

Corner-Cutting Tunneling in Hydride Transfer Between NAD^+ Analogues

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Dedicated to Professor Jacob Bigeleisen on the occasion of his 70th birthday

If hydride transfer from a donor, $\text{A}_\text{J}\text{H}$, to an acceptor, A_I^+ , involves tunneling, phenomenological theory suggests a characteristic functional relation between rate constants and the equilibrium constant, i.e. between $\ln(k_{\text{ij,H}}/k_{\text{ij,D}})$ and $\ln K_{\text{ij}}$. Tunneling occurs at a heavy atom separation larger than that of the transition state (saddle point). This gives the critical configuration (point of no-return) for H-transfer a larger heavy atom separation than that for D-transfer and leads to the pattern described through a corollary of Marcus theory of atom transfer. The theory is called corner-cutting because it shortens the path which represents the reaction in multi-dimensional potential energy space. If the reactions are moderately spontaneous and the variation in structure which generates the variation in $k_{\text{ij,H}}$, $k_{\text{ij,D}}$ and K_{ij} is in the acceptor, the slope of the plot of $\ln(k_{\text{ij,H}}/k_{\text{ij,D}})$ against $\ln K_{\text{ij}}$ is expected to be negative; if the structure variation is in the donor it is expected to be positive. Similar results are expected for proton and hydrogen atom transfer.

This behavior has now been observed, for hydride transfer between various nitrogen heterocycles (all of which may be regarded as analogues of the enzymatic cofactor, NAD^+). These reactions have $k_{\text{ij,H}}/k_{\text{ij,D}} \sim 5$. The increase of $k_{\text{ij,H}}/k_{\text{ij,D}}$, with increasing K_{ij} , reported in this paper, is particularly hard to explain without corner-cutting. The present results, therefore, support the view that some tunneling is involved in most hydrogen transfer reactions, even when no anomalies are obvious.

Introduction

It is a pleasure to dedicate this paper to Jake Bigeleisen on the occasion of his 70th birthday. His pioneering work on the theory of kinetic isotope effects provides the foundation for all subsequent work, including the present paper.

For some time, now, theory developed in a number of groups has indicated that tunneling is significant in most hydrogen transfer reactions, and that the heavy atom framework in which this tunneling takes place is different from that yielding the saddle point of the potential energy surface connecting products and reactants [1–12]. The critical configuration of such a reaction – defined as the most probable structure for crossing the surface that separates reactants from products in potential energy hyperspace – is expected

to be more expanded, with a larger donor – acceptor distance, for H-transfer than for D-transfer. It was pointed out [1] that this should have observable, testable consequences in solution reactions where the rate constant cannot be calculated with useful accuracy. Among these, the primary kinetic isotope effect (KIE) should be increased if the approach of the donor to the acceptor is sterically inhibited. For D-transfer, Δv^\ddagger should be smaller than Δv^\ddagger for the corresponding H-transfer, so the KIE should be reduced if the reaction is carried out under pressure. A characteristic pattern of variation of the KIE with the reaction equilibrium constant within a family of reactions is anticipated. The steric effect on the KIE [1, 13, 14] and the pressure effect on the KIE [1, 15] had been observed before the theory was formulated. Some evidence for the expected variation of the KIE with the equilibrium constant was presented [1]. In the present paper we present additional evidence for this pattern of effects, which we believe is more compelling.

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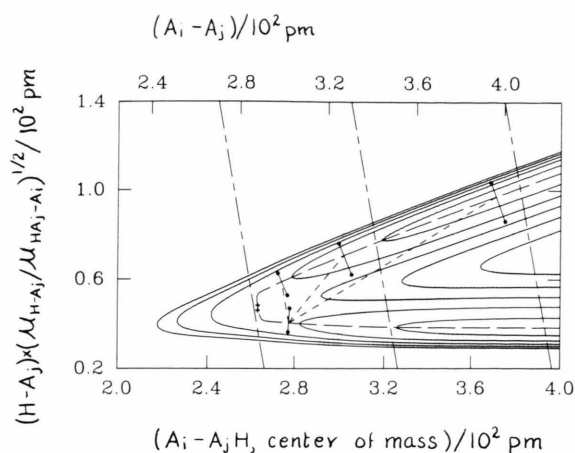


Fig. 1. Potential energy contours, tunneling paths, and vibrational cuts for $A_i + HA_j$ as a colinear, triatomic reaction with zero exoergicity. A_i and A_j have masses of 15 Daltons each. Mass-scaled coordinates are used as the axes. The upper horizontal scale indicates the A_i -to- A_j distance, and the long-short dashed curves are lines of constant A_i -to- A_j distance at 270, 330, and 400 pm. The solid curves are contours for 5, 15, 25, 35, and 45 kcal mole $^{-1}$. The zero of energy is defined as the bottom of the reactant vibrational well. The saddle point is shown as \pm . The minimum energy path is shown as a long-dashed curve. The vibrational cuts are shown as solid line segments; these are the classical turning points in the vibrationally adiabatic potential curves for the lowest allowed stretching vibration in the reactant channel, and for the first three vibrational levels in the product channel, at a total energy of 20.9 kcal mole $^{-1}$. The dots are the turning points in the stretching motion for the same total energy. The short dashed lines are the large-curvature tunneling paths connecting the initial state in its lowest vibrational level at its transitional turning point to the first three product vibrational states at their turning points. The total energy shown is that for which the integrand, $P^G(E) \exp(-E/kT)$, of the transmission coefficient peaks at 300 K. The three final states shown are those most populated by the tunneling process at this energy. The lowest vibrational state of the products is the most heavily populated. The next two states receive successively and substantially smaller, but still significant fractions of the total product. Details of the calculations are given in [1]. — This figure is reprinted with permission from [1]. Copyright 1986 American Chemical Society.

The expansion of the critical configuration for tunneling is shown in Figs. 1 and 2. These figures show the dynamics of H-transfer in linear, triatomic systems, the donor and acceptor being given masses of 15. They show the potential energy surface in a mass-scaled, orthogonal coordinate system. On such a surface the motion of a single point of fixed mass accurately represents the colinear motions of the 3-atom system [1]. There is no failure of the Born-Oppenheimer approximation. The two surfaces are identical functions of the internuclear distances. They differ in appearance because the heavier mass of deuterium

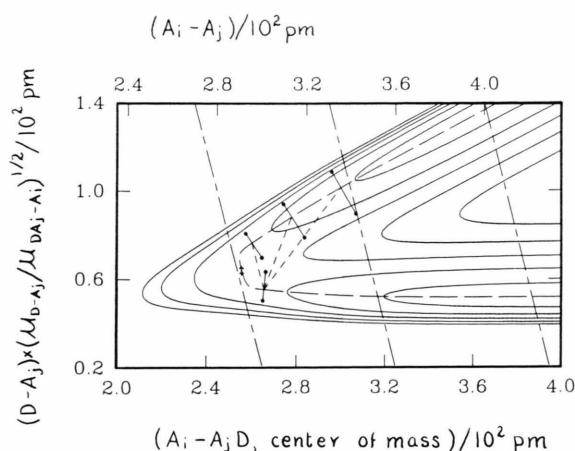


Fig. 2. The symbols have the same meaning as in Figure 1. The reaction is $A_i + DA_j$. The vibrational cuts are for a total energy of 20.90 kcal mole $^{-1}$, which is 0.21 kcal mole $^{-1}$ above the energy at which the integrand of the transmission coefficient for this reaction peaks. This energy was chosen so as to be essentially equal to that used in Figure 1. This figure is reprinted with permission from [1]. Copyright 1986 American Chemical Society.

leads to a differently scaled ordinate. In both cases the transmission coefficient through the dividing surface peaks at larger heavy atom distances than those of the saddle point (conventional transition state) because this leads to shorter paths through the region of negative kinetic energy. Because the tunneling paths are shorter than the minimum energy path through the saddle point they are said to cut the corner. For the particular, somewhat arbitrary, potential surface depicted in Figs. 1 and 2 the heavy atom separation in the critical configuration for H-transfer is ~ 5 pm larger than the separation in the critical configuration for D-transfer.

The expansion of the donor-acceptor distance decreases *both* the H-donor bond order and the H-acceptor bond order in the critical configuration. It thereby *increases* the Brønsted α if the substituents are in the donor, because, from the vantage point of the donor, the critical configuration looks more like products than does the conventional transition state. But the expansion decreases the Brønsted α if the substituents are in the acceptor, because the critical configuration looks more like the reactants than does the conventional transition state from that viewing point [16, 17].

Using Marcus theory of atom transfer, this treatment has been formalized [16, 17], leading to an equation which gives the Brønsted α in terms of the Marcus

parameters [16, 18]:

$$\alpha = \chi \pm 0.5 (\tau - 1) \mp 0.5 (RT \ln K_{ij} / \lambda)^2 (\tau - 1), \quad (1)$$

$$\chi \equiv 0.5 \{1 - [(RT/\lambda) \ln K_{ij}]\},$$

$$(\tau - 1) \equiv d(\ln k_{ii})/d(\ln K_{ij}).$$

Equation (1) deals with the series of reactions symbolized by



where both in the original paper [16] and the present work X is H or D. The equilibrium constant for some member of the set is K_{ij} and k_{ij} , is the rate constant for that reaction. The rate constant for a degenerate reaction A_i^+ with $A_i H$ is k_{ii} and that for reaction of A_j^+ with $A_j H$ is k_{jj} . The Marcus theory pictures these reactions taking place in three stages; first the formation of a precursor configuration (PC) from the reactants, with a standard free energy of W^r ; then the passage through the dividing surface via the critical configuration, resulting in the covalency changes and leading to a successor configuration (SC); then the conversion of the SC to the products. The standard free energy of formation of the SC from the products is W^p . The overall standard free energy of reaction is ΔG° , given by $-RT \ln K_{ij}$, and the standard free energy of conversion of the PC to the SC is $\Delta G^{\circ'}$ given by

$$\Delta G^{\circ'} = \Delta G^\circ - W^r + W^p. \quad (3)$$

Since $-RT \ln(k_{ij} h / \tilde{k} T) = \Delta G^*$, one obtains k_{ij} from

$$\Delta G^* = W^r + [1 + (\Delta G^{\circ'} / \lambda)]^2 \lambda / 4. \quad (4)$$

The standard free energy of the second step (covalency change) is ΔG^\ddagger , and is given by $[1 + (\Delta G^{\circ'} / \lambda)]^2 \lambda / 4$. The intrinsic barrier, $\lambda/4$, is ΔG^\ddagger for the special case that $\Delta G^{\circ'} = 0$. It is estimated using the equation [19, 20]

$$\lambda = (\lambda_i + \lambda_j) / 2. \quad (5)$$

The last term in (1) is a crossterm [16a] which is small in most cases and very small in the cases discussed in the present paper, so it will be neglected.

A measure of the tightness of the critical configuration is given by $(\tau - 1)$ [16]. When k_{ij} is changed by changing the structure of A_i^+ , the hydride acceptor, the derivative used to define $(\tau - 1)$ is -1 ($\tau = 0$) if the critical complex is completely exploded, because an increase in A_j-H bond strength will produce an equal increase in $-\Delta G^{\circ'}$, but it will not change ΔG^\ddagger because no A_i-H bonding yet exists in the critical con-

figuration. In the same way $(\tau - 1)$ is $+1$ ($\tau = 2$) if the critical configuration is so compressed that both A_i-H bonds have the strength of the A_i-H bond in the product (or reactant) and $(\tau - 1)$ is zero ($\tau = 1$) if both A_i-H bonds have half their normal bond strength. Since tunneling tends to expand the critical configuration it tends to make τ smaller. Thus τ_H , which is τ for H-transfer, should be smaller than τ_D , which is τ for D-transfer. This difference leads to the prediction of a characteristic structure-sensitivity of the KIE.

The upper signs are used in (1) if the structure variation which leads to the variation in k_{ij} and K_{ij} is in the acceptor, A_j^+ , and the lower signs are used if the structure variation is in the donor, $A_i H$. Therefore, α_H , the Brønsted α for H-transfer, should be smaller than α_D , the Brønsted α for D-transfer if the structure variation is in the acceptor, while α_H should be larger than α_D if the structure variation is in the donor. These relations are expressed in the equations

$$\ln k_{ij,H} = \ln k_{ij,H}^0 + \alpha_H \ln K_{ij}, \quad (6)$$

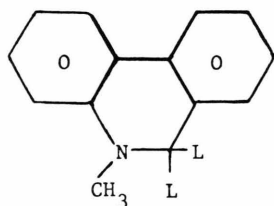
$$\ln k_{ij,D} = \ln k_{ij,D}^0 + \alpha_D \ln K_{ij}, \quad (7)$$

$$\ln(k_{ij,H}/k_{ij,D}) = \ln(k_{ij,H}^0/k_{ij,D}^0) \pm 0.5 \ln K_{ij} (\tau_H - \tau_D) - 0.5 RT (\ln K_{ij})^2 (1/\lambda_H - 1/\lambda_D). \quad (8)$$

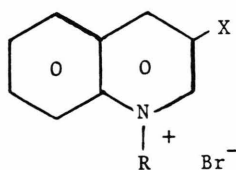
In these equations the crossterm from (1) has been neglected. It has been assumed that K_{ij} is isotopically insensitive. The rate constant for the member of the series with $K_{ij} = 1.00$ is k_{ij}^0 . The subscripts H or D indicate a rate constant for H-transfer or D-transfer. With the structure variation in the acceptor, the anticipated decrease in $\ln(k_{ij,H}/k_{ij,D})$ with increasing $\ln K_{ij}$ has already been observed [1] and has been used to strengthen the case for tunneling in reactions with unexceptional isotope effects (around 5 in this case) [1]. However, there are other reasons to anticipate a change in this direction [21], if $K_{ij} > 1.00$, as it is in these cases. The observed trend was much stronger than that foreseen without tunneling [1]. Nevertheless, the observation that $\ln(k_{ij,H}/k_{ij,D})$ increases with increasing $\ln K_{ij}$, with $K_{ij} > 1$, and the structure variation in the donor would be much stronger evidence, because we are not aware that such a trend can be explained without introducing corner-cutting. Such a trend we now report.

The original measurements were made with **1** as the donor and **2** as the acceptors. It was not possible for us to study hydride transfer from deuterated dihy-

droquinolines to acridinium ion because we could not prepare deuterated dihydroquinolines in the required isotopic purity. We, therefore, used compounds **3** as the donors in the present work, with **2e** as the acceptor. These produce the corresponding acridinium ion, **4**, and 1-benzyl-3-cyanodihydroquinoline ion as products.

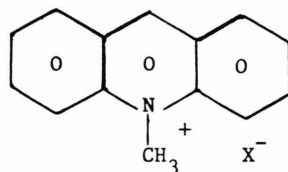


1 L = H or D (A_JH or A_JD)



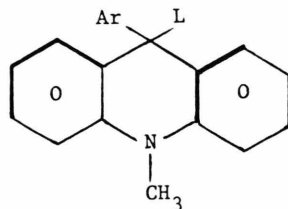
2 a–f (A_i^+)

- a R = CH₃; X = CONH₂
 b R = CH₂C₆H₅; X = CONH₂
 c R = CH₂C₆H₄pCN; X = CONH₂
 d R = CH₂C₆H₄pCH₃; X = CN
 e R = CH₂C₆H₅; X = CN [22]
 f R = CH₂C₆H₄pCN; X = CN



3 a–c

- a Ar = p(CH₃)₂NC₆H₄
 b Ar = pNH₂C₆H₄
 c Ar = pCH₃OC₆H₄
 d Ar = C₆H₅
 e Ar = pCF₃C₆H₄



3 a–e (L);
L = H or D (A_JH or A_JD)

Experimental

All kinetic measurements were made in a solvent consisting of 4 parts of isopropanol to one part of water, by volume, at 25 °C, to facilitate comparison

with a large body of analogous results already available in that solvent [1, 16, 23]. Distilled water was redistilled in the presence of a small amount of H₂SO₄. Isopropanol (Mallinckrodt ChromAr[®] HPLC) was also distilled from a small amount of H₂SO₄ before use. Rate constants were measured in acetic acid-acetate buffers with an ionic strength of 0.13. The pH of these solutions were between 3.5 and 5.5, depending on the pK_R of the oxidant and the pK_a of the reductant. The pH was measured after each reaction was completed, and never differed from the original value by more than 0.01.

Values of pH were determined electrometrically, with a radiometer pH-meter and combination electrode. It was calibrated in water at pH = 4.00 and pH = 7.00. A correction of −0.17 was applied to the mixed solvent pH values. The required correction was determined by measuring the pH values of four HClO₄ solutions, of concentration between 10^{−2} M and 10^{−4} M, in the mixed solvent.

Rate constants were determined spectrophotometrically, monitoring the absorption due to the acridinium ions produced from the variants of **3**. The acridinium ions derived from **3a** and **3b** have intense charge-transfer bonds with maxima ~550 nm, and the growth of these was monitored at 600 nm. The other acridinium ions were monitored at one of their vibronic maxima ~450 nm. These wave lengths are all free of interference from other species involved in these reactions. The reacting solutions were kept in the cell compartment of Cary 219 spectrophotometer. The temperature was maintained at 25.0 ± 0.2 °C by circulating water through the jacket of the cell compartment from a conventional thermostat. Isotope effects were determined from rate constants measured simultaneously to minimize errors due to temperature variations. Absorbances, A_t , were recorded automatically at regular intervals. (The subscript indicates the time of measurement.) Data were collected over a period of up to 10 hours. When longer reaction periods were used, spectroscopic evidence of an unidentified side reaction was observed, especially at concentrations of **2b** above 10^{−2} M.

All rate constants were measured with **2b** in at least 23-fold excess. Pseudo-first order rate constants, k_{obs} , were obtained from [24]

$$k_{\text{obs}} = t^{-1} \ln [(A_0 - A_\infty)/(A_t - A_\infty)] \quad (9)$$

and $k_{ij} = k_{\text{obs}}/\theta$. In simple cases $\theta = C_2$, where C_2 is the concentration of **2b**. However, **2** has a pK_R = 5.31 [25]

while **3a** and **3b** have pK_a 's of 4.17 and 4.06 [26], so that, in general, $\theta = C_2 f_i f_j$; where f_i is the fraction of **2** in the active, non-hydroxylated form, and f_j the fraction of **3** in the active, unprotonated form. In no case was $f_i f_j < 0.5$. To minimize any error in k_{obs} , rates were measured at the pH of maximum rate, given by $pK_R pK_A/2$. To further minimize any error in the isotope effect from this cause, $k_{ij,H}$ and $k_{ij,D}$ were determined at the same pH.

For reactions that went to >50% completion in 10 hours, best A_∞ values were determined, along best k_{obs} values, by an iterative computer program which finds the values of k_{obs} and A_∞ that minimize the sum of the squares of the discrepancies between measured absorbances and those calculated from (9). Discrepancies of not more than ± 0.002 , and the absence of systematic variations of discrepancies with time were regarded as indications of satisfactory fit. In general, the A_∞ values were within a few percent of those calculated from the known molar absorbances of the acridinium ions. For those reactions which did not achieve 50% completion in 10 hours, A_∞ was calculated from the molar absorbance of the acridinium ion. If the H-transfer did reach 50% completion and the D-transfer did not, the molar absorbance for use in the calculation of A_∞ for D-transfer was calculated from the A_∞ simultaneously determined for H-transfer.

In the calculation of $k_{ij,D}$, we also took account of the residual H-content of our **3** (D) samples, when it was detectable, by means of the relation

$$k_{ij,D} = (k_{obs} - k_{ij,H} \theta f_H) / \theta f_D. \quad (10)$$

The fractions of deterio- and hydridoacridan are f_D and f_H , respectively. In no case did the hydridoacridan constitute more than 1% of our sample, and the inclusion of the correction in no case changed the value of $k_{ij,D}$ by more than 5%.

Each rate constant, k_{ij} , and each isotope effect, $k_{ij,H}/k_{ij,D}$ was replicated 4–14 times. The probable errors of both quantities were 2–3%.

The preparation of **2b** has been previously described [16a]. **3a**, iodide, was prepared by the method of Chupakin, Trofimov, and Pushkaveva [27]. 10-Methyl-acridinium iodide [16] (21 g, 6 mmole), freshly vacuum distilled aniline (2 g, 22 mmole) and sulfur (0.36 g, 11 mmole) were heated together at 125 °C for 2.5 hours. The resulting dark solid was washed with 50 cm³ of ether and 20 cm³ of carbon tetrachloride. The residue was recrystallized from absolute ethanol

Table 1. Rate constants for reduction of 1-benzyl-3-cyanoquinolinium ions by 9-aryl-10-methylacridans.

Reductant	$k_{ij,H}/M^{-1} s^{-1}$	$k_{ij,D}/M^{-1} s^{-1}$	$\ln K_{ij}^a$
3a (L)	1.38×10^{-2}	2.36×10^{-3}	7.68
3b (L)	1.01×10^{-2}	1.74×10^{-3}	7.41
3c (L)	2.07×10^{-3}	3.90×10^{-4}	4.80
3d (L)	1.13×10^{-3}	2.08×10^{-4}	3.52
3e (L)	1.35×10^{-4}	2.76×10^{-5}	0.72

^a Determined by methods similar to those which have been described [25, 26].

to give a 78% yield of **3a**, iodide: m.p. 238–239 °C; lit. [27], 234 °C.

3b, iodide, was prepared in the same way and **3a** in 95% yield: m.p. 230 °C; lit. [27], 216 °C.

3a (H) was prepared by NaBH₄ reduction of the corresponding acridinium iodide. To 120 cm³ of H₂O was added 0.41 g (1 mmole) of **3a**, iodide. Then 0.2 g (5 mmole) of NaBH₄ dissolved in 20 cm³ of 0.1 M aqueous NaOH was added with vigorous stirring, under a blanket of N₂. The acridinium salt appeared to be converted to **3a** (H), a nearly colorless, water insoluble solid, almost immediately. However, stirring was continued overnight to minimize residual starting material. The product was then collected and recrystallized twice from 3:1, ethanol: water. The yield of **3a** (H) was over 70%: m.p. 146 °C (lit. [28], 153–154 °C) [28].

3b (H) was prepared similarly, but the recrystallizations were also carried out under an N₂ blanket because of the vulnerability of the NH₂ group to air oxidation. It had m.p. 142 °C; lit. [28], 148–149 °C.

Preliminary preparation of **3a** (D) and **3b** (D) was carried out in the same way as the hydride variants except that NaBD₄ (MSD Isotopes, 98% D) was used in place of NaBH₄. These preparations had ~5% contamination with the corresponding hydride compounds, as judged by their ¹H-NMR spectra. They were purified by sacrificial oxidation with 2,3,5,6-tetrachloroquinone (Chloranil). For **3a** (D), 0.2 g (0.8 mmole) of chloranil was dissolved in 130 cm³ of ether and added, dropwise, to a stirred solution of 0.5 g (1.6 mmole) of **3a** (D) (containing 5% **3a** (H)) in 100 cm³ of ether. Reaction appeared to take place immediately, but the mixture was allowed to stand overnight. The oxidation product – presumably **3a**, 2,3,5,6-tetrachlorophenate – precipitates, and was removed by filtration. The ether was allowed to evaporate from the unreacted **3a** (D), and the residue was

recrystallized several times from 10:1, ethanol : water. Because there is a large isotope effect on the oxidation of the acridan by chloranil [29] the **3a** (H) was selectively oxidized. Reisolated **3a** (D) showed no detectable signal for the 9-hydrogen in its ^1H -NMR spectrum. We estimate that 1% of isotopic contamination would have been easily detectable, so the isotopic purity of our **3a** (D) was >99%. Its m.p. was identical with that of **3a** (H).

3d (H) was prepared by addition of phenyl Grignard reagent to 10-methylacridinium iodide. Phenyl Grignard reagent was prepared from bromo benzene (1.5 g, 10 mmole) and magnesium (2 g, 80 mmole) in 100 cm³ of anhydrous ether. Using a double tipped needle and N₂ gas pressure, the ether solution of phenyl Grignard reagent was transferred to a 2-neck round bottomed flask equipped with a condenser and containing a stirred suspension of 10-methylacridinium iodide (1.5 g, 5 mmole) in 50 cm³ of anhydrous ether. The stirring was continued until the red, ether-insoluble acridinium iodide was entirely consumed. Five cm³ of methanol was added to destroy any unreacted Grignard reagent, whereupon a mass of white magnesium salts appeared. The white mass was removed by filtration, and the solvent was removed from the filtrate by evaporation under reduced pressure. The residue was a pale yellow solid. It was recrystallized from ethanol : water, 10 : 1, to give an 80% yield of **3d** (H): m.p. 109 °C, lit. [29], 104–106 °C.

3c (H) and **3e** (H) were prepared similarly. They do not appear to be previously reported.

3c (H) had m.p., 142 °C. Its IR spectrum in a KBr disk had bands at 3006 (w), 2877 (w), 2822 (w), 1593 (s), 1508 (s), 1476 (vs), 1345 (s), 1248 (s), 1063 (s), 807 (m) and 750 (s) cm⁻¹. Its ^1H -NMR spectrum in DCCl₃ had sharp singlets at $\delta = 3.41$ ($i = 3$), 3.72 ($i = 3$) and 5.12 ($i = 1$) p.p.m., in addition to a broad multiplet in the region of aromatic proton absorption.

Anal. calcd. for C₂₁H₁₉NO (m.w. = 301.37): C, 83.69; H, 6.35; N, 4.65. Found [30]: C, 83.61; H, 6.48; N, 4.74.

3e (H) had m.p., 130 °C. Its IR spectrum in a KBr disk had bands at 3014 (w), 2874 (w), 2821 (w), 1616 (s), 1594 (s), 1476 (vs), 1410 (m), 1325 (vs), 1281 (s), 1155 (s), 1114 (vs), 898 (m), 812 (m), and 754 (s) cm⁻¹. Its ^1H -NMR spectrum in DCCl₃ had sharp singlets at $\delta = 3.42$ ($i = 3$) and 5.26 ($i = 1$) ppm.

Anal. calcd. for C₂₁H₁₆F₃N (m.w. = 339.35): C, 74.32; H, 4.75; F, 16.80; N, 4.13. Found [30]: C, 74.20; H, 4.74; F, 16.67; N, 4.20.

3c, **3d**, and **3e**, all as perchlorates, were prepared by oxidizing **3c** (H), **3d** (H), and **3e** (H) with chloranil in ether; then converting the resulting 2,3,5,6-tetrachlorophenates to perchloroates with an excess of 70% perchloric acid [31].

3d (perchlorate) had m.p. 247 °C. Although this is a known substance [31], its m.p. appears not to have been previously reported. Its IR spectrum in a KBr disk had bands at 3128 (w), 3063 (w), 1612 (s), 1580 (s), 1551 (s), 1442 (s), 1382 (m), 1227 (m), 1092 (vs), 767 (s), 700 (s), and 625 (s) cm⁻¹. Its ^1H -NMR spectrum in DMSO-D₆ had only a singlet at $\delta = 4.96$ ppm ($i = 3$) in addition to multiplets in the region of aromatic absorption. Its electronic spectrum in isopropanol : water, 4 : 1, had λ_{max} (with log ϵ_{max} in parentheses) at 343 (3.95), 360 (4.28), 406 (3.69), and 424 (3.74) nm.

3c (perchlorate) appears not to be reported previously. It had m.p., 251 °C. Its IR spectrum in a KBr disk had bands at 3068 (w), 1610 (s), 1577 (m), 1551 (m), 1253 (s), 1179 (m), 1090 (vs), 765 (s), and 624 (s) cm⁻¹. Its ^1H -NMR spectrum in DMSO-D₆ had singlets at $\delta = 3.98$ ($i = 3$) and 4.94 ($i = 3$) ppm, in addition to bands in the region of aromatic absorption. Its electronic spectrum in isopropanol : water, 4 : 1, had λ_{max} (with log ϵ_{max} in parentheses) at 342 (3.94), 357 (4.27), and 432 (3.87) nm.

Anal. calcd. for C₂₁H₁₈ClNO₅ (m.w. = 399.81): C, 63.08; H, 4.54; Cl, 8.87; N, 3.50. Found [30]: C, 63.02; H, 4.60; Cl, 9.03; N, 3.38.

3e (perchlorate) had m.p. 251 °C. It is not previously reported. Its IR spectrum in a KBr disk had bands at 3079 (w), 1609 (m), 1577 (w), 1551 (m), 1330 (s), 1174 (s), 1109 (vs), 1087 (vs), 769 (m), and 625 (m) cm⁻¹. Its ^1H -NMR spectrum had only one singlet, at $\delta = 4.99$ ($i = 3$) ppm, in addition to bands in the region of aromatic absorption.

Anal. calcd. for C₂₁H₁₅ClF₃NO₄ (m.w. = 437.79): C, 57.61; H, 3.45; Cl, 8.10; F, 13.02; N, 3.20. Found: C, 57.68; H, 3.47; Cl, 8.04; F, 12.89; N, 3.18.

3c (D), **3d** (D), and **3e** (D) were prepared from the corresponding variant of **3**, perchlorate, and then purified by the methods described above for **3a** (D) and **3b** (D). All of these showed at least 99% isotopic purity, and the same m.p.'s as the corresponding H-variants.

Results

Rate constants are shown in Table 1 for five reactions of the type shown in (2), with A_i⁺ as **2e** and the

variants of **3** (L) as A_jH . These were all measured at 25.0 ± 0.2 °C in a solvent made up of four parts of isopropanol to one part of water. Equilibrium constants were also determined, under the same conditions, by methods which have been previously described [25, 26]. These are also listed in Table 1.

Because the last term on the right hand side of (8) is modest compared to the other terms in the equation, in the present case, and probably in many other cases of interest, it is convenient to test (8) by plotting $\ln(k_{ij,H}/k_{ij,D}) + 0.5 RT (\ln K_{ij})^2 (1/\lambda_H - 1/\lambda_D)$ against $\ln K_{ij}$. 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 , the negative for structure variation in A_jH . Figure 3 shows such plots for the present results and those obtained earlier, with **1** (L) as A_jH and the variants of **2** as A_i^+ [1]. Both plots are acceptably linear considering the uncertainties in the isotope effects and the small number of points. They have slopes of $\pm 0.0246 \pm 0.0030$ and -0.0074 ± 0.0014 , respectively [32]. In making these plots, values of λ_H and λ_D are required for both series of reactions. For reactions of **3** (L) with **2e**, $\lambda_H = 385$ and $\lambda_D = 401$ were used; for reactions of **1** (L) with **2**, values of 332 and 350; all in kJ mole^{-1} . These values are consistent with the rates and isotope effects under consideration, and previously reported λ values [16b]. In any event, the exact values taken are not critical, as the correction to $\ln(k_{ij,H}/k_{ij,D})$ is small. From these slopes, 0.049 ± 0.006 and 0.015 ± 0.003 are obtained for $\tau_D - \tau_H$.

As noted above, the scatter in replicated values of k_{ij} indicates a probable error of $\sim 2\%$ in these quantities. In addition, there are systematic errors, which may arise from errors in the K_R or K_a values; from errors in the molar absorptivities, when these were not determined directly from the kinetic data; from impurities, including isotopic impurities; or from side reactions or other sources that we are unaware of. We have attempted to minimize the effect of each of these on $k_{ij,H}/k_{ij,D}$. A substantial part of the scatter is the result of temperature fluctuations. We attempted to remove the influence of this factor on $k_{ij,H}/k_{ij,D}$ by carrying out the two reactions simultaneously. Since the H-transfer is inherently faster, we used higher concentrations of the reagent in excess, **2b**, for reactions of the D-variant than for reactions of the corresponding H-variants. This strategy could not be completely successful because we usually could not make the **2b** concentrations high enough to compensate for the isotope effect, but its partial success is indicated by the scatter in the

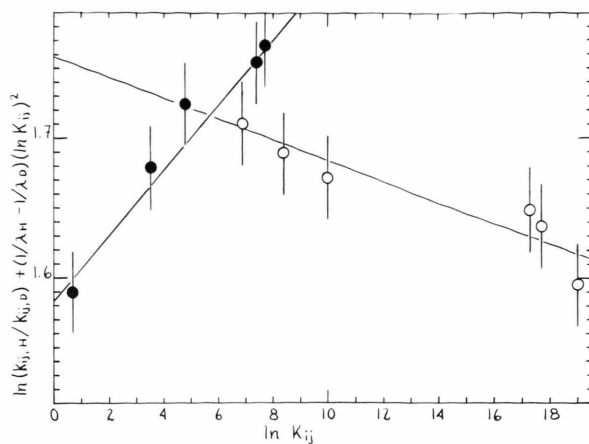


Fig. 3. A test of (8) leading to determinations of $(\tau_D - \tau_H)$. The open points are for reactions of **1** (L) with the variants of **2** [1]. The filled points are for the reactions of the variants of **3** (L) with **2e**. The vertical bars show the effects of errors of 3% in $k_{ij,H}/k_{ij,D}$. The lines through the points were selected by the method of least squares. The signs of the slopes are as anticipated and their magnitudes are reasonable, but the derived values of $(\tau_D - \tau_H)$ are significantly different; 0.049, from the solid points; and 0.015, from the open points.

isotope effect; 2% as measured by their probable error. The completely random occurrence of 2% errors in $k_{ij,H}$ and $k_{ij,D}$ would be expected to lead to a 3% error in their ratio. The impact of systematic errors on the isotope effect is harder to estimate, but, as recorded in the Experimental Section, we have tried to minimize them. We estimate a total uncertainty of 3–4% in $k_{ij,H}/k_{ij,D}$. The scatter of points from the two lines shown in Fig. 3 is $\sim 1\%$ in each case, which suggests that the foregoing error analysis may be a bit conservative, although the small number of points also improves the appearance of fit.

Discussion

These results closely resemble the expected consequences of corner-cutting tunneling. We are not aware of any other model that leads to the results shown in Figure 3 [33, 34]. For the present system the increase in the isotope effect with increasing k_{ij} , with $K_{ij} > 1.0$, is particularly hard to rationalize unless the critical complex for H-transfer is looser (has a smaller τ value) than that for D-transfer, and we see no reason that this should be so if there were no tunneling. The quasi-classical isotope effect can be expected to reach a maximum when the A_i-H and A_j-H force con-

stants are equal [33, 34], and the introduction of one-dimensional tunneling does not change this conclusion [34]. In general, the force constants need not be equal at $K_{ij}=1.0$ [21]. However, the present system is structurally very symmetrical. Further, rates of reactions very similar to the ones under discussion here conform quite accurately to Marcus theory of atom and group transfer [16b], and the symmetry of the potential energy hypersurface connecting reactants and products is a fundamental assumption of that theory [35, 36]. The probable errors cited above seem to reduce to $\ll 1\%$ the probability that both $\tau_D - \tau_H$ values are zero [37], and this is the result to be expected in the absence of corner-cutting tunneling.

Theory offers little guidance, at this time, as to the magnitude of $\tau_D - \tau_H$. Intuition and experience suggest that it should be small, and the values seem suitable. Indeed, if τ_D and τ_H were determined separately, their uncertainties, which arise from the approximate nature of the Brønsted catalysis law as well as the experimental uncertainties, would make it hard to be sure that they are different. In the formulation of (8) most of the approximations of the Brønsted catalysis law cancel out, and the systematic trends become clear.

The substantial difference between the two values of $\tau_D - \tau_H$ are, nevertheless, somewhat puzzling. One explanation, of course, is that both values are really the same; 0.02–0.03. The probability of this also seems quite small [37], but the small number of points makes

it difficult to exclude this possibility definitely. Another explanation would be based on the structural differences between the two reductants. It would require that the tunneling contribution to the isotope effect be larger for reactions of **3** than for reactions of **1**, and the quasi-classical contribution correspondingly smaller, since the overall isotope effects are similar.

Conclusion

We conclude that corner-cutting tunneling occurs in hydride transfers between NAD^+ analogues, and probably in most proton, hydride, and hydrogen atom transfer reactions, even when the magnitude of the isotope effect is not unusually large. A sensitive way to detect this is to examine the variation in the isotope effect with the equilibrium constant, for substitution in the donor, and, separately, for substitution in the acceptor, with $\Delta G^\circ \ll \Delta G^*$. As the equilibrium constant increases, a pattern of increasing isotope effect if the structure-variation is in the donor, but decreasing isotope effect if the structure variation is in the acceptor, strongly suggests corner-cutting tunneling.

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