and $CO-Pd^{47}$ systems, are examples of cases where the "structural" factor is of only minor importance. However, the equilibration of H_2 and D_2 on Pt is dependent on crystal face,[48] and preliminary evidence indicates that the interaction of ethylene with single crystal faces of platinum can be quite complex.[49] In contrast to the case of tungsten, where ethylene decomposition is concerted, similar decomposition on platinum occurs both by a concerted process and by a two-step process involving an acetylenic intermediate.[49]

Thus, it is clear in the case of tungsten that extensive crystal face dependence exists, and one may speculate that the face dependence may not be as extensive in the case of the fccub metals. However, there is just not enough evidence at the moment to make clear correlations of this type.

(43) K. Christmann, O. Schober, G. Ertl, and M. Neumann, *J. Chem. Phys.*, 60, 4528 (1974).

(44) J. C. Tracy, *J. Chem. Phys.*, 56, 2748 (1972).

(45) H. H. Madden, J. Kuppers, and G. Ertl, *J. Chem. Phys.*, 58, 3401 (1973).

(46) H. Conrad, G. Ertl, and E. E. Latta, *Surface Sci.*, 41, 435 (1974).

(47) H. Conrad, G. Ertl, J. Koch, and E. E. Latta, *Surface Sci.*, submitted for publication.

(48) K. E. Lu and R. R. Rye, *Surface Sci.*, in press.

(49) K. E. Lu, Ph.D. Thesis, Materials Science Center Report, Cornell University, Ithaca, N.Y.

What Makes Proton Transfer Fast?

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Proton transfer is an elementary chemical reaction of undeniable importance. It must occur, for example, in all changes which are catalyzed by Brønsted acids or bases, and acid–base catalysis of this sort is probably the most common means by which a chemical or biological reaction may be facilitated.

A central issue in the study of proton transfer concerns its rate: just what is it that makes some proton transfers fast while others are slow? This question has occupied the minds of a number of chemists for many years, and much insight into the matter has been obtained.

We, ourselves, have been especially interested in the effect of charge delocalization on the rate of proton transfer and the relationship which this bears to the identity of the atoms between which the transfer is taking place. Factors such as these may be classified as purely kinetic, but, before their importance can be assessed, thermodynamic effects must also be taken into account, i.e., allowance must be made for the extra drive a reaction might receive because it is exothermic or the impediment it suffers when it is endothermic.

Fast Proton Transfer to Carbon

It is common experience that proton transfer between electronegative atoms such as oxygen or nitrogen is very fast whereas that involving carbon is usually quite slow. This would seem to be related to the fact that the electron pair which receives the proton onto an oxygen or nitrogen base is generally localized on a single atom, as in ammonia or amines. The corresponding pair of a carbon base, on the other hand, except in unusual circumstances, is strongly delocalized away from the atom to which the proton becomes attached; this is so, for example, in nitronate and enolate ions, the reprotonations of which are classic examples of slow proton transfer.

If delocalization is indeed responsible for this striking difference in behavior, then confining an electron pair to a single carbon atom should produce a base which behaves like a nitrogen or oxygen species, i.e., which protonates very rapdily. Unfortunately, substances with which this hypothesis can be tested are rare, but some do exist, among them the acetylide ion. When an acetylenic carbon–hydrogen bond ionizes as an acid, the electron pair is left behind in an sp hybrid orbital which is orthogonal to the π system of the carbon–carbon triple bond; in this circumstance charge delocalization cannot take place, and the electron pair remains localized on a single carbon atom.

We began our search for fast proton transfer to carbon by studying the acid–base behavior of acetylenes, choosing phenylacetylene as a representative substrate. This material is an easily handled liquid which reacts with ordinary bases in aqueous solution at convenient rates;[1] these rates, moreover, can be measured readily by using tritium as a tracer (eq 1).

$$C_6H_5C{\equiv}CT + H_2O \xrightarrow{B} C_6H_5C{\equiv}CH + HTO \quad (1)$$
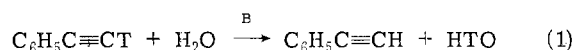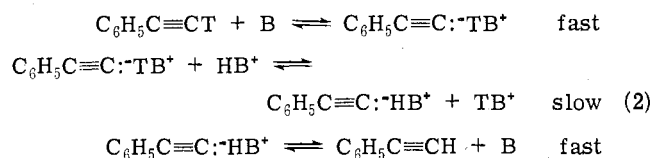
In our hands this hydrogen-exchange reaction proved

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(1) E. A. Halevi and F. A. Long, *J. Am. Chem. Soc.*, 83, 2809 (1961).

to be cleanly first order for as many as 10–12 half-lives. It shows general base catalysis, and the data give a good Brφnsted plot with $\beta = 1.11 \pm 0.04$ for a series of thirteen amines. Furthermore, the reaction occurs with no primary isotope effect: $k_H/k_D = 0.95 \pm 0.09$ for hydroxide ion as the catalyst and 1.2 ± 0.5 for N-methylimidazole.[2]

The absence of a primary isotope effect indicates that proton transfer does not occur in the rate-determining step of this reaction. The large value of the Brφnsted exponent ($\beta \simeq 1$) suggests further that transfer occurs *before* rather than *after* the rate-determining stage, and that leads to the hypothesis that proton transfer is fast and subsequent separation of the proton transfer products, the acetylide ion and the conjugate acid of the catalyzing base, is slow (eq 2).

$$C_6H_5C{\equiv}CT \ + \ B \ \rightleftharpoons \ C_6H_5C{\equiv}C{:}^-TB^+ \qquad \text{fast}$$

$$C_6H_5C{\equiv}C{:}^-TB^+ \ + \ HB^+ \ \rightleftharpoons$$

$$\qquad C_6H_5C{\equiv}C{:}^-HB^+ \ + \ TB^+ \qquad \text{slow} \quad (2)$$

$$C_6H_5C{\equiv}C{:}^-HB^+ \ \rightleftharpoons \ C_6H_5C{\equiv}CH \ + \ B \qquad \text{fast}$$

The exothermic reverse reaction, recombination of an acetylide ion with acid, must therefore be an encounter-controlled process. This conclusion is supported by the fact that the rate constants measured in this study, when combined with $pK_a = 21$ for phenylacetylene,[3] lead to specific rates of recombination which are of the order of $10^{10} \ M^{-1} \ \text{sec}^{-1}$; this is the magnitude expected for an encounter-controlled reaction in aqueous solution at 25°. Since no bimolecular reaction can occur more rapidly than the rate at which its reactants can encounter, it does seem that localization of an electron pair on a single carbon atom has produced a very fast proton transfer reaction.

The reprotonation of carbanions derived from certain cyanocarbons, such as 1,4-dicyano-2-butene or malononitrile and its 2-bromo and 2-*tert*-butyl derivatives, is also a very fast process;[4] it was therefore suggested at one time that these, too, might be encounter-controlled proton transfers to carbon.[4b,c] More recent work, however, has shown that the Brφnsted exponent for detritiation of *tert*-butylmalononitrile-2-*t* is not as great as originally reported.[5] It has also been found that the rate of tritium loss from 1,4-dicyano-2-butene does not respond to changes in solvent viscosity in a manner characteristic of an encounter-controlled process.[6] These new results, of course, are consistent with the fact that the cyano group can stabilize an adjacent negative charge through resonance as well as by a purely polar field or inductive effect. These carbanions, therefore, very probably do not have completely localized electron pairs.

The carbanion derived from chloroform (eq 3), on

$$CHCl_3 \ \rightleftharpoons \ H^+ \ + \ CCl_3^- \qquad (3)$$

the other hand, is a species for which no formal resonance structures can be written. It is significant, therefore, that reprotonation in this case does appear to be encounter controlled. The evidence is much the same as in the case of phenylacetylene: the reaction shows no primary isotope effect (with hydroxide ion as the proton acceptor, $k_H/k_D = 1.42 \pm 0.01$[7] or 1.11 ± 0.05[8]), and it gives a Brφnsted relation with near-unit slope. The latter piece of information was at first based upon a somewhat tenuous argument using medium effects in Me_2SO–water solvent mixtures when a search for general base catalysis in aqueous buffer solutions proved to be fruitless.[7] Since then, however, general base catalysis in wholly aqueous amine buffers has been definitely established,[8] thus substantiating an earlier claim of its existence.[9] A Brφnsted relation with $\beta = 1.15 \pm 0.07$, based upon seven amines, is now available.

These studies demonstrate that proton transfer to carbon can be very fast provided that the electron pair which receives the proton is completely localized on a single carbon atom. Unfortunately, however, they do not establish conclusively that such proton transfers are equally fast as proton transfers to localized pairs on oxygen or nitrogen, inasmuch as all of these localized carbon systems have appreciably exothermic recombination reactions and some of their great rapidity may be just the "extra drive" which exothermicity can bestow upon a chemical reaction. This thermodynamic contribution to reaction rates will now be discussed in more detail.

Thermodynamic Effects

A particularly simple example of a thermodynamic contribution to a reaction barrier may be seen in any endothermic process. Here the free energy of activation must be at least as large as the free energy of reaction, and, provided that the latter is sufficiently great, even an intrinsically very fast process will occur quite slowly. For example, the self-ionization of water, eq 4, is a reaction which is uphill by some 20

$$H_2O \ + \ H_2O \ \longrightarrow \ H_3O^+ \ + \ HO^- \qquad (4)$$
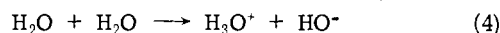
kcal/mol, and this process therefore has a rate constant of the order of $10^{-5} \ \text{sec}^{-1}$ despite the fact that it is a simple proton transfer between two electronegative oxygen atoms.

An obvious way of correcting for this thermodynamic effect is to subtract the free energy of reaction from the free energy of activation. The kinetic barrier, KB, so obtained, however, might still be a poor measure of purely kinetic effects, for it could still be subject to some thermodynamic influence. This, in fact, is just what is required by the Hammond postulate,[10] which holds that activated complexes of strongly endothermic reactions will resemble the reaction products more closely, and thus differ from

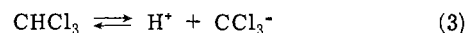(2) A. J. Kresge and A. C. Lin, *J. Chem. Soc., Chem. Commun.*, 761 (1973).

(3) D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, N.Y., 1965, p 48.

(4) (a) E. A. Walters and F. A. Long, *J. Am. Chem. Soc.*, **91**, 3733 (1969); (b) F. Hibbert, F. A. Long, and E. A. Walters, *ibid.*, **93**, 2829 (1971); F. Hibbert and F. A. Long, *ibid.*, **94**, 2647 (1972).

(5) R. F. Pratt and T. C. Bruice, *J. Org. Chem.*, **37**, 3563 (1972).

(6) M. M. Kreevoy, J. Dolmar, and J. T. Langland, 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 26–31, 1973, Abstract No. PHYS-148.

(7) (a) Z. Margolin and F. A. Long, *J. Am. Chem. Soc.*, **94**, 5108 (1972); (b) *ibid.*, **95**, 2757 (1973).

(8) A. C. Lin, Ph.D. Thesis, Illinois Institute of Technology, Chicago, Ill., 1974.

(9) J. Hine, r. C. Peek, and B. D. Oaks, *J. Am. Chem. Soc.*, **76**, 827 (1954).

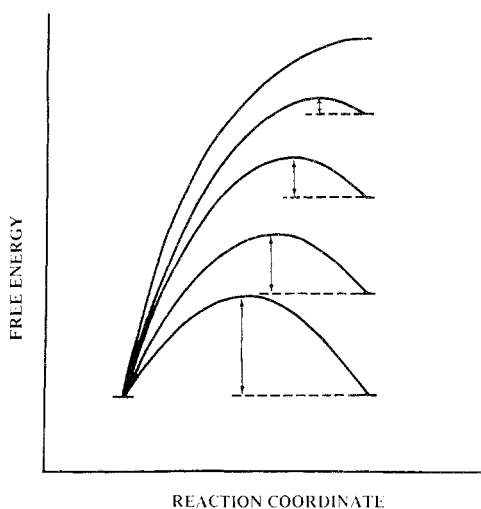(10) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

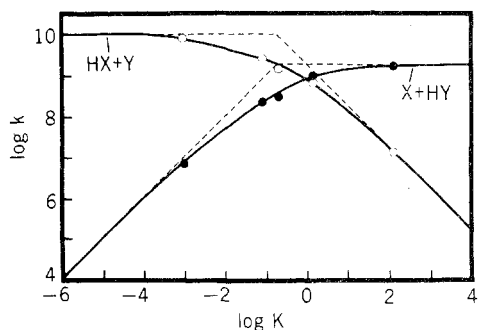**Figure 1.** The Hammond postulate. The arrows indicate changes in the magnitude of the kinetic barrier, KB.

Figure 2. Brϕnsted plot for proton transfer from a series of oxygen acids to ammonia.

Figure 3. Brϕnsted plot for the reaction of carbonyl compounds with bases.

Table I
Aromatic Protonation by the Hydronium Ion

Substrate	$\Delta G^{\circ\,a}$	$\Delta G^{\ddagger\,a}$	$d\Delta G^{\ddagger}/d\Delta G^{\circ}$
Guaiazulene	-4.0	17.0	0.43
Azulene	$+0.6$	19.1	0.47
1,3,5-Trimethoxybenzene	5.0	20.7	0.55
2,4-Dimethoxytoluene	10.9	25.0	0.62
Anisole	18.7	30.0	0.72
Benzene	30.3	38.9	0.87

^{a} kcal/mol.

them less in free energy, than will activated complexes of more nearly thermoneutral systems. Along a series of reactions in which the kinetic factors that contribute to the reaction barrier remain constant, but ΔG° nevertheless increases, KB may therefore be expected to diminish and eventually go to zero. This is shown schematically in Figure 1. Exothermic systems will, of course, give corresponding behavior, inasmuch as they are simply the reverse of endothermic processes, and here KB will therefore also decrease as the system moves away from thermoneutrality; strong exothermicity can thus "pull a reaction along", making it faster than it would otherwise be.

Some insight into whether or not real systems do behave in this way may be obtained by considering processes in which KB does not change with ΔG°. In this situation, $\Delta G^{\ddagger} = \Delta G^{\circ} + $ a constant (KB), and $d\Delta G^{\ddagger}/d\Delta G^{\circ}$ must therefore be either unity (when $\Delta G^{\circ} + $ KB > 0) or zero (when $\Delta G^{\circ} + $ KB < 0 and $\Delta G^{\ddagger} = 0$). These derivatives may of course be identified with the exponents α and β in the Brϕnsted relation, and systems with constant KB should therefore give biphasic Brϕnsted plots with linear arms of unit and zero slope joined by sharply curved transition regions. Such Brϕnsted plots are, in fact, observed in proton transfer between oxygen and nitrogen acids and bases, where KB is effectively zero and therefore constant. An example from the classic work of Eigen[11] is shown in Figure 2, where it may be seen that the transition from unit to zero slope occurs over

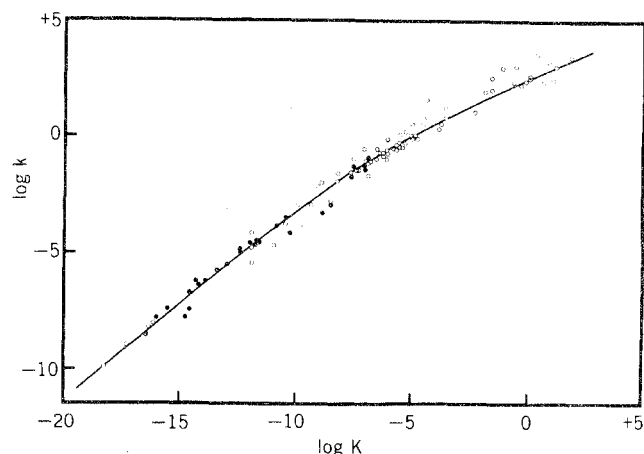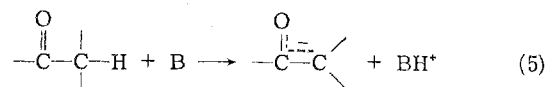(11) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).

the fairly narrow interval $\Delta pK \simeq -2$ to $+2$, which corresponds to a change in ΔG° of only 5 kcal/mol.

Most Brϕnsted plots, of course, are not biphasic. Brϕnsted exponents, moreover, are usually neither zero nor unity: they commonly lie somewhere between these limits and change only slowly. It is not unusual, in fact, to find the variation in exponent over the experimentally accessible range to be so small as to escape detection; it then becomes necessary to change the substrate as well as the catalyst in order to demonstrate curvature.

A well-documented example of this situation is provided by proton transfer from a series of carbonyl compounds to a variety of bases (eq 5); here, $d\Delta G^{\ddagger}/$

$$\underset{|}{\overset{\overset{\displaystyle O}{\|}}{-C}}-\overset{|}{C}-H \; + \; B \; \longrightarrow \; \overset{\overset{\displaystyle O}{\|\cdots}}{-C}-C\overset{/}{\underset{\backslash}{}} \; + \; BH^{+} \qquad (5)$$

$$HAr \; + \; H_3O^{+} \; \longrightarrow \; HArH^{+} \; + \; H_2O \qquad (6)$$

$d\Delta G^{\circ}$ $(=\beta)$ changes from 0.4 to 0.9 over the range $\Delta G^{\circ} = -5$ to $+25$ kcal/mol (Figure 3).[12] Another case is the protonation of a series of aromatic substrates by the hydronium ion (eq 6); some of the data upon which this Brϕnsted relation is based are listed in Table I, where it may be seen that a variation in ΔG° of 35 kcal/mol is required to change $d\Delta G^{\ddagger}/d\Delta G^{\circ}$ $(=\alpha)$ from 0.4 to 0.9.[13]

Slowly curving Brϕnsted relations such as this require KB to be a slowly changing function of ΔG°. This means that, despite the fact that KB is obtained

(12) R. P. Bell, "The Proton in Chemistry", 2nd ed., Cornell University Press, Ithaca, N.Y., 1973, p 203.
(13) A. J. Kresge, S. G. Mylonakis, Y. Sato, and V. P. Vitullo, *J. Am. Chem. Soc.*, **93**, 6181 (1971).

by eliminating ΔG° from $\Delta G^{\ddagger}$, it still contains a thermodynamic component and is only free of all thermodynamic influences when ΔG° itself is zero. If KB is to be used as a reliable measure of purely kinetic effects, it must therefore be corrected for whatever thermodynamic effects it still contains, i.e., it must be converted to the value it would have at $\Delta G^{\circ} = 0$.

A formalism first proposed by Marcus[14] provides a particularly simple way of doing this. Marcus theory expresses the barrier to a proton-transfer reaction, $\Delta G^{\ddagger}$, in terms of ΔG° and just one other parameter, $\Delta G^{\ddagger}_0$ (eq 7). The latter is the value of $\Delta G^{\ddagger}$ at $\Delta G^{\circ} =$

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_0 (1 + \Delta G^{\circ}/4\Delta G^{\ddagger}_0)^2 =$$
$$\Delta G^{\ddagger}_0 + \Delta G^{\circ}/2 + (\Delta G^{\circ})^2/16\Delta G^{\ddagger}_0 \quad (7)$$
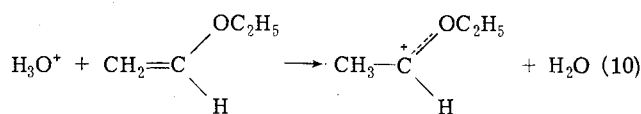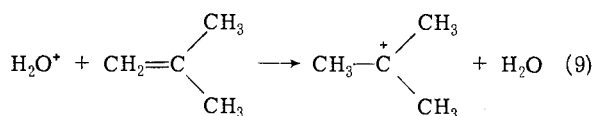
0, which is of course also KB at $\Delta G^{\circ} = 0$, and $\Delta G^{\ddagger}_0$ is therefore just the quantity needed for assessing purely kinetic effects; Marcus, in fact, calls it an "intrinsic" kinetic barrier.

The quadratic form of Marcus' equation is the simplest relationship between $\Delta G^{\ddagger}$ and ΔG° which will give a curved Brønsted plot; it is also consistent with the Hammond postulate, and a simple quantitative interpretation of that postulate in fact leads to the Marcus equation.[15] This equation is also attractive in that it relates the extent of curvature of a Brønsted plot to the speed of the reactions which the plot correlates: eq 8,

$$d^2\Delta G^{\ddagger}/d(\Delta G^{\circ})^2 = d\alpha/d\Delta G^{\circ} = 1/8\Delta G^{\ddagger}_0 \quad (8)$$

which is the second derivative of eq 7, shows that a small value of $\Delta G^{\ddagger}_0$, which through eq 7 corresponds to a small barrier and a fast reaction, gives a rapid change of α with ΔG° (sharp curvature), whereas a large value of $\Delta G^{\ddagger}_0$ gives the opposite behavior. This is consistent with chemical experience: the proton transfers between oxygen and nitrogen acids and bases which give sharply curved Brønsted plots are all very rapid, whereas those proton transfers which provide nearly linear Brønsted plots are invariably quite slow.

It is illuminating to apply eq 7 to the protonation of a carbon–carbon double bond in two different kinds of substrate, isobutylene (eq 9) and ethyl vinyl ether (eq 10). The specific rate of the former reaction

$$H_2O^+ + CH_2=C\begin{smallmatrix}CH_3\\\\CH_3\end{smallmatrix} \longrightarrow CH_3-\overset{+}{C}\begin{smallmatrix}CH_3\\\\CH_3\end{smallmatrix} + H_2O \quad (9)$$

$$H_3O^+ + CH_2=C\begin{smallmatrix}OC_2H_5\\\\H\end{smallmatrix} \longrightarrow CH_3-\overset{+}{C}\begin{smallmatrix}OC_2H_5\\\\H\end{smallmatrix} + H_2O \quad (10)$$

is available from measurements of the rate of acid-catalyzed hydration of isobutylene to tert-butyl alcohol,[16] a reaction known to occur via rate-determining protonation of the carbon–carbon double bond,[17] while the specific rate of the latter is available from studies of the hydrolysis of ethyl vinyl ether,[18] a pro-

Table II
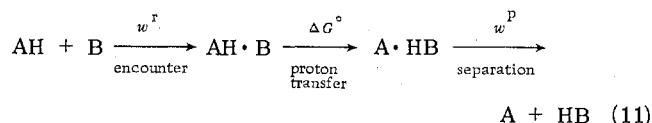### Carbon–Carbon Double Bond Protonation by the Hydronium Ion

Substrate	k, $M^{-1}\,sec^{-1}$	$\Delta G^{\ddagger a}$	$\Delta G^{\circ},{}^a$	$\Delta G_0^{\ddagger}$
Isobutylene	0.00037	22.1	22	6
Ethyl vinyl ether	1.8	17.1	10	12

^{a} kcal/mol.

cess which also occurs by rate-determining double bond protonation.[18,19] The equilibrium constants for these reactions have not been measured directly, but an estimate for the process involving isobutylene has been made using information from related reactions,[20] and a similar treatment has been applied to the protonation of ethyl vinyl ether.[21]

These data are summarized in Table II, where it can be seen that the proton transfer to isobutylene is by far the slower process, by a factor of 5000 in rate constant or a difference of 5 kcal/mol in $\Delta G^{\ddagger}$. The isobutylene reaction, however, is also the more endothermic by a considerably greater margin. The result is that its intrinsic barrier is just half that for the protonation of ethyl vinyl ether, and that makes the latter the intrinsically slower process. This conclusion, perhaps surprising at first, is wholly consistent with the fact that the cation formed in the ethyl vinyl ether reaction is a charge-delocalized species, whereas the charge on the cation formed in the other reaction is formally confined to a single atom.

This example is a somewhat oversimplified application of Marcus theory: it neglects the fact that work must be done to bring the reactants together and that this work will contribute an amount to the reaction barrier which is very likely unrelated to the reaction's exo- or endothermicity. This feature may be taken in to account by using a three-step mechanism to describe the proton-transfer process: (1) encounter of the reactants, (2) proton transfer, and (3) separation of the products (eq 11). The Marcus equa-

$$AH + B \xrightarrow[\text{encounter}]{w^r} AH \cdot B \xrightarrow[\substack{\text{proton}\\\text{transfer}}]{\Delta G^{\circ}} A \cdot HB \xrightarrow[\text{separation}]{w^p}$$
$$A + HB \quad (11)$$

tion (eq 7) is then taken to apply only to the proton-transfer step, but the observed reaction barrier is of course equal to the barrier for this step plus the work term w^r: $(\Delta G^{\ddagger})_{obsd} = \Delta G^{\ddagger} + w^r$. It is possible, by fitting experimental data to a quadratic expression based upon this model, to evaluate both $\Delta G^{\ddagger}_0$ and w^r (and in favorable cases w^p as well).[22]

Several reaction series have now been analyzed in this way; some of the results obtained are collected in Table III. These data offer further evidence for a connection between charge delocalization and intrinsic or purely kinetic reaction barriers. For example, the largest value of $\Delta G^{\ddagger}_0$ listed, 10 kcal/mol, is for ar-

(14) R. A. Marcus, J. Phys. Chem. 72, 891 (1968).

(15) J. R. Murdoch, J. Am. Chem. Soc., 94, 4410 (1972).

(16) F. G. Ciapetta and M. Kilpatrick, J. Am. Chem. Soc., 70, 639 (1948).

(17) A. J. Kresge, Y. Chiang, P. H. Fitzgerald, R. S. McDonald, and G. H. Schmid, J. Am. Chem. Soc., 93, 4907 (1971).

(18) A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, J. Am. Chem. Soc., 93, 413 (1971).

(19) P. Salomaa, A. Kankaanpera, and M. Lajunen, Acta Chem. Scand., 20, 1790 (1966); A. J. Kresge and Y. Chiang, J. Chem. Soc. B, 53, 58 (1967); M. M. Kreevoy and R. Eliason, J. Phys. Chem., 72, 1313 (1968).

(20) N. C. Deno, Prog. Phys. Org. Chem., 2, 136 (1964).

(21) P. Salomaa and A. Kankaanpera, Acta Chem. Scand., 20, 1802 (1966).

(22) A. J. Kresge, Chem. Soc. Rev., 2, 475 (1973).

Reaction	$\Delta G_0^{\ddagger\ a}$	$w^{r\ a}$
1. Aromatic protonation	10	10
2. Ionization of carbonyl compounds[c]	8	6
3. Dehydration of acetal-dehyde hydrate[d]	5	13
4. Protonation of diazo compounds[e]	1–5	8–14
5. Proton transfer from acetic acid or phenol to "normal" oxygen and nitrogen bases[f]	2	3

[a] kcal/mol. [b] Reference 13. [c] Reference 12. [d] R. P. Bell and W. C. E. Higginson, *Proc. R. Soc. London, Ser. A,* 197, 141 (1949). [e] Reference 24 and W. J. Albery, A. N. Campbell-Crawford, and J. S. Curran, *J. Chem. Soc., Perkin Trans. 2,* 2206 (1972). [f] Data listed in ref 12, p 128, compiled from ref 11, M. Eigen, *Pure Appl. Chem.,* 6, 97 (1963), and M. L. Ahrens and G. W. Maass, *Angew. Chem., Int. Ed. Engl.,* 7, 818 (1964).

omatic protonation, a reaction which destroys a benzene or other aromatic ring and gives a highly delocalized cation. Protonation of a diazo compound, on the other hand, involves much less electronic reorganization, and $\Delta G^{\ddagger}_0$ is only 1 to 5 kcal/mol. The ionization of carbonyl compounds, in this case mostly β-diketones and β-keto esters, occupies an intermediate position.

The dehydration of acetaldehyde hydrate provides an apparent exception to this general trend, inasmuch as little delocalization is involved and yet $\Delta G^{\ddagger}_0$ = 5 kcal/mol. There is good evidence, however, that this reaction occurs through a cyclic transition state which includes the catalyst, the substrate, and at least one more water molecule;[23] this reaction is therefore slowed by the need for considerable heavy atom reorganization rather than charge delocalization.

The last entry in Table III represents proton transfer between normal oxygen and nitrogen acids and bases. This process is generally considered to require no activation energy and thus to be completely encounter controlled. It is interesting, therefore, that this analysis gives this reaction an intrinsic barrier of 2 kcal/mol, which is less, but not much less, than the barrier for diffusion of simple molecules in aqueous solution at 25°.

Perhaps the single most striking feature of the results presented in Table III is the magnitude of w^r: except for the last entry, this parameter has values which are much too large to represent simple encounter of two reactant molecules. It has been proposed, therefore, that this term includes also the energy needed to convert an encounter complex into a reaction complex, i.e., to orient an already juxtaposed reactant pair properly so that proton transfer may take place.[24] For reactions between normal acids and

carbon bases, such as entries 1, 2 (reverse process), and 4 of Table III, this will involve, among other things, removal of a solvent molecule which is hydrogen bonded to the acidic site of the proton donor, and replacement of this molecule by the proton acceptor. Since the latter is a carbon base with a delocalized electron pair, no new hydrogen bond will be formed, and w^r will be increased by an amount corresponding to the strength of the hydrogen bond broken; this has been estimated to be of the order of 6 kcal/mol for an ordinary normal acid in aqueous solution.[24] Consistent with this idea is the fact that w^r is only 3 kcal/mol for proton transfer from normal acids to normal bases (Table III, entry 5): here a new hydrogen bond between proton donor and proton acceptor *is* formed, and w^r is therefore reduced correspondingly.

It is likely, however, that real proton transfer reactions do not conform exactly to the simple Marcus equation, and that some of the work terms listed in Table III are therefore greater than true values. This is suggested by some semiempirical theoretical studies in which the proton transfer process was simulated by two intersecting harmonic oscillators[25] and also by the BEBO method.[26] In both cases, relationships between $\Delta G^{\ddagger}$ and $\Delta G°$ were obtained which are more complex than the simple quadratic expression of eq 7. Nevertheless, these relationships are approximately quadratic over much of their range, and data generated by either model can be fitted to the Marcus equation quite successfully. The values of $\Delta G^{\ddagger}_0$ obtained in this way, however, are less than the true intrinsic barriers, sometimes by appreciable amounts. Thus, insofar as these models represent real behavior, simple Marcus theory tends to underestimate $\Delta G^{\ddagger}_0$ and consequently to overestimate w^r.

Although these semitheoretical studies are not in quantitative agreement with simple Marcus theory, they do give the same sort of qualitative relationship between $\Delta G^{\ddagger}$ and $\Delta G°$ as the simple theory predicts; i.e., for a series of closely related reactions, $\Delta G^{\ddagger}$ increases with $\Delta G°$ from a zero or near-zero limit for strongly exothermic systems to a maximum value near $\Delta G° = 0$; beyond this point, $\Delta G^{\ddagger}$ for the reverse reaction decreases until it too approaches a zero or near-zero limit for strongly endothermic variants of the process. There would seem to be no reason, therefore, to doubt the real existence of a purely thermodynamic effect on the rate of proton transfer which makes strongly exothermic and strongly endothermic reactions faster than they would otherwise be.

Slow Proton Transfer to Nitrogen

Corollary to the hypothesis that localization of an electron pair on a single atom can make proton transfer to carbon fast is the idea that delocalization of the basic pair on oxygen or nitrogen might make protonation of these atoms slow. Nitrogen bases would seem the better suited for testing this idea, inasmuch as they, e.g. amines, generally possess only one pair of unshared electrons, whereas oxygen bases, e.g. car-

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boxylate or phenoxide ions, commonly have at least two. We therefore began our study of this aspect of the general problem "What makes proton transfer fast?" by seeking to determine whether or not delocalization of the unshared pair on amine nitrogen can have any appreciable effect on the rate of protonation of such an atom.

We started with a system in which the amine is conjugated with a benzene ring. It is convenient here to use N,N-dimethylaniline rather than aniline itself, for rates of proton transfer can then be determined from the shape of the methyl group NMR signal of the N,N-dimethylanilinium ion: under conditions of rapid exchange of the acidic proton, this signal is a singlet, whereas, when exchange is slow, it becomes a doublet. Rates can be measured by this method with this substrate only in concentrated acid solutions where deprotonation is sufficiently slow, and acidity functions rather than acid concentrations must then be used to analyze the data. Fortunately, an acidity function exactly appropriate to the present situation is available: H_0''' is in fact based upon N,N-dimethylaniline indicators.

This acidity function does correlate the deprotonation rates quite well, but more important than the good linearity shown by the relationship between log k and H_0''' is the fact that its slope is exactly unity: 1.004 ± 0.030.[27] This implies that the transition state of the slow step in the deprotonation process closely resembles the final state of the indicator reaction (eq 12), where the amine molecule has lost its proton

$$C_6H_5NH(CH_3)_2{}^+ \underset{k_{H^+}}{\overset{k_{-H^+}}{\rightleftharpoons}} C_6H_5N(CH_3)_2 + H^+ \quad (12)$$
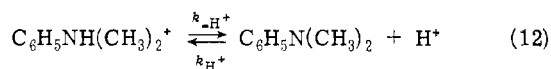
completely. This in turn suggests that proton transfer is complete at the rate-determining transition state, and that can be so only if proton transfer is rapid and separation of the proton-transfer products is slow. Consistent with this conclusion is the fact that extrapolation of the data to dilute solution, and combination of the specific rate of deprotonation so obtained (k_{-H^+}, eq 12) with the acidity constant of N,N-dimethylanilinium ion, gives 4×10^{10} M^{-1} sec^{-1} for the specific rate of recombination, k_{H^+}. This is the order of magnitude expected for an encounter-controlled process.

It is not surprising, in retrospect, that conjugation of an amine electron pair with the otherwise unsubstituted benzene ring should fail to show protonation of the nitrogen atom, for the energy of the resonance interaction here is not very great and delocalization therefore cannot be very extensive. The magnitude of this interaction can be increased somewhat by introducing an appropriate substituent into the para position of the benzene ring; for example, the barrier to rotation about the nitrogen atom–phenyl group bond increases from 5 kcal/mol in N,N-dimethylaniline to 8 kcal/mol in N,N-dimethyl-p-nitroaniline.[28] Preliminary results suggest, however, that the added delocalization afforded by a p-nitro group is still not enough to slow proton transfer appreciably: by both of the criteria used in the case of N,N-dimethylani-

line itself, reprotonation of N,N-dimethyl-p-nitroaniline appears to be an encounter-controlled process.[29]

These experiments with N,N-dimethyl-p-nitroaniline already use the most concentrated aqueous acids which it is practical to employ, and extension of the work to still more highly delocalized, and therefore less basic, anilines is not feasible. It is possible, however, to gain information about proton transfer to another kind of amine nitrogen electron pair where delocalization is quite strong, that of an amide, by combining data already present in several places in the literature. The resonance energy of amides has been estimated at 21 kcal/mol,[30] which is nearly three times that between the amino side chain and the rest of the system in N,N-dimethyl-p-nitroaniline.

Amides protonate predominantly on oxygen in aqueous media (eq 13). The existence of N-proton-

$$\underset{\text{R—C—NH}_2}{\overset{\text{O}}{\|}} + H^+ \longrightarrow \underset{\text{R—C—NH}_2}{\overset{\text{OH}^+}{\|}} \quad (13)$$
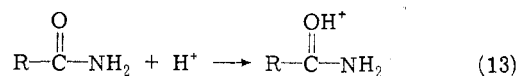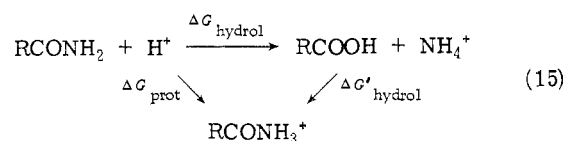
ated conjugate acids as minor species present in low concentration can nevertheless be inferred from, for example, N–H hydrogen-exchange studies. It is possible, in fact, to estimate a pK_a for nitrogen protonation from these exchange rate constants provided that some assumption is made about the specific rate of the reverse reaction, eq 14. When this is set at 10^{10}

$$\underset{\text{R—C—NH}_3{}^+}{\overset{\text{O}}{\|}} + H_2O \longrightarrow \underset{\text{R—C—NH}_2}{\overset{\text{O}}{\|}} + H_3O^+ \quad (14)$$
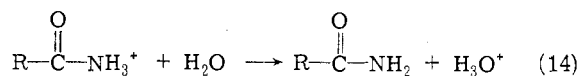
M^{-1} sec^{-1}, which is the value expected if this exothermic process is encounter controlled, the value $pK_N = -8$ is obtained.[31]

Another estimate of this quantity may also be made in a complete different manner by using the thermodynamic cycle shown in eq 15.[32] The free

$$RCONH_2 + H^+ \xrightarrow{\Delta G_{\text{hydrol}}} RCOOH + NH_4{}^+$$
$$\Delta G_{\text{prot}} \searrow \qquad \nearrow \Delta G'_{\text{hydrol}} \quad (15)$$
$$RCONH_3{}^+$$

energies of hydrolysis of unprotonated amides have been determined empirically,[33] and the free-energy change for the reaction in the top line of eq 15, ΔG_{hydrol}, may therefore be calculated. This differs from the free energy of hydrolysis of an N-protonated amide, $\Delta G'_{\text{hydrol}}$, only by the free energy for N-protonation, ΔG_{prot}, and, since $\Delta G'_{\text{hydrol}}$ may be estimated from measurements made on acetylpyridinium ions,[34] the cycle affords ΔG_{prot}. This method also gives $pK_N = -8$ for a simple aliphatic amide.

Since these two estimates of nitrogen basicity are in good agreement with one another, the assumption upon which the first one rests, namely that the deprotonation of an N-protonated amide is an encoun-

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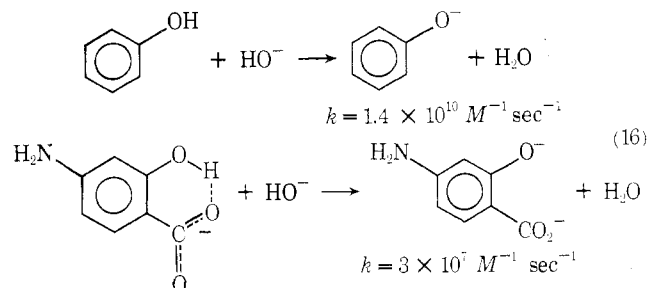(34) A. R. Fehrst and W. P. Jencks, *J. Am. Chem. Soc.*, **92**, 5432 (1970).

ter-controlled process, must be a reasonably good one. It would seem, therefore, that even the fairly extensive delocalization of an amine electron pair present in the amide molecule cannot slow proton transfer to a nitrogen atom very much. This suggests that delocalization is not the only factor responsible for the striking rate difference generally observed between proton transfers involving carbon and those limited to oxygen and nitrogen acids and bases alone, but that some other property of the atoms themselves must be involved as well.

Intramolecular Hydrogen Bonding

Proton transfers involving only oxygen and nitrogen acids and bases can be slowed, sometimes dramatically, by a phenomenon quite different from charge delocalization. It was shown quite early in the study of proton transfer reactions by modern fast reaction techniques that incorporation of an acidic proton into an internal hydrogen bond can slow its rate of transfer to a base by several orders of magnitude.[11] For example, the reactions of phenol and p-aminosalicylate ion (eq 16) with hydroxide are both exother-

mic processes, and yet the specific rate of the latter is three orders of magnitude less than the encounter-controlled rate of the former.[35] Internal hydrogen bonding of this kind may well be responsible for the slowness of the transfer of the second acidic proton from ethylenedinitramine to ammonia, for which a rate constant well below the encounter-controlled limit has been reported despite the fact that this is an exothermic process.[36]

An especially interesting example of the effect of hydrogen bonding on the rate of proton transfer is to be found in the chemistry of Proton Sponge,[37] 1,8-bis(dimethylamino)naphthalene (1). This substance is an unusually strong base—the pK_a of its conjugate acid is 12.3[38]—because the proton accepted is placed in a particularly tight hydrogen bond.[39] That, plus the steric inaccessibility provided by two N,N-dimethyl groups constrained to lie in planes perpendicular to the naphthalene ring, makes removal of this proton quite difficult and therefore slow; for example, the rate constant for proton transfer to the hydroxide (eq 17) is only $2 \times 10^5\ M^{-1}\ \text{sec}^{-1}$.[40]
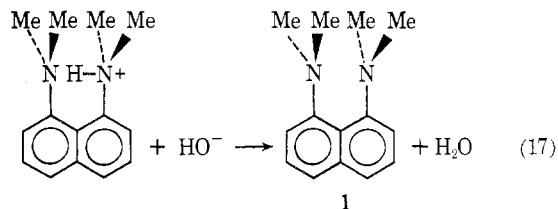
Even greater reluctance to give up protons is shown by the macrobicyclic amines produced by a group at Du Pont[41] and the proton cryptates made by Lehn.[42] Lehn, in fact, reports that the diammonium ion shown in eq 18 remains unchanged after
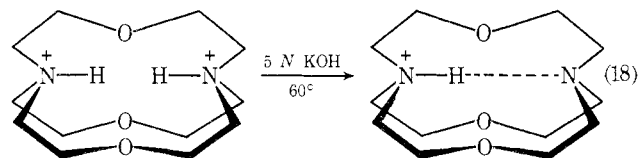
treatment for 18 days with 5 N KOH, but that it does give up a single proton to this reagent at 60° with a half-life of 80 hr.[42] That gives this proton transfer to hydroxide ion a rate constant of $5 \times 10^{-7}\ M^{-1}\ \text{sec}^{-1}$ and puts the reaction barrier some 23 kcal/mol above that expected for an exothermic encounter-controlled process!

Two different hypotheses have been advanced to account for the low reactivity of protons situated in internal hydrogen bonds. One of these assumes the internally hydrogen-bonded acid to be in equilibrium with a species bound externally to a solvent molecule; the latter gives up its proton at an encounter-controlled rate much as any other externally solvated oxygen or nitrogen acid, but the overall rate of transfer is low because the externally bound species is present in low concentration.[12,35] The other mechanism proposes that breaking of the internal hydrogen bond and proton transfer occurs simultaneously through a single transition state. In this transition state, however, the breaking and forming bonds are not collinear, and the geometry is therefore not optimum for a proton-transfer reaction; consequently, the rate is slowed.[43] Definitive evidence to support one or the other of these mechanisms is unfortunately not yet available.[44]

The difference between these two mechanisms is an interesting one. In one scheme, the heavy atom reorganization which must be accomplished takes place *before* the proton begins to move, whereas in the other, the two kinds of motion occur *simultaneously*. This basic distinction, i.e., whether proton transfer to oxygen or nitrogen and heavy atom reorganization take place in a stepwise or a concerted fashion, has been a fundamental issue in acid–base catalysis for some time. The question is as yet far from settled; perhaps a detailed study of the very slow proton transfers afforded by proton cryptates can provide an answer.

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