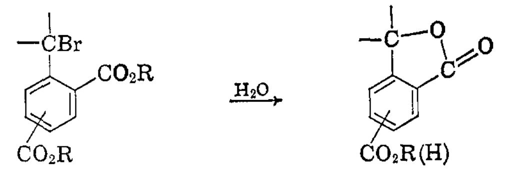
thoxy groups in the reaction of V is extensive enough so that there is significantly less hydration of the activated complex and correspondingly less change in entropy than in the other reactions. The carbomethoxy groups themselves are probably very nearly properly positioned even before activation occurs. From the thermodynamic standpoint the unusual reactivity of V must be accounted for entirely in terms of the favorable entropy of activation, since the energy of activation for hydrolysis of this halide is as large as that for hydrolysis of any of the halides under consideration.

The Products of Hydrolysis of the Dicarbomethoxy-Substituted Benzyl and Phenylethyl Bromides. The product which has been isolated from the hydrolysis of *o*-carbomethoxybenzyl bromide is the lactone, phthalide.[1] It has not been established whether this is the immediate reaction product or whether *o*-carbomethoxybenzyl alcohol is first formed and is then converted to phthalide. Lactones have also been obtained by hydrolysis of the dicarbomethoxy-substituted benzyl and phenylethyl bromides (eq 2).



(2)

In some of the reactions, the second carbomethoxy group was hydrolyzed, undoubtedly through catalysis by hydrogen bromide generated in the solvolysis of the organic bromide.

Acknowledgment. The authors are indebted to the National Science Foundation for a grant in support of this research. Some of the work on the manuscript was done at the Chemistry Department, The University of Hull, Hull, England, which served as a kind host to L. J. Andrews during his stay there as a Fulbright–Hays Research Scholar, 1967–1968. M. J. S. is further indebted to the National Science Foundation for a Predoctoral Cooperative Fellowship.

Some Relationships between the Hydrolysis of Imidate Esters and the Mechanisms of Related Acyl Transfer Reactions

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New Haven, Connecticut 06510. Received January 23, 1968

Abstract: Quantitative relationships are presented relating the effects of pH and general acid–base catalysts on the yields of the hydrolysis products of imidate esters to the rates and mechanisms of related acyl transfer reactions. Mechanisms including tetrahedral addition intermediates in acid–base equilibrium are found to account satisfactorily for parallel observations made in both types of systems. The kinetics of acyl transfer in O-acetylethanolamine are reinterpreted and conclusions are drawn concerning the influence of pH on the nature of the products formed by hydrolysis of 2-methylthiazoline, 2-methyloxazoline, and N-hydroxythioimidate esters.

The chemistry of the tetrahedral addition intermediates formed in many nucleophilic reactions at the acyl carbon atom has become the focus of intense investigation.[1] An understanding of the factors which control the formation and decomposition of these metastable intermediates should furnish the basis for a complete description of the acyl transfer reaction. For reactions in aqueous solution, particular attention must be directed at the following questions. (1) Do there exist several tetrahedral intermediates in acid–base equilibrium with each other? (2) What is the effect of pH variation on the distribution of these species? (3) What is the mode of decomposition of each species of the intermediate? (4) How is the decomposition of each species affected by the presence of general acid–base catalysts? Answers to the first three questions lead to a definition of the influence of pH on the nature of the rate-determining step. The understanding of the mechanism of general acid–base catalysis of the over-all reaction is dependent on the answer to the fourth question.

In earlier reports,[2–5] we have shown that studies of the hydrolysis of imidate esters provide valuable information concerning the mechanism of related acyl transfer reactions. If proton transfers are sufficiently rapid to allow acid–base equilibrium to occur between tetrahedral intermediates generated from different reactants (see, for example, Scheme I) knowledge of the behavior of the intermediates generated in imidate hydrolysis is sufficient for the complete kinetic description of the two related nucleophilic acyl transfer processes. The validity of this assumption has been partially demonstrated in one instance: the effects of

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(1) (a) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (b) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964); (c) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1966; (d) S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

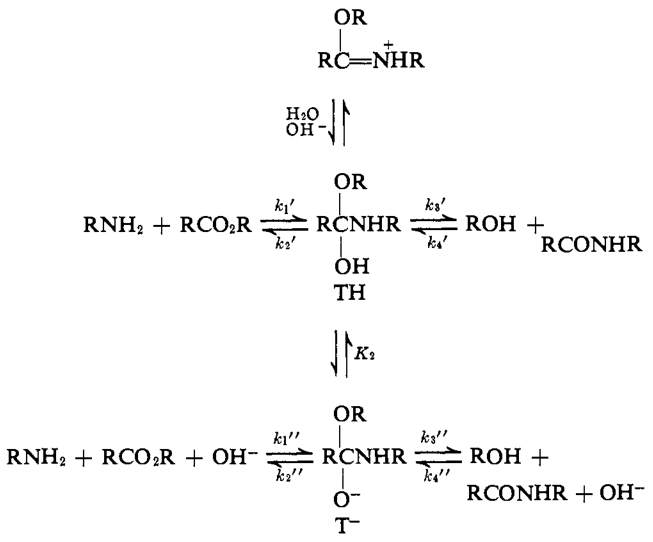
(2) G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, **87**, 5692 (1965).

(3) B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

(4) B. A. Cunningham and G. L. Schmir, *ibid.*, **89**, 917 (1967).

(5) R. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *ibid.*, **89**, 6984 (1967).

Scheme I



pH and of acid–base catalysts on the products of hydrolysis of the iminolactone 2-(N-phenylimino)tetrahydrofuran led to the prediction that the conversion of 4-hydroxybutyranilide to aniline and butyrolactone should be subject to bifunctional catalysis. The kinetics of the latter reaction were in quantitative agreement with expectation.[2-4]

The variation of the products of imidate hydrolysis with pH is probably a widespread phenomenon. With imidates and thioimidates, we suggested that this observation resulted from the different modes of decomposition of tetrahedral addition intermediates in acid–base equilibrium. Based on this hypothesis, it will be shown in what follows that accurate knowledge of the nature of the products of imidate hydrolysis as a function of pH should allow quantitative description of the pH–rate profile for the acyl transfer reactions leading to the interconversion of the hydrolysis products. In principle, the first three questions stated above can be completely answered simply by analysis for the products of imidate hydrolysis. It may be found, however, that some of the desired information is experimentally inaccessible in this manner; such might be the case when the yield of a given product is nearly zero or 100% and is thus difficult to measure accurately. Alternatively, if the products undergo rapid interconversion, none of the questions may be answerable from the study of imidate hydrolysis. It will be shown that, in these instances, it should be possible to rely solely on the study of the kinetics of one of the acyl transfer reactions. Finally, the effects of acid–base catalysts on the nature of the products of imidate hydrolysis bear direct and predictable relationships to the effects of these catalysts on the rates and mechanism of the acyl transfer reactions; several cases will be considered from a quantitative viewpoint.

We emphasize that the relationships elaborated in the remainder of this paper are critically dependent on the above-stated assumption of rapid proton transfers between tetrahedral intermediates. Failure to observe in an acyl transfer reaction the kinetic behavior predicted from the study of the products of hydrolysis of the related imidate may be evidence for the existence of a rate-determining proton transfer.

The Influence of pH on the Initial Products of Hydrolysis of Imidates and on the Rates of Interconversion of the Products

Case I (Scheme I). A. The Products of Hydrolysis of the Imidate Ester. Assumptions: The hydrolysis of the imidate proceeds *via* the formation of *neutral* (TH) and *anionic* (T^-) tetrahedral intermediates. Each species of the intermediate gives rise to different ratios of the possible pairs of products (*i.e.*, $k_2'/k_3' \neq k_2''/k_3''$). The rate of interconversion of the product pairs, *via* steps k_1', k_1'', k_4', and k_4'', is negligible under the conditions of imidate hydrolysis (*i.e.*, amine + ester $\not\rightleftharpoons$ amide + alcohol). For simplicity, it is also assumed that hydration of the protonated imidate by water or hydroxide ion is the rate-determining step of the hydrolysis reaction in the pH range under consideration. Numerous kinetic studies of the hydrolysis of Schiff bases,[6] thiazolines,[7] oxazolines,[8] and other imidate[2,9] and thioimidate[5] esters support this assumption. The steady-state approximation is applied to all species of the intermediate.

The fraction of amine in the total product is given[10] by eq 1.

$$\%\ \text{amine} = \frac{\left(\dfrac{k_2'}{k_2' + k_3'}\right)[\mathrm{H}^+] + \left(\dfrac{k_2''}{k_2'' + k_3''}\right)K'}{[\mathrm{H}^+] + K'} \tag{1}$$

The mechanism of Scheme I thus predicts that the yield of amine formed on hydrolysis of the imidate will vary with pH as the sigmoid curve characteristic of the dissociation of a univalent acid of dissociation constant $K' = K_2(k_2'' + k_3'')/(k_2' + k_3')$ (Figure 1A). The yield of amine obtained asymptotically at low pH is $k_2'/(k_2' + k_3')$ and describes the partitioning of the neutral intermediate TH. The yield of amine formed at high pH is given by $k_2''/(k_2'' + k_3'')$ and similarly describes the partitioning of the anionic intermediate to amine or amide. The constant K' is determined both by the partitioning ratios of TH and T^- and by the dissociation constant K_2 of the neutral intermediate.

B. The pH–Rate Profile for Ester Aminolysis. Assumptions: The formation of imidate by acid-catalyzed dehydration of TH does not occur in the pH range under consideration. Alcoholysis of the amide is negligible ($k_4' = k_4'' = 0$). The steady-state approximation is applied to TH and T^-.

The second-order rate constant with respect to amine free base varies with pH as eq 2. The pH–rate profile thus defined is of the general shape shown in Figure 1B when log k_{obsd}/[free amine] is plotted *vs.* pH. Four

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(6) (a) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, 84, 832 (1962); (b) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963); (c) K. Koehler, W. Sandstrom, and E. H. Cordes, *ibid.*, **86**, 2413 (1964).

(7) (a) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *ibid.*, 81, 5089 (1959); (b) R. B. Martin and A. Parcell, *ibid.*, 83, 4830 (1961); (c) G. L. Schmir, *ibid.*, 87, 2743 (1965).

(8) (a) R. B. Martin and A. Parcell, *ibid.*, 83, 4835 (1961); (b) R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, 41, 1662 (1963).

(9) (a) M. Kandel and E. H. Cordes, *J. Org. Chem.*, **32**, 3061 (1967); (b) R. K. Chaturvedi and G. L. Schmir, *J. Am. Chem. Soc.*, in press.

(10) The detailed derivation of a similar expression may be found in ref 2, Appendix, parts B and C. The numerator of eq 20 in the reference should be corrected to read $[\mathrm{H}]k_3(k_1 + k_7[\mathrm{OH}])/k_2$. In that case, it could be assumed that TH gave exclusively amine ($k_2' \gg k_3'$) and that T^- gave exclusively amide ($k_3'' \gg k_2''$).

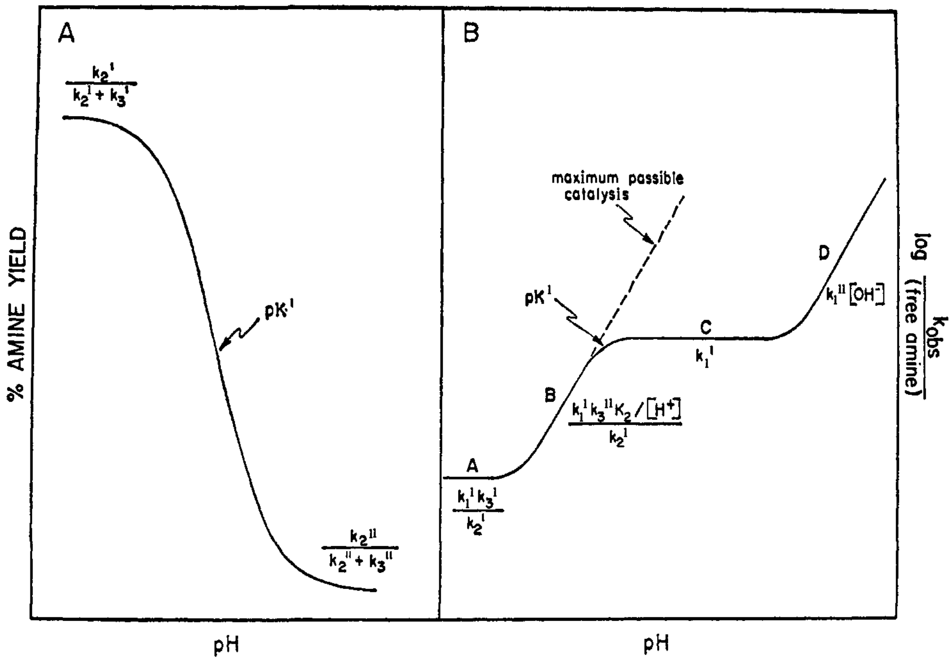

Figure 1. Effect of pH on tetrahedral intermediates obeying the relationships of Scheme I. A, Effect of pH on yield of amine formed by hydrolysis of the imidate ester. Rate constant ratios describing the asymptotes refer to steps of Scheme I. B, Effect of pH on rate of ester aminolysis. The terms describing the four regions of the pH profile are from Table I and refer to the special case of $k_2' \gg k_3'$ and $k_3'' \gg k_2''$.

$$\frac{k_{\text{obsd}}}{[\text{free amine}]} = \frac{(k_3' + k_3''K_2/[\text{H}^+])(k_1' + k_1''[\text{OH}^-])}{(k_2' + k_3') + (k_2'' + k_3'')K_2/[\text{H}^+]} \qquad (2)$$

distinct regions (A–D) appear, two of which are of unit slope (B and D) while the other two are pH ranges where the second-order rate constant is independent of pH. In terms of the rate and equilibrium constants of Scheme I, the four regions are described by the expressions listed in Table I (column 3). These expressions are derived from eq 2, using the equilibrium constraints of eq 3 and the assumptions listed

$$k_1'/k_2' = k_1''[\text{OH}^-]/(k_2''K_2/[\text{H}^+]) \qquad (3)$$

in Table I (column 2). The general formulations for the four regions of the pH profile are reduced to simpler terms (Table I, column 4) in the extreme case where $k_2' \gg k_3'$ and $k_3'' \gg k_2''$, *i.e.*, when TH yields almost exclusively amine and T^- breaks down almost solely to amide.

Certain additional conclusions drawn from the foregoing analysis are summarized in Tables I and II. The displacements of regions B and D, or C and A, from each other are a function of the partitioning ratios of the intermediates. In the extreme case, the B/D ratio, equivalent to the distance between inflection points 2 and 3 along the pH axis, is a direct measure of the partitioning of T^-; the C/A ratio, equivalent to the distance between inflection points 1 and 2 along the pH axis, defines the corresponding term for TH. Table II also lists the hydrogen ion concentrations at which the inflection points separating the various regions will occur.

Table I. The pH–Rate Profile for Aminolysis of Esters According to Scheme I

pH range[a]	Assumptions	k_{obsd}/[free amine]: General case	k_{obsd}/[free amine]: Extreme case[b]	Rate-determining step	Main pathways: Attack	Main pathways: Product formation
A	$k_3' > k_3''K_2/[\text{H}^+]$ $k_1' > k_1''[\text{OH}^-]$ $k_2' > k_3''K_2/[\text{H}^+]$	$\frac{k_1'k_3'}{k_2' + k_3'}$	$\frac{k_1'k_3'}{k_2'}$	Breakdown of TH	k_1'	k_3'
B	$k_3''K_2/[\text{H}^+] > k_3'$ $k_1' > k_1''[\text{OH}^-]$ $k_2' > k_3''K_2/[\text{H}^+]$	$\frac{k_1'k_3''K_2/[\text{H}^+]}{k_2' + k_3'}$	$\frac{k_1k_3''K_2/[\text{H}^+]}{k_2'}$	Breakdown of T^-	k_1'	k_3''
C	$k_3''K_2/[\text{H}^+] > k_3'$ $k_1' > k_1''[\text{OH}^-]$ $k_3''K_2/[\text{H}^+] > k_2'$	$\frac{k_1'k_3''}{k_2'' + k_3''}$	k_1'	Nucleophilic attack	k_1'	k_3''
D	$k_3''K_2/[\text{H}^+] > k_3'$ $k_1''[\text{OH}^-] > k_1'$ $k_3''K_2/[\text{H}^+] > k_2'$	$\frac{k_1''k_3''[\text{OH}^-]}{k_2'' + k_3''}$	$k_1''[\text{OH}^-]$	Hydroxide ion catalysis of nucleophilic attack	k_1''	k_3''

[a] See Figure 1B. [b] $k_2' \gg k_3'$; $k_3'' \gg k_2''$.

Table II. Quantitative Relationships of the pH–Rate Profile for Ester Aminolysis According to Scheme I

Calculation[a]	General case	Extreme case[b]
Ratio B/D	$\dfrac{1 + k_3''/k_2''}{1 + k_3'/k_2'}$	k_3''/k_2''
Ratio C/A	$\dfrac{1 + k_2'/k_3'}{1 + k_2''/k_3''}$	k_2'/k_3'
Ratio B/C	$\dfrac{(k_2'' + k_3'')K_2}{(k_2' + k_3')[\mathrm{H}^+]} = \dfrac{K'}{[\mathrm{H}^+]}$	$\dfrac{k_3''K_2}{k_2'[\mathrm{H}^+]}$

Inflection point[c]	$[\mathrm{H}^+]$[d]
1 (A–B)	$k_3''K_2/k_3'$
2 (B–C)	$\dfrac{(k_2'' + k_3'')K_2}{(k_2' + k_3')} = K'$
3 (C–D)	$k_2''K_2/k_2'$

[a] Based on the formulations listed in Table I. [b] $k_2' \gg k_3'$; $k_3'' \gg k_2''$. [c] The intersection of lines extending the regions of slope 0 and +1 of Figure 1B. [d] Hydrogen ion concentration at which inflection point occurs.

It should be noted that the aminolysis reaction undergoes a transition from rate-determining breakdown of the intermediates to rate-determining addition of amine to ester at the pH where regions B and C meet. The numerical value of the pH where this transition occurs (pK') is identical with the pH where transition occurred between the two possible sets of products formed on hydrolysis of the imidate ester (Figure 1A). Thus, knowledge of the nature of the products of imidate hydrolysis leads to an unambiguous definition of the nature of the rate-limiting steps in the corresponding aminolysis reaction. In addition, the partitioning ratios for TH and T$^-$ determine the asymptotes of the sigmoid curve of Figure 1A and the relative positions of the various regions of the pH–rate profile of Figure 1B, and may be calculated from either type of data.

C. The Alcoholysis of Amides. If ester aminolysis may be negelected ($k_1' = k_1'' = 0$), the second-order rate constant for alcoholysis of the amide depends on pH as eq 4. This equation is the counterpart of eq 2

$$k_{\text{obsd}} = \frac{(k_2' + k_2''K_2/[\mathrm{H}^+])(k_4' + k_4''[\mathrm{OH}^-])}{(k_2' + k_3') + (k_2'' + k_3'')K_2/[\mathrm{H}^+]} \qquad (4)$$

and describes a pH–rate profile identical in shape with that for ester aminolysis (Figure 1B). Without need for detailed analysis, it may be stated that, at low pH, the rate-limiting step of the alcoholysis reaction is the formation of the tetrahedral intermediates. At pH = pK', transition takes place to rate-determining breakdown of the intermediates.

D. Some Experimental Observations. a. The Hydrolysis of Imidate Esters. Plots of amine yield *vs.* pH for the hydrolysis of an iminolactone[2] and three acyclic imidate esters derived from aniline,[9b] α-methylphenethylamine,[9b] and morpholine[11] are accurately sigmoid in shape. The inflection points (pK') of these plots lie in the pH range 7.1–8.4, leading to the prediction that the related ester aminolyses and amide alcoholyses should undergo transitions in rate-determining step at weakly alkaline pH. The yields of product formed at the asymptotes of the sigmoid curve could not be determined with high accuracy, so that the complete aminolysis pH profile is not predictable.

b. The Aminolysis of Methyl Formate.[11] Kinetic evidence for transitions from rate-determining breakdown of tetrahedral intermediates at low pH to rate-determining attack of the amine at high pH has been obtained for the reaction of methyl formate with five amines. With hydrazine, the pH–rate profile for aminolysis corresponds to regions A–B–C of Figure 1B, while with glycinamide and morpholine, rate data were obtained for regions B–C–D. In all cases, transition occurs in the pH range 6.3–8.4. For the reaction with morpholine, the value of pK' (7.4) deduced from ester aminolysis was found to be in reasonable agreement with that obtained by study of the hydrolysis of the corresponding imidate (pK' = *ca.* 7.7).

The results of Blackburn and Jencks allow calculation of some partitioning ratios for TH and T$^-$, information which would be accessible only with difficulty from imidate hydrolysis. The imidate ester corresponding to methyl formate and hydrazine would be converted to amine in a yield of about 96% at acid pH (breakdown of TH). The formimidates obtained from glycinamide and morpholine should exhibit partitioning ratios k_3''/k_2'' of about 230 and 780, respectively.

c. The Hydrolysis of 2-Methyloxazoline. The interesting question of the influence of pH on the *initial* products of the hydrolysis of 2-methyloxazoline has not been answered by direct study of oxazoline hydrolysis.[8,12] It is known that, at pH <7, the exclusive hydrolysis product is O-acetylethanolamine; however, the rapid base-catalyzed isomerization[12–14] of O-acetyl- to N-acetylethanolamine masks the possibility that, at alkaline pH, oxazoline ring cleavage yields N-acetylethanolamine directly. If the hydrolysis of 2-methyloxazoline obeys the mechanism of Scheme I, kinetic study of the interconversion of the hydrolysis products should disclose the desired information. The precise rate measurements of Hansen[13] for acetyl transfer from O-acetylethanolamine lend themselves well to such analysis.[15] The general eq 2 is equivalent to eq 5 when the assumption is made that TH yields predominantly amine ($k_2' \gg k_3'$). The following values[16a] were assigned to the constants of eq 5: pK' = 7.6; $k_1' = 2.2 \times 10^{-3}$ sec^{-1}; k_1'' = 180 M^{-1} sec^{-1}; and $k_3''/(k_2'' + k_3'')$ =

$$\frac{k_{\text{obsd}}}{[\text{free amine}]} = \frac{K'k_3''(k_1' + k_1''[\mathrm{OH}^-])}{([\mathrm{H}^+] + K')(k_2'' + k_3'')} \qquad (5)$$

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(11) G. M. Blackburn and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 2638 (1968).

(12) G. R. Porter, H. N. Rydon, and J. A. Schofield, *J. Chem. Soc.*, 2686 (1960).

(13) B. Hansen, *Acta Chem. Scand.*, **17**, 1307 (1963).

(14) R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 3197 (1964).

(15) (a) Mechanism bb proposed by Hansen[13] does not seem to account completely for his rate measurements at high pH. In the notation of Scheme I of our paper, Hansen invokes uncatalyzed aminolysis of the ester (steps k_1' and k_2') followed by breakdown of an anionic intermediate to products (steps K_2 and k_3''). We find it necessary to postulate an additional base-catalyzed aminolysis path (steps k_1'' and k_2'') to obtain satisfactory agreement between calculated pH–rate profile and Hansen's data. The need to consider hydroxide-ion catalysis of acetyl transfer in this system has been previously recognized.[14] (b) We are grateful to Dr. B. Hansen for kindly providing us the numerical values of the data shown in Figure 1 of ref 13.

(16) (a) It should be noted that the four terms of eq 5 to which numerical values are assigned are not independently variable. Because of the

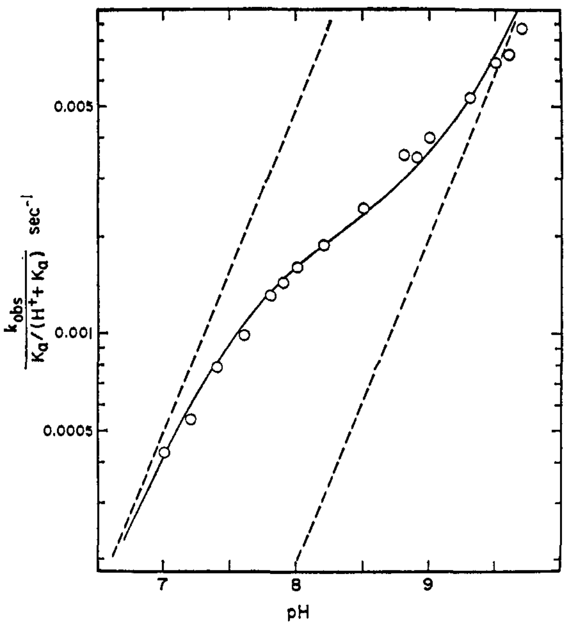


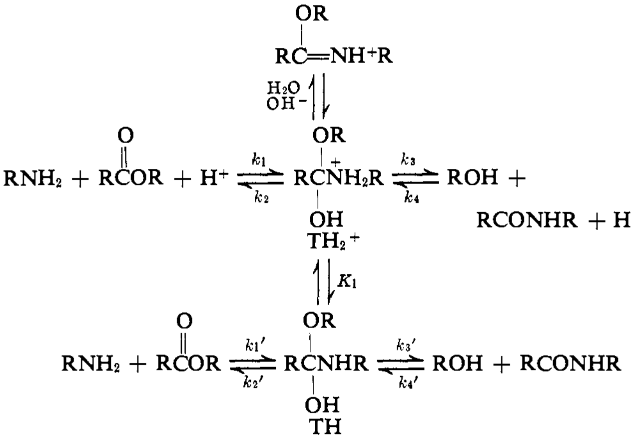
Figure 2. Effect of pH on rate of O → N acetyl transfer in O-acetylethanolamine. Data are from ref 13 and also supplied by Dr. B. Hansen. Observed first-order rate constants are divided by the fraction of substrate in the free base form, using pK_a = 8.94.[13] Solid curve is calculated from eq 5, using the constants given in the text. Dashed lines are drawn with slope = 1.

0.96. The satisfactory agreement of the assumed mechanism with the experimental data is seen in Figure 2, thus explaining the anomalous fractional-order dependence of the rate of acetyl transfer on hydroxide ion concentration. With respect to oxazoline hydrolysis, it is then possible to conclude that hydrolysis at acid pH yields mainly O-acetylethanolamine (from TH) and hydrolysis at alkaline pH gives predominantly N-acetylethanolamine (T^- partitioning about 96% to the N-acetyl isomer) and that the transition between the two modes of ring cleavage occurs at pH 7.6.

d. The Alcoholysis of 4-Hydroxybutyranilide.[4] The pH-rate profile for the appearance of aniline by intramolecular alcoholysis of 4-hydroxybutyranilide was studied in regions C–D of Figure 1B. These rate data as well as additional information from catalysis experiments (see below) were used to calculate a transition point (pK') of 7.13, in good accord with the value of 7.07 observed in experiments with the corresponding imidate ester.[2] The partitioning ratio (k_3''/k_2'') for the anionic tetrahedral intermediate was calculated to be 1500, a result not easily obtainable from studies of iminolactone hydrolysis.

Case II (Scheme II). A. The Products of Hydrolysis of the Imidate Ester. Assumptions: The hydrolysis of the imidate proceeds *via* the formation of *cationic* (TH_2^+) and *neutral* (TH) tetrahedral intermediates. Each species of the intermediate gives rise to different products, whose rate of interconversion is negligible under the conditions of imidate hydrolysis. It is again assumed that hydration of the protonated imidate by water or hydroxide ion is the rate-determining step of the hydrolysis reaction. The steady-state approximation is applied to all species of the intermediate.

Scheme II



The fraction of amine in the total product is given by eq 6, where $K' = K_1(k_2' + k_3')/(k_2 + k_3)$.

$$\%\ \text{amine} = \frac{\left(\dfrac{k_2}{k_2 + k_3}\right)[\mathrm{H}^+] + \left(\dfrac{k_2'}{k_2' + k_3'}\right)K'}{[\mathrm{H}^+] + K'} \qquad (6)$$

As with case I, the mechanism of Scheme II predicts that the yield of amine formed on hydrolysis of the imidate will vary as the titration curve of an acid of dissociation constant K' (Figure 3A). The asymptotic yields at low and high pH are $k_2/(k_2 + k_3)$ and $k_2'/(k_2' + k_3')$ and describe the partitioning of TH_2^+ and TH, respectively.

B. The pH–Rate Profile of Ester Aminolysis. The assumptions made are the same as for case I, part B. The second-order rate constants with respect to amine free base varies with pH according to eq 7. The corresponding pH–rate profile is shown schematically in Figure 3B, and differs significantly from that of case I.

$$\frac{k_{\text{obsd}}}{[\text{free amine}]} = \frac{(k_3 + k_3'K_1/[\mathrm{H}^+])(k_1[\mathrm{H}^+] + k_1')}{(k_2 + k_3) + (k_2' + k_3')K_1/[\mathrm{H}^+]} \qquad (7)$$

Four regions (A–D) are discernible, the slopes of which are alternately −1 and 0. In Table III (column 3) are listed the terms describing each region of the pH profile, based on eq 7 and the equilibrium condition of eq 8. In the extreme case where TH_2^+ gives largely

$$\frac{k_1}{k_2} = \frac{k_1'}{k_2'K_1} \qquad (8)$$

amine and TH breaks down mainly to amide, simplified expressions are obtained (Table III, column 4). Other quantitative features of the pH–rate profile appear in Table IV.

The aminolysis reaction undergoes a transition from rate-determining breakdown of tetrahedral intermediates to rate-determining attack of amine at the inflection point linking regions B and C. This point (pK') is again identical with the midpoint of the sigmoid profile of the product–pH curve of Figure 3A. As

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equilibrium restriction of eq 3, it follows from the definition of K' (with $k_3' = 0$) that $k_3''/(k_2'' + k_3'') = 1 - (k_1''K_w/k_1'K')$. Selection of values for k_1'', k_1', and K' thus completely determines the curve defined by eq 5. K_w = ion product of water. (b) By analogy to the hydrolysis of imidates and other imines, we previously[5] favored Scheme I to account for the effect of pH on the products of hydrolysis of thioimidate esters. Although the kinetics of aminolysis of thiol esters provide support for Scheme II, the existence of the unresolved "thiazoline dilemma"[14] is evidence of our imperfect knowledge of the mechanisms of these reactions.

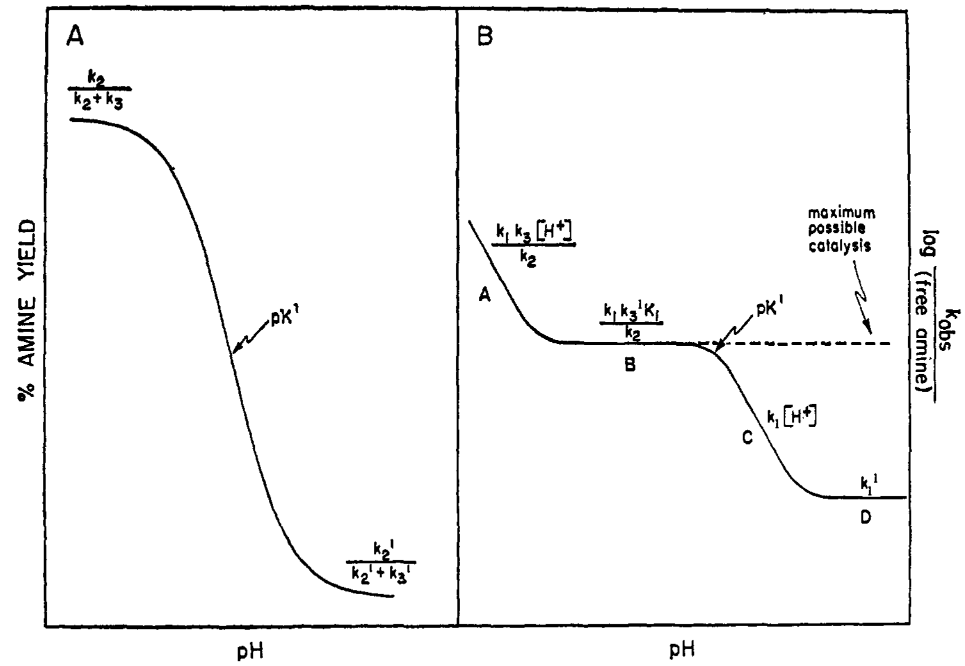

Figure 3. Effect of pH on tetrahedral intermediates obeying the relationships of Scheme II. A, Effect of pH on yield of amine formed by hydrolysis of the imidate ester. Rate constant ratios describing the asymptotes refer to steps of Scheme II. B, Effect of pH on rate of ester aminolysis. The terms describing the four regions of the pH profile are from Table III and refer to the special case of $k_2 \gg k_3$ and $k_3' \gg k_2'$.

set forth in detail for case I, knowledge of the nature of the products of imidate hydrolysis as a function of pH leads to the complete description of the related aminolysis pH profile, and *vice versa.*

Table III. The pH–Rate Profile for Aminolysis of Esters According to Scheme II

pH range[a]	Assumptions	k_{obsd}/[free amine] General case	k_{obsd}/[free amine] Extreme case[b]	Rate-determining step	Main pathways Attack	Main pathways Product formation
A	$k_3 > k_3'K_1/[H^+]$ $k_2 > (k_2' + k_3')K_1/[H^+]$ $k_1[H^+] > k_1'$	$\frac{k_1k_3[H^+]}{(k_2 + k_3)}$	$\frac{k_1k_3[H^+]}{k_2}$	Breakdown of TH_2^+	k_1	k_3
B	$k_3'K_1/[H^+] > k_3$ $k_2 > (k_2' + k_3')K_1/[H^+]$ $k_1[H^+] > k_1'$	$\frac{k_1k_3'K_1}{k_2 + k_3}$	$\frac{k_1k_3'K_1}{k_2}$	Breakdown of TH	k_1	k_3'
C	$k_3'K_1/[H^+] > k_3$ $(k_2' + k_3')K_1/[H^+] > k_2$ $k_1[H^+] > k_1'$	$\frac{k_1k_3'[H^+]}{k_2' + k_3'}$	$k_1[H^+]$	Acid-catalyzed nucleophilic attack by amine	k_1	k_3'
D	$k_3'K_1/[H^+] > k_3$ $(k_2' + k_3')K_1/[H^+] > k_2$ $k_1' > k_1[H^+]$	$\frac{k_1'k_3'}{k_2' + k_3'}$	k_1'	Nucleophilic attack by neutral amine	k_1'	k_3'

[a] See Figure 3B. [b] $k_2 > k_3$; $k_3' > k_2'$.

C. Some Experimental Observations. a. The Hydrolysis of Thiomidate Esters.[5] The effect of pH on the products of hydrolysis of two acyclic thioimidate esters derived from aniline and ammonia conforms closely to the expected sigmoid relationship, with p*K*' = 2.7–2.9. While these data do not distinguish between the mechanisms of Schemes I and II, studies of the aminolysis of thiol esters (see below) lend support to the hypothesis that the hydrolysis of thioimidates is described by Scheme II.[16b]

b. Acetyl Transfer in S-Acetyl-β-mercaptoethylamine and the Hydrolysis of 2-Methylthiazoline. The pH–rate profile for S–N acetyl transfer in S-acetyl-β-mercaptoethylamine[17] agrees with regions B–C–D of Figure 3B and has been interpreted[14,18] in terms of a mechanism analogous to that of Scheme II. The transition in rate-determining step (p*K*') is calculated for pH 3.08 (25°) and leads to the prediction that the product of hydrolysis of 2-methylthiazoline should vary with pH according to Figure 3A, with a midpoint at about pH 3. This conclusion is supported by the previously cited observation[5] that acyclic thioimidate esters yield predominantly amine and thiol ester at pH <2 and amide and mercaptan at higher pH, transition occurring at pH 2.7–2.9. Because of rapid

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(17) R. B. Martin and R. I. Hedrick, *J. Am. Chem. Soc.*, 84, 106 (1962).

(18) Martin and coworkers[14] have emphasized the fact that certain aspects of this proposal conflict seriously with the mechanism presented for the hydrolysis of 2-methylthiazoline.[7] These apparent contradictions have not yet been reconciled.

Table IV. Quantitative Relationships of the pH–Rate Profile for Ester Aminolysis According to Scheme II

Calculation[a]	General case	Extreme case[b]
Ratio B/D	$\dfrac{1 + k_3'/k_2'}{1 + k_3/k_2}$	k_3'/k_2'
Ratio C/A	$\dfrac{1 + k_2/k_3}{1 + k_2'/k_3'}$	k_2/k_3
Ratio B/C	$\dfrac{(k_2' + k_3')K_1}{(k_2 + k_3)[\mathrm{H}^+]} = \dfrac{K'}{[\mathrm{H}^+]}$	$\dfrac{k_3'K_1}{k_2[\mathrm{H}^+]}$
Inflection point[c]	**$[\mathrm{H}^+]$[d]**	
1 (A–B)	$k_3'K_1/k_3$	
2 (B–C)	$\dfrac{(k_2' + k_3')K_1}{(k_2 + k_3)} = K'$	
3 (C–D)	$k_2'K_1/k_2$	

[a] Based on the formulations listed in Table III. [b] $k_2 \gg k_3$; $k_3' \gg k_2'$. [c] The intersection of lines extending the regions of slope −1 and 0 of Figure 3B. [d] Hydrogen ion concentration at which inflection point occurs.

S-N acyl transfer at pH >2, it is difficult to obtain corroborative evidence by direct examination of the products of thiazoline hydrolysis. Nevertheless, the suggestion[7a,14] that the ratio of S-acyl to N-acyl products in the hydrolysis of thiazolines is independent of pH should be treated with caution.

c. The Hydroxylaminolysis of Thiol Esters. In an important paper, Bruice and Fedor[19,20] described kinetic evidence for the existence of tetrahedral intermediates in acid–base equilibrium during the reaction of hydroxylamine with thiol esters. The data of these authors may be analyzed according to Scheme II and lead to the interesting conclusion that the transition in rate-determining step in the hydroxylaminolysis of several thiol esters occurs at pH 6.0–6.9, with the corollary that pK' for the hydrolysis of the corresponding N-hydroxythioimidate esters is in the same pH range. If it is assumed that $\mathrm{TH_2}^+$ breaks down almost exclusively to thiol ester and hydroxylamine, it follows that the yield of amine obtained at high pH from TH ranges from 9 to 31% for the several cases considered.

In view of the observations that in imidate hydrolysis,[9b,11] pK' increases somewhat with increasing basicity of the amine and that with thioimidates,[5] pK' lies below pH 3 for compounds derived from aniline or ammonia, it is surprising that pK' for N-hydroxythioimidates should be predicted to occur at pH 6–7.

General Acid–Base Catalysis

The first part of this paper has dealt with the effects of pH on the formation and decomposition of tetrahedral intermediates, *i.e.*, with the effects of catalysis by water and hydronium and hydroxide ions. The influence of general acid–base catalysts will now be briefly considered, with attention to quantitative relationships between the manifestations of such effects on the products of imidate hydrolysis and on the rates of aminolysis reactions.

For clarity, the system to be examined will be a hypothetical one conforming to Scheme I, with the added simplification that in the absence of catalysts, TH and T^- yield exclusively amine and amide, respectively ($k_3' = k_2'' = 0$). The examples discussed are meant solely to illustrate an approach to such phenomena; it is certain that more elaborate explanations will be required in some experimental situations.

A. Interaction of TH with a Nonionizable Catalyst. Consider Scheme I, modified by the added reaction of TH with a catalyst $\mathrm{B_T}$ to yield amine (eq 9).

$$\mathrm{TH} \underset{k_1'''[\mathrm{B_T}]}{\overset{k_2'''[\mathrm{B_T}]}{\rightleftharpoons}} \mathrm{RNH_2} + \mathrm{RCO_2R} \qquad (9)$$

a. The Products of Imidate Hydrolysis. Plots of per cent yield of amine *vs.* concentration of catalyst $\mathrm{B_T}$ are rectangular hyperbolas (eq 10). The intercept

$$\%\ \text{amine} = \frac{(k_2'/k_2''') + [\mathrm{B_T}]}{(k_2'/k_2''')([\mathrm{H}^+] + K')/[\mathrm{H}^+] + [\mathrm{B_T}]} \times 100 \qquad (10)$$

on the *y* axis ($[\mathrm{B_T}] = 0$) indicates the effect of pH alone on the amine yield (*cf.* eq 1). As catalyst concentration approaches infinity, amine yield tends to 100%. At fixed pH, the first term in the denominator of eq 10 (K_{app}) is constant and is equal to the concentration of catalyst required to achieve half the possible increase in amine yield (from the intercept value to 100%). The ratio k_2'''/k_2' is a measure of the effectiveness of the catalyzed conversion of TH to amine relative to the uncatalyzed (or water-catalyzed) process and may be calculated from K_{app} if K' is known. The three parameters characterizing the hyperbola of eq 10 may be evaluated by computer curve-fitting procedures[5] or, if the amine yield in the absence of catalyst is known, by the customary double-reciprocal plots.[3,21] At low concentrations of catalyst (or with ineffective catalysts), plots of amine yield *vs.* $\mathrm{B_T}$ are approximately linear (eq 11). From the slope ($1/K_{\mathrm{app}}$) and intercept

$$\text{amine yield} = [\mathrm{H}^+]/([\mathrm{H}^+] + K') + ([\mathrm{H}^+]/([\mathrm{H}^+] + K'))(k_2'''/k_2')[\mathrm{B_T}] \qquad [11)$$

of such plots may be calculated the catalytic coefficient (k_2'''/k_2') characteristic of the given catalyst.

Scheme I and eq 9 predict that, at high catalyst concentration, the yield of amine at any pH approaches the yield of amine formed at low pH in the absence of catalyst (*i.e.*, from TH alone).

Hyperbolic dependences of amine yield on buffer concentration have been observed in the hydrolyses of cyclic[3] and acyclic[9b] imidate esters and of thioimidate esters.[5]

b. The Aminolysis of Esters. In the presence of the catalyst $\mathrm{B_T}$, the rate of aminolysis reaction in the pH range of rate-determining amine attack (Figure 1B, region C) is given by eq 12 (derived from Scheme I and

$$\frac{k_{\mathrm{obsd}}}{[\text{free amine}]} = \frac{(K'k_2'/k_2'''[\mathrm{H}^+])(k_1' + k_1'''[\mathrm{B_T}])}{(k_2'/k_2''')([\mathrm{H}^+] + K')/[\mathrm{H}^+] + [\mathrm{B_T}]} \qquad (12)$$

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(19) T. C. Bruice and L. R. Fedor, *J. Am. Chem. Soc.*, **86**, 4886 (1964).

(20) Mechanism 29 of ref 19 is in accord with the observed kinetic behavior but predicts that hydrolysis of the corresponding thioimidates will yield exclusively amide and mercaptan at low pH (from $\mathrm{TH_2}^+$), with increasing amounts of amine as pH increases. In view of the known effects of pH on the products of hydrolysis of thioimidates,[5] we prefer the alternative formulation of Scheme II. With $k_3 = 0$, eq 7 of the present paper becomes identical in form with eq 30 of Bruice and Fedor.

(21) The relative merits of several alternative linear transformations of hyperbolic curves have been critically discussed by J. E. Dowd and D. S. Riggs, *J. Biol. Chem.*, 240, 863 (1965).

Table V. Influence of Catalytic Mechanism on K_{app} and Maximum Yield of Amine in Imidate Hydrolysis

Catalyzed reactions[a]	K_{app}	Maximum amine yield[b]
(1) $\mathrm{TH} \underset{k_1'''[\mathrm{B_T}]}{\overset{k_2'''[\mathrm{B_T}]}{\rightleftharpoons}} \mathrm{RNH_2}$	$\dfrac{k_2'([\mathrm{H^+}] + K')}{k_2'''[\mathrm{H^+}]}$	1
(2) $\mathrm{TH} \underset{k_1'''[\mathrm{BH}]}{\overset{k_2'''[\mathrm{BH}]}{\rightleftharpoons}} \mathrm{RNH_2}$	$\dfrac{k_2'([\mathrm{H^+}] + K')([\mathrm{H^+}] + K_a)}{k_2'''[\mathrm{H^+}]^2}$	1
(3)[c] $\mathrm{TH} \underset{k_1'''[\mathrm{B}]}{\overset{k_2'''[\mathrm{B}]}{\rightleftharpoons}} \mathrm{RNH_2}$	$\dfrac{k_2'([\mathrm{H^+}] + K')([\mathrm{H^+}] + K_a)}{k_2'''[\mathrm{H^+}]K_a}$	1
(4) $\mathrm{TH} \underset{k_1'''[\mathrm{B_T}]}{\overset{k_2'''[\mathrm{B_T}]}{\rightleftharpoons}} \mathrm{RNH_2}$ $\mathrm{TH} \underset{k_4'''[\mathrm{B_T}]}{\overset{k_3'''[\mathrm{B_T}]}{\rightleftharpoons}} \mathrm{RCONH_2}$	$\dfrac{k_2'([\mathrm{H^+}] + K')}{(k_2''' + k_3''')[\mathrm{H^+}]}$	$\dfrac{k_2'''}{k_2''' + k_3'''}$

[a] $\mathrm{B_T}$ = nonionizable catalyst; BH and B are the conjugate acid and conjugate base forms, respectively, of a catalyst of dissociation constant K_a. [b] Expressed as fraction of total product. [c] Kinetically identical with reaction of T with BH.

eq 9). It is therefore expected that the rate of aminolysis will vary with catalyst concentration as a rectangular hyperbola, with linear dependence on catalyst at low catalysts concentration, becoming independent of catalyst at high concentrations.

At high catalyst concentration, the rate of aminolysis approaches eq 13 as a limit (Figure 1B, dashed line).

$$\frac{k_{\mathrm{obsd}}}{[\text{free amine}]} = k_1'''k_2'K'/k_2'''[\mathrm{H^+}] = k_1'k_3''K_2/k_2'[\mathrm{H^+}] \quad (13)$$

As a result of catalysis on steps k_1' and k_2', the rate-determining step in the aminolysis reaction in region C has been changed from amine attack to breakdown of the intermediate, assumed in this instance to be unaffected by the presence of catalyst. Consequently, the maximum rate achieved is a function of pH and the maximum catalysis possible in region C increases with pH. From similar considerations, it may be shown that the maximum possible catalysis for systems obeying Scheme II is given by the dashed line of Figure 3B, assuming catalysis on steps k_1' and k_2'.

The denominators of eq 10 and 12 are identical. Knowledge of K_{app} for amine formation from the imidate ester thus immediately indicates the buffer concentration required to achieve half the maximal possible rate increase in the aminolysis reaction. At low catalyst concentration, the rate of aminolysis varies linearly with catalyst (eq 14) and the catalytic co-

$$\frac{k_{\mathrm{obsd}}}{[\text{free amine}]} = k_1'K'/([\mathrm{H^+}] + K') + [\mathrm{B_T}]k_1'''K'/([\mathrm{H^+}] + K') \quad (14)$$

efficient k_1'''/k_1' is obtained from the slope and intercept of such plots. Since $k_1'''/k_1' = k_2'''/k_2'$, quantitative knowledge of the effects of the catalyst on the amine yield from the imidate is sufficient for the prediction of the parallel effects on the rates of aminolysis reactions.

In several instances, nonlinear dependences of rate on buffer concentration in acyl transfer reactions have been interpreted in terms of changes in rate-limiting steps.[4,14,22] With 4-hydroxybutyranilide,[4] the rate constants approached at high buffer concentration were used to calculate the partitioning ratio of the anionic tetrahedral intermediate $\mathrm{T^-}$ since region B of the pH–rate profile, normally used for such calculations (see Table II), was not readily accessible experimentally.

B. Some Other Mechanisms. A number of possible mechanisms involving interaction between catalysts and one or more species of tetrahedral intermediates will lead to hyperbolic plots of amine yield *vs.* catalyst concentration, and hence to nonlinear rate–catalyst dependences in the related acyl transfer reactions. Some of these mechanisms are distinguishable from each other by studies of the pH dependence of K_{app} and of maximum amine yield; a few possible cases are briefly considered here and are summarized in Table V.

a. Interaction of TH with the Conjugate Acid BH of a Catalytic Buffer of Acid Dissociation Constant K_a. The maximum yield of amine is 100%; K_{app} is independent of pH at lowest pH and becomes inversely proportional to $[\mathrm{H^+}]^2$ as pH increases. Several examples of this behavior have been found in imidate hydrolysis.[3,9b]

b. Interaction of TH with the Conjugate Base B of the Catalyst. Maximum yield of amine is 100%; K_{app} varies with pH as the reciprocal of a bell-shaped curve, with a minimum value (maximum effectiveness of the catalyst) at pH = $(\mathrm{p}K' + \mathrm{p}K_a)/2$. The reaction of $\mathrm{T^-}$ with BH follows the same pattern. Buffer effects on product yields in the hydrolysis of thioimidates were in agreement with this mechanism.[5]

c. Interaction of TH with a Nonionizable Catalyst to Yield Amine (Step k_2''') and Simultaneous Interaction (at a Different Rate, k_3''') to Yield Amide. The maximum yield of amine formed at all pH values is less than 100% and is given by $k_2'''/(k_2''' + k_3''')$. According to this mechanism, it is possible to obtain a smaller yield of amine in the presence of the catalyst than in its absence.

A large variety of other possibilities involving interactions of TH or $\mathrm{T^-}$ with BH, B, or combinations of both species suggest themselves. For example, iminolactone hydrolysis was affected by phosphate buffer in a manner consistent with the interaction of TH with both species of the buffer to yield amine.[3] It is evident

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(22) (a) R. B. Martin, A. Parcell, and R. I. Hedrick, *J. Am. Chem. Soc.* **86**, 2406 (1964); (b) G. E. Lienhard and W. P. Jencks, *ibid.*, **87**, 3855 (1965); (c) S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, **20**, 1892 (1966); (d) S. O. Eriksson and L. Bratt, *ibid.*, **21**, 1812 (1967); (e) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc*, **86**, 5616 (1964); (f) D. R. Robinson and W. P. Jencks, *ibid.*, **89**, 7098 (1967).

that each mode of tetrahedral intermediate–catalyst interaction found in imidate hydrolysis will have its quantitative counterpart in the related acyl transfer reactions. Use of this reasoning led to the verifiable prediction that the alcoholysis of 4-hydroxybutyranilide should be subject to bifunctional catalysis by certain general acid–base catalysts.[3,4] Finally, we have omitted from consideration the most general and at the same time most complex situation, that involving simultaneously three tetrahedral intermediates, TH_2^+, TH, and T^-, each giving rise to different products on breakdown and each subject to particular catalytic influences. Clearly, a thorough analysis of the general case should provide the framework for the description of many acyl transfer reactions.

Conclusions

Two qualitative observations derived from the study of the products of hydrolysis of imidate esters have provided strong support for the existence of tetrahedral intermediates in such reactions: (1) the effect of pH variation on the nature of the products of hydrolysis is not related to the effect of pH on the over-all reaction rate; (2) at constant pH, catalysts alter the yields of hydrolysis products without affecting the over-all rate of hydrolysis. In the present paper, it has been shown that a number of additional quantitative conclusions may be stated concerning the effects of pH and general acid–base catalysts on the rates and mechanisms of certain acyl transfer reactions. It appears that many aspects of the chemistry of the elusive addition intermediates formed at the acyl carbonyl group will be amenable to study by these indirect methods.

Acknowledgment. Support of this work by the National Institutes of Health is gratefully acknowledged (Grant No. AM-04288). We wish to thank Professor W. P. Jencks for informing us of the results of the study of ester aminolysis prior to publication.

The Acid-Catalyzed Hydrolysis of a Series of Phosphoramidates[1]

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Abstract: The acid-catalyzed hydrolysis of a series of six 2,4-dichlorophenyl methyl N-alkylphosphoramidates (I) has been studied. Most of the reactions were carried out in 25% dioxane in water (v/v) in the presence of 0.19 *M* HCl, with the concentration of phosphoramidate being 0.002 *M*. The reactions were followed kinetically by ultraviolet spectrophotometry and were found to be first order in phosphoramidate. Product determination experiments showed that the hydrolysis involved P–N bond cleavage with negligible liberation of 2,4-dichlorophenol or alcohol. The product of acid hydrolysis is thus the appropriate alkylamine salt of 2,4-dichlorophenyl methyl phosphoric acid (II). Activation energies and entropies were calculated, the highly negative value of the latter showing the reaction to be bimolecular. The hydrolysis is first order in hydronium ion as shown by pH dependence studies. The phosphoramidates hydrolyzed faster by a factor of 2 in D_2O than in H_2O, indicating a fast prior protonation of the substrate. A small increase in the rate of hydrolysis of the methyl phosphoramidate was observed with increasing percentage of water in the solvent at the same pH. Linear free-energy relationships were used to determine the effect of the N-alkyl substituent on the rate of hydrolysis. It was concluded that both steric and polar substituent effects operate, with an increase in bulk of the substituent hindering the reaction slightly while electron withdrawal aids the reaction. Possible mechanisms are proposed for the acid hydrolysis of the phosphoramidate diesters.

Phosphoramidates are important as pesticides and several of them, including schradan (octamethylpyrophosphoramide), Ruelene (4-*t*-butyl-2-chlorophenyl methyl N-methylphosphoramidate), and Zytron (2,4-dichlorophenyl methyl N-isopropylphosphoramidothiolate), are now on the market. There is evidence that diesters of phosphoramidic acid should act as phosphorylating agents in nucleotide synthesis,[3] and these compounds have been found useful as chemical reagents for the synthesis of unsaturated organic nitrogen compounds.[4]

Phosphoramidates are esters of phosphoramidic acid, $(HO)_2P(O)NH_2$. Much of the chemical interest in this class of compounds is due to the presence of the phosphorus-to-nitrogen bond and its susceptibility to cleavage in aqueous acidic solution. (Hydrolysis in alkaline solution leads principally to P–O bond cleavage.[5]) Although there is recorded a relatively large

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(1) (a) Presented in part at the 18th Southeastern Regional Meeting of the American Chemical Society, Louisville, Ky., Oct 1966. (b) Mention of products and manufacturers in this publication is for identification only and does not imply endorsement by the Federal Water Pollution Control Administration or the United States Department of the Interior.

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(3) A. R. Todd, *Proc. Chem. Soc.*, 199 (1962).

(4) W. S. Wadsworth and W. D. Emmons, *J. Org. Chem.*, **29**, 2816 (1964).

(5) J. E. Berger and E. Wittner, *J. Phys. Chem.*, 70, 1025 (1966).