

## Enforced General Acid-Base Catalysis of Complex Reactions and its Limitations<sup>1</sup>

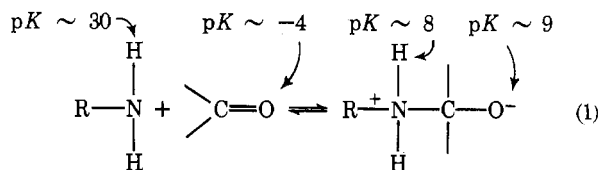
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Many biochemical and chemical reactions involve at least one proton transfer, and the most common mechanism of catalysis of these reactions, by enzymes or in the laboratory, involves some sort of facilitation of this proton transfer.

The driving force for general acid-base catalysis of carbonyl addition and related reactions arises ultimately from the sudden large change in  $pK$  of reacting groups when there is a change in the bonding of heavy atoms, such as the increase in acidity of the amine of some 22  $pK$  units and the increase in basicity of the carbonyl oxygen atom of  $\sim 13$   $pK$  units when an amine adds to a carbonyl group (eq 1). These large changes in



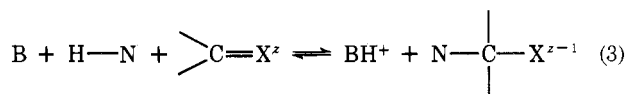
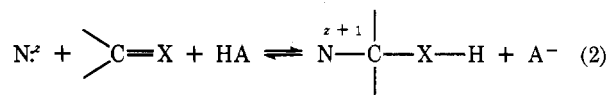
$pK$  commonly give rise to unstable intermediates and transition states, and catalysis can accelerate the reactions either by trapping such intermediates or by stabilizing or by-passing the transition states leading to their formation.

It has not been clear why some reactions of this kind are subject to general acid-base catalysis while others are not, or what is the driving force and maximum rate advantage for such catalysis. The purpose of this Account is to review some reactions in which catalysis *must* occur because of the properties of unstable intermediates.<sup>2</sup> These reactions provide partial answers to the above questions and some insight into the mechanism of general acid-base catalysis.

### Class e-s and n-s Reactions

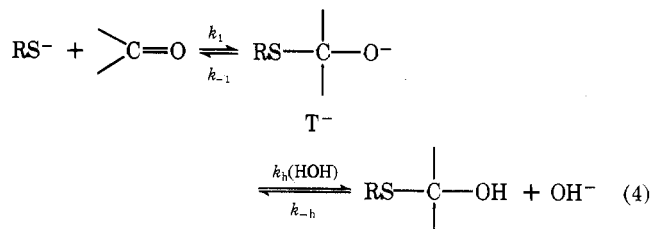
General acid-base catalysis of this type of reaction generally represents either class e reactions (eq 2), in which the catalyst donates a proton to the electrophilic

reagent in one direction and removes it in the reverse direction, or class n reactions (eq 3), in which the cata-



lyst facilitates proton transfer from or to the nucleophilic reagent,  $\text{H}-\text{N}$ .<sup>3</sup> In class e-s and n-s reactions (s refers to a relatively slow proton transfer) the  $pK$  of the initially formed addition intermediate is such that the intermediate is not immediately trapped by proton transfer to or from the solvent; i.e. in e-s reactions the  $pK_a$  of  $\text{N}-\text{R}_2\text{C}-\text{XH}$  is below 14 and in n-s reactions the  $pK_a$  of  $^+\text{HN}-\text{R}_2\text{C}-\text{X}$  is above 0.

**A. Trapping by Simple Proton Transfer.** When a nucleophile is expelled faster than the initially formed addition compound is trapped by solvent-mediated proton transfer there must be catalysis by general acids or bases. Such reactions, in which proton transfer is required to form a stable product, are therefore subject to enforced general acid-base catalysis. Consider the addition of thiol anions to the carbonyl group (eq 4) as



an example of a class e-s reaction. The rate at which the anionic addition intermediate  $\text{T}^-$  is trapped by proton

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(2) For an earlier Account, see R. E. Barnett, *Acc. Chem. Res.*, **6**, 41 (1973); see also L. D. Kershner and R. L. Schowen, *J. Am. Chem. Soc.*, **93**, 2014 (1971).

(3) These designations indicate the site, not the mechanism of catalysis. Class e and n are used in preference to  $\beta$  and  $\alpha$ , respectively (R. L. Schowen, *Progr. Phys. Org. Chem.*, **9**, 275 (1972)) in order to avoid possible confusion with Brønsted coefficients.

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**Table I**  
Examples of Reactions for Which Catalysis Has Been  
Attributed to Trapping

		References
RNH <sub>2</sub> and		
aldehydes	Carbinolamine formation	9, 14
imines		
cyanic acid	Transimination	a
esters	Urea synthesis	15
thiol esters	Ester aminolysis	18
acetylimidazole	Ester aminolysis	16, b
and acetyltriazole	Amide aminolysis	6, c
formamidine		
trinitrobenzenes	Methenyl-THFA model	d
	Nucleophilic aromatic substitution	e
triaryl carbonium ions	Addition to carbon	f
RS <sup>-</sup> and aldehydes	Hemithioacetal formation	4, 13
ROH and thiol esters	Ester hydrolysis	g
amides	Amide hydrolysis	h
C <sup>-</sup> and aldehydes	Aldol condensation	23

<sup>a</sup> J. P. Fox and J. M. Chalovich, personal communication; J. Hogg, D. Jencks, and W. P. Jencks, in preparation. <sup>b</sup> R. K. Chaturvedi and G. L. Schmir, *J. Am. Chem. Soc.*, **91**, 737 (1969); G. M. Blackburn, *Chem. Commun.*, 249 (1970). <sup>c</sup> M. Page and W. P. Jencks, *J. Am. Chem. Soc.*, **94**, 8828 (1972). Although the initial intermediate appears to be trapped by diffusion-controlled encounter with a catalyst, the subsequent breakdown has been attributed to a concerted mechanism. <sup>d</sup> W. P. Bullard, L. J. Farina, P. R. Farina, and S. J. Benkovic, *J. Am. Chem. Soc.*, **96**, 7295 (1974). <sup>e</sup> C. F. Bernasconi and C. L. Gehringer, *J. Am. Chem. Soc.*, **96**, 1092 (1974); C. F. Bernasconi and F. Terrier, *ibid.*, **97**, 7458 (1975). <sup>f</sup> C. A. Bunton and S. K. Huang, *J. Am. Chem. Soc.*, **96**, 515 (1974). <sup>g</sup> R. J. Zygmunt and R. E. Barnett, *J. Am. Chem. Soc.*, **94**, 1996 (1972). <sup>h</sup> D. Drake, R. L. Schowen, and H. Jayaraman, *J. Am. Chem. Soc.*, **95**, 454 (1973); M. F. Aldersley, A. J. Kirby, P. W. Lancaster, R. S. McDonald, and C. R. Smith, *J. Chem. Soc., Perkin Trans. 2*, 1487 (1974).

transfer from the solvent depends on its basicity and is given by  $k_h = k_{-h}K_w/K_a$ , in which  $K_a$  is the acid dissociation constant of the hemithioacetal and  $k_{-h}$  represents the diffusion-controlled abstraction of a proton by hydroxide ion with a value of approximately  $10^{10} \text{ M}^{-1} \text{ s}^{-1}$ . The addition of the weakly basic methyl mercaptoacetate anion to acetaldehyde is subject to general acid catalysis because the initially formed unstable intermediate breaks down to reactants at a rate ( $k_{-1} \approx 2 \times 10^8 \text{ s}^{-1}$ ) that is comparable to the rate at which it is trapped by proton abstraction from water ( $k_h \approx 2 \times 10^8 \text{ s}^{-1}$  determined by its  $\text{p}K_a$  of 12.4).<sup>4-6</sup> Therefore, diffusion-controlled protonation of T<sup>-</sup> upon encounter with a low concentration of a buffer acid provides an additional route to product by trapping the anionic intermediate, and thereby increases the observed rate. The more basic ethanethiol anion is expelled more slowly ( $k_{-1} = 5 \times 10^6 \text{ s}^{-1}$ ), so that every time the anionic intermediate is formed it abstracts a proton from water faster than it reverts to reactants ( $k_h = 7 \times 10^8 \text{ s}^{-1}$ ) and no catalysis is observed.<sup>4,7</sup>

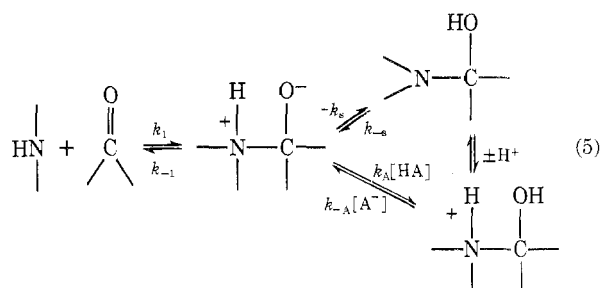
(4) H. F. Gilbert and W. P. Jencks, *J. Pure Appl. Chem.*, in press.

(5) Based on a measured  $\text{p}K_a$  of 12.4 for HOEtSCH<sub>2</sub>OH (R. Kallen, personal communication) and structure-reactivity correlations.<sup>6</sup>

(6) J. P. Fox and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 1436 (1974).

(7) G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3982 (1966).

If the attacking nucleophile contains a proton that becomes acidic when the addition compound is formed, the solvent-mediated proton transfer is likely to occur through a "proton-switch" mechanism with a rate constant,  $k_s$ , of approximately  $10^6$ – $10^8 \text{ s}^{-1}$ .<sup>8</sup> Thus, the zwitterionic intermediate T<sup>±</sup> that is formed from the attack of methoxyamine on *p*-chlorobenzaldehyde (eq 5) abstracts a proton from solvent slowly ( $k_h \approx 3 \times 10^4$



$\text{sec}^{-1}$ ) because of its relatively low basicity but is trapped by a proton switch, probably through two solvent molecules, with a rate constant of  $k_s = 6 \times 10^6 \text{ s}^{-1}$ . Since the intermediate reverts to reactants faster than this, with  $k_{-1} = 3 \times 10^8 \text{ s}^{-1}$ , protonation by buffer acids gives catalysis by trapping.<sup>9</sup> The more stable intermediate that is formed from trimethylamine, a more basic amine, and formaldehyde, a more reactive aldehyde, breaks down to reactants more slowly ( $k_{-1} = 3.4 \times 10^3 \text{ s}^{-1}$ ) and shows no catalysis by trapping because every molecule of intermediate that is formed abstracts a proton from water ( $k_h = 4 \times 10^5 \text{ s}^{-1}$ ).<sup>10</sup>

A group of reactions is listed in Table I for which the observed catalysis has been attributed to trapping by an e-s mechanism or by the corresponding n-s mechanism, in which the addition intermediate is trapped by proton removal after encounter with a buffer base. An important characteristic of such reactions is that their properties, such as structure-reactivity correlations and isotope effects, depend only upon the equilibrium constant for formation of the addition intermediate and the rate constant for proton transfer, not the rate constant for attack of the nucleophile. The following are some examples of the experimental manifestations of this type of catalysis.

(1) The Brønsted slopes  $\alpha$  and  $\beta$  for catalysis by relatively strong acids and bases are close to zero because trapping of the intermediate is diffusion controlled and independent of the  $\text{p}K$  of the catalyst when the proton transfer is strongly favorable thermodynamically. This is observed for catalysis of methoxyamine addition to *p*-methoxybenzaldehyde by protonated amines of  $\text{p}K \leq 7$ , for example (Figure 1).<sup>9</sup> As the  $\text{p}K$  of the catalyzing acid is increased so that the proton transfer becomes thermodynamically unfavorable, the slope of the Brønsted line changes toward a limiting value of  $\alpha = 1.0$  following an "Eigen curve" for simple proton transfer reactions; in this region the rate of the proton-transfer step approaches the diffusion-controlled limit in the reverse direction.<sup>11</sup> The breakpoint in the curve ( $\Delta\text{p}K$

(8) E. Grunwald, C. F. Jumper, and S. Meiboom, *J. Am. Chem. Soc.*, **85**, 522 (1963); E. Grunwald and S. Meiboom, *ibid.*, **85**, 2047 (1963); Z. Luz and S. Meiboom, *ibid.*, **85**, 3923 (1963).

(9) S. Rosenberg, S. M. Silver, J. M. Sayer, and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7986 (1974).

(10) T. D. Stewart and H. P. Kung, *J. Am. Chem. Soc.*, **55**, 4813 (1933); J. Hine and F. C. Kokesh, *ibid.*, **92**, 4383 (1970).

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

= 0, Figure 1) occurs when the  $pK$  of the catalyst is equal to that of the protonated intermediate and the observed break, at  $pK = 8.6$ , is close to the estimated  $pK$  of the intermediate of 9.1.<sup>9</sup> The proton and hydroxide ion exhibit positive deviations of 10–50-fold from such curves because of their faster rates of diffusion-controlled proton transfer.<sup>11</sup> In spite of its apparent simplicity, the demonstration that a Brønsted plot follows an Eigen curve is by no means a trivial matter, largely because of differences in the behavior of different types of catalysts.

(2) As the buffer concentration is increased, the rate of addition of methyl mercaptoacetate to acetaldehyde (eq 4) first increases, but then levels off as all of the molecules of the anionic addition intermediate are trapped by encounter with HA and the observed rate is limited by the rate of the uncatalyzed addition step,  $k_1$ .<sup>4</sup> Such a change in rate-determining step will generally be detectable if the rate constant  $k_{-1}$  is in the region of  $10^9 \text{ s}^{-1}$  or less and provides unequivocal evidence for a two-step reaction and an intermediate if it can be shown that the leveling off is not caused by association of the catalyst or by salt or solvent effects.<sup>12</sup> If the rate constant for the diffusion-controlled trapping step can be estimated, the observation of a change in rate-determining step provides a "clock" that permits the calculation of  $k_{-1}$  and the equilibrium constant  $K_1 = k_1/k_{-1}$ . For example, when the change in rate-determining step and leveling off is half-complete, the intermediate breaks down to reactants and products at equal rates and  $k_{-1} = k_{\text{HA}}[\text{HA}]$ .

(3) The observed rate constants for hydroxide ion catalyzed expulsion of acidic thiols from hemithioacetals (eq 4, right to left) are  $0.8\text{--}1.0 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ , in the range expected for a diffusion-controlled reaction.<sup>4,13</sup> The absolute values of the rate constants estimated from overall equilibrium and dissociation constants for the addition of methyl mercaptoacetate to acetaldehyde and for catalysis of other carbonyl addition reactions in this group are also in the range expected for diffusion-controlled trapping.<sup>4,9,14</sup>

(4) The rate of urea formation from cyanic acid exhibits general acid and base catalysis and a large dependence on the basicity of the attacking amine for weakly basic amines ( $\beta_{\text{nuc}} = 0.8$ ), but no buffer catalysis and a small dependence on basicity for strongly basic amines ( $\beta_{\text{nuc}} = 0.3$ ).<sup>15</sup> Weakly basic amines are expelled rapidly from the unstable zwitterionic addition intermediate to give reactants ( $k_{-1} > k_s$ ), so that the rate is increased by buffer-catalyzed trapping, but strongly basic amines are expelled more slowly, so that the more stable intermediate always goes on to products ( $k_{-1} < k_s$ ) and the rate-determining step changes to the uncatalyzed formation of the intermediate.

(5) Similar absolute values of the rate constants for catalysis by strong acids and bases are found for urea formation from cyanic acid and aniline, as would be expected if both types of catalysis involve diffusion-controlled encounter of the catalyst with the same unstable zwitterionic intermediate,  $T^\pm$ .<sup>15</sup>

(12) E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, **97**, 6221 (1975).

(13) R. E. Barnett and W. P. Jencks, *J. Am. Chem. Soc.*, **91**, 6758 (1969).

(14) H. Diebler and R. N. F. Thorneley, *J. Am. Chem. Soc.*, **95**, 996 (1973); R. N. F. Thorneley and H. Diebler, *ibid.*, **96**, 1072 (1974).

(15) A. Williams and W. P. Jencks, *J. Chem. Soc., Perkin Trans. 2*, 1753, 1760 (1974).

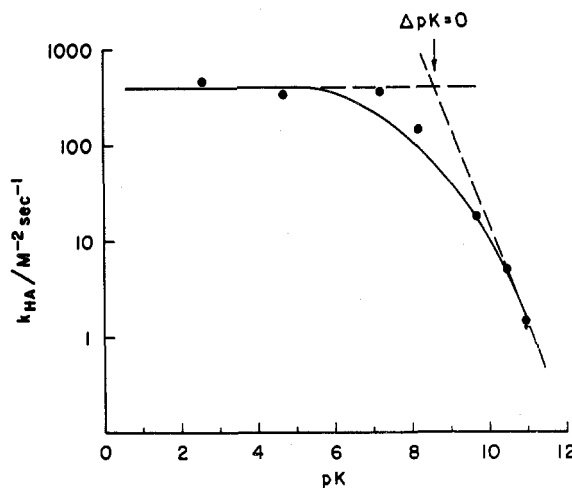
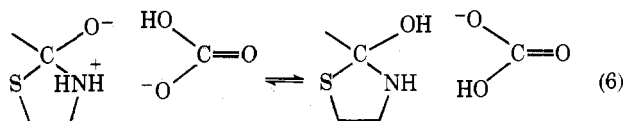


Figure 1. Brønsted plot for the addition of methoxyamine to *p*-methoxybenzaldehyde, showing the "Eigen curve" for catalysis by triazolium, methoxyammonium, imidazolium, cyanoethylammonium, methoxyethylammonium, methoxypropylammonium and ethylammonium ions (from left to right).<sup>9</sup>

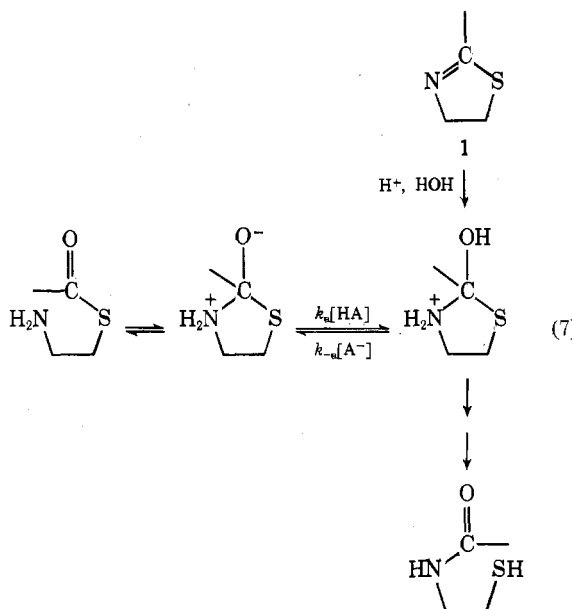
(6) Bicarbonate ion, which can act as a bifunctional acid and base catalyst, exhibits a 30-fold positive deviation from the Eigen curve for *e-s* catalysis by monofunctional general acids of the intramolecular aminolysis of *S*-acetylmercaptoethylamine.<sup>16</sup> Such bifunctional catalysts can trap a dipolar intermediate through a proton-switch mechanism (eq 6), which gives them an



advantage over monofunctional catalysts when proton transfer becomes thermodynamically unfavorable and slower than diffusion controlled.

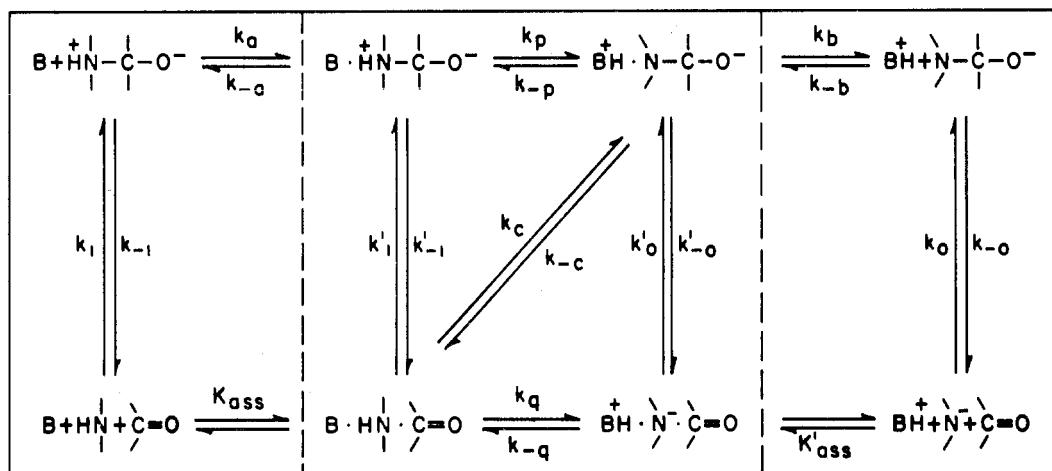
(7) The kinetics of this reaction requires that it proceed through at least three sequential steps. Since only two of these steps can represent formation and breakdown of an addition intermediate, one of them must represent a proton transfer.<sup>16</sup>

(8) The rate-determining step for diffusion-controlled acid catalysis of thiol ester aminolysis ( $k_a$ - $k_{-a}$ , eq 7)



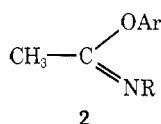
(16) R. E. Barnett and W. P. Jencks, *J. Am. Chem. Soc.*, **91**, 2358 (1969).

Scheme I



corresponds to a product-determining step when 2-methyl- $\Delta^2$ -thiazoline (1) undergoes hydrolysis through the same tetrahedral addition intermediates to thiol ester and amide.<sup>16</sup> This step shows the decrease with increasing viscosity in 0–60% glycerol that is expected for a diffusion-controlled reaction; there is little effect of viscosity on the non-diffusion-limited steps.<sup>17</sup>

(9) Similarly, hydrolysis of phenyl acetimidates (2)



generates the same tetrahedral addition intermediates that are formed in the acid-catalyzed aminolysis of phenyl esters. Eigen-type Brønsted plots are observed for general acid catalysis of the partitioning of these intermediates to give ester and amine. This suggests that the product-determining step of imidate hydrolysis and the rate-determining step of general acid catalyzed ester aminolysis is a stepwise proton transfer. The partitioning of the intermediate in the absence of catalyst is almost unchanged by electron-withdrawing substituents on the phenol, as is expected if proton transfer and not phenolate expulsion controls the partitioning.<sup>18</sup>

(10) Solvent deuterium isotope effects on these reactions are usually determined by secondary isotope effects on any initial equilibrium steps and a small effect on the rate of diffusion. The small isotope effect of  $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.25$  for the hydroxide ion catalyzed breakdown of the hemithioacetal of acetaldehyde and thioacetic acid is in the expected range for a diffusion-controlled reaction.<sup>13</sup>

**B. Preassociation Mechanisms.** *When the rate of breakdown of the addition intermediate is faster than the rate of separation of the intermediate and catalyst the reaction must proceed through a preassociation mechanism.*<sup>19</sup> If the rate constants for breakdown of the addition intermediate  $\text{T}^\pm$  formed from *p*-chlorobenzaldehyde and methoxyamine ( $\text{p}K = 4.7$ ,  $k_{-1} = 3 \times 10^8 \text{ s}^{-1}$ )<sup>9</sup> and semicarbazide ( $\text{p}K = 3.9$ ,  $k_{-1} = 2 \times 10^9 \text{ s}^{-1}$ )<sup>20</sup>

are extrapolated to the  $\text{p}K$  of 1.2 for the conjugate acid of 2-methylthiosemicarbazide, the estimated value of  $k_{-1}$  for this reaction is  $\sim 5 \times 10^{11} \text{ s}^{-1}$ . Since this rate constant is larger than that for the diffusional separation of an encounter pair  $\text{B}^+\text{H}_2\text{NR}-\text{CHR}'-\text{O}^-$  ( $k_{-a}$ , Scheme I), such an addition intermediate would break down to reactants within the ion pair with the rate constant  $k'_{-1}$  faster than the catalyst can diffuse away. If this is the lowest energy path for the breakdown of the encounter complex to reactants, it is also the lowest energy path for its formation from reactants (Figure 2), so that the formation of the addition complex *must* take place by a preliminary association of the reactants and catalyst followed by amine addition to give  $\text{T}^\pm$  with the rate constant  $k'_1$  (Scheme I).

In the presence of a strong base this is followed by a fast proton jump ( $k_p$ ) that traps the intermediate. With weaker bases the proton transfer itself (and associated solvation changes) will become rate determining, and with still weaker bases the separation of  $\text{BH}^+$  from  $\text{T}^-$  ( $k_b$ ) becomes rate determining. The latter two steps are the same as in simple proton transfer reactions. Consequently, the preassociation mechanism will follow the normal Eigen-type curve for weak bases but will follow the lower energy preassociation pathway with larger rate constants for strong bases (upper line, Figure 3), so that the break in the curve occurs at higher  $\text{p}K$  values than in a simple trapping mechanism (arrows, Figure 3). The observed break for the 2-methylthiosemicarbazide reaction is at  $\text{p}K = 4.5$ , 1.4 units above the estimated  $\text{p}K$  of 3.1 for  $\text{T}^\pm$ , and the absolute values of the observed rate constants agree with those calculated from the observed overall equilibrium constant and estimated  $\text{p}K$  values, using a value of  $5 \times 10^{11} \text{ s}^{-1}$  for  $k_{-1}$ .<sup>21</sup> These results provide support, but not conclusive proof, for a preassociation mechanism in this reaction.

In addition to (1) a shifted  $\text{p}K$  of the breakpoint in the Brønsted plot, the experimental manifestations of a preassociation mechanism that may distinguish it from a simple trapping mechanism are (2) independence of the rate on viscosity of the medium, (3) the absence of a change in rate-determining step with increasing

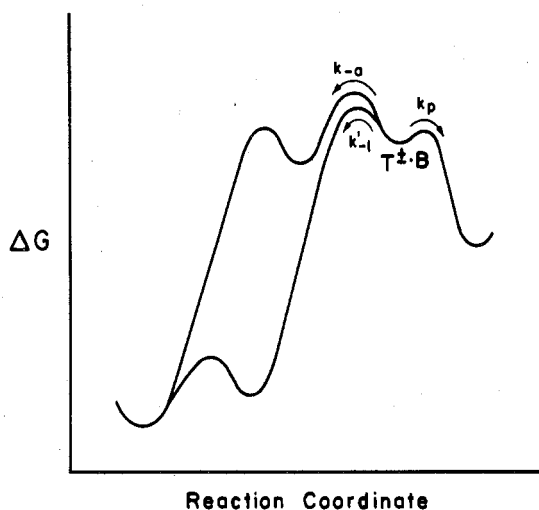
(17) C. Cerjan and R. E. Barnett, *J. Phys. Chem.*, **76**, 1192 (1972).

(18) A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7018, 7031 (1974).

(19) W. P. Jencks and K. Salvesen, *J. Am. Chem. Soc.*, **93**, 1419 (1971); L. D. Kershner and R. L. Schowen, *ibid.*, **93**, 2014 (1971).

(20) Calculated from the data of Sayer et al. (J. M. Sayer, B. Pinsky, A. Schonbrunn, and W. Washtien, *J. Am. Chem. Soc.*, **96**, 7998 (1974)) for addition to *p*-nitrobenzaldehyde. The rate constants for expulsion of methoxyamine do not differ significantly for the addition compounds formed from *p*-chlorobenzaldehyde and *p*-nitrobenzaldehyde.<sup>9</sup>

(21) J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **95**, 5637 (1973).

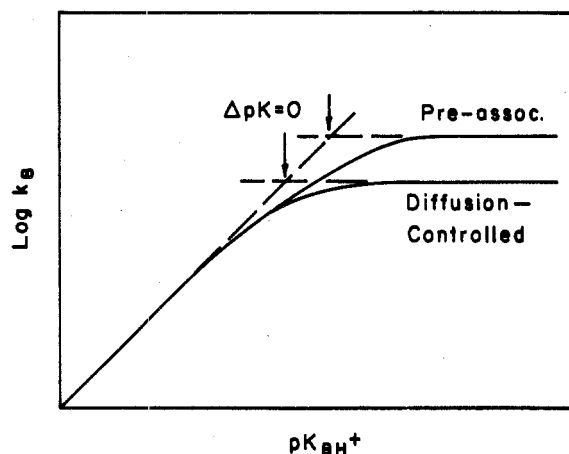


**Figure 2.** Reaction coordinate diagram to illustrate that a preassociation mechanism is preferred to a trapping mechanism when the intermediate  $T^{\ddagger}$  breaks down faster ( $k'_{-1}$ ) than it separates from B ( $k_{-a}$ ).

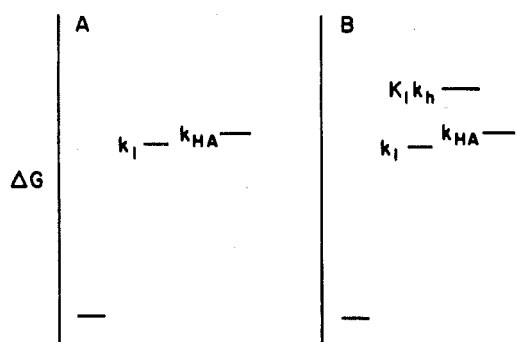
buffer concentration, and (4) solvent and heavy atom isotope effects and structure-reactivity correlations (such as  $\beta_{\text{nuc}}$  and  $\rho\sigma$ ) that are characteristic of rate-determining nucleophilic attack ( $k'_1$ ) rather than proton transfer to or from a fully formed intermediate ( $k_a$ ). The general acid catalyzed aminolysis of phenyl acetate by methoxyamine exhibits a nonlinear Brønsted plot with a break below that for the analogous methylamine reaction and is not slowed by increasing solvent viscosity in aqueous glycerol.<sup>22</sup> The rate constant  $k_{-1}$  for breakdown of the analogous intermediate formed from methylamine ( $\text{p}K = 10.6$ ) has been estimated<sup>18</sup> to be  $3 \times 10^9 \text{ s}^{-1}$ , so that it is not unreasonable that the less basic methoxyamine ( $\text{p}K = 4.7$ ) should be expelled faster and react through a preassociation mechanism.

**C. Hydrogen Bonding.** When the lifetime of an intermediate is sufficiently short that the reaction proceeds through a preassociation mechanism with the catalyst in the correct position for subsequent proton transfer, an *e-s* reaction must exhibit catalysis by hydrogen bonding to HA with  $\alpha > 0$  when the carbonyl oxygen atom in the transition state is basic enough to perturb the H-A bond. An analogous situation holds for n-s reactions with respect to hydrogen bonding of a base to an acidic proton on the nucleophile in the transition state.

Extrapolation of the rate constants  $k_{-1}$  for breakdown of the intermediates formed from the attack of basic thiol anions on acetaldehyde gives values of  $k_{-1} = 10^{11} \text{ s}^{-1}$  for the expulsion of thiols of  $\text{p}K \sim 3$ , so that a preassociation mechanism is expected for the attack of weakly basic thiols. The observed Brønsted slope of  $\alpha = 0.2$  for general acid catalysis of the attack of  $\text{C}_6\text{F}_5\text{S}^-$  ( $\text{p}K = 2.7$ ) by acids of  $\text{p}K$  2 to 9 is in the range expected for hydrogen bonding and suggests that the reaction is subject to enforced catalysis by hydrogen bonding to the developing negative charge on the oxygen atom of  $T^-$  ( $\text{p}K \sim 12$ ).<sup>4</sup> The addition of 2-methylthiosemicarbazide to *p*-chlorobenzaldehyde also exhibits general acid catalysis with  $\alpha = 0.2$ , and the catalytic constants are approximately tenfold larger than those for general base catalysis, for which  $\beta \approx 0$ .<sup>21</sup> This is consistent with a



**Figure 3.** Brønsted plots to show how the break point for general base catalysis by a preassociation mechanism is shifted from  $\Delta\text{p}K = 0$ .



**Figure 4.** Gibbs free energy diagram to show how a general acid catalyzed reaction ( $k_{\text{HA}}$ , diagram A) that is less favorable than an uncatalyzed reaction ( $k_1$ ) can become a low-energy path for reaction when trapping ( $K_1k_h$ ) becomes rate determining for the uncatalyzed reaction (diagram B).

preassociation mechanism in which there is a modest rate acceleration from hydrogen bonding to acids, but not to bases, in the transition state. A change in rate-determining step with increasing buffer concentration and the curvature of the Brønsted plots for general acid catalysis suggest that the addition of weakly basic carbanions to acetaldehyde is catalyzed by concurrent trapping and hydrogen-bonding mechanisms.<sup>23</sup>

The attack of strongly basic nucleophiles on reactive carbonyl compounds generally does not exhibit detectable buffer catalysis; catalysis is seen for "hard" reactions of weak nucleophiles, "when it is most needed". The reason for this is that there is an additional advantage for catalysis by hydrogen bonding relative to the buffer-independent reaction for all reactions in which the lifetime of the intermediate is short enough to require a preassociation or a trapping mechanism.

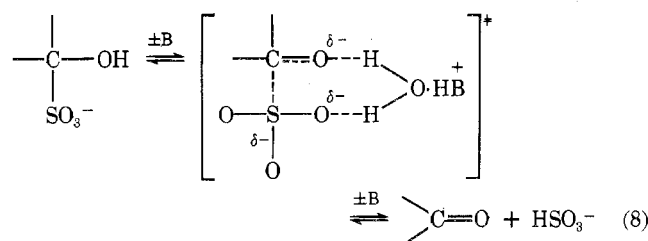
Consider a reaction, such as the addition of basic thiolate anions to acetaldehyde, for which the transition state for general acid catalyzed attack ( $k_{\text{HA}}$ ) is not sufficiently stable compared to that for uncatalyzed attack ( $k_1$ ) to make general acid catalysis detectable (Figure 4A).<sup>7</sup> With less basic thiols the intermediate breaks down faster, proton transfer from the solvent ( $k_h$ ) becomes rate determining, and general acid catalysis appears.<sup>4,13</sup> The transition state for the hydrogen-bonding mechanism ( $k_{\text{HA}}$ ) is now of lower energy than that for the rate-determining buffer-independent reaction ( $K_1k_h$ ), even though it maintains the same energy rel-

(22) M. Cox and W. P. Jencks, in preparation.

(23) W. N. White and W. P. Jencks, in preparation.

ative to  $k_1$  (Figure 4B), so that catalysis by hydrogen bonding with  $\alpha \approx 0.2$  becomes more significant as the basicity of the thiol decreases. The additional advantage for catalysis by hydrogen bonding in this situation is given by the ratio of the rate constants for breakdown of the intermediate and for solvent-mediated proton transfer,  $k_{-1}/(k_h + k_s)$ . Hydrogen bonding stabilizes the transition state for a preassociation mechanism in these reactions so as to provide catalysis with addition compounds of intermediate stability.

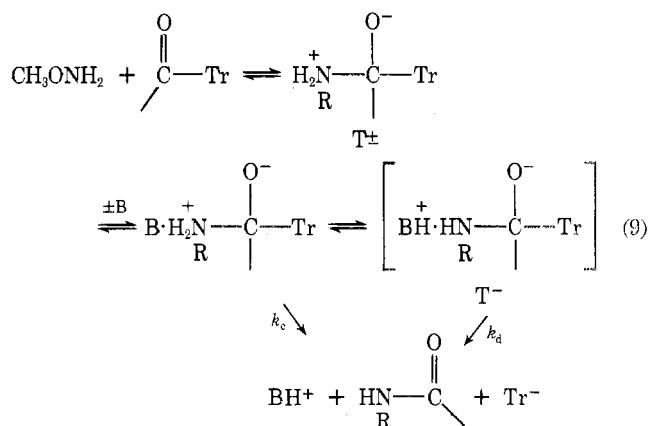
We can then ask whether buffer catalysis is observed *only* for reactions in which the short lifetime of the intermediate provides this additional advantage. The answer is no, because catalysis has been observed for the breakdown of the bisulfite addition compound of *p*-methoxybenzaldehyde, for which proton transfer is faster than breakdown of the intermediate dianion ( $k_h = 2.3 \times 10^6 \text{ s}^{-1}$ ,  $k_{-1} = 2.6 \times 10^4 \text{ s}^{-1}$ ).<sup>24</sup> The catalytic constants are correlated with the equilibrium constants for association of sulfite dianion with acids and cations, suggesting that the catalysis involves stabilization by hydrogen bonding to the dianionic transition state. A possible mechanism is shown in eq 8.



**D. Concerted Catalysis.** *If the lifetime of an intermediate in a catalyzed reaction becomes shorter than that for a preassociation mechanism, the "intermediate" no longer exists and the reaction must proceed through a concerted mechanism.* A species must exist for longer than a vibration frequency,  $10^{13}$ – $10^{14} \text{ s}^{-1}$ , to qualify as an intermediate, and a reaction that cannot proceed in steps through an intermediate must proceed without steps through a concerted mechanism. This will occur when (a) there is no barrier for the expulsion of a nucleophile from the addition compound or (b) there is no barrier for the proton-transfer step.

The former situation is particularly likely to arise for acyl-transfer reactions, in which there are generally two atoms that can donate electrons to expel the attacking nucleophile or leaving group and form a resonance-stabilized product. The most unstable species of the addition compound will be those in which the leaving group is protonated and the other electronegative atoms are not, and buffer catalysis of the breakdown of a more stable ionic species *must* be concerted when the immediate product of the proton transfer is so unstable that it has no significant lifetime. The methoxyaminolysis of acetyltriazole may provide an example of this situation.<sup>6</sup>

The rate constants for catalysis by strong acids and bases approach the same limiting,  $\text{pK}$ -independent value, suggesting that the initially formed addition intermediate  $\text{T}^{\pm}$  (eq 9) breaks down upon diffusion-controlled encounter with either type of catalyst. However, the break in the nonlinear Brønsted plot for general base



catalysis is more than 2  $\text{pK}$  units below the estimated  $\text{pK}$  of the intermediate  $\text{T}^{\pm}$ . This cannot be accounted for by a preassociation mechanism<sup>6</sup> and suggests that the intermediate breaks down rapidly upon encounter with even relatively weak bases; i.e. the immediate product of proton removal is so unstable that concerted breakdown occurs rapidly with only partial proton removal ( $k_c$ , eq 9).

With still weaker bases the breakdown step,  $k_c$ , becomes rate determining, and the observed rate constants follow a Brønsted slope of  $\beta = 0.6$ . Such a mechanism will be found when the "intermediate"  $\text{T}^-$  does not exist ( $k_d > 10^{13} \text{ s}^{-1}$ ) and appears reasonable because triazole ( $\text{pK} = 10$ ) is a good leaving group and the product is a resonance-stabilized amide. An analogous concerted mechanism involving protonation of the leaving triazole group is probable for the acid-catalyzed reaction, for which the breakpoint of the Brønsted plot is shifted more than 2  $\text{pK}$  units above the estimated  $\text{pK}$  of the protonated addition compound, but an alternative mechanism involving protonation of the oxygen atom of  $\text{T}^{\pm}$  is also possible.<sup>6</sup>

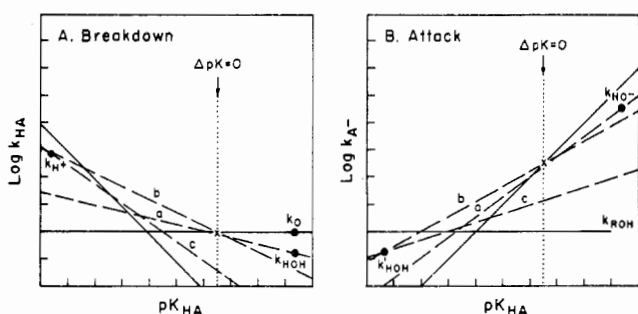
### Class n-f and e-f Reactions

*When the  $\text{pK}$  of the initially formed addition intermediate is such that the intermediate will be trapped by a single thermodynamically favorable proton transfer to or from solvent, any observed general acid-base catalysis must represent transition-state stabilization in a hydrogen bonding or concerted mechanism and not catalysis by trapping.* Such a thermodynamically favorable proton transfer is very fast, hence the designations n-f and e-f for these reactions. If the  $\text{pK}$  of an addition intermediate  $\text{T}^{\pm}$  in an n-f reaction is 0 or less, for example, the intermediate will be trapped by rapid proton donation to 55 M water faster than 1 M added base, so that trapping of the intermediate by added base will be insignificant and any observed catalysis by base must represent stabilization of the transition state for attack of the nucleophile. The analogous situation holds for general acid catalysis of an e-f reaction when a strongly basic intermediate is generated.

Nucleophilic attack on an uncharged imine generates such a basic intermediate. Thus, general acid catalysis of the addition of hydroxide ion to an imine, an e-f reaction that involves general base catalysis of carbinolamine breakdown in the reverse direction (eq 10,  $\text{R} = \text{H}$ ), *must* represent transition state stabilization through hydrogen bonding or a concerted mechanism. The estimated  $\text{pK}$  and observed rate constant for the







**Figure 5.** Brønsted plots to illustrate the limitations to the existence of significant general acid–base catalysis for an  $n - 2$  reaction, such as acetal hydrolysis, in the direction of leaving group departure with general acid catalysis by HA (A) and nucleophile attack with general base catalysis by  $A^-$  (B).

in principle and in experimental detection. These limitations may be illustrated by considering the Brønsted plots for an  $n$ -f reaction, such as the acid-catalyzed cleavage of an acetal (Figure 5). The vertical dotted line in the figure is at the  $pK_a$  of the leaving alcohol or phenol.

(1) The Brønsted line for catalysis by *hydrogen bonding of the acid to the leaving oxyanion* will pass through (or near)  $k_{HOH}$ , the second-order rate constant for catalysis by water, and will have a slope on the order of  $\alpha = 0.2$  (line a, Figure 5A). (a) In order for buffer catalysis to be significant the catalytic constant  $k_{HA}$  must be larger than  $k_0$ , the pseudo-first-order rate constant for the water reaction ( $k_0 = 55k_{HOH}$ ). (b) Since hydrogen bonds between conjugate acid–base pairs do not have appreciable net stability in water, the Brønsted line must fall below the point x at the  $pK$  of the leaving group,  $\Delta pK = 0$ . (c) Catalysis will be experimentally significant only if  $k_{HA}$  falls above the solid line of slope  $-1.0$  that is drawn 1.7 log units above the rate constant for catalysis by the proton,  $k_{H^+}$ .<sup>34</sup> Therefore, the range of  $pK$  in which catalysis can be detected is small in many reactions and absent in some.

(2) A Brønsted line b for *concerted catalysis* must be above the line for any catalysis by hydrogen bonding in order to be significant but must pass through or below  $k_{H^+}$  and x, and must be below  $k_{HOH}$ . The latter two limitations are based on a rule which states that *an initially unfavorable proton transfer to or from the catalyst must become thermodynamically favorable in the course of a reaction in order to provide the driving force for concerted general acid or base catalysis*.<sup>31,35</sup> One reason for this limitation is apparent from a consideration of the reverse reaction, the general base catalyzed attack of ROH on the oxocarbenium ion with the rate constant  $k_{A^-}$  (Figure 5B). Buffer catalysis with a  $pH$  and a  $pK$  of the catalyst above the  $pK$  of ROH would require that  $RO^-$  undergo a thermodynamically unfavorable protonation to give the less reactive ROH, followed by partial proton removal by the base  $A^-$  in the transition state for nucleophilic attack. Since the partially deprotonated species  $[A \cdots H \cdots OR]^-$  is not expected to be as reactive as the fully deprotonated species  $RO^-$ , concerted catalysis is not expected in either direction when the  $pK$  of the catalyst is above the  $pK$  of ROH.

The observed rate in the region to the right of the dotted lines in Figure 5 will be dominated by the uncatalyzed expulsion of  $RO^-$  ( $k_0$ , Figure 5A) and the attack of  $RO^-$ , which is equivalent to the (specific) hydroxide ion catalyzed attack of ROH ( $k_{HO^-}$ , Figure 5B).

(3) The Brønsted line c for catalysis by *hydrogen bonding of  $A^-$  to the attacking and leaving ROH* must pass through (or near)  $k'_{HOH}$ , the third-order rate constant for catalysis by water (Figure 5B), and the catalytic constant  $k_{A^-}$  must be larger than  $k_{ROH}$ , the observed second-order rate constant for the water reaction, in order to be significant ( $k_{ROH} = 55k'_{HOH}$ ). The point x in Figure 5B corresponds to  $k_{RO^-}$ , the rate constant for the attack of  $RO^-$ , and the rate constant for general base catalyzed attack of ROH is expected to be smaller than this. The catalytic constant  $k_{A^-}$  must also fall above the diagonal solid line that is determined by  $k_{HO^-}$  in order to be significant. The Brønsted slope is expected to be on the order of  $\beta = 0.2$  for the attack direction and  $\alpha = 0.8$  for the breakdown direction. Again, there is only a limited range in which catalysis can be observed.

The Brønsted line for general acid catalysis of the hydrolysis of methyl *m*-nitrophenyl benzaldehyde acetal passes through the limiting intersection point x at  $\Delta pK = 0$ , increases sharply with increasing acidity with a slope of  $\alpha = 0.5$ , and passes well below the rate constant  $k_{HOH}$  for expulsion of the phenoxide ion with hydrogen bonding.<sup>33</sup> These data support a concerted mechanism of catalysis for this reaction and the fact that the Brønsted slope is frequently close to  $\alpha = 0.5$ , as well as the reasons described earlier, suggest that general acid catalysis of alcohol expulsion in the breakdown of acetals and related reactions generally occurs through a concerted mechanism.

The range of catalyst  $pK$  over which significant catalysis can occur is also limited by the lifetime and selectivity of the immediate product of the breakdown reaction,  $>C=OR^+$ . If the reaction of this oxocarbenium ion with ROH is diffusion controlled or the selectivity toward the nucleophile is small, then the rate constants  $k_{ROH}$  and  $k_{RO^-}$  will be similar or identical, both solid lines in Figure 5B (and also in Figure 5A) will pass through or near point x, no rate increase can result from either partial or complete proton removal from ROH, and buffer catalysis will not be observed.<sup>36</sup> This is the case for the hydrolysis of the mixed *O*-ethyl *S*-phenyl thioacetal of benzaldehyde, for example.<sup>36,37</sup>

If the reaction of ROH with  $>C=OR^+$  is diffusion controlled and  $k_{ROH} \approx k_{RO^-}$ , the reaction *must* exhibit specific acid catalysis in the reverse direction, provided only that the protonated acetal can exist. The uncatalyzed attack of ROH in one direction corresponds to preequilibrium protonation of the acetal followed by expulsion of ROH in the other direction, i.e., to specific acid catalysis. An unselective or diffusion-controlled mechanism will be favored for the reactions of basic alcohols and unstable carbonium ions. This may help to account for the experimental observation that general acid catalysis of this type of reaction becomes significant when the attacking or leaving alcohol is more acidic and the oxocarbenium ion is more stable.<sup>30,33,37,38</sup>

(34) This can be more easily seen by considering the reverse reaction. Proton catalysis of alcohol leaving ( $k_{H^+}$ ) corresponds to the "water" reaction of alcohol attack in the reverse direction ( $k'_{HOH}$ , Figure 5B). Catalysis by 1 M buffer must be comparable to catalysis by 55 M water ( $k_{ROH} = 55k'_{HOH}$ , Figure 5B) to be significant. The horizontal line through  $k_{ROH}$  in Figure 5B corresponds to the line of slope  $-1$  in Figure 5A.

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