The Mechanism of the Aminolysis of Methyl Formate[1]

G. M. Blackburn[2] and W. P. Jencks

Contribution No. 557 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154. *Received December 14, 1967*

Abstract: The aminolysis of methyl formate by *n*-propylamine, methoxyethylamine, morpholine, hydrazine, glycinamide, and glycylglycine in aqueous solution proceeds predominantly by general base catalyzed attack of free amine at high pH; hydroxide ion and water-catalyzed reactions also occur. The rate decreases with decreasing pH at a constant concentration of free amine. This is evidence for a change in rate-determining step and the existence of an intermediate on the reaction path. A change in rate-determining step is also observed with increasing buffer concentration at constant pH. The hydrolysis of N-(methoxymethylene)morpholinium methosulfate gives amide in basic solution and ester in acidic solution. This permits an assignment of the rate-determining step for the reaction of morpholine with methyl formate as the attack step at high pH and breakdown of a tetrahedral addition intermediate at low pH. Hydrazine exhibits an enhanced rate of expulsion as well as attack; *i.e.*, the α effect is manifested to a greater extent in the rate constant than in the equilibrium constant for adduct formation.

The aminolysis of esters is subject to general base catalysis by a second molecule of the amine,[3-5] but the detailed mechanism of this complex reaction has not been established directly.[6] Three questions are of special interest: first, whether or not a tetrahedral addition intermediate is formed along the reaction path; second, whether the attack or the breakdown of the intermediate is rate determining, if such an intermediate is formed; and third, which of the several kinetically equivalent mechanisms accounts for the observed general base catalysis of the rate-determining step. The rate of the intramolecular aminolysis of ethanolamine acetate exhibits a dependence on pH which is indicative of a change of rate-determining step and, therefore, an intermediate on the reaction path.[7] This reaction is subject to catalysis by borate buffer.[8] In an important series of papers, Schmir and Cunningham have shown that the tetrahedral intermediate formed during the hydrolysis of 2-phenyliminotetrahydrofuran breaks down to expel alcoholate ion in a hydroxide ion catalyzed reaction and to expel amine in a pH-independent reaction which is markedly accelerated by bifunctional buffers.[9] These data were used successfully to predict the kinetic behavior of the intramolecular alcoholysis of 4-hydroxybutyranilide, one of the products of imidate breakdown, indicating that this reaction proceeds through the same addition intermediate; according to the principle of microscopic reversibility, the reverse aminolysis reaction must proceed by the same mechanism, although it has not been studied directly.

Although it is possible to combine the experimental results obtained with these several different systems and construct a mechanism for general base catalysis of ester aminolysis, we felt that it would be desirable to examine a system in which the mechanism of the reaction of an aliphatic ester with an aliphatic amine might be determined in a single reaction series in the absence of perturbations which might be introduced by cyclic systems. In this paper we describe the characteristics of the reactions in aqueous solution of methyl formate with aliphatic amines of $pK = 8$–11.

Experimental Section

Materials. Commercially available amines and methyl formate were distilled before use. Tetramethylammonium chloride and other amine hydrochlorides were recrystallized from ethanol and stored in a desiccator. Tetramethylammonium hydroxide was prepared by ion-exchange chromatography from the chloride using Dowex 1 in the hydroxide form. Glass-distilled water was used throughout, and the ionic strength was maintained at 1.5 *M* with tetramethylammonium chloride except where otherwise indicated. Stock solutions of commercially available hydroxylamine hydro-

(1) Supported by grants from the National Science Foundation and the National Institute of Child Health and Human Development of the Public Health Service (HD-01247).

(2) Department of Chemistry, University of Sheffield, Sheffield, England.

(3) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, 82, 665 (1960).

(4) W. P. Jencks and J. Carriuolo, *ibid.*, 82, 675 (1960).

(5) T. C. Bruice and M. F. Mayahi, *ibid.*, 82, 3067 (1960).

(6) Arguments were presented previously[4] in support of a mechanism for general base catalysis of ester aminolysis which is the same as that which has been shown directly to be correct by the experiments reported here. One of these arguments is that a mechanism which explains a fourfold rate increase by general acid catalysis of phenolate expulsion at pH 10 is improbable, because in the reverse reaction under the same experimental conditions this would require that the partial removal of a proton from phenol by a general base catalyst should give a more reactive nucleophilic species than the completely ionized phenolate ion which is present in a concentration equal to that of phenol at this pH. Since complete proton removal at pH 10 could give at most a twofold increase in rate it is unlikely that partial removal could give a fourfold rate increase. T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, 89, 2106 (1967), have taken issue with this argument on the grounds that although general acid–base catalysis would not be important above the pK of the phenol, the reverse reaction might proceed by direct attack of phenolate ion on the amide under these conditions. We reject this criticism on the following grounds. Under a given set of experimental conditions the transition states for the several pathways by which a reaction proceeds will have certain relative energies which determine the fraction of the total reaction which proceeds through each pathway. This is true for the reverse as well as the forward reaction, so that the same fraction of the total reaction must proceed through each transition state of a given charge and composition in each direction; this is essentially a statement of the principle of microscopic reversibility. The argument presented by Bruice, *et al.*, evidently requires that at pH 10 general acid–base catalysis be important in the forward, but not the reverse, reaction and that the reverse reaction proceed predominantly through an ionic transition state which is not observed for the forward reaction under these conditions. We believe that the original argument[4] is still valid.

(7) B. Hansen, *Acta Chem. Scand.*, 17, 1307 (1963). Hansen has presented an argument for the assignment of the two steps of the reaction as a function of pH. The conclusion (mechanism bb) is correct, but the argument appears to violate the principle of microscopic reversibility by postulating an equilibrium between the free amine and an uncharged addition intermediate which involves hydroxide ion as a reactant in one direction only (mechanism ba).

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

(9) G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, 87, 5692 (1965); B. A. Cunningham and G. L. Schmir, *ibid.*, 88, 551 (1966); 89, 917 (1967).

chloride (4 *M*) and ferric chloride hexahydrate (20% in 0.3 *M* hydrochloric acid) were used for hydroxamic acid assays.

Substituted formamides were prepared by reaction of equivalent amounts of methyl formate and the appropriate amine in anhydrous ethanol at 25° and were purified by distillation or by crystallization from ethyl alcohol: **N-formylhydrazine**, mp 57–59° (lit.[10] 54°); **N-formylmorpholine**, bp 103–104° (13 mm) (*Anal.* Calcd for $C_5H_9NO_2$: C, 52.15; H, 7.9; N, 12.2. Found: C, 52.0; H, 8.0; N, 12.2); infrared spectrum (film) ν_{max} 1675 cm^{-1}; **N-formyl-2-methoxyethylamine**, bp 112.5–113° (13 mm) (*Anal.* Calcd for $C_4H_9NO_2$: C, 46.6; H, 8.8; N, 13.6. Found: C, 46.6; H, 8.7; N, 13.8); ν_{max} 3300, 1670, and 1540 cm^{-1}.

N-(Methyoxymethylene)morpholinium Methosulfate. N-Formylmorpholine (0.1 mol) was thoroughly mixed with methyl sulfate (0.1 mol, redistilled) under anhydrous conditions.[11] The viscosity of the liquid increased and gave an oil which was insoluble in ether, but completely soluble in water. After several days at 0°, the oil completely solidified to a mass of colorless needles. The *product* had mp 45–48° (*Anal.* Calcd for $C_7H_{15}NO_6S$: N, 5.8. Found: N, 5.8); infrared (supercooled liquid film) ν_{max} 1675 cm^{-1} was significantly different from that of the reaction mixture immediately after mixing, notably in the appearance of a sharp doublet at 892 and 870 cm^{-1} and in the change in profile of the group of peaks at 1200–1270 cm^{-1}. The spectrum was unchanged in samples heated for 10 min at 110° or maintained at 50° at 10^{-1} mm for several hours. A supercooled sample remained liquid at 25° unless crystallization was induced by seeding or scratching.

Kinetics. Aminolysis reactions were initiated by the addition of 0.5 ml of aqueous methyl formate (0.1–0.2 *M*) to the amine buffer solution (19.5 ml) preincubated at 25 ± 0.05°, with thorough mixing. Aliquots of 1.0 ml were withdrawn at intervals and incubated at 25° with a freshly prepared hydroxylamine buffer (1.0 ml, prepared from 4 *M* hydroxylamine hydrochloride, 3.5 *M* sodium hydroxide, 2 *M* tris(hydroxymethyl)aminomethane base, 10:11:4 v/v, and ethylenediaminetetraacetic acid to 10^{-4} *M*) for 10.0 min. The intensity of the coloration produced by the addition of 4.0 ml of ferric chloride solution (20% in 0.3 *M* hydrochloric acid) was determined at 540 mμ in 1-cm cells with a Zeiss PMQ II spectrophotometer. The intensity did not vary significantly between 10 and 30 min after the addition of ferric chloride. No differences were observed in the velocities of reactions performed in open and stoppered tubes but the latter were employed routinely for reactions having a half-time greater than 5 min. The same assay was used to study the hydrolysis of methyl formate. An alternative assay involving the quenching of 1-ml aliquots into 2 ml of 1 *M* hydrochloric acid and determination of the optical density of the amide solution at 220 mμ was occasionally used and gave the same observed velocity as the hydroxamic acid assay, but was less sensitive.

The hydroxamic acid assay for glycylglycine and glycinamide produced an initial red color which faded on standing and gave reproducible results only if the optical density was determined 20.0 min after addition of ferric chloride. Attempted assays on solutions containing cyanomethylamine and 2-cyanoethylamine gave intense red colorations and were unreliable. Reactions involving hydrazine were either followed by the hydroxamic acid assay or by direct observation of the formation of formylhydrazine. The amine buffer solution in 3.0 ml was transferred to a 1-cm cuvette in a brass block in the cell compartment of a Gilford Model 2000 spectrophotometer thermostated at 25 ± 0.05°. The reaction was initiated by the addition of 0.01 ml of 2 *M* methyl formate with a plastic rod with a flattened cup at one end, which was also used to mix the solution. The optical density was recorded at 230 mμ. Experiments with half-times of less than 1 min generally were run in duplicate.

The hydrolysis of methoxymethylenemorpholinium methosulfate was followed by the addition of *ca.* 2 mg of liquid ester into 3 ml of buffer solution in a 1-cm cuvette, as above, and observing the diminution in optical density at 230 mμ. Complete mixing could be effected in 2 sec.

At the end of reactions, the solutions were brought to 25°, and the pH was determined with a Radiometer PMH 4c pH meter with G200 B or C glass electrodes. Initial pH values were determined where necessary.

Rate constants were calculated from the dependence on amine concentration and pH of the observed pseudo-first-order rate constants as described previously.[4] The observed pseudo-first-order rate constants were corrected for methyl formate hydrolysis from measurements of the pH in each reaction mixture and a rate constant for alkaline hydrolysis of 1.95 ± 0.1 M^{-1} min^{-1}, based on hydroxide ion activity, which was determined from a series of eight experiments in the pH range 7.7–10.6 in 0.05 *M* buffers at ionic strength 1.5 *M*. The rate of hydrolysis was shown to be independent of buffer concentration under the conditions of the experiments for several of the buffers which were used. This rate constant was found to agree satisfactorily with the observed rate constants in the aminolysis experiments extrapolated to zero amine concentration.

Product Analysis. From the reaction of aqueous morpholine (2 *M*) with methyl formate (1.5 *M*) at 25° was isolated a sample of N-formylmorpholine identical with the compound described above. The observed extinction coefficients in hydrochloric acid of aliquots of completed reactions of methyl formate with hydrazine and with 2-methoxyethylamine were in quantitative agreement with those calculated from the ultraviolet spectra of the corresponding amides. Assay of the products of the reactions of methyl formate with morpholine and methoxyethylamine by the method for amide determination described above, using authentic samples of the appropriate amides as controls, showed the predominant products of the reaction to be the expected amide; *i.e.*, there is no large contribution from amine-catalyzed hydrolysis to the observed reaction rate.

Product analysis of methoxymethylenemorpholinium methosulfate hydrolysis was determined as follows. The liquid ester, ~20 mg, was introduced from a 0.05-ml pipet, weighed before and after transfer, into 10 ml of buffer solution in a stoppered tube preincubated at 25 ± 0.05° and was completely dissolved by vigorous shaking. After a standard time interval (10 min at low pH, 2 min above pH 9), 1.0-ml aliquots were withdrawn and assayed for ester by the hydroxamic acid procedure described above. Amide produced was assayed by treating 1.0-ml aliquots with 0.01 ml of 2 *M* sodium hydroxide for 1 min at 25°, then adding 1 ml of hydroxylamine buffer (4 *M* hydroxylamine hydrochloride, 3.5 *M* sodium hydroxide, 10:6, and EDTA to 10^{-4} *M*) and incubating at 40° in a stoppered tube for 20 hr, then cooling, adding 4 ml of ferric chloride solution (20% in 0.3 *M* hydrochloric acid), and determining the optical density at 540 mμ as before. N-Formylmorpholine was used as a standard. Under these conditions, formic acid gave a small positive coloration and so necessitated a correction for the amount of ester produced at each pH. The effect of formate was somewhat enhanced in Tris buffers.

The product of hydrolysis of methoxymethylenemorpholinium methosulfate at pH 11.5 exhibited the same velocity of reaction with the hydroxylamine assay as did an authentic sample of N-formylmorpholine. The predominant product below neutrality was shown to be methyl formate as follows. A sample of the imidate ester (0.15 g) was added to 0.1 *M* phosphate buffer (15 ml, pH 5.9) in a closed system. A stream of nitrogen gas was used to stir the solution and sweep volatile products into a receiver cooled at −40°. The colorless, volatile liquid collected was treated with hydroxylamine mix (2.5 ml, pH 9.0) and water (2.5 ml) and incubated at 25° for 10 min. Ferric chloride assay showed the formation of 0.58 mol of hydroxamic acid/mol of imidate.

Results and Discussion

The aminolysis of methyl formate (Table I) was found to proceed rapidly in aqueous solution without serious interference by hydrolysis under most of the experimental conditions examined. The dependence of the pseudo-first-order rate constants for the reaction with morpholine (Figure 1) and other amines on the amine concentration at constant pH reveals a greater than first-order dependence on amine concentration which is characteristic of general base catalysis by a second mole of amine, according to the rate law of eq 1.[3-5] Plots of the apparent second-order rate constants for aminolysis, $(k_{obsd} - k_{hyd})$/[free amine], against amine concentration reveal small intercepts and large slopes at the higher pH values, as shown for the reaction with hydrazine in Figure 2. This indicates that most of the ob-

$$k_{obsd} - k_{hyd} = k_1[R_2NH] + k_2[R_2NH][R_2NH] \quad (1)$$

(10) G. Pellizzari, *Gazzetta*, 24, II, 225 (1894).
(11) H. Bredereck, F. Effenberger, and G. Simchen, *Chem. Ber.*, 96, 1350 (1963).

Table I. Aminolysis of Methyl Formate at 25° [a]

Amine	pK_a[b]	k_1, M^{-1} min^{-1}	k_2, M^{-2} min^{-1}	k_3, M^{-2} min^{-1}	k_{-1}/k_4, M^{-1}	k_{-2}/k_4, M^{-1}	k_5/k_4, M^{-1}	k_6/k_4, M^{-1}
t-Butylamine[c]	11.01	0.17	6.0					
n-Propylamine[d]	10.92	1.0[e]	180		2.61×10^8	0.563		
$CH_3OCH_2CH_2NH_2$	9.63	0.35	7.5		1.2×10^8	0.61		
$HOCH_2CH_2NH_2$[f]	9.80	0.44	16.6					
Morpholine[g]	8.84	0.27	3.9	1500[g]	2.3×10^7	0.47		
Hydrazine	8.30	5.0	170		5.5×10^8	90	1.2	2.5×10^6
Glycinamide[h]	8.40	0.018	0.73	3500	2.2×10^6	0.312		
Glycylglycine[i]	8.35	0.02	0.75					

[a] Ionic strength maintained at 1.5 with tetramethylammonium chloride. [b] Determined under the conditions of the kinetic experiments. [c] Determined from six runs with 0.2–1.4 *M* total amine, 10% free base. [d] Determined from three experiments of five to seven runs each with amine concentrations in the range 0.1–1.5 *M* at 5, 10, and 15% free base as well as the data shown in Figure 4. [e] Approximate value. [f] Determined from seven runs with 0.05–0.5 *M* total amine, 50% free base. [g] Determined from four experiments of five to seven runs each with amine concentrations in the range 0.07 to 2.0 *M* at 10, 25, 50, and 80% free base as well as the data shown in Figure 4. [h] Determined from two experiments of six to seven runs each with amine concentrations in the range 0.1–1.0 *M* at 50 and 70% free base as well as the data shown in Figure 4. [i] Determined from seven runs with 0.085–0.95 *M* total amine, 70% free base.

served reaction at moderate concentrations of amine is accounted for by the amine-catalyzed component of the reaction.

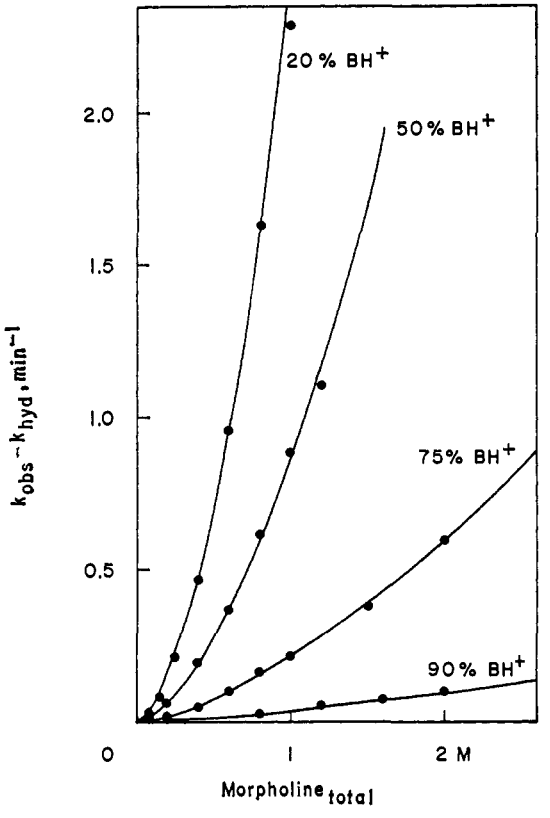


Figure 1. Pseudo-first-order rate constants for the reaction of methyl formate with morpholine as a function of morpholine buffer concentration at 25°, ionic strength 1.5 *M*, at different fractions of amine neutralization from 10 to 80% free base. Theoretical curves are calculated from eq 3 and the rate constants in Table I.

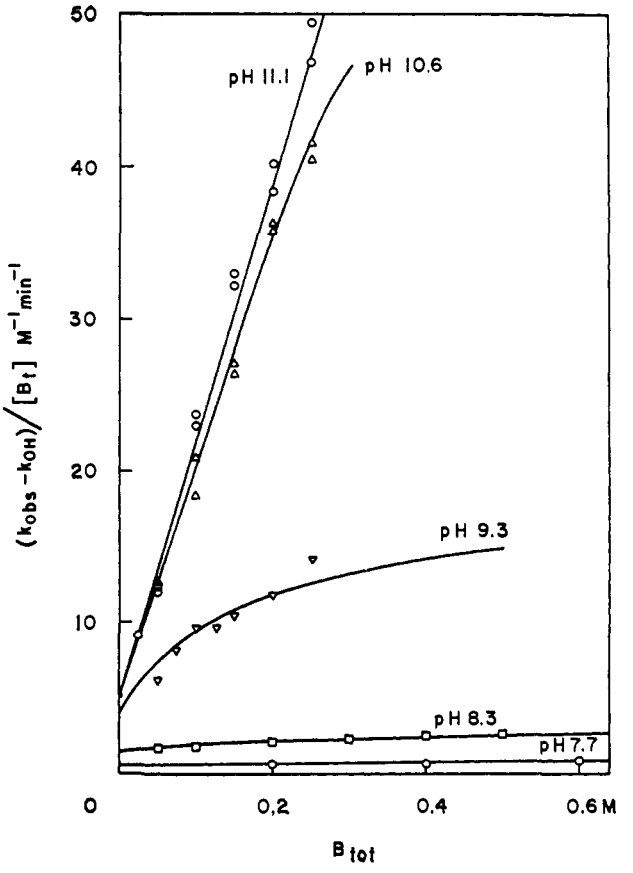


Figure 2. Apparent second-order rate constants for the reaction between methyl formate and hydrazine at 25°, ionic strength 1.5 *M*, at different pH values in hydrazine or 0.1 *M* *t*-butylamine buffers. Theoretical curves are calculated from the rate constants in Table I.

As the pH is decreased in a series of experiments *at a constant concentration of free amine* the rate of the reaction with hydrazine is at first constant, then decreases, and finally approaches a new plateau (Figure 3). The reaction at high pH involves a reaction of the free amine and an amine-catalyzed reaction of free amine (Figure 2). The decrease in rate with decreasing pH at constant free amine concentration means that the reaction no longer follows the simple rate law which is followed at high pH. This is evidence for a change in rate-determining step and an intermediate on the reaction path.[12,13] The reaction at high pH proceeds through the transition states with no net charge. At intermediate pH there is a change to a transition state with a negative charge, which is reflected in the slope of 1.0 in the logarithmic plot of Figure 3, and at low pH

(12) S. L. Johnson, *Advan. Phys. Org. Chem.*, 5, 237 (1967).
(13) W. P. Jencks, *Progr. Phys. Org. Chem.*, 2, 63 (1964).

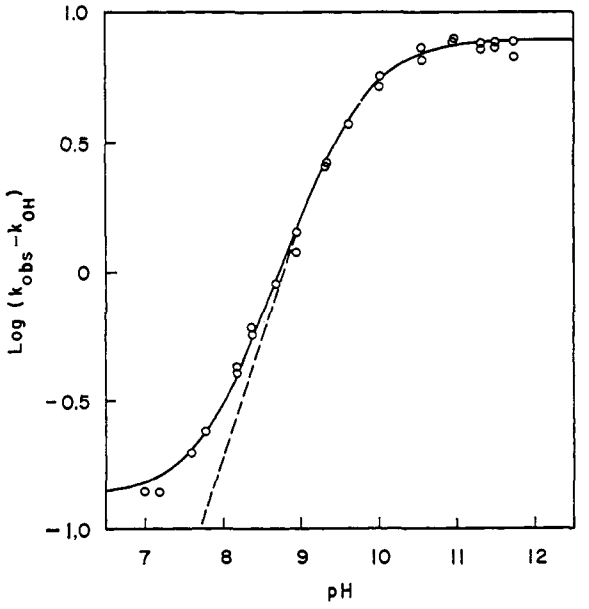


Figure 3. Pseudo-first-order rate constants for the reaction between methyl formate and hydrazine as a function of pH at 25°, ionic strength 1.5 M, with [hydrazine$_{free}$] constant at 0.2 M. Hydrazine buffers used below pH 10, 0.1 M t-butylamine buffers above pH 10. Theoretical curves are calculated from the rate constants in Table I (solid line) and from the same data but with $k_5 = k_6 = 0$ (dashed line).

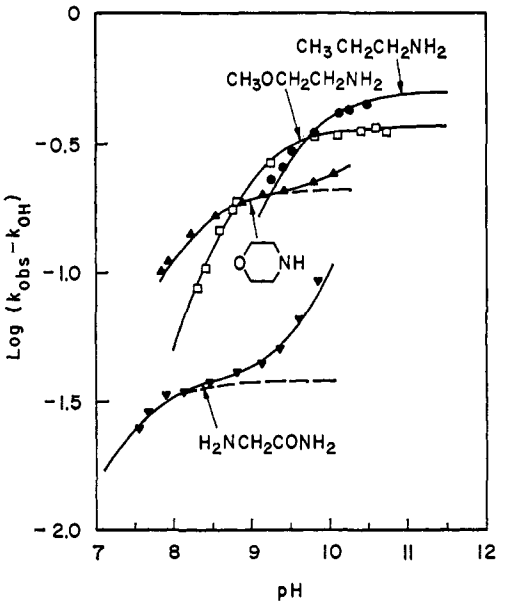


Figure 4. Pseudo-first-order rate constants for the reaction between methyl formate and n-propylamine, 2-methoxyethylamine, morpholine, and glycinamide as a function of pH at 25°, ionic strength 1.5 M, [amine$_{free}$] constant at 0.2 M (n-propylamine at 0.05 M). Theoretical curves were calculated from the rate constants in Table I (solid lines) and additionally for morpholine and glycinamide with $k_3 = 0$ (dashed lines).

a different transition state with no net charge becomes predominant.

The change in rate-determining step is also evident in plots of the apparent second-order rate constants against amine concentration (Figure 2). These show a levelling with increasing amine concentration and a decrease in slope with decreasing pH which are characteristic of a transition from a reaction which is strongly catalyzed by a second molecule of amine to one which shows little or no such catalysis.[12,13] It should be noted, however, that the reaction at pH 7.7 does show a small increase in rate constant with increasing amine concentration and experiments carried out with total amine concentration of up to 1.4 M indicated nearly a doubling of the apparent second-order rate constant, from 0.73 to 1.30 M^{-1} min^{-1}. This suggests that the rate-determining step at low pH is also subject to buffer catalysis, although to a much smaller extent than the rate-determining step at high pH.

The reactions of methyl formate with propylamine, methoxyethylamine, morpholine, glycinamide (Figure 4), and glycylglycine (not shown) also proceed through an intermediate and undergo a change in rate-determining step, as shown by the decrease in rate constant with decreasing pH at constant concentration of free amine. However, with these amines it was not possible to measure the rate at sufficiently low pH values to detect the levelling off which was observed with hydrazine. The reaction with glycinamide and probably that with morpholine shows an increase in rate at the highest pH values which is indicative of hydroxide ion catalysis of the step which is rate determining at high pH.

The effects of concentrated salts and dioxane on the rate of the reaction with morpholine are shown in Figure 5. These results are difficult to interpret according to a unified theory, but they do indicate that tetramethylammonium chloride, which was used to maintain a constant ionic strength of 1.5 M in the other experiments, does not affect the rate and that solvent effects are not responsible for the kinetic phenomena shown in Figures 1–4, although they may influence the numerical value of the derived rate constants.

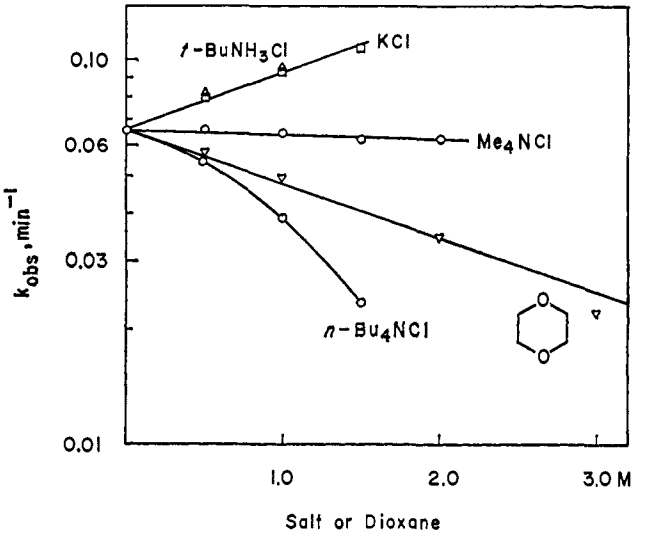


Figure 5. Observed rate constants for the reaction between methyl formate and 0.2 M morpholine buffer, 50% neutralized, at 25°, with additions of salt or dioxane as shown.

The observation of a change in rate-determining step demonstrates that there is a change from rate-determining formation to rate-determining breakdown of the intermediate with changing pH or buffer concentration, but does not indicate whether the breakdown or the attack step is rate determining at the high and low pH values and buffer concentrations. For reasons which

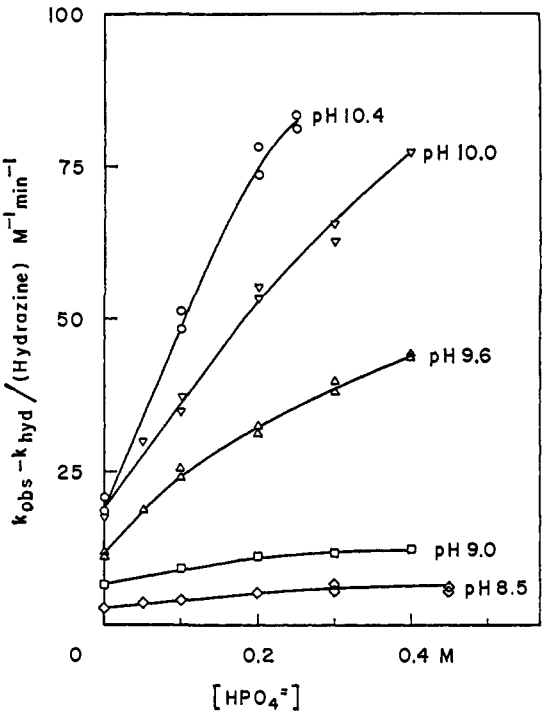


Figure 6. Apparent second-order rate constants for the reaction between methyl formate and hydrazine at 25°, ionic strength 1.5 *M*, as a function of phosphate dianion concentration at the indicated pH values.

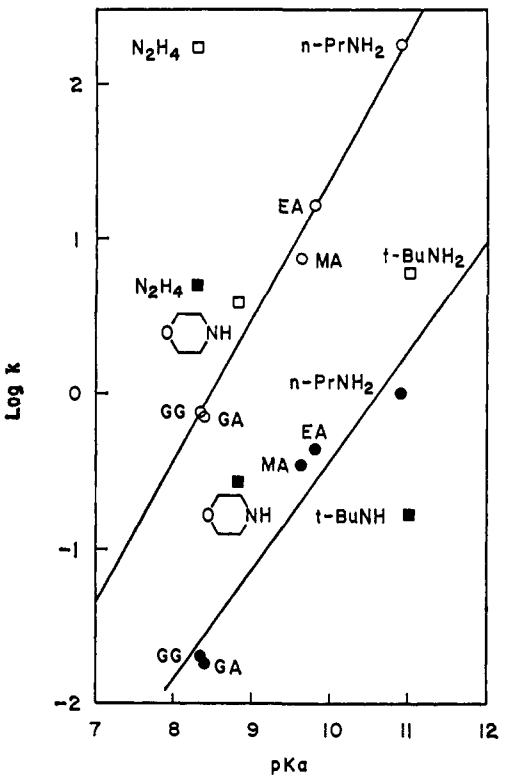
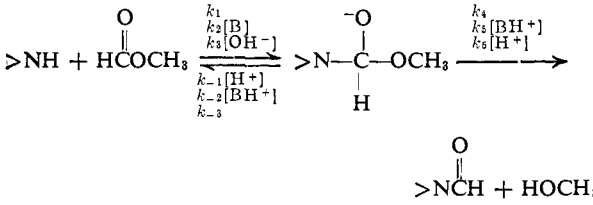


Figure 7. Plot of the logarithm of the rate constants for the aminolysis of methyl formate against the pK_a values of the conjugate acids of the amines: ○, □, amine-catalyzed aminolysis, k_2; ●, ■, water-catalyzed (uncatalyzed) aminolysis, k_1.

will become apparent later, we will assume that amine attack is rate determining at high pH and low buffer concentration and that breakdown of the intermediate is rate determining at low pH and high buffer concentration. The kinetic terms which have been demonstrated experimentally for these steps with one or more of the amines examined are shown in eq 2. The attack



$$>NH + HCOCH_3 \underset{k_{-1}[H^+] + k_{-2}[BH^+] + k_{-3}}{\overset{k_1 + k_2[B] + k_3[OH^-]}{\rightleftharpoons}} >N-C(-O^-)(H)-OCH_3 \xrightarrow{k_4 + k_5[BH^+] + k_6[H^+]} >NCH + HOCH_3 \quad (2)$$

step occurs predominantly through the amine-catalyzed pathway, k_2, with smaller contributions of water-catalyzed and hydroxide ion catalyzed terms. The breakdown step occurs predominantly through an anionic transition state corresponding to the rate constants, k_4, with a small contribution of the water-catalyzed and general acid catalyzed pathways in the reaction with hydrazine at low pH. The steady-state rate treatment of this mechanism gives eq 3. Rate

$$\frac{\text{rate}}{[B][\text{ester}]} = \frac{k_1 + k_2[B] + k_3[OH^-]}{1 + \dfrac{k_{-1}[H^+] + k_{-2}[BH^+] + k_{-3}}{k_4 + k_5[BH^+] + k_6[H^+]}} \quad (3)$$

constants for this mechanism were evaluated from the observed rates under conditions in which one or the other step is almost entirely rate determining and are summarized in Table I. The solid lines in Figures 1–4 were calculated from these rate constants and eq 3 and show satisfactory agreement with the experimental data.

Phosphate buffer catalysis of the reaction of hydrazine with methyl formate is shown in Figure 6. There is a levelling off of the rate with increasing buffer concentration and a decrease in catalysis with decreasing pH similar to that observed for hydrazine catalysis of the reaction. A detailed quantitative analysis of these data was not attempted because of small changes in pH with changing buffer concentration and the probability that the substitution of phosphate for tetramethylammonium chloride at constant ionic strength causes a specific salt effect on the reaction, but the data indicate that the catalytic constant for phosphate is at least 280 M^{-2} min^{-1} at pH 10.4 and extrapolation to a limiting value at higher pH suggests a maximum value of not less than 400 M^{-2} min^{-1}. This is larger than the catalytic constant for the more basic hydrazine molecule of 170 M^{-2} min^{-1} (Table I). This suggests that phosphate has a special catalytic ability attributable to its bifunctional character which is analogous to but smaller than that observed for aniline expulsion from the tetrahedral intermediate formed in the hydrolysis of 2-phenyliminotetrahydrofuran.[9] Phosphate catalysis is observed at low pH values and gives rate constants higher than those for the reaction under conditions in which the uncatalyzed breakdown step is rate determining. This is further evidence that the breakdown step, as well as the attack step, is subject to buffer catalysis.

The rate constants for the attack of amines on methyl formate are plotted logarithmically as a function of the basicity of the amine in Figure 7. The slopes of the lines, β, are 0.9 for the amine-catalyzed reaction and 0.7 for the water-catalyzed reaction; the amine-cata-

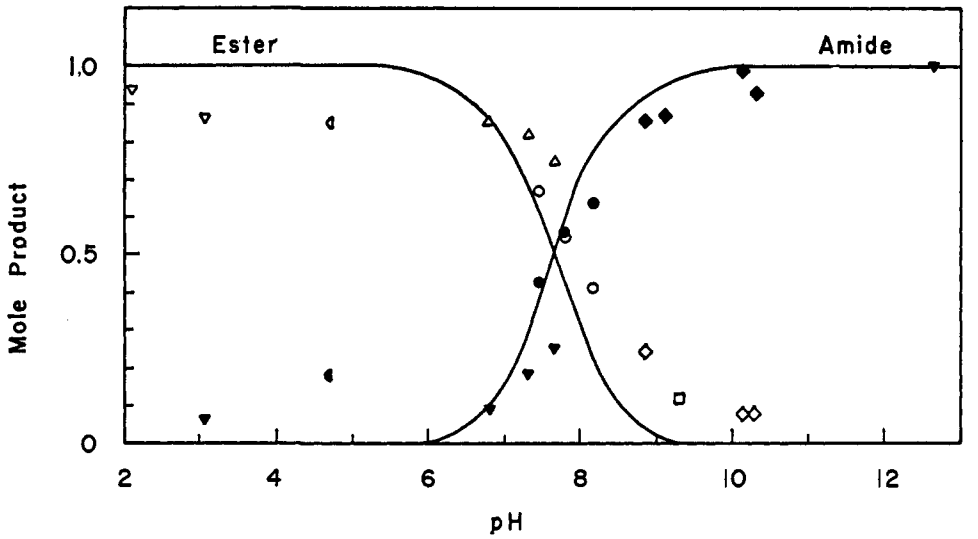
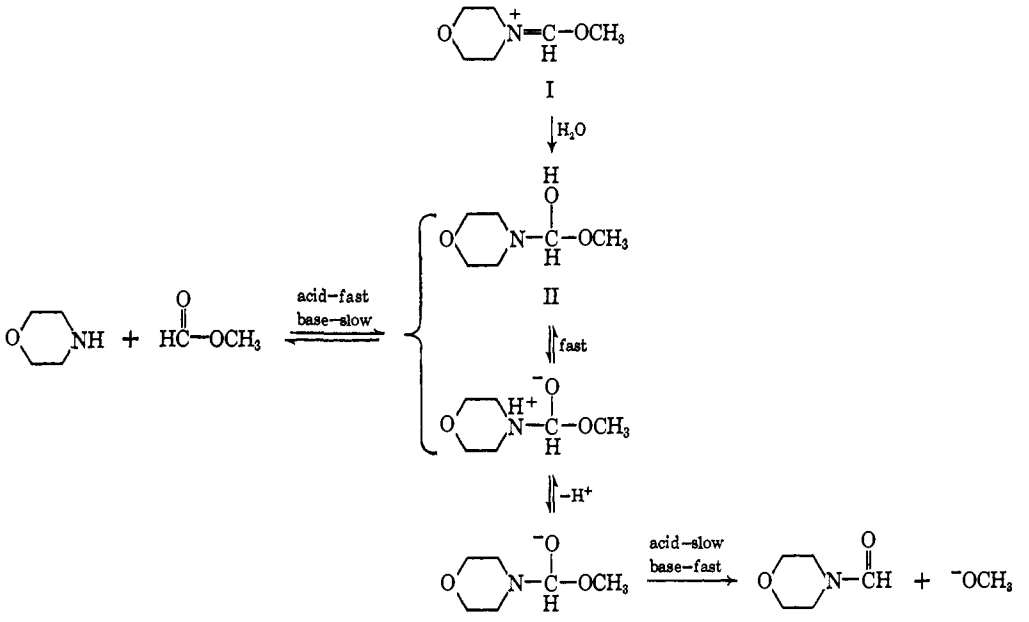


Figure 8. Products of the hydrolysis of N-(methoxymethylene)morpholinium methosulfate (I) as a function of pH. Buffers used were hydrochloric acid (▽), 0.05 *M* acetate (◁), phosphate (△), tris(hydroxymethyl)aminomethane (○), *t*-butylamine (◇), phenol (□), and sodium hydroxide (▽). Open symbols show ester formation and closed symbols amide production.

lyzed term accounts for the greater part of the observed reaction under most experimental conditions so that the rate constants and slope for this term are more accurate than those for the water-catalyzed term. The slopes, β, are similar to those observed for phenyl acetate aminolysis, with a large positive deviation for hydrazine, suggesting that the nature of the rate-determining step is similar for these two reactions.[4,14,15]

the aminolysis of methyl formate, it was of interest to determine the products of hydrolysis of the methoxymethylenemorpholinium cation I, which should generate the same tetrahedral intermediate upon hydrolysis as is formed in the reaction of methyl formate with morpholine (II, eq 4). The experiments were technically difficult because of the rapid rate of hydrolysis of this imidate and the fact that its direction of breakdown is



If a tetrahedral addition intermediate is formed in an acyl transfer reaction, it is possible to determine which way this intermediate breaks down most rapidly and, therefore, the rate-determining step of the reaction by generating the same intermediate from a different reaction and simply observing the predominant breakdown products under a given set of experimental conditions.[9,16–18] Knowing that there is an intermediate in

affected by the buffer used to maintain a constant pH. For example, the hydrolysis in 0.1 *M* phosphate buffer gave approximately 96% ester at pH 8, whereas only 50% ester was obtained in 0.05 *M* tris(hydroxymethyl)-aminomethane buffer at this pH and an increase in the concentration of carbonate buffer from 0 to 0.13 *M* in the presence of a phenol buffer at pH 9.7 gave an increase in the yield of ester from 20 to 55%. In spite of these difficulties, the results of a series of experiments

(14) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968).
(15) See Bruice, *et al.*[6]
(16) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959).
(17) R. B. Martin and A. Parcell, *ibid.*, **83**, 4830, 4835 (1961); R. B. Martin and R. I. Hedrick, *ibid.*, 84, 106 (1962).
(18) M. Kandel and E. H. Cordes, *J. Org. Chem.*, **32**, 3061 (1967).

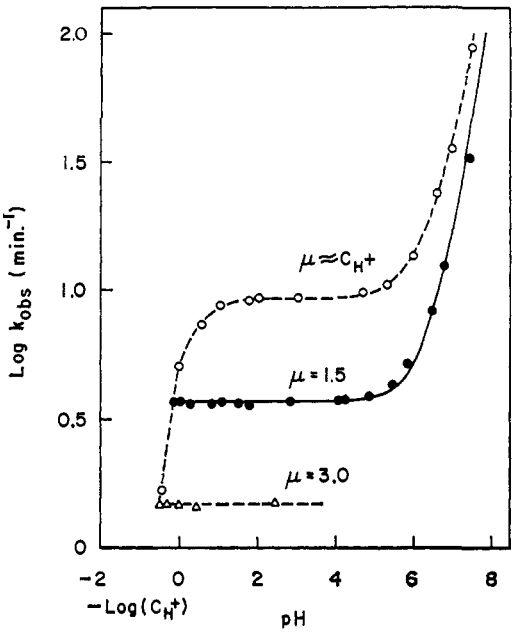


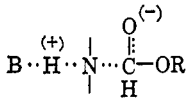
Figure 9. Observed rates for the hydrolysis of N-(methoxymethylene)morpholinium methosulfate (I) as a function of acid concentration. Lithium chloride was added to maintain ionic strength at 3.0 *M* (open triangles) and 1.5 *M* (closed circles); no addition (open circles). The solid curve was calculated from $k_{hyd} = (3.70 + 1.4 \times 10^8[a_{OH^-}])$ min^{-1}.

carried out in dilute acid, base, or buffer solutions show unequivocally that in acid solution breakdown occurs to methyl formate and morpholine, whereas in basic solution breakdown occurs to N-formylmorpholine and methanol (Figure 8). This means that in acid solution the tetrahedral intermediate II expels amine faster than alcohol, so that breakdown of the intermediate is the rate-determining step of ester aminolysis, and that in alkaline solution it expels alcohol faster than amine, so that attack of amine on the ester is the rate-determining step of ester aminolysis (eq 4). The curve in Figure 8 is calculated for a crossover point at pH 7.7, whereas the calculated crossover point from the rate constants for the reaction of methyl formate with morpholine (Table I) is at pH 7.4. This difference is probably not significant in view of the difficulty of correcting for buffer effects and of maintaining a constant local pH during the rapid solution and hydrolysis of the imidate. The change in the direction of breakdown of the intermediate with pH is similar to that observed with 2-phenyliminotetrahydrofuran.[9] Imidates ordinarily undergo hydrolysis to esters,[19] but there are a few other instances in which imidates with electron-withdrawing substituents on the nitrogen atom have been shown to give amides upon hydrolysis in neutral or alkaline solution.[20] It was found that all buffers examined cause an increase in the yield of ester relative to amide, but the special effectiveness of phosphate in this respect is similar to that observed in the hydrolysis of 2-phenyliminotetrahydrofuran[9] and suggests that bifunctional acid–base catalysis is particularly effective in catalyzing the addition and expulsion of morpholine.

(19) A. Pinner, "Die Imidoather und ihre Derivate," Oppenheim, Berlin, 1892; R. Roger and D. C. Nielson, *Chem. Rev.*, **61**, 179 (1961).
(20) D. F. Elliott, *Biochem. J.*, **45**, 429 (1949); I. Brown and O. E. Edwards, *Can. J. Chem.*, **43**, 1266 (1965); K. D. Berlin and M. A. R. Khayat, *Tetrahedron*, **22**, 975 (1966).

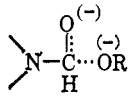
The rate of hydrolysis of I was examined in neutral and acidic solution (Figure 9). Between pH 1 and 5 the rate is independent of pH and at higher pH values a base-catalyzed reaction becomes predominant. This base-catalyzed reaction with a cationic substrate has a neutral transition state and corresponds to the pH-independent hydrolysis of imidates of primary amines at alkaline pH, which occurs by the attack of hydroxide ion on the protonated imidate.[9] In acid solution, there is an inhibition of the reaction which, in the absence of other information, might be taken as evidence for a change in rate-determining step. However, if the reaction is carried out at constant ionic strength, substituting hydrogen ion for lithium ion as the acid concentration is increased, there is no such acid inhibition. This demonstrates clearly that the acid inhibition is a salt effect and does not represent a change in rate-determining step. The fact that the appearance of the hydroxide ion catalyzed reaction between pH 5 and 6 does not correspond to the change in product formation at pH 7–8 suggests that, as in the case of 2-phenyliminotetrahydrofuran hydrolysis,[9] the partitioning of the tetrahedral intermediate is kinetically distinct from the rate of its formation; *i.e.*, that the rate-determining step is the attack of water or hydroxide ion to form a tetrahedral intermediate and the product-determining step is the breakdown of the intermediate.

With this information it is possible to describe the mechanism of the aminolysis of methyl formate by aliphatic amines in some detail. At high pH the rate-determining step is amine attack, whereas at low pH the rate-determining step is the breakdown of the tetrahedral intermediate which is formed on the main reaction path. The general agreement of the results from the kinetic experiment and the hydrolysis of the morpholine imidate suggests that the *same* intermediate is formed in both reactions; *i.e.*, the intermediate has a sufficient lifetime to permit proton-transfer steps to occur. The formation of the intermediate occurs through water-catalyzed, amine-catalyzed, and hydroxide ion catalyzed pathways with a Bronsted slope of approximately 0.3–0.4 for these three catalysts. The ionization of a free aliphatic amine to the unstable amine anion (pK about 30) is so unfavorable energetically that the subsequent attack of amine anion on the ester would have to occur many orders of magnitude faster than a diffusion-controlled reaction in order to account for the observed rate of the reaction. This effectively rules out any mechanism which requires such a preliminary ionization. The mechanism of the attack step is therefore defined as III without kinetic ambiguity.



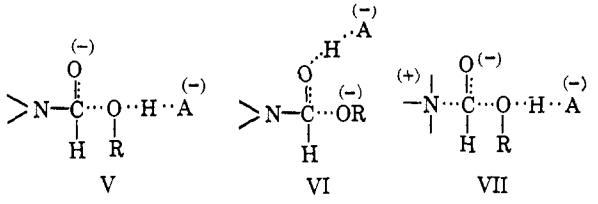
III

The breakdown step proceeds principally by a hydroxide ion catalyzed reaction, through the anionic transition state IV. At lower pH values the breakdown



IV

of the anionic intermediate is subject to catalysis by the solvated proton and general acids according to transition states V, VI, or VII; the hydroxide ion reaction may be considered as a special case of mechanism V or VI in which HA = HOH or $A^- = OH^-$. By analogy with



V VI VII

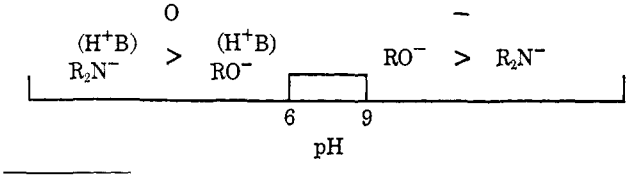
the preferred mechanism for base-catalyzed additions to aldehydes and imines and according to the hypothesis that catalysis occurs in such a way as to avoid the formation of the most unstable intermediates or products[13] (methoxide ion in this reaction) mechanism V is perhaps more probable than mechanism VI. Mechanism VII (HA = HOH) is almost certainly the pathway for the aminolysis of phenyl esters by tertiary amines.[14] The reaction may occur by a "one-encounter" mechanism in which the same molecule of catalyst removes a proton from the neutral intermediate and donates it to the leaving alcoholate ion.[21,22]

The effect of varying amine structure on the reaction may be analyzed as follows. The "break point" of the change in rate-determining step, *i.e.*, the pH at which the intermediate breaks down at equal rates in both directions (in the absence of general base catalysis by amine) is the pH at which $k_{-1}[H^+] = k_4$. This pH increases steadily from 6.3 for glycinamide (pK = 8.4) to 8.4 for propylamine (pK = 10.9), but is 8.7 for hydrazine (pK = 8.3); it is 1.3 to 2.5 pH units below the pK of the amine for all amines except hydrazine, for which it is above the pK. Consider an anionic tetrahedral intermediate that can expel methoxide ion directly or can add a proton to the nitrogen atom and expel amine. An increase in amine basicity is expected to cause a small increase in the rate of methoxide expulsion, a large increase in the amount of amine protonation, and a moderate decrease in the leaving ability of the protonated amine. The fact that k_{-1}/k_4 increases so that the break point occurs at higher pH with more basic amines means that amine expulsion is preferred to methoxide expulsion over a wider pH range for such amines. This means that the effect of amine structure on the concentration of protonated amine must outweigh its effects on the rates of expulsion of methoxide and protonated amine. This trend cannot be extrapolated to 2-phenyliminotetrahydrofuran, which gives equal rates of expulsion of aniline (pK = 4.9) and alkoxide at pH 7;[9] evidently the ring structure, the large size of aniline, and/or a greater basicity of the alkoxide ion favor amine expulsion from the tetrahedral intermediate formed during the hydrolysis of this imidate. The large k_{-1}/k_4 ratio and high pH of the break point for hydrazine indicate that the rate of expulsion as well as the rate of attack of this α-effect compound must be unusually large. The fact that the over-all rates k_1k_4/k_{-1} under conditions in which base-catalyzed breakdown of the intermediate is rate determining are almost the same for hydrazine and glycinamide, although the rate of attack of hydrazine is 280 times larger than that of glycinamide, suggests that the α effect is manifested to a larger extent in the rate constant for the attack step than in the equilibrium constant for adduct formation, k_1/k_{-1}, in spite of the known high affinity of hydrazine for the carbonyl group.[23]

Except in the case of the hydrazine reaction it was not possible to follow the rates to pH values low enough for the breakdown step to become fully rate determining or for the pH-independent breakdown pathway to become evident. By analogy with the hydrazine reaction, it would be expected that this pH-independent breakdown should become significant at a pH value which is not very far below that at which the change in the rate-determining step occurs; *i.e.*, the differences in rate constants which lead to a change in rate-determining step are not large. If the alcohol is made a better leaving group, oxygen expulsion should be favored over amine expulsion and the attack step should become partially or entirely rate determining over a wide range of pH. This appears to be the case in the reactions of phenyl acetate with amines.[14,18]

The change in rate-determining step at high pH is a consequence of the fact that transition states of different charge are favored for departure of alkoxide and of amine: alkoxide is a far better leaving group than amine anion and is expelled through an anionic transition state at high pH, so that amine attack is rate determining, whereas amine expulsion (pK = 8–11) is preferred to alcohol expulsion (pK = *ca.* 15) through a neutral transition state. With phenolate as the leaving group it appears that phenolate expulsion is only slightly preferred to methylamine expulsion through a neutral transition state;[14] *i.e.*, the reaction is near a break point. The mechanism for the aminolysis of methyl formate may be summarized schematically by Scheme I, which shows the preferred mode of leaving group expulsion from the addition intermediate and the charge of the transition state for this expulsion as a function of pH.

Scheme I



(21) M. Eigen, *Discussions Faraday Soc.*, **39**, 7 (1965).
(22) G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, 88, 3982 (1966).
(23) W. P. Jencks, *ibid.*, **81**, 475 (1959).