

Encounter-Limited Rate-Determining Steps in Carbonyl and Acyl Group Reactions

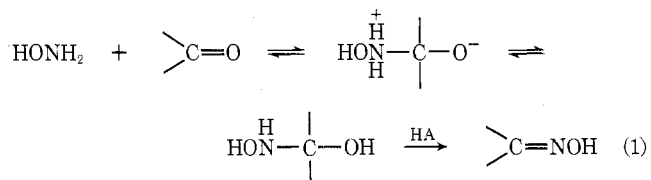
Ronald E. Barnett

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota

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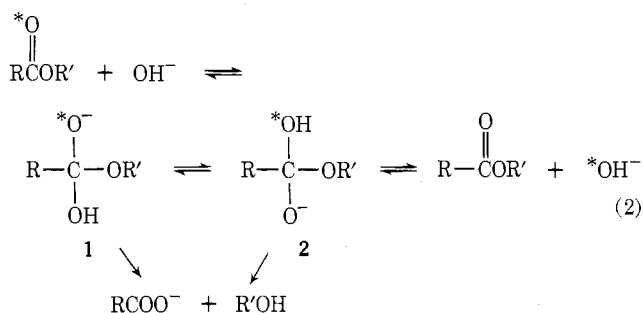
Pick up any standard textbook on physical organic chemistry and you will find that it is generally assumed that encounter-controlled processes, such as thermodynamically favorable proton transfers between electronegative atoms, are too fast to be rate limiting. For example, in Ingold's "Structure and Mechanism in Organic Chemistry,"¹ in a discussion of ester hydrolysis is found the statement that "all proton transfers are regarded as effectively instantaneous." It is hoped that after reading this Account the reader will be aware that for many common reactions this assumption is unjustified.

Tetrahedral intermediates have been shown to be formed in a variety of carbonyl and acyl group reactions.² For many of these reactions the initially formed intermediate must undergo at least one proton transfer before it can break down to products. For example, in oxime formation the initially formed intermediate is a zwitterion which must be converted to the neutral species before dehydration to the oxime can occur (eq 1).³ It is such proton transfers



that have generally been assumed to be too fast to be rate determining.

One of the earliest suggestions that this may not be so comes from Moffat and Hunt.⁴ Alkaline hydrolysis of alkyl benzoates is accompanied by ¹⁸O exchange between the ester and water (eq 2). Bender noted that hydrolysis occurred faster than exchange and interpreted this to mean that formation of the intermediate is rate determining.⁵ Moffat and Hunt noted that the lifetime of the intermediates 1 and 2



may be so short that their equilibration by proton transfer may not be complete, and so the greater rate of hydrolysis compared to exchange may be due to rate-limiting proton transfer in the exchange reaction which does not have to occur in the hydrolysis reaction.

The principal factor in determining whether encounter-controlled steps can be rate determining is the lifetime of the intermediate. The breakdown of tetrahedral intermediates can occur quite rapidly. The expulsion of hydroxylamine from the aminol formed with *p*-chlorobenzaldehyde³ has been estimated to occur with a rate constant of near 10⁹ sec⁻¹ and the expulsion of amine from the intermediate formed in the aminolysis of thiol esters^{6,7} has a rate constant of 10⁸-10⁹ sec⁻¹. Expulsion of water from 3⁸ or of weakly basic thiol anions from 4⁸ and 5⁹ occurs with rate constants ranging from 10⁸ sec⁻¹ to greater than 10¹⁰ sec⁻¹.

Even lifetimes as long as 10⁻³ to 10⁻⁴ sec (corresponding to rate constants for breakdown of 10³-10⁴

(1) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1971, p 1145.

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

(3) J. E. Reimann and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3973 (1966).

(4) A. Moffat and H. Hunt, *J. Amer. Chem. Soc.*, **81**, 2082 (1959).

(5) M. L. Bender, *J. Amer. Chem. Soc.*, **73**, 1626 (1951).

(6) R. E. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 4199 (1968); **91**, 2358 (1969).

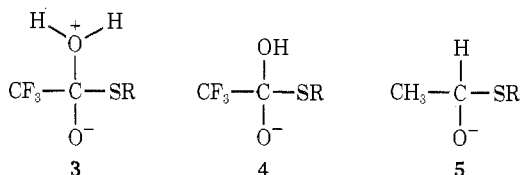
(7) R. K. Chaturvedi and G. L. Schmir, *J. Amer. Chem. Soc.*, **91**, 2358 (1969); G. M. Blackburn, *Chem. Commun.*, 249 (1970).

(8) R. E. Barnett and W. P. Jencks, *J. Org. Chem.*, **34**, 2777 (1969); R. J. Zygumt and R. E. Barnett, *J. Amer. Chem. Soc.*, **94**, 1966 (1972).

(9) R. E. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **89**, 5963 (1967); **91**, 6758 (1969).

Ronald E. Barnett was born in Pueblo, Colorado, in 1942. He received his B.A. in chemistry from the University of Colorado and his Ph.D. under W. P. Jencks from Brandeis University. He was a postdoctoral fellow with H. M. McConnell at Stanford University for the year 1968-1969, and has since been an Assistant Professor of Chemistry at the University of Minnesota. Besides his interest in the mechanisms of carbonyl and acyl group reactions, he is actively involved in studies of membrane biochemistry, especially with respect to energy-dependent membrane transport systems.

sec⁻¹) may be short enough for encounter-controlled processes to be rate determining. Eigen reports the second-order rate constant for protonation of imidazole by hydronium ion¹⁰ to be $1.5 \times 10^{10} M^{-1} \text{sec}^{-1}$.



At pH 7 this corresponds to a pseudo-first-order rate constant of $1.5 \times 10^3 \text{sec}^{-1}$. Water-mediated protonation has a comparable rate constant of $1.3 \times 10^3 \text{sec}^{-1}$.

The overall rate of reaction can be quite slow even though the rate-determining step is encounter-controlled. All that is required is that the rate-determining step be preceded by an unfavorable preequilibrium. Unfortunately, when the encounter-controlled step is preceded by an unfavorable preequilibrium, it is often difficult to demonstrate that the rate-determining step is the encounter-controlled step. Much of this Account deals with an examination of the criteria for determining whether a reaction has an encounter-controlled rate-limiting step and application of these criteria to specific reactions.

There are a limited number of approaches for determining whether a reaction has an encounter-controlled rate-limiting step:

(1) If the first step of a reaction is rate determining, show that the rate constant is near $10^{10} M^{-1} \text{sec}^{-1}$, the expected value for an encounter-controlled process.^{9,10} If the reaction has more than one step, it must be unambiguously demonstrated that the first step in the reaction is rate determining.

(2) Demonstrate by kinetic methods that there must be at least three *sequential* steps, each of which is rate determining for some reaction conditions.⁶

(3) For reactions which are subject to general acid or general base catalysis, show that the Bronsted plot is biphasic for nonsolvent catalysts.^{6-8,11} Eigen has observed that proton transfers between simple acids and bases, such as proton transfer from phenol to a series of amines, exhibit biphasic Bronsted plots.¹⁰ The limiting slopes should be zero and unity and the transition region relatively sharp (Figure 1). The midpoint of the transition should be approximately equal to the pK_a of the species being protonated and deprotonated.

(4) Show by an analysis of transition-state acidities that the mechanism is inconsistent with rate-determining bond formation or bond breaking to carbon.¹² This method can be applied only to analogous

(10) M. Eigen, *Angew. Chem. Int. Ed. Engl.*, **1**, 1 (1964); M. Eigen and L. DeMaeyer in "Technique of Organic Chemistry," Vol. VIII, Part II, A. Weissberger, Ed., Interscience, New York, N. Y., 1963, p 1031.

(11) The Bronsted equation for general base catalysis has the form $\log k_B = \beta pK_{BH^+} + \log G$, where k_B is the rate constant for general base catalysis by the base B, β is the Bronsted coefficient for the reaction, pK_{BH^+} is the pK_a of the conjugate acid of the catalyst, and G is a constant characteristic of the reaction. The corresponding equation for general acid catalysis is $\log k_{HA} = -\alpha pK_{HA} + \log G$.

(12) J. L. Kurz, *J. Amer. Chem. Soc.*, **85**, 987 (1963); J. L. Kurz and J. I. Coburn, *ibid.*, **89**, 3528 (1967).

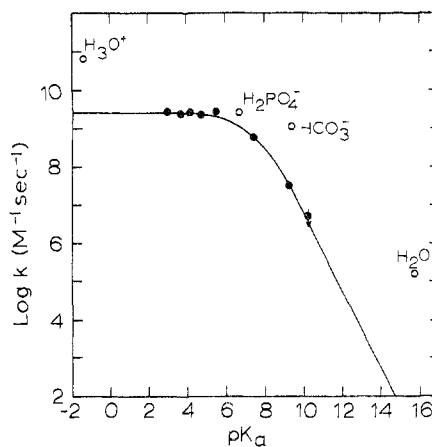


Figure 1. Bronsted plot for general acid catalysis of the intramolecular aminolysis of S-acetylmercaptoethylamine.⁶

reactions which have transition states differing only by the presence or absence of a proton and water of solvation.

(5) Show that the rate of the reaction is inversely proportional to the viscosity of the medium.¹³⁻¹⁵ Encounter-limited processes proceed with rates inversely proportional to viscosity, while reactions which are not encounter controlled should be unaffected by a change in viscosity.

A substantial fraction of the common carbonyl and acyl group reactions may have encounter-limited rate-determining steps. As indicated above, such reactions should exhibit biphasic Bronsted plots. However, within the rather large body of data on general acid and general base catalysis, there are few reports of biphasic Bronsted plots. Furthermore, the reported Bronsted slopes are generally in the range of 0.2 to 0.8. These data suggest that reactions which have an encounter-limited rate-determining step are rare.

A great deal of care must be taken in interpreting such data. For example, consider the deprotonation of phenol by a series of amines (Figure 2), a reaction which has an encounter-limited rate constant in the thermodynamically favorable direction.¹⁰ The dashed line is calculated from Eigen's theory for proton transfer between simple acids and bases. Ideally the transition region between the limiting slopes should be about 2 pK_a units. For deprotonation of phenol the transition region is relatively broad, covering 5-6 pK_a units, and the data consistently fall below the calculated curve. Moreover, encounter-controlled proton transfer involving the solvent species hydronium ion, hydroxide ion, or water is often 10-30 times faster than one would predict extrapolating from nonsolvent acids and bases.¹⁰ (However, in *slow* proton transfer reactions, hydronium ion is often an abnormally *poor* donor.) For example, protonation of ammonia by hydronium ion has a rate constant of $4.3 \times 10^{10} M^{-1} \text{sec}^{-1}$, while the limiting value for protonation by strong nonsolvent acids is about $2 \times 10^9 M^{-1} \text{sec}^{-1}$. As a consequence of the relatively broad transition region between the limiting slopes

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

(14) P. Debye, *Trans. Electrochem. Soc.*, **82**, 265 (1942).

(15) A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms," Wiley, New York, N. Y., 1961, p 271.

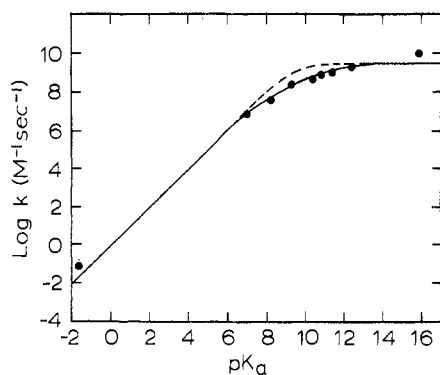


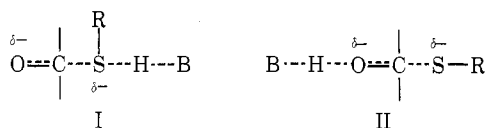
Figure 2. Rate constants for proton transfer from phenol to a series of bases.¹⁰

and of the positive deviation of the solvent rates, it is possible to obtain a respectable looking, although misleading, Bronsted plot with $\beta \approx 0.3$ for deprotonation of phenol (Figure 3).

A further problem is that in the transition region different classes of acids or bases, such as ammonium ions and carboxylic acids, do not lie on the same curve. If a Bronsted plot is to be used as a criterion for determining whether a reaction has an encounter-limited rate-determining step, the catalysts used should be limited to a single class of compounds, the acidities or basicities of the catalysts should cover at least five orders of magnitude, and solvent points should be excluded.

Reactions with Encounter-Limited Rate-Determining Steps. The hydroxide ion catalyzed breakdown of hemithioacetals of acetaldehyde is strongly dependent on the pK_a of the departing thiol, with a Bronsted $\beta = 1$ for the leaving group.¹⁶ However, as the pK_a of the thiol is decreased, the rate constant for decomposition becomes pH independent, with a limiting value of $1 \times 10^{10} M^{-1} sec^{-1}$.⁹ The reaction is also subject to general base catalysis, and hydroxide ion is probably functioning as a general base.

The two possible mechanisms for catalysis are illustrated by transition states I and II. Mechanism I



corresponds to the rapid formation of the hemithioacetal anion in a preequilibrium step, followed by general acid catalysis of the expulsion of the thiol. In the direction of hemithioacetal formation it corresponds to general base catalysis by removal of a proton from the attacking thiol. Mechanism II corresponds to general base catalysis of the elimination of thiol anion and, in the reverse direction, to general acid catalysis of the addition of thiol anion by proton donation to the carbonyl group.

The mechanism of transition state I can be ruled out if one considers the process from the direction of hemithioacetal formation. Catalysis is observed at pH 5 for the thioacetic acid-acetaldehyde system. At this pH the thiol is already more than 98% ionized to

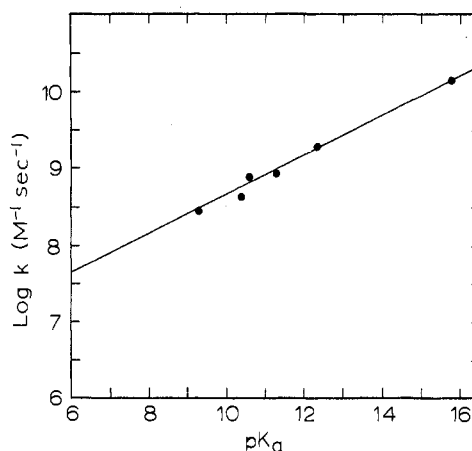
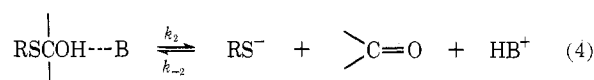
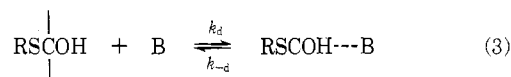


Figure 3. Rate constants for proton transfer from phenol to a series of bases.¹⁰

the anion (the pK_a of thioacetic acid is 3.20), so that catalysis by partial proton removal from the small amount of free thiol present could hardly give rise to a significant rate increase. The observed catalysis in the 0.5 M acetate at this pH corresponds to a rate increase of more than eightfold. With hydroxide ion as the catalyzing base the third-order rate constant required for hemithioacetal formation according to mechanism I is $4.6 \times 10^{11} M^{-2} sec^{-1}$. This is greater than the second-order rate constant for an encounter-controlled reaction,¹⁰ and it does not appear possible to divide this reaction into a series of bimolecular reactions which would proceed at less than diffusion-controlled rates. This leaves the mechanism of transition state II, as shown in eq 3-4, as the most



probable mechanism.

If the Bronsted plots for general base catalysis of the decomposition of the hemithioacetals of acetaldehyde and thioacetic acid, *p*-nitrobenzenethiol, and benzenethiol are extrapolated to the pK_a of hydroxide ion, the rate constants predicted for hydroxide ion are in excess of $10^{10} M^{-1} sec^{-1}$. This implies that, if the mechanism of eq 3-4 is correct, catalysis by hydroxide ion should be encounter controlled (k_d of eq 3 rate determining for hydroxide ion, k_2 of eq 4 rate determining for weaker bases) with a rate constant near $10^{10} M^{-1} sec^{-1}$. This is in fact observed. Moreover, the energy of activation for hydroxide ion catalyzed decomposition is 2-3 kcal/mol, and the solvent deuterium isotope effect, $k(\text{H}_2\text{O})/k(\text{D}_2\text{O})$, is 1.25, both of which are consistent with an encounter-limited reaction.^{17,18}

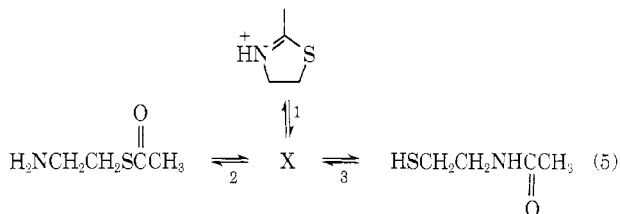
The rate-determining step of thiol ester aminolysis above pH 2 seems to be a simple encounter-controlled proton transfer.⁶ This can be seen from the following arguments. The hydrolysis of 2-methyl- Δ^2 -thiazoline undergoes a change in rate-determining

(16) G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3983 (1966).

(17) Z. Luz and S. Meiboom, *J. Amer. Chem. Soc.*, **86**, 4768 (1964).

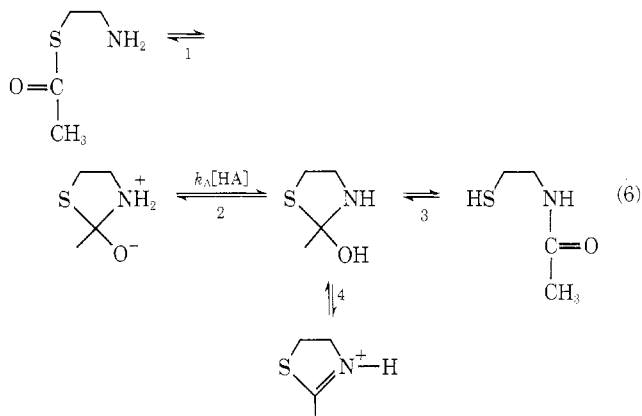
(18) R. J. Day and C. N. Reilly, *J. Phys. Chem.*, **71**, 1588 (1967).

ing step requiring that there be an intermediate in the reaction.¹⁹ Below pH 2 approximately equal amounts of thiol ester and amide are produced and the ratio of amide to ester is pH independent. Martin, *et al.*,¹⁹ determined that breakdown of the intermediate formed in thiazoline hydrolysis is rate determining below pH 2. The same intermediate should be formed in the hydrolysis of thiazoline to thiol ester and amide as is formed in the aminolysis of the thiol ester (eq 5). Since equal amounts of thiol ester and amide are formed below pH 2 and since breakdown of the intermediate is rate determining, both steps 2 and 3 of eq 5 must be partially rate determining in thiol ester aminolysis.



Furthermore, since the ratio of thiol ester to amide formed in thiazoline hydrolysis is pH independent, steps 2 and 3 must proceed through transition states of the same net charge. This implies for thiol ester aminolysis that a change in rate-determining step should not occur from changing the pH. However Martin, *et al.*,²⁰ found that a change in rate-determining step in thiol ester aminolysis occurs near pH 2, contradicting the inferences obtained from examining thiazoline hydrolysis. The data for thiazoline hydrolysis and thiol ester aminolysis can be reconciled if some step other than steps 2 and 3 of eq 5 becomes rate determining above pH 2.⁶

A mechanism which is consistent with all the data is shown in eq 6, where steps 1 and 3 would be each



partially rate determining below pH 2, and step 2, an encounter-controlled proton transfer, rate determining above pH 2. Consistent with this mechanism are the observations that (1) the value of α for general acid catalysis by carboxylic acids and phosphate monoanion of thiol ester aminolysis is zero, as ex-

pected for an encounter-controlled proton transfer; (2) the catalytic constant for the solvated proton is 24 times higher than for carboxylic acids and phosphate monoanion, corresponding to the known rapid rate of proton transfer from this species; (3) catalytic constants for catalysts with $\text{p}K_a$ values greater than 7.4 approach the expected Bronsted slope of $\alpha = 1.0$ for weak acids in a simple proton-transfer reaction in the thermodynamically unfavorable direction (Figure 1); and (4) the break in the Bronsted plot of *S*-chloroacetylmercaptoethylamine occurs 1.5 $\text{p}K$ units lower than for the acetyl compound, as predicted from the reduced basicity of the addition intermediate in this reaction. Similar conclusions have been drawn for intermolecular thiol ester aminolysis.⁷

One property which should be characteristic of an encounter-limited reaction is an inverse dependence on the viscosity of the medium.^{14,15} Equilibrium constants and nonencounter-limited processes should be independent of viscosity. One way of increasing the viscosity of an aqueous medium is to add glycerol. Water and glycerol form relatively ideal mixtures,^{21,22} glycerol has a relatively high dielectric constant (42.5), and water activity seems to be linearly correlated with water mole fraction,²² so this system looks promising for the continuous variation of viscosity. This method has been applied to the hydrolysis of 2-methyl- Δ^2 -thiazoline to thiol ester and amide.¹³ It was found that the encounter-limited step is proportional to the reciprocal of the viscosity, while equilibria and nonencounter-limited steps are relatively unaffected in going from water to 60% glycerol. Variation of viscosity using aqueous glycerol is a technique of considerable promise as probe for encounter-limited rate-determining steps.

Another apparent case of a diffusion-limited acyl group reaction is hydrolysis of the thiol ester, methyl *S*-trifluoroacetylmercaptoacetate.⁸ In acid solution the rate of hydrolysis decreases below the pH-independent rate of hydrolysis observed at higher pH values. This decrease is not due to a change in activity coefficients, and so there is a kinetically demonstrable intermediate. The rate-determining step in acid solution has an anionic transition state and must be a breakdown of an anionic intermediate, since an anionic transition state for formation of the intermediate, *i.e.*, attack of hydroxide ion on the thiol ester, would have to have a rate constant of $10^{13} \text{ M}^{-1} \text{ sec}^{-1}$. Such a rate constant is considerably greater than an encounter-controlled rate constant, and so the mechanism can be eliminated.

The pH-independent rate of hydrolysis must therefore represent rate-determining formation of the intermediate through a transition state of zero charge. This step is also subject to general base catalysis, and so the pH-independent rate probably represents attack of water general base catalyzed by water.

A reaction scheme which is consistent with the data is shown in eq 7. Below pH 1 k_2 becomes rate determining with $k_{\text{obsd}} = (k_1/k_{-1})k_2$. Since $K_{\text{H}}K_a =$

(19) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Amer. Chem. Soc.*, **81**, 5089 (1959); R. B. Martin and A. Parcell, *ibid.*, **83**, 4830 (1961).

(20) R. B. Martin and R. I. Hedrick, *J. Amer. Chem. Soc.*, **84**, 106 (1962); R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 3197 (1964).

(21) R. H. Stokes and R. A. Robinson, *J. Phys. Chem.*, **70**, 2126 (1966); R. A. Robinson and R. A. Stokes, "Electrolytic Solutions," 2nd ed, Wiley, New York, N. Y., 1959, pp 241-245.

(22) L. L. Schaleger and C. N. Richards, *J. Amer. Chem. Soc.*, **92**, 5565 (1970).

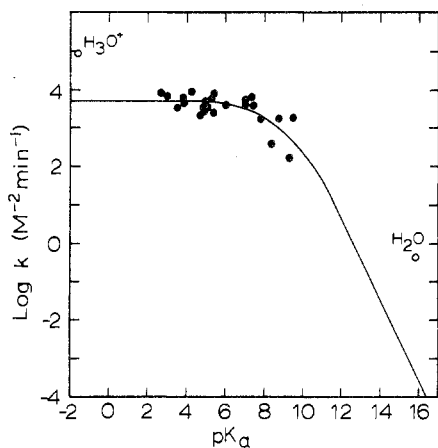
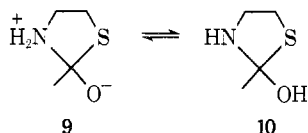


Figure 5. Bronsted plot for the reaction of semicarbazide with *p*-chlorobenzaldehyde.²⁵

stant of $5 \times 10^{10} M^{-1} \text{sec}^{-1}$ for hydronium ion catalyzed protonation of 8,¹⁰ the value for several carboxylic acids is about $3 \times 10^9 M^{-1} \text{sec}^{-1}$. This may be compared to values of $2-3 \times 10^9 M^{-1} \text{sec}^{-1}$ for carboxylic acid catalyzed protonation of 9, the intermediate formed in intramolecular thiol ester aminolysis.⁶ The rate constant for direct conversion of 8 to 7 catalyzed by water, $1.5 \times 10^7 \text{sec}^{-1}$, is similar to the rate constant of $9 \times 10^6 \text{sec}^{-1}$ for the direct conversion of 9 to 10 in thiol ester aminolysis.⁶ It must

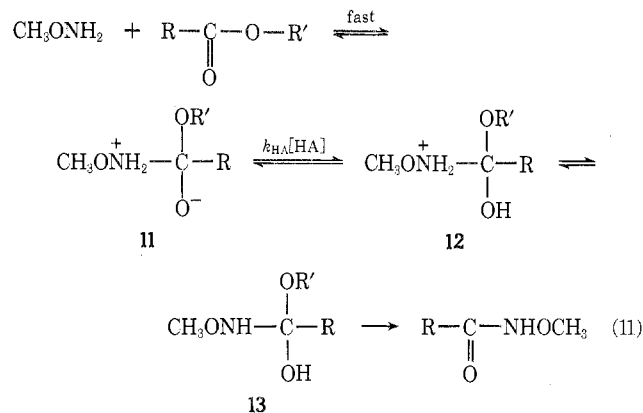


be concluded that the mechanism of eq 10 cannot be ruled out from the existing data.

The methoxyaminolysis of *p*-nitrophenyl acetate is general acid catalyzed with $\alpha \approx 0$ for several carbox-

ylic acids.²⁶ For less acidic ammonium ion catalysts α increases with the transition occurring for catalysts with pK_s 's near 5.5. The authors proposed that the difference in the value of α for carboxylic acids and ammonium ions may be due to bifunctional catalysis on the part of the carboxylic acids.

However, another explanation is consistent with the experimental observations. This is illustrated by the mechanism of eq 11, which is virtually identical



with the proposed mechanism for thiol ester aminolysis.^{6,7} The rate-determining step would then be conversion of 11 to 12. The transition from $\alpha = 0$ to $\alpha = 1$ should occur for catalysts with pK_a 's near the pK_a of the OH group of 12. Using a $\Sigma\sigma_I-pK_a$ correlation for alcohols²³ the predicted pK_a of 18 is 5.3 to 7.5. The observed transition at 5.5 is consistent with this prediction, and so the mechanism of eq 11 cannot be ruled out as a possibility.

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(26) L. do Amaral, K. Koehler, D. Barlenbach, T. Pletcher, and E. H. Cordes, *J. Amer. Chem. Soc.*, 89, 3537 (1967).

Organic Ion Pairs as Intermediates in Nucleophilic Substitution and Elimination Reactions¹

Richard A. Sneen

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

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A particularly unfortunate, although perhaps inevitable, consequence of the recognition of carbonium ions as reaction intermediates in certain substitutions at saturated carbon was the tendency to as-

sume that they are more universal than is in fact the case. Very soon after their recognition disquieting experimental data were forthcoming that could be forced into the carbonium ion picture only by making certain *ad hoc* assumptions about their behavior. Thus the partial inversion of configuration accompanying solvolysis of optically active 2-octyl halides in various solvents was ascribed to partial shielding of

Richard A. Sneen is a native of Wisconsin and attended St. Olaf College and then the University of Illinois (Ph.D., 1955, E. J. Corey). He was then a research associate at UCLA in the laboratory of the late Saul Winstein. Since 1956 he has been on the staff at Purdue University where he is now Professor. His research interests are concentrated in the field of organic reaction mechanisms with special emphasis on the roles of ion pairs in substitution and elimination reactions.

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