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(KBr) 3300–2500 (br), 1728, 1462, 1430, 1408, 1270, 1253, 1225, 1104, 760, 695, 676 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_6$: C, 55.47; H, 4.23. Found: C, 55.34; H, 4.24.

2,3-*O*-Benzylidene-*N*,*N*′-dibenzyl-*N*,*N*′-ethylenetartramide.[17] A solution of benzylidenetartaric acid (1.19 g, 5.0 mmol), dibenzylethylenediamine (1.18 mL, 5.0 mmol, Aldrich), and Et_3N (4.2 mL, 30 mmol) in dry $CHCl_3$ (80 mL) was added dropwise over 5 h to a refluxing solution of *N*-methyl-2-chloropyridinium iodide (3.83 g, 15.0 mmol) in dry $CHCl_3$ (80 mL). The solution was refluxed overnight, extracted with saturated aqueous $NaHCO_3$ (150 mL), washed with water (2 × 150 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (on several occasions the product crystallized at this stage) and filtered through 50 g of 60–230-mesh silica gel, using 1:1 hexane–EtOAc as eluant, to give 1.15 g (52%) of the title compound as a crystalline solid. This material was generally recrystallized from CH_2Cl_2–hexane before the next step. This reaction is somewhat less efficient when performed in CH_3CN (35–40% yield; 20-mmol scale): mp 110–111 °C; $[\alpha]_D^{25}$ +58.6° (*c* 1, $CHCl_3$) for the (*R*,*R*) isomer; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.7–7.74 (m, 2 H), 7.20–7.45 (m, 13 H), 6.24 (s, 1 H), 4.96 (A of AB, J = 6.7 Hz, 1 H), 4.84 (B of AB, J = 6.7 Hz, 1 H), 4.77 (d, J = 14.7 Hz, 1 H), 4.75 (d, J = 14.7 Hz, 1 H), 4.44 (d, J = 14.8 Hz, 2 H), 3.15–3.44 (m, 4 H); ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ 170.6, 168.4, 136.6, 136.4, 134.9, 129.9, 129.0, 128.9, 128.4, 128.3, 128.1, 128.0, 127.6, 106.6, 76.6, 76.4, 52.0, 51.7, 49.2; IR ($CHCl_3$) 1680, 1495, 1470, 1455, 1435, 1235, 1110 cm^{-1}; mass spectrum (EI, 270 °C) m/z 442 (M^+). Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.29; H, 5.92; N, 6.33. Found: C, 72.91; H, 5.89; N, 6.30.

***N*,*N*′-Dibenzyl-*N*,*N*′-ethylenetartramide (DBETA, 4).** A solution of the benzylidene acetal (3.35 g, 7.57 mmol) in HOAc (30 mL) and H_2O (10 mL) was heated at reflux for 17 h. The solvent was then removed at reduced pressure and dried by coevaporation with heptane and absolute EtOH. The crude product was crystallized from 30 mL of 2:1 $CHCl_3$–Et_2O, giving 2.32 g (87%) of **4**. A second crystallization from 21 mL of 7:3 EtOH–H_2O gave analytically pure material that was used in all allylboration experiments: m.p. 202–203 °C; $[\alpha]_D^{25}$ −73.9° (*c* 1, dioxane, after 15-min equilibration) for the (*R*,*R*) isomer; ^1H NMR ($DMSO d_6$, 90 °C) δ 7.18–7.38 (m, 10 H), 4.31 (s, 2 H), 4.27 and 4.13 (AB system, J = 14.7 Hz, 4 H, CH_2Bzl), 3.65–3.80 (m, 2 H), 3.40–3.60 (m, 2 H); IR (KBr) 3375, 1620, 1452, 1066, 743, 698 cm^{-1}; mass spectrum (EI, 250 °C) m/z 354 (M^+). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.56; H, 6.43; N, 8.04.

Allylboronate 5. A suspension of **4** (200 mg, 0.56 mmol) in dry CH_2Cl_2 (5 mL) was treated with triallylborane (98 μL, 0.56 mmol) at 23 °C. The suspension became a clear solution within a few minutes and was stirred for 3 h before being concentrated in vacuo with exclusion of moisture. The resulting white foam was stripped overnight at 0.1 mmHg to give reagent **5**, which was used directly in the experiments described in Tables I and II: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18–7.33 (m, 10 H), 5.87–6.05 (m, 1 H), 5.11 (d, J = 17.1 Hz, 1 H), 4.96–5.02 (m, 1 H), 4.98 (s, 2 H, C*H*O), 4.73 (d, J = 14.0 Hz, 2 H), 4.40 (d, J = 14 Hz, 2 H), 3.35 (d, J = 15.0 Hz, 2 H), 3.14 (d, J = 15 Hz, 2 H), 2.01 (d, J = 7.3 Hz, 2 H, CH_2B); ^{13}C NMR ($CDCl_3$, 76.7 MHz) δ 169.7, 136.4, 132.8, 129.0, 128.4, 128.1, 115.9, 77.0, 52.0, 49.3.

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Registry No. (*R*,*R*)-**4**, 112897-01-5; (*R*,*R*)-**5**, 112897-02-6; **6**, 38270-72-3; **7**, 140-28-3; **8a**, 97826-89-6; **8b**, 112897-04-8; **8c**, 79026-61-2; **9a**, 112897-05-9; **9b**, 112897-06-0; **9c**, 94233-73-5; **10a**, 112897-07-1; **10b**, 112897-08-2; **10c**, 94233-74-6; **11**, 15186-48-8; **12**, 79364-35-5; **13**, 87604-46-4; *c*-$C_6H_{11}CHO$, 2043-61-0; C_6H_5CHO, 100-52-7; *t*-C_4H_9CHO, 630-19-3; (TBDPS)OCH_2CH_2CHO, 112897-03-7; $BzlOCH_2CHO$, 60656-87-3; (*S*)-c-$C_6H_{11}CH(OH)CH_2CH{=}CH_2$, 94340-22-4; (*S*)-$C_6H_5CH(OH)CH_2CH{=}CH_2$, 77118-87-7; (*S*)-*t*-$C_4H_9CH(OH)CH_2CH{=}CH_2$, 67760-86-5; (*R*)-(TBDPS)-$OCH_2CH_2CH(OH)CH_2CH{=}CH_2$, 112897-09-3; (*S*)-$BzlOCH_2CH(OH)CH_2CH{=}CH_2$, 88981-35-5; 2,3-*O*-benzylidene tartaric acid, 83529-41-3; *N*-methyl-2-chloropyridinium iodide, 14338-32-0; 2,3-*O*-benzylidene-*N*,*N*′-dibenzyl-*N*,*N*′-ethylene tartrate, 112897-00-4; *N*,*N*′-ethylene tartrate triallylborane, 688-61-9.

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[17] We thank Dr. Kaori Ando and Dan Powers for assisting with the optimization of this reaction.

On the Electron–Proton–Electron Mechanism for 1-Benzyl-1,4-dihydronicotinamide Oxidations

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Abstract: The reaction of 1-benzyl-1,4-dihydronicotinamide (BNAH) with several ferrocenium (Fc^+) salts in aqueous propanol was studied. The mechanism was shown to involve electron–proton–electron transfer with rate-limiting electron transfer from BNAH to Fc^+. From the rate constants and $E°(Fc/Fc^+)$ values, the $E°(BNAH/BNAH^{\bullet+})$ was estimated to be 0.89 V (SCE). The electrochemistry of BNAH was investigated in order to evaluate a previously determined $E°(BNAH/BNAH^{\bullet+})$. A reconsideration of the literature data for (non-DDQ) quinone oxidations of reduced nicotinamide adenine dinucleotide (NADH) in water and BNAH in CH_3CN shows that the data are consistent with a hydride-transfer mechanism and inconsistent with an electron–proton–electron mechanism involving free $NADH^{\bullet+}$. A mechanism in which the hydride is transferred by electron–proton–electron transfer within one complex cannot be excluded.

The mechanisms of nonenzymatic oxidations of reduced nicotinamide adenine dinucleotide (NADH) and NADH model compounds like 1-benzyl-1,4-dihydronicotinamide (BNAH) have attracted continuing attention.[1] An issue of particular interest has been the three-step mechanism involving sequential electron–proton–electron transfer (e–p–e) as an alternative to a one-step hydride transfer for conversion of NADH to NAD^+. Evidence has been reported to support the e–p–e mechanism for reactions involving thermal,[2-5] photochemical,[5-10] and electrochemical[10-15] oxidation. Each of these cases involved strong

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Table I. $E°$ Estimates

couple	$E°$, V (SCE)	solvent	method[a]	ref
BNAH/BNAH$^{•+}$	0.76	CH_3CN	Fl	6b
BNAH/BNAH$^{•+}$	0.60	CH_3CN	Fl	10
BNAH/BNAH$^{•+}$	0.57	CH_3CN, 0.1 M Bu_4NClO_4	CV	10
NADH/NADH$^{•+}$	0.90	propanol/H_2O, 0.1 M $NaClO_4$, pH 7.0[b]	Fc	2
NADH/NADH$^{•+}$	0.81	propanol/H_2O, pH 7.0[c]	Fc	2
NADH/NADH$^{•+}$	0.76	H_2O, pH 7.0[d]	Fc′	15

[a] Fl, fluorescence quenching of excited BNAH by electron acceptors; CV, cyclic voltammetry; Fc, kinetic studies of ferrocenium oxidations by using spectroscopy; Fc′, kinetic studies of ferrocenmium oxidations with cyclic voltammetry. [b] 1-Propanol/water, 1:1 by volume, 0.1 M $NaClO_4$, 0.01 M phosphate buffer. [c] Same as *b* without $NaClO_4$. [d] Sorenson buffer.

one-electron oxidants with minimal hydride-acceptor properties. Evidence has also been offered to support the hydride-transfer mechanism, not e–p–e, for reactions in which NADH model compounds are oxidized by NAD$^+$ model compounds.[16,17] There are, however, a number of reactions that are superficially of the hydride type for which e–p–e type mechanisms may hold.

One such reaction type is quinone oxidations of NADH and its model compounds. NADH reactions were studied by McFarland and co-workers[18] and by Carlson and Miller (CM),[19] while BNAH and other models were studied by Tanaka and co-workers.[20] Fukuzumi, Kommitsu, Hironaka, and Tanaka (FKHT) summarized the considerable volume of their previous work, offered some new interpretive methods, commented on the CM paper, and concluded that quinones oxidize NADH and its model compounds by an e–p–e type mechanism.[1] Here, we offer new experimental evidence on BNAH oxidations and offer several alternative interpretations to those advanced by FKHT.

Results and Discussion

Table II. Cyclic Voltammetry and Vis Spectral Data for Ferroceniums[a]

Fc$^+$	substituents	$E°$, mV (SCE)[b]	λ_{max} (ϵ)[c]
1$^+$	1,1′-dimethyl	198	650 (320)
2$^+$	1,1′-diethyl	179	660 (310)
3$^+$	3-ethyl-1,1′-dimethyl	160	676 (280)
4$^+$	1,1′,3-triethyl	150	674 (300)
5$^+$	1,1′,2,2′-tetramethyl	80	678 (400)

[a] Measured in 50% aqueous 1-propanol containing 0.1 M $NaClO_4$ and 0.01 M phosphate buffer, pH 7.0. [b] From cyclic voltammetry on the ferrocene. Average of at least 10 runs at 100 mV s^{-1}. [c] As $Fc^+PF_6^-$ in the absence of oxygen.

Table III. Reaction Rates for BNAH with Fc$^+$ [a]

ferrocenium	$\bar{k}_2$,[b] M^{-1} s^{-1}	no. of runs
1$^+$	4.62 ± 0.10	5
2$^+$	2.23 ± 0.08	8
2^{+c}	2.26 ± 0.17	6
3$^+$	1.30 ± 0.04	7
4$^+$	0.90 ± 0.03	9
5$^+$	0.11 ± 0.01	10
5^{+d}	0.14 ± 0.01	10
5^{+e}	0.28 ± 0.03	8

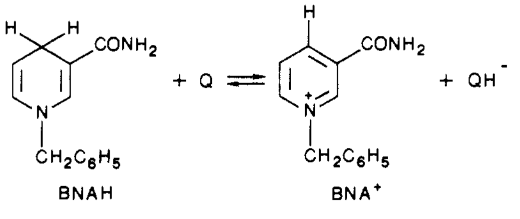
[a] In 50% aqueous 1-propanol, 0.01 M pH 7.0 phosphate buffer, 0.1 M $NaClO_4$. [b] Average second-order rate constant obtained by dividing the pseudo-first-order rate constant by the initial concentration of the BNAH. [c] 0.2 M $NaClO_4$. [d] Solvent mixture contained no added $NaClO_4$. [e] In CH_3CN, 0.1 M $NaClO_4$

Table IV. Cyclic Voltammetry Data for BNAH Oxidation[a]

ν, mV s^{-1}		200	100	50	20
E_P, mV	C	343	333	323	310
	Pt	323	306	297	287
$E_{P/2}$, mV	C	262	253	240	225
	Pt	246	219	211	197
$(E_P - E_{P/2})$, mV	C	81	80	83	85
	Pt	87	87	86	90
$i_p/C_{BNAH}A$, μA mM^{-1} cm^{-2}	C	431	301	208	130
	Pt	419	263	181	113

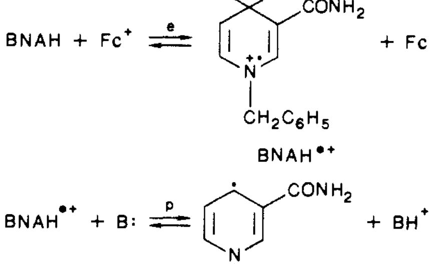
[a] At carbon [BNAH] = 0.54 mM, 0.1 M Bu_4ClO_4. At Pt [BNAH] = 0.80 mM, 0.5 M Bu_4ClO_4.

The mechanisms of interest here are hydride transfer and e–p–e.[21] In hydride transfer the 4-hydrogen is transferred in one step to the oxidant. As illustrated with BNAH and a quinone (Q) as oxidant, BNA$^+$ is produced directly.

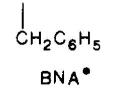


(1)

The e–p–e mechanism has two important variants. In one, electron transfer from BNAH to the oxidant is followed by separation of the resulting pair, providing BNAH$^{•+}$ free in the solution. This BNAH$^{•+}$ is then deprotonated by a base to give BNA$^•$, and finally a second oxidant molecule removes the second electron. Illustrated for ferrocenium (Fc$^+$) as oxidant:



(2)



(3)

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(21) The alternative mechanism involving hydrogen-atom transfer followed by electron transfer in one complex is not treated here. CM concluded it was consistent with their data. FKHT found it inconsistent with their data. It is suggested that unless NAD$^•$, QH$^•$ is a discreet, metastable intermediate, this mechanism is moot.

$$\mathrm{BNA^{\cdot} + Fc^{+} \rightarrow BNA^{+} + Fc} \qquad (4)$$

The second variant, which will be denoted $\overline{\text{e–p–e}}$, is one where a two-electron oxidant also acts to accept the proton, so that all three steps take place within one complex. As illustrated for a quinone (Q) oxidant, BNAH and Q come together and react by $\overline{\text{e–p–e}}$; when the pair separates, the products are those of a net hydride transfer:

$$\mathrm{BNAH + Q} \rightleftarrows \overline{\mathrm{BNAH, Q}} \overset{\mathrm{e}}{\rightleftarrows} \overline{\mathrm{BNAH^{\cdot +}, Q^{\cdot -}}} \overset{\mathrm{p}}{\rightleftarrows}$$
$$\overline{\mathrm{BNAH^{\cdot}, QH^{\cdot}}} \overset{\mathrm{e}}{\rightleftarrows} \overline{\mathrm{BNA^{+}, QH^{-}}} \rightleftarrows \mathrm{BNA^{+} + QH^{-}} \qquad (5)$$

This $\overline{\text{e–p–e}}$ mechanism will be difficult to distinguish from hydride transfer. Accurate descriptions[22] would take into account both tunneling and the details of solvent motion. These naturally cloud the simple distinction between hydride and $\overline{\text{e–p–e}}$. Even in simpler descriptions, if there are no metastable intermediates along the potential energy surface, the question of one step vs three is moot.

A number of one-electron oxidants have been used to oxidize NADH and its analogues by the e–p–e mechanism.[2-10] In these cases kinetic studies have given results, e.g., reaction order, isotope effects, pH effects, and agreement with Marcus theory, consistent with expectations. An appropriate CIDNP effect has also been observed.[24] It has been realized that $\mathrm{NADH^{\cdot +}}$ and $\mathrm{BNAH^{\cdot +}}$ are rather unstable so it takes rather powerful one-electron oxidants to generate them, and they react rapidly and irreversibly with base. Because of this energetic situation, e–p–e reactions show either the first step (eq 2) rate limiting (an example is NADH with $\mathrm{Fc^{+}}$ in aqueous propanol)[2] or a reversible first-step with rate-limiting deprotonation (eq 3) (an example is N-methylacridan with ferricyanide in the presence of ferrocyanide in aqueous $\mathrm{CH_3CN}$[3b]).

The comparison of kinetic and thermodynamic data for these oxidations has played a central role in previous considerations. Of special interest here are rates and equilibria for electron transfer from NADH and BNAH (as a typical model compound) to various oxidants. In this regard the $E°(\mathrm{BNAH/BNAH^{\cdot +}})$ and $E°(\mathrm{NADH/NADH^{\cdot +}})$ are fundamental to our understanding.[25] The problem is that $\mathrm{NADH^{\cdot +}}$ and $\mathrm{BNAH^{\cdot +}}$ are so unstable that the $E°$ cannot be directly measured. These values have, however, been estimated from kinetic data. Table I gives values of BNAH in $\mathrm{CH_3CN}$ and for NADH in aqueous media. There are a number of concerns with these values and their use. (1) In general, insufficient attention has been given to the variations in $E°$ with solvent and electrolyte.[2,26] (2) There is a specific concern that BNAH and NADH experiments have used different solvents. This is addressed herein. (3) The accuracy of entry 3 is of concern for several reasons discussed below. (4) There is also a concern about $E°(\mathrm{BNAH/BNAH^{\cdot +}})$ in $\mathrm{CH_3CN}$ determined by fluorescence quenching. Entries 1 and 2 in Table I were determined by using the same method, with many of the same oxidant quenchers, and produced rate constants that were in agreement. Even so, the $E°$ values that were calculated from this data by using Rehm–Weller theory are quite different.[6b,10] We are unable to comment on this discrepancy.

BNAH Oxidized by Ferroceniums. In a previous study it was shown that a series of $\mathrm{Fc^{+}}$ reacted with NADH in aqueous propanol by rate-limiting electron transfer.[2] The rate constants and the $E°$ of the various $\mathrm{Fc^{+}/Fc}$ couples were used to estimate $E°(\mathrm{NADH/NADH^{\cdot +}})$. In the present study, this approach was extended to BNAH. Since the oxidants and the solvent were the same, we are thus able to know if BNAH behaves the same as NADH (in detail) and to estimate the $E°(\mathrm{BNAH/BNAH^{\cdot +}})$ in this protic medium. Substantial solvent effects on the thermodynamics and kinetics are possible, and because NADH has two anionic phosphates, while BNAH is neutral, some effects are possible that do not directly relate to the dihydropyridine moiety, which is the site of oxidation.

The ferrocenes **1**–**5** were purchased or prepared. The ferrocenium hexafluorophosphates $\mathbf{1^{+}}$–$\mathbf{5^{+}}$ were prepared and characterized spectroscopically. The vis spectra (Table II) of the $\mathrm{Fc^{+}}$ were used to follow the reaction rate. The $E°(\mathrm{Fc/Fc^{+}})$ were measured by cyclic voltammetry against SCE in a solvent consisting of 50% aqueous 1-propanol containing 0.1 M $\mathrm{NaClO_4}$, and 0.01 M phosphate buffer pH 7.0. (This mixture including electrolyte will be called 50% aqueous propanol.) In each case the electrochemistry was reversible as indicated by $\Delta E_{\mathrm{p}} = 58 \pm 2$ mV and by equal anodic and cathodic peak currents.

Kinetic runs were also made as before[2] in 50% aqueous propanol. In general, BNAH was initially present in 15–20-fold excess over the $\mathrm{Fc^{+}PF_6^{-}}$. The solutions were degassed with argon as it was determined that oxygen reacted with $\mathrm{Fc^{+}}$ and affected the results. The rate at 30 °C was measured by following the disappearance of $\mathrm{Fc^{+}}$. The pseudo-first-order rate constants were good (correlation 0.999) over at least 3 half-lives. Table III summarizes the results.

The reaction of $[4,4\text{-}^{2}\mathrm{H}_2]$- or $[4\text{-}^{2}\mathrm{H}]$BNAH with 1,1′,3-triethylferrocenium ($\mathbf{3^{+}}$) showed that $k_{\mathrm{H}}/k_{\mathrm{D}}$ was 1.0 ± 0.2. When the oxidation of BNAH with $\mathbf{5^{+}}$ was run without added $\mathrm{NaClO_4}$, the rate did not change. Also, when BNAH was oxidized with $\mathbf{2^{+}}$ by using 0.2 M $\mathrm{NaClO_4}$, the observed rate constants were within experimental error of those determined in 0.1 M $\mathrm{NaClO_4}$ (Table III). Thus, there is no appreciable isotope effect, consistent with rate-limiting electron transfer, and there is no salt effect, which is consistent with a reaction involving no change in the net charge.

These rate constants can be compared with the driving force by a plot of log k vs $E°$ for the various $\mathrm{Fc^{+}}$. This plot is linear (correlation 0.999) with a slope of 13.52 $\mathrm{V^{-1}}$ and an intercept of −5.30. As we have previously indicated,[2] such data indicate that the rate is determined by endothermic rate-limiting electron transfer, where the separation of the $\mathrm{BNAH^{\cdot +}}$, Fc pair is the actual rate-limiting process. Extrapolation of this line to the diffusion-controlled limit provides a method for the estimation of $E°$.[27] Choosing log $k_{\mathrm{diff}} = 10$ leads to a value of $E°(\mathrm{BNAH/BNAH^{\cdot +}}) = 0.89$ V (SCE).[28]

In comparison with previous results using $\mathrm{Fc^{+}}$ with NADH in this solvent,[2] the results are extremely similar. In 50% aqueous propanol, $E°(\mathrm{NADH/NADH^{\cdot +}})$ is 0.90 V. In this solvent in the absence of the 0.1 M $\mathrm{NaClO_4}$, $E°(\mathrm{NADH/NADH^{\cdot +}})$ is 0.81 V. Kinetically, using BNAH with dimethylferrocenium in 50% aqueous propanol as an example, BNAH reacts 6.3 times faster than NADH.

Since $E°(\mathrm{Fc/Fc^{+}})$ are electrolyte dependent[2] but BNAH rate constants are not, this indicates that $E°(\mathrm{BNAH/BNAH^{\cdot +}})$ is electrolyte dependent, just like $\mathrm{Fc/Fc^{+}}$, so the driving force effects balance. In the case of the dianionic NADH, these effects do not balance, and the NADH rate varies with electrolyte concentration.

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(25) This paper will follow the literature in this field in that "$E°$" is used to designate a thermodynamic value that might be better designated an apparent $E°$. Activity coefficients are not considered and the effects of electrolyte concentration are often treated superficially. The reader should, of course, be aware that changes in apparent $E°$ with solvent and electrolyte may be due to changes in liquid junction potential between the reaction medium and the reference electrode medium. In this paper, all potentials are referred to SCE.

(26) A previous estimate of $E°(\mathrm{NADH/NADH^{\cdot +}}) = 0.76$ V (SCE) in water, Sorenson buffer determined by Masue et al.[15] should be considered the best value available for water-electrolyte solution.

(27) Andrieux, C. P.; Blochman, C.; Dumas-Bouchiat, J. M.; Saveant, J. M. *J. Am. Chem. Soc.* **1979**, *101*, 3431. Evans, D. H.; Xie, N. *J. Am. Chem. Soc.* **1983**, *105*, 315.

(28) To estimate the variation in $E°(\mathrm{BNAH/NAH^{\cdot +}})$ induced by extrapolation with the theoretical 16.6 $\mathrm{V^{-1}}$ slope, rather than the experimental slope, one can take a data point and make it part of a theoretical 16.6 $\mathrm{V^{-1}}$ line. Using the $\mathbf{3^{+}}$ point with log $k = 0.11$ and $E° = 160$ mV, this procedure leads to $E°(\mathrm{BNAH/BNAH^{\cdot +}}) = 0.75$ V. This variation points out the limitations of this method, which involves a long extrapolation of the log k vs $E°$ plot.

It is concluded that, when compared in the same solvent, BNAH and NADH electron-transfer reactions are thermodynamically and kinetically very similar. The variations in E° shown in Table I are due to normal solvent–electrolyte effects or due to inaccuracies in the kinetic estimates.

In view of the concerns with entries 1–3 in Table I, it was of interest to extend the BNAH data to CH_3CN solvent. The E° and reaction rate constant were measured as before with 1,1′,2,2′-tetramethylferrocenium as oxidant. The rate in CH_3CN, 0.1 M $NaClO_4$ was 2.5 times that for 50% aqueous propanol. The $E^\circ(Fc/Fc^+)$ value in this electrolyte was correspondingly larger by 20 mV. Thus, it can be concluded that the small rate increase was due to the small change in $E^\circ(Fc/Fc^+)$. This suggests that $E^\circ(BNAH/BNAH^{\bullet+})$ in CH_3CN, 0.1 M $NaClO_4$ is very similar to that in 50% aqueous propanol, that is about 0.89 V (SCE). This value is larger than the values previously estimated, and we turn now to examine one of those literature values.

BNAH Electrochemistry. Cyclic voltammetry has been used by FKHT to estimate $E^\circ(BNAH/BNAH^{\bullet+})$, $E^\circ(BNA^\bullet/BNA^+)$ and the similar one-electron E° values for other model compounds. In this section, we report experimental results on BNAH oxidation and begin by briefly commenting on their approach to cyclic voltammogram analysis. Because the voltammograms showed irreversible behavior due to product, e.g., $BNAH^{\bullet+}$, instability, the E° values were not measured directly. Instead a new, general theory was developed to allow an estimate of E° values from irreversible cyclic voltammograms for cases where the heterogeneous electron transfer is rate limiting. The approach uses Marcus theory to derive the following relationship between the cyclic voltammetry peak potential (E_p) and E° for the one-electron process of interest, i.e., $E^\circ(BNAH/BNAH^{\bullet+})$,

$$E_p = E^\circ(BNAH/BNAH^{\bullet+}) + 4(1 - 2\beta)\Delta G_0^* \quad (6)$$

β is the transfer coefficient for the rate-limiting heterogeneous electron transfer and ΔG_0^* is the activation free energy for the reaction when the driving force is zero. In practice E_p and $E_{p/2}$ values were measured at several sweep rates for BNAH oxidation. $E_p - E_{p/2}$ was used to calculate β from eq 7. A plot of E_p vs $4(1 - 2\beta)$ was then extrapolated to $\beta = 0.5$, and this potential was taken as E°.

$$E_p - E_{p/2} = 1.857(RT/\beta F) \quad (7)$$

This treatment involves four untested assumptions. (1) It is assumed that the transfer coefficient, β, which depends on potential, can be evaluated at E_p by using eq 7. β may[29] or may not[30] vary with E, and its measurement is nontrivial. Indeed, most treatments of heterogeneous electron transfer kinetics avoid the problem by assuming β is independent of E. The derivation of eq 7[31] assumes that β does not change, and an obvious implication of the form of eq 7 is that there is one value of β at both E_p and $E_{p/2}$. The BNAH experiments[1] gave ($E_p - E_{p/2}$) values as large as 200 mV with the assumption that β does not change with E over this range. These experiments gave a total variation in the other parameter, E_p, as ν changed less than 200 mV, with the assumption that β changes with E. This seems incongruous. (2) The assumption that $\beta = 0.5$ at E° is not necessarily valid. It is, however, a reasonable assumption. (3) It is assumed that a measured potential, i.e., E_p, can be taken as a measure of the Marcus theory driving force, ΔG°. Most authors[29,30] have assumed that the measured potential must be corrected for double-layer effects to obtain theoretically relevant transfer coefficients. This would seem necessary if potential dependence of the transfer coefficient is to be revealed. Beyond that it must be recognized that the choice of E_p to represent the driving force was arbitrary. E_p has no thermodynamic significance, and if some other point along the voltammogram was chosen, a different E° would be obtained. (4) It is assumed that the voltammetric wave shape only reflects the intrinsic kinetic properties of the $BNAH/BNAH^{\bullet+}$ reaction. The BNAH reactions are not the simple one-electron transfers treated by theory, and the complexity of the overall reaction chemistry might affect the experimental observations. In particular, the kinetics of heterogeneous electron transfer reactions are sensitive to surface structure, and this structure can change as the concentrations of the various products build up during a single cyclic voltammetric sweep.

In light of these problems, it is suggested that the FKHT method may not give reliable E° values.

Turning now to experimental results, it has been reported that for BNAH oxidation in CH_3CN, the cyclic voltammetric peak width depends substantially on sweep rate.[1] We have now reinvestigated this point as well as some preparative aspects of BNAH oxidation.

BNAH electrochemistry in CH_3CN was explored with 0.1 M Bu_4NClO_4 in purified, degassed solvent. An extensive investigation was carried out to determine the effect of electrode material and electrode pretreatment on the voltammograms. It was determined that good reproducibility was obtained by use of a polished glassy carbon electrode and by limiting the potential range of the scan to −100 to 640 mV (vs Ag/0.01 M $AgClO_4$). Identical cyclic voltammograms were observed under conditions where the working electrode was removed, repolished, and sonicated after one cycle or under conditions where the electrode was not removed and successive cycles were recorded at various sweep rates, or, finally, under conditions where the electrode was electrochemically pretreated in the solvent-supporting electrolyte before BNAH was added by recording 10 consecutive CV's over the −100 to +640 mV range at 100 mV s^{-1}. In all these cases a peak width of 80 ± 5 mV was obtained along with a reproducible E_p (±5 mV) at a given scan rate. Table IV contains representative data for a cyclic voltammetry experiment in which the scan rate (ν) was varied in the 20–200 mV s^{-1} range. Similar data were obtained for 1.0 mM BNAH solutions. In all cases E_p vs log ν plots gave slopes of 30 ± 5 mV/decade with correlation coefficients ≥0.99. Also, i_p vs $\nu^{1/2}$ plots were linear indicating diffusion-limited oxidation of BNAH.

With use of a platinum working electrode, which had been cleaned by soaking it in concentrated nitric acid[1] for 10 min followed by a water wash and drying, similar results were obtained (Table IV shows data for 0.5 M Bu_4ClO_4). Before reproducible CV's could be obtained in the −200 to +540 mV range, the potential was scanned from −200 to +1600 to −1600 mV at 100 mV/s for two cycles (reproducible CV's in the −200 to +540 mV range were obtained by pretreating either before or after the addition of BNAH). The data reported in Table IV was obtained after such an electrochemical pretreatment. Without scanning the potential cathodic very broad, featureless CV's were obtained in the −200 to +540 mV range.

Further details of BNAH electrochemistry are provided below, but it is emphasized that our experimental results do not show peak widths that vary significantly with sweep rate. The variation found by FKHT might have resulted from uncompensated resistance or electrode surface effects. In any electrochemical reaction involving rate-limiting electron transfer, the nature of the electrode surface is extremely important. This has been previously demonstrated for NADH oxidations where product adsorption broadened the peaks.[12] In the $BNAH/CH_3CN$ case, the electrode pretreatment and restriction of the range over which the electrode potential was swept were shown to be important in obtaining reproducible voltammograms (with narrow peak widths).

It has been known since the pioneering study of Haas and Blaedel[14] that BNAH oxidation in CH_3CN is complicated and does not lead to BNA^+ cleanly. This could be involved in the problem of a reliable E° determination, and we present here several observations. As studied by Haas, BNAH oxidation in CH_3CN in the absence of base gives little BNA^+, mostly the dimeric product **6**. We have also isolated this product, characterized its structure spectroscopically, and studied its electrochemical reactivity. Because (1) BNAH plus acid in CH_3CN gives the dimer,

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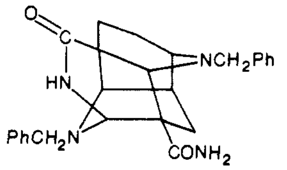
[29] Saveant, J. M.; Tessier, D. *Faraday Discuss. Chem. Soc.* **1982**, *74*, 57.

[30] See references in Gileadi, E. *J. Electrochem. Soc.* **1987**, *134*, 117. Anson, F. C.; Weaver, M. J. *J. Phys. Chem.* **1976**, *80*, 1861.

[31] Nicholson, R. S.; Shain, I. *Anal. Chem.* **1964**, *36*, 706.

(2) BNAH oxidation in CH_3CN with added pyridine does not give the dimer, and (3) the anodic oxidation of BNAH without pyridine in CH_3CN consumes only 0.7 F mol^{-1}, it is concluded that the dimer formed in the electrochemical cell comes not by anodic oxidation, but by reaction of BNAH with electrogenerated acid.

The cyclic voltammograms of BNAH and of the dimer **6** indicate that **6** is formed during a single sweep. Thus, the BNAH voltammogram in CH_3CN shows two peaks. The E_p of the second peak corresponds to that for **6**. Addition of pyridine to the BNAH solution increases the first peak height and causes the second peak due to **6** to disappear.



Thus, it is shown that the acid-catalyzed chemistry affects the BNAH voltammogram. This means that the assumption made by FKHT for their $E°$ determination that the reaction was simply formation of BNA^+ by e–p–e is incorrect. It may be possible to make that assumption for BNAH oxidation in the presence of pyridine. However, using excess pyridine in CH_3CN–0.1 M Bu_4NClO_4 we again find an essentially constant peak width (90 ± 5 mV) as the scan rate is varied.

These experiments have shown that under experimental conditions described here (1) the peak widths are narrow and do not vary substantially with sweep rate and (2) the oxidation product in the absence of pyridine is mainly **6** not BNA^+. These observations give concern that under the very similar conditions used by FKHT that the voltammetric measurements were not only controlled by the intrinsic kinetics of $BNAH/BNAH^{\bullet+}$. Combined with the concern about the assumptions made in using eq 6 and 7, it is concluded that the $E°(BNAH/BNAH^{\bullet+}) = 0.57$ for CH_3CN, 0.1 M Bu_4ClO_4 may not be accurate.

Oxidation by Quinones. Quinone oxidations of NADH and its model compounds are of interest in part because they provide a "risky test" for the intercession of electron transfer. Since phenoxides (Q^-), phenoxy radicals ($QH^\bullet$), and semiquinones ($Q^{\bullet-}$) are all energetically accessible, one must consider hydride, e–p–e, and $\overline{\text{e–p–e}}$ mechanisms as reasonable.[19] CM, following an earlier study by McFarland and co-workers, studied NADH oxidation by quinones in 0.5 M aqueous KCl solution and concluded that the data were consistent with hydride transfer but inconsistent with e–p–e. FKHT studied BNAH and other model compounds in acetonitrile and concluded that the mechanism was $\overline{\text{e–p–e}}$ followed by reaction of QH^- and Q generating QH_2 and $Q^{\bullet-}$. It is our goal here to reconcile these conclusions and to respond to several points raised by FKHT.

The CM study encompassed both *o*- and *p*-quinones (but not DDQ or dicyano quinone) at pH 7.0 in aqueous 0.05 M phosphate buffer, 0.5 M KCl. It was shown that the reaction was first order in NADH and first order in quinone. There was no pH effect on the rate. There was a primary kinetic isotope effect when NADH-d_2 was employed. These data ruled out e–p–e, since if the first e step was rate limiting there would be no isotope effect and if the p step was rate limiting there would be a pH effect.

The substituent effects were treated by plotting log k vs $E°(Q/QH^-$ at pH 7).[32] This gave one line for *o*-quinones and a separate line for *p*-quinones. The slopes of these lines were essentially the same and lead to a calculation of Brønsted $\alpha = 0.5$. It was thus concluded that the substituent effects were consistent with a hydride transfer mechanism.

This reasoning was criticized by FKHT, who suggested: "However, if the intrinsic barrier of the reaction (i.e. the activation Gibbs energy when the Gibbs energy change is zero) is sufficiently large, any homologous series of reactions gives a linear Gibbs energy relationship between log k_{obsd} and the Gibbs energy change of the reaction with $\alpha = 0.5$, providing no definitive information on the nature of the transition states." In response we simply point out that according to this quotation, if the mechanism is hydride transfer, there *must* be a linear log k vs $E°(Q/QH^-)$ plot. As CM had concluded, the data fulfill that obligation. The e–p–e mechanism (with rate-limiting p) cannot be tested in this way because thermodynamic data for $Q/Q^{\bullet-}$ in water at pH 7.0 are unavailable.

Another argument put forward by CM was that quinones reacted too rapidly to be involved in e–p–e. The argument was based on success in using Marcus theory to calculate the rates of NADH oxidations, which involved e–p–e mechanisms, and lack of success in calculating the rates where hydride transfer has been strongly implicated,[2] i.e., transfer between NAD^+ and NADH model compounds. In those cases the experimental rates were much larger than those calculated, assuming an e–p–e mechanism. Using $E°(NADH/NADH^{\bullet+}) = 0.69$ V (SCE),[33] CM found that *p*-quinones reacted 10^4 times faster than the prediction from Marcus theory, while *o*-quinones reacted 10^6 times faster than predicted.[33] Since an e–p–e reaction cannot be more rapid than the first e step, it was concluded that this was inconsistent with e–p–e.

FKHT criticized this conclusion, indicating that the CM calculation had ignored the work term, w_p. This term, which is the negative of the energy required to separate the $NADH^{\bullet+}{\cdot}Q^{\bullet-}$ pair, was indeed explicitly ignored by CM, under the assumption that it was small. FKHT argued that it is large.

The question concerns the calculation of the rate of the hypothetical reaction, single-electron transfer from NADH to Q. The answer can be found by considering eq 8, which describes

$$NADH + Q \rightleftarrows \overline{NADH, Q} \overset{\epsilon}{\rightleftarrows} \overline{NADH^{\bullet+}, Q^{\bullet-}} \rightleftarrows NADH^{\bullet+} + Q^{\bullet-} \quad (8)$$

the electron transfer in detail. Because Marcus theory treats the electron-transfer step (ϵ) within the pair, while the $E°$ values are concerned with the separated reactants and separated product ions, there need to be correction terms included to account for the energy change involved when the separated species are brought together. The "work term" of interest is w_p, the Coulombic energy gained when the product ions are brought together. Thus, the driving force for the electron transfer process should be

$$2.3RT \log K_\epsilon = F[E°(NADH/NADH^{\bullet+}) - E°(Q/Q^{\bullet-})] - w_p \quad (9)$$

In order for theory to satisfactorily account for the fast rate of *p*-quinones as suggested by FKHT, w_p would have to be about −8 kcal mol^{-1}. For *o*-quinones, w_p would have to be about −11 kcal mol^{-1}.[33] We contend that these values are too large. There are numerous w_p values in the literature for electron-transfer reactions in aqueous solutions. Calculations based on Debye–Hückel theory[34] indicate that w_p is smaller than −1 kcal mol^{-1} for monocation–monoanion pairs in water without KCl. If the dianionic phosphates of NADH are ignored, w_p is calculated for a monocation–monoanion pair in aqueous 0.5 M KCl to be a few tenths of a kilocalorie negative. If the net charge of NADH is used, the w_p is calculated for a pair of anions ($NADH^{\bullet+,2-}$, $Q^{\bullet-}$) to be slightly positive.

We conclude that it is unlikely that w_p is as large as −8 to −11 kcal mol^{-1} for NADH, quinone reactions in aqueous KCl. Therefore, within the limits of the low quality thermodynamic data the electron-transfer rates for NADH with quinones in

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[32] At pH 7 the stable product is QH_2. A plot of log k vs $E°(Q/QH_2)$ was nonlinear. This leads to the conclusion that the driving force for the kinetics is not QH_2 formation.

[33] The value $E°(NADH/NADH^{\bullet+}) = 0.76$ V determined for water with Sorenson buffer[15] is a more accurately determined value than 0.69 V for water and more appropriate for comparison with the 0.5 M aqueous KCl used for quinone oxidations. If $E° = 0.76$ V is used to calculate electron-transfer rates from NADH to quinones, these rate constants are 10^5 (para) to 10^7 (ortho) smaller than the experimental rate constants.

[34] See, for example: Haim, A.; Sutin, N. *Inorg. Chem.* **1976**, *15*, 476.

Table V. Isotope Effects on Oxidations by Quinones in CH_3CN

quinone	$E°(Q/Q^{\bullet-})$, V	k_H/k_D
2,3-dichloro-5,6-dicyano-*p*-benzoquinone	0.51	2.6
2,3-dicyano-*p*-benzoquinone	0.28	2.6
p-chloranil	0.01	5.3
p-bromanil	0	5.2
2,6-dichloro-*p*-benzoquinone	−0.18	5.6
2,5-dichloro-*p*-benzoquinone	−0.18	5.5
chloro-*p*-benzoquinone	−0.34	6.1
p-benzoquinone	−0.50	6.2
methyl-*p*-benzoquinone	−0.58	5.9
2,6-dimethyl-*p*-benzoquinone	−0.67	5.6
trimethyl-*p*-benzoquinone	−0.75	5.6

aqueous 0.5 M KCl are calculated to be much (10^5–10^7) slower than the experimental rates. Since the overall e–p–e or $\overline{\text{e–p–e}}$ reaction rate cannot be faster than the initial e step, this argues against these mechanisms. The rapid rate can of course, be explained if a concerted hydride transfer is involved, which avoids the high energy $NADH^{\bullet+}$.

With regard to BNAH, Q reactions in CH_3CN, Debye–Hückel theory leads to w_p of about −2 kcal mol^{-1}. Tanaka and co-workers measured w_p = −1.2 to −2.6 kcal mol^{-1} for $BNAH^{\bullet+}$, nitroaromatic$^{\bullet-}$ pairs in CH_3CN.[10] Martens and Verhoeven chose −1.5 kcal mol^{-1} for this same reaction with Debye–Hückel theory.[6b] Nitroaromatic anion radicals should be excellent models for $Q^{\bullet-}$.

FKHT have used the reaction of DDQ with BNAH in CH_3CN to estimate the w_p for $BNAH^{\bullet+}$, $DDQ^{\bullet-}$. They used

$$2.3RT \log k_{et} = F[E°(BNAH/BNAH^{\bullet+}) - E°(Q/Q^-)] - w_p \tag{10}$$

and employed their value of $E°(BNAH/BNAH^{\bullet+})$ = 0.60 V to calculate w_p = −7.1 kcal mol^{-1}. If, however, one uses the Martens and Verhoeven value of $E°(BNAH/BNAH^{\bullet+})$ = 0.76 V,[6b] which is in better agreement with our estimate, w_p is calculated to be −2.6 kcal mol^{-1}. It is concluded that even in CH_3CN without electrolyte, w_p should be smaller than about −3 kcal mol^{-1}.

Finally, we turn to the discussion of reasons why FKHT preferred the $\overline{\text{e–p–e}}$ mechanism to hydride transfer for quinone oxidations. There were two lines of argument that are of interest. One was isotope effects. The data (see also their Figure 7)[1] are in Table V for BNAH reacting with quinones in CH_3CN. FKHT argued that if hydride transfer with constant α = 0.5 was involved, k_H/k_D should be independent of the driving force for the reaction. Since this was not true, hydride transfer seemed unlikely compared to $\overline{\text{e–p–e}}$. We point out that the k_H/k_D values in Table V are essentially constant at 5.7 ± 0.5 except for two compounds, DDQ and dicyano quinone. These two quinones are powerful one-electron oxidants, and we agree that they do not react by hydride transfer. Instead an e–p–e or $\overline{\text{e–p–e}}$ mechanism is probably involved.

Having recognized that DDQ and dicyano quinone probably react by an e–p–e or $\overline{\text{e–p–e}}$ mechanism, this does not mean that the other quinones react by $\overline{\text{e–p–e}}$ as well. The dramatic change in k_H/k_D shows a change in mechanism, and it could well be true that most quinones react by hydride transfer. The observed $k_H/k_D \simeq 5.7$ is consistent with isotope effects for other reactions[16,17] where hydride transfer has been invoked, and it seems unwise to use the FKHT results to argue for $\overline{\text{e–p–e}}$, not hydride for quinones other than DDQ and dicyano quinone.

Second, we wish to comment on the calculations made by FKHT in which they dissected the thermodynamics of eq 5 for BNAH, Q reactions in CH_3CN. The concern here is simply that the thermodynamic values employed may be poorly chosen, leading to inaccurate conclusions. Comment has been made about $E°(BNAH^{\bullet+}/BNAH)$ and $E°(BNA^{\bullet}/BNA^+)$ and w_p for $BNAH^{\bullet+}$, $Q^{\bullet-}$. In addition we note that the values for $E°(QH^{\bullet}/QH^-)$ and $pK_a(Q^{\bullet-}/QH^{\bullet})$ were taken from aqueous solution studies. The transfer of these values from water to CH_3CN may not be proper because of the different hydrogen-bond characteristics of the two solvents. Indeed, a comparison of phenol pK_a's in water and acetonitrile is instructive in showing the substantial differences expected for equilibria involving QH^- in the two solutions.[35]

Considering these concerns with isotope effect interpretation and inaccurate thermodynamic values, we believe it is unwise to conclude that $\overline{\text{e–p–e}}$ not hydride transfer is the mechanism for the CM quinone oxidations of NADH in aqueous solution or for the (non-DDQ) quinone oxidations of BNAH in CH_3CN. The CM data clearly rule out e–p–e and argue on extrathermodynamic grounds that $\overline{\text{e–p–e}}$ is improbable. This latter conclusion is, however, based on an estimate for $E°(NADH/NADH^{\bullet+})$ and cannot be considered entirely conclusive. We suggest that an appropriate and challenging view is that one-step hydride transfer should not be replaced by the more complicated three-step $\overline{\text{e–p–e}}$ mechanism until evidence appears that unequivocally discriminates between these pathways. It should be recognized that an accurate description of the process must include solvent motion and tunnelling. Stepwise mechanisms and classical transition state theory may be insufficient for an accurate description of the process.

Experimental Section

Ferrocenes. 1,1′-Dimethylferrocene was purchased from Aldrich (97%) and recrystallized from $EtOH/H_2O$. 1,1′-Diethylferrocene was prepared via the Clemmensen reduction of 1,1′-diacetylferrocene[36] (97%, Aldrich). 3-Ethyl-1,1′-dimethylferrocene was prepared via the acetylation of 1,1′-dimethylferrocene[37] followed by $LiAlH_4/AlCl_3$ reduction of the 3-acetyl-1,1′-dimethylferrocene isomer. 1,1′,3-Triethylferrocene was prepared via the acetylation of 1,1′-diethylferrocene followed by $LiAlH_4/AlCl_3$ reduction the 3-acetyl-1,1′-diethylferrocene isomer.[38] 1,2,1′,2′-Tetramethylferrocene was synthesized according to Ozman,[39] beginning with the esterification of crotonic anhydride with 2-propanol in benzene at reflux catalyzed by methanesulfonic acid, which proceeded in 61% yield. Cyclization of dimethylcyclopent-2-en-1-one was effected in 54% yield by reaction of isopropyl crotonate with polyphosphoric acid at 100 °C for 1 h with constant mechanical stirring. To a three-necked round-bottom flask equipped with a septum, addition funnel, and condenser was added 2.3 g of $LiAlH_4$ along with 200 mL of dry ether and a stir bar. The flask was cooled in a salt/ice bath. Dimethylcyclopent-2-en-1-one isomers (16 g) in 75 mL of ether were added to the flask, under a continuous stream of argon, slowly. After 30 min, the unreacted $LiAlH_4$ was quenched with distilled H_2O, and then 130 mL of 15% HCl was added. The flask was removed from the ice bath and brought to reflux for an additional 4 h. Conventional workup gave a yellow-green liquid (12.5 g, >90% yield). To avoid oligomerization, this liquid was *immediately* transferred to a three-necked flask equipped with an addition funnel, septum, and condenser along with 200 mL of benzene and a stir bar; 90 mL of a 1.4 M CH_3Li in ether solution was added slowly, and then the solution was refluxed for 4 h. The flask was then placed in ice/salt bath for 30 min prior to the addition of a THF solution (125 mL) containing 6.15 g of $FeCl_3$ (anhydrous) and 1.3 g of Fe dust also at 0 °C before addition. After addition the flask was removed from the ice bath and allowed to react for 12 h at room temperature with stirring. The reaction mixture was poured on ice, and unreacted CH_3Li was quenched with 15% NH_4Cl. Conventional workup gave an orange-red liquid. The mixture was chromatographed on silica with hexane followed by benzene, giving **5**: ^1H NMR ($CDCl_3$) δ 1.89 (12 H), 3.81 (6 H); mass spectrum base peak at m/e 242 due to molecular ion, $M^{\bullet+} - CH_3$ peak (11% of base peak) at m/e 227.

^1H NMR and mass spectra were obtained on all ferrocenes, corroborating their proposed structure.

Ferrocenium Hexafluorophosphate Salts. The ferrocenium hexafluorophosphate salts were prepared for the following ferrocene derivatives: 1,1′-dimethyl, 1,1′-diethyl, 3-ethyl-1,1′-dimethyl, 1,1′,3-triethyl, and 1,2,1′,2′-tetramethyl. The general procedure[40,41] for preparing the

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Table VI. Elemental Analysis Results for Ferrocenium Hexafluorophosphate Salts

		% composition[a]		
Fc^+	mol formula (mol wt)	% C	% H	% P
1^+	$C_{12}H_{14}FePF_6$ (359)	40.14 (40.33)	3.93 (3.89)	8.63 (8.41)
2^+	$C_{14}H_{18}FePF_6$ (387)	43.44 (43.68)	4.69 (4.73)	8.00 (7.88)
3^+	$C_{14}H_{18}FePF_6$ (387)	43.44 (43.71)	4.69 (4.77)	8.00 (7.83)
4^+	$C_{16}H_{22}FePF_6$ (415)	46.29 (46.37)	5.34 (5.13)	7.46 (7.61)
$5^{+\,b}$	$C_{14}H_{18}FePF_6$ (387)	43.44 (43.22)	4.69 (4.70)	8.00 (7.81)

[a] Theoretical values in parentheses. [b] Recrystallized from dilute H_2SO_4.

$Fc^+PF_6^-$ salts used oxidation with concentrated H_2SO_4 followed by NH_4PF_6.

Yields were 70–80%. The elemental analysis results of these derivatives are found in Table VI. These derivatives were also characterized from their FTIR spectra as KBr pellets. All derivatives had an intense absorption in the 833–839-cm^{-1} range due to the hexafluorophosphate anion. All other major bands were in accord with their proposed structure, and the pellets remained blue.

BNAH, [4-^{2}H]BNAH, [4,4-$^2H_2$]BNAH. 1-Benzylnicotinamide chloride (BNA^+Cl^-) was prepared by alkylating nicotinamide with benzyl chloride,[42] mp 239–241 °C (lit. mp 241 °C). 1-Benzyl-1,4-dihydronicotinamide (BNAH) was prepared via the dithionite reduction of BNA^+Cl^- in the presence of sodium bicarbonate in distilled H_2O,[43,44] mp 116–117 °C (lit. mp 110–114 °C). The ^{1}H and ^{13}C NMR, FTIR (as KBr pellets), and mass spectra confirm their structure. [4-^{2}H]BNAH was prepared from BNA^+Cl^- by conducting the dithionite reduction in D_2O rather than H_2O.[44] [4,4-$^2H_2$]BNAH was prepared by carrying out three cycles of oxidation of [4-^{2}H]BNAH by chloranil in DMF followed by dithionite reduction in D_2O. Melting points for [4-^{2}H]BNAH and [4,4-$^2H_2$]BNAH were similar to that observed for nondeuteriated BNAH. The deuterium incorporation in the 4-position was determined to be 50% for [4-^{2}H]-BNAH and 90% for [4,4-$^2H_2$]BNAH by ^{1}H NMR spectroscopy (58% and 87% by electron-impact mass spectrometry).

Kinetics. The solvent consisted of a 50/50 by volume mixture of 1-propanol (distilled from K_2CO_3) and 0.02 M pH 7.0 phosphate buffer. This was used to make up solutions that were 0.1 M in $NaClO_4$. A series of kinetic experiments were also carried out in CH_3CN containing 0.1 M $NaClO_4$. The CH_3CN was HPLC grade and stored over 4-Å molecular sieves. The 1-propanol and 0.02 M pH 7.0 phosphate buffer were bubbled for at least 2 h with argon that had been deoxygenated and dried by passage through a column of activated Ridox (Fisher Scientific) followed by Drierite, respectively. After mixing, the solvent was bubbled an additional 15 min. Acetonitrile was bubbled for at least 2 h with purified argon before use.

A standard UV cuvette with graded seal (Hellma Cells, Inc.) was modified by attaching a glass piece containing a stopcock and 14/20 female ground-glass joint. The cell was so constructed to allow deaeration of the cell contents with purified argon prior to the addition of the ferrocenium solution, while maintaining a positive pressure of argon during the kinetic experiments. The standard ferrocenium and BNAH solutions were prepared in an argon purged glovebag. For all experiments, 2.0 mL of the desired concentration of ferrocenium was added to the septum-capped deaerated UV cell. BNAH solutions were prepared in an ordinary cuvette, which was septum-capped before removing from the glovebag. These two cuvettes were thermostated at 30.0 ± 0.2 °C in the cell holder (HP 89075 programmable multicell transport) of a Hewlett-Packard HP 8451 diode array spectrophotometer for at least 15 min prior to a kinetic run. A Neslab RTE-4 refrigerated circulating bath regulated the temperature of cell holder. The cuvette contents were stirred.

Typically, a volume in the 100–250-μL range of 0.100 M BNAH was added to the 2.0 mL of ferrocenium solution (0.41–0.55 mM), such that at least a 15-fold initial excess of BNAH was maintained. For all kinetic experiments the reaction of BNAH with ferrocenium was complete; that is, the absorbance at infinity for the ferrocenium oxidant was essentially zero. Time vs absorbance readings were evaluated through the use of integrated rate equations.

Electrochemistry. A. Ferrocene Derivatives. A BAS-100 Electrochemical Analyzer (Bioanalytical Systems, Inc., West Lafayette, Indiana) was used. IR compensation was achieved before each cyclic voltammogram was recorded. Solutions were typically ~1 mM ferrocene derivative in 50/50 by volume 1-propanol, 0.02 M pH 6.96 phosphate buffer. All solutions were 0.1 M in $NaClO_4$ and degassed for at least 10 min before recording CV's. A 0.04-cm^2 glassy carbon working electrode, which had been polished successively in 0.3 and 0.05 M alumina (Buehler), sonicated for 5 min, and dried with a kim-wipe, was used in all measurements. A graphite rod auxiliary electrode and SCE reference electrode were used. These electrodes along with a Luggin probe were assembled in a four-necked one-compartment cell. The cyclic voltammetry data reported is the average of at least 10 separate runs; the error associated with the given $E°$ is ± 2 mV.

B. BNAH. All electrochemistry (including cyclic voltammetry and bulk electrolysis) was carried out with a PAR Model 173 Potentiostat/Galvanostat. For cyclic voltammetry a PAR Model 175 universal programmer was used in conjunction with the potentiostat. CV's were recorded on a Kipp & Zonen BD-90 X-Y recorder. The same glassy carbon working electrode used above was used here also, with identical surface pretreatment. A 0.020-cm^2 Pt working electrode sealed in Kel-F was purchased from Bioanalytical Systems, Inc. This electrode was polished and sonicated as above before cleaning in concentrated nitric acid. A Pt/Ir coil auxiliary electrode concentric with the working electrode was used in all CV experiments. The reference electrode used in all nonaqueous experiments consisted of a silver wire immersed in a glass tube with semiporous ceramic junction (Bioanalytical Systems, Inc.) containing a filling solution of 0.1 M Bu_4ClO_4 and 0.01 M $AgClO_4$ in CH_3CN (+300 mV vs SCE). A two-compartment electrochemical cell was used with a separate reference electrode chamber connected to the main chamber via a Luggin probe. The cell was provided with an inlet and outlet port for a controlled argon atmosphere.

BNAH solutions were prepared from HPLC grade acetonitrile (Fisher), which had sat overnight over activated 4-Å molecular sieves (EM Science) prior to passage through a column of activated neutral alumina (Fisher Scientific). The alumina was activated overnight at >500 °C and then placed in dessicator over P_2O_5 to cool. Tetrabutylammonium perchlorate was purchased from Southwestern Analytical Chemicals and recrystallized from ethanol before use. FTIR of Bu_4ClO_4 as a KBr pellet revealed the presence of no hydroxylic impurities.

C. BNAH Dimer. The BNAH dimer was prepared via preparative electrolyses of BNAH in dried acetonitrile containing 0.1 M $LiClO_4$.[45] A large-area carbon felt working electrode, graphite rod auxiliary electrode, and Ag/Ag^+ reference electrode were used. A three-compartment cell was used in which the working and reference electrode compartments were separated from the auxiliary electrode compartment by a fine-porosity frit. The working and auxiliary electrode chambers were provided with separate inlet and outlet lines for argon atmosphere. The presence of stopcocks on the inlet lines allowed argon to pass into the bottom of the cell through a porous frit or over the solution after deaeration. Typically, ~50 mL of 0.1 M $LiClO_4/CH_3CN$ solution was added to the cell and deaerated for 15 min. To the working electrode chamber was added a certain weight of BNAH. The solution was then redeaerated and stirred to dissolve the added BNAH. Constant-potential electrolysis at or beyond the oxidation peak for BNAH was maintained until the current attained a very low value. Typically 0.7 ± 0.1 F mol^{-1} were passed under the prescribed conditions. The contents of the working and reference electrode compartments were transferred to a seperatory funnel. A CH_2Cl_2/H_2O extraction was performed. The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated to dryness by rotary evaporation under aspirator vacuum. The solid remaining in the flask was dissolved in a small volume of acetonitrile and transferred to a smaller flask. It was observed that a white precipitate formed in the bottom of the vial after ~30 min. The white product (with yellow impurities) from several electrolyses was collected. The amount remaining in solution was retrieved via flash chromatography (silica; acetonitrile). The collected crude white product was recrystallized from ethanol twice giving white crystals, mp 212–214 °C.

A high-resolution electron-impact (70 eV) mass spectrum of this compound **6** gave a molecular ion at m/e 428. A significant intensity

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(45) The BNAH dimer could also be prepared by adding a 1:10 molar ratio of $HClO_4$ to BNAH in acetonitrile. X-ray analysis of the product of the acid decomposition of 1-methyl-1,4-dihydronicotinamide gives the molecular structure of the dimer as displayed in **6** with methyl groups replaced by benzyl groups. Ammon, H. L.; Jensen, L. H. *Acta Crystallogr.* **1967**, *23*, 805.

M − 91 peak was also observed. The base peak in the spectrum was at 91. Elemental analysis. Found: C, 72.67; H, 6.67; N, 12.95. Calcd: C, 72.87; H, 6.59; N, 13.07. The structure of the dimer was confirmed by ^{1}H and ^{13}C NMR. A proton-coupled and -decoupled ^{13}C spectrum was performed. No olefinic carbon atoms were observed. All resonances besides those due to the two amide carbonyl carbon and aromatic carbons were in the 16–72 ppm range: ^{13}C NMR (CDCl$_3$) δ 176.3 (2 H), 175.8 (2 H), 138.4 (0 H), 137.7 (0 H), 128.9 (1 H), 128.7 (1 H), 128.6 (1 H), 128.4 (1 H), 127.7 (1 H), 127.4 (1 H), 69.9 (1 H), 63.5 (1 H), 57.2 (1 H), 56.6 (2 H), 54.3 (2 H), 52.7 (1 H), 49.3 (0 H), 46.0 (0 H), 35.6 (1 H), 29.4 (2 H), 20.6 (2 H), 17.9 (2 H); ^{1}H NMR (CDCl$_3$) δ 7.28 (m, 10 H), 6.17 (s, 1 H), 6.05 (d, 1 H), 4.91 (m, 2 H), 4.03 (d, 1 H), 3.84 (d, 1 H), 3.69 (d, 1 H), 3.50 (d, 1 H), 3.13 (m, 1 H), 2.86 (s, 1 H), 2.72 (d, 1 H), 2.37 (m, 2 H), 2.10 (m, 4 H), 1.60 (s, 1 H).

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Marcus Theory of Hydride Transfer from an Anionic Reduced Deazaflavin to NAD$^+$ Analogues[1]

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Abstract: Eighteen rate constants, k_{ij}, for hydride transfer from the conjugate base of 1,5-dihydro-3,10-dimethyl-5-diazaisoalloxazine to a variety of pyridinium, quinolinium, phenanthridinium, and acridinium ions have been determined. (All the oxidizing agents can be regarded as analogues of NAD$^+$.) The k_{ij} values span 7 powers of 10 and the corresponding equilibrium constants, K_{ij}, span more than 13 powers of 10. For reactions with $\Delta G°$ near zero, the k_{ij} values are close to those given by modified Marcus theory (ref 10). However, with more negative $\Delta G°$ values, the observed k_{ij} increase more strongly than the calculated values. Agreement can be produced by making the standard free energy of precursor complex formation, symbolized $W^r_\pm$ here, to indicate that it applies to reactants of opposite charge, a linear function of $\Delta G°$, and treating the slope and intercept of the linear relation as adjustable parameters. The best fit is obtained with $W^r_\pm$ (in kJ mol^{-1}) = $-9.4 + 0.11\Delta G°$. An average discrepancy between calculated and observed ln k_{ij} values of 0.5 is achieved, which is as good as the overall fit achieved for hydride transfer from neutral NADH analogues to NAD$^+$ analogues (ref 10). The form and the parametrization of W^r are shown to be a physically reasonable approximation for reactions with $\Delta G° < 0$. These results strengthen the conclusion (ref 10) that a wide range of hydride transfer rates can be quantitatively understood without introducing high-energy metastable intermediates (radicals and radical ions).

In most applications of the Marcus theory[2-7] (eq 1–5) the standard free energy of forming the precursor configuration[7] from the reactants, W^r, is considered to be structure-invariant and equal to the standard free energy of forming the successor configuration from the products, W^p.[4-8] (Sometimes both have been taken as zero.[5,9])

$$\Delta G^* = W^r + \lambda/4 + \Delta G°'/2 + \Delta G°'^2/4\lambda \qquad (1)$$

$$\Delta G°' = \Delta G° - W^r + W^p \qquad (2)$$

$$\lambda = (\lambda_i + \lambda_j)/2 \qquad (3)$$

$$k = \tilde{k}T/h \exp(-\Delta G^*/RT) \qquad (4)$$

$$K = \exp(-\Delta G°/RT) \qquad (5)$$

In eq 1–5, $\tilde{k}$ is Boltzmann's constant, k is a rate constant, K is an equilibrium constant, λ is $4(\Delta G^* - W^r)$ for the case that $\Delta G°'$ is zero, λ_i and λ_j are λ for special cases in which the reactions are structurally as well as energetically symmetrical. It is reasonable to assume that W^r and W^p are equal and structure-insensitive for reactions in which a unicharged ion reacts with a neutral to give another unicharged ion and another neutral, particularly if the reactants and products are structurally similar. With these assumptions, eq 1–5 have been shown to work well in hydride-transfer reactions of the type shown in eq 6.[10] (We

$$A_i^+ + A_jH \rightleftarrows A_iH + A_j^+ \qquad (6)$$

have established[7,10,11] and shall maintain the convention that A_i^+ is the oxidizing agent when the reaction is written in the forward—not necessarily spontaneous—direction.)

In the present paper we describe results for reactions of the type shown in eq 7. The substances, A_i^+ are all analogues of the enzyme cofactor, nicotinamide adenine dinucleotide (NAD$^+$). They are

$$A_i^+ + A_jH^- \rightleftarrows A_iH + A_j \qquad (7)$$

pyridinium ions, **1**, quinolinium ions, **2**, phenanthridinium ions, **3**, or an acridinium ion, **4**. The A_iH are the corresponding dihydro derivatives, **1H–4H**. A_jH^- is the conjugate base of 1,5-dihydro-3,10-dimethyl-5-deazaisoalloxazine, dihydrodeazaflavin, **5H**, and A_j is the corresponding deazaflavin, **5**. For reactions of the charge type shown in eq 7, it is no longer reasonable that W^r and W^p should be regarded as equal, since the reactants are oppositely charged ions, which will be attracted by coulombic forces, while the products are neutral. W^r is also no longer safely considered structure-insensitive, as will be shown. On the other hand, the covalency changes involved in the present reactions are very similar to those that accompany hydride transfer between cationic NAD$^+$ analogues (eq 6). Since rate constants for reactions of the type

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