# Concurrent General Acid and General Base Catalysis in the Hydrolysis of an Imidate Ester. I. Monofunctional Catalysis

Yin-Nan Lee and Gaston L. Schmir*

Contribution from the Department of Molecular Biophysics and Biochemistry, Yale University School of Medicine, New Haven, Connecticut 06510. Received May 5, 1978

Abstract: The effect of general acid–base catalysis on the breakdown of the tetrahedral intermediate generated by the hydration of the imidate ester I has been studied in 0.5% acetonitrile–water at 30 °C, $\mu = 0.5$. In terms of a neutral tetrahedral intermediate, amine formation is effectively catalyzed by general acids ranging in pK from 3 to 10. The Brønsted plot exhibits a sharp break at catalyst pK about 5.5. Catalysis by stronger acids is essentially independent of catalyst pK; catalytic constants for acids of p$K > 6$ fall on a line of slope = 1.00 ± 0.07. General base catalysis of the breakdown of a neutral intermediate is correlated by a Brønsted line of slope $\beta = 0.17 \pm 0.03$. These observations suggest that general acid catalysis involves a kinetically significant proton transfer step, while protonation and cleavage of the carbon–nitrogen bond may be concerted in the general base catalyzed reaction. The proposed mechanism accounts for these findings, as well as for the observation that the buffer-independent transition in products from amine to amide with increasing pH is not correlated with the effect of pH on the rate of hydrolysis of the imidate ester.

Studies of the effects of general acid–base catalysts on the nature of the products of hydrolysis of imidate esters have had several important consequences. First, the observation that certain buffers increase the yield of amine with little or no change in the overall rate of hydrolysis has provided compelling evidence for the existence of intermediates on the reaction pathway, with the catalyst acting mainly on the product-determining breakdown of the intermediates, and not on the rate-determining formation step(s) (e.g., eq 1).[1-4] Second, the

(1)

buffer catalysis
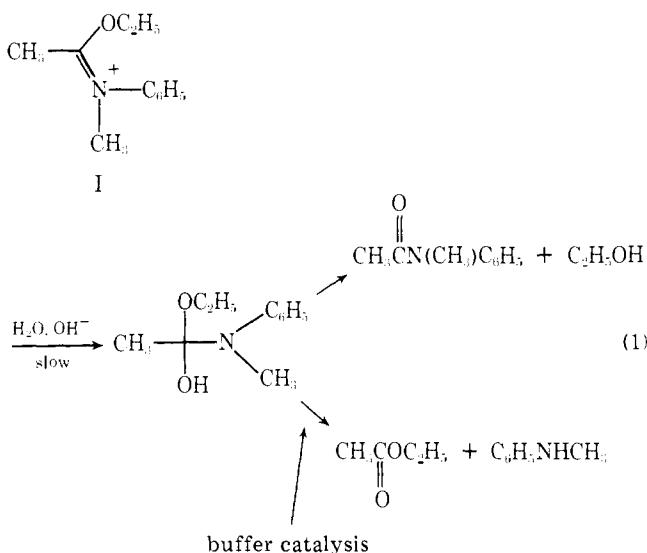
remarkable superiority of some catalysts (e.g., phosphate and bicarbonate ions) over others of the same pK_a in controlling the direction of breakdown of the imidate ester has led to the suggestion that this process may represent an instance of (more or less) concerted bifunctional acid–base catalysis, a relatively rare occurrence in aqueous solution.[1,2,6] Third, evidence for kinetically important proton transfer steps has been obtained from the dependence of catalytic ability on the pK of the catalysts.[3,7] Finally, owing to the close relationship between the tetrahedral intermediates of imidate hydrolysis and those formed in some acyl transfer reactions (e.g., the aminolysis of esters), an improved understanding of catalytic mechanisms in acyl transfer reactions has been attained.[6,8]

The interaction of bifunctional acid–base catalysts with the tetrahedral intermediates derived from imidate esters has not been extensively studied. For example, the structural and electronic factors in the catalyst required for effective bifunctional catalysis of the decomposition of the intermediate

of eq 1 have not been clearly defined. Nor are the features which render the tetrahedral intermediate particularly susceptible to bifunctional acid–base catalysis well understood. In view of the implications of this phenomenon for the mechanism of catalysis of acyl transfer reactions both in model and in enzymatic systems, further investigation of the chemistry of bifunctional catalysis seemed desirable.

The primary criterion used to detect the possible existence of unusual modes of catalysis consists of the observation of enhanced reactivity of a catalyst in comparison to other acid–base catalysts of the same acidic or basic strength. With two exceptions,[3,7a] previous studies have yielded only fragmentary data on the reactivity of simple catalysts (e.g., alcohols, amines) on the breakdown of tetrahedral intermediates generated by hydration of imidate esters. A detailed study of the influence of general acid–base catalysts on the products of hydrolysis of phenyl (and substituted phenyl) *N*-methylacetimidate has been reported by Satterthwait and Jencks.[3] Although Brønsted plots for different classes of general acids generated slightly different lines, catalytic constants for general acids of the same pK_a were within a factor of 3 of each other.

The imidate ester I used in the present study was selected for the following reasons: (a) tetrahedral intermediates wherein the resident amine is an aniline derivative appear to be much more sensitive to the influence of bifunctional catalysts than similar intermediates containing an aliphatic amine;[9] (b) unlike protonated imidates, N,N-disubstituted imidate salts cannot undergo deprotonation at alkaline pH to the frequently much less reactive neutral imidate; and (c) the mechanism of hydrolysis of imidate I in the absence of added buffer varies in some aspects from that for phenyl imidates (see Discussion), and it is of interest to determine to what extent the buffer-dependent pathways resemble or differ from those found with phenyl imidates.

The present paper describes our findings concerning the interaction of monofunctional acid–base catalysts with imidate I, an understanding of which is required prior to the evaluation of potential bifunctional catalysts.

Results

The pH–rate profile (extrapolated to zero buffer concentration) for the hydrolysis of imidate I in 0.5% acetonitrile–water (30 °C, $\mu = 0.5$) has been previously shown to follow the equation

$$k_{obsd} = k_w + k_{OH}[OH^-] \qquad (2)$$
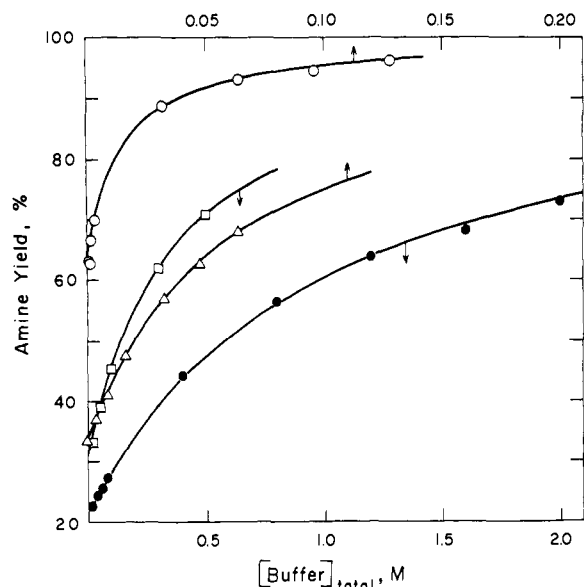
Figure 1. Effect of buffers on yield of N-methylaniline formed on hydrolysis of imidate ester 1: O, imidazole, pH 7.61, in presence of 0.032 M Tris; □, N-methylmorpholine, pH 8.23; △, p-nitrophenol, pH 8.39, in presence of 0.030 M Tris; ●, Tris, pH 8.76. Curves are calculated from the equation given in note 13b, using constants in Table 1.

Figure 2. pH dependence of amine yield in hydrolysis of imidate 1. Yields are extrapolated to zero buffer concentration. Curve is calculated from equation for the dissociation of a monovalent acid, with $pK' = 7.49$, and asymptotes at 100 and 17%.

in the range of pH 2-9, and has been interpreted in terms of rate-determining addition of water (k_w) and hydroxide ion (k_{OH}) to the cationic imino group.[10] Rate measurements in dilute HCl solution yielded a value of $k_w = 1.84 \times 10^{-4}$ s^{-1}; determination of k_{OH} from experiments in Tris or imidazole buffers at pH 7-9, with k_{obsd} extrapolated to zero buffer concentration, gave a value of $7.3 \pm 0.3 \times 10^3$ M^{-1} s^{-1} for k_{OH}, which was confirmed by a measurment at pH 12.2 (sodium hydroxide buffer).[11a] The rate of addition of water is equal to the rate of addition of hydroxide ion at pH 6.4.

In the pH range of interest (7-9), buffer effects on the rate of hydrolysis were quite small. For example, Tris buffers of concentration up to 0.1 M caused rate increases of no more than 20% over the rate extrapolated to zero buffer concentration.

When kinetic measurements were carried out on reactions containing hexafluoro-2-propanol buffer (up to 0.2 M), erratic changes in optical densities were obtained, and the final values could be changed appreciably by vigorously shaking the spectrophotometer cuvette, though no turbidity was seen. This behavior appeared associated with the fact that the imidate ester was introduced into the reaction mixture as a small volume of a stock solution in acetonitrile (see Experimental Section). Addition of the substrate as a stock solution in *water* led to well-behaved absorbance changes. Possibly, addition of acetonitrile to the water-hexafluoro-2-propanol solvent causes local, noninstantaneous changes in solvent structure which are responsible for the observed behavior.

pH Dependence of Amine Yield. The yield of amine (or ester) formed on hydrolysis of imidate esters is frequently highly dependent on pH and on the nature and concentration of added buffers (e.g., Figure 1). If the imidate is particularly susceptible to buffer effects, careful extrapolation is required to determine accurately the dependence of product yield on pH alone. Amine yields were measured in experiments carried out at low buffer concentrations (0.01-0.05 M) and were extrapolated to zero buffer concentration (Figure 2). As previously reported for this imidate,[10] the dependence of the yield of N-methylaniline on pH follows a simple sigmoid curve characteristic of the dissociation of a monovalent acid. The yield of amine reached asymptotically at low pH is 100 ± 1% and that at high
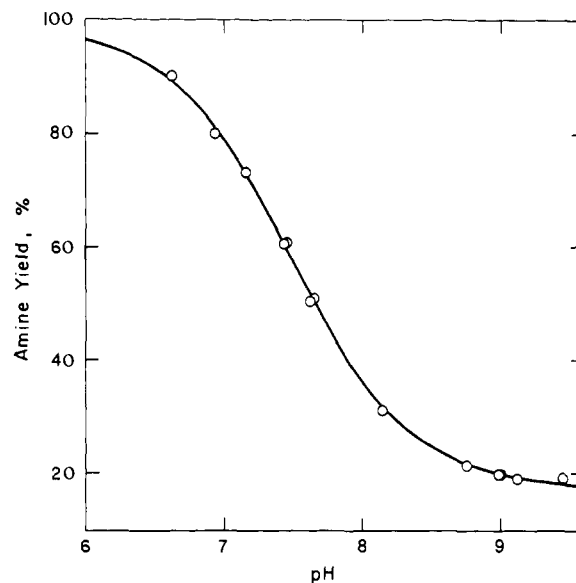
pH is 17 ± 0.5%. The midpoint of the product transition (pK') is at pH 7.49 ± 0.02, in contrast to the reported[10] value of 7.9. This difference is probably the result of incorrect extrapolation to zero buffer in the earlier study, owing to the fact that simple amine buffers are more effective catalysts than had been thought (see, for example, imidazole in Figure 1). Clearly, if the concentrations of buffer used are not sufficiently low, extrapolated yields will be erroneously high, and the derived pH value for the midpoint of the product transition will be too high.
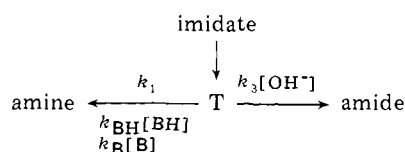
Effects of Buffers on Amine Yield. The dependence of amine yield on total buffer concentration is described by a rectangular hyperbola with yields approaching 100% when reactive buffers are used (Figure 1). A simplified version of the reaction mechanism is shown in Scheme I (where T = tetrahedral intermediate), from which is obtained eq 3, which relates amine

$$\% \text{ amine} = \frac{k_1/k_2 + [\text{B}]_\text{T}}{(k_1 + k_3)/k_2 + [\text{B}]_\text{T}} = \frac{k_1/k_2 + [\text{B}]_\text{T}}{K_{\text{app}} + [\text{B}]_\text{T}} \quad (3)$$

yield to total buffer concentration $[\text{B}]_\text{T}$.[11b] The constant K_{app} is equivalent to the buffer concentration required to produce half of the total possible increase in amine yield and is used to calculate the relative abilities of various buffers to catalyze the formation of amine. Two methods were used to evaluate K_{app} from data such as those of Figure 1. The first method consisted of nonlinear least-squares computer fitting to the equation for the two-parameter rectangular hyperbola.[12] This method requires knowledge of the yield at "zero" buffer concentration (i.e., in the absence of the buffer whose concentration is being varied) and could be used when the concentration of a reactive buffer was varied in the presence of a constant concentration of a relatively unreactive buffer, added to maintain constant pH. The constant thus obtained will be denoted K'_{app}, and must be corrected for the effect of the constant buffer to give the true K_{app} characteristic of the variable buffer (see below). The amine yield (A_0') at zero concentration of the variable buffer is directly measured and includes a contribution by the constant buffer. Correction of A_0' for the effect of the constant buffer gives the true buffer independent amine yield (A_0). When the hydrolysis of the imidate was performed in the presence of a single buffer, so that the amine yield at zero

Figure 3. pH dependence of the effectiveness of buffers in catalyzing the formation of N-methylaniline in hydrolysis of imidate 1: (A) Tris, (B) 3-chloroquinuclidine. Solid curve is calculated using eq 9 and constants of Table 11. Dashed curves are for acid or base catalysis only, and are calculated from eq 9, with k_B and $k_{BH} = 0$, respectively. $pK' = 7.49$.

Scheme I

$$\text{amine} \underset{k_2[\text{B}]_\text{T}}{\overset{k_1}{\rightleftharpoons}} \overset{\text{imidate}}{\underset{}{\text{T}}} \overset{k_3}{\longrightarrow} \text{amide}$$

Scheme II

$$\text{amine} \underset{\substack{k_2[\text{B}]_\text{T} \\ k_2''[\text{B}'']_\text{T}}}{\overset{k_1}{\longleftarrow}} \overset{\text{imidate}}{\underset{}{\text{T}}} \overset{k_3}{\longrightarrow} \text{amide}$$

buffer could not be directly measured, the amine yield at zero buffer was taken as that value which gave the best computer fit to the data.

The second method employed to evaluate K_{app} made use of linear plots of (amine yield)/(amide yield) vs. total buffer concentration,[3] according to

$$\% \text{ amine}/\% \text{ amide} = k_1/k_3 + (k_2/k_3)[\text{B}]_\text{T} \qquad (4)$$

which is derived from Scheme I. The slope k_2/k_3 of these plots is used to calculate K_{app} (or K'_{app} when two buffers are used) by means of

$$K_{app} = 1/\text{slope}(\Delta A_{max}) = (k_1 + k_3)/k_2 \qquad (5)$$

where ΔA_{max} is the maximum possible increase in amine yield over the yield in the absence of the variable buffer. It should be noted that eq 4 and 5 are applicable only if the amine yield approaches 100% at infinitely high buffer concentration.[13a] Values of K_{app} (or K'_{app}) calculated by both methods were in good agreement, as were the calculated amine yields at zero buffer concentration, which are obtained either from the y-axis intercept of eq 4 or from the computer-fitting procedure described above. Since the second buffer (present at fixed concentration) is itself capable of catalyzing the conversion of the intermediate to the amine product (Scheme II, k_2'' step), its presence will result in making the variable buffer seem less effective than it really is; i.e., K'_{app} will be greater than K_{app}. Correction for the effect of the second buffer is made as follows. Consider Scheme II, where B refers to the buffer whose concentration is being varied, and B'' is the second buffer, present at fixed concentration. The dependence of amine yield on the concentration of B is given by eq 6, from which K'_{app} is evaluated as discussed above. If the effectiveness of the second buffer, as given by K''_{app} ($=(k_1 + k_3)/k_2''$) has been independently determined, then the true K_{app} for the variable

Figure 4. pH dependence of the effectiveness of buffers in catalyzing the formation of N-methylaniline in hydrolysis of imidate I: (A) 2,4-lutidine, (B) 3-chloropropionic acid. For calculation of curves, see legend to Figure 3.

buffer is calculated from eq 7. The correction generally did not exceed 20% of the value of K'_{app} and was frequently much smaller.

$$\% \text{ amine} = \cfrac{\dfrac{k_1 + k_2''[\text{B}'']_\text{T}}{k_2} + [\text{B}]_\text{T}}{\dfrac{k_1 + k_3 + k_2''[\text{B}'']_\text{T}}{k_2} + [\text{B}]_\text{T}}$$

$$= \cfrac{\dfrac{k_1 + k_2''[\text{B}'']_\text{T}}{k_2} + [\text{B}]_\text{T}}{K'_{app} + [\text{B}]_\text{T}} \qquad (6)$$

$$K_{app} = K'_{app}\left(1 - \frac{[\text{B}'']_\text{T}}{K''_{app} + [\text{B}'']_\text{T}}\right) \qquad (7)$$

The results of experiments with amine, alcohol, and carboxylic acid buffers are summarized in Table I.[14] Limited data obtained in earlier studies with other imidates had shown that amine buffers had little effect on the direction of breakdown of the tetrahedral intermediate.[2,9] This is clearly not the case with some of the catalysts listed in Table I (e.g., imidazole). Even Tris buffer, which has been employed in this and earlier studies to maintain constant pH, has a significant effect on the amine yield, especially at pH <8. For instance, the presence of 0.012 M Tris buffer at pH 7.5 causes a 6% increase in amine yield, over the buffer-independent yield of 58%.[13b] The values of the buffer-independent amine yields (A_0) calculated from these experiments are listed in Table I and are in good agreement with those obtained from experiments at lower buffer concentration (Figure 2).

The effectiveness of buffers in increasing amine yield is markedly dependent on pH, as illustrated in Figures 3 and 4. Two factors place rather narrow limits on the pH range in which buffer catalysis may be studied with imidate I: (a) at pH >9, K_{app} for most buffers approaches or exceeds 1 M, so that it may become difficult to separate buffer catalysis from possible solvent and salt effects; (b) at pH 7 and below, the yield of amine at zero buffer concentration is greater than 80%, and it becomes difficult to accurately measure increases caused by added buffers.

Use was made of Scheme III for the analysis of the dependence of K_{app} on pH. This formulation includes the assumption that the conversion of the intermediate to amine is catalyzed both by the buffer acid (BH) and its conjugate base (B). It is also proposed that hydroxide ion catalyzes the conversion of the intermediate to amide; the latter assumption accounts for

Scheme III

imidate
$\downarrow$ $k_3[OH^-]$
amine $\xleftarrow{\quad k_1 \quad}$ T $\xrightarrow{\quad\quad}$ amide
$k_{BH}[BH]$
$k_B[B]$

the pH dependence of amine yield at zero buffer concentration (Figure 2).[15] The dependence of amine yield on pH and total buffer concentration follows eq 8, where K_a is the acid dissociation constant of the buffer. The expression for K_{app} can be rearranged to eq 9, where $K' = k_3 K_w / k_1$ (K_w being the ion product of water). Fitting data such as those of Figures 3 and

$$\% \text{ amine} = \frac{\dfrac{k_1([H^+] + K_a)}{k_{BH}[H^+] + k_B K_a} + [B]_T}{\dfrac{(k_1 + k_3[OH^-])([H^+] + K_a)}{k_{BH}[H^+] + k_B K_a} + [B]_T}$$

$$= \frac{\dfrac{k_1([H^+] + K_a)}{k_{BH}[H^+] + k_B K_a} + [B]_T}{K_{app} + [B]_T} \quad (8)$$

$$K_{app} = \frac{k_1}{k_{BH}} \left(\frac{[H^+] + K'}{[H^+]} \right) \left(\frac{[H^+] + K_a}{[H^+] + k_B K_a / k_{BH}} \right) \quad (9)$$

4 to eq 9 provides the values of $k_{BH}/k_1 (=k_{AH})$ and of k_B/k_1 ($=k_A$) which describe general acid and general base catalysis, respectively, of the breakdown of the tetrahedral intermediate to amine (Table II). It should be noted that eq 9 contains only two adjustable parameters, which are k_1/k_{BH} and k_B/k_{BH}. The other two constants are K_a, the value of which is known, and K', which is determined from the dependence of amine yield on pH at zero buffer concentration (Figure 2), where pK' is equal to the pH (7.49) at the midpoint of the transition in products. Changing the value of the ratio k_B/k_{BH} will affect the shape of the curve describing the variation of K_{app} with pH. The other variable parameter (k_1/k_{BH}) is simply a scale factor, changes in which translate the computed curve along the vertical axis without any alteration in shape. The dashed curves in Figures 3 and 4 represent the expected dependence of K_{app} on pH for mechanisms involving solely general acid ($k_B = 0$) or general base ($k_{BH} = 0$) catalysis, and were calculated using the appropriate modification of eq 9 and the same values of k_{AH} or k_A that were used to compute the solid curve. Clearly, the experimental data shown in Figures 3 and 4 cannot be fitted by either of the curves calculated for simple general acid or general base catalysis. The intersection of the dashed curves represents the pH value at which general acid and general base catalysis contribute equally to amine formation from the tetrahedral intermediate, and is given by the expression pH = pK_a − log (k_A/k_{AH}). Accurate determination of both k_{AH} and k_A requires that K_{app} values be measured in the vicinity of this intersection point. With chloroacetate buffers, the intersection point is estimated to be at pH 6.2, so that the contribution of the acid-catalyzed pathway at the lowest pH examined (7.44) is negligible and could be estimated as an upper limit only.

Replacing the potassium chloride used to maintain constant ionic strength by other salts (at 0.4 M) has a negligible effect on the amine yield at either pH 7.7 or 8.7, except for sodium perchlorate (Table III). If it is assumed that perchlorate ion is a suitable model for carboxylate ions, then correction of the amine yields in the presence of chloroacetate or methoxyacetate buffers for the (presumed) salt effect of the carboxylate ion causes a reduction of no more than 25% in the effectiveness of these buffers as general acid or general base catalysts. Experiments with trifluoroacetate ion at pH 7.73 and 8.25 led to a catalytic constant of $k_A = 2$–3 M^{-1} for general base catalysis. If it is assumed that this "general base catalysis" is really

Table II. Constants for General Acid and General Base Catalysis of Amine Formation in Imidate Hydrolysis

buffer	pK_a[a]	k_{AH}, M^{-1}	k_A, M^{-1}
3-chloropyridine (CPY)	3.13	3.3×10^4	9.9
pyridine (PY)	5.37	1.5×10^4	7.5
4-picoline (PI)	6.16	4.8×10^3	7.2
3,4-lutidine (3,4 LU)	6.60	2.4×10^3	17
2,4-lutidine (2,4 LU)	6.80	8.3×10^2	25
imidazole (IM)	7.10	1.1×10^3	32
N-methylmorpholine (NMM)	7.63	50	10
Tris	8.16	26	20
2-amino-2-methylpropanediol (APD)	8.86	19	38
3-chloroquinuclidine (CQD)	8.86	5.6	56
2-amino-2-methyl-1-propanol (AP)	9.80	0.94	1.1×10^2
chloroacetic acid (CA)	2.72	3×10^4 [b]	12
methoxyacetic acid (MA)	3.41	2.5×10^4	10
3-chloropropionic acid (CPA)	3.94	1.6×10^4	13
acetic acid (AA)	4.60	2.1×10^4	10
p-nitrophenol (PNP)	6.96	2.8×10^3	56
hexafluoro-2-propanol (HFP)	9.19	35	1.1×10^2

[a] Taken as the pH of the half-neutralized buffer solution at 30 °C and $\mu = 0.5$. The buffer concentration was sufficiently high so that the pH did not change when the buffer was diluted by half. [b] Upper limit only.

Table III. Effect of Added Salts on Amine Yield[a]

salt[b]	pH[c]	% amine	pH[d]	% amine
KCl	7.74	52.3	8.70	25.0
NaCl	7.68	51.8	8.65	24.7
NaClO₄	7.67	65.2	8.63	31.1
(CH₃)₄NCl	7.69	50.4	8.67	24.0
KNO₃	7.75	54.0	8.69	26.2

[a] At 30 °C, 0.5% acetonitrile-water, $\mu = 0.5$. [b] [Salt] = 0.4 M; the ionic strength made up to 0.5 with NaCl and Tris hydrochloride. [c] 0.015 M Tris. [d] 0.020 M Tris.

entirely a salt effect, then the catalytic constants for the other carboxylate buffers are again reduced by no more than 25%. The use of either model leads to the conclusion that the increases in amine yield caused by chloroacetate and methoxyacetate result largely or entirely from general acid-base catalysis and not from medium effects. With carboxylic acids of higher pK such as acetic acid, the possibility of salt effects is even less likely owing to the lower buffer concentrations used with these catalysts.

Addition of organic solvents (0.5 M) caused small increases in amine yield at pH 7.7 and negligible changes at pH 8.7. The effect increases with decreasing dielectric constant (Table IV). Since the solvent effect is most pronounced at low pH, where the amine buffers are most effective as catalysts, no significant correction is required.

The possibility that the buffer-induced increase in amine yield results from nucleophilic attack by buffer components on the imidate ester can be excluded on kinetic grounds in several cases. A conceivable mechanism for a nucleophilic pathway is outlined in Scheme IV, where it is proposed that the imidate undergoes rate-determining addition of water and hydroxide ion (k_0) to give an intermediate, or undergoes nucleophilic attack (k_N) by a buffer species to form the amine product (either directly or via subsequent fast reactions). The observed first-order rate constant for imidate hydrolysis in the presence of excess buffer is given by

$$k_{obsd} = k_0 + k_N[B]_T \quad (10)$$

and the dependence of amine yield on buffer concentration is

Table IV. Solvent Effect on Amine Yield[a]

organic solvent[b]	dielectric constant[c]	% amine (pH 7.74)[d]	% amine (pH 8.69)[e]
none		53.1	24.7
formamide	111	54.8	25.1
dimethyl sulfoxide	47	56.9	25.0
acetonitrile	38	57.3	25.0
N,N-dimethylfor-mamide	37	56.6	24.9
methanol	34	58.8	26.7
tert-butyl alcohol	12	59.4	26.3

[a] At 30 °C, μ = 0.5, 0.5% CH_3CN-H_2O. [b] 0.5 M. [c] J. A. Riddick and W. B. Bunger, "Organic Solvents", 3rd ed, Wiley, New York, N.Y., 1970. [d] 0.015 M Tris, pH ± 0.02. [e] 0.020 M Tris, pH ± 0.02.

again a hyperbola:

$$\% \text{ amine} = \frac{\dfrac{k_1 k_0}{(k_1 + k_3)k_N} + [B]_T}{k_0/k_N + [B]_T} \qquad (11)$$

For this scheme, K_{app} is given by k_0/k_N and can thus be predicted from the kinetics of imidate hydrolysis. In the case of imidazole, Tris, and hexafluoro-2-propanol buffers, k_N was at least ten times too small to account for the effectiveness of these buffers in increasing the amine yield; i.e., the observed value of K_{app} was much smaller than would be predicted from the kinetics of imidate hydrolysis (eq 10). It should be noted, however, that both phenyl and alkyl imidates have been reported to react with some nucleophiles in aqueous solution.[16]

Discussion

In most respects, the hydrolysis of the imidate ester I conforms to the well-established behavior of previously studied imines. The rate law (eq 2) has been observed with quaternary Schiff bases,[17a] thiazolines,[17b] and acyclic thioimidates,[7a,17c] and with several cationic imidates.[3,6b,10] The sigmoid dependence of amine yield on pH is also a familiar feature of imidate hydrolysis.[6b,10,18] With most (but not all) imidates, there is no correspondence between the effect of pH on the rates and products of hydrolysis; this observation constitutes strong evidence for the existence of intermediates on the reaction pathway. In the present instance, the change in the rate law from water attack to hydroxide attack on the iminium center occurs at pH 6.4, while the midpoint in the product transition from amine to mainly amide takes place at pH 7.49. This difference, which is outside possible experimental error, will be used in the selection of a reaction mechanism. Finally, in accord with previous experience, the yield of amine in the hydrolysis product mixture is dependent on the nature and concentration of buffer species.[1-3] Once again, the independent influences of general acid-base catalysts on the rates and products of hydrolysis serve to support the existence of the postulated tetrahedral addition intermediates in imidate hydrolysis. Although early mechanistic proposals considered that the several ionic forms of the tetrahedral intermediates were in rapid acid-base equilibrium,[18,19] studies with cyclic[7b,20] and acyclic[7a] thioimidates indicated that rate- (or product-) determining diffusion-controlled proton transfer steps were kinetically important. More recently, the nonlinear Brønsted plots for the general acid-catalyzed expulsion of amine from the tetrahedral intermediates generated in the hydrolysis of phenyl imidates offered convincing evidence for the conclusion that some of the tetrahedral intermediates were not in equilibrium with respect to proton transport processes.[3]

In terms of the neutral tetrahedral intermediate, the product

Scheme IV
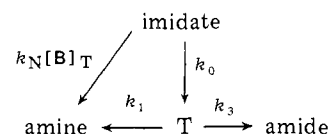
forming steps in the hydrolysis of imidate I may be formally considered to be subject to general acid and general base catalysis. In what follows, the term "general acid catalysis" refers to the process identified by the rate constant k_{BH} in Scheme III and eq 9. For convenience, this process is considered to involve the interaction of the conjugate acid of the buffer with a neutral tetrahedral intermediate, even though the correct description of the chemical process probably consists of the kinetically equivalent reaction of the conjugate base of the buffer with a cationic tetrahedral intermediate. Similarly, "general base catalysis" refers to the process identified by the rate constant k_B, although the reaction again probably is best described as involving the kinetically equivalent interaction of the buffer conjugate acid with an anionic intermediate. The statistically corrected[21] Brønsted plot for general acid catalysis of the breakdown of the tetrahedral intermediate (Figure 5) exhibits marked nonlinear character. Amines of pK >6 fall on or near a line of unit slope. The data, obtained over a range of about 4 pK units, could not be correlated by a line of significantly lesser slope. There occurs a sharp change in slope at about pK 5.5 to a line of approximately zero slope, defined by four carboxylic acids and one amine. In view of the diversity of structural types among the catalysts studied, it is not surprising that a number of deviations from the line of unit slope are seen, the largest being a fourfold negative deviation shown by *N*-methylmorpholine. Reduced reactivity ascribed to steric or conformational factors has been reported for several reactions in which morpholines acted as general acid-base catalysts.[22] Steric hindrance by the *o*-methyl substituent may reduce the catalysis by 2,4-lutidine.[23] Similar steric hindrance might have been expected for tris(hydroxymethyl)aminomethane (Tris) and its two less oxygenated analogs 2-amino-2-methylpropane-1,3-diol (APD) and 2-amino-2-methylpropan-1-ol (AP); the data are not consistent on this point, APD showing an approximately twofold positive deviation from the line of unit slope. The positive deviations exhibited by the two alcohols hexafluoro-2-propanol and *p*-nitrophenol may represent favorable electrostatic interactions between catalyst and tetrahedral intermediates (see below).[22c,24]
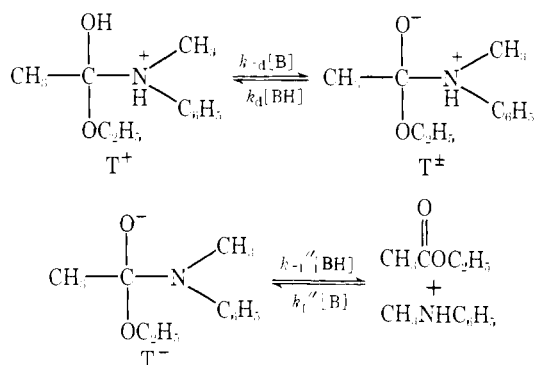
The statistically corrected Brønsted plot for general base catalysis of amine expulsion from a neutral tetrahedral intermediate is strikingly different from that for acid catalysis, and yields β = 0.17 ± 0.03 over the range of 3-10 in catalyst pK (Figure 6). In view of the large uncertainty in the pK_a value for trifluoroacetic acid (pK_a values ranging from 0.5 to −0.9 have been reported),[25a-d] and the possibility that a significant portion of its catalytic constant may represent a salt effect, the result for this acid was not used in this calculation. The deviations from the least-squares line are magnified by the shallow slope and, in fact, are generally smaller than those for general acid catalysis. In contrast to general acid catalysis, there is no indication of a significant change in slope over the range of 7 pK units. The relatively large estimated error limits for pyridine and 4-picoline result from the large acid catalysis and weak base catalysis by these buffers of low pK, so that the observed catalytic effect reflects mainly acid catalysis in the pH range examined.

The principal features of the reaction mechanism (Scheme V) which is proposed to account for the hydrolysis of imidate I are as follows: (a) the rate-determining step is the addition of water or hydroxide ion to the cationic imine to form a neutral tetrahedral intermediate (T^0); the latter is in equilibrium with
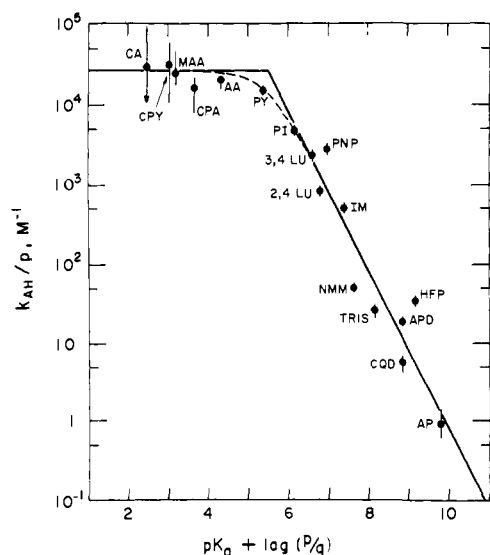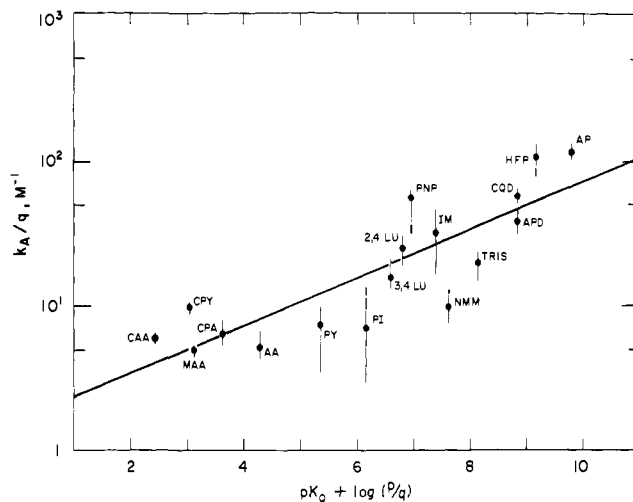
Figure 5. Brønsted plot for general acid catalysis of amine formation from imidate. Error bars are estimated variation in catalytic constant assuming that K_{app} values are accurate to $\pm 10\%$. Point for chloroacetic acid (CA) is upper limit only. Dashed line is calculated from $k_{AH} = (8.6 \times 10^9 \, M^{-2})K_a/(1 + 10^{-\Delta pK})$, where K_a is the acid dissociation constant of the catalyst, $\Delta pK = pK(\text{catalyst}) - pK(\text{intermediate})$, and $\Delta pK = 0$ at $pK_a = 5.5.$[30] Solid lines are limiting slopes of 1 and 0.

Figure 6. Brønsted plot for general base catalysis of amine formation from imidate. Error bars are estimated variation in catalytic constant assuming that K_{app} values are accurate to $\pm 10\%$. Least-squares line has slope $\beta = 0.17$.

cationic (T^+) and anionic (T^-) species; (b) in the absence of buffer, amine is formed from a zwitterionic intermediate ($T^\pm$) to which T^0 is converted by a proton switch mechanism; (c) the precursor of the amide product is T^-, which is also converted in part to amine, possibly in a reaction involving proton donation by water to the nitrogen of T^- concerted with the cleavage of the carbon–nitrogen bond; (d) general acid catalysis of amine formation from a neutral intermediate consists in fact of the kinetically equivalent conversion of T^+ to $T^\pm$ by general bases; (e) general base catalysis of amine formation from a neutral intermediate is suggested to represent instead

Scheme V

version to T^-, and the observed catalytic constant is sharply diminished.

The nonlinear Brønsted plot for general acid catalysis (Figure 5) is characteristic of proton transfer reactions, the rates of which approach the diffusion-controlled limit in the thermodynamically favorable direction (slope = zero) and reach a limiting slope of one when the proton donor is a much weaker acid than the conjugate acid of the proton acceptor.[25e] The break in the curve is expected to occur at $\Delta pK = 0$ between donor and acceptor. In view of the uncertainty in the estimated value[10] of 7.3 for pK_d, the observed break at about $pK = 5.5$
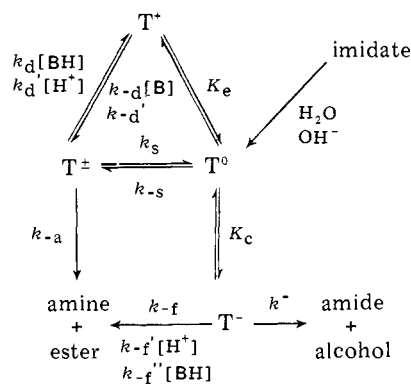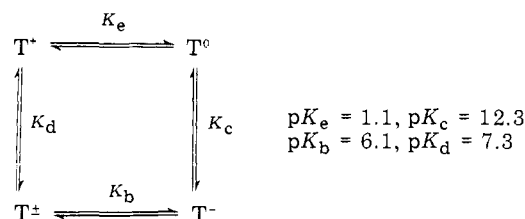

the general acid catalyzed breakdown of T^- in a reaction where proton transfer is concerted with the expulsion of the amine.

The mechanism of Scheme V is similar to one considered but found not to be applicable to the hydrolysis of phenyl imidates.[3] Two experimental observations made in the present study appear to require modification of the favored phenyl imidate mechanism in the case of the hydrolysis of imidate I: (a) the pH value at which the rate law (eq 2) changes from addition of water to addition of hydroxide ion is 1.1 units lower than the pH where the transition in products takes place (7.49); (b) the marked loss in effectiveness of buffer catalysis of amine formation with increasing pH (Figures 3 and 4) is quantitatively consistent with a mechanism where the buffer conjugate acid and base interact with a neutral intermediate (or any other kinetically equivalent formulation); with increasing pH, the concentration of the neutral intermediate is reduced by con-

$pK_e = 1.1$, $pK_c = 12.3$
$pK_b = 6.1$, $pK_d = 7.3$

is reasonably consistent with a mechanism which proposes that buffer catalysis consists of the abstraction by buffer bases of the hydroxyl proton of T^+ to convert it to $T^\pm$, and not of the kinetically equivalent protonation of T^0 on nitrogen to give T^+ ($pK_e \sim 1.1$). If the difference of about 1.8 units between pK_d and the break point of the Brønsted plot is considered significant, more complex proton transfer mechanisms may be envisaged.[26-28] One possible cause for a difference between the position of the break and the point where $\Delta pK = 0$ may be found by considering the symmetrical or unsymmetrical nature

of the encounter processes in the forward and reverse direction with respect to the charges of the reacting species. That the break should occur at $\Delta pK = 0$ is expected only in symmetrical situations (e.g., anionic bases abstracting a proton from a neutral acid). For unsymmetrical cases, the break may differ from $\Delta pK = 0$ by over 1 pK unit.[25e] The proposed interaction of the buffer conjugate base with T$^+$ offers a possible explanation for the enhanced reactivity of hexafluoro-2-propanol and p-nitrophenol, since these anionic bases might react more readily with the cationic intermediate than would the neutral amine bases.

The general base-catalyzed process (in terms of neutral intermediate) shows little dependence on the pK of the catalyst over the entire range studied, with no evidence of the change in slope expected for a simple proton transfer reaction. Possible reactions in which the proton transfer is concerted with the cleavage of the carbon–nitrogen bond involve either the reaction of T^0 with the conjugate base form of the catalyst or the reaction of T$^-$ with the conjugate acid of the catalyst. There are no grounds to suppose that abstraction of the hydroxyl proton of T^0 by buffer bases would assist the expulsion of the amine, especially since it is proposed that conversion of T^0 to T$^-$ by hydroxide ion results mainly in the formation of amide and alcohol. The kinetically indistinguishable alternative which consists of the protonation of the nitrogen of T$^-$ by general acids is an attractive possibility were it not for the suggestion[29] that a concerted mechanism is expected only when a thermodynamically unfavorable proton transfer is converted to a favorable one as the reaction proceeds. This requirement does not seem to be met by the more acidic catalysts, from which proton transfer to the nitrogen atom of T$^-$ (p$K \sim 6.1$) is in the favorable direction, and which would therefore be expected to effect a stepwise protonation of T$^-$ to T$^\pm$. The argument that T$^\pm$ may be too unstable to exist, and hence that the breakdown of T$^-$ must be concerted, is not applicable, since Figure 5 provides evidence for the formation of T$^\pm$ in the general acid-catalyzed amine formation.[31]

When the steady-state approximation is applied to the intermediates in Scheme V, a general expression which relates the amine yield to pH and buffer concentration is derived (Appendix, eq 14).[14] At zero buffer concentration, the general equation is reduced to the equation for a simple sigmoid curve (eq 15) as expected from the data in Figure 2. The following values can be assigned to the parameters of this equation: the term $k_{-f}/(k_{-f} + k^-) \equiv P^- = 0.173$ describes the partitioning of T$^-$ between amine and amide, and is equivalent to the amine yield at high pH; the term $K' = (k_{-f} + k^-)K_c/(k_{-s} + k_{-f}'K_c) = 3.23 \times 10^{-8}$ M (p$K' = 7.49$) corresponds to the midpoint of the product transition (Figure 2).

The complete equation can be rearranged to the form of eq 3; i.e., the dependence of amine yield on buffer concentration is described by a rectangular hyperbola (Appendix, eq 16). The term equivalent to K_{app} in eq 3 is given by eq 17 and can be rearranged to the form of eq 9. Comparison of eq 18 and 19 to eq 9 shows that the constant k_{AH} for general acid catalysis and the constant k_A for general base catalysis are given by eq 12 and 13, respectively. The constant k_{AH} is directly proportional to the rate constant k_{-d} for deprotonation of T$^+$, while k_A is proportional to k_{-f}'', which is the rate constant for proton donation to T$^-$ concerted with expulsion of amine.

$$k_{AH} = \frac{k_{-d}K_a}{(k_{-s} + k_{-f}'K_c)K_e} = \frac{k_{-d}K_a}{\text{constant}} \qquad (12)$$

$$k_A = \frac{k_{-f}''K_c}{(k_{-s} + k_{-f}'K_c)K_a} = \frac{k_{-f}''}{K_a} \text{ (constant)} \qquad (13)$$

Combination of eq 12 and 13 leads to the expression $k_{-f}'' = k_A k_{-d}K_a^2/k_{AH}K_cK_e$, in which all terms have been measured or estimated, except for k_{-d}. For relatively strong acidic

catalysts, the value of the latter constant is estimated as follows. The constant K_d for the dissociation of T$^+$ to T$^\pm$ is taken as 3.2×10^{-6} (p$K_d = 5.5$) from the break point of the Brønsted plot. Since $[T^\pm][BH]/[T^+][B] = K_d/K_a = k_{-d}/k_d$, assumption of a value of k_d allows the calculation of k_{-d}, and hence of k_{-f}''. In the case of methoxyacetic acid, the step k_d represents proton transfer from the catalyst to T$^\pm$ in the thermodynamically favorable direction, and is taken as 10^9 M^{-1} s^{-1}, yielding $k_{-f}'' = 1.2 \times 10^{10}$ M^{-1} s^{-1}. With weaker acids (e.g., protonated 3-chloroquinuclidine), k_{-d} is diffusion controlled and is assumed to be 10^9 M^{-1} s^{-1}, giving $k_{-f}'' = 4.8 \times 10^5$ M^{-1} s^{-1}.

These calculations suggest that k_{-f}'' has reached the diffusion-controlled limit with methoxyacetic acid, and would exceed this value with more acidic catalysts. Despite the necessarily approximate nature of the calculation of k_{-f}'' (for example, the use of a value of pK_d closer to the original estimate of 7.3 would significantly reduce k_{-f}''), the proposed concerted pathway for the base-catalyzed formation of amine may not be applicable to catalysts of low pK. It should be noted that when similar calculations are made for the kinetically equivalent mechanism involving general base-catalyzed abstraction of a proton from T^0 concerted with amine expulsion, the resulting rate constants are far below the diffusion limit. As discussed above, however, this alternative mechanism does not seem acceptable on chemical grounds.

The rate constants k_{-f} and k^- which describe the partitioning of T$^-$ to amine and amide can be calculated from eq 12 and the values of K' and P^- given above, and are $k_{-f} = 1.6 \times 10^4$ s^{-1} and $k^- = 7.9 \times 10^4$ s^{-1}.

The imidate I is far more sensitive to general acid catalysis of amine formation from the tetrahedral intermediate than the phenyl imidates studied earlier, as evidenced by the limiting values of k_{AH} (Figure 5) of about 3×10^4 M^{-1}, in contrast to values of about 2 M^{-1} found with phenyl imidates.[3] Since both reactions consist of a diffusion-controlled encounter of the catalyst with the tetrahedral intermediate, the large difference in susceptibility to catalysis must reflect properties of the intermediate alone, such as relative values of the equilibrium constant K_e and of the proton switch rate constant k_{-s}. In terms of the mechanism of Scheme V, it is evident that small values of K_e and of k_{-s} will favor the buffer-catalyzed pathway, the first constant by shifting the equilibrium between T$^+$ and T^0 in favor of T$^+$, and the second constant by reducing the rate of the competing, solvent-catalyzed, route to T$^\pm$, and hence to amine.

Experimental Section

Materials. Methyl [α-(ethoxy)ethylidene]phenylammonium tetrafluoroborate[10] (I) was recrystallized from ethanol–ether prior to use. The purification procedure for acetonitrile has been described.[1] Reagent grade inorganic salts and tris(hydroxymethyl)aminomethane (Tris, Sigma) were used without further purification. Organic liquids were distilled except for hexafluoro-2-propanol (99+%, Aldrich), and all organic solids were recrystallized. Freshly boiled, glass-distilled deionized water was used in all experiments.

Stock solutions of the imidate salt in acetonitrile were stored in the refrigerator in glass vials sealed with a Hamilton three-layer silicone septum through which aliquots were withdrawn using a glass syringe equipped with a stainless-steel hypodermic needle.

Product Analysis. The yield of N-methylaniline produced on hydrolysis of the imidate salt at 30 °C and ionic strength 0.5 was determined by colorimetric assay.[7a] The procedure used in a typical experiment is as follows. A 5-mL sample of aqueous buffer solution ($\mu = 0.5$, maintained with KCl) was placed in a capped test tube and kept in a constant-temperature water bath at 30 °C. After temperature equilibration (generally 30 min), 25 μL of the stock solution of the imidate salt (0.03 M) in acetonitrile was introduced into the buffer solution by means of a 50 μL Hamilton syringe. The reaction mixture was thoroughly stirred and kept at 30 °C for at least 10 half-lives of reaction before assay.

This procedure, where a single buffer was used, was followed with buffers (e.g., Tris, *N*-methylmorpholine) of relatively low catalytic effect whose buffering capacity is reasonably high in the experimental pH range (7–9). In cases where low concentrations of buffer were used because of a high catalytic effect (e.g., imidazole) or where buffering capacity was insufficient (e.g., acetic acid), a second buffer (usually Tris) was used to maintain the pH. Tris was chosen for this purpose because of its good buffering capacity in the pH range of interest, and its relatively low catalytic effect.

The pH of the final reaction mixture was measured using a Radiometer pH meter, Model 4d, standardized just prior to use.

Kinetics. The rates of hydrolysis of the imidate salt were followed at 30.0 ± 0.1 °C and ionic strength 0.5 with the use of a Cary Model 15 recording UV spectrophotometer. Reactions were initiated by adding ca. 15 μL of the stock solution of the imidate salt in acetonitrile into a 3-mL cuvette which contained the buffer solution equilibrated at 30 °C. The final concentration of the imidate salt was ca. 1.5×10^{-4} M, and the final solution contained 0.5% acetonitrile. When the pH of the reaction mixture was higher than 5, the appearance of *N*-methylaniline was observed at 240 nm. In cases where the buffer also absorbs in this region, 283 nm was used. When the pH is lower than 5, the disappearance of the imidate salt at 235 nm was followed. For fast reactions (pH >10), rates were measured with a Durrum-Gibson stopped-flow spectrophotometer.

First-order rate constants were evaluated from the slope of plots of $\log |A - A_\infty|$ vs. time. Good linear relationships were observed for at least 3 half-lives. The pH of the reaction mixture was measured at the end of the reactions.

Supplementary Material Available: Table I, buffer catalysis of amine formation in imidate hydrolysis, and Appendix, eq 14–19 (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) B. A. Cunningham and G. L. Schmir, *J. Am. Chem. Soc.*, **88**, 551 (1966).
(2) T. Okuyama, D. J. Sahn, and G. L. Schmir, *J. Am. Chem. Soc.*, **95**, 2345 (1973), and references cited therein.
(3) A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7031 (1974).
(4) Earlier conclusions that tetrahedral addition intermediates are formed in the hydrolysis of Schiff bases, imidates, and thioimidates were based mainly on the effects of pH and buffers on the *rates* of hydrolysis of these imines.[5]
(5) W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 63 (1964).
(6) (a) B. A. Cunningham and G. L. Schmir, *J. Am. Chem. Soc.*, **89**, 917 (1967); (b) G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2683 (1968).
(7) (a) R. K. Chaturvedi and G. L. Schmir, *J. Am. Chem. Soc.*, **91**, 737 (1969); (b) R. E. Barnett and W. P. Jencks, *ibid.*, **91**, 2358 (1969); (c) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972); (d) *Acc. Chem. Res.*, **9**, 425 (1976).
(8) (a) G. L. Schmir, *J. Am. Chem. Soc.*, **90**, 3478 (1968); (b) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, Chapter 10; (c) A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7018 (1974).
(9) R. K. Chaturvedi and G. L. Schmir, *J. Am. Chem. Soc.*, **90**, 4413 (1968).
(10) V. F. Smith, Jr., and G. L. Schmir, *J. Am. Chem. Soc.*, **97**, 3171 (1975).
(11) (a) The previously reported[10] value of $k_{OH} = 5.5 \times 10^3$ M^{-1} s^{-1} is in error. (b) For all equations derived from Schemes I–V, the steady-state approximation is applied to the tetrahedral intermediates.
(12) K. R. Hanson, R. Ling, and E. Havir, *Biochem. Biophys. Res. Commun.*, **29**, 194 (1967).
(13) (a) If the maximum yield of amine is significantly less than 100%, modified equations must be used.[3] (b) The increase in amine yield caused by a buffer is most easily calculated from the expression $\Delta A / \Delta A_{max} = [\text{buffer}]/([\text{buffer}] + K_{app})$, where ΔA = increase in amine yield as compared with yield at zero buffer concentration; ΔA_{max} = maximum increase possible.
(14) See paragraph at end of paper regarding supplementary material.
(15) This treatment ignores the observation that the product of imidate I hydrolysis at high pH is not solely the amide but that it also contains amine in 17% yield. This omission has no effect on the analysis of the pH dependence of K_{app}.
(16) (a) E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 3505 (1962); (b) M. Kandel and E. H. Cordes, *J. Org. Chem.*, **32**, 3061 (1967); (c) Y. Pocker, M. W. Beug, and K. L. Stephens, *J. Am. Chem. Soc.*, **96**, 174 (1974).
(17) (a) K. Koehler, W. Sandstrom, and E. H. Cordes, *J. Am. Chem. Soc.*, **86**, 2413 (1964); (b) R. B. Martin and A. Parcell, *ibid.*, **83**, 4830 (1961); (c) G. E. Lienhard and T.-C. Wang, *ibid.*, **90**, 3781 (1968).
(18) G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, **87**, 5692 (1965).
(19) (a) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968); (b) T. Okuyama, T. C. Pletcher, D.J. Sahn, and G. L. Schmir, *ibid.*, **95**, 1253 (1973).
(20) C. Cerjan and R. E. Barnett, *J. Phys. Chem.*, **76**, 1192 (1972).
(21) R. P. Bell and P. G. Evans, *Proc. R. Soc. London, Ser. A*, **291**, 297 (1966).
(22) (a) J. Hine and J. Mulders, *J. Org. Chem.*, **32**, 2200 (1967); (b) M. I. Page and W. P. Jencks, *J. Am. Chem. Soc.*, **94**, 8828 (1972); (c) J. M. Sayer and W. P. Jencks, *ibid.*, **95**, 5637 (1973); (d) A. Williams and W. P. Jencks, *J. Chem. Soc., Perkin Trans. 2*, 1760 (1974).
(23) F. Covitz and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 1773 (1963).
(24) W. K. Chwang, R. Eliason, and A. J. Kresge, *J. Am. Chem. Soc.*, **99**, 805 (1977).
(25) (a) A. L. Henne and C. J. Fox, *J. Am. Chem. Soc.*, **73**, 2323 (1951); (b) J. L. Kurz and J. M. Farrar, *ibid.*, **91**, 6057 (1969); (c) E. Grunwald and J. F. Haley, *J. Phys. Chem.*, **72**, 1944 (1968); (d) A. K. Covington, J. G. Freeman, and T. H. Lilley, *ibid.*, **74**, 3773 (1970); (e) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(26) The estimated pK values which interrelate the four ionic forms of the tetrahedral intermediate are probably accurate to within 1 pK unit.[27] Possible sources of error include the assumption that the value $\rho_I = 8.4$ correlates the acidities of N,N-disubstituted anilines, and the assumption of $\sigma_I = 0.18$ for the *N*-methyl-*N*-phenylamino group, for which no σ_I value is available. Effects of ionic strength and temperature may also cause small errors in the estimated pK values.
(27) J. P. Fox and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 1436 (1974).
(28) For other estimates of the pK values of related tetrahedral intermediates see (a) J. P. Guthrie, *J. Am. Chem. Soc.*, **96**, 3608 (1974); (b) J. Fastrez, *ibid.*, **99**, 7004 (1977).
(29) W. P. Jencks, *J. Am. Chem. Soc.*, **94**, 4731 (1972).
(30) R. P. Bell, "The Proton in Chemistry", 2nd ed, Cornell University Press, Ithaca, N.Y., 1973, Chapter 7.
(31) If T$^\pm$ is too unstable to exist, the principal objection to a concerted pathway for the breakdown of T$^-$ is removed. The nonlinear Brønsted plot of Figure 5 would then represent the encounter-controlled breakdown of T$^+$ by strong bases (zero slope) and a concerted pathway for the breakdown of T$^+$ catalyzed by weak bases. An analogous mechanism has been suggested for the general acid–base catalyzed reaction of methoxyamine with acetyltriazole.[27] In the latter reaction, the observed Brønsted slopes of 0.6–0.7 for weak acids or bases offer support for the proposed concerted reaction. The fact that it would be difficult to draw a line of slope significantly less than 1 for the data of Figure 5 speaks against this alternative mechanism in the hydrolysis of imidate I.