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Reinterpretation of the Brønsted α for Redox Reactions Based on the Effect of Substituents on Hydride Transfer Reaction Rates between NAD$^+$ Analogues

In-Sook Han Lee,* Young Ran Ji, and Eun Hee Jeoung[†]

Department of Science Education, Kangwon National University, Chunchon 200-701, Korea

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Rate and equilibrium constants have been determined spectrophotometrically for two sets of hydride transfer redox reactions between acridine and benzothiazoline derivatives and between pyridine and benzimidazoline derivatives that can be regarded as NAD$^+$/NADH analogues. According to generally accepted ideas of the relation between equilibrium constants, *K*, and rate constants, *k*, these reactions would all have Brønsted α values close to 0.5 since the equilibrium constants, *K*, for these reactions range from 10^{-1} to 10^{2}. However, when the structural variation is in the hydride acceptor, the Brønsted α is less than 0.5 (0.38 and 0.42, respectively), and when the structural variation is in the hydride donor, the Brønsted α is greater than 0.5 (0.63 and 0.61, respectively) for the present systems. The Marcus theory of atom and group transfer can explain the difference of α values in terms of the tightness factor in the critical configuration. When the transition state is loose and symmetrical, the deviation of the Brønsted α from 0.5 can be obtained by adding or subtracting a tightness factor that depends on the location of the substituents.

Introduction

Reaction rate−equilibrium relationships provide powerful tools for probing the structures of transition states. These relations have been of special interest to physical organic chemists because they provide insight into the nature of the energy surface that is responsible for the structure of the transition state. Changes in substituent polarity that lead to mutually reinforcing changes in structure and electron density have been of especially great interest.[1] One proposed model for interpreting rate−equilibrium relationships upon changes in substiuents is the Marcus equation, relating rates to the intrinsic barrier and the standard free energy of reaction.[2]

In a one-step reaction of the type shown in eq 1

$$A_i^+ + D_jH \rightarrow A_iH + D_j^+ \qquad (1)$$

the Brønsted α, defined by

$$\alpha = d(\Delta G^*)/d(\Delta G^\circ) \qquad (2)$$

depends on the structural variation *i* in acceptor, A_i^+, or the structural variation *j* in donor, D_jH, on the tightness of the critical configuration, and on the resemblance of the critical configuration to reactants or products. The dependence on the nature of the critical configuration reflects the fact that structural changes with similar effects on *K* can have quite different effects on intrinsic reactivity and, consequently, on *k*.[3] The critical configuration has been defined as the most probable configuration for crossing the hardest-to-attain dividing surface that separates products from reactants.[4,5] Marcus theory provides a way to approximate the free energy of the critical configuration, which is identified with the Gibbs free energy of activation, ΔG^*, and to correlate this with the equilibrium constant, *K*, written in terms of the overall Gibbs free energy of reaction, ΔG°.[2,5−7]

In this paper, we report the dependence of the Brønsted α on the location of substituents for hydride transfer reactions between NAD$^+$ analogues. NAD$^+$ (nicotinamide adenine dinucleotide) and its reduced form, NADH, are important redox coenzymes for biological systems; over 400 enzymatic redox reactions depend on these coenzymes. Interconversion of NAD$^+$ and NADH involves transferring a hydride equivalent. The mechanistic details of interconversion continue to be controversial,[8] and three mechanisms have been proposed: direct hydride transfer (one-step mechanism), electron transfer followed by hydrogen transfer, and sequential electron, proton, and electron transfer (stepwise mechanism). The related nonenzymatic reactions in which simple NAD$^+$ and NADH analogues act as hydride acceptors and donors can be good models for the enzymatic reaction as well as serving practical purposes in organic synthesis.[9]

In the present article, two sets of NAD$^+$ analogue reactions are considered. One set involves a series of 10-substituted benzylacridinium ions, **1**$^+$, reacting with a series of 3-methyl-2-substituted phenylbenzothiazoline compounds, **2H**, as shown in eq 3, and the other set is a series of 1-substituted benzyl-3-carbamoylpyridinium ions, **3**$^+$, reacting with a series of 1,3-dimethyl-2-substituted phenylbenzimidazoline compounds, **4H**, as shown in eq 4.

Next, we describe the use of Marcus theory to predict the effect of differing locations of substituents on the Brønsted α. In this discussion, we will find it useful to discuss the two symmetrical reactions

$$A_i^{*+} + A_iH \rightleftarrows A_i^*H + A_i^+ \qquad (5)$$

$$D_j^{*+} + D_jH \rightleftarrows D_j^*H + D_j^+ \qquad (6)$$

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* To whom correspondence should be addressed. E-mail: ishl@kangwon.ac.kr.

[†] Present address: Department of Chemistry, Kangnung National Univerisity, Kangnung 210-702, Korea.

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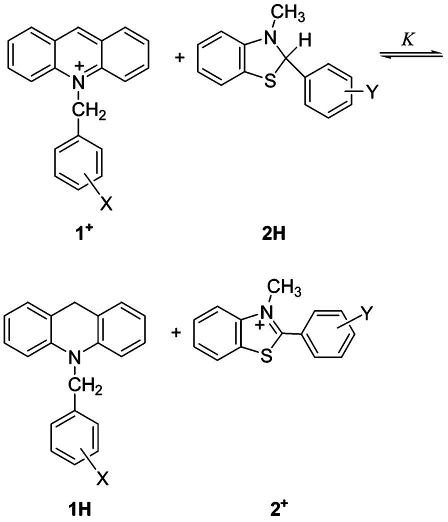
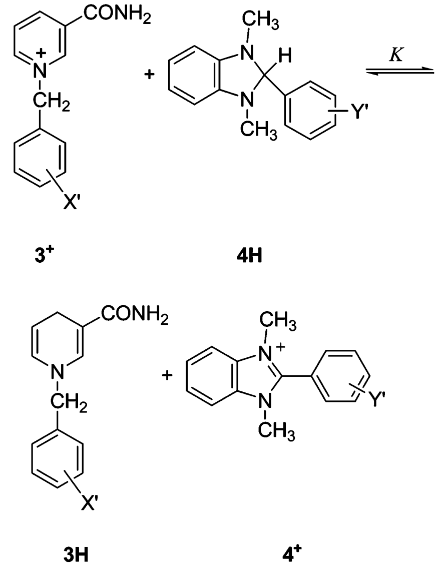


(3)

X: **a**, *p*-CH$_3$; **b**, H; **c**, *p*-F; **d**, *p*-Br; **e**, *m*-F; **f**, *m*-Br; **g**, *m*-CF$_3$; **h**, *p*-CF$_3$; **i**, *p*-CN

Y: **a**, *p*-OCH$_3$; **b**, *p*-CH$_3$; **c**, H; **d**, *p*-F; **e**, *p*-Cl; **f**, *m*-F; **g**, *m*-Cl



(4)

X': **a**, *p*-CH$_3$; **b**, H; **c**, *p*-F; **d**, *p*-Br; **e**, *m*-F; **f**, *m*-Cl; **g**, *p*-CN

Y': **a**, *p*-CH$_3$; **b**, H; **c**, *p*-F; **d**, *p*-Cl; **e**, *m*-F; **f**, *m*-Cl; **g**, *m,m'*-Cl$_2$

Marcus Theory. In general, we rewrite the reaction in eq 1 as

$$A_i^+ + D_jH \xrightarrow{W^r} PC \xrightarrow{\Delta G^{\circ\prime}} SC \xrightarrow{-W^p} A_iH + D_j^+ \qquad (1a)$$

where PC and SC denote a precursor complex and a successor complex, respectively, and the quantities above the arrows are the free energy changes for each step. Note that

$$\Delta G^\circ = \Delta G^{\circ\prime} + W^r - W^p \qquad (7)$$

If the reactants and the products are structurally related and of the same charge type, it can be assumed that W^r is the same as W^p. In that case, the Marcus relations[2,10] predict that the free energy of activation is given by

$$\Delta G^* = W^r + (1 + \Delta G^\circ/\lambda)^2\lambda/4 \qquad (8)$$

where λ is the intrinsic barrier given by

$$\lambda = (\lambda_i + \lambda_j)/2 \qquad (9)$$

where λ_i and λ_j are the free energies of activations for the two related degenerate reactions shown as eqs 5 and 6, and the two free energies are related to the equilibrium constant and the rate constant by

$$K = \exp(-\Delta G^\circ/RT) \qquad (10)$$

$$k = k_BT/h \exp(-\Delta G^*/RT) \qquad (11)$$

Notice that $\lambda = 4(\Delta G^* - W^r)$ when ΔG° is zero. The subscripts *i* and *j* label the hydride acceptor and donor, respectively, as in eqs 1 and 1a. In eq 1a, PC and SC were originally regarded as true metastable reaction intermediates. However, it now appears that they are simply points along the reaction path that identify the portion of the free energy of reaction that correlates with the free energy of activation, ΔG^*.[10] In other words, W^r is a phenomenological parameter that permits the quadratic relation in eq 8 to give a useful correlation of the results.[10] W^r has been taken as −8 kJ/mol for the reaction shown as eq 1.[11−14] For values between 8.4 and −8.4 kJ/mol, the choice of W^r has very little impact on the correspondence between Marcus theory and the experimental results.[7]

From eqs 8−11, we derive the following expression for the Brønsted α.

$$\alpha = \chi \pm (\tau - 1)/2 \mp (RT \ln K/\lambda)^2(\tau - 1)/2 \qquad (12)$$

where χ, called the Leffler−Hammond parameter or the resemblance parameter, depends on the magnitude of *K* according to

$$\chi = [1 - (RT \ln K/\lambda)]/2 \qquad (13)$$

and τ, called the tightness parameter, is given by

$$(\tau - 1) = d(\ln k_i)/d(\ln K^\circ) \qquad (14a)$$

in terms of the rate constant, k_i, for the reaction in eq 5, or

$$-(\tau - 1) = d(\ln k_j)/d(\ln K^\circ) \qquad (14b)$$

in terms of the rate constant, k_j, for the reaction in eq 6. The equilibrium constants, K°, in eqs 14a and 14b represent the equilibrium constants for the hydride transfer reactions from some standard donor to a series of acceptors, A_i^+, and from some standard acceptor to a series of donors, D_jH, and can be written as $\Delta G^{\circ\circ}$ in terms of change in the overall Gibbs free energy of reaction. In practice, for historic reasons and reasons of convenience, 10-methylacridan has been used as the standard donor.[15]

The upper signs in eq 12 can be used for the structural variation in the hydride acceptor, A_i^+, and the lower signs are used for the structural variation in the hydride donor, D_jH. Note that χ gives a quantitative measure of the relative weights of the reactant structure and the product structure in the critical configuration. When *K* becomes larger, the reaction becomes more spontaneous, leading to a smaller value of χ. When χ becomes smaller, the critical configuration becomes more similar to the reactant.[16] Thus, χ has the properties formerly ascribed to α,[16] in particular, it is $\delta(\ln k)/\delta(\ln K)$ or $\delta(\Delta G^*)/\delta(\Delta G^\circ)$ at constant λ. On the other hand, τ appears to have a qualitative significance rather than a quantitative one.[10] It was originally defined as the sum of the orders of the reacting bonds to the in-flight atom or group at the critical configuration,[15] but more generally, it is a phenomenological parameter related to the

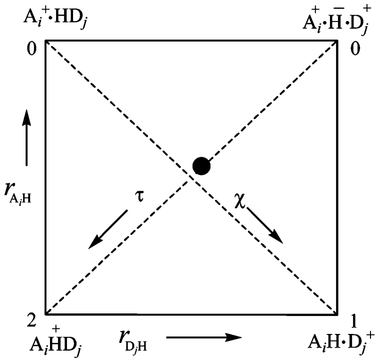


Figure 1. A 2-D critical configuration map for hydride transfer between A_i^+ and D_jH. The closed circle indicates the location of the critical configuration for the present system in the map.

distance between the end groups as well as the partial charge on the in-flight atom or group. Equation 14 shows that τ is an experimentally accessible quantity if the rate constants for the symmetrical exchange reactions, k_i, or k_j, can be measured.

The last term in eq 12 is a cross-term that is likely to be small in most applications because $(RT/\lambda)^2$ will usually be very small. Thus, the Bronsted α can be the value smaller or larger than χ by the tightness factor depending on the location of substituents as shown in eq 12.

The fact that the upper signs apply for the structural variation in the acceptor and the lower signs for one in the donor may be interpreted in terms that were first explicitly discussed by Thornton,[17] and hence, this aspect of the variation of k with $K°$ is called a Thornton effect. The right side of either in eq 14 can be written as $d(\lambda/4)/d(\Delta G°°)$ as we change the hydride affinity of the donor or the acceptor. When we increase the hydride affinity by changing the acceptor, A_i^+ in eq 1, the reaction becomes more spontaneous ($\Delta G°°$ more negative). When the critical configuration is loose (dissociative), λ, the average of λ_i and λ_j, will increase with an increase in hydride affinity at either site. Changes in the acceptor, A_i^+, cause $d(\lambda_i/4)$ to be positive and thus $d(\lambda_i/4)/d(\Delta G°°)$ becomes negative.[5,15]

On the other hand, when we increase the hydride affinity by changing the donor, D_jH in eq 1, the reaction becomes less spontaneous ($\Delta G°°$ more positive), causing $d(\lambda_j/4)/d(\Delta G°°)$ to be positive. Thus, for a loose (dissociative) critical configuration, $d(\lambda_i/4)/d(\Delta G°°)$ is negative, and it makes a negative contribution to $d(\Delta G^*)/d(\Delta G°)$ if the structural variation is in the acceptor, but $d(\lambda_j/4)/d(\Delta G°°)$ is positive and makes a positive contribution to $d(\Delta G^*)/d(\Delta G°)$ if the structural variation is in the donor.

For the reaction of eq 1, a two-dimensional (2-D) critical configuration map (an Albery−More−O'Ferrall−Jencks diagram) is given in Figure 1.

Points on such a diagram represent critical configurations for various reactions (this diagram should not be confused with a potential energy surface or free energy surface for a given reaction). As mentioned above, χ is a quantitative measure of the relative resemblance of the critical configuration to the reactant structure and the product structure, and τ is a quantitative measure of the charge distribution and reactive bond lengths of the critical configuration. In the diagram, the critical configuration in the upper left corner ($\chi = 0$) is identical to reactants which are in contact and properly positioned. The critical configuration in the lower right corner ($\chi = 1$) is identical to the products which are fully formed but not yet separated or disoriented. The critical configuration in the upper right ($\tau = 0$) is a hypothetical one, in which the hydride is in contact with both A_i^+ and D_j^+ but has no covalent bond to either. The critical configuration in the lower left ($\tau = 2$) is also hypothetical, and it represents a hypervalent hydrogen that has covalent bonds with both A_i and D_j and has a full positive charge. If the critical configuration lies along the upper right−lower left diagonal, the bonds to donor and acceptor are of equal strength and the equilibrium constant equals unity ($\chi = {}^1/_2$).

Let us consider the symmetrical exchange reactions between A_i^+ and A_iH as shown in eq 5, where, to measure the rate constants, k_i, the acceptors, A_i^{*+}, can be isotopically labeled at a position remote from the reacting site. We assume that such isotopic substitution does not significantly affect the rates. For a single family of reactions, it is assumed[7] that τ is constant and the critical configuration is always located in the same place in Figure 1. If the critical configuration is at $\tau = 0$ (upper-right in the map in Figure 1), the original A_iH bond is completely broken but the new bond in A_iH is not formed at all in eq 5. Referring to eq 14a, if the free energy of the A_iH bond is increased, then $K°$ and $\ln K°$ will increase, because A_iH is one of the products in eq 1, but k_i and $\ln k_i$ will decrease by an equal amount in eq 5, because the bond being broken (A_iH) in the critical configuration is stronger and the new bond A_iH in the product has not yet begun to form. Thus, $[\delta \ln k_i/\delta \ln K°]_j = -1$ in this case, and $\tau = 0$. At the crossing of the two diagonals, the free energies of the old and new bonds are equal. Therefore, all k_i values will be equal, $[\delta \ln k_i/\delta \ln K°]_j$ will be 0, and τ will be 1. In a similar way, if the critical configuration is at $\tau = 2$ (lower-left in the map), then the original A_iH is preserved as it was and the new bond A_iH is also completely formed in eq 5. When the A_iH bond is strengthened, $K°$ and $\ln K°$ will increase and k_i and $\ln k_i$ will increase by an equal amount because the bond being formed (A_iH) in the critical configuration is stronger. Thus, $[\delta \ln k_i/\delta \ln K°]_j = 1$ in this case, and $\tau = 2$.

We can apply the same treatment to symmetrical reactions between D_j^+ and D_jH as shown in eq 6 to give the opposite results.

We also consider an unsymmetrical reaction with $\tau < 1$ and $K = 1$, in which case the critical configuration is loose (dissociative) and the in-flight H has a hydridic character. If the structural variation is in the acceptor, A_i^+, and the donor is constant, then $\ln k$ will increase by less than half the increase in $\ln K$ because the new bond (A_iH) is less than half formed. On the other hand, if the structural variation is in the donor, D_jH, and the acceptor is constant, then $\ln k$ will increase by more than half the increase in $\ln K$ because the old bond (D_jH) is more than half broken. However, eq 13 shows that χ should be ${}^1/_2$ in both cases because $K = 1$. Something must be added to χ if the donor structure is varied but subtracted from χ if the acceptor structure is varied when the critical configuration is loose (dissociative), $\tau < 1$.

In other words, by locating substituents on the acceptor or the donor, we can design reaction sequences with variable Brønsted α, corresponding to the addition or subtraction of the tightness factor (τ) from the resemblance parameter (χ) in eq 12.

Experimental Section

Compounds **1a**−**i**$^+$ were prepared by nucleophilic addition reaction processes. One equivalent of acridine was heated with 1.2 equiv of the appropriate benzyl bromide in a pressure tube at 105 °C for 5 h. The resulting black solids were washed with benzene and small amount of CH_2Cl_2 to remove unreacted reactants. The crude products were recrystallized from absolute ethanol to give a greenish yellow solid. Yields were around

50%. The benzyl bromides used for the preparation of $\mathbf{1g}^+$ and $\mathbf{1h}^+$ were prepared from the corresponding alcohols.[18] Compounds **1Ha−i** were prepared from the reduction of $\mathbf{1a{-}i}^+$ by $NaBH_4$ to give pale yellow crystalline compounds and purified by recrystallization from ethanol−H_2O (2:1 v/v). Yields were around 70%. Their melting points and spectroscopic properties agreed with those previously reported.[19] Compounds $\mathbf{3a{-}g}^+$ and **3Ha−g** are well-known substances reported previously[20] and identified by their physical and spectroscopic properties. Compounds $\mathbf{4a{-}g}^+$ and **4Ha−g** have also been reported previously.[12] Compounds $\mathbf{2a{-}h}^+$ were prepared by the method of Craig et al. with a slight modification.[21]

Illustrative Procedure for the Preparation of $\mathbf{2}^+$ and 2H. A mixture of 1.3 equiv of benzoic acid (3.00 g, 2.46×10^{-2} mol) and 1 equiv of 2-aminothiophenol (2.38 g, 1.9×10^{-2} mol) and polyphosphoric acid (6.39 g) were heated with stirring at 150 °C for 2 h and then cooled to around 50 °C to give brown solids. Fifty mL of 7% NH_4OH was added to neutralize the unreacted acids. The stirring was continued for 2 h. The yellow solid was filtered off, thoroughly rinsed with the NH_4OH solution (50 mL), and dried to give 2-phenylbenzothiazole (3.99 g), mp 113 °C (lit.[22] 112−113 °C). The yield was generally over 95%. The product was identified by ^1H NMR. Without further purification, this product (3.98 g, 1.88×10^{-2} mol) was heated with methyl iodide (12.6 g, 8.88×10^{-2} mol) at 120 °C for 12 h in a pressure tube to give dark brown solids. The crude product was rinsed with a small amount of acetone to remove unreacted reactants and recrystallized from absolute ethanol to give yellow crystalline solids ($\mathbf{2c}^+\ \mathbf{I}^-$). The yield was over 90%. The iodide counterion ($\mathbf{2c}^+\ \mathbf{I}^-$) was exchanged by perchlorate ion ($\mathbf{2c}^+\ \mathbf{ClO_4}^-$) as follows: $\mathbf{2c}^+\ \mathbf{I}^-$ (3.00 g, 8.50×10^{-3} mol) was dissolved in 100 mL of hot water and treated with 30 mL of hot aqueous solution containing an excess of $NaClO_4$ (10.0 g, 8.17×10^{-2} mol). The exchange reaction took place instantaneously and then the perchlorate salt precipitated. The pale yellow solid of $\mathbf{2c}^+\ \mathbf{ClO_4}^-$ was recrystallized from absolute ethanol to give over 80% yield. Iodide ion has been known to form the charge-transfer complex with some of NAD^+ analogues.[12] Therefore, the iodide counterion was exchanged with the perchlorate ion in order to prevent the formation of the complex. An aqueous solution (20 mL) of $\mathbf{2c}^+\ \mathbf{I}^-$ (2.50 g, 7.08×10^{-3} mol) was reduced by $NaBH_4$ (1.90 g, 5.02×10^{-2} mol) dissolved in 0.05 M NaOH solution (25 mL) to give a white solid. The white solid was recrystallized from ethanol−H_2O (2:1 v/v) to give a colorless crystalline product **2Hc**. The yield was over 70% (1.12 g).

The melting points, spectroscopic properties, and elemental analyses for $\mathbf{2a{-}g}^+$ and **2Ha−g** are given in the Supporting Information.

Measurements. All kinetic measurements were conducted in a solvent containing four parts of 2-propanol to one part of water by volume at 25 ± 0.1 °C to facilitate comparison with a large body of analogous results which have been reported.[7,11−14] 2-Propanol and water were distilled before use. The forward reactions of $\mathbf{1}^+$ with **2Hc** and $\mathbf{1b}^+$ with **2H** were monitored by the decay of the absorption of the reactant, $\mathbf{1}^+$, in the presence of excess **2H**, at 420 nm, whereas the reverse reactions of **1Hb** with $\mathbf{2}^+$ and **1H** with $\mathbf{2c}^+$ were monitored by the growth of the absorption of the product, $\mathbf{1}^+$. The reactions of $\mathbf{3}^+$ with **4Hb** and $\mathbf{3b}^+$ with **4H** were monitored by the growth of the absorption of product, **3H**, in the excess of **4H**, at 360 nm, whereas the reverse reactions of **3H** with $\mathbf{4b}^+$ and **3Hb** with $\mathbf{4}^+$ were monitored by the decay of the absorption of reactant, **3H**. All kinetic experiments were carried out with at least a 25−250-fold excess of the spectroscopically inactive constituents, $\mathbf{2}^+$ and **2H** and $\mathbf{4}^+$ and **4H**. Therefore, k_{obs} was obtained from the first-order rate law in the usual way.[23] The second-order rate constant for the forward reaction, k_{ij}, was obtained from k_{obs} by dividing by the concentration of the excess substrate. All kinetic experiments were performed at least four times in separate experiments with the various concentrations in excess. The average deviations from the mean values of k_{obs} were less than 5%. To get the equilibrium constants, K ($= k_{ij}/k_{ji}$), for the reaction of $\mathbf{3}^+$ with **4Hb**, the reverse reaction rate constants, k_{ji}, were needed. The reverse reactions of **3H** with $\mathbf{4b}^+$ are slower than the forward reactions, and they reached equilibrium with substantial amounts of both reactants still present, so the rate constants for reverse reactions, $k_{ji,}$ were evaluated using[24]

$$k_{ji}C = [x_e/(2a - x_e)]t^{-1} \ln\{[ax_e + x_t(a - x_e)]/a(x_e - x_t)\} \tag{15}$$

The initial concentration of the limiting reactant is a, x_e is the equal concentration of the two products at equilibrium, and x_t is the concentration of the product at time t. This was determined from the stoichiometry of the reaction mixture and its absorbance at 360 nm, which was entirely due to the dihydropyridine, **3H**. C is the concentration of the reactant in excess by at least a factor of 25. A value of K is also required, to calculate x_e, since these reactions are too slow to follow to completion. A trial value of K gave a first estimate of x_e. With this value of x_e, k_{ji} was evaluated. Then K was reevaluated, and a new value of x_e was obtained. The cycle was repeated until consistency was achieved. Usually no more than two iterations were necessary. The average deviations from the mean values of K obtained from the iteration were less than 10%. It should be noted that compound **3H** under the present conditions was found to undergo self-oxidation. Self-oxidation takes place very slowly (half-life around one month) but still makes a nonnegligible contribution to the apparent rate constants for the oxidation of **3H** with $\mathbf{4}^+$. We were not aware of any systematic change in the measurement of the rate constant between **3Hb** and **3Ha** (electron-releasing group) and **3Hi** (electron-withdrawing group). Therefore, we used the value obtained from **3Hb** (2.4×10^{-7}), and the values of $k_{ji}C$ were corrected by subtracting the rate constant of self-oxidation, then they were used to calculate the k_{ji} values.

Results

Rate constants were determined experimentally for forward and reverse reactions when possible, but in some cases, the equilibrium constants, K ($= k_{ij}/k_{ji}$), are not accessible experimentally because the rate in one direction is too fast or too slow to be measured. Rate and equilibrium constants for the reactions of $\mathbf{1}^+$ with **2Hc** and for the reactions of $\mathbf{1b}^+$ with **2H** in eq 3 are given in Table 1, and those for the reactions of $\mathbf{3}^+$ with **4Hb** and $\mathbf{3b}^+$ with **4H** in eq 4 are given in Table 2.

It is interesting to compare the reactivities for reductants such as **2H** and **4H**. On the basis of the magnitude of the rate constants for the reactions with $\mathbf{1b}^+$, **4H** ($2.94 \times 10^2\ M^{-1}\ s^{-1}$ for **4Hb**)[25] is much greater than **2H** ($1.18 \times 10^{-1}\ M^{-1}\ s^{-1}$ for **2Hc**) in reducing power even though N in **4H** is more electronegative than S in **2H**, which substantially decreases the reducing power of **4H**. It is believed that the resonance effect resulting from the better overlapping of the N and C in the **4H** → $\mathbf{4}^+$ conversion as compared with the S and C orbitals in the **2H** → $\mathbf{2}^+$case is larger than the inductive effect resulting from

TABLE 1: Rate and Equilibrium Constants for the Reactions of 1^+ with 2H in eq 3

X	k (M^{-1} s^{-1})[a]	K[a]	Y	k (M^{-1} s^{-1})[b]	K[b]
a	1.00×10^{-1}	4.39×10	**a**	2.80×10^{-1}	3.01×10^{2}
b	1.18×10^{-1}	5.99×10	**b**	2.06×10^{-1}	1.59×10^{2}
c	1.28×10^{-1}	8.95×10	**c**	1.18×10^{-1}	5.99×10
d	1.41×10^{-1}	1.19×10^{2}	**d**	7.00×10^{-2}	3.08×10
e	1.60×10^{-1}	1.47×10^{2}	**e**	4.10×10^{-2}	1.49×10
f	1.70×10^{-1}	1.77×10^{2}	**f**	2.34×10^{-2}	5.05
g	1.82×10^{-1}	2.25×10^{2}	**g**	2.05×10^{-2}	4.12
h	2.00×10^{-1}	2.34×10^{2}			
i	2.20×10^{-1}	3.64×10^{2}			

[a] These values were obtained from the reactions of 1^+ with **2Hc**. [b] These values were obtained from the reactions of $1b^+$ with **2H**.

TABLE 2: Rate and Equilibrium Constants for the Reactions of 3^+ with 4H in eq 4

X'	k (M^{-1} s^{-1})[a]	K[a]	Y'	k (M^{-1} s^{-1})[b]	K[b]
a	1.59×10^{-3}	2.27×10	**a**	2.96×10^{-3}	6.58×10
b	1.85×10^{-3}	3.60×10	**b**	1.80×10^{-3}	3.60×10
c	1.96×10^{-3}	3.90×10	**c**	1.03×10^{-3}	1.72×10
d	2.28×10^{-3}	6.08×10	**d**	7.00×10^{-4}	4.46
e	2.37×10^{-3}	6.97×10	**e**	4.72×10^{-4}	2.52
f	2.62×10^{-3}	7.92×10	**f**	3.49×10^{-4}	1.65
g	3.72×10^{-3}	1.70×10^{2}	**g**	5.02×10^{-5}	1.12×10^{-1}

[a] These values were obtained from the reactions of 3^+ with **4Hb**. [b] These values were obtained from the reactions of $3b^+$ with **4H** in ref 12.

their electronegativity difference, which compensates enough for **4H** to be a better reductant than **2H**.

Another way to compare the reactivities of the reductants is to measure the magnitude of reduction potential. The equilibrium constant for the reaction of 10-methylacridinium ion with **4Hb** in the same solvent system has been reported as 1.23×10^{11} with a reduction potential, $E_{red}°$, of −407 mV for $4b^+$.[12] We also measured[25] an equilibrium constant of 5.08 for the reaction of 10-methylacridinium ion with **2Hc**. With this value of K, a reduction potential, $E_{red}°$, of −100 mV can be obtained[26] for $2c^+$ by means of

$$RT \ln K = nF\Delta E° \tag{16}$$

where F is the Faraday constant and n is the number of electrons transferred, that is, two in this case. This value is much less negative than the reported[27] value of −1.40 V.

For all the present systems, Brønsted plots were made by plotting the value of ln k against the value of ln K for the reactions shown in eqs 3 and 4. Figure 2 shows that the plots for the reactions shown in eq 3 are reasonably linear and the slopes, which are the Brønsted α, have values of 0.38 ± 0.02 (α for the structural variation in 1^+) and 0.63 ± 0.02 (α for the structural variation in **2H**), respectively.

Figure 3 shows that the plots for the reaction shown in eq 4 are also linear, with slopes of 0.42 ± 0.02 (α for the structural variation in 3^+) and 0.61 ± 0.04 (α for the structural variation in **4H**), respectively. The slopes and their uncertainties were evaluated by the method of least squares.[28]

Figure 4 shows that the rate constants for reactions with structural variations in the acceptors, 1^+ and 3^+, are linearly correlated with the Hammett σ parameter, giving slopes (ρ values) of 0.41 and 0.43, respectively.

Figure 5 shows that the rate constants for reactions with structural variations in the donors, **2H** and **4H**, also give a good linear correlation of ln k with σ, giving ρ values of −1.80 and −1.92, respectively.

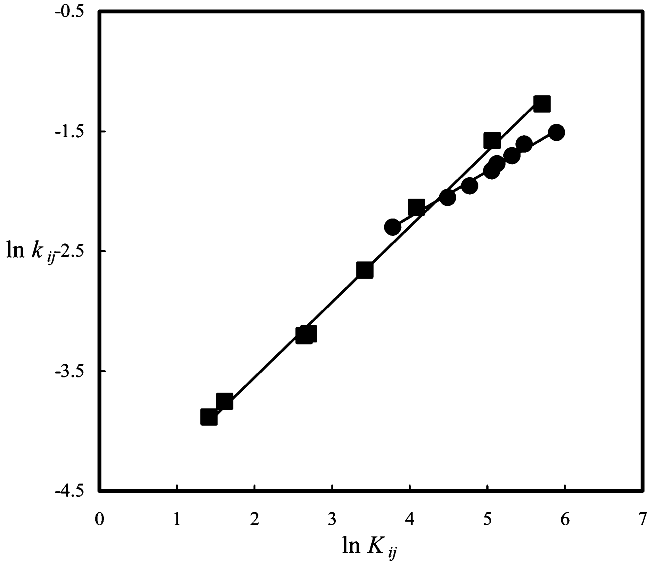


Figure 2. ln k_{ij} as a function of ln K_{ij} for the reactions of 1^+ with **2Hc** (circles) and $1b^+$ with **2H** (squares) in eq 3. The slopes, which are the values for the Brønsted α, are 0.38 ± 0.02 (r = 0.986) and 0.63 ± 0.02 (r = 0.996), respectively.

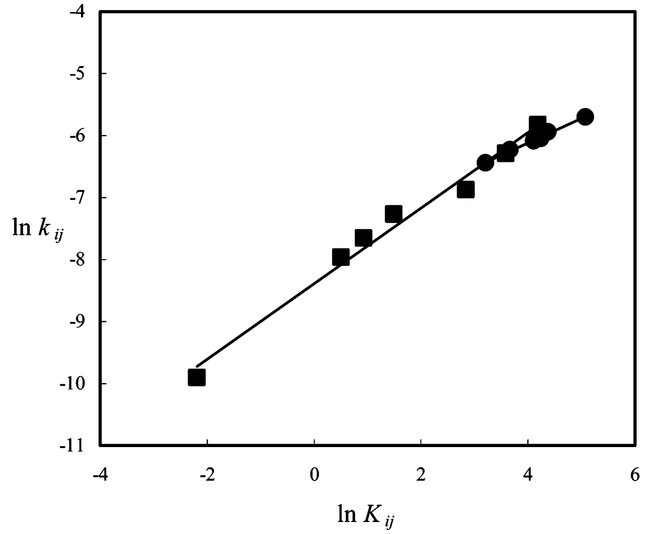


Figure 3. ln k_{ij} as a function of ln K_{ij} for the reactions of 3^+ with **4Hb** (circles) and $3b^+$ with **4H** (squares) in eq 4. The slopes are 0.42 ± 0.02 (r = 0.990) and 0.61 ± 0.04 (r = 0.983), respectively.

For the reaction described in eq 3, ln K values range from 3.8 to 5.9 in the acceptor variation series and from 5.1 to −0.5 in the donor variation series. The ln K value of −0.5 (in the case of p-CN) for the series with donor variation was obtained by extrapolating the plot of ln K as a function of σ in order to get the same reaction range as that for the series with acceptor variation, so as to get well-balanced average values of χ for the application of the Marcus equation. The same method for extrapolation described above was applied for the value of ln k (in the case of p-CN). To apply eq 13, we calculated λ from ΔG^*, $\Delta G°$, W^r, and eq 8. The values of χ are calculated from eq 13 with the average values of ln K (4.84 and 2.33) and ln k (−1.91 and −3.31), and 0.47 and 0.49 are obtained, respectively, because they are the same reactions except for the different location of the substituents in the reactants. It should be noted that structural variation in the donor or the acceptor does change the value of χ, but change in χ is too insignificant to be measurable unless the system has a very wide range of equilibrium constant. For example, χ changed from 0.49 to 0.41

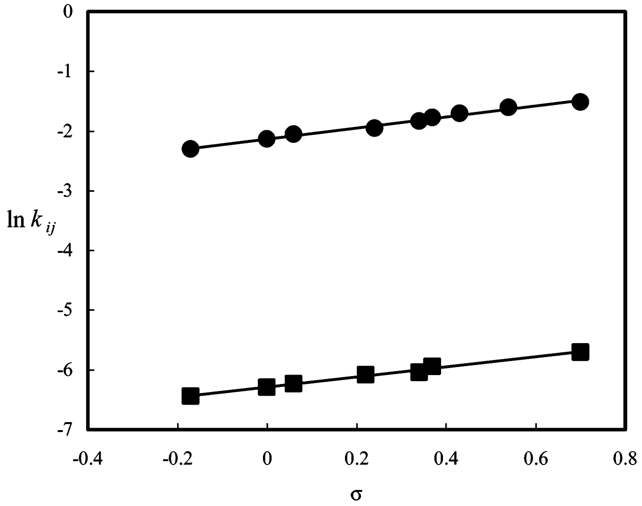


Figure 4. ln k_{ij} as a function of σ for the reactions in eqs 3 and 4 with the structural variation in the acceptors, $\mathbf{1}^+$ (circles) and $\mathbf{3}^+$ (squares), respectively. The slopes, which are the value of ρ, are 0.41 ± 0.04 ($r = 0.991$) for the variation of $\mathbf{1}^+$ and 0.43 ± 0.04 ($r = 0.979$) for the variation of $\mathbf{3}^+$, respectively. Their ρ values are divided by 2.3 from the slopes to put on the usual scale.

when the equilibrium constant changed from 10 to 10^{12}.[12] Since the average equilibrium constants are similar (~100 and 10), one expects similar critical configuration; nevertheless, the two series (acceptor variation and donor variation) give quite different α values (0.38 and 0.63). Strikingly, one is less than 0.5 and the other is greater than 0.5, as shown in Figure 2.

For the reaction described in eq 4, we applied the same method as used for eq 3 to get the average values of ln K and ln k for the same ranges. (We also obtained the values of ln K and ln k for the compound, *m,m′*-$\mathrm{Cl_2}$, by extrapolation.) The values of χ can be calculated with the average values of ln K (4.12 and 1.00) and ln k (−6.01 and −7.86) for the reactions, and 0.49 and 0.50 are obtained, respectively. Also, despite the similar values of χ for both reactions, the two series give different Brønsted α values of 0.42 and 0.61, respectively, as shown in Figure 3.

Discussion

It is very reasonable that the signs of Hammett ρ values are opposite and the magnitudes of the absolute values of ρ are larger for reactions with structural variation in the donors, **2H** and **4H**, than those with structural variation in the acceptors, $\mathbf{1}^+$ and $\mathbf{3}^+$, because in compounds **2H** and **4H** a positive charge is being developing during the course of the reaction, while in compounds $\mathbf{1}^+$ and $\mathbf{3}^+$ the positive charge is partially diminished. Furthermore, the phenyl ring having the substituent in compounds **2H** and **4H** is directly attached to the reacting center, whereas the phenyl ring in compounds $\mathbf{1}^+$ and $\mathbf{3}^+$ is insulated from the reacting center by the methylene group. More interesting is that the Brønsted α values are found to be less than 0.5 (in particular, 0.38 and 0.42) for structural variation in the acceptor and to be greater than 0.5 (in particular, 0.63 and 0.61) for structural variation in the donor, even though the equilibrium constants are close to unity. Lewis and co-workers have shown this phenomenon for methyl transfer reactions and indicated that it should be considered in interpreting Brønsted α values.[29] Grunwald[30] also presented a theoretical analysis similar to that employed in ref 15 and here, in particular being based on a modified Marcus theory and diagrams similar to Figure 1. Bernasconi[31,32] have studied several reactions in which substituents were introduced in various location in the reactants. They observed phenomenon similar to what was observed here in that the Brønsted α depends on the location of the substitution, and they interpreted this in terms of a principle of nonperfect sychronization rather than by the extended Marcus theory treatment used here. However, Bernasconi showed that approaches of the type used by Grunwald and in ref 15 and here can be related to the principle of nonperfect synchronization by a change of variables. Truhlar and co-workers[33] have observed a similar phenomenon for an enzyme-catalyzed hydride transfer reaction. In interpreting the secondary kinetic isotope effect, they showed that the changes of hybridization states of the hydride donor and acceptor do not occur synchronously along the reaction coordinate but rather they are unbalanced in the transition state.[33] The present results and these previous examples provide evidence that a 1-D interpretation of α in terms of the Hammond postulate is insufficient for understanding structure−reactivity relationships in oxidation−reduction reactions involving $\mathrm{NAD^+}$, NADH, and similar compounds.

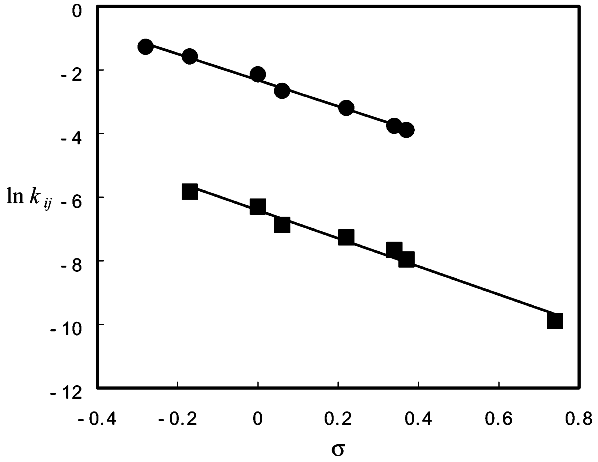


Figure 5. ln k_{ij} as a function of σ for the reactions in eqs 3 and 4 with the structural variation in the donors, **2H** (circles) and **4H** (squares), respectively. The slopes are −1.80 ± 0.18 ($r = 0.991$) for the variation of **2H** and −1.92 ± 0.28 ($r = 0.979$) for the variation of **4H**, respectively. Their ρ values are divided by 2.3 from the slopes to put on the usual scale.

As mentioned in the Introduction, τ is orthogonal to the reaction coordinate. From the related hydride transfer reactions for $\mathrm{NAD^+}$ analogues, a τ value of 0.81 was experimentally obtained[7] and can be used for the present work. This value is similar to the value 0.87 obtained in another study[10] and somewhat larger than a more recent value,[11] 0.66. An extensive discussion of this difference is provided elsewhere;[11] here, we use the median value 0.81, which we believe to be more generally reliable. With the values of χ and τ, the critical configuration of the present system in eqs 3 and 4 is located at the closed circle in Figure 1. The present system has the in-flight atom with a partially negative charge and greater distance between the reactants, the donor, and the acceptor, than that for a system with the positively charged in-flight atom.

When the above-mentioned values of χ, τ, and W^r are inserted in eq 12, the Brønsted α values for structural variation in the acceptor can be calculated to give values of 0.38 and 0.39 in eqs 3 and 4, respectively. On the other hand, the Brønsted α values for structural variation in the donor are calculated to give values of 0.59 and 0.60 in eqs 3 and 4, respectively. These are in a fairly good agreement with the experimental values. Since Marcus theory is based on a one-step model of the reaction, it may be argued that this good agreement constitutes evidence that the present system undergoes a one-step hydride transfer.

Mayr and co-workers have reported[34] α values for the hydride transfer reactions of disubstituted propenes with disubstituted allyl cations by using various levels of ab initio and DFT quantum chemical calculations. Interestingly, their results were quite opposite to ours, giving rise to a smaller value of α with the donor variation and a larger value of α with the acceptor variation. In their system, the value of 1.22 was obtained for τ from the correlation of intrinsic barriers with the standard free energy of the reaction. This value of τ indicates that the critical configuration is tight (associative) and that the in-flight hydrogen has a partial positive charge, nominally +0.22, according to the extended Marcus theory employed here. They[34] found by calculation [MP2/6-31+G(d,p)//RHF/631+G(d,p)] that the in-flight hydrogen bears a positive charge of +0.15, which is in quite good agreement with the value (+0.22) obtained by the extended Marcus theory. The distance between the hydride acceptor and donor is shorter in their system and greater in our system than it would be if τ were unity. Therefore, experimental and computational results indicate that the Brønsted α should not be interpreted as a measure of the resemblance of the transition state to the reactants and products if τ is not 1.0. The extended Marcus theory used here can, however, predict the location effect of the substituent on the Brønsted α in the hydride transfer reaction quite accurately.

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Supporting Information Available: The melting points, spectroscopic properties, and elemental analyses for **2a−g**$^+$ and **2Ha−g**, Hammett σ values, and Table 3, which contains rate and equilibrium constants, α, χ, λ, and τ for hydride transfer reactions in eqs 3 and 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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