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Primary Kinetic Isotope Effects on Hydride Transfer from Heterocyclic Compounds to NAD$^+$ Analogues

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Primary kinetic isotope effects (KIEs), k_H/k_D, have been determined spectrophotometrically for the reactions of NAD$^+$ analogues (acridinium ions, **1a**−**e**$^+$, and quinolinium ion, **2**$^+$) with heteroaromatic compounds such as 3-methyl-2-phenylbenzothiazoline, **3H(D)**, and 1,3-dimethyl-2-phenylbenzimidazoline, **4H(D)** in a mixed solvent containing four parts 2-propanol and one part water at 25.0 ± 0.1 °C. The KIEs decrease from 6.24 to 3.93 as the equilibrium constant, *K*, is increased from about 1 to 10^{12} by the structural variation in the hydride acceptor. The Marcus theory of atom transfer in a linear, triatomic model of the reaction, with tunneling, can explain the variation of KIE with *K*. The Marcus theory is based on a model involving no high-energy intermediates, leading to a one-step mechanism. The present system satisfies this condition.

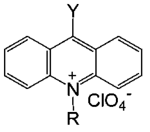
1. Introduction

A primary kinetic hydrogen isotope effect (KIE) provides a probe of the reaction mechanism as well as the structure of transition state because it provides information about the participation of the bonds to the isotopically substituted atom in the rate-determining step of the reaction. In organic molecules, it is often found that the rate of a reaction involving cleavage of a C−D bond is several times slower than that of a C−H bond if the cleavage takes place in the rate-determining step. According to quantum mechanical dynamical theory, the KIEs result from the quantization of molecular vibrations and from turnneling.[1]

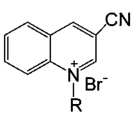
For a series of reactions, the primary kinetic isotope effect (KIE) may be related to the equilibrium constant, *K*, by a linear or quadratic free energy relationship, which may also give insight to the reaction mechanism. The Marcus theory[2] of atom transfer can provide such a relation by calculations based on a series of potential energy surfaces on which the ridge separating reactants from products changes systematically as the strengths of the donor and acceptor bonds change.[3] Marcus theory also predicts that changing *K* will not have the same effect on the KIE when the acceptor is changed as it does when the donor is changed.[4−6]

In the present paper we report measurements of primary kinetic isotope effects (KIE) for the reactions of acridinium ions, **1**$^+$, and quinolinum ion, **2**$^+$, with heterocyclic compounds such as 3-methyl-2-phenylbenzothiazoline, **3H**, and 1,3-dimethyl-2-phenylbenzimidazoline, **4H**, with the structural variation in the hydride acceptor. The hydride acceptors **1**$^+$ and **2**$^+$ are of special interest because they are analogs of the commonly occurring coenzyme NAD$^+$ (nicotinamide adenine dinucleotide). Furthermore, the hydride donors **3H(D)**, and **4H(D)** are analogs of the reduced form, NADH, of the coenzyme.[7] These donors are particularly well suited to theoretical analysis because they have only one hydrogenic atom at the donation center, and therefore there is no involvement of secondary kinetic isotope effects to be considered.

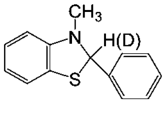
We will also show how an extended Marcus-type analysis incorporating the tunneling effect can explain the data and provide insight into the detailed dynamics.



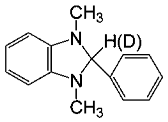
1$^+$



2$^+$



3H(D)



4H(D)

1a$^+$, Y = H, R = CH_3 **2**$^+$, R = $C_6H_5CH_2$

1b$^+$, Y = H, R = $C_6H_5CH_2$

1c$^+$, Y = CN, R= CH_3

1d$^+$, Y = C_6H_5, R = CH_3

1e$^+$, Y = 3,5-$Cl_2C_6H_3$, R = CH_3

2. Theory

2.1. Marcus Theory for a Series of Related Reactions.

Marcus theory was originally derived to account for the quasi-thermodynamic part of the activation energy for outer-sphere electron transfer reactions.[2a,b] It has been extended in various ways to atom, ion, and group transfer reactions,[2c−h,3,4] and to include transmission coefficients and their associated contribution to the free energy of reaction.[2f,h,3,4] Marcus theory is most useful when one considers reactions in which the reactants and products should be structurally similar so that the potential surface has the same general shape on either side of a ridge separating reactants and products.[9] Nitrogen-containing heterocyclic compounds that are structurally related to the coenzyme NAD$^+$ (nicotinamide adenine dinucleotide), allow a wide variety of ring substitutious and therefore can serve as members of series that meet this requirement when a hydride is transferred from an NADH-like hydride donor to an NAD$^+$-like hydride acceptor.[8] Here we consider a series of hydride transfer reactions

$$A_i^+ + D_jX \rightarrow A_iX + D_j^+ \tag{1}$$

where subscripts *i* and *j* label substituents at the hydride acceptor and donor, respectively, and X indicates H or D in hydride

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transfer reaction. The reactants and products are structurally related and of the same charge type.

In Marcus theory,[2-4] the Gibbs free energy of activation, ΔG^*, for each reaction in the series consists of two parts.

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

where W^r, is the work term, ΔG^* is the free energy of reaction, and $\lambda/4$ is the intrinsic barrier. In eq 2, the first term, W^r, is that part of ΔG^* that is independent of the Gibbs free energy of reaction, ΔG°.[3] The work term, W^r, was originally regarded as the free energy required to form a metastable "encounter complex" or "reaction complex"[10,11] from the separated reactants. Formally though, it represents only that part of ΔG^* which is insensitive to the value of ΔG°.[3] Nonzero values of W^r were required to fit computed rate constants to the Marcus theory even when the potential energy surfaces from which they were calculated had no metastable intermediates.[8] Ultimately, this can be explained in terms of an analysis of the bonding and charge transfer contributions to the activation energy.

The second term in eq 2 is a function of ΔG°. If $\Delta G^\circ = 0$, the second term becomes $\lambda/4$, which is called the intrinsic barrier, and $\lambda/4 = \Delta G^* - W^r$. The intrinsic barrier for the reaction is the average of the intrinsic barriers for the two symmetric reactions, λ_i and λ_j, shown in eq 3.

$$\lambda = (\lambda_1 + \lambda_j)/2 \qquad (3)$$

Note that ΔG° and ΔG^* can be related to the equilibrium constant, K, and the rate constant, k, through the standard thermodynamic and quasi-thermodynamic expressions:[2]

$$K = \exp(-\Delta G^\circ/RT) \qquad (4)$$

$$k = (k_B T/h)\exp(-\Delta G^*/RT) \qquad (5)$$

Using eqs 2−5, the Brønsted α ($\equiv$d(ln k)/d(ln K)) can be derived in terms of Marcus parameter shown in eq 6.

$$\alpha = \chi \pm 0.5(\tau\text{-}1) \mp 0.5(RT \ln K/\lambda)^2(\tau - 1) \qquad (6)$$

$$\chi = 0.5[1 - (RT \ln K/\lambda)] \qquad (7)$$

$$\tau - 1 = \mathrm{d}(\ln k_i)/\mathrm{d}(\ln K^\circ) \qquad (8)$$

The effect of the first term on the right-hand side of eq 6 is called the parallel effect, or the Leffler−Hammond effect.[12] The parameter, χ, called the resemblance parameter, depends on the magnitude of K as follows: When K is unity, χ is 0.5, and the critical configuration equally resembles the reactants and the products. When the reaction is more spontaneous, K becomes larger, χ becomes smaller, and the critical configuration becomes more reactant-like.[12] The value of λ determines the sensitivity of χ to changes in K as shown in eq 7. In a dissociative reaction, to make the affinity of one of either side, A_i^+ or D_j^+, for X^- stronger, λ will be larger in any case. But the Brønsted α will be larger or smaller depending on the location of the structural variation in A_i^+ or D_j^+.[8e] For example, when K is increased by making the affinity of A_i^+ for X^- stronger the reaction goes faster not only because ΔG° is more negative but also because λ becomes larger, leading to the decrease of the value of Brønsted α by increase in λ in eq 6. On the other hand, when K is increased by making the affinity D_j^+ for X^- weaker, the reaction goes faster not only because ΔG° is more negative but also because λ becomes smaller, leading to the increase of the value of the Brønsted α by decrease in λ in eq 6. Therefore, the effect of changing K by changing the affinity of acceptor A_i^+ for X^- is opposite to the effect of an equal change in the donor, D_j^+.

The second term on the right-hand side of eq 6 accounts for the perpendicular effect, or Thornton effect.[13] The parameter, τ, called the tightness parameter, is given by eq 8.

In eq 8, K° represents the equilibrium constants for the reactions of the various A_i^+ with a standard hydride. In practice, for historical reasons and reasons of convenience, 10-methylacridan, **1Ha**, has been used as the standard donor.[8b]

Next we consider a series of symmetrical reactions of the type:

$$A_i^{*+} + A_iH \rightarrow A_i^*H + A_i^+ \qquad (9)$$

For such a series the rate constants, k_i will change systematically with the affinity of A_i^+ for X^- even though all the equilibrium constants are all unity. Using eq 8, the variation in rate constants of symmetrical reactions with K° can be used to evaluate the parameter τ. For hydride transfer between NAD$^+$ analogues, τ_H was found to be reasonably constant with an average value of 0.81,[8b] and this value is used in the present work. The third term is negligible in most cases because $(RT/\lambda)^2$ will usually be very small. It has been shown that both of the first two terms in eq 6 are required for a satisfactory estimate of α.[8] The choice of signs in eq 6 depends on the location of the structural variation.[8e] The upper signs are used in eq 6 if the structural variation is in the acceptor, and the lower signs are used if the structural variation is in the donor.[8] The present system has the structural variation in the hydride acceptor so we used the upper signs consistently.

Note that τ was originally defined as the sum of the bond orders of the in-flight hydrogen at the critical configuration,[8a] but more generally, it is a phenomenological parameter related to the distance between the end groups as well as the partial charge on the in-flight atom or group.[3] Theoretical work suggests[2] that it is approximately constant over a broad range of K values, as long as the end groups are unchanged.

2.2. Application of Marcus Theory to Kinetic Isotope Effects. Because the deuterium has the greater mass than the hydrogen, its zero-point energy is lower, and these vibrational energies are proportionately reduced when the critical configuration is formed.[1] Furthermore, the zero-point energy for modes orthogonal to the reaction path contributes to the effective energy requirement for reaction, both for classical motion over the barrier[14] and for tunneling.[15] Therefore, since λ, despite its name, is not an internal energy barrier, but rather 4 times the free energy of activation of a degenerate rearrangement reaction, this effect plus the fact that more tunneling is expected for hydride transfer than for deuteride transfer makes the intrinsic barrier for hydride transfer, λ_H, smaller than that for deuteride transfer, λ_D. The most probable distance for tunneling is larger than that in the classical transition state.[4,16,17] Thus, the acceptor−donor distance for hydride transfer should be larger than that for deuteride transfer. Since τ is inversely correlated with the donor−acceptor distance, τ_H is less than τ_D. That is, the critical configuration for reaction (averaged over a thermal ensemble) is expected to be more dissociative for hydride transfer than for deuteride transfer.

Since the Brønsted α is a function of λ and τ, and both of these are expected to change on isotopic substitution of the in-flight hydrogen, separate Brønsted relations are expected for hydride and deuteride transfer as shown in eqs 10 and 11.

$$\ln k_{\mathrm{H}} = \ln k_{\mathrm{H}}^{\circ} + \alpha_{\mathrm{H}} \ln K \tag{10}$$

$$\ln k_{\mathrm{D}} = \ln k_{\mathrm{D}}^{\circ} + \alpha_{\mathrm{D}} \ln K \tag{11}$$

where k_{H}° and k_{D}° indicate the rate constants for hydride and deuteride transfer, respectively, for the special case that K is unity.

When ln k_{D} is subtracted from ln k_{H} and appropriate substitution is made for τ and KIE is defined as $k_{\mathrm{H}}/k_{\mathrm{D}}$, we obtain:

$$\ln \mathrm{KIE} = \ln \mathrm{KIE}^{\circ} + 0.5[\ln K(\tau_{\mathrm{H}} - \tau_{\mathrm{D}})] - 0.5RT(\ln K)^2(1/\lambda_{\mathrm{H}} - 1/\lambda_{\mathrm{D}}) \tag{12}$$

where the third term on the right-hand side of eq 6 is neglected, which can be justified as follows. The isotopic sensitivity of χ, arising from the isotopic sensitivity of λ, is shown by eq 7, has been neglected because it has a negligible effect on the ln KIE values which we will discuss in this paper. The second term on the right-hand side of eq 12 represents the perpendicular effect on ln KIE and should be linear against ln K. As a result, Westheimer theory[18] that ln KIE should be a bell shaped function of ln K with a maximum at $K = 1.0$ has been challenged.[19] As mentioned above τ_{H} is smaller than τ_{D}, and $(\tau_{\mathrm{H}} - \tau_{\mathrm{D}})$ should be negative. When the structural variation is in the hydride acceptor, A_i^+, the slope of the plot of ln KIE + C ($C = 0.5RT(\ln K)^2\ (1/\lambda_{\mathrm{H}} - 1/\lambda_{\mathrm{D}})$) against ln K is negative as shown in eq 12. The third term on the right side of eq 12 represents the parallel effect due to the relation with λ and should be parabolic against ln K.

3. Synthesis

Compounds **1a**−**b**$^+$ are well-known substances obtained by methylation and benzylation of acridine using methyl iodide[5] and benzyl bromide,[8e] respectively, and followed by an ion exchange reaction with $\mathrm{NaClO_4}$. Compound **1c**$^+$ was prepared by addition of KCN to **1b**$^+$ followed by oxidation reaction with *p*-chloranil and perchloric acid.[20] Compounds **1d**−**e**$^+$ were prepared by addition of Grignard reagent to **1b**$^+$ followed by oxidation reaction with *p*-chloranil and perchloric acid.[5] Compound **2** was prepared from benzylation of 3-cyanoquinoline.[8a] All the acridine compounds and the quinoline compound were identified by their physical and spectroscopic properties. Compounds **3H** and **4H** were prepared by the method of Craig and co-workers[21] with small modifications. A typical procedure is as follows:

A mixture of benzoic acid (1.2 equiv), *o*-aminothiophenol (1eq), and polyphosphoric acid (3 times the weight of the acid) was heated with stirring at 150 °C for 2 h and then cooled to room temperature. An aqueous solution of $\mathrm{NH_4OH}$ (7%) was added to neutralize unreacted acids (benzoic acid and polyphosphoric acid). The solid was filtered and, thoroughly rinsed with the $\mathrm{NH_4OH}$ solution to give 2-substituted phenylbenzothiazole. The yields were generally over 90%. Without further purification, the product was treated with methyl iodide (3eq). The reaction mixture was heated at 110 °C overnight in a pressure tube. The crude product was recrystallized from absolute ethanol to give **3**$^+$ (yields, over 80%). To a solution of **3**$^+$ (1eq) in methanol (25 mL/g) was slowly added $\mathrm{NaBH_4}$ (3eq). The reaction mixture was stirred vigorously for 1 h under $\mathrm{N_2}$. After removal of the solvent under reduced pressure the solid was treated with water to remove the inorganic compound. The solid was recrystallized from EtOH−$\mathrm{H_2O}$ (2:1, v/v) to give a colorless crystalline product, **3H** (yields, over 70%). Compound **3D** was prepared by the same method as **3H** except using $\mathrm{NaBD_4}$ for reduction. This preparation had 2−6% of contamination with **3H**, as determined by its ^{1}H NMR spectrum. It was purified by sacrificial oxidation with *p*-chloranil. *p*-Chloranil (0.3 equiv) was partially dissolved in ether and added to the solution of **3D** in ether slowly with stirring. Reaction took place immediately to give a brownish yellow precipitate. The stirring was continued for 1 h under $\mathrm{N_2}$. The solvent of the filtrate was allowed to evaporate from the unreacted **3D**. The residue was recrystallized twice from EtOH−$\mathrm{H_2O}$ (2:1, v/v) to give colorless crystals in 50% yield. There was no detectable signal for **3H** in the ^{1}H NMR (400 MHz). We estimated from this that the isotopic purity of **3D** was >99%. Its melting point was identical with that of **3H** (mp 112 °C). The deuterium content of **3D** was confirmed by comparison of a mass spectrum of **3H** and that of **3D**, employing the electron impact ionization technique and introduction via a direct insertion probe inlet system:

3H *m/z* (%): 227 ($\mathrm{M^+}$, 81), 226 ($\mathrm{M^+}$ − H, 44), 150 ($\mathrm{M^+}$ − $\mathrm{C_6H_5}$, 100), 109 ($\mathrm{M^+}$ − $\mathrm{C_6H_5}$, C, and $\mathrm{NCH_3}$, 33)

3D *m/z* (%): 228 ($\mathrm{M^+}$, 54), 226 ($\mathrm{M^+}$ − D, 14), 151 ($\mathrm{M^+}$ − $\mathrm{C_6H_5}$, 100), 110 ($\mathrm{M^+}$ − $\mathrm{C_6H_5}$, C, and $\mathrm{NCH_3}$, 9)

4. Kinetics Measurements

All kinetics measurements were conducted in a solvent containing four parts 2-propanol to one part water by volume at 25.0 ± 0.1 °C to facilitate comparison with a large body of analogous results already available in this solvent system.[5,6,8] 2-Propanol and water were distilled before use. For most reactions, the reaction rates were moderate and a spectrophotometer was used to monitor the decay of the absorption at 420 nm for compounds **1**$^+$ and the decay at 280 nm for compound **2**$^+$. For faster reactions, such as the reaction of **1b**$^+$ with **4H,** whose half-life is less than 1 s, the reaction rate constant was determined with a stopped-flow apparatus (Hi-Tech Scientific, SFA-20) attached to the spectrophotometer (Beckmann DU-7500). All the reactions went to completion in the presence of excess of the reducing agents, **3H** and **4H**. All the products were identified by ^{1}H NMR and UV−vis spectroscopy. All kinetic experiments were carried out with at least 25−100-fold excess of the spectroscopically inactive constituents, **3H** and **4H**, for the present system. Therefore, k_{obs} was obtained from the first-order rate law in the usual way as shown in eq 13.[22]

$$k_{\mathrm{obs}} = t^{-1} \ln[(A_{\mathrm{o}} - A_{\infty})/(A_t - A_{\infty})] \tag{13}$$

The second-order rate constants, k, were given by k_{obs}/C, where C is the concentration of the substance in excess. All kinetic experiments were performed at least 4 times, in separate experiments. For the fast reaction of **1b**$^+$with **4H**, more than 20 experiments were performed because the stopped-flow apparatus required small volumes, which give rise to greater-than-usual uncertainties in the concentrations. The average deviations from the mean values of k_{obs} were around 2% for

TABLE 1: Rate, Equilibrium Constants, and KIE for Hydride Transfer Reactions

oxidant	reductant	k_H(M^{-1}s^{-1})	K	KIE(exptl)
1a$^+$	**3H**	$(2.85 \pm 0.05) \times 10^{-2}$	5.08	6.24 ± 0.35
1b$^+$	**3H**	$(1.18 \pm 0.04) \times 10^{-1}$ [a]	5.99×10 [a]	6.18 ± 0.25
1c$^+$	**3H**	$(3.96 \pm 0.05) \times 10^{-1}$	4.43×10^3 [b]	5.59 ± 0.33
2$^+$	**3H**	$(1.60 \pm 0.04) \times 10^{-2}$	1.12×10^2 [b]	5.83 ± 0.14
1a$^+$	**4H**	$(2.94 \pm 0.12) \times 10^2$ [d]	1.23×10^{11} [c]	3.95 ± 0.32 [d]
1b$^+$	**4H**	$(9.80 \pm 0.35) \times 10^2$ [e]	1.45×10^{12} [d]	3.93 ± 0.25
1d$^+$	**4H**	$(1.92 \pm 0.07) \times 10^{-1}$ [d]	7.81×10^{10} [d]	4.44 ± 0.26 [d]
1e$^+$	**4H**	$(7.43 \pm 0.59) \times 10^{-1}$ [d]	6.35×10^{12} [d]	4.05 ± 0.32 [d]
2$^+$	**4H**	$(2.08 \pm 0.09) \times 10^2$ [d]	2.73×10^{12} [d]	4.18 ± 0.33 [d]

[a] This value was taken from ref 8e. [b] Determined by the ladder procedure. (The estimated uncertainty is 10−25%.)[20] [c] This value was taken from ref 8c. [d] These values were obtained from ref 6. [e] This value was taken from ref 23.

TABLE 2: Intrinsic Barrier, λ_H, Perpendicular Effect, A, and Parallel Effect, B, for Hydride Transfer Reactions

oxidant	reductant	λ_H (k/mol)	A[a]	B[b]
1a$^+$	**3H**	369	0.02	0
1b$^+$	**3H**	367	0.05	0
1c$^+$	**3H**	373	0.10	0.01
2$^+$	**3H**	387	0.06	0
1a$^+$	**4H**	385[c]	0.31[d]	0.09[c]
1b$^+$	**4H**	383	0.34	0.10
1d$^+$	**4H**	458[c]	0.30[d]	0.08[c]
1e$^+$	**4H**	473[c]	0.35[d]	0.11[c]
2$^+$	**4H**	402[c]	0.34[d]	0.11[c]

[a] These values were obtained from the second term on the right-hand side in eq 12. [b] These values were obtained from the third term on the right-hand side in eq 12. The estimated error for A is less than 5% and that for B is less than 10% due to the estimated uncertainty of K. [c] These values were obtained from ref 6. [d] These values are slightly different from those in ref 6 due to the slightly different value of the slope obtained from Figure 1.

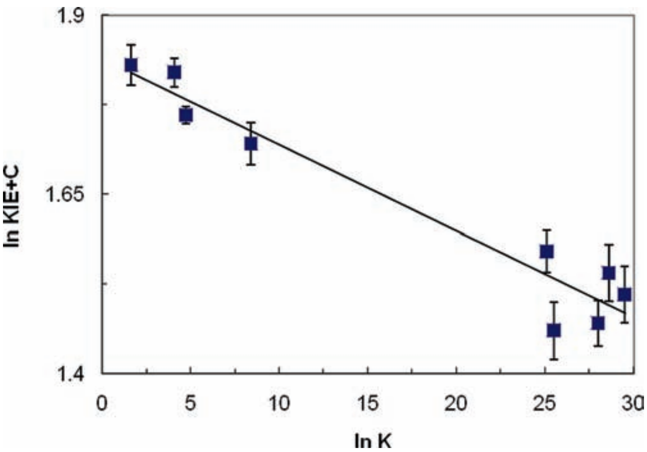

Figure 1. ln KIE + C [$C = 0.5RT(\ln K)^2(1/\lambda_H - 1/\lambda_D)$] as a function of ln K for hydride transfer reactions. The two points [(ln K, ln KIE + C): (3.58, 1.84), (14.4, 1.65)] obtained from ref 6 are added in this plot because they are the reactions of 1-benzyl-3-carbamoylpyridinium ion and 5-benzylphenanthridium ion with **4H**, respectively, which are the same family of the present system. The slope of the plot, which is $+0.5(\tau_H - \tau_D)$, is -0.012 ± 0.002 ($r = 0.938$).

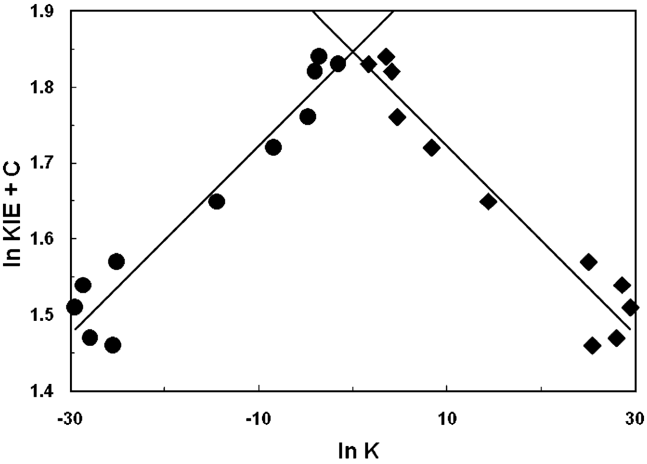

Figure 2. ln KIE + C [$C = 0.5RT(\ln K)^2(1/\lambda_H - 1/\lambda_D)$] as a function of ln K for hydride transfer reactions. The KIEs for the reverse reactions (circles) were obtained from the assumption that the present system has the EIE close to unity. The ln KIE + C has a maximum value when ln K is 0. When there is no intermediate and $K = 1$, the KIE will be maximized by the quasiclassical isotope effect and also by a maximum contribution of tunneling.[18]

the moderate reactions and 5% for the fast reactions. Isotope effects for the most reactions were determined by simultaneous measurement of k_H and k_D, to minimize errors due to temperature fluctuation. The measurement of isotope effect for the reaction of **1b**$^+$ with **4D** was also replicated more than 20 times. The values of KIE were obtained by dividing k_H, the average value out of more than 20 values, by k_D obtained in the same way as in k_H. The average deviation from the mean values was less than 7%. Most of the scatter is probably due to variation in temperature and solvent composition.

5. Results

Rate constants, equilibrium constants, and KIEs for the reactions shown in eq 1 are given in Table 1. The equilibrium constants, K, for reactions of **1c**$^+$ and **2**$^+$ with **3H** were obtained by using a ladder procedure from the K values for the reactions of **2**$^+$ with **1aH**,[8a] for **1a**$^+$with **3H**, and **1c**$^+$with **2H**,[23] respectively. The intrinsic barriers, λ_H and λ_D, can be obtained from eq 2 with the value of W^r, rate constants, and equilibrium constants leading to ΔG^* and ΔG^o using eqs 4 and 5, respectively. For reactions of the present type, W^r has been taken as −8 kJ/mol.[8] The values of λ_H are given in Table 2. The intrinsic barrier of **4H**, $\lambda_{\mathbf{4H}}$, has been reported as 413 kJ/mol.[8c] With this value we can calculate the individual intrinsic barrier for the acridine and the quinoline compounds by applying eq 3. The calculated values are 353 kJ/mol for $\lambda_{\mathbf{1a}+}$, 357 kJ/mol for $\lambda_{\mathbf{1b}+}$, and 391 kJ/mol for $\lambda_{\mathbf{2}+}$, respectively. When these values are applied to eq 3 for the estimation of $\lambda_{\mathbf{3H}}$, the values of $\lambda_{\mathbf{3H}}$ are obtained as 381 kJ/mol with $\lambda_{\mathbf{1a}+}$, 381 kJ/mol with $\lambda_{\mathbf{1b}+}$, and 383 kJ/mol with $\lambda_{\mathbf{2}+}$, respectively. They are in fairly good agreement. The more reactive the reductant is, the greater the intrinsic barrier is. Therefore, this value (382 kJ/mol) is reasonable when compared with **4H** because **3H** is less reactive than **4H**. The plots of ln KIE + C [$C = 0.5RT(\ln K)^2(1/\lambda_H - 1/\lambda_D)$] as a function of ln K for hydride transfer reactions are shown in Figures 1 and 2. The perpendicular effect and the parallel effect on ln KIE as a function of ln K for hydride transfer reactions is shown in Figure 3.

6. Discussion

Marcus theory predicts the relationship between K and KIE with the structural variation. The present system has the structural variation in the acceptor, A_i^+. In eq 12, the slope of the plot of ln KIE + C [$C = 0.5RT(\ln K)^2\ (1/\lambda_H - 1/\lambda_D)$] against ln K should be linear and negative because $(\tau_H - \tau_D)$ is negative. The anticipation is realized as shown in Figure 1. The slope of the plot, which is $+0.5(\tau_H - \tau_D)$, is −0.012

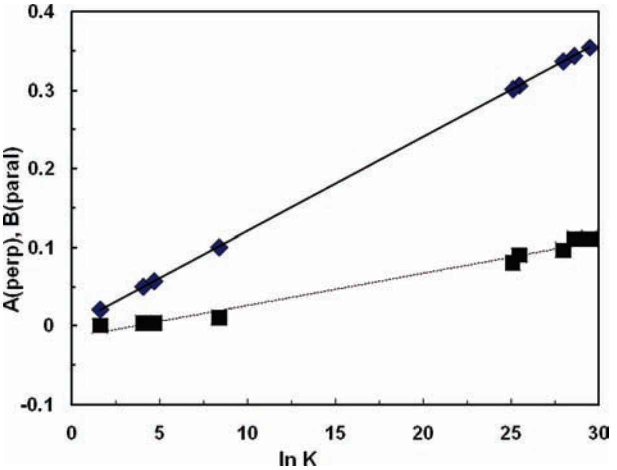

Figure 3. Perpendicular effect (diamonds) and the parallel effect (squares) on ln KIE as a function of ln *K* for hydride transfer reactions. The perpendicular effect is a linear function of ln *K* and the parallel effect is a parabola function of ln *K* according to the Marcus theory shown in eq 12.

± 0.002 ($r = 0.938$). In this plot are added the two values reported previously[6] for the reactions of **4H** with 1-benzyl-3-carbamoylpyridinium ion and 5-benzylphenanthridinium ion, which can be regarded as the same family for the present system. The value of the slope leads to the difference between τ_H and τ_D, giving a value of 0.025. This value is the same as the value obtained from the computation by ICVT (improved canonical variational transition state theory)-plus-LCT (large curvature ground-state tunneling) method.[3] A family of three-body potential energy surfaces was used[3] for calculation of rate constants, *k*, and primary kinetic isotope effects. The bimolecular rate constant, k_2, can be approximated by eq 14 when tunneling is taken into account.[24]

$$k_2 = k(\text{ICVT})\kappa(\text{LCT}) \qquad (14)$$

where *k*(ICVT) represents the quasi-classical rate constant and κ(LCT) represents the transmission coefficient calculated by the large curvature tunneling (LCT) approximation. For the calculation of the rate constants, *k*, the standard donor C−H bond energy was assumed to be 305 kJ/mol and the full range of bond dissociation energies for the reactions considered in the three-body model were to be D_e(CH) of 242−347 kJ/mol.[3] The quasi-classical kinetic isotope effect is $k_H(\text{ICVT})/k_D(\text{ICVT})$, which is determined by changes in zero-point energy and vibrational and rotational partition functions. The transmission coefficient, κ, is the ratio of the thermally averaged quantal transmission probability to the thermally averaged overbarrier transmission probability with classical reaction coordinate. The tunneling contribution to the kinetic isotope effect is $\kappa_H(\text{LCT})/\kappa_D(\text{LCT})$. The total KIE for hydride transfer reaction, which is the product of the quasiclassical contribution to the KIE and the tunneling contribution to the KIE, increases significantly when the C−H bond energy decreases and consequently the donor−acceptor distance increases.[3]

The equilibrium isotope effect (EIE) on the reduction of NAD^+ to NADH (isotopic substitution of H at the 4-position) has been reported to be 0.89.[25] On the other hand, the value of the EIE for the oxidation of a secondary alcohol by NAD^+ has been reported to be 1.18.[25] Therefore, it may be reasonable to assume that the present system, which is fairly similar to the reported one, would have the value of EIE close to unity.[25] In that case the KIE for the forward reaction (KIE_f) is similar to that for the reverse reaction (KIE_r). If this is the case, we can plot the KIE_r for the reverse reaction of the present system as a function of ln *K*, as shown in Figure 2. The ln KIE + *C* has a maximum value when ln *K* is 0 in Figure 2. It is predicted that the KIE will be maximized when *K* is close to unity and there is no intermediate. These conditions maximize the quasiclassical isotope effect and also give a maximum contribution of tunneling.[18]

The perpendicular effect and the parallel effect calculated by the Marcus formalism shown in eq 12 are listed in Table 2. The plot of the perpendicular effect which is the second term in the right -hand side in eq 12 against ln *K* is linear while the plot of parallel effect which is the last term in eq 12 against ln *K* is a parabola as expected in the Marcus theory. As shown in Figure 3 the perpendicular effect is much larger than the parallel effect on the Brønsted α, and this appears to be the main reason for the change in the KIE. In other words, the corner-cutting tunneling contribution to the KIE plays a very significant role for the present system when a hydride is transferred. This is also in good agreement with the maximum value of KIE at $K = 1$.[18]

In conclusion, our analysis is consistent with the present system undergoing a direct hydride transfer in one-step mechanism. The extension of the phenomenological Marcus theory used here explains quite accurately the effect of tunneling on the hydride transfer by using the relationship of the equilibrium constants with the KIE.

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