J. Am. Chem. Soc. 1988, 110, 3989-3993

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]

In-Sook Han Lee,*[†] Dražen Ostović,[‡] and Maurice Kreevoy*[‡]

Contribution from the Department of Science Education, Kangweon National University, Chuncheon 200, Korea, and Chemical Dynamics Laboratory, Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455. *Received December 14, 1987*

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 ΔG° near zero, the k_{ij} values are close to those given by modified Marcus theory (ref 10). However, with more negative ΔG° 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 ΔG°, 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}) = $-9.4 + 0.11\Delta G^\circ$. 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 $\Delta G^\circ < 0$. 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])

$$\Delta G^* = W^r + \lambda/4 + \Delta G^{\circ\prime}/2 + \Delta G^{\circ\prime 2}/4\lambda \qquad (1)$$

$$\Delta G^{\circ\prime} = \Delta G^\circ - W^r + W^p \qquad (2)$$

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

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

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

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 $\Delta G^{\circ\prime}$ 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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[†] Kangweon National University.

[‡] University of Minnesota.

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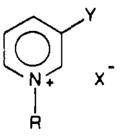
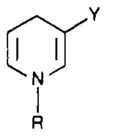
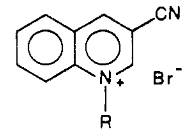


1



1H



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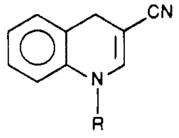
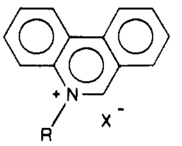


2H

a: R = $C_6H_5CH_2$, Y = CN; X = Br
b: R = $C_6H_5CH_2$; Y = CO_2CH_3; X = Br
c: R = $C_6H_5CH_2$; Y = $CONH_2$; X = Br
d: R = CH_3; Y = $CONHCH_2C_6H_5$; X = I
e: R = CH_3; Y = CONH-*n*-C_8H_{17}; X = I

a: R = *p*-$CH_3C_6H_4CH_2$
b: R = $C_6H_5CH_2$
c: R = *p*-$FC_6H_4CH_2$
d: R = *p*-$BrC_6H_4CH_2$
e: R = *m*-$FC_6H_4CH_2$
f: R = *p*-$CNC_6H_4CH_2$
g: R = *m*-$CF_3C_6H_4CH_2$
h: R = *p*-$CF_3C_6H_4CH_2$



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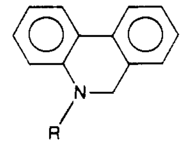
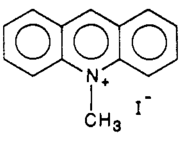
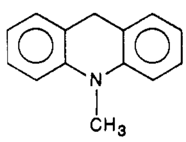


3H

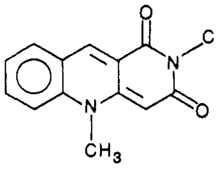


4

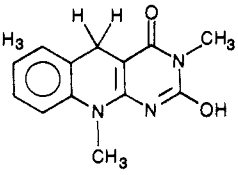
a: R = CH_3; X = I
b: R = $C_6H_5CH_2$, X = Br
c: R = *p*-$CF_3C_6H_4CH_2$, X = Br
d: R = *p*-$CNC_6H_4CH_2$, X = Br



4H



5



5H

shown in eq 6 are very well accommodated by eq 1–5,[10] these equations should also hold for the present reaction if we can find proper formulations for W^r and W^p.

Since the products are both neutral, we assume that W^p is −8.4 kJ mol^{-1} (−2 kcal mol^{-1}) and structure-independent. This is the same value we have used before for cationic oxidants reacting with neutral reductants.[10] W^r should be more negative than W^p, because of the coulombic interaction between the oppositely charged reactants and because of the probably more important charge-transfer interaction. Further, that charge-transfer interaction becomes more important still as the reaction becomes more spontaneous, other things being equal. The energy separation between the highest occupied molecular orbital (HOMO) of the reductant and the lowest unoccupied molecular orbital (LUMO) of the oxidant, ΔE, should be reduced as the spontaneity of the overall oxidation increases. The relation between the HOMO–LUMO ΔE and the $\Delta G°$ for the reactions of eq 7 will probably not be perfectly regular. The reaction is much more complicated than an electron transfer. Nevertheless, it does involve a net transfer of negative charge from the reductant to the oxidant, and a rough relation between its $\Delta G°$ and the HOMO–LUMO ΔE should exist. Since the charge-transfer delocalization energy is inversely proportional to ΔE,[12] it should be approximately proportional to $\Delta G°$. Bruice and co-workers have observed that a variety of flavins form complexes with tryptophan and β-resorcylic acid (presumably charge transfer complexes). The logarithms of these formation constants are directly proportional to the logarithms of the rate constants for the reactions of the same flavins with NADH or with 1,4-dihydro-1-propylnicotinamide.[13] We will, therefore, use eq 8 for W^r in the case that the reactants

$$W^r_{\pm} = a_w + b_w \Delta G° \qquad (8)$$

have opposite charges. We designate this special W^r, $W^r_{\pm}$. The quantities, a_w and b_w, are treated as adjustable parameters. In view of their justification, a_w should be somewhat more negative than −8.4 kJ mol^{-1} and b_w should be positive. The results are consistent with these expectations.

In order to use eq 3, the rate constants for the relevant symmetric reactions are required. The rate constant for reaction of ^{13}C-labeled **5** with the unlabeled anion of **5H** was measured, with NMR spectroscopy. The rate constant obtained was assumed to be equal to that for the degenerate reaction. Rate constants for the other symmetrical reactions were available.[10] They already incorporate structure sensitivity and dependence on $\Delta G°$.[10]

The required equilibrium constants, K_{ij}, are available from our previous work.[10,14] Thus, we are able to evaluate all the quantities required by eq 1 for reactions of the type shown in eq 7.

Experimental Section

Materials. All the oxidants, **1a–e**, **2a–h**, **3a–d**, **4**, and **5**, have been previously described.[10,11,14] Compound **5H** was not isolated as a pure solid. Instead, it was prepared prior to the kinetic measurement by reduction of **5** with $NaBH_4$ in situ. A predetermined weight of **5** was dissolved in a smallest possible amount of the solvent employed for the kinetic measurement (*i*-PrOH–H_2O, 4:1, v/v), and a freshly prepared solution of $NaBH_4$ solution was added until the reduction of **5** was seen to be complete by observing that the yellow color of **5** had disappeared. The solution was allowed to stand in the dark for 2–3 h so that the excess $NaBH_4$ could be destroyed by reaction with the solvent. This solution was then diluted with buffer solution to the desired concentration and used promptly.

Compound **5** with a [^{13}C]methyl group in the 3-position, 3,10-[3-^{13}C]dimethyl-5-deazaisoalloxazine, was prepared in the same way as the unlabeled material,[14] except that iodo[^{13}C]methane was used in the final methylation. The iodo[^{13}C]methane was obtained from Aldrich Chemical Co., with 99% ^{13}C specified. It had an appropriate ^1H NMR spectrum, with a ^{13}C–^1H coupling constant of 140.7 Hz. Acetic acid–acetate buffers were made up by partially neutralizing acetic acid solutions of known concentration with sodium hydroxide of known concentration. 2-Propanol was Mallinckrodt ChromAR grade, 99.8% assay. This was distilled from a very small quantity of H_2SO_4 before use. The mixed solvent was made up from this solvent and distilled water in a 4:1 ratio, by volume, at temperatures between 20 and 25 °C. Inorganic reagents were of analytical reagent[15] quality and were used without further purification.

Measurements. All rate constants were measured in the 4:1 mixture of 2-propanol and water, described above, at 25.0 ± 0.2 °C. Reactions were carried out with at least a 20-fold excess of the oxidizing agent, so the pseudo-first-order rate law was obeyed,[14] leading to pseudo-first-order rate constants, k_1. For reactions with half-lives of several minutes or more, rate constants were measured by a standard spectrophotometric technique.[14] For reactions with half-lives between 0.2 and 200 s, rates were measured with a remote probe light-guide colorimeter in a reaction vessel that was immersed in a thermostat and efficiently stirred to provide fast mixing.[16] Absorbance was recorded continuously, before, during, and after the addition of the limiting agent, which was added as quickly as possible with a syringe. The rise time of this apparatus was 0.1 s. The average deviation from the mean k_1 values was typically ±20%. As described below, k_1 was pH-sensitive, and the principal cause of scatter is thought to be our inability to reproduce the pH values exactly. The standard error of k_1 was reduced to less than 10% by replication.

Rates of the near-symmetric reactions of labeled **5** with **5H** were carried out in solutions buffered to pH values between 6 and 7.4, with reactant concentrations around 10^{-2} M. The decrease of the ^{13}C signal of **5** at 26.38 ppm and the growth of the **5H** signal at 25.62 ppm were monitored in a Varian XL-100 NMR spectrometer, with use of 12-mm sample tubes with acetone-d_6 in a coaxial insert to lock the field. The temperature of the reacting solution was maintained at 25.0 ± 0.2 °C. Since the peak shapes appeared identical, the ratio of [^{13}C]-**5** to [^{13}C]-**5** plus [^{13}C]-**5H**, *R*, was evaluated from the peak heights. The rate constant, k_2, was then evaluated by using eq 9,[17] in which *t* is time elapsed since mixing, quantities in parentheses are concentrations, and subscripts indicate the times of reference of the various time-dependent quantities.

$$k_2 = \ln\,[1 - F]/[(\mathbf{5})_0 + (\mathbf{5H})_0]t \qquad (9)$$

$$F = (R_0 - R_t)/(R_0 - R_\infty)$$

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Table I. Rate Constants for Hydride Transfer from **5H** to Oxidizing Agents, A_i^+

no.	λ	A_i^+	pK_R^a	$\ln k_{ij}^b$	$\ln K_{ij}$
1	410	**1a**		2.04	11.06
2	398	**1b**		0.29	4.58
3	390	**1c**		−3.34	0.11
4	381	**1d**		−5.06	−4.26
5	381	**1e**		−5.26	−4.46
6	388	**2a**	5.44	10.21	24.81
7	389	**2b**	5.31	10.33	25.16
8	389	**2c**	5.20	10.40	25.33
9	390	**2d**	5.00	10.64	25.76
10	390	**2e**	4.95	10.67	25.89
11	391	**2f**	4.62	10.81	26.48
12	392	**2g**	4.63	10.98	26.80
13	391	**2h**	4.78	10.75	26.30[c]
14	365	**3a**	9.66	2.94	7.55
15	371	**3b**	8.78	5.40	10.92
16	374	**3c**	8.03	5.93	12.38
17	376	**3d**	7.79	6.34	13.69
18	352	**4**	7.74	11.17	22.06

[a] For A_i^+. [b] The units of k_{ij} are $M^{-1}\ s^{-1}$; values are formally divided by 1.00 $M^{-1}\ s^{-1}$ to get dimensionless quantities so that logarithms can be taken. [c] Obtained from the correlation of rate constants for reduction of **2** by **4H**.[11] The directly measured value fails to fit that and other correlations.[11]

To get k_{jj}, k_2 was divided by the fraction of **5H** that was in the active, anionic form.[14]

In formulating rate or equilibrium constants for reactions of oppositely charged ions, ionic strength effects on activity coefficients, $\gamma_\pm$, were dealt with by means of eq 10.[18,19] (The ionic strength is I.)

$$-\log \gamma_\pm = 1.87I^{1/2}/(1 + 4.05I^{1/2}) \tag{10}$$

Results

Measurements were facilitated, but the interpretation of results was complicated by the fact that both reactants enter into acid–base reactions. Compound **5H** dissociates as an acid, losing its hydroxylic proton, with a dissociation constant of 2.51×10^{-9} in our solvent system.[14] We designate **5H** A_jH_2 and its conjugate base A_jH^-. The oxidants are pseudoacids.[20] The present measurements were made in the pH range 4–7. In this pH range, none of the pyridinium ions, **1**, are significantly alkoxylated, but **4** and all the variants of 2 and 3 are significantly alkoxylated. The equilibrium constants for reactions of the type shown in eq 11 are

$$A_i^+ + ROH \rightleftarrows A_iOR + H^+ \tag{11}$$

designated K_R. In our present solvent mixture, R may be either H or 2-propyl, though we believe that, for the most part, it is H. The relevant pK_R values have been previously reported,[11,14] and they are shown in Table I.

The alkoxylated oxidants were assumed to be inert to reduction. However, A_jH_2 as well as A_jH^- is shown by the following argument to be a potentially significant reducing agent under the present conditions.

$$A_i^+ + A_jH_2 \xrightleftharpoons{K'_{ij}} A_iH + A_jH^+ \tag{12}$$

The equilibrium constants, K_{ij} and K'_{ij}, for reductions by A_jH^- and A_jH_2, are related by eq 13, where eq 14 and 15 describe the

$$K'_{ij} = K_{ij}K_{14}/K_{15} \tag{13}$$

acid dissociation of **5H** and protonated **5**, respectively. As noted,

$$A_jH_2 \xrightleftharpoons{K_{14}} A_jH^- + H^+ \tag{14}$$

$$A_jH^+ \xrightleftharpoons{K_{15}} A_j + H^+ \tag{15}$$

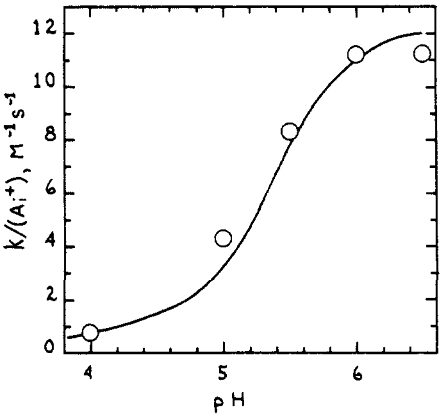

Figure 1. Observed values of k_1 (A_i^+) (circles) and values calculated according to eq 16 (solid line) with parameter values given in the text. The oxidizing agent is **2b**.

K_{14} is 2.51×10^{-9}.[14] A pK_a of 1.8 has been reported for protonated 3,6,7,10-tetramethyl-5-deazaisoalloxazine in water.[21] Since eq 15 involves no change in charge type, K_{15} probably has a similar value, or a little larger, in our mixed solvent.[22] We have, therefore, adopted a value of 10^{-1} for K_{15}, leading to a value of 2.5×10^{-8} for K'_{ij}/K_{ij}. Since Brønsted α values around 0.5 are observed for systems like this,[10] the ratio of rate constants, k'_{ij}/k_{ij} should be about 10^{-4}. It is, therefore, anticipated that reduction by A_jH_2 contributes only about 1% of the total reduction rate at a pH of 6.5 but contributes about 80% at a pH of 4.

Taking all the foregoing into account, eq 16 is expected to give k_1. (The activity of H^+ is a_H.) For the reaction of **2b** with **5H**,

$$\frac{k_1}{(A_i^+)} = \frac{k_{ij}K_{14}\gamma_\pm + k'_{ij}a_H}{a_H + K_R\gamma_\pm} \tag{16}$$

k_1 was measured at five pH values between 4.0 and 6.5. The best values of k_{ij} and k'_{ij}, 2.7×10^4 and $2 \times 10^{-1}\ M^{-1}\ s^{-1}$, respectively, were obtained by minimizing the sums of the squares of the fractional discrepancies between calculated and observed values of k. Figure 1 shows the fit of the theoretical curve to the experimental points. The ratio, k'_{ij}/k_{ij}, is 0.8×10^{-5}, which is 1 order of magnitude smaller than the estimated value. However, the agreement is tolerable in view of the substantial uncertainties in K_{15} and α. With the experimental value of k'_{ij}/k_{ij}, only 1% of k is due to the $k'_{ij}a_H$ term in eq 16 at a pH of 5.5, and this percentage should be approximately independent of the oxidizing agent, according to the logic of the preceding paragraph. Accordingly, all the rest of the k values were determined in solutions with pH values at or above 5.5, and the $k'_{ij}a_H$ term in eq 16 was neglected. The values of k_{ij} given by $[k/(A_i^+)](a_H + K_R\gamma_\pm)/K_{14}\gamma_\pm$ are collected in Table I. Each of these was replicated at least four times, and, typically, the average deviation from the mean value was about 5%.

The rate constant for the symmetrical reaction of A_j with A_jH^-, k_{jj}, was measured four times, giving a value of 2.8 $M^{-1}\ s^{-1}$, with an average deviation from the mean of 0.36. There was no systematic variation of k_{jj} with pH. From k_{jj}, λ_j was evaluated, for **5**, by using eq 1 and 4, with $W^r = W^p = -8.4$ kJ mol^{-1} and $\Delta G^{\circ\prime} = 0$. The value obtained was 315.4 kJ mol^{-1}. For the oxidants, λ_i was available from our previous work.[10] By averaging λ_i and λ_j, as shown in eq 3, a λ value was obtained for each reaction. These are shown in Table I.

The best values of a_w and b_w were then evaluated by minimizing the sum of the squares of discrepancies, Δ, between the observed and calculated values of $\ln k_{ij}$. This was done by calculating all the $\ln k_{ij}$ values with eq 1–5 and 8 for a grid of a_w and b_w values separated by 1.0 kJ mol^{-1} on the a_w axis and 0.01 on the b_w axis. After the rectangle of minimum $\sum\Delta^2$ was identified, a parabolic interpolation was used to estimate the particular values that would

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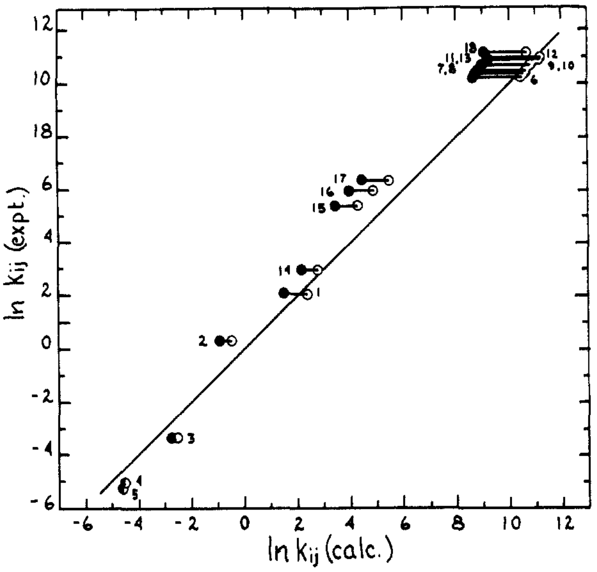

Figure 2. The relation between theoretical (eq 1–5) and observed values of ln k_{ij}. For the closed circles, $W^r = W^p = -8.4$ kJ mol^{-1}. For the open circles $W^p = -9.4 + 0.11\Delta G°$ kJ mol^{-1}. The numbers identify the points with entries in Table I. The two calculated values of ln k_{ij} are not visibly different for points 4 and 5. The solid line is the line of perfect agreement.

minimize $\sum\Delta^2$. They are $a_w = -9.4$ kJ mol^{-1} and $b_w = 0.11$.

The comparison between calculated and observed values of ln k_{ij} is shown in Figure 2. For all of these calculations, $W^p = -8.4$ kJ mol^{-1} was used, and $\Delta G°'$ was evaluated according to eq 2. Figure 2 also shows the comparison between calculated and observed values of ln k_{ij} if $W^r = W^p = -8.4$ kJ mol^{-1} is assumed. With this latter assumption, the average discrepancy is 1.4, the largest discrepancy is 2.1, and it is clear that the experimental values systematically exceed the calculated, the discrepancies getting larger as the values themselves increase. When W^r, with the selected parameters, is used instead, the average discrepancy falls to 0.5, the largest discrepancy falls to 1.1, and the points now appear more or less randomly distributed about the line of perfect agreement, although some segregation into families is still evident.

Discussion

These results show that hydride transfer from the deazaflavin, A_jH^- to NAD$^+$ analogues, is mechanistically very similar to hydride transfer among the NAD$^+$ analogues themselves. The same tightness parameter, τ,[10,11] which measures the total bond order to the in-flight hydrogen at the critical configuration,[7] was used. The same intrinsic barriers that were used for hydride transfer among NAD$^+$ analogues[10] serve for the present reactions as well. However, the intrinsic barrier for **5**, 315 kJ mol^{-1}, is smaller than the intrinsic barrier for **4**, 357 kJ mol^{-1}, and considerably smaller than the intrinsic barrier for nicotinamide derivatives; 390 kJ mol^{-1} for benzylnicotinamide, **1c**. This, as well as its charge, makes **5**H a kinetically more competent reducing agent than nicotinamide derivatives, in the absence of an enzyme.

The values of a_w and b_w accommodate the charge type of the reaction and are physically reasonable. W^r and $W^r_\pm$ are standard free energies of formation of precursor configurations[7] from separated reactants. If the reactants are oppositely charged, one would expect the formation of a complex from them to be more spontaneous than the formation of a similar complex from neutral and cationic reactants. Further, analogues of A_jH^- are known to act as charge-transfer donors with electron acceptors,[13] while compounds like **1**–**4** have been shown to act as charge-transfer acceptors.[23-25] Both ion–ion interactions,[26] and charge-transfer interactions[13] would become stronger as electron-withdrawing structural features are introduced in the oxidants. Electron-withdrawing structural features in the oxidant generally make hydride transfer reactions much more spontaneous. Thus, one would expect the formation of all the precursor configurations in the present series to be more spontaneous than the formation of precursor configurations from these same oxidatns with neutral reductants and to become more spontaneous, yet, as $\Delta G°$ for the overall reaction becomes more negative. These expectations are met. The best value of a_w is 1 kJ mol^{-1} more negative than W^r, and b_w gives W^r about 0.1 of the sensitivity of $\Delta G°$ to structural changes.

It is also gratifying that the global best value of b_w makes the theoretical value of the Brønsted α,[7,27,28] given by eq 17, for the 3-cyanoquinolinium ions (**2**) 0.40, in essentially perfect agreement with the experimental value, 0.39 ± 0.02. When eq 2 and 8 are

$$\alpha = \mathrm{d}\ \ln k_{ij}/\mathrm{d}\ \ln K_{ij} \qquad \alpha = \mathrm{d}\Delta G^*_{ij}/\mathrm{d}\Delta G°_{ij} \tag{17}$$

incorporated in eq 1, the result is eq 18. Differentiation gives eq 20, from which the theoretical value of α was obtained by inserting the average values of λ, $\Delta G°$, and W^r for compounds **2**. In this

$$\Delta G^* = C_0 + C_1\Delta G° + C_2\Delta G°^2 \tag{18}$$

$$C_0 \equiv \frac{W^p + a_w}{2} + \frac{\lambda}{4} + \frac{(W^p - a_w)^2}{4\lambda}$$

$$C_1 \equiv \frac{1 + b_w}{2} + \frac{(1 - b_w)(W^p - a_w)}{2\lambda}$$

$$C_2 \equiv \frac{(1 - b_w)^2}{4\lambda}$$

differentiation the previously derived[11] relation, eq 19, was used.

$$\mathrm{d}\lambda/\mathrm{d}(\Delta G°) = 2(\tau - 1) \tag{19}$$

τ was given its previously determined value, 0.81.[10] The experimental α was determined by the method of least squares, assuming a linear relation between ln k_{ij} and ln K_{ij}. Compounds **2** form a closely related family, with the substituents that produce the variation in k_{ij} and K_{ij} far removed from the reaction site so as to minimize idiosyncratic effects. The measurements were made

$$\mathrm{d}(\Delta G^*)/\mathrm{d}(\Delta G°) = C_0' + C_1'\Delta G° + C_2'(\Delta G°)^2 \tag{20}$$

$$C_0' = \frac{\tau - 1}{2} - \frac{(W^p - a_w)^2(\tau - 1)}{2\lambda} + \frac{1 + b_w}{2} + \frac{(1 - b_w)(W^p - a_w)}{2\lambda}$$

$$C_1' \equiv \frac{(1 - b)^2}{2\lambda} - \frac{(1 - b_w)(W^p - a_w)(\tau - 1)}{\lambda^2)}$$

$$C_2' \equiv \frac{-(1 - b_w)^2(\tau - 1)}{2\lambda^2}$$

with great care, with a view to interpreting α. On the other hand, the range of k_{ij} is relatively small. The adjustment of a_w and b_w to fit the data was bound to produce reasonable agreement between calculated and observed values of ln k_{ij}, but this procedure did not assure good agreement between calculated and observed values of α.

All this being said, it must be acknowledged that the present model is not unique in fitting the results and probably cannot be rigorously tested by measuring rates of reaction. Setting aside, for the moment, the weak dependence of λ on $\Delta G°$,[10,11] eq 18 is a quadratic in $\Delta G°$, and, in the most favorable case, only one check would be available after two parameters had been adjusted. In practice, the departure from linearity is small; there is some

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uncertainty in the experimentally determined quantities, λ, ΔG°, and ΔG^*. The present data could also be pretty well accommodated by arbitrarily adjusting τ or by adding a linear dependence on ΔG° to λ in eq 3. The final exprssions for ΔG^* would differ slightly from eq 18, but it would not be possible to choose among them on the basis of their fit to the data after the parameters had been optimized. We believe that a better approach to testing eq 8 lies in the examination of formation constants for complexes that are similar to our present precursor configurations but that cannot carry out the hydride transfer. Until such results are obtained we believe that the general reasonableness of the outcome is the best available support for the model.

In addition, eq 8 cannot give more than a rough approximation of $W^r_\pm$. For substantially positive ΔG°, the values of $W^r_\pm$ given by eq 8 become more positive than W^p. Since the reactants are oppositely charged while the products are neutral, this cannot be realistic, and it is only the absence of this sort of results that makes this characteristic acceptable. It is also possible that $W^r_\pm$ is structure-sensitive in ways that are not reflected in ΔG° at all. This may be one cause of the slight segregation of points into families, by ring system, which is detectable in Figure 2. The present rate constants for reaction of phenanthridinium ions with **5H** are, systematically, a bit above the calculated values (points 14–17 in Figure 2). They are slightly *below* the calculated values for hydride transfer between NAD$^+$ analogues.[10] This role reversal suggests that these discrepancies do not arise out of an artifact, since the same intrinsic barriers and relative equilibrium constants were used in both studies. We believe that the discrepancies are due to structure-specific interactions between the reacting molecules which are not reflected in the theory.

It is common to write α as a partial derivative,[3,4] rather than a total derivative, as in eq 17. The original implication was that temperature and pressure, and perhaps solvent composition, were constant. However, it is inappropriate to use eq 1, or any of its variants, and compare $(\partial\Delta G^*/\partial\Delta G^\circ)$ with the experimental α. There is no general reason for λ and W^r to be independent of ΔG°. λ is usually a function of ΔG°,[11,29] and, in this paper, we have shown that W^r may be as well. In the present case the two effects are compensatory. The variation of W^r with ΔG° adds about 0.1 to α; the variation of λ with ΔG° (the Thornton effect[30]) subtracts about the same amount. But there is no apparent reason that this should be general. The practice of regarding α as a measure of the relative strength of the new and the old bonds, which rests on the partial derivative formulation, has no quantitative validity.

The derivation of Marcus theory of atom transfer[3] takes no specific account of either zero-point energy or tunneling. Both undoubtedly influence hydride transfer reactions. Some of the consequences of tunneling have been identified.[31] Marcus theory nevertheless accommodates the rate constants because these effects also influence the symmetric reactions, and fall off systematically as $|\Delta G^\circ|$ increases. Thus, the quantum effects become incorporated in the empirically determined parameters. It has been shown[31] that Marcus formalism can provide a useful framework for understanding the rate constants even when quantum factors alter them by several powers of 10.[31]

The present results add further weight to our previous conclusion[10] that no high energy intermediates intervene between reactants and products in hydride transfer reactions between NAD$^+$ analogues. Marcus theory postulates a one-step conversion of the precursor configuration, which resembles the reactants, to the successor configuration, which resembles the products. Since the rate limiting step resembles the overall process, there is a strong correlation between ΔG° and ΔG^*. Since the activation free energy of the rate-limiting step is large, $(\partial\Delta G^*/\partial\Delta G^\circ)_{\lambda,W^r}$ remains as high as 0.42 even when ln k_{ij} exceeds 10.[11] This permits k_{ij} for the cyanoquinolinium ions, **2**, to approach that for **4**, even though the latter has a smaller intrinsic barrier.

The chief rival mechanism to the one-step hydride transfer is the electron–proton–electron (EPE) mechanism.[32,33] In that mechanism the rate-limiting step is the proton transfer. The first step is the strongly endergonic formation of A_i and A_jH (both neutral radicals, in this case) from the reactants. Since the activation free energy of the proton transfer (ΔG_H) plus the standard free energy of the first step must approximate the observed ΔG^*, ΔG_H must be modest, and the structure sensitivity of ΔG^* should principally reflect the relative stability of the radicals, A_i, since A_jH is invariant in this case. In this situation it seems very implausible that k_{ij} for cyanoquinolinium ions, which would give a benzylic free radical, would approximate k_{ij} for the 10-methylacridinium ion, which gives a much more stabilized diphenylmethyl radical. Thus, we believe that the EPE mechanism must again be rejected.

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