GENERAL ACID–BASE CATALYSIS OF COMPLEX REACTIONS IN WATER[1]

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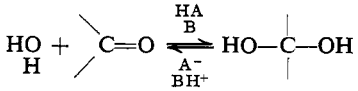
I. Introduction

A large fraction of chemical reactions and an even larger fraction of biochemical reactions involve the >C=O or >C=N– group. Many of these reactions, such as hydration of the carbonyl group (eq 1), involve the reversible addition of a nucleo-



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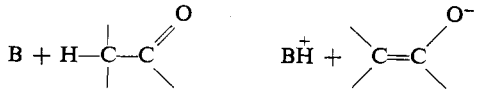
philic reagent to the electrophilic carbon atom and are subject to general acid–base catalysis by increasing concentrations of buffers at constant pH in aqueous solution. Reactions of this kind, in which one or more proton transfers accompany another, often more difficult process such as the making or breaking of bonds to carbon, may be defined as complex general acid–base catalyzed reactions. In simpler reactions, such as the ionization of carbon acids (eq 2), the proton transfer



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itself constitutes the primary reaction and is the only part of the reaction that involves the formation and cleavage of σ bonds in the transition state. In spite of the importance of these complex reactions, the mechanism of their catalysis by simple acids and bases and by enzymes is poorly understood, in large part because they involve the formation and breaking of bonds to as many as five different atoms during a very short period of time. In particular, we would like to know more about the nature of the driving force that is responsible for catalysis of these reactions, the interrelationship between the proton transfer process and the formation or breaking of bonds to carbon, and the way in which changes in one part of the reaction affect the other part. The three-dimensional reaction-coordinate contour diagrams that More O'Ferrall has applied to carbon elimination reactions[2] are very useful in approaching these and related questions, and in this review we propose to describe how these reactions may be examined in terms of these diagrams, making the simplest possible assumptions regarding the nature of the free-energy–reaction coordinate cross sections for the diagrams. We also propose to explore further the proposition that, although hydrogen bonding in the transition state[3] can certainly exist, the driving force for general acid–base catalysis of most complex reactions is more properly described as arising ultimately from the proton transfer process itself.[4,5]

The questions we wish to approach are concerned with how, where, when, and why general acid–base catalysis and its associated proton transfer facilitate complex reactions. Specifically, we would like to know what determines how much of a rate acceleration can be expected from general acid–base catalysis in chemical and enzymic processes and whether a reaction proceeds by specific acid or base catalyzed, uncatalyzed ("water"), stepwise acid–base catalyzed, or "concerted" reaction mechanisms. Must the proton be in a stable potential well in the transition states of these reactions?[3-5] In kinetically ambiguous reactions is there a reasonable basis for predicting which of the kinetically equivalent sites of catalysis will be favored[6-8] (*e.g.*, does catalysis take place in such a way as to avoid the most unstable intermediate? Does catalysis occur "where it is most needed"?). What are the effects of structural changes in the reactants on the mechanism of catalysis and the Brønsted slopes α and β?[6-10] Many of the

(1) This work was supported by grants from the National Science Foundation (GB 5648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD 01247). Publication No. 863 of the Graduate Department of Biochemistry, Brandeis University.

(2) R. A. More O'Ferrall, *J. Chem. Soc. B*, 274 (1970).
(3) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Amer. Chem. Soc.*, **87**, 1553 (1965).
(4) J. E. Reimann and W. P. Jencks, *ibid.*, **88**, 3973 (1966).
(5) R. L. Schowen, *Progr. Phys. Org. Chem.*, **9**, 275 (1972).
(6) C. G. Swain and J. C. Worosz, *Tetrahedron Lett.*, **36**, 3199 (1965).
(7) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 4319 (1962).
(8) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).
(9) G. S. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955).
(10) G. E. Lienhard and W. P. Jencks, *ibid.*, **88**, 3982 (1966).

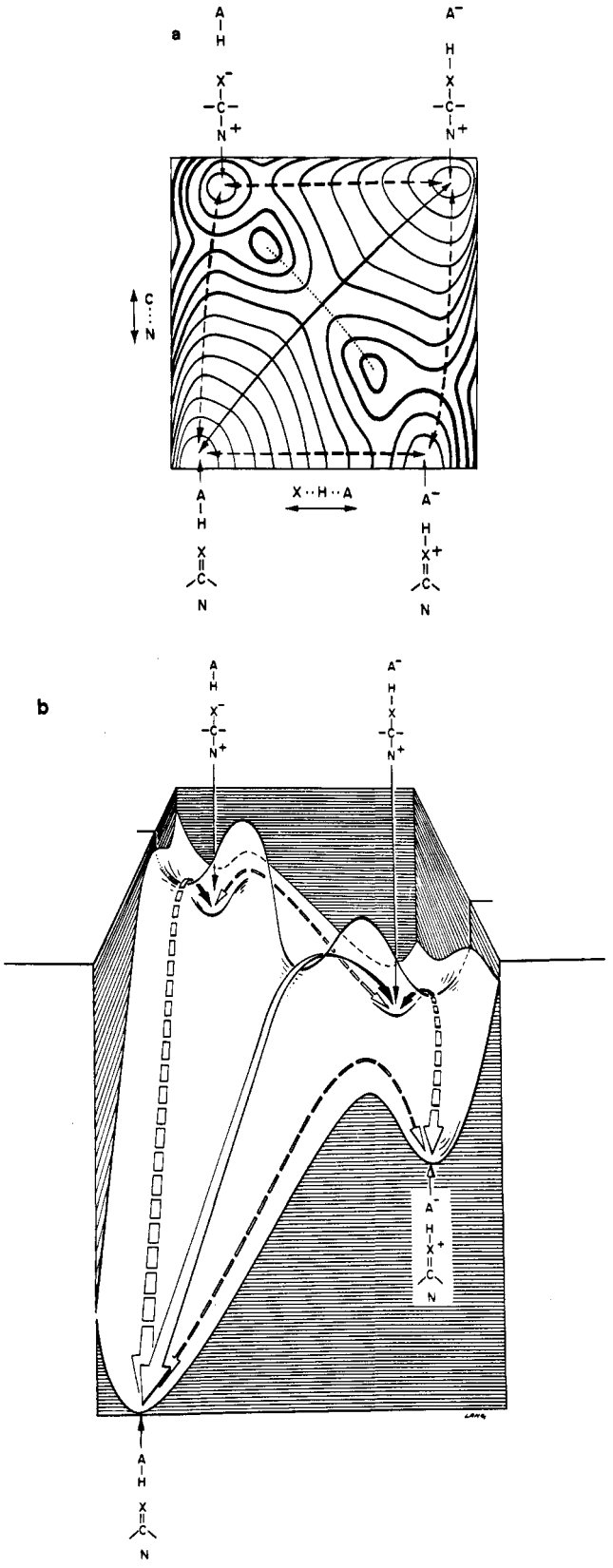
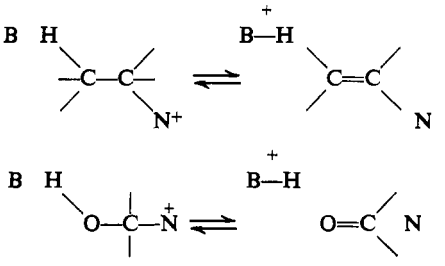


Figure 1. (a) Reaction coordinate contour diagram for the addition of a nucleophilic reagent to an unsaturated center >C=X, such as a carbonyl group, catalyzed by a general acid HA. Motion of the proton is shown on the horizontal axis and formation and cleavage of the carbon–nucleophile bond is shown on the vertical axis. The two intermediates are highly unstable relative to the starting materials and products. (b) A perspective drawing of the contour diagram.

conclusions of this approach may be applied directly to enzymic catalysis of these reactions if it is kept in mind that the environment of the substrate and catalyst in the active site of an enzyme is different from that in aqueous solution and that the geometric relationship of catalytic group and bound substrate may be fixed in the active site, with no need or opportunity for diffusion of one to the other. Carbon elimination reactions (eq 3)[2] are formally similar to the complex reactions we are considering (eq 4) and some of the conclusions may be applied to both classes of reaction.



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II. Three-Dimensional Contour Diagrams

A. DESCRIPTION AND ASSUMPTIONS

The contour diagrams are constructed with separate axes for making and breaking of bonds to the central carbon atom and for the proton transfer process, as shown in Figure 1a for general acid catalysis of the attack of a weakly basic nucleophile, N, on the carbonyl group. The distances along the reaction coordinates parallel to each axis are determined principally by the bond orders of the C–N and H–A bonds, and the position of the transition state along each of these axes is approximately (but not exactly) proportional to the Brønsted α or β coefficient for acid or base catalysis and to the Swain–Scott s parameter[11] or β_{nuc} for the nucleophile (β_{nuc} is the slope of a plot of log k against the pK of the nucleophile). A perspective drawing of the contour diagram is shown in Figure 1b. We will adopt the following simplifying assumptions for the purposes of this discussion. Complex reactions of this kind obviously cannot be described completely or quantitatively with only three dimensions and two reaction coordinates, but the simplifications are not different in kind from those in the widely utilized compression of three-dimensional energy surfaces to two-dimensional reaction coordinate diagrams and, as in the case of the latter diagrams, even grossly oversimplified diagrammatic representations of the reaction course may prove to be useful in the interpretation and prediction of experimental results.

(a) It is assumed that interatomic distances that are not explicitly indicated on the reaction coordinates (the C–X distance in Figure 1a, for example) will adjust to their most stable values.

(b) The three-dimensional surface is constructed from the expected free energy profiles for the stepwise reactions that are shown on the four borders of the square and analogous curves for the cross sections that describe one reaction coordinate at a given position of the other. In Figure 1a, for example, the cross sections for proton transfer along the horizontal reaction coordinate, at varying degrees of C–N bond formation, can represent the double or single potential wells that have been proposed for hydrogen bonds and proton

(11) C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, **75**, 141 (1953).

transfer reactions, but not triple potential wells, such as occur in the cross sections of More O'Ferrall's diagrams for carbon elimination reactions.[2] Similarly, the energy of one reaction coordinate is taken as a simple function of the position of the other; for example, the electron density and basicity of the carbonyl oxygen atom is assumed to reach its maximum value when the carbon–nucleophile bond is fully formed and to be smaller at intermediate degrees of carbon–nucleophile bond formation.[12] This important point is equivalent to the assumption that the transition state can be treated like other chemical species and does not have special properties, such as an enhanced polarizability,[3] that might increase the basicity of this oxygen atom toward the proton. The proton transfer may occur through one or more intermediate water molecules.

(c) Although the diagrams are helpful in visualizing the kinds of processes that can account for catalysis in these reactions, they obviously cannot provide a definitive answer to the difficult problem of defining the exact timing and nature of the processes that occur at or near the rate-determining transition state, such as the nature of the coupling between the motions along the two coordinates. We assume that tunneling of the proton, if it exists, occurs at a rate that can be described by an effective free energy of activation, even though the energy surface separating two potential wells is uncertain. For the purposes of this discussion we will take "concerted" to mean that the rate-determining transition state occurs in the central region of the diagram with significant movement along both coordinates, whereas "stepwise" refers to a reaction that follows a path around the border of the diagram and involves two distinct transition states and an intermediate.

(d) We will assume that an electron-donating substituent on a nucleophile increases its basicity, its nucleophilicity, and the stability of the immediate product of nucleophilic attack (in the absence of proton removal). Reactions in which these properties are not correlated can be considered in the same way, but are likely to be more complicated.

B. PROPERTIES OF THE DIAGRAMS

Two related conclusions follow immediately from the diagram of Figure 1a.

1. A Concerted Reaction Mechanism

A concerted mechanism of catalysis that follows a diagonal path across the diagram is possible, at least in principle, without postulating any special stabilization of hydrogen bonds in the transition state. The proton in this diagram is, in fact, at an energy *maximum* in the transition state with respect to movement along the horizontal axis between the carbonyl oxygen atom and the catalyst. This diagram, then, serves to illustrate an earlier proposal that the primary reason for the existence of concerted general acid–base catalysis lies in the avoidance of the highly unstable intermediates, and the transition states leading thereto, that would be required in the absence of such catalysis.[4,13,14] The reaction follows the lowest energy path between the Scylla and Charybdis of the two unstable intermediates and the energy minimum in the saddle point for this concerted pathway lies along the diagonal dotted line between the quite *different* transition states for the two stepwise, uncatalyzed reaction pathways. Thus, the energy for the dissociation of a hydrogen bond in the transition state (as measured along the horizontal axis) is not necessarily a relevant quantity; what one usually wishes to compare is the energy of the transition state for a concerted reaction with the energies of the different transition states for uncatalyzed or stepwise reaction paths. This point should be kept in mind when calculating the equilibrium constant for the dissociation of a proton or other catalyst from a transition state.[3,15] The basicity of the oxygen atom in the transition state of the concerted catalyzed reaction of Figure 1, for example, is very different from that in the transition state of either of the stepwise pathways with their different degrees of carbon–nucleophile bond formation. Since it is known that hydrogen bonds between two solute molecules in aqueous solution have little or no net stability (because of competition from the solvent), it is reassuring that there is a mechanism for catalysis by general acids and bases that does not depend on the stability of such hydrogen bonds.

Reactions which might be described by the diagram of Figure 1a, with concerted acid–base catalysis, include the addition of urea, thiourea, and water to aldehydes catalyzed by carboxylic acids and other moderately strong acids.[16–18] Catalysis of these reactions by carboxylic acids, which do not have pK values near the pK of the reactants or products, exhibits linear Brønsted correlations with α values in the range 0.27–0.45, rather than the values approaching 0 or 1.0 that are expected for a stepwise reaction mechanism with rate-determining proton transfer when there is a large ΔpK between the proton donor and acceptor.[19,20] Concerted catalysis of these reactions serves to avoid the formation of the unstable intermediates N^+—CR_1R_2—O^- and >C=OH^+.

2. Requirements and Asymmetry for a Concerted Mechanism

Unless the two intermediates for the stepwise reaction paths in Figure 1a are highly unstable, concerted catalysis of this kind will not be possible and the reaction will proceed by a stepwise reaction mechanism. Two cases in which the intermediate is not very unstable will be considered separately.

a. Consequences of Stable Intermediates

First, consider the case in which the intermediate is more stable than the starting material or the product. For acid catalysis of carbonyl addition reactions this situation applies to catalysis by any acid, including water, that is less acidic than the hydroxyl group of the product (eq 5, $K < 1$). In this

(12) There are a few situations in which this assumption is not expected to hold. In a (hypothetical) acyl transfer reaction that proceeds through a concerted reaction mechanism without the intermediate formation of a tetrahedral addition compound, for example, the carbonyl oxygen atom would generally be more basic in the transition state than in either the starting material or product. For such a reaction general acid catalysis without net proton transfer is possible, at least in principle.

(13) Essentially the same conclusion has been reached by Hine in another connection.[14]

(14) J. Hine, *J. Amer. Chem. Soc.*, **94**, 5766 (1972).
(15) J. L. Kurz, *ibid.*, **85**, 987 (1963).
(16) R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 1 (1966).
(17) Y. Ogata, A. Kawasaki, and N. Okumura, *Tetrahedron*, **22**, 1731 (1966).
(18) K. Dušek, *Collect. Czech. Chem. Commun.*, **25**, 108 (1960).
(19) M. Eigen, *Angew. Chem. Int. Ed. Engl.*, **3**, 1 (1964).
(20) R. E. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 2358 (1969).

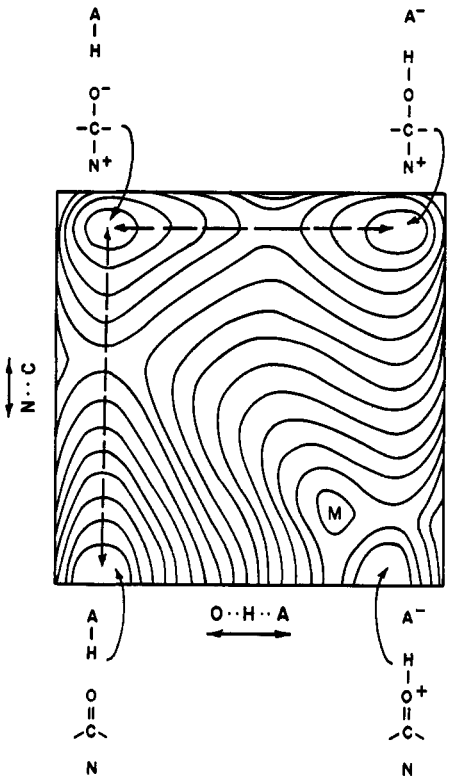


Figure 2. Contour diagram showing the preferred stepwise path for the addition of a nucleophile to the carbonyl group when the catalyst is a weaker acid than the hydroxyl group of the product. M refers to an energy maximum.

$$\overset{+}{\text{N}}\text{—C—O}^- + \text{HA} \underset{}{\overset{K}{\rightleftharpoons}} \overset{+}{\text{N}}\text{—C—OH} + \text{A}^- \qquad (5)$$

situation the energy surface (Figure 2) will have an overall downhill slope from right to left at all N–C distances, and the stepwise will always be favored over the concerted reaction path. In other words, if the free energy of proton transfer from the catalyst to both the starting material and the intermediate is unfavorable, it will also be unfavorable to the transition state, because the basicity of the transition state is less than that of the dipolar product. General acid catalysis by water in the forward direction corresponds to general base catalysis by hydroxide ion of the breakdown of the addition compound in the reverse direction and, as long as the dipolar addition compound has a sufficient lifetime to exist, it is clear that proton removal by hydroxide ion will occur first, in a close to diffusion-controlled reaction, followed by breakdown of the dipolar adduct in a second step. This situation has been summarized in the form of a rule,[21] which states that: *Concerted general acid–base catalysis of complex reactions in aqueous solution can occur only (a) at sites that undergo a large change in pK in the course of the reaction, and (b) when this change in pK converts an unfavorable to a favorable proton transfer with respect to the catalyst; i.e., the pK of the catalyst is intermediate between the initial and final pK values of the substrate site.* The same principle has been used as a criterion to distinguish the preferred site of catalysis in a number of kinetically ambiguous general acid–base catalyzed reactions.[22]

If carbon–nucleophile bond formation is the rate-determining step, the reaction can follow the stepwise path without a requirement for the presence of the catalyst molecule in the transition state. Since the fully concerted reaction path requires the additional loss of entropy for the inclusion of a properly located catalyst molecule in the transition state as well as any additional energy needed to transfer the proton at the same time that carbon–nucleophile bond formation or cleavage is taking place (*cf.* the "principle of least motion"),[23] the concerted mechanism will seldom be significant compared to the stepwise mechanism unless there is a *large* free energy difference (favorable ΔpK) for proton transfer between the intermediates and catalyst, as shown in Figure 1a for catalysis of carbonyl addition reactions by relatively strong acids.

i. Changing pK of the Catalyst. Addition of Hydrogen Peroxide to the Carbonyl Group. If we start with a concerted mechanism that has a large favorable ΔpK for proton transfer and change the pK of the catalyst so that the ΔpK becomes small or changes sign, the free energy of proton transfer will become small or positive and the concerted reaction path should then become insignificant and be replaced by the stepwise path. This provides an explanation for the fact that the points for water and hydroxide ion are frequently found to deviate from Brønsted correlations for a series of general acid or base catalysts. For any carbonyl addition reaction the rule requires that water cannot act as a simple general acid catalyst and hydroxide ion cannot act as a general base catalyst for the addition of a hydroxylic compound through the concerted mechanism. The addition of hydrogen peroxide to *p*-chlorobenzaldehyde, for example, is subject to general base catalysis by carboxylate ions with a β value of 0.66, but the point for catalysis by hydroxide ion shows a large positive deviation from the Brønsted line for the carboxylate ions, suggesting that it proceeds by a different mechanism.[24] General base catalysis by carboxylate ions (eq 6) is consistent with a con-

$$\text{B} + \text{HOOH} + \text{C=O} \rightleftharpoons \text{BH}^+ + \text{HOOC—O}^- \qquad (6)$$

certed mechanism because there is a large ΔpK between the carboxylate ion and both hydrogen peroxide and the intermediate

$$\text{HOO}^+\text{H—C—O}^-$$

However, proton transfer from hydrogen peroxide (pK 11.6) to hydroxide ion is thermodynamically favorable, so that this reaction is expected to proceed through a stepwise mechanism, in this case the uncatalyzed attack of free hydroperoxide ion (eq 7 and 8).

$$\text{HOOH} + \text{OH}^- \overset{\text{fast}}{\rightleftharpoons} \text{HOO}^- + \text{H}_2\text{O} \qquad (7)$$

$$\text{HOO}^- + \text{C=O} \rightleftharpoons \text{HOOC—O}^- \qquad (8)$$

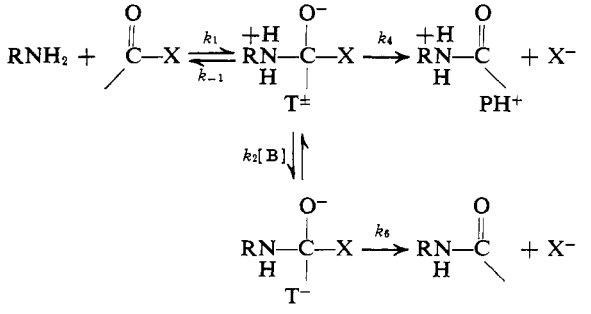
(21) W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 4731 (1972). The rule does not apply to certain diffusion-controlled reactions in which separate proton transfer steps are not possible. It does apply to the separate steps of reactions proceeding through intermediates so long as these intermediates have a significant lifetime; if there are no such intermediates it should be applied to the overall reaction.

(22) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapters 3 and 10.

(23) J. Hine, *J. Org. Chem.*, **31**, 1236 (1966).

(24) E. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 4377 (1968).

ii. Acyl Aminolysis. General base catalysis of acyl aminolysis reactions by a second molecule of the attacking amine should not occur by a concerted mechanism, according to these considerations, if a tetrahedral addition compound is an intermediate in the reaction. The pK of the addition compound $T^{\pm}$ (eq 9) is not very different from that of the protonated



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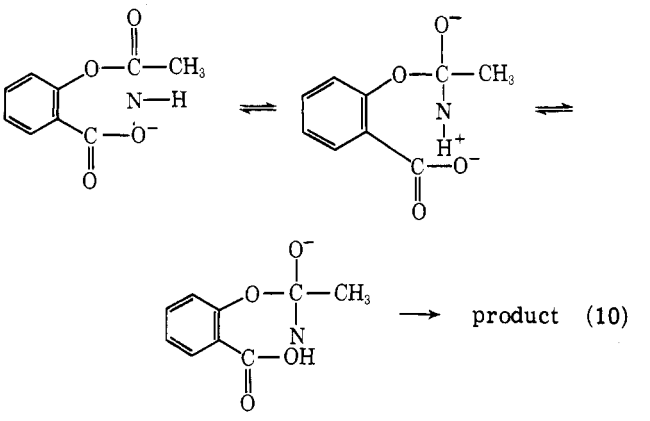
catalyst RNH_3^+[20,25] so that there is not a large favorable free energy for proton transfer to the catalyzing base and concerted catalysis will not ordinarily be expected for either the formation or breakdown of the addition intermediate. Nevertheless, it is highly desirable to remove a proton from the intermediate $T^{\pm}$ at some point in the reaction in order to avoid the formation of the unstable N-protonated amide product PH^+, which has a pK on the order of -7.6.[26] A stepwise mechanism of general base catalysis, through the k_2 and k_6 steps of eq 9, is therefore to be expected and the nonlinear Brønsted plots, with slopes approaching limiting values of 0 and 1.0, that have recently been observed for several such reactions are consistent with such a mechanism.[27] A similar stepwise mechanism has been proposed for the addition of basic amines to carbon dioxide.[28] There is evidence for a stepwise mechanism of general acid catalysis of aminolysis reactions that can be rationalized in the same manner.[20,27,29,30] If, however, the intermediate $T^{\pm}$ or T^- is too unstable to permit proton transfer to take place in a discrete step before its breakdown, a concerted mechanism of catalysis is possible in order to avoid the formation of PH^+ as the first product.

Intramolecular general base catalysis of the reactions of the acyl group of aspirin and related compounds is most important with weakly basic nucleophiles.[31,32] This is expected from the stepwise mechanism of general base catalysis because the weakly basic proton acceptor can easily remove a proton from the addition compound formed from a weakly basic nucleophile (eq 10), but this proton transfer will be thermodynamically unfavorable and correspondingly less important for the addition compound formed from strongly basic nucleophiles.

The interpretation of the "water" reaction in the aminolysis of methyl formate presents a special problem. For aminolysis reactions of acyl compounds with a moderately good leaving



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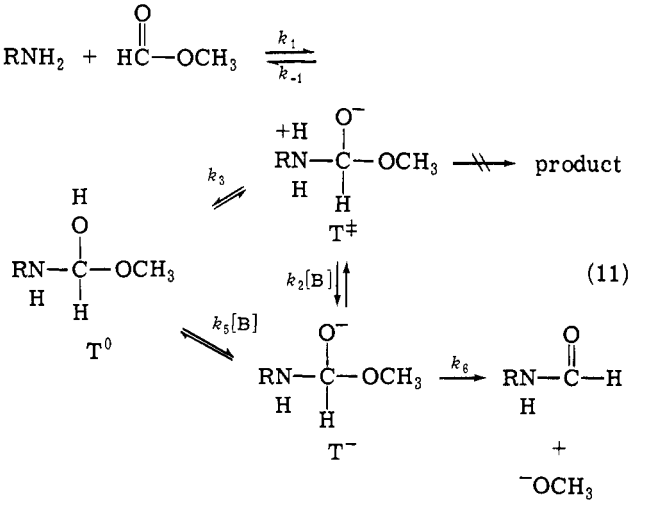
group it may be assumed that the formation of the intermediate (k_1, eq 9) is fast and the rate-determining step is either the uncatalyzed breakdown of $T^{\pm}$ (k_4) or the trapping of $T^{\pm}$ by reaction with an acid or base catalyst. However, methyl formate has a relatively poor leaving group and the breakdown of $T^{\pm}$ cannot be rate determining in the "water" reaction of methyl formate aminolysis because the kinetics of this reaction require that the pH-independent step be followed by a step that involves breakdown of the addition intermediate through an anionic transition state.[33] The water reaction is too fast, relative to the general base catalyzed reaction, to be accounted for as a simple proton removal by water, but a mechanism in which water makes possible the trapping of the intermediate $T^{\pm}$ by conversion to T^0 through a proton switch mechanism followed by a fast proton abstraction (k_3 and k_5, eq 11) provides a reasonable explanation for this reaction. The steady-



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state rate equation for this mechanism is the same as that described previously,[34] and estimated rate constants for the individual proton transfer steps appear to be in the expected range.

These aminolysis reactions are representatives of a class of

(25) J. Hine and F. C. Kokesh, *J. Amer. Chem. Soc.*, **92**, 4383 (1970); J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *ibid.*, **92**, 5194 (1970).

(26) A. R. Fersht, *ibid.*, **93**, 3504 (1971).

(27) J. P. Fox, M. I. Page, A. Satterthwait, and W. P. Jencks, *ibid.*, **94**, 4729 (1972).

(28) M. Caplow, *ibid.*, **90**, 6795 (1968).

(29) R. K. Chaturvedi and G. L. Schmir, *ibid.*, **91**, 737 (1969).

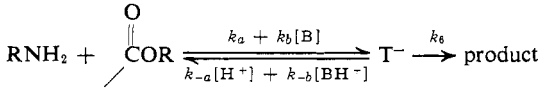
(30) G. M. Blackburn, *Chem. Commun.*, 249 (1970); M. F. Aldersley, A. J. Kirby, and P. W. Lancaster, *J. Chem. Soc., Chem. Commun.*, 570 (1972).

(31) T. St. Pierre and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 3817 (1968).

(32) S. M. Felton and T. C. Bruice, *ibid.*, **91**, 6721 (1969).

(33) G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968).

(34) Since amine addition ($k_1 - k_{-1}$) is fast, the equilibrium for the formation of $T^{\pm}$ may be incorporated into a rate constant and the system described by the simplified equation



as long as the pH or base concentration is sufficiently high that the k_5 step is fast.

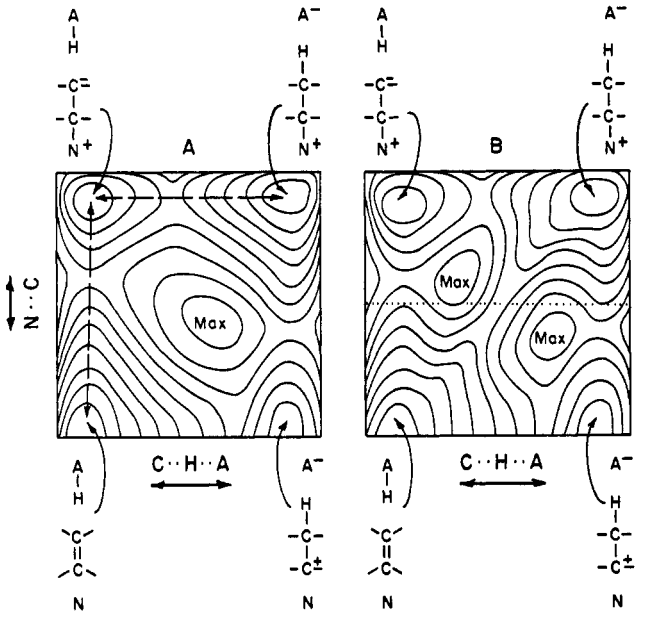


Figure 3. (A) Contour diagram showing the stepwise mechanism for a carbon elimination reaction when the intermediate carbanion is not extremely unstable relative to the starting material. (B) The same system, showing that a triple potential well cross section for motion of the proton (dotted line) is required if a valley corresponding to a concerted reaction mechanism is cut through the central energy maximum of Figure 3A.

multistep reactions in which concerted catalysis of one step is not energetically favorable, but a proton transfer is desirable at some point in the reaction in order to prevent the intermediate from reverting to starting materials and to make possible the formation of a stable product in a subsequent step. This proton transfer occurs in a separate step that may become rate-determining if the intermediate has a short lifetime and is not at equilibrium with the bulk solution with respect to proton transfer.

b. Intermediates of Moderate Stability

i. Requirement for Asymmetry. Second, consider the case in which the intermediates are only moderately unstable relative to the starting material or product. The concerted pathway in the diagram of Figure 1a and in analogous diagrams for carbon elimination reactions is made possible only by the asymmetry of the system that results from the great instability of the intermediates. According to the Hammond postulate and related considerations,[9,35] the transition state of a strongly endergonic reaction will be located in an asymmetric position near the product, and it is precisely this asymmetry that makes possible the concerted reaction path. If the intermediates are not of sufficiently high energy, the transition states for their formation will occur near the center of the reaction coordinates for the stepwise pathways. This is shown in the two vertical axes for N···C bond breaking in Figure 3A for a carbon elimination reaction. This system exhibits an energy *maximum*, with no saddle point, in the central region, so that a concerted mechanism is impossible and the reaction must proceed through a stepwise mechanism. If a channel is cut diagonally through the center of this diagram to permit a concerted reaction mechanism (Figure 3B), triple potential wells are introduced for the cross sections, as shown for the motion of the proton by the dotted line. A triple potential well cross section will be introduced into any system in which the degree of asymmetry is insufficient to prevent overlap in any cross section of the contour lines of a given energy that surround the two energy maxima (compare Figures 1a and 3B). Thus, if the carbanion or carbonium ion intermediate is moderately stable and if triple potential well cross sections are excluded, the reaction should proceed through this intermediate rather than by a concerted E2 elimination, and the geometric properties of these diagrams provide a simple rationale for the long-standing problem of why stabilization of a carbanion intermediate, for example, can make the reaction proceed through this intermediate ("anti-Hammond effect") rather than through a transition state that does not resemble a carbanion ("Hammond effect").[2,36-38]

ii. Stepwise and Preassociation Mechanisms. The stepwise mechanisms, corresponding to the pathways along the borders of the diagrams of Figures 1–3, may be divided into two general classes, depending on which step is rate determining: (1) if the C–N step is rate determining and the proton transfer step is fast, the reaction mechanism ordinarily corresponds to specific acid or base catalysis (*i.e.*, a rapid equilibrium proton transfer) in one direction and no catalysis (a "water" reaction) in the other direction; for the two stepwise paths of eq 12 and 13 for carbonyl addition, this corresponds to the k_1–k_{-1} and the k_4–k_{-4} steps being rate determining. The proton donor or acceptor molecule need not be present in the rate-determining transition state of this mechanism if the intermediates have a lifetime sufficient to allow diffusion away of the catalyst molecule before their breakdown.

$$N + \underset{\diagdown\ \diagup}{C{=}O} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overset{+}{N}{-}\underset{|}{C}{-}O^- \underset{k_{-2}[A^-]}{\overset{k_2[HA]}{\rightleftharpoons}} \overset{+}{N}{-}\underset{|}{C}{-}OH \qquad (12)$$

$$\underset{\diagdown\ \diagup}{C{=}O} \underset{k_{-3}[A^-]}{\overset{k_3[HA]}{\rightleftharpoons}} \underset{\diagdown\ \diagup}{C{=}\overset{+}{O}H} \underset{k_{-4}}{\overset{k_4[N]}{\rightleftharpoons}} \overset{+}{N}{-}\underset{|}{C}{-}OH \qquad (13)$$

However, the possibility also exists that the catalyst is present during the k_1 or k_4 step in an encounter complex or hydrogen bonded to the substrate (preassociation or "spectator" mechanism).[39,40] In the latter case the value of α or β may differ somewhat from 1.0 or 0 as a consequence of this hydrogen bonding.[10,14,41] This mechanism will be preferred when the intermediate is so unstable that it breaks down before diffusion away of the catalyst (for example, when the rate of breakdown of $[^+N{-}CR_1R_2{-}O^-\cdot HA]$ to starting materials is faster than the diffusion away of HA from this complex; *cf.* section II.C.3). Values of α or β near 0.5 are not easily accommodated by this mechanism since they imply a nearly symmetrical hydrogen bond with an effective single potential well, *i.e.*, a concerted mechanism.

(2) In the second class the separate proton transfer step (k_2–k_{-2}) is rate determining for the mechanism of eq 12 (the analogous case for eq 13 is improbable) and the intermediate reacts more rapidly than proton transfer takes place. The pro-

(35) J. E. Leffler, *Science*, **117**, 340 (1953).

(36) J. F. Bunnett, *Surv. Progr. Chem.*, **5**, 53 (1969).
(37) E. R. Thornton, *J. Amer. Chem. Soc.*, **89**, 2915 (1967).
(38) F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).
(39) W. P. Jencks and K. Salvesen, *J. Amer. Chem. Soc.*, **93**, 1419 (1971).
(40) L. D. Kershner and R. L. Schowen, *ibid.*, **93**, 2014 (1971).
(41) J. E. Gordon, *J. Org. Chem.*, **26**, 738 (1961).

ton transfer ordinarily approaches a diffusion-controlled rate in the favorable direction and the Brønsted correlations are nonlinear with α and β values that approach limiting values of 0 and 1.0.[19,20] However, the possibility does exist that linear Brønsted plots with values of α or $\beta \neq 0$ or 1.0 may be observed if the proton transfer itself is rate-determining in a "one-encounter" mechanism that involves two sequential proton transfers without dissociation of the catalyst from the reacting complex[40] or in a preassociation mechanism.[39,40] Kershner and Schowen have suggested that breakdown of the addition intermediate in the alkaline hydrolysis of substituted trifluoroacetanilides occurs through a stepwise mechanism in which proton transfer is mainly rate determining for anilides with relatively basic leaving groups and through a concerted mechanism with solvation of the leaving group when the leaving group is less basic. The former compounds show a small sensitivity of the overall rate to the basicity of the aniline and a positive solvent deuterium isotope effect, whereas the latter group shows a rate increase with electron-withdrawing substituents and a smaller or inverse isotope effect.[40]

C. MODIFICATIONS AND FURTHER CONSIDERATIONS

So far we have considered the rather stringent requirements which may permit concerted mechanisms for reactions in which there is at least a small free energy barrier for both steps of the reaction, *i.e.*, reactions in which the intermediates correspond to energy minima on the diagrams, with a significant barrier for breakdown along either reaction coordinate and a lifetime corresponding to at least a few vibrations. This situation is reasonable for a number of reactions, especially when the proton is bound to carbon and a considerable amount of geometric reorganization of the system is required for its removal. However, concerted mechanisms are more likely to be found in reactions in which there is no significant free energy barrier for one or the other step. When this is the case the intermediates have no finite existence and the reaction must proceed by a more or less concerted, rather than a stepwise, mechanism (although it is not required that both reaction coordinates be at energy maxima, in a fully coupled reaction). This is especially likely for reactions that involve proton transfer to or from atoms, such as O, N, or S, that are known to undergo very rapid proton transfer and that have lone pair as well as bonding electrons, so that different orbitals may be involved in the two parts of the reaction.[2,5,40] The problem is equivalent to the question of whether the cross sections that describe one reaction coordinate (*e.g.*, proton transfer) at different distances along the axis for the other (*e.g.*, the C–N reaction) represent single or double wells.

1. Single Potential Well System

The limiting assumption of no barrier at all for the proton transfer reaction requires that the proton exist at all times in a single potential well that shifts its position of minimum energy steadily during the course of the reaction, as shown in Figure 4A for a carbonyl addition reaction.[10,42] The existence of a symmetrical, single potential well hydrogen bond is very probable for the bifluoride ion,[43] and there is evidence that certain proton transfer reactions between weak bases occur with little or no free energy of activation.[44,45] However, although this limiting case is possible, we do not believe it is general because (a) the great majority of hydrogen bonds between bases of comparable or equal pK are asymmetrical, with the proton located nearer one of the bases,[43] and (b) there is a significant free energy of activation for a proton transfer process that takes place between two bases of equal pK, as shown by the fact that such proton transfers generally occur one or two orders of magnitude more slowly than the rate of diffusion-

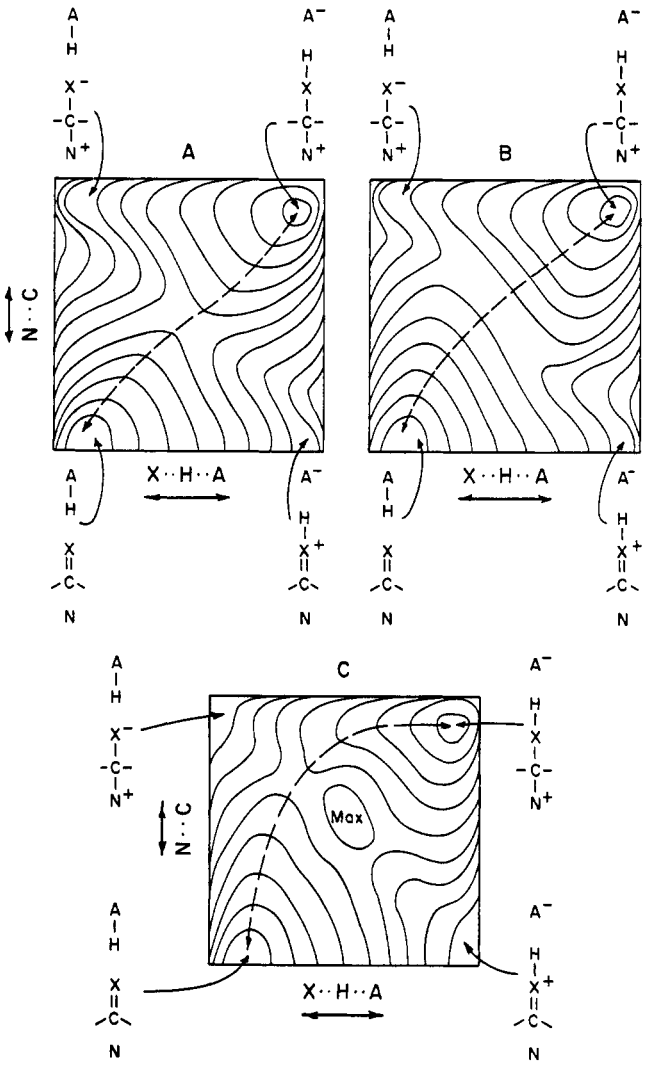


Figure 4. (A) Contour diagram showing the concerted pathway for general acid catalyzed addition to the carbonyl group when the cross section for motion of the proton is a single potential well at all N··C distances. (B) The same system, with no potential barrier for proton transfer when it is thermodynamically favorable but a small barrier when the donor and acceptor atoms are of similar basicity. (C) The same system, but with no activation energy for motion along either reaction coordinate from the two unstable intermediates.

(42) E. H. Cordes, *Progr. Phys. Org. Chem.*, 4, 1 (1967).

(43) G. C. Pimentel and A. L. McClellan, *Annu. Rev. Phys. Chem.*, 22, 347 (1971).

(44) M. M. Kreevoy and C. A. Mead, *Discuss. Faraday Soc.*, 39, 166 (1965).

(45) D. E. Irish and H. Chen, *J. Phys. Chem.*, 74, 3796 (1970).

controlled encounter of the reactants.[19,46,47] An additional opportunity for a free energy barrier arises from the possibility that the most favorable mechanism for proton transfer may well involve one or more intermediate water molecules.

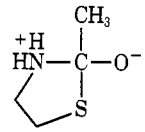
Although the single potential well model for the proton would seem to provide an attractive explanation for the small or negligible solvent deuterium isotope effects that are frequently seen in reactions of this kind,[3,5] there are alternative explanations and the model itself is not entirely adequate in this respect. Small observed solvent deuterium isotope effects may also be accounted for by coupling of the different atomic motions in the transition state,[48] by asymmetry of the transition state,[49] by secondary solvent isotope effects, and by equilibrium isotope effects that precede the rate-determining step;[50] furthermore, the broad potential well in the transition state of Figure 4A will have a low vibration frequency and zero-point energy for the proton which should give rise to a significant isotope effect.

2. *Single and Double Potential Wells. Lifetimes of Intermediates*

An intermediate situation is that in which there is no significant free energy barrier for proton transfer in the favorable direction from a highly unstable intermediate, but a small barrier exists in intermediate regions of the diagram, where the basicities of the donor and acceptor atoms are similar. In this case the proton can exist in either of two valleys that overlap to give a double well cross section for motion of the proton in the central region of the diagram (Figure 4B). This situation is reasonable for many complex general acid–base catalyzed reactions, especially those involving O, N, or S atoms because (a) experimentally, the free energy barrier for proton transfer between appropriately located O, N, or S atoms is small or zero when the proton transfer is strongly favored thermodynamically, because the rate of the observed reaction is limited only by the rate of encounter of the reactants,[19,51] and (b) the calculated potential surfaces for proton transfer reactions in the gas phase between HCl and NH_3 and between hydride ion and several proton donors have revealed no activation energy for transfer in the favorable direction.[52]

The same situation is probable for the carbon–nucleophile reaction coordinate in a number of reactions. For a carbonyl group reaction, for example, this is likely when the nucleophile is weakly basic or the carbonyl group is strongly resonance stabilized, as in an amide, so that the intermediate dipolar addition compound $N^+–CR_1R_2–O^-$ is not stable enough to exist for even a short time. As shown in Figure 4C, the reaction must then proceed by a concerted path in which the catalyst and reactant(s) come together before the transition state for C–N bond formation or cleavage is reached, and the proton transfer is required in order that a stable product may be formed. It should be noted that even though a stepwise process proceeding through an intermediate is not possible in this situation, one, or even both, of the cross sections for the reaction coordinates representing motion of the proton and of the C–N system can exhibit potential wells in the transition state. If the proton is in a potential well, the catalysis could be regarded as a form of "solvation" even though the proton has moved significantly from its position in the starting material. This situation illustrates the difficulty of drawing a sharp dividing line between "concerted" and "stepwise" mechanisms based upon whether or not the transition state corresponds to an energy maximum or minimum for particular atomic motions.

A small extrapolation from the known rates of breakdown of tetrahedral addition intermediates suggests that this case may not be uncommon. For example, the rate constant for



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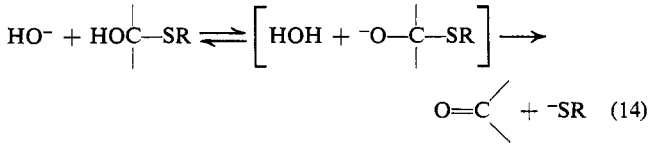
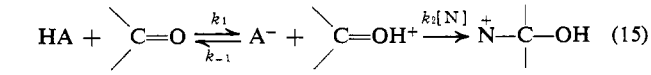
the expulsion of amine from the dipolar addition compound **1** has been estimated[20] to be 6.6×10^8 sec^{-1}, and the adduct of acetaldehyde with acidic thiols breaks down at a diffusion-controlled rate in the presence of hydroxide ion, so that the intermediate anion must decompose more rapidly than the catalyst and substrate diffuse apart (eq 14).[53] Addition com-



(14)

pounds formed from less basic nucleophiles with a smaller affinity toward carbon than sulfur and from acyl and carbonyl compounds with a greater degree of resonance stabilization will be considerably less stable. This instability could account for the occurrence of concerted general base catalysis in the addition of the weakly basic thiourea molecule to formaldehyde,[18] for example.

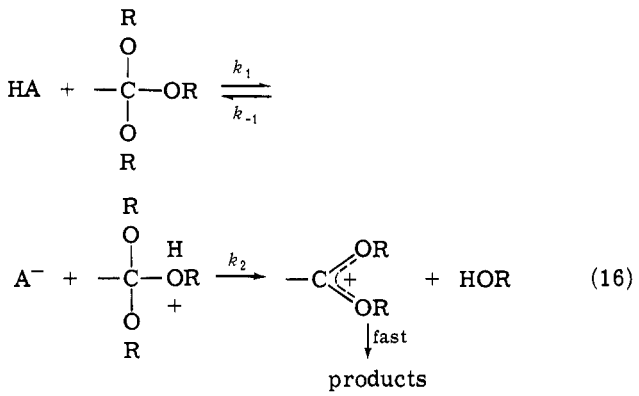
There are other reactions in which the intermediates that would be required for a stepwise mechanism are so unstable that they cannot be formed and react further at a rate that is fast enough to account for the observed overall reaction rate; the free energy for their formation is comparable to or considerably greater than the observed free energy of activation of the overall reaction and rate constants greater than the diffusion-controlled limit would be required to account for the observed reaction rate. Intermediates which have been shown to be unlikely or impossible for this reason include protonated aldehydes in reactions with amines[7,54] (eq 15), protonated



(15)

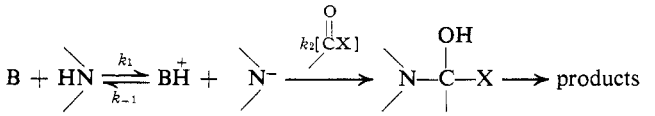
ortho esters and orthocarbonates[55] (eq 16), and anions of aliphatic and aromatic amines as attacking or leaving groups

(46) E. Grunwald and M. Cocivera, *Discuss. Faraday Soc.*, **39**, 105 (1965).
(47) M. L. Ahrens and G. Maass, *Angew. Chem. Int. Ed. Engl.*, **7**, 818 (1968).
(48) A. M. Katz and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **91**, 4469 (1969).
(49) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).
(50) W. P. Jencks, ref 22, Chapter 4.
(51) E. Grunwald, *Progr. Phys. Org. Chem.*, **3**, 317 (1965).
(52) E. Clementi, *J. Chem. Phys.*, **46**, 3851 (1967); C. D. Ritchie and H. F. King, *J. Amer. Chem. Soc.*, **90**, 825, 833, 838 (1968).
(53) R. E. Barnett and W. P. Jencks, *ibid.*, **91**, 6758 (1969).
(54) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5851 (1966).
(55) C. A. Bunton and R. H DeWolfe, *J. Org. Chem.*, **30**, 1371 (1965).



(16)

in transacylation reactions (eq 17) and carbamate formation.[28,33,56]



(17)

The previous conclusion that concerted catalysis will occur only if there is a favorable free energy for proton transfer between the catalyst and the immediate product will generally apply also to these situations; otherwise the valleys of Figures 4A-C would remain on the left-hand side of the diagrams, and no significant stabilization by interaction of the catalyst with either the product or transition state would be expected.

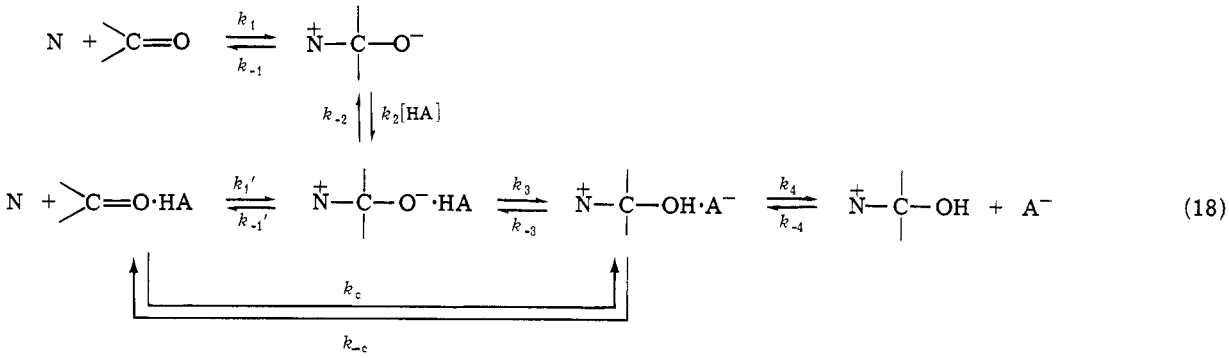
3. *A Limiting Classification o Mechanisms of Catalysis*

All of these examples are consistent with the proposition that the primary driving force for concerted general acid-base catalysis is the avoidance of extremely unstable intermediates. The extreme conclusion that follows from this line of reasoning is that concerted catalysis occurs *only* when intermediates are too unstable to exist for a finite time or to give products at a significant rate without requiring rate constants larger than expected for diffusion-controlled encounter or separation of the reactants. Although this extreme conclusion has certainly not been established, there do not appear to be experimental data available at this time which conclusively demonstrate the occurrence of concerted catalysis in reactions in which the intermediates for the stepwise mechanism have an appreciable lifetime in the presence of catalyst. If the lifetime of the intermediate is the critical factor determining the mechanism of catalysis, these reactions can be divided into four classes.

(1) The intermediate has a lifetime sufficient to allow complete equilibration of proton transfer steps with the bulk solvent without the aid of a general acid or base catalyst. The rate-determining step is C–N bond formation or cleavage and the reaction is uncatalyzed in one direction and is usually specific acid or base catalyzed in the other. For carbonyl addition reactions (eq 18) in which the product $^{+}N–CR_1R_2–OH$ has a pK of 9 (this and subsequent numbers in this section are approximate values, for purposes of illustration), this means that the intermediate $^{+}NCR_1R_2O^{-}$ must decompose to starting materials with a rate constant k_{-1} of less than 10^4 sec^{-1}, since protonation of this intermediate by water will have a rate constant of approximately $55 \times 10^{10} \times 10^{(9-15.7)} = 10^5$ sec^{-1} (from a value of 10^{10} M^{-1} sec^{-1} for the reaction with hydroxide ion and the relationship $k_f = k_r K_{eq}$[19]). The addition of trimethylamine to formaldehyde,[25] with a value of $k_{-1} = 3.4 \times 10^3$ sec^{-1}, is an example of this class.

(2) The intermediate decomposes to starting materials faster than it equilibrates with water, but may be trapped by diffusion-controlled proton transfer involving a general acid or base. This stepwise mechanism with k_2 or k_4 rate determining can occur when the intermediate breaks down with a rate constant $k_{-1} = 10^4$–10^{11} sec^{-1}. This is a reasonable explanation, for example, for the nonlinear Brønsted plot observed in the general base catalyzed addition to *p*-chlorobenzaldehyde of 2-methylthiosemicarbazide,[57] which has a more basic attacking nitrogen atom than thiourea. A change in rate-determining step (to k_1) may occur with increasing catalyst concentration, as has been observed for the addition of amine to a thiol ester.[20]

(3) The intermediate has an extremely short lifetime in the range 10^{-11}–10^{-13} sec, so that the hydrogen-bonded complex $^{+}NCR_1R_2O^{-}\cdot HA$ breaks down to starting materials by expulsion of the nucleophile (k_{-1}') faster than HA diffuses away. If the lowest energy path for breakdown contains the catalyst molecule in an encounter complex, the lowest energy path for the formation of $^{+}NCR_1R_2O^{-}\cdot HA$ must also contain HA initially, from the principle of microscopic reversibility, and the reaction will occur through a preassociation mechanism corresponding to the k_1'–k_{-1}' step of eq 18.



(18)

(4) The intermediate has no significant lifetime (k_{-1} and $k_{-1}' > 10^{13}$ sec^{-1}), so that the reaction can occur only by the concerted reaction mechanism k_c.

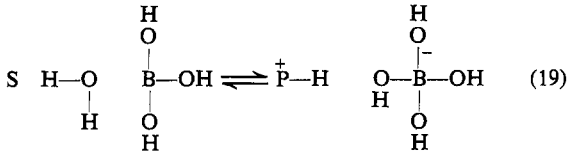
(56) D. R. Robinson and W. P. Jencks, *J. Amer. Chem. Soc.*, **89**, 7088 (1967).

(57) J. M. Sayer and W. P. Jencks, *ibid.*, **94**, 3262 (1972).

4. Catalysis by the Proton and by Boric Acid

One might ask how it is possible for the proton ever to act as a general acid catalyst for carbonyl addition reactions in view of the fact that at sufficiently high acidity the proton can add to the carbonyl group to form its conjugate acid. Under these conditions the protonated carbonyl group is the thermodynamically favored species and, according to the above rule, no concerted general acid catalysis is to be expected. The explanation is presumably that the proton donor is a different species in dilute and in concentrated acid solutions. In dilute solutions the fully solvated proton is a relatively weak acid that does not protonate an ordinary carbonyl group to an appreciable extent at equilibrium, so that concerted catalysis is possible. However, in concentrated acid solutions the protonating species is a much stronger acid, such as H_3O^+ or an undissociated mineral acid that will fully protonate the carbonyl group at equilibrium and concerted catalysis is not expected.

The importance of the proton transfer itself in catalysis provides a possible reason why boric acid is effective as a catalyst for some reactions and not others. Unhydrated boric acid is unlikely to form a hydrogen bond by the mechanism available to most acids, but can act as an effective proton donor by utilizing an intermediate water molecule for the proton transfer process (eq 19).



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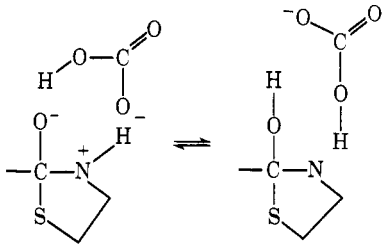
5. Bifunctional Acid–Base Catalysis[58]

These considerations suggest that the requirements for concerted catalysis are more stringent and the occurrence of such catalysis is consequently less widespread than has often been assumed. In particular, it is not surprising that examples of coupled, bifunctional acid–base catalysis in aqueous solution, in which the donation and removal of the two protons occur simultaneously with bond formation or cleavage at carbon, are rare or nonexistent. Such catalysis could involve two different catalyst molecules that are both present in the transition state to give a term in the rate law of the form of eq 20 or it could involve catalysis by a single molecule with sites for both proton donation and removal. In addition to the

$$v = k[S][HA][B] \quad (20)$$

requirements for properly locating one or two catalyst molecules in order that the two coupled proton transfers may take place and for breaking several bonds simultaneously,[23,59,60] such catalysis requires that the requirements of the above rule be met for two sites in the reactant and catalyst and that the free energies for both proton transfers be sufficiently large to provide the stabilization needed for a concerted transition state. These requirements are unlikely to be met often, if ever, but an enhanced activity of bifunctional acid–base catalysts may be observed in two situations.

(1) The two proton transfers take place in a step or steps that occur before or after bond formation or cleavage at carbon. This appears to be the case in the intramolecular aminolysis of thiol esters, in which the positive deviations from the Brønsted plot of 10^2 to 10^4 that are observed for bicarbonate and water have been attributed to bifunctional catalysis of the interconversion of dipolar and neutral tetrahedral addition intermediates (eq 21).[20] It may well be the



(21)

explanation for the special effectiveness of bifunctional catalysts in the expulsion of amine from the tetrahedral intermediates formed from an *N*-phenyliminolactone and trifluoroacetanilide.[61,62] This mechanism will ordinarily give rise to an unusual effectiveness of bifunctional catalysts only when proton transfer by a monofunctional catalyst of the same pK is ineffectual or slow because it is thermodynamically unfavorable (otherwise, both catalysts will react at the same, diffusion-controlled rate).

(2) One proton transfer takes place immediately before or during C–N bond formation or cleavage and the second proton is transferred in a subsequent step without diffusion away of the catalyst molecule; without this second step the reaction would be abortive and any intermediates that are formed would revert to starting materials. A mechanism of this kind may account for the unusual effectiveness of carboxylic acids, compared to the solvated proton, for catalysis of the addition of hydrogen peroxide to *p*-chlorobenzaldehyde. The Brønsted α value for general acid catalysis of the addition of this weakly basic nucleophile is 1.0, suggesting that essentially complete proton transfer from the catalyst has taken place in the transition state. According to one of several possible mechanisms for this catalysis (eq 22), formation of the unstable intermediate **2** is rate determining, but the stable product is formed only after a fast proton transfer to the carboxylate ion (k_2). An electron-donating substituent on the benzaldehyde causes an increase in the rate of breakdown of the addition compound that is too large to be accounted for by proton transfer alone, suggesting that some cleavage of the C–O bond has occurred in the transition state.[24]

A different, but related, mechanism has been suggested for monofunctional catalysts in "one-encounter" reactions in which the reaction is made possible, for example, by proton donation from an acid in one step followed by the removal of a different proton by the conjugate base of the acid before it diffuses away from the reaction complex.[22,63] The individual steps in this type of catalysis are expected to obey the same rules and structure–reactivity relationships as in the simpler

(58) We will use the term "bifunctional" for catalysis that involves both an acid and a base rather than "concerted," which is used in a different sense in this paper.

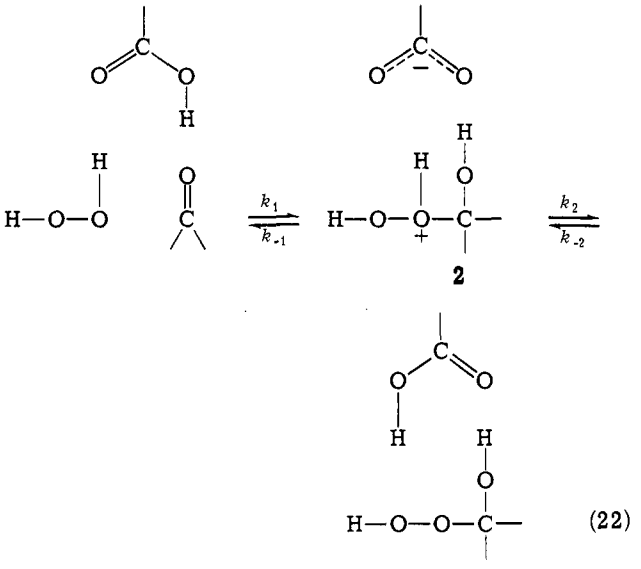
(59) R. P. Bell, J. P. Millington, and J. M. Pink, *Proc. Roy. Soc., Ser. A*, **303**, 1 (1968).

(60) G. E. Lienhard and F. H. Anderson, *J. Org. Chem.*, **32**, 2229 (1967).

(61) B. A. Cunningham and G. L. Schmir, *J. Amer. Chem. Soc.*, **88**, 551 (1966).

(62) S. O. Eriksson, *Acta Chem. Scand.*, **22**, 892 (1968).

(63) M. Eigen, *Discuss. Faraday Soc.*, **39**, 7 (1965).



(22)

mechanisms. Other cyclic reaction mechanisms are possible involving proton transfer through water molecules, even with a monofunctional catalyst.[59,63] Although some of these mechanisms appear to be reasonable, they are too complex to be considered in the present context and it is sometimes difficult to define the driving force for the rate acceleration that is provided by the catalyst.

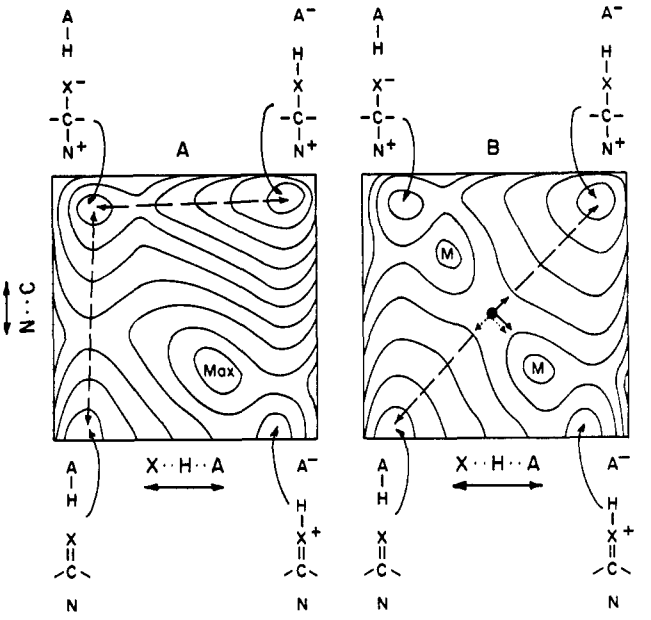


Figure 5. (A) Contour diagram showing the preferred stepwise path for the acid-catalyzed addition of a basic nucleophile to an unstable carbonyl compound to give a dipolar intermediate that is not highly unstable relative to the starting materials. (B) The same system, showing the concerted mechanism for the addition of a weakly basic nucleophile to a more stable carbonyl compound.

III. Structure–Reactivity Relationships

In this section we will consider in more detail the effects of polar substituents on the mechanism of a complex general acid–base catalyzed reaction and the interrelationships between substituent effects on different parts of the reaction. In particular, we would like to know whether there is a rationale for generalizations such as the "solvation rule,"[3,6] the "anthropomorphic rule,"[4] and the Cordes equations[7,8,10] that describe these interrelationships and have been used to distinguish between kinetically equivalent reaction mechanisms. Does the transition state adjust itself to resemble an intermediate or product that is stabilized by a change in substituent (anti-Hammond behavior, effect perpendicular to the reaction coordinate, upward curvature of the potential surface) or does it change so as to resemble an intermediate or product that is destabilized by a substituent effect (Hammond behavior, effect parallel to the reaction coordinate, downward curvature of the potential surface)?[2,9,35,37] There is a shortage of experimental data to provide a basis for answering these questions. Probably the most complete data are available for general acid catalyzed additions of nucleophilic reagents to the carbonyl group, which show a more or less steady increase in the value of α from zero, for strongly basic nucleophiles such as aliphatic amines, cyanide ion, and sulfite dianion, to 0.7–1.0 for weakly basic nucleophiles such as uncharged thiols and hydrogen peroxide.[8,22,64]

The response to a structural change may take two forms which should be considered separately: (1) a change from a concerted mechanism, with a reaction path passing diagonally through the center part of the reaction coordinate diagram, to a stepwise mechanism, with a path around the periphery of the diagram and (2) a change in the position of the transition state in the central region of the diagram for a concerted mechanism. In some cases the effects of substituents are opposite in direction for stepwise and for symmetrical, concerted reaction mechanisms. When this is the case there will be a transition region of asymmetrical transition states in which the opposing effects overlap so that an unambiguous prediction is not possible.

A. CONCERTED *vs.* STEPWISE MECHANISMS

The circumstances under which a change in mechanism is expected have been considered in section II.B.2.a for the case in which a change in the acidity or basicity of the catalyst or reactant leads to a change from a concerted to a stepwise reaction mechanism and *vice versa*. The consequences of other changes in structure are similar, but less obvious. Consider, for example, the attack of a strongly basic nucleophile on the carbonyl group that results in the formation of a relatively stable dipolar intermediate and shows stepwise (if any) catalysis by an acid of moderate acidity (Figure 5A). Now, if the nucleophile is made weaker and less basic, there will be relatively little change in the basicity of the oxygen atom of the dipolar intermediate, which is two atoms removed from the nucleophile, but a change to a concerted mechanism is to be expected as a consequence of product destabilization. The less stable products formed from the weaker nucleophile correspond to an increase in the energy of both addition compounds in the upper portion of the diagram, without a large change in the energy of the proton transfer (Figure 5B). Since the top of the diagram is raised more than the central region, this structural change favors the transition state for the concerted relative to that for the stepwise reaction mechanism. With a further weakening of the nucleophile, the dipolar intermediate will become still more unstable until it finally

(64) L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *J. Amer. Chem. Soc.*, **88**, 2225 (1966).

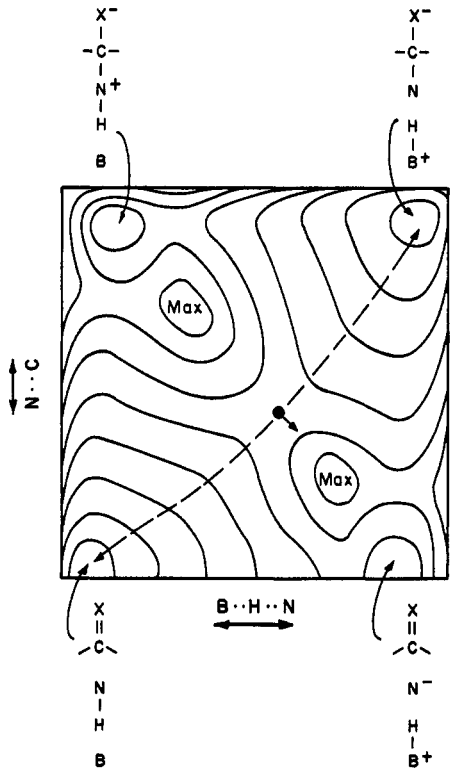


Figure 6. Contour diagram for the general base catalyzed addition of a nucleophile to an unsaturated center, such as a carbonyl group, with a preferred concerted pathway. The arrow shows the expected change in the position of the transition state (perpendicular to the reaction coordinate) when an electron-withdrawing substituent is added to the nucleophile.

ceases to exist as an identifiable species and only a concerted mechanism is possible. The observed change from an uncatalyzed ($\alpha = 0$) mechanism for strong nucleophiles to a general acid catalyzed mechanism ($\alpha > 0$) for weakly basic nucleophiles attacking the carbonyl group is consistent with this interpretation.

B. EFFECTS OF STRUCTURE IN CONCERTED MECHANISMS

1. General Acid Catalysis of Carbonyl Addition Reactions

The changes in the position of the transition state of a concerted reaction that result from structural changes in the reactants and catalyst are correlated by the Cordes equations[7,8,10] and are conveniently discussed in that context. The prediction of substituent effects is far simpler if the shift in position of the transition state is first evaluated in the directions parallel and perpendicular to the more or less diagonal reaction coordinate for the concerted reaction, and then along the individual reaction coordinates for proton transfer and carbon–nucleophile bond formation.[2,37] For example, in addition reactions to the carbonyl group catalyzed by general acids, an electron-withdrawing substituent that causes a decrease in basicity and nucleophilic reactivity, n, of the attacking group will increase the energy of the products and raise the upper half of the diagram of Figure 5B relative to the bottom half, as we have just seen. Such an increase in the energy of the products will move the transition state in the direction along the diagonal reaction coordinate toward the product in the upper right corner, in accord with the Hammond postulate. However, it will also shift the transition state toward the lower right corner in the direction perpendicular to the reaction coordinate; this shift causes the transition state to resemble the intermediate that is stabilized and is in an "anti-Hammond" direction. These shifts are indicated by the solid arrows in the figure. The directions of these shifts are a simple geometric consequence of the curvature of the energy surface of the saddle point in a downward direction from the transition state in both directions along the reaction coordinate and upward in both directions perpendicular to the reaction coordinate.[37] Since both shifts are to the right along the reaction coordinate for motion of the proton the structural change is expected to give a transition state with more proton transfer and a larger value of α (eq 23). However, the two arrows point

$$n_k = c_2(\alpha_0 - \alpha_k) \tag{23}$$

in opposite directions along the reaction coordinate for C–N bond formation, so that the net change in position is ambiguous and no firm prediction can be made regarding the amount of C–N bond formation in the transition state.

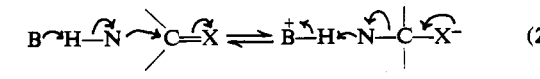
Following the same line of reasoning, an increase in the acidity of the catalyst (decrease in pK_2) will lower the right-hand side of the diagram and shift the transition state toward the lower left (parallel effect) and lower right (perpendicular effect) as shown by the dotted arrows in Figure 5B. This results in an unambiguous movement of the transition state backward along the N···C···X coordinate to give an earlier transition state with less C–N bond formation and a smaller sensitivity s_2 to the nucleophilicity of the attacking reagent, according to the complementary relationship shown in eq 24.

$$pK_2 - pK_1 = c_2(s_2 - s_1) \tag{24}$$

In this case there is no unambiguous prediction for the amount of proton transfer because of the opposing effects of the shifts parallel and perpendicular to the reaction coordinate. This cancellation of effects provides an explanation for the maintenance of a near constant value of α or β over a wide range of variation of the acidity or basicity of a catalyst in some reactions, in apparent contradiction to the Hammond postulate.

2. General Base Catalysis

Analogous considerations apply to structural changes in the general base catalyzed addition of nucleophiles to unsaturated centers (eq 25). These relationships are described by eq 26 and 27, illustrated in Figure 6, and summarized in Table I. The



(25)

$$n_i c_5 = \beta_0 - \beta_i \tag{26}$$

$$pK_2 - pK_1 = c_5(s_1 - s_2) \tag{27}$$

different behavior expected in acid and base catalyzed reactions when the structure of a reactant or catalyst is changed may be utilized as a method for distinguishing between these two mechanisms in cases in which they are kinetically ambiguous, according to the rate law of eq 28. For example, an

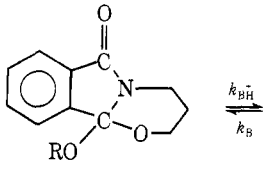
$$v = k_{HA}[HN][>C{=}X][HA] = k_B[A^-][HN][>C{=}X^+H] \tag{28}$$

increase in the basicity and nucleophilicity of the attacking reagent should result in a decrease in α for general acid catalysis and a decrease in β for general base catalysis, according to eq 23 and 26. Since $\beta = 1 - \alpha$ for kinetically ambiguous situations like that in eq 28, the opposite behavior expected for the two mechanisms provides a method for distinguishing between them.[10]

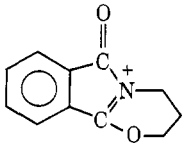
3. *Stabilization or Destabilization of Intermediates*

The prediction of substituent effects that influence principally the stability of the two ionic intermediates at the corners of the diagram is usually unambiguous and much simpler. For example, in the addition of alcohols to carbonyl compounds or imines, an electron-withdrawing substituent on the alcohol will destabilize the cationic intermediate and stabilize the oxyanion intermediate. This lowers the energy of the lower right corner and raises the energy of the upper left corner of the diagram of Figure 6 (a perpendicular effect) and results in an unambiguous increase in anionic character of this group in the transition state as shown by the arrow (increased β for general base catalysis and less C–N bond formation; decreased α for general acid catalysis and more C–N bond cleavage in the reverse direction). This kind of situation provides the simplest example of a transition state adjusting to take advantage of a structural change that stabilizes an intermediate.

An example of this behavior is found in the general acid catalyzed breakdown of the tetrahedral intermediate **3** (eq 29).[65] As electron-withdrawing substituents are added to the



3

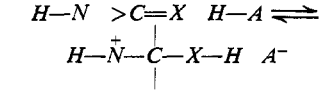


+ ROH $\xrightarrow[\text{fast}]{\text{HOH}}$ products (29)

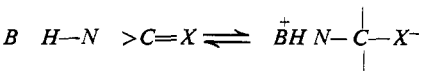
leaving alcohol RO^- in the series ethanol to trifluoroethanol, there is a progressive decrease in the value of α from 0.74 to 0.49 and an accompanying decrease in the relative rate for expulsion of less basic alcohols catalyzed by stronger acids.[65] These are the changes expected from a destabilization of the upper left-hand corner of the diagram of Figure 6. They are described by eq 26 and 27 (keeping in mind that general acid catalysis in one direction is general base catalysis in the other (eq 25) and that $\alpha = 1 - \beta$). The net charge development on the attacking or leaving nucleophile in the transition state of this type of reaction is the resultant of the opposing effects of charge development from the forming and breaking of the N–C and the H–N bonds, so that the absolute sensitivity of the rate to substituents on the nucleophile is likely to be small and may even change sign as the strength of the catalyst is varied. This is observed for the decomposition of **3**, for which electron-donating substituents in the nucleophile cause a small increase in the rate of the proton-catalyzed reaction

Table I

Summary of Predicted Structure–Reactivity Relationships for Concerted General Acid–Base Catalysis



	Proton transfer α	*N–C bond formation*
Electron-donating substituent on N	↓	±
Electron-donating substituent on C		
Case A[a]	↑	±
Case B[a]	±	↓
Electron-donating substituent on X	↑	↓
Electron-donating substituent on A	±	↑

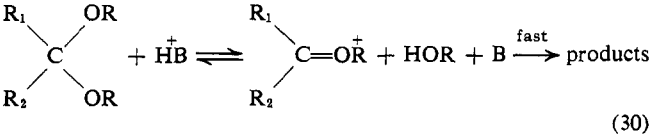


	β	
Electron-donating substituent on B	±	↓
Electron-donating substituent on N	↓	↑
Electron-donating substituent on C	↑	±
Electron-donating substituent on X	↑	±

[a] The effect of an electron-donating substituent on carbon depends on whether it causes a larger change in the energy of >C=X (case A) or H–N⁺–C–X–H (case B). The relative changes in energy will be different, for example, for >C=O and >C=N– (see text).

($\beta_{lg} = +0.2$; β_{lg} is the slope of a plot of log k against the pK_a of the leaving group) and a decrease in the rate of the acetic acid-catalyzed region ($\beta_{lg} = -0.3$). It should be noted that because of these opposing effects the effect of polar substituents in the nucleophile on the amount of C–N bond formation in the transition state is in the opposite direction from that predicted from the Hammond postulate for symmetrical reactions of this type. It should also be kept in mind that the value of β or α for catalysis is in no sense a direct measure of the amount of C–N bond formation or cleavage in the transition state, as is sometimes assumed.[32]

The hydrolysis of acetals and ortho esters (eq 30) is another



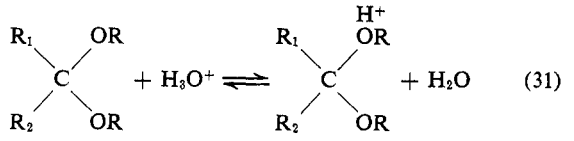
(30)

example of this reaction class. The hydrolysis of acetals is usually specific acid catalyzed (*i.e.*, $\alpha = 1.0$), but general acid catalysis of these reactions becomes detectable (*i.e.*, α decreases to a value well below 1.0) when the leaving group becomes more acidic and when the oxocarbonium ion is stabilized by electron-donating substituents.[66–70] These findings are also understandable from the diagram of Figure 6 if it is assumed that the reactions proceed through a concerted mechanism, since both of these structural changes are expected to move the transition state to the right along the axis for proton transfer. For acetals with a relatively basic leaving group, such as ethanol, there will be little driving force

(65) N. Gravitz and W. P. Jencks, in preparation.

(66) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081 (1968).
(67) E. Anderson and B. Capon, *J. Chem. Soc. B*, 1033 (1969).
(68) R. H. DeWolfe, K. M. Ivanetich, and N. F. Perry, *J. Org. Chem.*, **34**, 848 (1969).
(69) A. Kankaanperä and M. Lahti, *Acta Chem. Scand.*, **23**, 2465 (1969).
(70) T. H. Fife and E. Anderson, *J. Org. Chem.*, **36**, 2357 (1971).

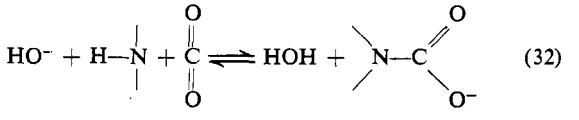
for concerted catalysis by the proton because of the small ΔpK between the catalyst and starting material (eq 31),[71] so



(31)

that the concerted mechanism of catalysis is not likely to be significant unless the oxocarbonium ion is unusually stable.

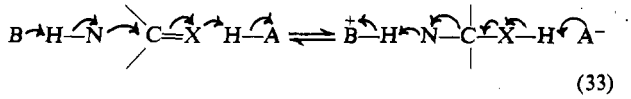
The change in sensitivity to the nucleophile with changing basicity of the catalyst that is predicted by eq 27 is observed in the addition of amines to carbon dioxide.[28] The rate of the hydroxide ion catalyzed reaction (eq 32) shows little or no



(32)

dependence on the basicity of amines of pK 3 to 11, although the "water" reaction shows a large rate increase over the same range. The hydroxide ion reaction probably involves concerted catalysis because the small sensitivity to amine basicity means that proton transfer from $R_2N^+HCOO^-$, in which the nitrogen atom carries a positive charge, is not rate determining and the amine anion is too unstable to be an intermediate.

The role of general base catalysis in this type of reaction is to increase the effective basicity and nucleophilicity of the attacking reagent. We have seen that such an increase will tend to lower the α value for general acid catalysis of the same reaction to a point at which general acid catalysis is not significant or detectable (eq 23). This situation provides



(33)

another reason why concerted bifunctional acid–base catalysis (eq 33) is unlikely to give rise to significant rate accelerations.

4. Other Effects of Structure

The predicted effects of other structural changes are summarized in Table I and in eq 34–39, in which σ and ρ refer

$$\sigma = C_1(\alpha_0 - \alpha_i) \quad (34)$$

$$pK_2 - pK_1 = C_1(\rho_2 - \rho_1) \quad (35)$$

$$\sigma_i = c_4(\beta_0 - \beta_i) \quad (36)$$

$$pK_1 - pK_2 = c_4(\rho_2 - \rho_1) \quad (37)$$

$$\sigma_i = C_3(s_i - s_0) \quad (38)$$

$$n_1 - n_2 = C_3(\rho_1 - \rho_2) \quad (39)$$

to substituent effects on the central carbon atom; they will not be described in detail here. In most cases it is clear from inspection of the appropriate diagram whether an unambiguous substituent effect may be predicted and, if it is unambiguous, what its direction will be for the different components of the transition state. However, in a few cases the predictions may be different for substituent effects on the central carbon atom and may even involve changes in the sign of the constants C or c depending on (a) the amount of destabilization of the starting material relative to the product by electron-withdrawing substituents and (b) the relative amounts of C–N and of X–H bond formation that determine whether the transition state will be in the lower right or upper left portions of the appropriate diagram. For example, the >C=O group is more destabilized by electron-withdrawing substituents than the less electronegative >C=N– group, so that for >C=O reactions the substituent effect will be manifested to a greater extent on the energy of the bottom part of the diagram and for >C=N– reactions the changes in the energy of the right-hand side of the diagram will be relatively more important.

The application of these diagrams and equations to the prediction of substituent effects does not depend on the assumption that the individual reaction coordinate cross sections for both proton transfer and C–N bond formation are at energy maxima in the transition state. As long as the reaction follows a more or less diagonal path across the diagram the predictions should be followed even if the proton is in a potential well in the transition state, because the geometry of the surface surrounding the saddle point requires that the curvature of the surface around the transition state will be downward in the direction of the diagonal reaction coordinate and upward in the direction perpendicular to the reaction coordinate.

These diagrams and predicted substituent effects provide no basis for distinguishing the mechanisms of complex reactions involving N, O, or S atoms from those of carbon elimination reactions[2] in spite of the fact that the poor hydrogen-bonding ability of the C–H group and the availability of lone pair orbitals to interact with protons on O, N, and S atoms suggest that the detailed mechanisms may differ significantly. In cases in which the prediction of a substituent effect is ambiguous because of opposing perpendicular and parallel effects (*e.g.*, Figure 5B) the net effect depends on the degree of curvature of the energy surfaces in the two directions.[37] Although resolution of the ambiguity is possible if the relative amounts of curvature can be estimated, we will not attempt such an estimation here.

Critchlow[72] has independently considered some of the problems considered here, using calculations based on a model in which the component parts of a complex reaction are interrelated by linear energy gradients, and has reached several conclusions similar or identical with those described here.

Acknowledgments. We are grateful to many colleagues, especially Jane Sayer and Ronald Barnett, for helpful discussions, and to Jack Hine and Richard Schowen for communication of manuscripts before publication.

(71) A. Kankaanperä, *Acta Chem. Scand.*, **23**, 1723, 1728 (1969).

(72) J. Critchlow, *Faraday Trans. 1, J. Chem. Soc.*, in press.