J. Am. Chem. Soc. **2001,** *123,* 7492−7496

Primary Kinetic Isotope Effects on Hydride Transfer from 1,3-Dimethyl-2-phenylbenzimidazoline to NAD$^+$ Analogues

In-Sook Han Lee,*,† Eun Hee Jeoung,† and Maurice M. Kreevoy*,‡

Contribution from the Department of Science Education, Kangwon National University, Chuncheon 200-701, Korea, and Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455-0431

Received December 11, 2000

Abstract: Primary kinetic isotope effects (KIE) have been determined spectrophotometrically for the reaction of NAD$^+$ analogues (pyridinium, quinolinium, phenanthridinium, and acridinium ions) with 1,3-dimethyl-2-phenylbenzimidazoline in a 4:1 mixture of 2-propanol and water by volume at 25 °C. The values of KIE varied systematically from 6.27 to 4.06 as the equilibrium constant changed from around 10 to around 10^{12}. This is consistent with Marcus theory of atom transfer, assuming that there are no high-energy intermediates. Within this theory, the perpendicular effect is responsible for most of the change in KIE. The Marcus theory of atom transfer is consistent with a linear, triatomic model of the reaction. Perpendicular effects arise from the systematic decrease of bond distances and increase of bond orders in the critical complexes of the two related degenerate hydride transfer reactions as their C−H bonds become stronger. The parallel effect (Leffler−Hammond effect) is attenuated by the fairly high intrinsic barrier ($\lambda/4$ is around 92 kJ/mol) and makes a smaller contribution to the change in the KIE.

Introduction

Kinetic isotope effects, especially primary kinetic hydrogen isotope effects (KIE), are among the simplest and most direct manifestation of the quantum nature of matter. Within the Born−Oppenheimer approximation isotopic replacement does not affect the potential energy surface of the molecule nor does it perturb the electronic energy levels. Only molecular vibrations, rotations, and translations change. Mainly it is changes in vibrations which change reaction rate and which carry mechanistic information.[1,2]

An expression for the relation between primary kinetic hydrogen isotope effect and equilibrium constant, *K*, comes out of the Marcus theory of atom transfer.[3] The Marcus theory[4] is consistent with a linear, triatomic model of an atom transfer reaction.[5] This model provides an approximate but quantitative potential energy surface for the reaction, in which the ridge separating reactants from products changes systematically as the strength of the donor and acceptor bonds changes.[5] The most essential requirement for the applicability of Marcus theory is that the reactants and products should be structurally similar, so that the potential surface has the same general shape on either side of the ridge.[6] Reactions in which hydride is transferred from one carbon to another meet this requirement, and Marcus theory gives a very good approximation of the change in the Gibbs free energy of activation, ΔG^*, with the change in the overall Gibbs free energy of reaction, $\Delta G°$.[7−9]

Marcus theory is summarized in eqs 2 and 3 for a one-step reaction of the type shown in eq 1

$$A_i^+ + A_jX \rightarrow A_iX + A_j^+ \tag{1}$$

$$\Delta G^* = W^r + (1 + \Delta G°/\lambda)^2 \cdot \lambda/4 \tag{2}$$

$$\lambda = (\lambda_i + \lambda_j)/2 \tag{3}$$

The subscripts *i* and *j* indicate the hydride acceptor and donor, respectively. In the absence of a subscript the subscript *ij* can be inferred. W^r was originally regarded as the free energy required to form a metastable “encounter complex”[3,4] or “reaction complex”[10,11] from the separated reactants. In fact, it appears to represent only that part of ΔG^* which is insensitive to the value of $\Delta G°$.[5] Nonzero values of W^r were required to fit computed rate constants to Marcus theory, even though the potential energy surfaces from which they were calculated had

---

[†] Kangwon National University.

[‡] University of Minnesota.

(1) Melander, L.; Saunders, W. H, *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980; pp 152−154.

(2) (a) Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265−273. (b) Bunton, C. A.; Shiner, V. J. *J. Am. Chem. Soc.* **1961**, *83*, 3214−3220. (c) Albery, W. J. *Trans. Faraday Soc.* **1967**, *63*, 200−206. (d) Kreevoy, M. M. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds; Elsevier: New York, 1976; Vol. 2, pp 1−31. (e) Tucker, S. C.; Truhlar, D. G. In *New Theoretical Concepts for Understanding Organic Reactions*; Berfran, J., Csizmadia, I. G., Eds.; Kluwer Academic Publishers: New York, 1989; pp 299−346. (f) Duan, X.; Scheiner, S. *J. Am. Chem. Soc.* **1992**, *114*, 5849−5856. (g) Benedict, H.; Limbach, H.-H.; Wehlan, M.; Fehlhammer, W.-P.; Golubev, N. S.; Janoschek, R. *J. Am. Chem. Soc.* **1998**, *120*, 2939−2950. (h) Kohen, A.; Klinman, J. P. *Chem. Biol.* **1999**, *6*, R191−R198. (i) The foregoing is only a small sample for a very large literature.

(3) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*. 891−899.

(4) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155−196.

(5) Kim, Y.; Truhlar, D. G.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 7837−7847.

(6) Magnoli, D. E.; Murdoch, J. R. *J. Am. Chem. Soc*. **1981**, *103*, 7465−7469.

(7) Kreevoy, M. M.; Ostović, D.; Lee, I.-S. H.; Binder, D. A.; King, G. W. *J. Am. Chem. Soc.* **1988**, *110*, 524−530.

(8) Albery, W. J.; Kreevoy, M. M. *Adv. Phys. Org. Chem*. **1978**, *16*, 87.

(9) Lee, I.-S. H.; Jeoung, E. H.; Kreevoy, M. M. *J. Am. Chem. Soc*, **1997**, *119*, 2722−2728.

(10) Kreevoy, M. M.; Konasewich, D. E. *Adv. Chem. Phys.* **1971**, *21*, 243−252.

(11) Hassid, A. I.; Kreevoy, M. M.; Liang, T.-M. *Symp. Faraday Soc.* **1975**, *10*, 69−77.

10.1021/ja004232+ CCC: $20.00

no metastable intermediates.[5,12] Thus W^r is little more than an adjustable parameter that enables this very simplified theory to give a faithful account of the results. For reactions of the present type W^r has been taken as −8 kJ/mol.[5] We used this value for the present work. $\lambda/4$ is called the intrinsic barrier. It is $(\Delta G^* - W^r)$ for the reaction of this type in which $\Delta G°$ is zero. For the nondegenerate reactions λ is the average of λ_i and λ_j, the values of $4(\Delta G^* - W^r)$ for the two related degenerate reactions. $\Delta G°$ and ΔG^* can be related to the equilibrium constant, K, and the rate constant, k, through the standard thermodynamic and quasithermodynamic expressions, shown in eqs 4 and 5.

$$K = \exp(-\Delta G°/RT) \tag{4}$$

$$k = [k_B T/h] \exp(-\Delta G^*/RT) \tag{5}$$

From eqs 2−5 the Brønsted α can be derived in terms of the Marcus parameters[12,13] with the result shown in eqs 6−8.

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

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

$$\tau - 1 = \mathrm{d}(\ln k_{ii})/\mathrm{d}(\ln K_{ij}{}^{o}) \tag{8a}$$

$$-(\tau - 1) = \mathrm{d}(\ln k_{jj})/\mathrm{d}(\ln K_{ij}{}^{o}) \tag{8b}$$

The equilibrium constant for some member of the set is K and the rate constant for a degenerate reaction A_i with A_iX is k_{ii}. Equations 7 and 8 define χ and τ, quantities which carry information about the structure of the critical configuration[13,14] and considerably simplify the form of eq 6.

The Leffler−Hammond parameter is χ. It is 0.5 when K is unity. Since the general shape of the reactant valley and the product valley in the potential surface is the same, a K value of unity implies that the critical configuration equally resembles the reactants and the products. As the reaction becomes more spontaneous, and K becomes larger, the critical configuration occurs closer to the reactant.[15] This is indicated by a smaller value of χ. The value of λ determines the sensitivity of χ to changes in K. It has often been assumed that α has the physical significance of χ.[16] The two are only the same for the special case that $\tau = 1.0$.

In a series of degenerate reactions of the type shown in eq 1 the rate constants, k_{ii}, will usually change systematically with the affinity of A^+ for X^- even though all the equilibrium constants are all unity.[13,14] In Marcus theory this can be accommodated by a systematic variation in λ with the affinity of A^+ for X^-. The tightness parameter, τ, is designed to achieve this. It is defined in eqs 8.[13,14] The slope of a logarithmic plot of k_{ii} or k_{jj} as a function of $K_{ij}{}^{o}$ determines τ. This is *not* a Brønsted plot. The $K_{ij}{}^{o}$ are equilibrium constants for the transfer of X^- from a standard donor to the various $A_i{}^+$ or from the various A_jX to a standard acceptor. Ln $K_{ij}{}^{o}$ is a measure of the affinity of the various $A_i{}^+$ for X^-. The sign changes because X^- is transferred to the $A_i{}^+$ from the standard donor, but from the A_jX to the standard acceptor.

The reactions for which k_{ii} are the rate constants all have equilibrium constants of unity. However, the k_{ii} vary systematically with the affinity of $A_i{}^+$ for X^- because twice the affinity of $A_i{}^+$ for X^- in the critical configuration is, in general, different than the affinity of $A_i{}^+$ for X^- in the reactant or product. Equation 8 defines τ so that it will be zero if the critical configuration is completely dissociative. In that case, if the affinity of $A_i{}^+$ for X^- increases, as indicated by an increase in $K_{ij}{}^{o}$, then k_{ii} will decrease by the same factor, making $\mathrm{d}(\ln k_{ii})/\mathrm{d}(\ln K_{ij}{}^{o})$, in eq 8a, equal to −1, and giving τ the indicated value, zero. If bond making and bond breaking are perfectly coordinated, so that twice the affinity of $A_i{}^+$ for X^- in the critical configuration is just equal to the affinity of $A_i{}^+$or X^- in the reactant, then the derivative would have the value zero, and τ would have the value +1. If X is divalent in the critical configuration (not possible if X is H), an increase in $K_{ij}{}^{o}$ will lead to an equal increase in k_{ii}. In that case the derivative is 1.0, and τ has the value +2.

In nondegenerate reactions, the effect of changing K by changing the affinity of the donor for X^- is opposite, in some respects, to the effect of an equal change in K, achieved by changing the affinity of the acceptor. In a partially dissociative reaction, if K is decreased by making the affinity of $A_j{}^+$ for X^- stronger the reaction goes slower not only because $\Delta G°$ is more positive but also because λ becomes larger. The Brønsted α is increased by the increase in λ. However, if K is decreased by reducing the affinity of $A_i{}^+$ for X^-, λ becomes smaller (eq 3), making the decrease in rate smaller, and thus decreasing α. But the change in τ is the same, because an increase in the affinity of $A_j{}^+$ for X^- has the same effect on τ as a decrease in the affinity of $A_i{}^+$ for X^- (eqs 8 and eqs 8 and 9 of ref 5). Hence the choice of signs in eq 6 depends on the location of the structural variation. The upper signs are used if structure is varied in the acceptor, the lower signs are used if structure is varied in the donor.

At least qualitatively, the critical configuration donor−acceptor distance and the charge on the in-flight atom or group, X, should be correlated with the value of τ. A large critical configuration donor−acceptor distance leads to weak $A^+{-}X^-$ affinity in the critical configuration, a large partial negative charge for X in the critical configuration, and a value of τ less than unity. A value of τ near 1.0 implies that the in-flight X is near-neutral.[13,14] The distance in the critical configuration is only a little more than twice the normal A−X. One of the virtues of this treatment is that eqs 8 permit a quantitative, experimental determination of τ, and thereby give insight into the charge distribution and reactive bond distances in the critical configuration.

In the present case $A_j{-}X$ is an NADH-like hydride donor, and $A_i{}^+$ is an NAD^+-like hydride acceptor. The sum of the hydride affinities of the donor and acceptor in the critical configuration is less than the reactant hydride affinity, so τ is less than unity. $K_{ij}{}^{o}$ is the equilibrium constant for hydride transfer from a standard donor, $A_j{-}H$, to acceptors, $A_i{}^+$. $K_{ij}{}^{o}$ measures the strength of the $A_i{-}H$ bond. For reasons of practical convenience, 9,10-dihydro-10-methylacridine has been used as the standard donor.[7] A value somewhat less than unity was found for τ.

Perpendicular effects on reactivity ($\tau \neq 1.0$) are examples of Bernasconi's principle of nonperfect synchronicity, which provides an evaluation of the transition state imbalance.[17] The formation of the new bonds is not perfectly coupled with the

---

(12) Kreevoy, M. M.; Ostović, D.; Truhler, D. G. *J. Phys. Chem*. **1986**, *90*, 3766−3774.

(13) Kreevoy, M. M.; Lee, I.-S. H. *J. Am. Chem. Soc*. **1984**, *106*, 2550−2583.

(14) Lewis, E. S.; Hu, D. D. *J. Am. Chem. Soc*. **1984**, *106*, 3292−3296.

(15) (a) Leffler, J. E. *Science* **1953**, *117*, 340−341. (b) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334−338.

(16) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p 148.

(17) (a) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9−16. (b) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119−238.

breaking of the old bonds. Bernasconi's treatment, however, can be qualitatively related to ideas such as resonance and solvation, which are widely used to systematize organic chemistry. Williams has explored parallel and perpendicular effects very effectively in a wide range of reactions by measuring Brønsted parameters for the same reaction at a number of sites.[18] Both Williams and Bernasconi have reached conclusions similar to ours.

Since the lowest allowed vibrational energy of a deuterium compound is less than the lowest allowed vibrational energy of the corresponding hydrogen compound, and these vibrational energies are proportionately reduced when the critical configuration is formed,[1] it is clear that λ_H, for hydride transfer, should generally be smaller than λ_D, for deuteride transfer. Less obviously, τ_H and τ_D are also probably different. In the minimum energy path for hydride transfer the A_i-A_j distance is compressed. Then the hydride (or deuteride) transfer occurs by tunneling. The most probable A_i-A_j distance for tunneling is larger than that in the classical transition state, saving compression energy.[19] Because of the greater mass of deuterium, deuteride tunneling occurs at an A_i-A_j distance smaller than the hydride transfer distance.[12,19] Since τ is inversely correlated with the donor−acceptor distance, τ_H is less than τ_D. That is, hydride transfer is more dissociative than deutride 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. These are shown in eqs 9 and 10. When ln k_D is subtracted from ln k_H and appropriate substitution is made for τ, eq 11 is obtained. The KIE is k_H/k_D. Rate constants and KIE for the special case that K is unity are superscripted with zero. In deriving eq 11, the isotopic sensitivity of χ, arising from the isotopic sensitivity of λ, has been neglected because it has a negligible effect on the ln KIE values which this paper will report. The novel aspect of eq 11 is the second term on the right-hand side, which represents the perpendicular effect on ln KIE, and is linear in ln K. As a result, the common belief that ln KIE should be a bell shaped function of ln K, with a maximum at $K = 1.0$, is challenged.[20,21]

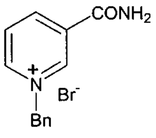
$$\ln k_H = \ln k_H{}^\circ + \alpha_H \ln K \tag{9}$$

$$\ln k_D = \ln k_D{}^\circ + \alpha_D \ln K \tag{10}$$

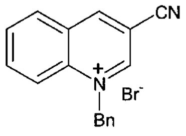
$$\ln \mathrm{KIE} = \ln \mathrm{KIE}^\circ \pm 0.5 \ln[K(\tau_H - \tau_D)] - 0.5RT(\ln K)^2(1/\lambda_H - 1/\lambda_D) \tag{11}$$

The rate constant is k° when $K = 1$, and (ln $k_H{}^o$ − ln $k_D{}^o$) is ln KIE°. In eq 11 ($\tau_H - \tau_D$) should be negative because τ_H is smaller than τ_D, which means that the donor−acceptor distance is larger for H than for D in their critical configurations. In the Marcus formalism, shown in eq 11, the second term on the right-hand side corresponds to the perpendicular effect while the last term corresponds to the parallel effect.

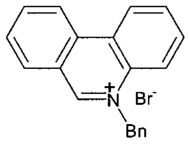
In the present paper we report the primary kinetic hydrogen isotope effect for the reactions of NAD$^+$ (nicotinamide adenine dinucleotide) analogues such as pyridinium (**1**), quinolinium (**2**), phenanthridinium (**3**), and acridinium ions (**4a**−**c**), with 1,3-dimethyl-2-phenylbenzimidazoline (**5H**(**D**)), which is also regarded as an NADH analogue.[22] **5H**(**D**) was chosen as the reducing agent for exploring the primary kinetic isotope effects because it is powerful and regioselective and has only one equivalent hydrogen for efficient reduction.[19] (It should be noted, however, that the reduction potential of **5H** has been greatly overestimated in a previous paper.[24])



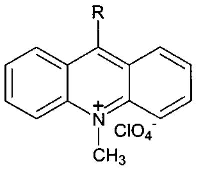
1



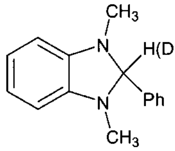
2



3



4



5H(D)

R: **a**, H; **b**, C_6H_5, **c**, 3,5-$Cl_2C_6H_3$

Experimental Section

Compounds **1**−**3** are well-known substances which were prepared by benzylation using benzyl bromide of the corresponding bases. The compounds were identified by their physical and spectroscopic properties.[25] Compounds **4a**−**c** were also prepared by methods that have been previously described.[26] Their melting points and spectroscopic properties agreed with previously reported values.[25] The perchlorate of **4a** was prepared by ion-exchange reaction of the corresponding iodide, using an excess of $NaClO_4$. Acridine was methylated with methyl iodide to get the iodide of **4a**. Compound **5H** was prepared by the method of Craig et al.[27] with a slight, previously described modification.[9] Compound **5D** was prepared by the same method as **5H** except using $NaBD_4$ instead of $NaBH_4$ for reduction. The yield was 90%. This preparation had 2−6% of contamination with the corresponding hydride compound, **5H**, as determined by its ^{1}H NMR spectrum. It was purified by sacrificial oxidation with *p*-chloranil. *p*-Chloranil (0.1 g, 0.4 mmol) was partially dissolved in ether (30 mL) and added to the solution of 0.5 g (2.2 mmol) of **5D** in ether (30 mL) slowly, with stirring. Reaction began immediately, to give a dirty yellow precipitate. The stirring was continued for 30 min. The solvent of the filterate was allowed to evaporate from the unreacted **5D**. The residual was recrystallized twice from EtOH−H_2O (6:1, v/v) to give ivory-colored crystals in 50% yield. There was no detectable signal for **5H** in the ^{1}H NMR (500 MHz) spectrum of **5D**. We estimated from this that the isotopic purity of **5D** was >99%. Its melting point was identical with that of **5H** (mp 93−4 °C).[9] The deuterium content of **5D** was confirmed by comparison of a mass spectrum of **5D** with that of **5H**, employing the electron impact ionization technique and introduction via a direct insertion probe inlet system.

5H *m/z* (%): 224 (M^+, 56), 223 (M^+ − H, 58), 147 (M^+ − C_6H_5, 100), 132 (M^+ − C_6H_5 and CH_3, 14%).

---

[18] Williams, A. *Adv. Phys. Org. Chem.* **1992**, *27*, 1−55.

[19] Kim, Y.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 7116−7123.

[20] Reference 1, p 134.

[21] Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman and Hall: New York, 1980; pp 98−105.

[22] Tanner, D. D.; Chen, J. J. *J. Org. Chem.* **1989**, *54*, 3842−3846.

[23] Chikashita, H.; Ide, H.; Itoh, K. *J. Org. Chem.* **1986**, *51*, 5400−5405.

[24] Timofeeva, Z. N.; El'tsov, A. V. *Zh. Obshch. Khim.* **1967**, *37*, 2599−2602.

[25] Robert, R. M. G.; Ostović, D.; Kreevoy, M. M. *Faraday Discuss. Chem. Soc.* **1982**, *74*, 257−265.

[26] Kreevoy, M. M.; Lee, I.-S. H. *Z. Naturforsch.* **1989**, *44a*, 418−426.

[27] Craig, J. C.; Ekwuribe, N. N.; Fu, C. C.; Walker, K. A. *M. Synthesis* **1981**, 303−305.

Table 1. Rate, Equilibrium Constants, KIE, Perpendicular Effect (*A*), Parallel Effect (*B*), and λ_H for Hydride Transfer Reactions

oxidant	k_H($M^{-1} s^{-1}$)	K^b	KIE(exptl)	A^c	B^c	λ_H (kJ/mol)
1	$(1.85 \pm 0.05) \times 10^{-3}$	36^a	6.27 ± 0.31	0.04	0.00	406
2	$(2.08 \pm 0.09) \times 10^2$	2.73×10^{12a}	4.18 ± 0.33	0.36	0.11	402
3	1.13 ± 0.06	1.78×10^{6a}	5.05 ± 0.35	0.18	0.03	392
4a	$(2.94 \pm 0.12) \times 10^2$	1.23×10^{11a}	3.95 ± 0.32	0.32	0.09	385
4b	$(1.92 \pm 0.07) \times 10^{-1}$	7.81×10^{10}	4.44 ± 0.26	0.31	0.08	458
4c	$(7.43 \pm 0.59) \times 10^{-1}$	6.35×10^{12}	4.05 ± 0.32	0.37	0.11	473

[a] Values are obtained from ref 9. [b] Determined by the ladder procedure. (The estimated uncertainty is 10−25%.)[30] [c] Absolute values are obtained from eq 11 (*A* is the second term and *B* is the third term on the right-hand side in the equation). The estimated error for *A* is less than 3% and that for *B* is less than 10% due to the estimated uncertainty of *K*.

5D *m/z* (%): 225 (M^+, 70), 223 ($M^+ - D$, 41), 148 ($M^+ - C_6H_5$, 100), 133 ($M^+ - C_6H_5$ and CH_3, 24%). Mass 224 was less than 1% after correction for the ^{13}C satellite from 223.

Measurement. Rate constants, *k*, were all measured spectrophotometrically in a solvent containing 4 parts of 2-propanol to one part of water by volume at 25 ± 0.2 °C. For slow (**1**) and moderate (**3**, **4b**,**c**) reactions a conventional spectrophotometer was used and isotope effects were determined by simultaneous measurement of k_H and k_D, to minimize errors due to temperature fluctuation. For fast reactions (**2**, **4a**) which have a half-life less than 10 s, k_{obs} values were measured with a stopped-flow apparatus (Hi-Tech scientific SFA-20) which was attached to the spectrophotometer (Beckman DU-7500). When the stopped-flow apparatus was used, scatter due to temperature fluctuation was not avoidable, since simultaneous measurement was not possible. This makes individual rate constants less reliable. To compensate, k_H and k_D were each measured more than 20 times and average values were used to get KIE values. All kinetic experiments were carried out with a 25−100-fold excess of the spectroscopically inactive constituent. In all cases reactions proceeded very close to completion. Therefore, the rate law for a pseudo-first-order reaction was used, as shown in eq 12.[28] In the case of very slow reactions (**1** with **5D**) A_t was estimated from measured A_t values by using a standard computer program.[26]

$$k_{obs} = t^{-1} \ln[(A_o - A_\infty)/(A_t - A_\infty)] \qquad (12)$$

The second-order rate constant, k_2, was obtained from k_{obs} divided by the concentration of the excess substrate.

For the reactions of **1** with **5H**, the compound **1** was used in excess. The growth of **1H** was monitored at 360 nm. **2** was also used in excess for reactions with **5H**, but the growth of **5** was monitored at 280 nm. The solution of **2** was made acidic using 4.5×10^{-3} M $HClO_4$ solution to give the reaction mixture a pH of 3.4, to prevent hydroxylation of **2**. **5H** was stable enough at this pH for the period of the measurement, which was no more than several minutes. For the reactions of **3** and **4a**−**c** with **5H**, compound **5H** was used in excess. The decay of **3** was monitored at 380 nm while **4a**−**c** was monitored at 420 nm.

The primary kinetic isotope effect is very sensitive to the isotopic purity of the substrates. However, the results cited above establish that the isotopic purity of **5H** is >99%, which is sufficient to make this an insignificant source of error.

Results and Discussion

Rate and equilibrium constants and primary kinetic isotope effects (KIE) for hydride transfer reactions with **5H**(**D**) are given in Table 1. All values of KIE were replicated more than 4 times. For the fast reactions using the stopped-flow apparatus the values of KIE were obtained from 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 deviations from the mean values were 3−8% and probable errors of the mean values were 2−4%. Most of the scatter is probably due to variation in temperature and solvent composition.

The equilibrium constants, *K*, for reaction of **4b** and **4c** with **5H** were calculated with the aid of *K* values for the reaction of **1** with **5H** and for **4b** and **4c** with **2H**.[26] Values of *K* for reaction of **1** with **2H** are known.[9]

In the Marcus formalism λ_H and λ_D can be obtained from eq 2 with the value of −8 kJ/mol for W^r and rate constants and equilibrium constants leading to $\Delta G^*$and $\Delta G°$ using eqs **4** and **5**, respectively. The values of λ_H are given in Table 1. λ_H and λ_D for **4c** should be similar to those for **4b**, and they are.

Marcus theory predicts that the effect of a change in *K* and the KIE depends on which reactant is altered to change *K*. Since $(\tau_H - \tau_D)$ is expected to be negative,[5,12] an increase in *K* produced by altering the acceptor is expected to reduce the KIE more than a similar change in *K* produced by altering the donor. To increase *K* by altering the acceptor, its bond to the hydride must be made stronger, in the critical configuration as well as in the product. This tends to partially offset the loss of binding to the donor, in forming the critical configuration. Therefore, the KIE is reduced. The converse is true if *K* is increased by altering the donor.[5,12,16] This is a major source of the scatter observed when the KIE is plotted against ΔpK, without regard for the location of the structure change.[20]

We can obtain $(\tau_H - \tau_D)$ by plotting ln KIE + $[0.5RT/(\ln K)^2](1/\lambda_H - 1/\lambda_D)$ against ln *K*, using KIE values obtained by altering only one of the reactants. Such a plot should be linear, with a slope of $\pm 0.5(\tau_H - \tau_D)$: the positive sign for structure variation in A_i, and the negative sign for structure variation in A_jX. The plot is shown in Figure 1. It is acceptably linear, and negative, as expected. The slope is -0.013 ± 0.002 ($r = 0.952$). $\tau_H - \tau_D$ is −0.025. The kinetic isotope effect for the reaction of a series of quinolinium compounds (**2**) with dihydrophenanthridine (**3H**), has been previously reported.[12] Those KIE data are also shown in Figure 1. The structure is altered in the acceptor, and the slope of the plot is −0.011 with a probable error of 0.001. Within experimental error the two slopes are the same, as expected. The intercepts would be expected to be different, but accidently, they are essentially the same.

The difference of τ values between H and D is almost the same as the difference computed by the VTST (variational transition state theory)-plus-LCG3 (large curvature ground-state tunneling) method, in which the potential energy surface of a three-body model shown in eq 1 can be used to calculate the rate constant *k* and primary kinetic isotopic effect.[5] In a three-body model the standard donor C−H bond energy is 305 kJ/mol.[5] The full range of reactions, used in the computation, have bond dissociation energy, De(CH), of 242−347 kJ/mol.

The quasiclassical kinetic isotope effect, $KIE_{qc,}$ is determined principally by changes in zero-point energy and rotational partition functions. The transition coefficient, κ, is the ratio of the thermally averaged quantal transmission probability to the thermally averaged classical transmission probability, obtained by the large curvature ground state (LCG3) tunneling ap-

---

(28) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*, 2nd ed.; Wiley: New York, 1961; p 29.

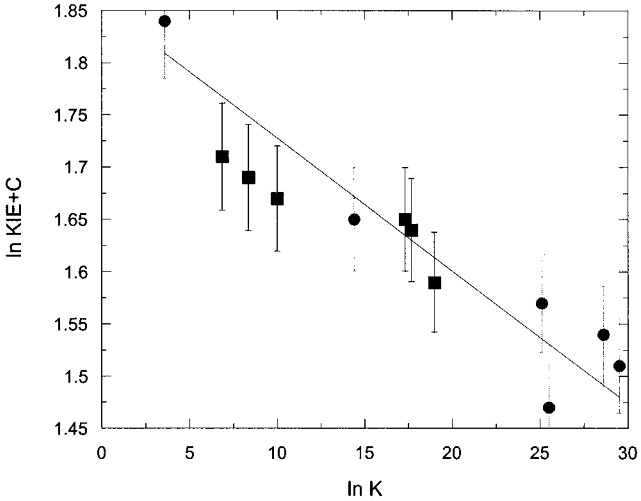


Figure 1. ln KIE + C [$C = \{0.5RT/(\ln K)^2\}(1/\lambda_H - 1/\lambda_D)$] as a function of ln K for hydride transfer reactions. The circle points are for the reactions of various oxidants with **5H**(**D**). The square points are for the reactions of variants of **2** with **3H**(**D**).[12] The vertical bars show the effect of errors of 3% in KIE. The line is obtained from eq 11, using the presently determined best value of ($\tau_H - \tau_D$) and the λ values obtained from the individual rate constants. The very slight scatter due to using individual values of λ is not observable on the plot. This plot shows how well eq 11 represents the variation in KIE with K.

proximation.[29] The tunneling contribution to the kinetic isotope effect is κ_H(LCG3)/κ_D(LCG3). When the quasiclassical contribution to the KIE and the tunneling contribution to the KIE for hydride transfer reactions are taken into account, the total KIE increases significantly as the C−H bond energy decreases[5] and as the donor−acceptor distance increases.[19]

The value of τ gives a semiquantitative measure of the effective charge on the in-flight atom. In the present case there is a fractional negative change on the in-flight hydrogen, as anticipated by theory.[13] Williams used a somewhat different approach for many examples bearing effective charges on the transferring groups when the group transfer reactions take place.[18] He demonstrated the dependence of the slope of a plot of the degenerate reaction rate constant on the pK_a of phenol for the reaction of the substituted phenolate ions with the substituted phenyl diphenylphosphates. The plot showed a nonlinearity indicating that the transition state structure changes as the nucleophile changes.[18]

In the Marcus formalism shown in eq 11 the perpendicular effect and the parallel effect on the KIE can be calculated. Those effects are listed in Table 1. The perpendicular effect which is the second term in the right-hand side in eq 11 is first order in ln K whereas the parallel effect which is the last term in eq 11 is second order. Thus, the plot of the perpendicular effect should be linear while the plot of the parallel should be a parabola. This expectation is shown in Figure 2. The perpendicular effect is much larger than the parallel effect on the Brønsted α. The slope of the perpendicular effect against ln K is the same as the slope of ln KIE against ln K shown in Figure 1, as it should be. The perpendicular effect depends on the typical transition state structure for the reaction in question and does not require a significant change in the structure. The parallel effect, on the other hand, depends on the change in structure within the series of reactions studied. For the present system the perpendicular effect, not the parallel effect, is the main reason for the change in the KIE.

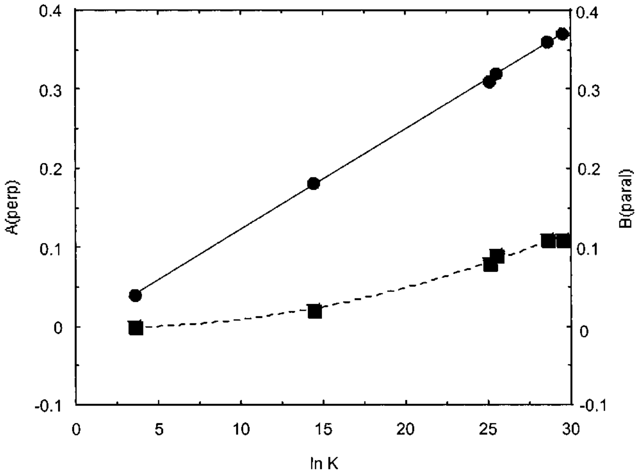


Figure 2. The perpendicular effect (circles) and the parallel effect (squares) on ln KIE as a function of ln K. (The perpendicular effect is first order in ln K which is the second term on the right-hand side of eq 11, using the present value of ($\tau_H - \tau_D$), while the parallel effect is second order, which is the third term on the right-hand side of eq 11, using the individually determined values of λ_H and λ_D.) This figure shows that the perpendicular effect on the KIE is much larger than the parallel effect at all accessible values of K.

It is noteworthy that the IR stretching and bending frequencies for **5H** and **5D** are quite normal. We would expect a nearly constant KIE value of around 2.0 if we only consider the quasiclassical kinetic isotope effect in the present range of the equilibrium constant.[19] This is not the case. Therefore, the corner-cutting tunneling contribution to the KIE plays a very important role for the present system.

In conclusion, the Marcus theory expresses the variation of rate with structure for hydride transfer quite accurately and also describes the variation of the KIE with structure very well. The present results also support the involvement of corner-cutting tunneling in most hydrogen transfer reactions.

Acknowledgment. This work was supported by grant No. 1999-2-123-003-5 from the Interdisciplinary Research Program of the KOSEF.

JA004232+

---

[29] Truhlar, D. G.; Isaacson, A. D.; Garret, B. C. In *Theory of Chemical Reaction Dynamics*; Baer, M., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. 4, p 65.

[30] Ostović, C.; Lee, I.-S. H.; Roberts, R. H. G.; Kreevoy, M. M. *J. Org. Chem.* **1985**, *50*, 4206−4211.