

GENERAL ACID-BASE CATALYSIS OF CARBONYL AND ACYL GROUP REACTIONS\*

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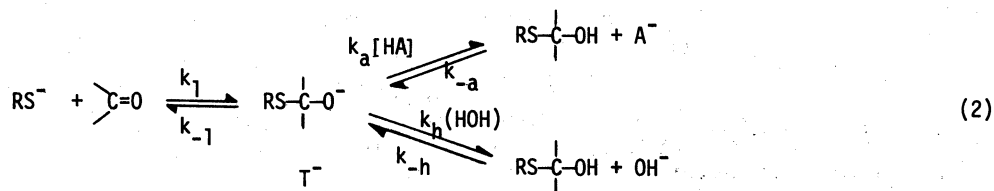
**Abstract** - The addition of thiols to the carbonyl group illustrates most of the range of mechanisms of general acid-base catalysis that are available for reactions of carbonyl and acyl groups. Strongly basic thiol anions add without significant acid catalysis to form an anionic intermediate  $T^-$ , which abstracts a proton from water to give the hemithioacetal in a subsequent fast step. Methyl mercaptoacetate anion generates a less stable intermediate,  $T^-$ , and exhibits catalysis through trapping by rate-determining stepwise protonation of this intermediate. Less basic thiol anions exhibit general acid catalysis by hydrogen bonding of HA to the carbonyl oxygen atom in the transition state, which becomes significant largely because of the short lifetime of the intermediate. General acid catalysis of the addition of RSH may represent concerted catalysis that is enforced by the nonexistence of the "intermediate"  $T^\ddagger$ .

Several aspects of our present understanding of the mechanism of catalysis of carbonyl and acyl group reactions may be illustrated by a consideration of the reversible addition of thiols to aldehydes and ketones (eq. 1). Reactions involving the thiol anion as the



attacking (or leaving) nucleophile are relatively simple because only a single proton transfer is required to form the stable product and the site of catalysis is unambiguous, i.e. proton transfer to and from the carbonyl oxygen atom. Similar mechanisms of catalysis are presumably involved in more complex reactions of other carbonyl and acyl compounds that commonly involve two bond forming or breaking steps of heavy atoms and two or more proton transfers.

The situation until recently was the following. (a) Basic thiol anions were known to attack the carbonyl group without detectable acid catalysis and with a very small dependence of the rate on the basicity of the thiol (1). The absence of detectable acid catalysis is typical for the attack of basic, strong nucleophiles and indicates that stabilization of the transition state by acids through hydrogen bonding or other mechanisms is of little or no significance in these reactions. (b) However, the addition of less basic anions of thiophenols and thioacetic acid had been shown to exhibit general acid catalysis with a Brønsted slope  $\alpha$  of approximately 0.2; this is equivalent, in the reverse direction, to general base catalysis of hemithioacetal breakdown with a Brønsted  $\beta$  value of 0.8 (2). It was suggested that the mechanism of this catalysis was, in some sense, "concerted" with significant perturbation of the proton in the transition state, as opposed to a stepwise mechanism involving rate-determining protonation of an initially formed anionic addition compound,  $T^-$  ( $k_a$ , eq. 2). (c) The rate of the reverse, breakdown reaction catalyzed by hydroxide ion



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was known to approach the diffusion controlled limit (2).

Although the rate constants for catalysis of the breakdown reaction by general bases do not follow the "Eigen curve" that would be expected if proton transfer were rate determining with these catalysts (3), the absolute values of the rate constants are close to those that would be expected for the proton transfer step,  $k_{-a}$ . The rate constants  $k_a$  and  $k_{-a}$  may be calculated from the estimated  $pK_a$  of the hemithioacetal (see Note a) and a value of  $k_a = 10^9 \text{ M}^{-1}\text{s}^{-1}$  for the protonation of  $T^-$  by a relatively strong acid (3). The rate constant  $k_h$  for protonation of  $T^-$  by water may be estimated from the  $pK_a$  in a similar manner, assuming that the reverse reaction of the hemithioacetal with hydroxide ion is diffusion controlled with  $k_{-h} = 10^{10} \text{ M}^{-1}\text{s}^{-1}$  (2). Such calculations showed that the rate of protonation of  $T^-$  by water was not fast enough to keep up with the known rate of formation of  $T^-$  by the attack of methyl mercaptoacetate anion on acetaldehyde in the absence of added catalysts. In other words, some of the molecules of  $T^-$  that are formed from the attack of  $RS^-$  on acetaldehyde return to reactants ( $k_{-1}$ ) before they are protonated by water ( $k_h$ ). The estimated values of  $k_{-1}$  and  $k_h$  for the methyl mercaptoacetate reaction were similar,  $2 \times 10^8 \text{ s}^{-1}$  and  $2.5 \times 10^8 \text{ s}^{-1}$ , respectively. In this situation the rate of product formation must be increased by the addition of buffer acids to the solution, because protonation of  $T^-$  by these acids provides an additional pathway for the proton transfer step and prevents the reversion of  $T^-$  to starting materials. It was predicted that the rate would increase with increasing concentration of added acid catalyst until all of the molecules of  $T^-$  that are formed are trapped by protonation ( $k_a[HA]$ ) and would then level off at the rate of the addition reaction,  $k_1$ .

This behavior was observed upon the addition of a number of different buffer acids to the reaction mixture and provides unequivocal evidence for a change in rate-determining step with increasing buffer concentration and, hence, a reaction mechanism for methyl mercaptoacetate that involves at least two steps and an intermediate. For a simple reaction of this kind, these steps must almost certainly be the attack of the thiol anion ( $k_1$ ) and protonation of the intermediate ( $k_a[HA]$  and  $k_h$ ). The values of  $k_{-1}$  and  $k_h$  may be calculated from the observed rate constants, assuming a value of  $k_a = 10^9 \text{ M}^{-1}\text{s}^{-1}$ , and the resulting values of  $k_{-1} = 1.3 \times 10^8 \text{ s}^{-1}$  and  $k_h = 5 \times 10^8 \text{ s}^{-1}$  are close to the predicted values. The values of  $k_{HA}$  for acid catalysis cannot be determined accurately because of the small and nonlinear increase in rate caused by the change in rate-determining step, but the results do show that (a) the catalytic effectiveness of acids with  $pK_a$  values in the range 2 to 9 is the same within experimental error, (b) the proton is more effective than other catalysts, and (c) weaker acids, of  $pK$  10 to 12, are less effective than other acids. This is the behavior expected for a simple stepwise proton transfer reaction and the approximate catalytic constants follow the nonlinear "Eigen curve" that is expected for such a proton transfer, with a break point at  $\Delta pK = 0$ , close to the estimated  $pK_a$  of the hemithioacetal product (Fig. 1, curve A).

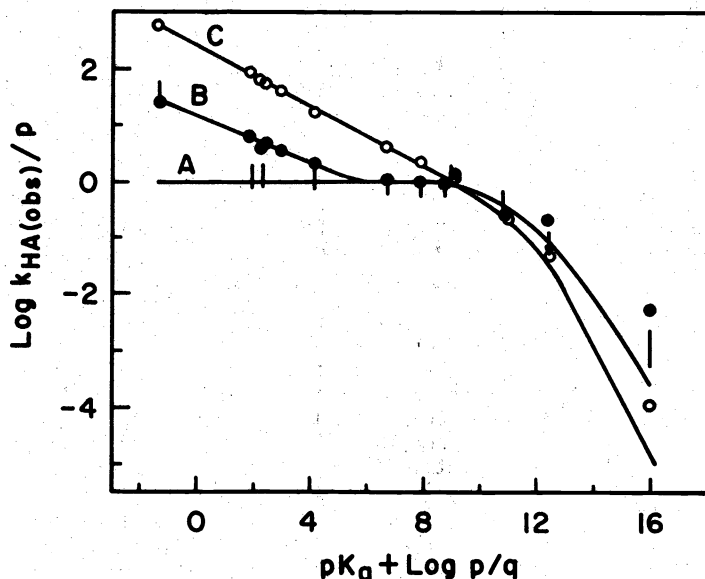


Fig. 1. Brønsted plots for catalysis by oxygen acids of the addition of thiol anions to acetaldehyde normalized to the same rate constant for catalysis by trapping of  $T^-$ . "Eigen curves" for simple proton transfer to  $T^-$  are drawn with  $\Delta pK = 0$  at 12.4 for A and B and 11.1 for C. Deviation of points above 0 represents hydrogen bond catalysis. (A) (○)  $\text{MeOOCCH}_2\text{SH}$ . (B) (●)  $\text{pMeOArSH}$ . (C) (○)  $\text{F}_5\text{ArSH}$ .

Note a. A  $pK$  value of 12.4 for  $\text{HOEtSCH}_2\text{OH}$  has been determined by R. G. Kallen (personal communication) and  $pK$  values of related compounds may be estimated from  $\rho_1\sigma_1$  correlations.

The reaction mechanism for methyl mercaptoacetate is illustrated by the reaction coordinate diagram of Fig. 2b. The barriers for reaction of the intermediate  $T^-$  to give reactants

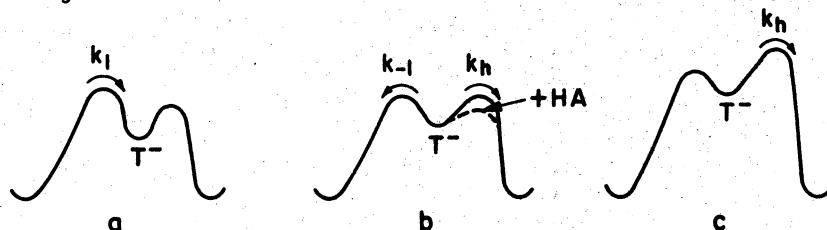
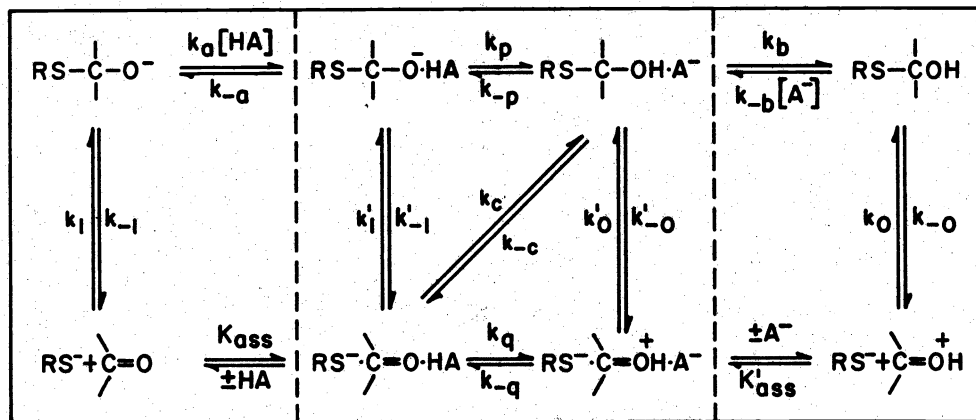


Fig. 2. Reaction coordinate diagrams for (a) rate-determining nucleophilic attack with basic thiol anions, (b) nucleophilic attack and proton transfer both partially rate determining in water and a change to rate-determining nucleophilic attack in the presence of added acid, and (c) rate-determining protonation of  $T^-$  that gives rise to general acid catalysis by trapping.

( $k_{-1}$ ) and products ( $k_h$ ) are similar so that both the  $k_1$  and  $k_h$  steps are partially rate determining. The addition of acid provides an additional, lower energy pathway for the proton transfer step ( $k_a$ ) so that the rate increases until the effective barrier for the proton transfer is decreased and  $k_1$  becomes fully rate determining. A more basic thiol anion, such as  $EtS^-$ , is a poorer leaving group ( $k_{-1}$  is smaller) so that  $k_1$  is always rate determining and no catalysis by trapping is observed (Fig. 2a). A less basic thiol anion, such as  $p-CH_3OPHS^-$ , is a better leaving group ( $k_{-1}$  is larger) so that the proton transfer step,  $k_h$ , is always rate determining (Fig. 2c) and the observed rate increases linearly with increasing concentration of acid catalyst.

For moderately strong acids, such as acetic acid, the rate-determining step of the proton transfer is the diffusion-controlled encounter of the acid and  $T^-$ , with the rate constant  $k_a$  (eq. 2 and Scheme I). However, there is another pathway to the species  $T^- \cdot HA$  that

#### SCHEME I



bypasses the diffusion-controlled step. This pathway involves a preliminary association of thiol anion, acetaldehyde and catalyst in an encounter complex ( $K_{ass}$ ) followed by nucleophilic attack ( $k_1'$ ) to give  $T^-$  with the catalyst already in position to trap the intermediate through a fast proton transfer ( $k_p$ ). If the transition state for the rate-determining  $k_1'$  step is sufficiently basic that it forms a stronger hydrogen bond to HA than to water, this pathway will be stabilized by such hydrogen bonding. If this hydrogen bonding is strong enough, buffer acids will stabilize  $k_1'$  relative to  $k_1$  and catalysis by hydrogen bonding will always be important. We know that this is not the case for the addition of basic thiol anions and other strong nucleophiles because little or no acid catalysis is observed when nucleophilic attack is rate determining. On the other hand, acid catalysis is significant for the attack of weakly basic thiol anions and exhibits a Brønsted  $\alpha$  value of 0.2. This Brønsted slope is inconsistent with the value of  $\alpha = 0$  that is expected for diffusion-controlled trapping by moderately strong acids, but is in the expected range for stabilization by hydrogen bonding.

Advantages of the hydrogen-bonding mechanism. In order to understand why catalysis by hydrogen bonding is more important with weakly basic than with strongly basic thiol anions, we must examine the effect of the stability of the addition intermediate on the relative importance of different reaction pathways. As the intermediate becomes progressively more unstable, catalysis by hydrogen bonding becomes progressively more important. We will

consider (a) the ratio of the observed rate constant,  $k_{HA}'$ , for catalysis through the  $k_1'$  pathway to the rate constant for the uncatalyzed or "water" reaction, (b) the ratio  $k_{HA}'/k_{HA}$  for catalysis by hydrogen bonding and by trapping, and (c) changes in the Brønsted coefficient  $\alpha$ .

(a) In order for catalysis by hydrogen bonding to be significant with strongly basic nucleophiles, for which  $k_1$  is rate determining, the transition state for the hydrogen bonding pathway ( $k_1'$ ) must be of comparable or lower energy than that for  $k_1$ . This is evidently not the case for basic thiol anions. However, with less basic thiols the rate-determining step is trapping through  $k_h$  (eq. 2,  $k_{HOH} = k_1 k_h / k_{-1}$ ), so that the hydrogen bonding pathway only has to be of lower energy than the transition state for the  $k_h$  step in order to be significant. Since the hydrogen bonding mechanism is expected to maintain approximately the same energy relative to  $k_1$ , but the observed rate constant  $k_{HOH}$  is now smaller than  $k_1$  by the factor  $k_h/k_{-1}$ , the hydrogen-bonding mechanism will become relatively more important. This additional advantage, by the factor  $k_{-1}/k_h$ , is the principal reason why catalysis by hydrogen bonding is more likely to be observed with weak nucleophiles that are easily expelled from the addition intermediate (large  $k_{-1}$ ).

(b) The factors that determine the relative importance of the pathways for acid catalysis by trapping ( $k_{HA}$ ) and by hydrogen bonding through the  $k_1'$  pathway ( $k_{HA}'$ ) may be illustrated by the reaction coordinate diagram of Fig. 3. (i) Consider first a reaction in which there

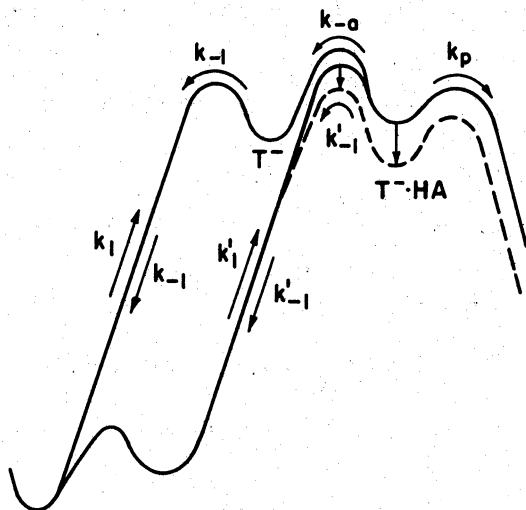


Fig. 3. Reaction coordinate diagram for general acid catalysis with rate-determining trapping (upper line) and rate-determining nucleophilic attack by a pre-association mechanism (lower lines). The dashed line and the vertical arrows indicate the additional stabilization brought about by hydrogen bonding to an acid HA.

is no stabilization of the transition state of the  $k_1' - k_{-1}'$  step by hydrogen bonding to HA ( $\alpha = 0$ ). This pathway (lower solid line, Fig. 3) will still be preferred to the trapping mechanism (upper line) when the intermediate  $T^- \cdot HA$  breaks down faster ( $k_{-1}'$ ) than HA can diffuse away from it ( $k_{-a}$ ). This pre-association or "spectator" mechanism (4-6) is useful because it generates the intermediate  $T^- \cdot HA$ , which is immediately trapped by an ultrafast proton transfer, by a pathway that avoids the diffusion-controlled step  $k_a - k_{-a}$ . The relative importance of the diffusion-controlled and pre-association pathways is given by the ratio  $k_{-1}/k_{-a}$  (in the absence of stabilization by hydrogen bonding,  $k_{-1}' = k_{-1}$ ).

(ii) If there is stabilization of the transition state of the  $k_1' - k_{-1}'$  step by hydrogen bonding (dashed line, Fig. 3) this stabilization is expected to increase with increasing acidity of HA, following a Brønsted coefficient  $\alpha$ . This additional advantage is given by  $\text{antilog } \alpha$  ( $15.74 - pK_{HA}$ ) and represents the increase in the ratio  $k_{-1}'/k_{-a}$  when the acid that is hydrogen bonded to the transition state is changed from water to HA. Since  $k_{-a}$  and  $k_{-1}'$  are both first order constants for reactions of  $T^- \cdot HA$ , this ratio is dimensionless and there is no ambiguity regarding standard states. For an  $\alpha$  value of 0.2 and an acid of  $pK$  4.7, the advantage from hydrogen bonding is by the factor  $\text{antilog } 2.2 = 160$ . The value of  $\alpha$ , and hence the advantage from hydrogen bonding, is expected to increase with increasing basicity of the transition state and will follow some relationship such as that proposed by Hine (7).

Thus, the relative importance of the stepwise trapping mechanism,  $k_{HA}$ , and the hydrogen bonding mechanism,  $k_{HA}'$ , is determined by (i) the hydrogen bond-independent factor  $k_{-1}/k_{-a}$  and (ii) the additional stabilization from hydrogen bonding (eq. 3). The relative energies of

$$k_{HA}'/k_{HA} = (k_{-1}/k_{-a}) \text{antilog } \alpha(15.74 - pK_{HA}) \quad (3)$$

the two pathways are shown by the upper solid line and the dashed line in Fig. 3.

A numerical example may clarify these points. Suppose that the basicity of a transition state for nucleophilic attack is such that  $\alpha = 0.1$  for stabilization by hydrogen bonding and  $k_h$  for trapping of the intermediate by water is  $2 \times 10^8 \text{ s}^{-1}$ . Then, if  $k_{-1} = 10^7 \text{ s}^{-1}$  or less, attack of the nucleophile ( $k_1$ ) is rate determining and the observed ratio of  $k_{HA}'/k_1$  for an acid of  $pK$  4.7 is  $\text{antilog}[0.1(15.7 - 4.7) - 1.74] = 0.23$ . Since this ratio gives only a 23% rate increase at 1 M acid, general acid catalysis would be of borderline significance, at best. The term 1.74 =  $\log 55$  in this calculation arises from the molarity of liquid water, which competes with the acid HA for hydrogen bonding to the transition state. However, if  $k_{-1}$  is  $10^9 \text{ s}^{-1}$  and the rate constant  $k_a$  for diffusion-controlled trapping of  $T^-$  by HA is  $10^9 \text{ M}^{-1}\text{s}^{-1}$ , then the ratio  $k_{HA}/k_{HOH} = k_a/k_h = 10^9/2 \times 10^8$  for catalysis by trapping is 5. The relative importance of catalysis by hydrogen bonding and by trapping (eq. 3) is  $k_{HA}'/k_{HA} = (0.1)\text{antilog } 0.1(15.7 - 4.7) = 1.26$ , assuming that  $k_{-a} = 10^{10} \text{ s}^{-1}$ . The ratio  $(k_{HA} + k_{HA}')/k_{HOH}$  is then  $5 + 1.26 \times 5 = 11$  and the observed rate will be doubled by less than 0.1 M added acid catalyst. If  $k_{-1}$  is  $10^{10} \text{ s}^{-1}$  the ratio  $(k_{HA} + k_{HA}')/k_{HOH} = 68$  and the observed rate will be doubled by 0.02 M acid. Thus, the importance of catalysis by hydrogen bonding increases sharply as the intermediate becomes less stable and  $k_{-1}$  increases. The effect of the lifetime of the intermediate ( $k_{-1}$ ) on the importance of the rate constants for general acid catalysis by trapping and by hydrogen bonding is summarized in Table 1.

TABLE 1. The relative importance of catalysis by trapping and by hydrogen bonding as the lifetime of  $T^-$  decreases ( $k_{-1}$  increases)<sup>a</sup>

$k_{-1}$ $\text{s}^{-1}$	$\frac{k_{HA}}{k_{HOH}}$ $\text{M}^{-1}$	$\frac{k_{HA}'}{k_{HOH}}$ $\text{M}^{-1}$	$\frac{k_{HA} + k_{HA}'}{k_{HOH}}$ $\text{M}^{-1}$	[HOAc] to double rate M	Percent of catalysis due to Trapping	H-bonding
$10^8$	<sup>b</sup>	0.6	0.6	1.6	<sup>b</sup>	100
$10^9$	5	6	11	0.1	45	55
$10^{10}$	5	63	68	0.015	7	93
$10^{11}$	5	630	635	0.0016	1	99

<sup>a</sup>Based on  $\alpha = 0.1$ ,  $k_a = 10^9 \text{ M}^{-1}\text{s}^{-1}$ ,  $k_{-a} = 10^{10} \text{ s}^{-1}$  and  $k_h = 2 \times 10^8 \text{ s}^{-1}$ .

<sup>b</sup>Catalysis by trapping can result in only a 50% rate increase over  $k_{HOH}$  before attack ( $k_1$ ) becomes rate determining; any additional catalysis must represent hydrogen bonding.

(c) Still another factor that may increase the importance of hydrogen-bond catalysis with weak nucleophiles is a "Hammond Postulate" type effect that leads to an increase in the Brønsted slope  $\alpha$ . With weak nucleophiles the transition state for nucleophilic attack may be reached later along the reaction coordinate and develop a larger negative charge and basicity on the carbonyl oxygen atom. This will lead to an increase in the Brønsted  $\alpha$  coefficient with a resulting increase in catalysis by moderately strong acids relative to water.

The shapes of some Brønsted curves for general acid catalysis that would be expected from these considerations are shown in Fig. 4. An "Eigen curve" for rate-determining trapping by proton transfer is shown in Fig. 4A, with the arrow indicating the break point at  $\Delta pK = 0$ . A pre-association mechanism with no stabilization by hydrogen bonding (Fig. 4B) shows a break point at a lower  $pK$  value (6). A reaction in which catalysis by hydrogen bonding is facilitated by the short lifetime of the addition intermediate (Fig. 4D) exhibits a Brønsted slope  $>0$ , but breaks to a steeper slope with weak acids as the proton transfer itself becomes rate determining. It is this break and the relatively small rate constant for water ( $k_{HOH} = k_h k_1 / k_{-1}$ ) that makes catalysis so significant experimentally. With a longer lifetime of the intermediate there is less facilitation of hydrogen-bond catalysis and this mechanism becomes important only for the stronger acids, so that there is an additional break in the Brønsted curve (Fig. 4C).

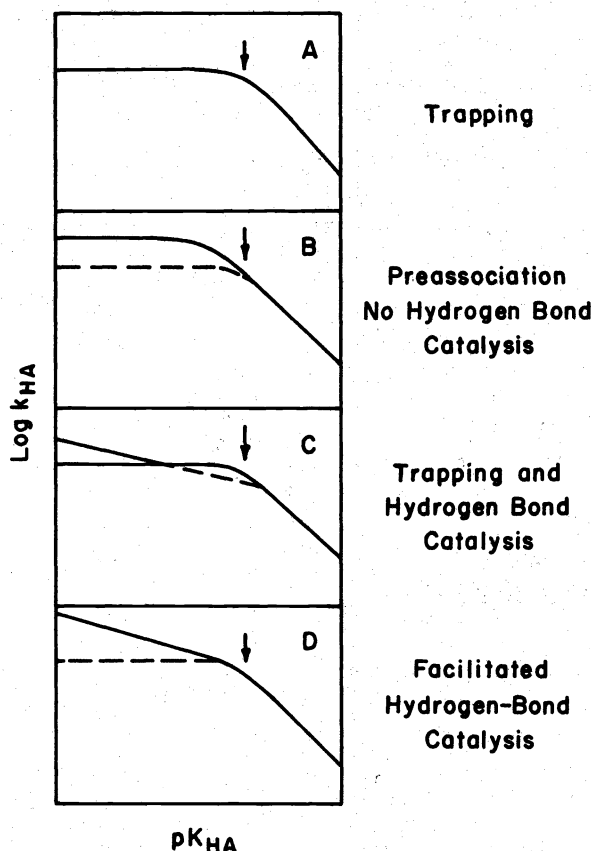


Fig. 4. Schematic Brønsted curves for general acid catalysis.

Although it is difficult to determine  $k_{-1}$  for the expulsion of thiol anions from  $T^-$  directly, this rate constant can be estimated from the  $pK$  and the observed rate constants for the breakdown of hemithioacetals of basic thiols. For expulsion of the anions of ethanethiol, methoxyethanethiol and methyl mercaptoacetate from  $T^-$  the values of  $k_{-1}$  are  $1.6 \times 10^7 \text{ s}^{-1}$ ,  $4.7 \times 10^7 \text{ s}^{-1}$ , and  $1.3 \times 10^8 \text{ s}^{-1}$ , respectively. The rate constants increase with decreasing basicity of the leaving group and extrapolation to the  $pK$  values of 6.5 and 2.7 for *p*-methoxythiophenol and pentafluorothiophenol gives values of  $k_{-1} = \sim 10^9 \text{ s}^{-1}$  and  $10^{10} - 10^{11} \text{ s}^{-1}$ , respectively, well into the range in which catalysis by hydrogen bonding should be facilitated. The Brønsted plot for general acid catalysis of the pentafluorothiophenol reaction (curve C, Fig. 1) exhibits a slope of  $\alpha = 0.26$  and suggests that facilitated hydrogen bonding is the predominant mechanism of catalysis for this compound, in accord with the large value of  $k_{-1}$ . The Brønsted plot for the *p*-methoxythiophenol reaction (curve B, Fig. 1) is clearly different from that for pentafluorothiophenol and is similar to that in Fig. 4C, suggesting that catalysis involves rate-determining trapping with weak acids and hydrogen bonding with a Brønsted slope  $\alpha > 0$  for stronger acids.

These results support the conclusion that catalysis by facilitated hydrogen bonding increases in importance as the intermediate becomes less stable and  $k_{-1}$  increases. The concentrations of acetic acid needed to give a twofold increase in the observed rate are 2.6 M, 0.4 M and 0.001 M for the reactions with methyl mercaptoacetate, *p*-methoxythiophenol and pentafluorothiophenol anions. Since no hydrogen-bonding catalysis can be observed with basic thiol anions ( $\alpha < 0.1$ ) and the observed Brønsted slope is 0.26 for pentafluorothiophenol anion, it is also probable that there is a later, more basic transition state and larger Brønsted  $\alpha$  with less basic thiols.

We do not know at this time what pathway is followed after the transition state of the rate-determining step for hydrogen bonding catalysis. Of the three pathways shown in the reaction coordinate diagram of Fig. 5 the simplest is (a), in which the immediate product is  $T^- \cdot HA$  and proton transfer occurs in a subsequent, separate step. We know that the intermediate  $T^-$  has a finite existence with respect to expulsion of  $RS^-$  for at least some thiols, but we do not know how fast a proton is transferred (possibly through a water molecule) from HA to  $T^-$  so that it is not certain that  $T^-$  can exist as a discrete intermediate. The other possible

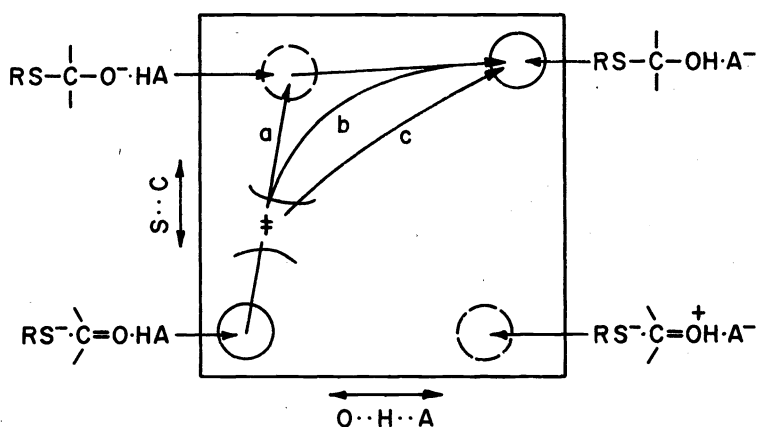
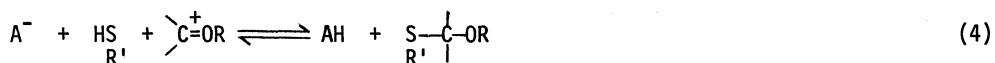


Fig. 5. Reaction coordinate diagram showing different pathways to products after a transition state with hydrogen bonding.

pathways are (b), which is similar to (a) except that it does not involve  $T^-$  as an intermediate, and (c), which is a fully concerted reaction mechanism with an early transition state.

Finally, we can ask what will be the mechanism of catalysis when the nucleophile is still weaker than pentafluorothiophenolate anion. Assuming that  $k_{-1}$  continues to increase as the nucleophile becomes less basic, a point will be reached at which the addition compound  $T^-$  ceases to exist as an intermediate with a significant lifetime when  $k_{-1}$  approaches  $10^{14} \text{ s}^{-1}$ , in the range of a vibration frequency. There are experimental obstacles to the study of such weakly basic anions, but the free thiols, RSH, are extremely weak bases and exhibit general acid catalysis of their addition to acetaldehyde (1). Although this reaction has not been studied in detail, the available data indicate that  $\alpha$  is large. It is unlikely that the reaction involves equilibrium protonation of the carbonyl group and catalysis of proton removal from the attacking thiol (eq. 4, R = H) because no buffer catalysis is observed in the analogous reaction of thiol expulsion from a mixed acetal (eq 4, R = Me)(8). It is



tempting to speculate that general acid catalysis of the addition of a free thiol represents concerted catalysis (path c, Fig. 5) which is enforced by the short lifetime, indeed the nonexistence of the initial addition "intermediate"  $^+ \text{RSHCHR}'\text{O}^-$ . Other addition reactions of weak bases, such as the addition of the nitrogen atom of urea (9,10) exhibit Brønsted  $\alpha$  coefficients near 0.5 and are also candidates for a concerted mechanism of catalysis that is enforced by the nonexistence of the addition compound that would be formed in the absence of proton transfer.

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