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Relative Rates and Kinetic Isotope Effects of Reactions in Solution

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Received February 3, 1978

Abstract: Recently, there has been considerable interest in relating curvature observed in rate–equilibrium relationships to "intrinsic" barriers for proton-transfer reactions. These results have attracted wide attention since many of the "intrinsic" barriers are surprisingly small and range between 1 and 5 kcal/mol. The overall rates of these reactions are far too slow to be accounted for by such small barriers, and it is necessary to assign the difference to an unusually large barrier for assembling the reactants together into a reactive configuration (i.e., an encounter step). The encounter step(s) may involve diffusion, solvent reorganization, orientation, or molecular distortions rather than bond formation which contributes to the "intrinsic" barrier. A fundamental implication of these results is that making and breaking chemical bonds is often *less* important than encounter as a contributor to the overall barrier.

Curvature can have an *intrinsic* component which is associated with changes in rate and equilibrium constants for the proton-transfer step, as well as a *coupling* component which arises from *coupling* of proton transfer with other steps in the overall reaction. It is the *intrinsic* contribution which is relevant for calculating "intrinsic" barriers, but in the past these two contributions have not been clearly delineated. In the present paper a relationship between the *intrinsic* and *coupling* components is derived. It is shown that variations in relative rates and kinetic isotope effects due to factors intrinsic to the proton transfer step cannot be easily distinguished from variations due to coupling of other steps with proton transfer. As a result, calculated "intrinsic" barriers can be too low by 75–100% for small barriers (e.g., 2 kcal) and by 5–13 kcal/mol, or more, for larger barriers (e.g., 25 kcal/mol). Corresponding errors in the opposite direction are introduced into the encounter contribution to the observed barrier. A significant point is that the *coupling* component of the curvature can be large enough to reverse the relative importance of bond formation and encounter as elements of the observed barrier.

I. Curvature in Rate–Equilibrium Relationships

Rate–equilibrium relationships have been of interest ever since Brønsted,[1] Bell,[2] and Evans and Polanyi[3] suggested empirical relationships between the activation energy and the thermodynamics of an overall reaction:

$$\Delta G^{\ddagger} = \alpha' \Delta G^\circ + \beta'$$

$$\Delta E_a{}^{\ddagger} = \alpha'' \Delta H^\circ + \beta''$$

The parameter α' provided a measure of the relative sensitivities of $\Delta G^{\ddagger}$ and ΔG° to substituent effects and was frequently interpreted as an indicator of the structural similarity between the transition state and the reactants or products of the reaction.[4] For many years it was thought that endergonic reactions should show a larger dependence on ΔG° than exergonic reactions, so that reactions with negative values of ΔG° should be associated with lower values of α' than reactions with positive ΔG°'s. This effect should give rise to curvature in plots of log k vs. ΔG°, but for almost 40 years no one was able to demonstrate *unambiguously* the anticipated dependence of α' on ΔG° until Eigen[5a] produced curved rate–equilibrium plots involving proton transfer between bases and acids containing O, N, and C.

Eigen[5a] and Ahrens and Maass[6] also showed that the curvature was significantly more pronounced for reaction series which had larger rate constants at $\Delta G^\circ = 0$, so that proton transfers between O and N gave sharply curved Brønsted plots, while proton transfer reactions involving carbon gave almost linear plots over extended regions of ΔpK.[5] This led to the idea that curvature in rate–equilibrium plots and the rate constant for the thermoneutral member of the reaction series were qualitatively related.

Since Eigen's original demonstration of curved rate–equilibrium relationships, numerous other examples of curvature have also appeared. These include proton-transfer reactions,[7-16] carbonyl additions,[17,18] nucleophilic attack,[19] radical-transfer reactions,[20] and fluorescence quenching by electron transfer,[21,22] to cite only a few examples. Observed curvature in rate–equilibrium relationships has been used to help choose between mechanistic alternatives[16,19,21,22] and to calculate "intrinsic" barriers for related series of reactions.[7-15,17,18] The "intrinsic" barrier is defined as the reaction barrier at $\Delta G^\circ = 0$ and a "related series of reactions" is often defined as those reactions sharing a common "intrinsic" barrier. These relationships have frequently been expressed through Marcus' equation[12]

$$\Delta G^{\ddagger} = (\Delta G^\circ)^2/16\Delta G_0{}^{\ddagger} + {}^1\!/_2\Delta G^\circ + \Delta G_0{}^{\ddagger} \tag{1}$$

$$\alpha = \left(\frac{\partial \Delta G^{\ddagger}}{\partial \Delta G^\circ}\right)_{\Delta G_0{}^{\ddagger}, T, P}$$

where ΔG° is the free energy of reaction for an *elementary* step, $\Delta G^{\ddagger}$ is the free energy of activation, and $\Delta G_0{}^{\ddagger}$ is the "intrinsic" barrier for the reaction.

Since eq 1 is a parabolic relationship, a plot of $\Delta G^{\ddagger}$ vs. ΔG° will show a degree of curvature which depends on the magnitude of $\Delta G_0{}^{\ddagger}$.[12] Recently, a number of authors[7-21] have made use of this fact in order to estimate intrinsic barriers for several classes of proton transfer and other types of reactions. Many of the intrinsic barriers are remarkably small, ranging in most

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cases from 1 to 5 kcal/mol.[7-9] Since the overall rates of the reactions are far too slow to be accounted for by such small barriers, it is necessary to assign the difference to an unusually large barrier for assembling the reactants into a reactive configuration. If valid, this result is of fundamental significance and has important implications for many aspects of chemical reactivity, both in the gas phase and in solution.[1-24,29]

Many workers[1-5] have recognized that curvature can also arise as a reaction becomes diffusion controlled in either direction. The rate constant of a diffusion-controlled reaction is usually independent of its equilibrium constant, so that the slope of a rate-equilibrium plot for a diffusion-controlled reaction is frequently close to zero. The slope for a rate-limiting proton-transfer reaction will generally be greater than zero, so that the transition from rate-limiting proton transfer to rate-limiting diffusion will result in a curved rate-equilibrium plot. This type of curvature is important when proton transfer becomes competitive or kinetically *coupled* with diffusion or perhaps other steps. Consequently, curvature of this type might be described as *coupling* curvature. Curvature due to the relationship between $\Delta G^{\ddagger}$ and ΔG° is an *intrinsic* property of a particular step of an overall reaction and may be related to the *intrinsic* barrier of that step (e.g., eq 1). Consequently curvature of this type might be described as *intrinsic* curvature. It should be clear that if observed curvature is to be indicative of the intrinsic barrier magnitude, then one necessary condition is that proton transfer must be rate limiting over the pK range for which the rate measurements are made.

One might raise the question of how proton transfer between substituted ammonium ions and diazoacetate could be rate limiting over 9-10 pK units if Kreevoy's suggestion[7c] regarding an intrinsic barrier of only 1.4 kcal/mol is correct. At $\Delta G^{\circ} = 0$, the rate constant for such a reaction would be on the order of $10^{12}\ \mathrm{s}^{-1}$, and, if proton transfer is to be rate limiting, one might expect the rate constants for separation of the products or the reacting molecules to equal or exceed this value.[24] Rotational relaxation is the fastest process which might conceivably lead to molecular separation or reorientation under normal conditions in solution. Experimental measurements of rotational relaxation times suggest that it will be unusual for $1/\tau$ to exceed $10^{12}\ \mathrm{s}^{-1}$. If this number is taken as an upper limit to a rate constant for the separation or reorientation of two molecules in solution, then an intrinsic barrier of 1.4 kcal/mol would permit rate-limiting proton transfer over a range no greater than ±½ pK unit rather than the 9-10 pK units reported by Kreevoy.[7c] Furthermore, an intrinsic barrier of 1.4 kcal/mol would result in the rate constant for the reverse reaction approaching $\kappa T/h$ near $\Delta G^{\circ} = 5.6$ kcal/mol[24b] for the proton-transfer step. This prediction should occur for all reactions of diazoacetate and ammonium ions whose pKs are greater than about 9.0-9.5,[31] and Kreevoy[7c] has provided about four examples in the pK region between 9 and 10.7. If Kreevoy's estimate of the intrinsic barrier is correct, which requires proton transfer to be rate limiting for these four reactions, then rate constants for separation of the diazonium acetate and the amines should be equal to or larger than $\kappa T/h$. This conclusion would seem to be unrealistic and is unsupported by the available experimental information on relaxation events in solution (see section II).

The fast rate constants ($\sim\kappa T/h$) for proton transfer required by an intrinsic barrier of 1.4 kcal/mol suggest that at least one of two variants of internal return[32-34] should be important for Kreevoy's proton-transfer reactions involving ammonium ion pKs higher than 9.0-9.5. These reactions are particularly significant since nearly all of the curvature from the "slow" end of his Brønsted plot comes from these four reactions, and it is widely known that internal return can result in a substantial increase in curvature.[24] Internal return can arise after the initial proton transfer to diazoacetate if the resulting base reabstracts a proton from the diazonium acetate zwitterion before separation of the two species into solution can occur.[32,33] If the two protons of the diazonium intermediate become equivalent before the occurrence of proton transfer to the base, the α hydrogens of the starting diazoacetate can exchange with solvent. If the two protons do not become equivalent, then internal return can still take place, but the simplest available method of detection is the indirect technique of Streitwieser and Sonnichson[32] using the Swain equation. The results of experiments for detecting internal return would be interesting, but the outcome will not affect the conclusion that Kreevoy's intrinsic barrier may be incorrect. If internal return is present, the intrinsic barrier can be revised upward,[24] and, if internal return is absent, it would seem unlikely that the rate constants for proton transfer (in the reverse direction at p$K_a \geq$ 9-9.5) actually approach $\kappa T/h$, as required by the intrinsic barrier of 1.4 kcal/mol. In either case some explanation other than a low intrinsic barrier would be necessary to account for all of the observed curvature.[35]

It has generally been assumed that curvature due to a change in rate-limiting step could be recognized by applying one or more of the widely accepted criteria for a rate-limiting step. These include substantial primary, secondary, or solvent isotope effects, Brønsted slopes between zero and unity, or free-energy correlations which do not exhibit sharp changes in slope. One result of the present paper is a test of the adequacy of these criteria by examining the influence of prior or subsequent steps on the observed pattern of relative rates and kinetic isotope effects. A related question is whether or not this influence of additional steps in a multistep mechanism can be distinguished from intrinsic variations due to changes in rate constants for the rate-limiting step. For reactions in solution, the simplest multistep reaction might involve an encounter or diffusion step(s) where two or more reacting molecules come together in a configuration suitable for reaction, a bond-forming step where structural and electronic reorganization take place, and finally a product separation step(s). A simple example is Eigen's three-step proposal for proton-transfer reactions[5a] (eq 2).

$$\mathrm{AH} + \mathrm{B}^- \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} [\mathrm{AH}\text{---}\mathrm{B}]^-$$

encounter

$$\underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} [\mathrm{A}\text{---}\mathrm{HB}]^- \underset{k_{-c}}{\overset{k_c}{\rightleftharpoons}} \mathrm{A}^- + \mathrm{HB} \qquad (2)$$

proton transfer separation

Under steady-state conditions[5]

$$k_{\mathrm{obsd}} = k_a k_b k_c/(k_{-a}(k_{-b} + k_c) + k_b k_c) \qquad (3)$$

$$K = k_a k_b k_c/k_{-a}k_{-b}k_{-c} \qquad (4)$$

$$\alpha = \mathrm{d}\log k_b/\mathrm{d}\log(k_b/k_{-b})$$

$$\alpha_{\mathrm{exp}} = \mathrm{d}\log k_{\mathrm{obsd}}/\mathrm{d}\log K$$

Combining eq 3 and 1 using transition-state theory, an expression for k_{obsd} in terms of ΔG°, $\Delta G_0^{\ddagger}$, k_a, k_{-a}, k_c, and k_{-c} can be obtained[24] that is valid regardless of which step is rate limiting. A comparison of k_b and k_{obsd} reveals the effect of coupling between proton transfer and prior or subsequent steps.[5b]

It should be emphasized that Kreevoy's suggestion regarding the small intrinsic barrier (1.4 kcal) for the diazoacetate reactions could be correct even though it would require rate constants comparable to $\kappa T/h$ or greater for reversal of the encounter step. In principle, this might be possible if encounter is accompanied by vibrational distortion of one or both reactants to form a new geometry which is better suited for proton transfer. The encounter could be effectively reversed in the time scale of a vibration ($\sim h/\kappa T$ s) without requiring reorientation or physical separation of the reacting molecules, if vibrational relaxation of the distorted geometry leads to a sufficiently large drop in energy.[64] Since the diazoacetate anion is presumably planar, this geometric distortion might include a change in hybridization of the 2 carbon from sp^2 toward sp^3. However, there appears to be little evidence that internal distortions make a significant contribution to encounter in reactions involving delocalized substrates which undergo hybridization changes.[28] Particularly striking are the observations that protonation of benzyl anion by methanol is close to a diffusion-controlled process ($k = 6 \times 10^9$ M^{-1} s^{-1})[28a] and that recombination of benzyl cation with I$^-$ proceeds with an even larger rate constant ($k = 5 \times 10^{10}$ M^{-1} s^{-1}).[28b] Furthermore, the numerous examples of internal return in radical reactions,[36-38] solvolysis reactions,[39] and proton-transfer reactions[32,33] provide ample demonstration that rate constants for reversal of the encounter step are frequently less than $\kappa T/h$ and comparable to rate constants for many chemical reactions.

These results suggest that for many reactions vibrational relaxation may be insignificant as a mechanism for reversal of the encounter step and that processes leading to molecular reorientation or separation are often necessary. Consequently, it would be of interest to examine four fundamental questions with regard to the recent observations[5-22] of curvature in rate-equilibrium relationships.

(a) What is the maximum limit and the range expected for rate constants for molecular separation in solution (section II)?

(b) How do *intrinsic* effects and *coupling* effects restrict the range of rate-limiting proton transfer and increase observed curvature (section III)?

(c) Can *intrinsic* curvature be distinguished from *coupling* curvature by examining patterns of relative rates and kinetic isotope effects (section IV)?

(d) How much curvature can be added by coupling additional steps to proton transfer (section V)?

II. How Fast Do Molecules Separate in Solution?

Since the detailed mechanism(s) of encounter and separation processes are obscure, the prediction of these rate constants on a case-by-case basis is a difficult question at present. Fortunately, there is extensive information on diffusion and relaxation events available in the literature. While this material cannot provide any specific numbers directly relevant to specific reactions, the data are adequate for obtaining an estimate of the maximum limit and the range that rate constants for separation might reasonably be expected to cover.

The dielectric relaxation times of small molecules with weak interactions such as benzene or CCl$_4$ are frequently on the order of 10^{-12} s ($1/\tau = 10^{12}$ s^{-1}).[40] For larger molecules, such as hexane[40] and didodecyl ether,[41] $1/\tau$ values range from 2.5×10^{11} to 8.4×10^9 s^{-1}.

Molecules showing significant interactions with each other or with solvent frequently have reduced values of $1/\tau$. For example, chloroform is known to self-associate to a slight degree,[42] and $1/\tau$ (30 °C) is 1.85×10^{11} s^{-1},[43] compared to about 10^{12} s^{-1} for CCl$_4$ or benzene. Good electron acceptors such as tetracyanoethylene (TCNE) and tetrachlorobenzoquinone show a similar effect in donor solvents: $1/\tau$ for TCNE (20 °C) is equal to 7.52×10^{10} s^{-1} in mesitylene solvent.[44] Hydrogen bonding might also be expected to reduce $1/\tau$, which for water has been found to range from 7.4×10^{10} (10 °C) to 2.08×10^{11} s^{-1} (50 °C).[45] Similarly, $1/\tau$ for methanol[46] varies from 1.42×10^{10} (5 °C) to 3.62×10^{10} s^{-1} (55 °C). A liquid crystal, cholesteryl chloride/cholesteryl myristate (7:4), provides an example of an exceptionally slow dielectric relaxation process: $1/\tau$ varies from 4×10^3 (21 °C) to 2×10^7 s^{-1} (57 °C).[47]

Lifetimes of amine-water complexes have been estimated using ^{1}H NMR by Grunwald and co-workers, who measured dissociation rate constants (20-30 °C) ranging from 5×10^8 to 8.3×10^{10} s^{-1} for various amines and pyridines.[48] Two notable exceptions to this range are the dissociation rate constants for the hydrogen-bonded complexes between ammonia and water (5×10^{11} s^{-1}, 25 °C)[48a] and the corresponding value for the complex of *tert*-butyl alcohol with *N*,*N*-diethyl-*m*-toluidine (2.6×10^5 s^{-1}, 25 °C).[48c] Significantly, the rate constants for dissociation show little or no correlation with the basicity of the amine, but do seem to depend inversely on the total steric bulk of the complex.[48d] This suggests that strong hydrogen bonding is not entirely responsible for some of the slower values.

Rate constants have also been measured by various techniques for dissociation of hydrogen-bonded dimers. Dimers of 2-pyridone,[49] benzoic acid,[50,51] and ϵ-caprolactam[52] have dissociation rate constants varying from 10^5 to 10^8 s^{-1} in solvents ranging from benzene and cyclohexane to dioxane and dimethylformamide.

The relationship between k_{-a} and k_c with $1/\tau$ derived from dielectric relaxation data may not be particularly simple, since processes leading to dipole reorientation in an oscillating electric field do not necessarily correspond to those leading to reversal of the encounter step. Nonetheless, the dielectric relaxation data is in reasonable agreement with the molecular rotation relaxation times derived from laser light scattering from simple molecules,[30] and it is unlikely that either reorientation of two molecules or their separation to free reactants or products can occur faster than molecular rotation of small, symmetrical, weakly interacting molecules such as benzene or CCl$_4$. Consequently, we may be reasonably certain that the maximum limit for k_{-a} and k_c in solution under ordinary conditions will be somewhere in the neighborhood of 10^{12} s^{-1}, and that values in the range 10^8–10^{10} s^{-1} may not be uncommon.

III. Curvature and the Range of Rate-Limiting Proton Transfer. Intrinsic Effects vs. Coupling Effects

The relationship between log k_c and $\Delta G_0^{\ddagger}$ which determines the maximum pK interval over which proton transfer can be rate limiting is illustrated in the two contour plots in Figures 1a and 1b.[53] In Figure 1a, each point on a contour line corresponds to a value of log k_c (left vertical axis) and a value of $\Delta G_0^{\ddagger}$ (lower horizontal axis). $\Delta G_0^{\ddagger}$ is directly related[12,24] to the pK interval where a barrier exists for proton transfer in both directions (upper horizontal axis). This pK interval is equivalent to the pK span over which both k_b and k_{-b} will be smaller than $\kappa T/h$, and is the transition region for α (Brønsted slope for proton-transfer step)[24] to change from zero to unity. Unless k_c and k_{-a} equal $\kappa T/h$, proton transfer will be rate limiting only over a fraction of the transition region, and this fraction is the value assigned to each contour line. For example, if $k_c = \kappa T/h$, an intrinsic barrier of 15 kcal/mol (lower horizontal axis) would correspond to a transition region for rate-limiting proton transfer of ±44 pK units (upper horizontal axis). If k_c is reduced to 10^{10} s^{-1} (left vertical axis), the contour line connecting log k_c and $\Delta G_0^{\ddagger}$ is the one marked 0.5, so that the rate-limiting region is reduced to 0.5 (±44) = ±22 pK units. This span of ±22 pK units would be the rate-limiting region associated with an intrinsic barrier of only 7.5 kcal/mol if it were incorrectly assumed that $k_c = \kappa T/h$.

In Figure 1b, an alternative contour plot is presented. The vertical and horizontal axes are identical with those of Figure 1a, but the contour lines represent the locus of all values of log k_c and $\Delta G_0^{\ddagger}$ corresponding to a fixed pK interval where proton transfer is rate limiting. Note that an interval of rate-limiting

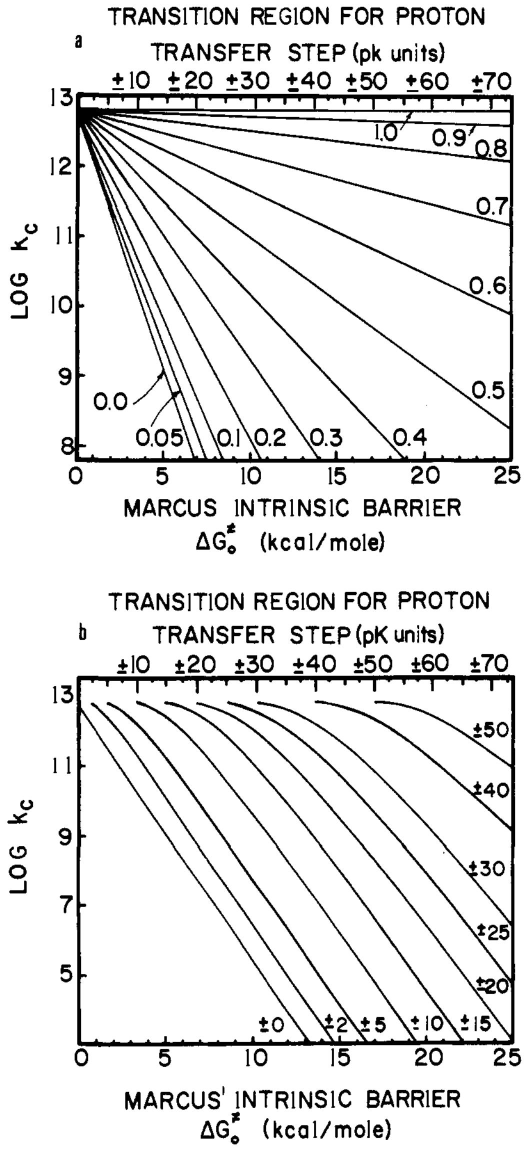

Figure 1. (a) Fraction of transition region where proton transfer is rate limiting. Each contour line corresponds to the fraction (e.g., 0.5, 0.6, etc.) and the transition region ($0 < \alpha < 1$) is indicated on the upper vertical axis. It can be shown that the contour lines fit the equation $\log k_c = -[(1 - f)(1 - f)]\Delta G_0^{\ddagger}/(2.3RT) + \log \kappa T/h$. (b) Region of ΔpK for rate-limiting proton transfer. The contour lines trace out the locus of all values of log k_c and $\Delta G_0^{\ddagger}$ which correspond to a given ΔpK interval of rate-limiting proton transfer. For example, if rate-limiting proton transfer is observed over an interval of ±5 pK units, the intrinsic barrier could range from 1.7 to 16.6 kcal/mol as k_c varies from $\kappa T/h$ to 10^3 s^{-1}. It can be shown that the contour lines fit the equation $\log k_c = \frac{1}{2}\Delta pK + \log \kappa T/h - (2.3RT(\Delta pK)^2)/(16\Delta G_0^{\ddagger}) - (\Delta G_0^{\ddagger}/2.3RT)$ where $|2.3RT\Delta pK| \leq 4\Delta G_0^{\ddagger}$. Note that for $\Delta G_0^{\ddagger} \gg \Delta pK$, log k_c and $\Delta G_0^{\ddagger}$ are almost linearly dependent.

proton transfer of ±5 pK units is consistent with an intrinsic barrier of ~2 kcal/mol if $k_c = \kappa T/h$, but could just as well represent an intrinsic barrier of 10 kcal/mol for $k_c = 10^8$ s^{-1} (Figure 1b). Since the expected range for k_c is about 10^8–10^{12} s^{-1} (section II), this 8 kcal/mol uncertainty for a 10^4 variation in k_c is significant, since it could account for a substantial portion of the observed[7-9] variation in intrinsic barriers between 2 and 10 kcal/mol.[54]

IV. Can Intrinsic Curvature Be Distinguished from Coupling Curvature?

A. Relative Rates. One of the questions of primary importance is whether the *curvature* produced by a low intrinsic barrier (e.g., 1.4 kcal/mol) can be imitated by a high intrinsic barrier (e.g., 12.5 kcal/mol) coupled with a slow step subsequent to proton transfer (i.e., $k_c \ll \kappa T/h$). To test this proposal, log k_{obsd} was calculated from eq 3 for $\Delta G°$ between 0 and 10 kcal/mol. Values for $\Delta G_0^{\ddagger}$ were selected (1.4–12.5 kcal/mol), and k_c was chosen so that the Brønsted curvature for $0 \leq \Delta G° \leq 10$ kcal/mol matched that calculated from eq 1 with $\Delta G_0^{\ddagger} = 1.4$ kcal/mol and $k_c > \kappa T/h$. A simple method of comparing curvatures is to tabulate the rates (relative to the rate at a reference value of $\Delta G°$) at different ΔG's for each intrinsic barrier.

Comparison of these relative rates for intrinsic barriers between 1.4 and 12.5 kcal/mol shows only marginal differences (Table I). The maximum deviation is only 0.14 log unit and most of the discrepancies are well within 0.1 log unit. In Figure 2a, Kreevoy's data[7c] (log k_{obsd} vs. log K_{HA} where K_{HA} is the ionization constant for the ammonium salt) is plotted, together with the line calculated from eq 1 using $\Delta G_0^{\ddagger} = 1.4$ kcal/mol, $k_c > \kappa T/h$, W_r[59] = 13.8 kcal/mol, and pK = +5 when $\Delta G° = 0$. In Figure 2b the same data are plotted, but the line is generated from eq 3 with $\Delta G_0^{\ddagger} = 12.5$ kcal/mol and $k_c = 4.5 \times 10^4$ s^{-1}. Log k_{obsd} is assumed to be identical for the two plots at pK = 5.[31] This last value is completely arbitrary and any reasonable value could be used by readjusting k_c. The results in Table I show that any value for the intrinsic barrier between 1.4 and 12.5 kcal/mol would be consistent with the observed curvature, and that values for k_c in the range of 10^8–10^{12} s^{-1} would permit intrinsic barriers up to 11 kcal/mol.

B. Isotope Effects. Kreevoy has also measured the primary kinetic isotope effect for the same reaction.[7c] The observation that $k^{\text{H}}/k^{\text{D}}$ declines from ~11 to ~1.4 over a span of ~7 pK units was regarded as being consistent with a low (i.e., 1.4 kcal/mol) intrinsic barrier. However, such a dropoff can also be produced by the combination of a high barrier at $\Delta G° = 0$ and a low value of k_c. In fact, the same values of k_c and $\Delta G_0^{\ddagger}$ that accounted for the curvature of the Brønsted plot will also produce essentially the same dropoff of the kinetic isotope effect (see Figure 3 and Table II). The differences which are seen are small compared to the experimental variation in Kreevoy's isotope effects[7c] and become insignificant when log $(k^{\text{H}}/k^{\text{D}})_{\text{obsd}}$ is considered. The results show that k_c and $\Delta G_0^{\ddagger}$ are both important in producing changes in $(k^{\text{H}}/k^{\text{D}})_{\text{obsd}}$ with variations in $\Delta G°$. For $\Delta G_0^{\ddagger} = 10$ kcal/mol, $k_b^{\text{H}}/k_b^{\text{D}}$ is greater than 11 over a pK range of more than 7 units, while $(k^{\text{H}}/k^{\text{D}})_{\text{obsd}}$ varies from 11.0 to 1.06 for the same region. Such behavior is simply a reflection of the well-known fact that k_{obsd} can be influenced by more than one elementary step at a time, and that discrete boundaries, with sharp changes in behavior, do not necessarily separate those regions where one elementary step is dominant over the others.

Two significant points emerge from this analysis: (1) Brønsted curvature and variation of observed isotope effects can provide only a *lower* limit to the intrinsic barrier of a reaction. (2) The intrinsic curvature and the curvature produced by a change in rate-limiting step appear indistinguishable unless data of unusually high precision are obtainable.

V. How Much Coupling Curvature Can Be Added? The "Apparent" Intrinsic Barrier

Since we have seen that a large intrinsic barrier (e.g., 12.5 kcal/mol) can appear to be only 1.4 kcal/mol, we might expect that it could also be reduced to any intermediate height, if k_{-a} and k_c assume appropriate values. Indeed, this is found to be the case as seen in Figure 4, where $\Delta G_0^{\ddagger}$ has been set equal to 12.5 kcal/mol and k_{-a}, k_c vary from 10^6 to 10^{10} s^{-1}. The theoretical transition region for α to go from 0 to 1 for $\Delta G_0^{\ddagger} = 12.5$ kcal/mol is about 73 pK units (25 °C). If we define the empirical transition region (ETR) as the pK interval for α_{exp}

Table I. Values[a] of Log k^x_{rel} Illustrating Curvature[g] as a Function of k_c and $\Delta G_0^{\ddagger}$

$\Delta G° - \Delta G°_{\mathrm{ref}}$, kcal/mol	$\Delta G_0^{\ddagger}$, kcal/mol									
	1.4[b]	1.65[b]	2.5[b]	5.0[b]	7.5[b]	10.0[b]	12.5[b]	10.0[d]	11.0[e]	12.5[f]
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2.00	0.86	0.92	0.92	0.90	0.89	0.89	0.89	0.99	0.96	0.92
4.00	1.99	2.10	2.09	2.04	2.03	2.02	2.02	2.13	2.09	2.06
5.60	3.08	3.18	3.16	3.11	3.10	3.09	3.10	3.17	3.13	3.11
6.50	3.74	3.83	3.79	3.74	3.73	3.73	3.73	3.79	3.75	3.74
9.00	5.57	5.66	5.58	5.54	5.54	5.54	5.54	5.56	5.54	5.54
10.00	6.30	6.39	6.31	6.26	6.27	6.27	6.27	6.29	6.26	6.27
curvature[g]	0.018	0.019	0.018	0.018	0.018	0.018	0.018	0.018	0.018	0.018
k_c, s^{-1} [c]	$\gg \kappa T/h$	$\kappa T/h$	10^{12}	1.45×10^{10}	2.1×10^{8}	3.1×10^{6}	4.5×10^{4}	10^{9}	10^{8}	1.15×10^{6}

[a] Log $k^x_{\mathrm{rel}} = \log k_{\mathrm{obsd}}(\Delta G°_{\mathrm{ref}})/k_{\mathrm{obsd}}(\Delta G°)$ where $k_{\mathrm{obsd}}(\Delta G°_{\mathrm{ref}}) = k_{\mathrm{obsd}}$ at $\Delta G°_{\mathrm{ref}}$ and $\Delta G_0^{\ddagger} = x$ kcal/mol. [b] $\Delta G°_{\mathrm{ref}} = 0.0$. [c] Value of k_c required to give close agreement between log $k^{1.4}_{\mathrm{rel}}$ and log k^x_{rel}. No attempt has been made to completely optimize the k_c values. [d] $\Delta G°_{\mathrm{ref}} = 7.625$ kcal/mol. [e] $\Delta G°_{\mathrm{ref}} = 6.6$ kcal/mol. [f] $\Delta G°_{\mathrm{ref}} = 4.0$ kcal/mol. [g] Log k^x_{rel} can be fit to a quadratic function, log $k^x_{\mathrm{rel}} = a + by + cy^2$, where $y = \Delta G° - \Delta G°_{\mathrm{ref}}$. The curvature can be defined as the quadratic coefficient, c. The quadratic coefficient is determined by least squares (a is fixed at 0.0 and b is fixed at 0.454). The standard deviation of the fit is 0.05 log unit..

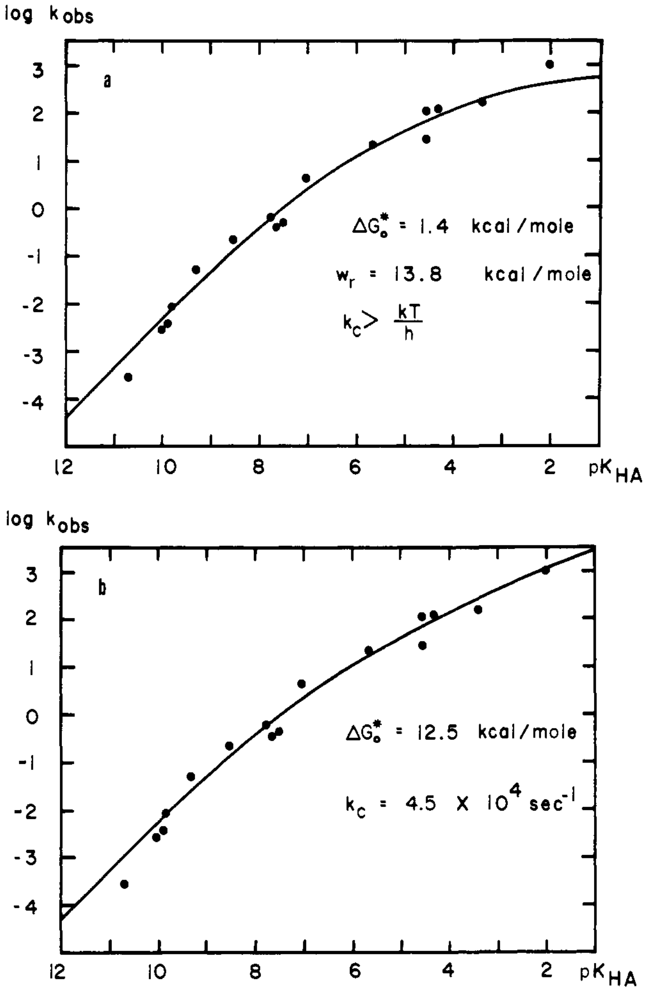

Figure 2. Constant curvature and $\Delta G_0^{\ddagger}$. (a) Kreevoy's data, ref 7, plotted using best parameters found in ref 7 for eq 1.[59] $\Delta G_0^{\ddagger} = 1.4$ kcal/mol; $W_r = 13.8$ kcal/mol; k_{-a}, $k_c > \kappa T/h$. (b) Same data plotted according to eq 3 where $\Delta G_0^{\ddagger} = 12.5$ kcal/mol, $k_c = 4.5 \times 10^4\ s^{-1}$, $k_{-a} > \kappa T/h$. Intrinsic barriers from 1.4 to 12.5 kcal/mol can reproduce the curvature over the pK range investigated by Kreevoy. The curvature at the low pK region can be increased by reducing k_{-a}.

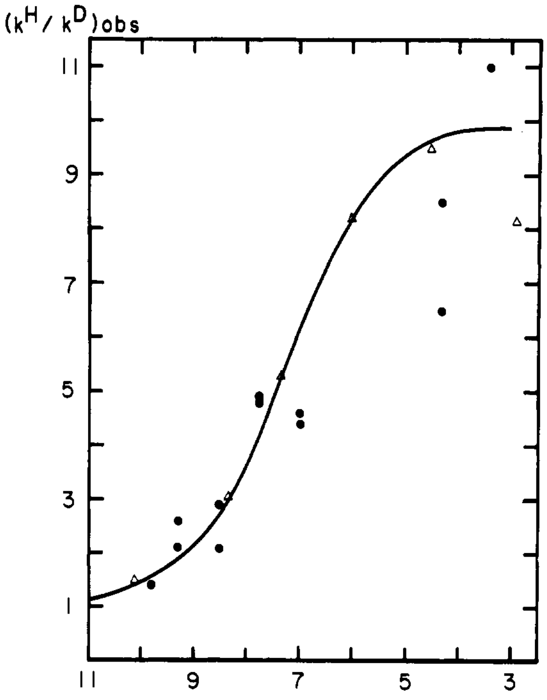

Figure 3. Variation of kinetic isotope effects with pK: (●) Kreevoy's experimental data (ref 7); (△) calculated $(k^H/k^D)_{\mathrm{obsd}}$ using $\Delta G_0^{\ddagger} = 1.4$ kcal/mol assuming $k_c > \kappa T/h$; (—) calculated $(k^H/k^D)_{\mathrm{obsd}}$ using eq 3 where $\Delta G_0^{\ddagger} = 12.5$ kcal/mol and $k_c = 4.5 \times 10^4\ s^{-1}$. Intrinsic barriers from 1.4 to 12.5 kcal/mol can reproduce the falloff of $(k^H/k^D)_{\mathrm{obsd}}$ with increasing pK. $\Delta G°_{\mathrm{ref}} = 0$ for $\Delta G_0^{\ddagger} = 1.4$ and $\Delta G°_{\mathrm{ref}} = -1.1$ for $\Delta G_0^{\ddagger} = 12.5$.

to change from 0.01 to 0.99,[53,54] then with $k_{-a} = k_c = 10^{10}\ s^{-1}$ the ETR is about 44 pK units. This would correspond to an "apparent" intrinsic barrier of ~7.5 kcal/mol if it were erroneously assumed that $k_{-a} = k_c = \kappa T/h$ ($6 \times 10^{12}\ s^{-1}$, 25 °C). If $k_{-a} = k_c = 10^8\ s^{-1}$, then the apparent intrinsic barrier is reduced to 4.8 kcal/mol (ETR = 28 pK units), while with $k_{-a} = k_c = 10^6\ s^{-1}$ the ETR of 18 pK units would yield an apparent intrinsic barrier of a mere 3.1 kcal/mol.

Comparison of α with α_{exp} (Table III) shows that proton transfer is rate limiting over a range of roughly ±11 pK units with $k_{-a} = k_c = 10^{10}\ s^{-1}$. When k_{-a} and k_c are reduced to $10^6\ s^{-1}$, the effective region for rate-limiting proton transfer is compressed into a span of ±1-2 pK units. Brønsted,[1] Bell,[2] Eigen,[5a] and other pioneer investigators anticipated that α_{exp} could be influenced by changes in the rate-limiting step, al-

Table II. Primary Kinetic Isotope Effect vs. k_c and $\Delta G_0^{\ddagger}$

$\Delta G° - \Delta G°_{ref}$, kcal/mol		$\Delta G_0^{\ddagger}$, kcal/mol										
		1.65[a]	2.5[b]	5.0[b]	7.5[b]	10.0[b]	12.5[b]	10.0[e]	11.0[f]	12.5[g]	12.5[c]	1.4[d]
0.00	$(k^H/k^D)_{obsd}$ =	11.0	11.1	11.1	11.0	11.0	11.0	10.2	10.5	10.9	9.5	9.5
	k_b^H/k_b^D =	11.6	12.0	12.0	12.0	12.0	12.0	11.1	11.4	11.8		
	k_c/k_{-b}^D =	188	130	128	126	125	124	113	123	124		
2.00	$(k^H/k^D)_{obsd}$ =	8.4	8.2	8.3	8.3	8.3	8.3	8.0	8.3	8.4	8.3	8.2
	k_b^H/k_b^D =	10.3	11.3	11.8	11.9	11.9	12.0	10.6	11.0	11.6		
	k_c/k_{-b}^D =	40	27	25	24	24	24	29	29	27		
4.00	$(k^H/k^D)_{obsd}$ =	4.8	4.5	4.4	4.3	4.2	4.1	4.9	4.9	4.6	5.3	5.3
	k_b^H/k_b^D =	7.2	9.3	11.1	11.6	11.7	11.8	10.0	10.6	11.3		
	k_c/k_{-b}^D =	11.0	6.8	5.7	5.2	5.0	4.8	7.9	7.5	6.1		
5.6	$(k^H/k^D)_{obsd}$ =	2.8	2.7	2.4	2.3	2.2	2.1	3.0	2.9	2.5	2.9	3.0
	k_b^H/k_b^D =	4.5	7.3	10.3	11.2	11.5	11.7	9.5	10.1	11.0		
	k_c/k_{-b}^D =	4.8	2.7	1.9	1.6	1.5	1.4	2.9	2.7	2.0		
6.5	$(k^H/k^D)_{obsd}$ =	2.1	2.1	1.9	1.7	1.7	1.6	2.3	2.2	1.9	2.0	2.1
	k_b^H/k_b^D =	3.3	6.2	9.8	10.9	11.3	11.6	9.2	9.9	10.9		
	k_c/k_{-b}^D =	3.3	1.7	1.1	0.9	0.8	0.7	1.7	1.5	1.1		
9.0	$(k^H/k^D)_{obsd}$ =	1.2	1.3	1.2	1.2	1.1	1.1	1.4	1.3	1.2	1.2	1.2
	k_b^H/k_b^D =	1.5	3.4	8.1	9.9	10.7	11.2	8.3	9.1	10.3		
	k_c/k_{-b}^D =	1.5	0.6	0.2	0.2	0.1	0.1	0.4	0.3	0.2		
10.0	$(k^H/k^D)_{obsd}$ =	1.1	1.2	1.1	1.1	1.1	1.1	1.2	1.2	1.1	1.1	1.0
	k_b^H/k_b^D =	1.2	2.5	7.4	9.5	10.5	11.0	7.9	8.8	10.1		
	k_c/k_{-b}^D =	1.2	0.4	0.1	0.1	0.1	0.1	0.3	0.2	0.1		
	k_c, s^{-1} =	$\kappa T/h$	10^{12}	1.45×10^{10}	2.1×10^8	3.1×10^6	4.5×10^4	10^9	10^8	1.15×10^6	4.5×10^4	$\gg \kappa T/h$

[a] $\Delta G^{\ddagger}_{oD} - \Delta G^{\ddagger}_{oH}$ = 1.454 kcal/mol = ZPE, $\Delta G°_{ref}$ = 0. kcal/mol. [b] ZPE = 1.473 kcal/mol, $\Delta G°_{ref}$ = 0. [c] ZPE = 1.353 kcal/mol, $\Delta G°_{ref}$ = −1.1. [d] ZPE = 1.335 kcal/mol, $\Delta G°_{ref}$ = 0.0. [e] ZPE = 1.473 kcal/mol, $\Delta G°_{ref}$ = 7.625. [f] ZPE = 1.473 kcal/mol, $\Delta G°_{ref}$ = 6.6. [g] ZPE = 1.473 kcal/mol, $\Delta G°_{ref}$ = 4.0.

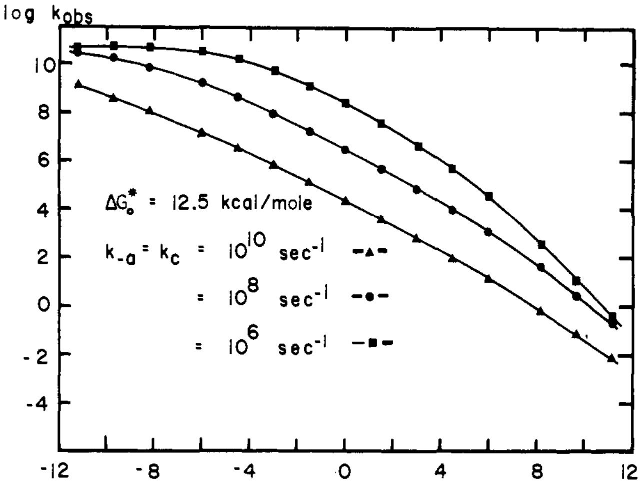

Figure 4. Influence of coupling on Brønsted slope. Rate constants for proton transfer (k_b) (Table III) have been calculated using eq 1 with $\Delta G_0^{\ddagger}$ = 12.5 kcal/mol. "Observed" rate constants (k_{obsd}) have been calculated using eq 3 where k_{-a}, k_c ($k_{-a} = k_c$) have been successively adjusted from 10^{10}, 10^8, and 10^6 s^{-1}.

though the contributions of intrinsic and coupling effects were never quantitatively delineated. The relative importance of these contributions to α_{exp} can be seen from eq 5,[60] and it is not surprising to find that the discrepancy between α and α_{exp} caused by a changeover in rate-limiting step can be significant only when k_{-b} approaches and exceeds k_c.

$$\alpha_{exp} = \alpha + (1 - \alpha)k_{-b}/(k_{-b} + k_c) \qquad (5)$$

However, it is apparent that the coupling contribution to α_{exp}, represented by the last term in (5), is not easily determined from curvature measurements, since a careful inspection of the three lines in Figure 4 shows no well-defined point where the rate-limiting step changes from a to b or from b to c. An analogous result can be derived for isotope effects,[60] and examination of k_b^H/k_b^D and $(k^H/k^D)_{obsd}$ (Table III) shows that the transition from one rate-limiting step to another can occur over 8–9 p*K* units and that $(k^H/k^D)_{obsd}$ can maintain a significant value over a large portion of this transition region.

An important point, which is not often appreciated,[33] is that values of α_{exp} greater than zero or less than unity or substantial values for $(k^H/k^D)_{obsd}$ do not necessarily prove that proton transfer is rate limiting.

VI. Conclusions

The results of the present paper show that it is not always possible to distinguish whether variations in kinetic measurements are due to factors intrinsic to the bond-making process or to a changeover in the rate-limiting step. An important point (Figure 1) is that the rate-limiting region with intrinsic barriers as large as 12.5 kcal/mol will be reduced by 30% or more, even when k_c is as high as 10^{12} s^{-1}. For smaller intrinsic barriers (e.g., Kreevoy's 1.4 kcal/mol) the transition region of about ±5 p*K* units ($k_c = \kappa T/h$) would be reduced to about ±½ p*K* unit with $k_c = 10^{12}$ s^{-1}. Since $\kappa T/h = 6 \times 10^{12}$ s^{-1} at 25 °C, it is clear that even small departures from $\kappa T/h$ for rate constants such as k_{-a} and k_c can have rather significant effects on the intrinsic barriers calculated assuming that $k_{-a} = k_c = \kappa T/h$. Furthermore, a considerable body of experimental evidence[30,40-52] supports the idea that rate constants for separation will commonly lie in the range of 10^8–10^{12} s^{-1}, and in special instances[48] may dip to 10^5 s^{-1} or even below. No claim has been made in the present paper that these values are directly related to any specific reaction, but it should be noted

Table III. Influence of Subsequent and Prior Steps on Observed Primary Isotope Effects and Changes in Relative Rates[a]

		α_{exp}				$(k^H/k^D)_{obsd}$[c]		
		$k_{-a} = k_c$				$k_{-a} = k_c$		
$-\Delta pK$	α	$10^{10}\ s^{-1}$	$10^8\ s^{-1}$	$10^6\ s^{-1}$	(k_b^H/k_b^D)[b]	$10^{10}\ s^{-1}$	$10^8\ s^{-1}$	$10^6\ s^{-1}$
14.94	0.296	0.213	0.007	0.000	8.28	6.25	1.18	1.00
12.70	0.327	0.303	0.037	0.000	9.17	8.59	1.94	1.01
11.21	0.347	0.339	0.101	0.001	9.73	9.53	3.55	1.04
9.71	0.367	0.364	0.215	0.005	10.25	10.19	6.41	1.13
8.22	0.388	0.387	0.325	0.019	10.72	10.70	9.14	1.48
5.98	0.418	0.418	0.408	0.122	11.30	11.29	11.06	4.01
4.48	0.439	0.439	0.436	0.282	11.60	11.59	11.54	7.82
2.99	0.459	0.459	0.459	0.411	11.81	11.81	11.80	10.67
1.49	0.480	0.480	0.480	0.469	11.94	11.94	11.94	11.68
0.00	0.500	0.500	0.500	0.500	11.99	11.99	11.99	11.89

[a] α and α_{exp} calculated as in ref 24. $\Delta G_0^{\ddagger} = 12.5$ kcal/mol; $k_{-a} = k_c$ (see columns 3–5 and 7–9). [b] Calculated from eq 1 with $\Delta G^{\ddagger}{}_{oD} - \Delta G^{\ddagger}{}_{oH} = 1.473$ kcal/mol (25 °C). [c] Calculated from eq 3.

that even a range of 10^4 in k_c could account for reductions up to 8–12 kcal/mol[54] in intrinsic barriers from 10 to 23 kcal/mol (Figure 1a).

A second point is that, since maximum rate constants for separation (i.e., k_{-a}, k_c) will be in the neighborhood of 10^{11}–10^{12} s^{-1},[30] encounter and/or separation will necessarily become rate limiting as the rate constant for the bond forming/breaking process approaches and exceeds 10^{11}–10^{12} s^{-1}. As a result, less and less information concerning the bond-forming or bond-breaking step becomes available so that the technique of examining the asymptotic behavior of a rate-equilibrium plot as $\Delta G°$ approaches $\pm\infty$ is unlikely to prove useful for measuring intrinsic barriers or for distinguishing alternatives to Marcus' theory (i.e., eq 1). In the limit of large $|\Delta G°|$, changes in rate will progressively reflect the changeover in rate-limiting step rather than intrinsic changes in the bond-forming step.

A third point is that the conclusions of the present paper do not depend upon the nature of the processes represented by k_{-a} or k_c. The results are applicable to situations where a sequence of bond reorganizing steps may be involved and where many of the rate constants may be orders of magnitude less than $\kappa T/h$. A few examples include base-catalyzed eliminations, carbonium ion rearrangements, nucleophilic addition and elimination reactions of carbonyl compounds, aromatic substitution reactions, and various internal rearrangements. Photochemical systems, where energy transfer and spin interconversion compete with bond reorganization, should also provide some interesting applications.

The aim of the present paper has been to test the uniqueness of the conclusions derived from a particular rate-equilibrium treatment[61] when applied in a form appropriate to a single kinetic step (e.g., eq 1). The results definitively demonstrate that distinguishing intrinsic effects on rate measurements from coupling effects is exceedingly difficult without knowledge of rate constants for so-called "fast" steps prior or subsequent to a rate-limiting process. At present, general methods for measuring such rate constants directly have not been developed,[62,63] but it seems clear that such information will play a central role in relating theoretical treatments of chemical reactivity to experimental results obtained in solution and in the gas phase.

Acknowledgment. The author would like to thank Professor Cheves Walling, Professor William McMillan, and Douglas Magnoli for their interest in this work and for many helpful discussions. This research was supported in part by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society, by the Pennwalt Corporation Grant of Research Corporation, by a USPHS Biomedical Research Grant (4-521355-24739) and by continued assistance from the University Research Committee (UCLA). J.R.M. also acknowledges a Regents' Junior Faculty Fellowship (1978–1979) and a UCLA Faculty Career Development Award (1979–1980).

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(53) Proton transfer can be defined as rate limiting when $k_{-a} \geq k_b$ and $k_c \geq k_{-b}$. This definition will tend to exaggerate the region of rate-limiting proton transfer.

(54) Figures 1a and 1b are drawn so that the region of rate-limiting proton transfer can be expressed as either a fraction of the theoretical region (Figure 1a) or in p*K* units (Figure 1b). The transition region for α_{exp} to vary from 0 to 1 will be somewhat larger than the transition region for rate-limiting proton transfer since $\alpha_{\mathrm{exp}} \simeq 1$ requires $k_{-b} > k_c$ rather than $k_{-b} = k_c$ as in footnote 53. Figures 1a and 1b can be used to estimate the transition region corresponding to the constraint $k_{-b} = Rk_c$ by replacing log k_c on the left vertical axis with log Rk_c. R can be estimated from the relationship $R = (\alpha_{\mathrm{l}} - (f+1)/2)/(1-\alpha_{\mathrm{l}})$, which can be derived from eq 11 and 12 in ref 24. f represents the transition region for α_{exp} to vary from $1-\alpha_{\mathrm{l}}$ to α_{T}, expressed as a fraction of the transition region for α to vary from 0 to 1. For example, if the transition region for α_{exp} to change from 0.05 to 0.95 is one-tenth of the transition region for α to change from 0 to 1, then $f = 0.1$, $\alpha_{\mathrm{l}} = 0.95$, and $R = 8$. Under these conditions, the apparent intrinsic barrier would be one-tenth of $\Delta G_0^{\ddagger}$. If f is changed to 0.5, R is decreased to 4. The value of k_c required to produce a given apparent intrinsic barrier can be found from $k_c = (1/R)k_{-b}$ and $k_{-b} = (\kappa T/h)\cdot e^{-\Delta G_0^{\ddagger}(1-2f+f\cdot f)/RT}$

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(59) The two encounter steps are often accounted for by rewriting eq 1 as

$$\Delta G^{\ddagger}{}_{\mathrm{exp}} = \frac{(\Delta G^{\circ}{}_{\mathrm{exp}} - W_r + W_p)^2}{16\Delta G_0^{\ddagger}} + \frac{1}{2}(\Delta G^{\circ}{}_{\mathrm{exp}} - W_r + W_p) + \Delta G_0^{\ddagger} + W_r \quad (6)$$

where W_r is the free energy necessary to assemble the first encounter complex from the reactants, W_p is the corresponding quantity for the formation of the second encounter complex from the products, and $\Delta G^{\circ}{}_{\mathrm{exp}}$ is the overall free-energy change for the entire sequence. The validity of (6) depends upon the assumption that k_{-a} and k_c are significantly faster than k_b and k_{-b}, so that the bond-forming steps, k_b and k_{-b}, must be rate limiting. If k_{-a} and k_c are comparable to $\kappa T/h$ ($6 \times 10^{12}\ \mathrm{s}^{-1}$, 25 °C), this will almost always be the case, so that the use of eq 6 will introduce no serious error beyond the inherent limitations of Marcus' theory. Note that the curvatures predicted by eq 1 and 6 are always identical since (6) implies that proton transfer is rate limiting in a strict sense.

(60) If $k_b = (\kappa T/h)e^{-\Delta G^{\ddagger}/RT}$ and $k_{-b} = (\kappa T/h)e^{-(\Delta G^{\ddagger} - \Delta G^{\circ})/RT}$, then $(\partial k_b/\partial k_{-b})_{T,P} = (k_b/k_{-b})\alpha/(\alpha - 1)$, where $\alpha = (\partial \Delta G^{\ddagger}/\partial \Delta G^{\circ})_{T,P}$. The expression for $(\partial k_b/\partial k_{-b})_{T,P}$ can be substituted into eq 11 of ref 24 to yield $\alpha_{\mathrm{exp}} = (k_{-a}k_c\alpha + k_{-b}k_{-a})/(k_{-a}(k_{-b} + k_c) + k_bk_c)$, which for $k_{-a} \gg k_b$ simplifies to eq 5. If $k_c \gg k_{-b}$, $\alpha_{\mathrm{exp}} = \alpha k_{-a}/(k_{-a} + k_b)$. Note that eq 5 does *not* depend on Marcus' theory and that the only restriction on α is that α exist. The analogous relation between $(k^{\mathrm{H}}/k^{\mathrm{D}})_{\mathrm{obsd}}$ and $k_b{}^{\mathrm{H}}/k_b{}^{\mathrm{D}}$ is given by $(k^{\mathrm{H}}/k^{\mathrm{D}})_{\mathrm{obsd}} = (k_b{}^{\mathrm{H}}/k_b{}^{\mathrm{D}})(k_{-a}(k_{-b}{}^{\mathrm{D}} + k_c) + k_b{}^{\mathrm{D}}k_c)/(k_{-a}(k_{-b}{}^{\mathrm{H}} + k_c) + k_b{}^{\mathrm{H}}k_c)$.

(61) An important question is whether the present results will be altered by replacing Marcus' theory with one of several alternative models which have been proposed (ref 9b, 12b, 13b, 20, 21, 23, 55–58). No comment will be made on the relative merits of these proposals, but it is well known that most of the alternatives give quantitative results which are not substantially different from Marcus' theory. If the analytical expressions for these alternatives are rewritten as expansions in terms of ΔG°, this similarity can be verified, and the near-linear dependence of log k_c and $\Delta G_0^{\ddagger}$ noted in Figure 1b for Marcus' theory is found for these other expressions. This suggests that the correlation between intrinsic curvature and kinetic curvature seen in Figures 1–4 is not unique to the particular form of Marcus equation.

(62) Many elegant methods for detecting internal return have been developed, including techniques based on isotopic scrambling and racemization,[38,39] relationships between hydrogen, deuterium, and tritium isotope effects,[32] and viscosity correlations.[36-38] These approaches often permit determination of ratios of rate constants (e.g., k_{-b}/k_c), but do not easily allow independent evaluation of k_c. Furthermore, when internal return is due to strong molecular association, rather than solvent "cage" effects, correlations with solvent viscosity may not necessarily be observed.

(63) There are two points worth noting about eq 5. First, the ratio k_{-b}/k_c is sufficient to obtain α from α_{exp}. In principle, several α's at different p*K*s could be used to calculate $\Delta G_0^{\ddagger}$. However, an independent check on $\Delta G_0^{\ddagger}$ at each point would require the ratio k_{-b}/k_c *and* either k_{-b} or k_c. These rate constants are not obtainable by the normal methods of detecting internal return.[62] The second point is that the discrepancy between α and α_{exp} can be much more significant than that between log k_b and log k_{obsd}. For example, if $k_{-b}/k_c = 1$, log k_b and log k_{obsd} may differ by only 0.3 log unit. The difference between α and α_{exp} is dependent on α. For $\alpha = 0.1$ and $k_{-b}/k_c = 1$, α_{exp} is 0.55. This corresponds to a relative error of 550%.

(64) The geometric distortion(s) could encompass displacement of solvent as well as changes in the internal coordinates (bond lengths, bond angles) of the reactants.