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# The Tightness Contribution to the Brønsted α for Hydride Transfer between NAD$^+$ Analogues

In-Sook Han Lee,* Kim-Hung Chow, 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*

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***Abstract:*** It has been shown that the rate of symmetrical hydride transfer reaction varies with the hydride affinity of the (identical) donor and acceptor. In that case, Marcus theory of atom and group transfer predicts that the Brønsted α depends on the location of the substituent, whether it is in the donor or the acceptor, and the tightness of the critical configuration, as well as the resemblance of the critical configuration to reactants or products. This prediction has now been confirmed for hydride transfer reactions between heterocyclic, nitrogen-containing cations, which can be regarded as analogues of the enzyme cofactor, nicotinamide adenine dinucleotide (NAD$^+$). A series of reactions with substituents in the donor gives Brønsted α of 0.67 ± 0.03 and a tightness parameter, $\tau$, of 0.64 ± 0.06. With substituents in the acceptor $\alpha = 0.32 \pm 0.03$ and $\tau = 0.68 \pm 0.08$. The reactions are all spontaneous, with equilibrium constants between 0.4 and $3 \times 10^4$, and the two sets span about the same range of equilibrium constants. The two $\tau$ values are essentially identical with an average value of 0.66 ± 0.05. These results can be semiquantitatively mimicked by rate constants calculated for a linear, triatomic model of the reaction. Variational transition state theory and a physically motivated but empirically calibrated potential function were used. The computed rate constants generate an α value of 0.56 if the hydride affinity of the acceptor is varied and an α of 0.44 if the hydride affinity of the donor is varied. The calculated kinetic isotope effects are similar to the measured values. A previous error in the Born charging term of the potential function has been corrected. Marcus theory can be successfully fitted to both the experimental and computed rate constants, and appears to be the most compact way to express and compare them. The success of the linear triatomic model in qualitatively reproducing these results encourages the continued use of this easily conceptualized model to think about group, ion, and atom transfer reactions.

## 1. Introduction

During the last century a number of empirical equations and semiquantitative relations have been developed to relate rate constants to one another and to equilibrium constants. These relations have systematized large areas of chemistry, facilitated teaching, and facilitated the identification of unusual behavior. They also have some predictive power. In recent years it has become possible to calculate the rate constants of specific reactions quantum mechanically, from first principles, with useful reliability. While these computations are more transparent than measured rate constants they do not easily lead to generalization. The physics underlying the empirical relations is still imperfectly understood. In this paper we continue our effort to use Marcus theory of atom and group transfer to provide a link between empirical correlation and physically motivated, though highly simplified calculation on a linear, triatomic model of hydride transfer between nicotinamide adenine dinucleotide (NAD$^+$) analogues.

Phenomenological Marcus theory, applied to atom or group transfer reactions, can provide a quantitative measure of the tightness of the critical configuration.[1−4] Tightness is related to the distance between the end groups, the bond order to the in-flight atom or group, and the partial charge on the in-flight atom or group.[1−4] The critical configuration has been defined as the most probable configuration for crossing the hardest to attain dividing surface that separates products from reactants.[5]

For a one-step hydride transfer reaction of the type shown in eq 1, Marcus theory can be formalized in eqs 2 and 3.

$$\mathrm{A}_i^{+} + \mathrm{A}_j\mathrm{H} \rightarrow \mathrm{A}_i\mathrm{H} + \mathrm{A}_j^{+} \tag{1}$$

$$\Delta G_{ij}^{*} = W^{\mathrm{r}} + (1 + \Delta G_{ij}^{\circ}/\lambda_{ij})^2 \lambda_{ij}/4 \tag{2}$$

$$\lambda_{ij} = (\lambda_{ii} + \lambda_{jj})/2 \tag{3}$$

$$K_{ij} = \exp\,(-\Delta G_{ij}^{\circ}/RT) \tag{4}$$

$$k_{ij} = k_{\mathrm{B}}T/h\,\exp(-\Delta G_{ij}^{*}/RT) \tag{5}$$

The subscripts *i* and *j* indicate the hydride acceptor and donor, respectively.

In eq 2, $W^{\mathrm{r}}$ was originally regarded as the free energy required to form a metastable reaction complex from the separated

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* Address correspondence to this author at Kangwon National University. E-mail: ishl@kangwon.ac.kr.

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reactants.[6] However, it appears only to represent that part of $\Delta G_{ij}$* which is insensitive to $\Delta G_{ij}°$.[7] In other words, $W^r$ is little more than an adjustable parameter that permits the theory to give a useful description of the results. Since the reactants and products are structurally related and of the same charge type, it can be assumed that $W^r$ is the same in both directions. In that case, the standard free energy of reaction, $\Delta G_{ij}°$, is the same as the standard free energy of reaction within a reactive complex, $\Delta G_{ij}°'$. This simplifies the Marcus formalism to the form shown as eqs 2 and 3. For the reaction shown as eq 1, $W^r$ has been taken as −8 kJ/mol.[7]

When $\Delta G_{ij}°$ is zero, $\lambda_{ij}/4$ is equal to ($\Delta G_{ij}^* - W^r$). This is the intrinsic barrier. For the nondegenerate reactions $\lambda_{ij}$ is the average of $\lambda_{ii}$ and $\lambda_{jj}$, for the two related degenerate reactions, $A_i^+$ with $A_iH$, and $A_j^+$ with $A_jH$, respectively.

$\Delta G°$ and $\Delta G^*$ can be related to the equilibrium constant $K_{ij}$ and the rate constants, $k_{ij}$, shown as eqs 4 and 5.

The Brønsted α is defined by eq 6.

$$\alpha = \mathrm{d}(\ln k_{ij})/\mathrm{d}(\ln K_{ij}) \tag{6a}$$

$$\alpha = \mathrm{d}(\Delta G_{ij}^*)/\mathrm{d}(\Delta G_{ij}°) \tag{6b}$$

From eqs 2−6, and the definitions given in eqs 8 and 9, the expression shown in eq 7 can be derived for the Brønsted α.[2]

$$\alpha = \chi \pm (\tau - 1)/2 \mp (RT \ln K_{ij}/\lambda_{ij})^2(\tau - 1)/2 \tag{7}$$

$$\chi = [1 - (RT \ln K_{ij}/\lambda_{ij})]/2 \tag{8}$$

$$(\tau - 1) = \mathrm{d}(\ln k_{ii})/\mathrm{d}(\ln K_{ij}) \tag{9}$$

Equations 8 and 9 define $\chi$ and $\tau$. $\chi$ is the Leffler−Hammond parameter. It gives a quantitative measure of the relative weights of the reactant structure and the product structure in the structure of the critical configuration. When the reaction becomes more spontaneous, $K$ becomes larger, leading to a smaller value of $\chi$, which indicates a critical configuration closer to the reactant.[8] This quantity has the properties formerly ascribed to α. It is $\delta(\ln k_{ij})/\delta(\ln K_{ij})$ or $\delta(\Delta G_{ij}^*)/\delta(\Delta G_{ij}°)$ at constant $\lambda$. On the other hand, the tightness parameter, earlier dubbed $\tau$,[9] is expected to have an important effect on the Brønsted α, as shown in eqs 1 and 7−9. (The last term in eq 7 is a small cross-term that is insignificant in the present case.) $\tau$ implies that the displacement of the critical configuration toward structures that do not resemble either reactants or products is needed to describe its charge distribution and reactive bond lengths.[2]

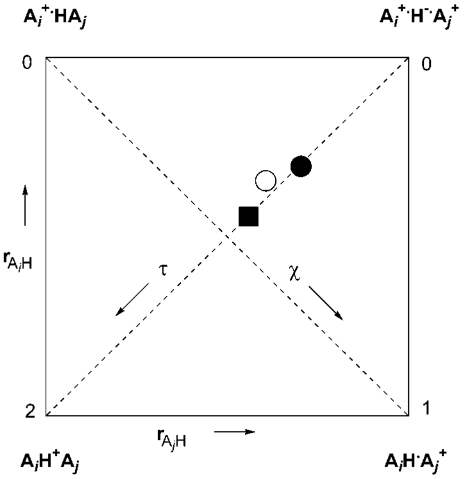

**Figure 1.** A two-dimensional cartoon for hydride transfer between $A_i^+$ and $A_j^+$. The closed circle indicates the illustrative case described in the text. The open circle indicates the location of the critical configuration for the present experimental system. The closed square indicates the location of the critical configuration of the computational results for the linear and triatomic model.

Since this paper will discuss hydride transfer between NAD$^+$ analogues, rate constants, $k_{ij}$, and equilibrium constants, $K_{ij}$, are defined with respect to eq 1, but the ideas involved are general, including also enzyme-catalyzed reactions. The equilibrium constant for the transfer of hydride from some standard donor to a series of acceptors, $A_i^+$, is $K_{ij}°$. In practice, for practical and historic reasons the standard donor is 10-methylacridan.[2] The rate constant for the symmetric transfer for hydride between one $A_i^+$ and another is $k_{ii}$. The variation of $k_{ii}$ with $K_{ij}°$ was first explicitly discussed by Thornton[10] and is called a Thornton effect. The most striking aspect of this development is that ($\tau - 1$)/2 is expected to take the positive sign in eq 7 (and the cross term to take the negative sign) if the structural changes which generate the changes in $k_{ij}$ and $K_{ij}$ are in the acceptor atom or group, while the opposite signs apply if the structural changes are in the donor.[2,4] This is most easily seen by considering $\mathrm{d}(\lambda/4)/\mathrm{d}(\Delta G°)$ as we change the hydride affinity of the donor or the acceptor. To make the reactions more spontaneous ($\Delta G°$ more negative) and faster, by changing the acceptor, we must increase its hydride affinity. To make the reactions more spontaneous, and faster, by changing the donor, we must decrease its hydride affinity. But $\lambda_{ij}$ is approximately the mean of the $\lambda$ values for symmetrical exchange in the donor and the acceptor, and increases with an increase in hydride affinity at either site.[2,4] Thus $\mathrm{d}(\lambda/4)/\mathrm{d}(\Delta G°)$ is negative, and makes a negative contribution to $\mathrm{d}(\Delta G^*)/\mathrm{d}(\Delta G°)$ if substitution is in the acceptor, but it is positive if substitution is in the donor.

An intuitive justification of this outcome is given in Figure 1, which is a two-dimensional cartoon.[2,9] As mentioned above, $\chi$ is a quantitative measure of the relative resemblance of the critical configuration to the reactant structure and the product structure. $\tau$ is a quantitative measure of the charge distribution and reactive bond lengths of the critical configuration. A critical configuration in the upper left corner is identical to reactants which are in contact and properly positioned. A critical configuration in the lower right corner is identical to fully formed products which have not yet separated or become

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disoriented. In the upper right corner there is a hypothetical critical configuration in which hydride is in contact with both acceptors but has no covalent bond to either. In the lower left corner is a hypothetical critical configuration with a hypervalent hydrogen, which has covalent bonds to *both* $A_i$ and $A_j$. In all critical configurations along the upper right−lower left diagonal the bonds to donor and acceptor are of equal strength and $K_{ij} = 1.0$. For all such critical configurations eq 8 shows that $\chi$ is $^1/_2$.

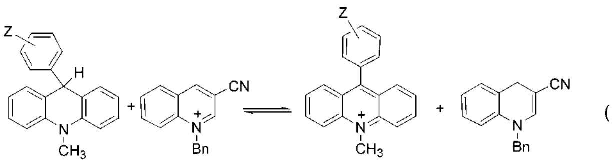
We first consider symmetrical rections in which the donor is $A_iH$, the acceptor is $A_i^+$, and the rate constants are $k_{ii}$. If the critical configuration for all of these reactions is in the upper right corner, the original $A_iH$ bond is completely broken, but the new $A_iH$ bond is not at all formed. Referring to eq 9, if the free energy of the $A_iH$ bond is increased, $K_{ij}°$ and $\ln K_{ij}°$ will increase, but $\ln k_{ii}$ will decrease by an equal amount, because the bond being broken is stronger and the new bond has not yet begun to form. Thus, $[\delta(\ln k_{ii})/\delta(\ln K_{ij}°)]_j = -1$ in this case and $\tau = 0$. At the crossing of the two diagonals the free energies of the old and new bonds are equal. Therefore, all $k_{ii}$ will be equal, $[\delta(\ln k_{ii})/\delta(\ln K_{ij}°)]_j = 0$, and $\tau$ will be 1. In a similar way, $\tau$ will be 2 if the critical configuration is in the lower left corner. For a single family of reactions it is assumed that $\tau$ is constant for our present discussion, and the critical configuration is always located in the same place on the cartoon. Using the two diagonals as coordinates in the cartoon, the upper right−lower left diagonal gives $\tau$, increasing in that direction, with the scale established by the values determined above. The value on the coordinate running from upper left to lower right gives the other variable, $\chi$.

We next consider a group of unsymmetrical reactions, in which the critical configuration is at the closed circle in the cartoon. If $A_i$ is varied and $A_j$ is constant (constant donor−variable acceptor) $\ln k_{ij}$ will increase by less than half the increase in $\ln K_{ij}°$ because the new bond is less than half formed. On the other hand, if we consider a group of unsymmetrical reactions in which $A_i$ is constant and $A_j$ is varied (constant acceptor−variable donor) with the same critical configuration location, the change in $\ln k_{ij}$ will be larger than half the change in $\ln K_{ij}°$, because more than half of the donor bond free energy is lost in making this critical configuration. However, eq 8 shows that $\chi$ should be $^1/_2$ in both cases, therefore, $\chi$ alone cannot be identified with $\alpha$. Something must be added if the donor structure is varied, but subtracted if the acceptor structure is varied. Mathematical manipulation of Marcus theory yields the form shown in eq 7.[2]

Lewis and co-workers have already shown the semiquantitative correctness of this prediction for methyl transfer reactions,[3,11] and in this paper, we do so for hydride transfer reactions.

The specific series used to illustrate the point are shown in eqs 10 and 11. In addition the solvolysis equilibria of the cations, eq 12, were examined, and $K_R$ values are reported, for comparison with the equilibrium constants for hydride transfer. To take advantage of a large body of information already available, a 4:1 2-propanol:water mixture was used as solvent. Therefore, R, in eq 12, may be either H or 2-propyl.

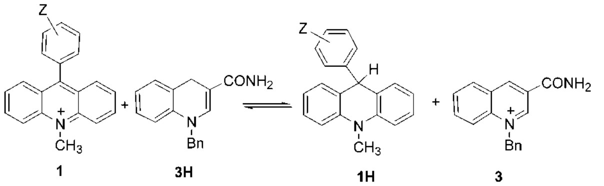
We also present some related computational results which help to clarify the origin and meaning of these observations. Rate constants were calculated by using improved canonical variational transition-state theory[12,13] (ICVT) with the large-curvature ground-state tunneling approximation.[12] These calculations were implemented by the program POLYRATE 3.0.[13] The calculations require a family of global potential energy surfaces. For the present work a previously obtained family of surface[7] was used. However, an error was found and corrected. These surfaces are based on the good general agreement between experimental reactivity patterns and rate constants calculated with use of the surfaces.[7] The computations are transparent and free of experimental error and the idiosyncracies of individual molecular structures. Unlike experimental results, the origin of computed effects is generally unambiguous.



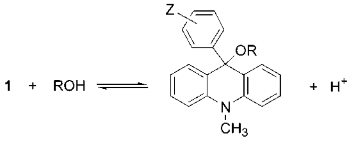
(10)

Z

**a**, 4-N(CH$_3$)$_2$
**b**, 4-NH$_2$
**c**, 4-OCH$_3$
**d**, H
**e**, 4-CF$_3$
**f**, 3,5-Cl$_2$



(11)



(12)

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## 2. Experimental Section

The 9-aryl-10-methylacridinium ions and their dihydro derivatives, and the quinoline derivatives, are all previousely reported compounds[14,15] and all had acceptable physical and spectroscopic properties.

The water used was distilled and then redistilled in the presence of a small amount of $H_2SO_4$. All other substances used were good quality commercial materials and were used without further purification. For reactions which would almost entirely consume one of the reactants, pseudo-first-order rate constants, $k_1$, were measured spectrophotometrically at 25.0 ± 0.2 °C in the usual way.[14] The ions **1a**−**f** all have

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***Table 1.*** Rate Constants and Equilibrium Constants for Reactions Represented by Equations 10−12

| | eq 10 | | eq 11 | | eq 12 |
|---|---|---|---|---|---|
| Z | $k_{ij}$[a] | $K_{ij}$[b] | $k_{ij}$[a] | $K_{ij}$[b] | $K_R$[c,f] |
| 4-$(CH_3)_2N$ | $1.38 \times 10^{-2}$[d] | $2.38 \times 10^{3}$[e] | $2.38 \times 10^{-3}$ | 4.3[f] | $5.37 \times 10^{-11}$ |
| 4-$NH_2$ | $1.10 \times 10^{-2}$[d] | $1.98 \times 10^{3}$[e] | $2.28 \times 10^{-3}$ | 5.7[f] | $1.00 \times 10^{-10}$ |
| 4-$CH_3O$ | $2.07 \times 10^{-3}$[d] | $1.21 \times 10^{2}$[e] | $7.04 \times 10^{-3}$ | $8.5 \times 10^{1}$[e] | $7.59 \times 10^{-10}$ |
| H | $1.13 \times 10^{-3}$[d] | $3.40 \times 10^{1}$[e] | $1.38 \times 10^{-2}$ | $3.0 \times 10^{2}$[e] | $2.69 \times 10^{-9}$ |
| 4-$CF_3$ | $1.35 \times 10^{-4}$[d] | 2.16[f] | $2.71 \times 10^{-2}$ | $5.0 \times 10^{3}$[e] | $1.95 \times 10^{-8}$ |
| 3,5-$Cl_2$ | $3.30 \times 10^{-5}$ | $4.07 \times 10^{-1}$[f] | $3.33 \times 10^{-2}$ | $2.5 \times 10^{4}$[e] | $1.62 \times 10^{-7}$ |

[a] In units of $M^{-1}$ $s^{-1}$ with probable errors of 5−10%, as estimated in the Experimental Section. [b] Dimensionless. [c] In units of M. [d] These values were taken from ref 15. [e] These equilibrium constants could not be measured directly, and were estimated by the method described in the text. Their reliability is discussed in the text. [f] With probable error of ∼10%[17]

distinctive electronic spectra in the visible range, and the intensities of these absorptions were monitored. A pH between 3.5 and 5.5 was maintained in the reacting solutions by means of an acetic acid−acetate buffer, with an ionic strength of 0.13.[16] The pH of these solutions was measured before and after $k_1$ was measured, and the two determinations never differed by more than 0.01.

A correction of 0.17 was subtracted from electrometrically measured pH values in the mixed solvent. The required correction was determined by measuring the pH values of four $HClO_4$ solutions, of known concentration between $10^{-2}$ and $10^{-4}$ M, in the mixed solvent.

At least a 23-fold excess of quinoline derivatives was used for all $k_1$ measurements. Second-order rate constants, $k_{ij}$, were given by $k_{ij} = k_1/C_2 f_1 f_2$. The stoichiometric concentration of quinoline derivatives is $C_2$. The quinolinium ions have solvolysis equilibria analogous to that represented in eq 12. While the p$K_R$ of **3** is above 9 in the 2-propanol/water solvent, and thus outside our present range of interest, the p$K_R$ of **2** is 5.11.[17] The fraction of **2** or **3**[18] actually present as free quinolinium ion was defined as $f_2$, and calculated by means of the appropriate equilibrium expression.[17] Compounds **1Ha** and **1Hb** are the conjugate bases of Brønsted acids, with p$K_a$ values of 4.17 and 4.06 in the 2-propanol/water mixture,[15] so they were partially converted to protonated forms which are inactive as reducing agents. The fraction of **1H** in the active form is defined as $f_1$, and calculated from a conventional equilibrium expression. Each $k_{ij}$ measurement was repeated 4−14 times, and the standard errors of the mean values, as judged by reproducibility, were 2−3%. However there are also systematic errors and errors due to inaccuracies in $K_R$ values and $K_a$ values. If $K_R$ and $K_a$ are uncertain by 10%,[17]that will introduce an uncertainty of 5−10% into the $k_{ij}$ values.

Several equilibrium constants, $K_{ij}$, were evaluated by measuring reaction rate constants in both directions.[17] In the less favorable direction these reactions come to equilibrium with substantial amounts of both reactants still present. The method to obtain values of $k_1$ for these reactions was also previously described[2] and second-order rate constants were calculated from them as described above. Some of the equilibrium constants, which could not be directly measured, were estimated by a method that is described in the Results section.

Values of $K_R$ were determined from the electronic spectra of compounds **1a**−**f**, in solutions of measured pH, in the same 4:1 2-propanol:water mixture in which rates were measured. The technique of these measurements has been previously described.[17] The $K_R$ have a standard error, based on their reproducibility, of ca. 5%. We are not aware of any systematic error in the measurement of the present $K_R$ values, so we believe that their accuracy is not much worse than their statistical standard error.

## 3. Potential Surfaces

The potential energy surfaces are very similar to those developed previously.[7] They have the general form shown in eq 13. $V_{ELEPS}$ is an extended LEPS function. It, along with the

$$V = V_{ELEPS} + V_W + V_{CD} + V_{solv} \tag{13}$$

widening term, expresses the covalent binding between the end atoms and the in-flight hydride ion. They also express the repulsion between the end atoms, which is the source of most of the activation energy. $V_W$ is a barrier-widening function. It augments the covalent binding and end-atom repulsion at an inter-end-atom distance somewhat greater than that at the saddle point. It has the effect of reducing the imaginary frequency, and therefore reducing the effect of tunneling on the calculated rate constants and isotopes effects. $V_{CD}$ is a term for charge-induced dipole interaction; and $V_{solv}$ is a generalized Born term, intended to approximate solvation energy, given by eq 14. All of these terms except $V_{solv}$ have been carried over from the

$$V_{solv} = -\frac{1}{2}\left(1 - \frac{1}{\epsilon}\right)\sum_{a}\frac{q_a^{\,2}}{r_a} - \frac{1}{2}\left(1 - \frac{1}{\epsilon}\right)\sum_{a}\sum_{b\neq a}\frac{q_a q_b}{r_{ab}} \tag{14}$$

previous work.[7] However, an error has been discovered in $V_{solv}$ and this has been corrected. In $V_{solv}$, $q_a$ is the charge on atom a, $r_a$ is the van der Waals radius of atom a, $r_{ab}$ is the internuclear distance between atom a and atom b, and $\epsilon$ is the dielectric constant. The double summation has the effect of inappropriately counting each atom−atom interaction twice. However this double counting is removed when the double summation is multiplied by $^1/_2$. In the earlier work[7] the double counting was arbitrarily eliminated, but the multiplication by $^1/_2$ was retained, making the contribution of atom−atom interactions to $V_{solv}$ too small (insufficiently negative). This was then compensated, in good part, by using too large a $\epsilon$ value (40) for the dielectric constant. We have now corrected the counting error. The potential function permits the three-atom model to give a good representation of a large and diverse body of data for polyatomic reactants.[7] This is the source of its usefulness and the best evidence that it is physically meaningful. To retain the original fit, $\epsilon$, in $V_{solv}$, was reduced from 40 to 1.4. This change leaves $V$, and the rate constants calculated from it, almost unchanged, without requiring us to recalibrate the other terms.

## 4. Results and Discussion

Table 1 gives $k_{ij}$ and $K_{ij}$ for reactions represented by eqs 10 and 11. Many of the required equilibrium constants could not be measured directly because the rates of the reactions from

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(16) Equations 10−12 all represent reactions of neutrals with cations, to give cationic products or critical configurations. The acid dissociations of protonated **1Ha** and **1Hb** do likewise. Therefore, the effect of ionic strength on activity cancels out their rate or equilibrium expressions in first approximation. The reported rate and equilibrium constants should be approximately valid in infinitely dilute solution.

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(18) The active fraction of **3** was always 1.0 in these experiments.

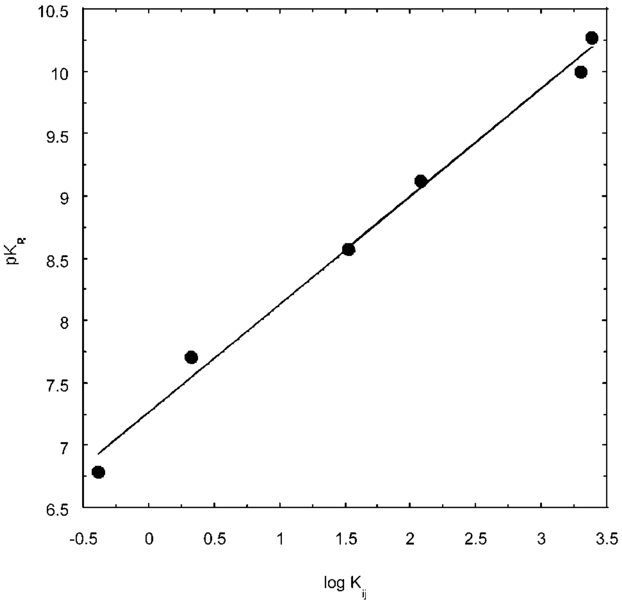

**Figure 2.** The correlation between $K_{ij}$, eq 10, and p$K_R$. The least-squares slope is 0.87 ± 0.04.

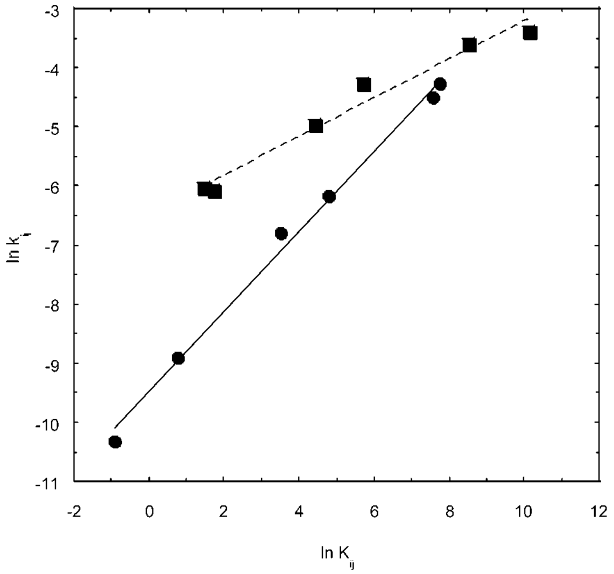

**Figure 3.** Brønsted plots for the reactions shown in eqs 10 (circles) and 11 (squares). The slopes, which are the values for the Brønsted α, are 0.67 ± 0.03 and 0.32 ± 0.03, respectively.

right to left are too slow, and side reactions (possibly air oxidation) intervene before a measurable fraction of the reaction of interest has occurred. To estimate the rate constants for the reactions represented by eq 10, right to left ($k_{ji}$), we take advantage of the similarity of those reactions to the reactions represented by eq 11, left to right. Two $k_{ji}$ were measured for reactions represented by eq 10. The more reliable of these is for reaction of **1f** with **2H**. It has a value of 8.1 × $10^{-5}$ $M^{-1}$ $s^{-1}$. It was assumed that the effect of altering the 9-aryl substituents on $k_{ji}$ for eq 10 would be the same as the effects these alterations would have on $k_{ij}$ for eq 11. Thus we estimate $k_{ji}$ for **1e** in eq 10 as $k_{ji}$ (**1f**, eq 10) × $k_{ij}$ (**1e**, eq 11)/$k_{ij}$ (**1f**, eq 11). The value obtained in this way for $k_{ji}$ (**1e**, eq 10) is 6.55 × $10^{-5}$. When 1.35 × $10^{-4}$, $k_{ij}$ for this reaction, is divided by $k_{ji}$, 6.55 × $10^{-5}$, a value of 2.1 is obtained. This may be compared with the value of 2.2, obtained experimentally. The other indirectly estimated $K_{ij}$ values in Table 1 were obtained in the same way. Those for eq 11, right to left, use the analogy with eq 10, left to right. The use of these analogies is equivalent to assuming that eq 10, left to right, has the same Hammett $\rho$[19] as eq 11, right to left. And eq 11, left to right, has the same Hammett $\rho$ as eq 10, right to left. While this is probably not exactly true, the two reactions are sufficiently similar that it seems to be a good approximation. In either case, if the two $\rho$ values are different by 0.1, which seems larger than the difference is actually likely to be for such similar reactions,[19] errors up to 35% would be introduced into $K_{ij}$.

Table 1 also gives the measured values of $K_R$. Figure 2 shows the correlation between the log of $K_{ij}$ for reactions represented by eq 10 and p$K_R$. The good linear correlation, with a slope of 0.87 ± 0.04, provides additional support for the estimated values of $K_{ij}$. Because of the way they were calculated the log $K_{ij}$ values for reactions represented by eq 11 must correlate with p$K_R$ exactly as well as those for reactions represented by eq 10. Values of $K_R$ have been used as a model for the equilibrium constants of reactions such as those represented by eqs 10 and 11.[2,20] While the model does not hold for a series of acceptors with a variety of heterocyclic ring systems, it appears to be valid for remote substitution in a single ring system.[2]

The slight departure of the slope from unity may not be significant, or it may be due to inaccuracy in the assumption that was made in estimating $K_{ij}$, but its direction is intuitively reasonable. In eq 10 the positive charge replaces a C−H bond of very little polarity, since the electronegativities of C and H are similar.[21] In eq 12 the positive charge replaces a C−O bond. Since the oxygen has a much higher electronegativity than carbon,[21] the carbon to which it is attached in **4** has a small partial positive charge. Thus the latter process would be a little less sensitive to substituents than the former.

Figure 3 shows plots of ln $k_{ij}$ against the ln $K_{ij}$ (Brønsted plots) for the reactions shown in eqs 10 and 11. For the first of these reactions the Brønsted plot is linear, as expected, and has a slope, $\alpha_{10}$, of 0.67 ± 0.03. The second also should be linear and it has been treated as such. It has a slope, $\alpha_{11}$, of 0.32 ± 0.03. The slopes and their uncertainties, which are probable errors, were evaluated by the method of least squares.[22]

For the reactions described by eq 10, a $\chi_{10}$ value, 0.49, can be obtained from eq 8, and similarly, the $\chi_{11}$ value is 0.48.[23] Combining these $\chi$ values with the α values based on all the data, $\tau$ values of 0.64 ± 0.06 and 0.68 ± 0.08 are obtained. These differ by much less than their combined probable error[24] and give a mean value of 0.66 ± 0.05. The near identity of the two $\tau$ values strongly supports eq 7, and the Marcus formalism from which it is derived.

The reactions described by eq 10 have ln $K_{ij}$ values ranging from −0.8 to 7.8, with an average of 3.5. Those described by

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(19) (a) Hammett, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970; Chapter 11. (b) Wells, P. R. *Chem. Rev.* **1963**, *63*, 171.

(20) Bunting, J. W.; Bolton, J. L. *Tetrahedron* **1986**, *42*, 1007.

(21) Levine, I. N. *Physical Chemistry*, 3rd ed.; McGraw-Hill: New York, 1988; p 655.

(22) Topping, J. *Errors of Observation and Their Treatment*; Chapman and Hall: London, 1962; pp 101−109.

(23) For each series of reactions its average $K_{ij}$ value was used, A typical $\lambda$ value of 88.5 kcal mol$^{-1}$ was used for both. These approximations are quite adequate for evaluating the small second term in eq 8 to the required accuracy.

(24) Livingston, R. *Physico Chemical Experiments*, 3rd ed.; Macmillan: New York, 1956; pp 22−30.

eq 11 have ln $K_{ij}$ values ranging from 1.5 to 10.1, averaging 5.8. As shown above, their $\chi$ values are similar. Despite their similar ranges of equilibrium constants (and the presumable similarity of their critical configurations) the two series give quite different $\alpha$ values. This result, which is entirely consistent with Marcus theory, emphasizes the shortcomings of a one-dimensional interpretation of $\alpha$, which would identify a large value with a critical configuration similar to the product structure and a small value with a critical configuration similar to the reactant structure. As described in the Introduction section, the critical configuration for the present system is at the open cicle in Figure 1. The distance in the critical configuration between the carbon donating the hydride and the carbon accepting the hydride increases as $\tau$ becomes smaller. In the present case it is larger than it would be if $\tau$ were unity. Also, the in-flight H takes on a partial negative charge as $\tau$ becomes less than unity.

Bernasconi and co-workers have provided many examples of reactions in which the introduction of substituents in any place in the reactants leads to a Brønsted relation (eq 6) but the value of $\alpha$ varies, depending on the location of the substitution.[25] Such observations have been identified with the imperfect synchronization of the various changes leading from reactant to product.[25] The present observations can be regarded as another example of this phenomenon; however, our treatment of them is somewhat different from that developed by Bernasconi. We now show how the two treatments are related, and attempt to illuminate both of them.

Marcus theory, eq 2, has been shown to be generally consistent with a linear triatomic model of the critical complex.[5,7] Such a model has only two, orthogonal, internal coordinates: the end atom breathing coordinate and the central atom (hydrogen) displacement coordinate. After the separation of the work term, $W^r$, the two variables of the Marcus theory are ln $K_{ij}$, or its energetic equivalent, and $\lambda_{ij}$, both of which are related to both coordinates of the model. Equations 8 and 9 define the two new coordinates, $\chi$ and $\tau$, in terms of ln $K_{ij}$ and $\lambda_{ij}$. Each of these depends, to a good approximation, on only one of the model coordinates: $\tau$ on the distance between the end atoms and $\chi$ on the donor−hydrogen distance. Equation 7 follows from the Marcus equation and the definitions of $\chi$ and $\tau$, eqs 8 and 9, without mathematical approximations.[2−4] Equations 8 and 9 permit $\chi$ and $\tau$ to be evaluated from experimentally measurable quantities, and $\tau$ can be evaluated in two, independent ways: directly, using eq 9, or from eqs 7 and 8.

In a similar way $\tau$ and $\alpha$ can be evaluated from rate constants computed for the model system. This permits the use of the transparent, easily manipulated model as a surrogate for the opaque experimental system. The price of this is loss of flexibility. In effect, the electron distribution and geometry of the model are completely specified when the values of the two coordinates are specified, leaving no way to account for redistribution of electrons due to structure changes within the real, polyatomic donor and/or acceptor.

Bernasconi's treatment always provides an evaluation of the "transition state imbalance". This quantity can be qualitatively related to ideas such as resonance and solvation, which are widely used to systematize organic chemistry.[25] However it does not appear possible to relate these imbalances to the properties of a model, short of very extensive (and expensive) quantum mechanical and dynamic calculations.

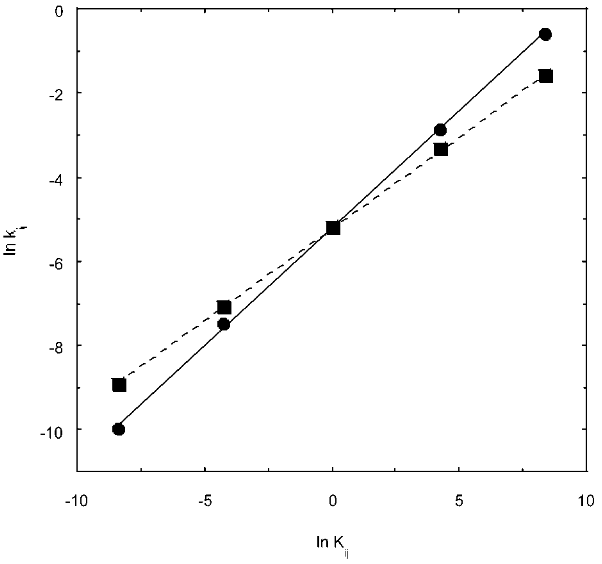

***Figure 4.*** Brønsted plots of computed rate constants for $A_i^+ + A_jH \rightarrow A_iH + A_j^+$. Circle points were generated by varying the $A_jH$ bond strength, using a bond strength of 73 kcal mol$^{-1}$ in $A_iH$. Square points were generated by varying the $A_iH$ bond strength and using a bond strength of 73 kcal mol$^{-1}$ in $A_jH$. The lower left-hand section of the figure corresponds to Figure 3.

The mean value of $\tau$ obtained in the present work, using eqs 7 and 8, is 0.66 ± 0.05. This is significantly less than the value, 0.81 ± 0.04, that was previously obtained by applying eq 9 to hydride transfer reactions of structurally similar but simpler classes of reactants.[1,15] We now attempt to find the origin of this discrepancy by examining computational results.

Three series were studied: one in which the donor C−H bond strength was varied; one in which the acceptor C−H bond strength was varied; and a series of symmetrical reactions in which both bond strengths were varied. A $\tau$ value of 0.87 was obtained by applying eq 9 to computational rate constants.[7] However, $\tau$ depends slightly on the range of $K_{ij}°$ values used. Using a range of $K_{ij}°$ values centering on 1.0, a value of 0.88 is obtained for $\tau$. With these values, the critical configuration of the triatomic model is located at the closed square in Figure 1. Also, Figure 4 shows Brønsted plots made with computed rate constants, taken from ref 7. They are very nearly linear. The $\alpha$ value is 0.56 if the donor bond strength is varied and 0.44 if the acceptor bond strength is varied. Since these Brønsted plots are both centered on $K_{ij} = 1.0$ (a luxury not available for the experimental results), $\chi$ is exactly 0.5 and the cross term in eq 7 is exactly zero. This permits $\tau$ to be evaluated from each $\alpha$ value, using eq 7. The two values are each 0.88, exactly the same as the value obtained with eq 9. Linearized Marcus theory applies very well to the computed rate constants. We conclude that the discrepancy between the present and earlier values of $\tau$ is not due to the use of eq 9 in one case and eqs 7 and 8 in the other.

The $\tau$ given by computed rate constants, $k$, was shown to decrease with decreasing donor and acceptor C−H bond energy,[7] but the effect is not large if the bond strength is kept within reasonable limits. For example, $\tau$ decreases from 0.88 to 0.85 if the bond energies of donor and acceptor in symmetrical reactions are decreased from 73 kcal mol$^{-1}$ to 58 kcal

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

***Table 2.*** The Effect of Equilibrium C−C Distance on Computed Rate Constants and $\tau$ Values for Symmetrical Hydride Transfers

| $r_{CC}$(e) Å | ln $k_{ii}$ | $\tau$ | KIE | $r_{CC}$(‡),[a] Å |
|---|---|---|---|---|
| 3.228 | −5.18 | 0.87 | 6.0 | 2.92 |
| 3.254 | −5.57 | 0.87 | 6.9 | 2.94 |
| 3.360 | −7.52 | 0.84 | 39.2 | 3.04 |
| 3.994 | −18.94 | 0.70 | $10^6$ | 3.60 |

[a] The C−C distance at the potential energy saddle point.

mol$^{-1}$.[7] This decrease in $\tau$ is accompanied by an increase of a factor of 29 in rate constant and an increase in KIE from 6.2 to 10.3.[7] Judged by the $K_{ij}$ values shown in Table 1, the hydride affinities of the donors used in the present studies are not strikingly different from those of previously used acceptors. And no increase in the isotope effect was noted.[26] We conclude that the decreased value of $\tau$ cannot be attributed to decreased C−H bond strength in the present examples. We now find that $\tau$ also decreases gradually as the equilibrium C−C distance, $r_{cc}$(e), increases, but the calculated rate constant falls and the primary kinetic isotope effect (KIE) rises very rapidly as the equilibrium C−C distance is increased.[26] To decrease the computed $\tau$ to ~0.7 by increasing $r_{cc}$(e), that distance would have to be increased from 3.228 Å to ~4.0 Å, which would reduce the computed rate constant by a factor of ~$10^6$ and increase the KIE to $10^6$! These results are shown in Table 2. The explosion of the KIE at larger equilibrium C−C distance is mainly due to tunneling.[26] The KIE also increases substantially as the C−H bond energy decreases.[7]

The decrease in the computed $k_{ij}$ is due to the energetic cost of the additional bond stretching that the longer donor−acceptor distance requires.

The reactions shown in eqs 10 and 11 appear to be more sterically hindered than those that were studied previously,[1,2] which might lead to a longer donor−acceptor distance in the critical configuration.[5] However, the rate constants recorded in Table 1 are only 1−2 orders of magnitude smaller than those previously reported for reactions with similar $K_{ij}$ values. And the primary kinetic isotope effects exhibited by the variants of eq 10 are in the range 4.9−5.8,[15] not significantly higher than the isotope effects observed in previously studied systems.[27] We conclude that steric hindrance, lengthening the donor−acceptor distance in the critical configuration, also cannot account for the lower values of $\tau$ we have now found.

Our model attempts to relate potential energy to the spacial relations of a small number of atoms undergoing covalency change. Trends in computed rate constants for hydride transfer in a linear, triatomic system can be made to resemble the trends observed in experimental rate constants for solution reactions.[7] The computed rate constants are very well reproduced by Marcus theory.[7] Using the same sets of computed rate constants, the $\tau$ values obtained with the two different, Marcus-theory-derived equations are identical, so the difference between the two experimental values does not arise from the difference in the method of evaluation. A change in the hydride affinity of the acceptors and a steric effect, leading to an increase in the donor−acceptor distance in the critical configuration, were also mimicked computationally. Neither seems able to reproduce the observed change in $\tau$.

Values of $\tau$ obtained from the model-calculated rate constants appear to be consistently larger than those obtained from experimental data, and more nearly constant. There does not appear to be any acceptable explanation for this discrepancy within the limits of the model and the framework of Marcus theory. It seems likely to us that the source of the smaller, and more variable, $\tau$ values is the possibility of delocalizing charge within the real, polyatomic donors and acceptors. The 9-phenylacridinium ions of the present study have an additional phenyl group into which charge is delocalized. The $\tau = 0.81$ value was obtained with all secondary carbocations.[1] This difference cannot be mimicked in the three-body model.

## 5. Conclusion

As indicated by Marcus theory of atom and group transfer, the tightness of the critical configuration either increases or decreases the Brønsted α for hydride transfer, depending on the location of the structure change, in the donor or in the acceptor. The size of the contributions differs somewhat from expectations based on related measurements using somewhat different compounds.

The discrepancy is not too large and oversimplification in the theory seems to be responsible for the discrepancy. The qualitative applicability of the theory is confirmed. The Brønsted α is not a simple indicator of the similarity of the critical configuration to reactant or product.

We believe that these conclusions are general, and this view is supported by the previous observation that they apply to methyl transfer reactions.[3,11] There is no evident reason that they should not also apply to enzyme to catalyzed reactions.

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**Note Added in Proof.** Mayr and co-workers have applied our theory successfully to hydride transfer reactions between carbocations.[28] Their $\tau$ value is larger than 1.0 (actually 1.24) that leads to different values of α for substitution in the donor and substitution in the acceptor. Their critical configuration represents the tighter critical complex between the donor and the acceptor and the positive charge on the in-flight hydrogen as confirmed by their electronic structure calculation.

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(27) Ostovic, D.; Roberts, R. M. G.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1983**, *105*, 7629.
(28) Würthwein, E.-U.; Lang, G.; Schappele, L. H.; Mayr, H. *J. Am. Chem. Soc.* **2002**, *124*, 4084.