an early transition state with little development of positive charge on nitrogen. It involves a different rate-determining step than the reaction in solution, which proceeds through a rapid and reversible addition of the amine.

(6) There is a rate-determining conformation change of the acyl-enzyme with a molecule of amine bound at the active site. It is difficult to explain the large differences in the reaction rates of specific and nonspecific substrates by this mechanism.

The formation and aminolysis of the acyl-enzyme intermediate exhibit a solvent deuterium isotope effect k_{H_2O}/k_{D_2O} of about 2–3 in the reactions of amines with *N*-acetyl-L-tyrosylchymotrypsin and in the hydrolysis of anilides.[34,36] A pH-dependent isotope effect has also been reported for the hydrolysis of *N*-acetyl-L-tryptophanamide.[44] If these isotope effects represent loss of the zero-point energy of the N–H proton in the transition state rather than a secondary isotope effect (*e.g.*, on the structure and catalytic activity of the protein), they serve to exclude Mechanisms 1, 5, and 6. A small, pH-dependent nitrogen isotope effect ($^{14}N/^{15}N$ = 1.006–1.010) has been observed for the hydrolysis of *N*-acetyltryptophanamide.[45] This result may be interpreted as evidence for rate-determining C–N bond cleavage in the transition state[45] or for a decrease in the C–N bond order upon conversion of the amide to the addition intermediate. A significant heavy-atom isotope effect has been observed upon formation of the addition intermediate in three reactions of methyl formate-*methoxyl*-^{18}O in which expulsion of alcohol is not occurring in the rate-determining step,[5] and the hydrolysis of *N*-benzoyl-L-argininamide by papain, in which C–N bond cleavage is presumably fully rate determining, exhibits a larger nitrogen isotope effect ($^{14}N/^{15}N$ = 1.022) and a small solvent deuterium isotope effect (k_{H_2O}/k_{D_2O} = 1.35).[46]

In our opinion the available data are insufficient to distinguish among Mechanisms 1–6 or other possible mechanisms for chymotrypsin at the present time. However, enough is now known about the mechanisms of nonenzymic reactions to indicate that mechanisms of this kind and their experimental implications deserve serious consideration with respect to the mechanism of catalysis by chymotrypsin and by other enzymes. We venture to express a slight preference for mechanisms 1 and 2 at this time.

The absence of an effect of polar substituents on the rate of reaction of alcohols with furoylchymotrypsin is consistent with a mechanism involving concerted general base catalysis of alcohol attack, as suggested previously.[35] The result is inconsistent or difficult to explain with mechanisms for alcohol attack analogous to 1, 5, and 6, but is not inconsistent with Mechanisms 2, 3 and 4.

Acknowledgment. We are grateful to Alan Fersht for helpful discussions.

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The Mechanism of Partitioning of the Intermediates Formed in the Hydrolysis of Phenyl Imidates[1]

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Abstract: The observed rate constants for the reactions of methylamine and dimethylamine with *p*-tolyl acetate remain constant over a range of pH in which a partial change in rate-determining step may be predicted from the observed change of the % ester/% amide product ratio in the hydrolysis of the corresponding *p*-tolyl imidates. Brønsted plots for general acid catalysis of ester formation from these imidates are curved, consistent with rate-determining proton transfer in the product-determining step. These results show that different, nonequilibrated ionic forms of the addition intermediate are formed in the aminolysis of the ester and in the hydrolysis of the corresponding imidate. Three predictions required by a proposed mechanism for imidate hydrolysis are supported experimentally: (1) the pH- and buffer-independent product ratio remains constant upon substitution of electron-withdrawing substituents into the phenyl group; (2) the decrease in ester yield with increasing pH is correlated with the fraction of the imidate that reacts with hydroxide ion; (3) the observed rate constants for general acid catalysis of ester formation remain almost constant as the buffer-independent ester yield decreases with increasing pH.

As discussed in the previous paper[2] and elsewhere,[3–6] an understanding of the mechanism of breakdown to ester and to amide of the tetrahedral intermediate that is formed during the hydrolysis of imidates is essential for an understanding of the mechanism of ester aminolysis. The mechanism we have proposed for ester aminolysis requires that under certain conditions

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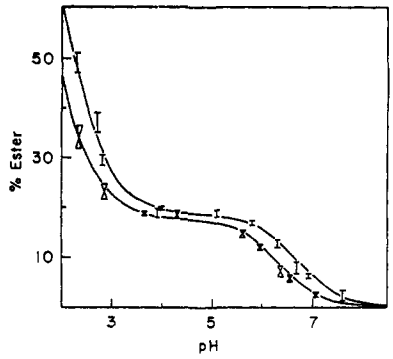
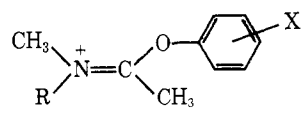


Figure 1. The buffer-independent yield of *p*-tolyl acetate from I as a function of pH at 25° (upper curve) and 50° (lower curve), ionic strength 1.0 (KCl). The buffers employed at pH <5.0 were substituted acetic acids and acetic acid and at pH >5.0 were N-substituted morpholines.

the addition intermediate that is formed in ester aminolysis is not in protonic equilibrium with the intermediate formed in imidate hydrolysis, so that the direction of breakdown of the latter intermediate does not necessarily identify the rate-determining step of ester aminolysis.[2] In this paper, we report experimental evidence that supports this requirement and suggests that the different ionic forms of the addition intermediate are interconvertible by simple proton transfer reactions that can be product determining in imidate hydrolysis and rate determining in ester aminolysis. The first evidence that simple proton transfer, to or from an unstable intermediate, can be rate determining in reactions of this kind was obtained for the aminolysis of a thiol ester and thiazoline hydrolysis,[7] and similar evidence has been obtained for product determination in the hydrolysis of an acyclic thiol imidate.[8]

A novel mechanism for imidate hydrolysis is presented in which different intermediates, T^+ and T^0, are formed by the attack of water and of hydroxide ion, respectively, on the cationic imidate. In the absence of added buffers, the partitioning of T^+ to ester and amide depends only on the relative rates of proton abstraction by water from the oxygen and nitrogen atoms of T^+, respectively. Buffers catalyze ester formation by facilitating the conversion of T^0 through T^+ to $T^\pm$, which expels amine rapidly to give ester. This mechanism is consistent with the previously proposed mechanism for ester aminolysis.[2] The results of three experimental tests support the mechanism and are not predicted by previously proposed mechanisms. The imidates that were examined are *p*-tolyl *N,N*-dimethylacetimidate (I)



I, R = CH_3; X = *p*-CH_3
II, R = H; X = *p*-CH_3
III, R = H; X = *p*-Cl
IV, R = H; X = *m*-NO_2

and *p*-tolyl, *p*-chlorophenyl, and *m*-nitrophenyl *N*-methylacetimidates (II–IV). A preliminary report of a portion of this work has appeared.[9]

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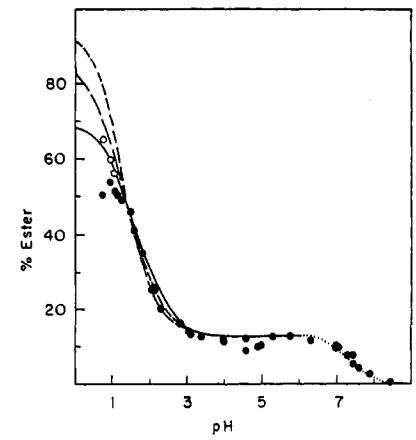

Figure 2. The buffer-independent yield of *p*-tolyl acetate from II as a function of pH at 25°, ionic strength 1.0 (KCl). Observed ester yield (●); corrected for ester hydrolysis (○). Hydrochloric acid was used to buffer the reaction at pH ≤2.0; otherwise buffers were as in Figure 1. The solid line is calculated from the partition equation for Mechanism 3 and the rate constants given in Table VI. The dashed lines at low pH are based on a % ester max of 85% and 95%. The dotted line at high pH is based on a pH-independent ester yield of 12.5% and a pK' = 7.30.

Results

Imidate Hydrolysis. The hydrolysis of *p*-tolyl *N,N*-dimethylacetimidate (I) was found to follow the rate law of eq 1, as expected for a cationic imidate.[5] The

$$k_{obsd} = k_1 + k_2 a_{OH^-} + k_B[B] \quad (1)$$

rate constants were evaluated carefully at 25 and 60° with at least 17 points at each temperature in the range pH 3 to 9; catalysis by the buffer was observed with acetate and hexafluoroacetone hydrate, and rate constants were extrapolated to zero concentration of these buffers. At 25 and 50°, the values of k_1 and k_2 were found to be 6.20×10^{-3} and 5.60×10^{-2} min^{-1}, and 1.24×10^5 and 4.55×10^5 M^{-1} min^{-1}, respectively (ionic strength 1.0, KCl). The values of k_B for acetate and hexafluoroacetone hydrate monoanions at 25° were found to be 0.020 and 0.027 M^{-1} min^{-1}, respectively; k_B for tetrafluoroacetone hydrate monoanion was found to be ≤ 0.55 M^{-1} min^{-1}. The other imidates exist as mixtures of *E* and *Z* isomers which hydrolyze at different rates and interconvert slowly so that hydrolysis does not follow first-order kinetics.[4,10]

Dependence of Product Yield on pH. The effect of pH on the yields of ester from the hydrolysis of I, II, and IV, determined by extrapolation of values of % ester/% amide to zero buffer concentration, are shown in Figures 1–3. The pH–product curves at intermediate pH values may be described by titration curves for monobasic acids[11] with values of pK'_a at 25° for I = 6.70, II = 7.30, and IV = 7.0; pK'_a for I at 50° is 6.35. The curves for II in the acid region are drawn in Figure 2 based on limiting values of ester yield at high acid concentration of 69% (solid line), 85%, and 95% (dashed lines); these are taken as the range of values of % ester max that are consistent with the data.

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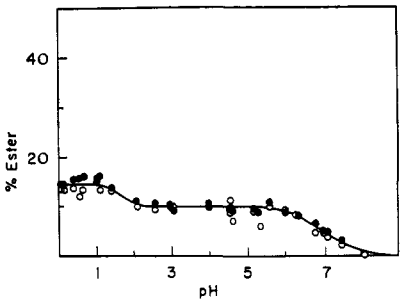

Figure 3. The yield of *m*-nitrophenyl acetate from IV as a function of pH at 25° and ionic strength 1.0 (KCl). Ester yield was determined using the alkaline hydrolysis (○) and hydroxamic acid (●) methods. Solutions were buffered as in Figures 1 and 2. No effect of buffer concentration (up to 0.5 *M*) on the yield of ester was observed. The solid line is based on pH-independent yields of ester between pH 0 and 1.0 of 14.5%, between pH 2.5 and 5.5 of 10%, a pK' = 1.6 at low pH, and a pK' = 7.0 at high pH

Table I. Ester Yield from III as a Function of pH and Buffer Concentration at Ionic Strength 1.0 (KCl), 25°

Buffer	Concentration, *M*	pH	No. of determinations	Average % ester
HCl	0.01	2.05	2	30[a]
Chloroacetate	0.05	2.91	4	12.3
(60% base)	0.50	2.85	2	14.3
Acetate	0.05	3.90	2	12.4
(17% base)			2	14.0
	0.50	3.91	2	12.6
Acetate	0.05	4.91	4	12.3
(70% base)	0.50	5.00	2	10.3

[a] A correction of +3% was made for hydrolysis of the ester product.

The effect of pH on the product yield from III is shown in Table I. The data for III and IV were obtained by Haggerty and Suva, respectively. The time course for the formation of ester was found to be the same as that for the release of phenol in the hydrolysis of II; *i.e.*, the biphasic time course of the hydrolysis of the mixture of *E* and *Z* isomers of II does not influence the product ratio.

An elimination mechanism for the hydrolysis of II at alkaline pH was excluded by showing that no deuterium is incorporated into the acetyl group of the *N*-methylacetamide product when the hydrolysis is carried out in deuterium oxide at pD 9.5.

Buffer Catalysis of Ester Formation in Imidate Hydrolysis. The acidic form of most buffers increases the yield of ester upon the hydrolysis of I and II but has no detectable effect with III and IV. For example, the ester yield from I increases from 33 to 71% as the concentration of methoxyacetate buffer (80% acid) is increased from 0.05 to 1.0 *M*, and the yield from II increases from 20 to 40% in the range 0.1 to 1.0 *M* of the same buffer. Relative catalytic constants for the acid species of the buffer, k_{cat}, were evaluated from the slopes of plots of % ester/% amide against buffer concentration, as illustrated in Figure 4. The data for II were also evaluated based on a limiting value of 70% for % ester max (Figure 2), as described in the Experimental Section, to give values of k'_{cat}. The relative values of k'_{cat} differ slightly from those of k_{cat} largely because of differences in the yield of ester, and hence the

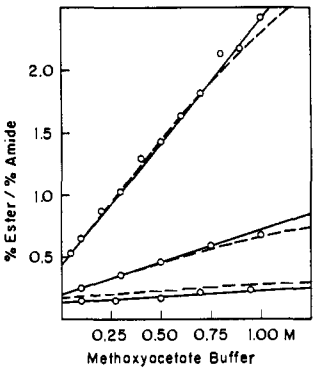

Figure 4. Methoxyacetic acid catalysis of ester formation from the tetrahedral intermediates generated from I and II at 25°, ionic strength 1.0 (KCl). The observed % ester/% amide ratio from I (upper line) and II (lower lines) is plotted as a function of methoxyacetate buffer (20% base, upper lines, and 80% base, lower line). The k_{cat} values reported in Tables II and III are based on the solid lines. The dashed lines were calculated from the partition equation for Mechanism 3 and the rate constants listed in Table VI.

size of the correction, with different buffers. The dashed lines in Figure 4 show the amount of curvature that would be expected with compound I if % ester max = 92%, which we take as a lower limit for this quantity. Since there is no difference in the relative values of k_{cat} and k'_{cat} for the different buffers if the data are calculated based on a value of % ester max = 90%, the results for this compound are adequately described by k_{cat}. The results are summarized in Tables II–IV.

Table II. General Acid Catalysis of Ester Yield from the Tetrahedral Addition Intermediates Generated from I at 25°, Ionic Strength 1.0 (KCl)

Acid	pK_a	pH	k_{cat},[a] M^{-1}
H_3O^+	−1.7		130 ± 10
Cyanoacetic (CNA)	2.33[b]	2.30	3.1 ± 0.5[c]
Chloroacetic (CA)	2.70[b]	2.70	1.9 ± 0.4[c]
Methoxyacetic (MA)	3.40[b]	2.80	2.5
Acetic (AC)	4.65[b]	4.00	2.5[d]
		4.00	2.2[e]
Cacodylic (CAC)	6.15[f]	4.00[g]	1.2
Hexafluoroacetone hydrate (HF)	6.45[h]	3.90[g]	1.8
Pentafluoroacetone hydrate (PF)	7.67[h]	3.90[i]	0.63
Hexafluoro-2-propanol (HFP)	9.22[b]	4.00[i]	0.07[j]
Tetrafluoroacetone hydrate (TF)	8.90[h]	5.50[k]	0.16
Trifluoroacetone hydrate (TRF)	10.45[h]	4.60[l]	0.06 ± 0.02
		4.00[i]	0.08 ± 0.03
		5.30[m]	0.06 ± 0.01
		5.20[m]	0.05 ± 0.01
		5.20[m]	0.04 ± 0.02
2,4-Lutidine-H$^+$ (2,4LU)	7.00[n]	4.00[g]	1.35
4-Dimethylaminopyridine-H$^+$ (DP)	9.84[h]	4.60[i]	≤0.04[o]

[a] Based on a % ester max of 100% and the acidic form of the buffer. Determined using the alkaline hydrolysis assay, except as noted. [b] J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 6353 (1969). [c] Small corrections were made for the hydrolysis of the ester product which occurred as the imidate was hydrolyzing. [d] I was added to the reaction mixture as the perchlorate salt. [e] Ionic strength 0.01–0.08 (potassium acetate). [f] J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **95**, 5637 (1973). [g] Buffered with 0.10 *M* acetate buffer (20% base). [h] Determined by titration of a 0.1 *M* solution of the acid form. [i] Buffered with 0.05 *M* acetate buffer (20% base). [j] Ionic strength 0.01 (potassium acetate) was required by the low solubility of hexafluoro-2-propanol. [k] Buffered with 0.05 *M* *N*-propargylmorpholine (50% base). [l] Buffered with 0.10 *M* acetate buffer (50% base). [m] Buffered with 0.05 *M* acetate buffer (80% base). [n] Estimated from partial neutralization of a 0.10 *M* solution. [o] The ester yield was determined using the hydroxamic acid assay.

Table III. General Acid Catalysis of Ester Yield from the Tetrahedral Addition Intermediates Generated from II at 25°, Ionic Strength 1.0 (KCl)[a]

Acid	pK_a	pH	k'_{cat},[b] M^{-1}	k_{cat},[c] M^{-1}
		Oxygen Acids		
H_3O^+	−1.7		38	20 ± 2
Difluoroacetic acid (DF)	1.13	2.13–2.21	4.2 ± 0.5	2.1 ± 0.3
Dichloroacetic acid (DC)	1.12[d]	2.12	4.5 ± 0.2	2.0 ± 0.2
Cyanoacetic acid	2.33	2.30	2.0 ± 0.2	0.8 ± 0.1
Chloroacetic acid	2.70	2.10	2.1	0.80
Methoxyacetic acid	3.40	2.80	1.3	0.65
		3.40	1.3	0.75
		4.0–4.2	1.1	0.55
Acetic acid	4.60	4.00	1.2	0.60
		4.00	1.2	0.60
		4.60	1.0	0.50
		5.00	0.8	0.50
Hexafluoroacetone hydrate	6.45	3.35[e]	0.79	0.41
		Alicyclic Tertiary Amines[f]		
Triethylenediamine dihydrochloride (Dabco)	3.47[g]	3.16–3.05		
		4.01	3.4	1.7
N,N'-Dimethylpiperazine dihydrochloride (DMP)[h]	4.60[i]	2.70–2.60[j]	1.6	0.80
N-Propargylmorpholine (PM)	5.60[k]	3.30[l]	0.62	0.30
N-(2-Chloroethyl)morpholine (CM)	6.30[i]	3.45[l]	0.32	0.18
N-Allylmorpholine (NAM)[i]	7.40[i]	3.40[l]	0.12	0.08
N-Methylmorpholine (NMM)[i]	7.83[k]	3.40[l]	0.08	0.05
		Pyridines[f]		
3-Chloropyridine (CP)[m]	3.30[d]	2.70–2.44	4.0[n]	2.1
Nicotinamide (NIC)[m]	3.55[d]	3.00–2.75	4.1	1.6
3-Iodopyridine (IP)[m]	3.70[o]	2.06	3.1	1.5
Pyridine (PY)	5.51[p]	3.40[l]	2.5	1.2
		5.60		1.2
2-Methylpyridine (2-MP)	6.30[d]	3.40[l]	1.0[m]	0.51[m]
		3.40[l]	0.86[h]	0.47[h]
4-Methylpyridine (4-MP)[m]	6.33[p]	3.40[l]	1.9	0.93
3,4-Lutidine (3,4-LU)[m]	6.79[p]	3.40[l]	1.4	0.70
2,4-Lutidine[h]	7.00	3.40[l]	0.50	0.30
		Imidazoles[f]		
5-Chloro-*N*-methylimidazole (CMI)	5.40[i]	3.40[l]	1.9	0.90
N-Methylimidazole (NMI)	7.20[q]	3.45[l]	0.41	0.23
Imidazole (IM)	7.24[r]	3.40[l]	0.62	0.33
1,2-Dimethylimidazole (DMI)	8.35[i]	4.60[s]	0.14	0.08
2-Methylimidazole (MI)	8.25[i]	4.00[t]	0.18	0.11

[a] The yield of ester was determined with the alkaline hydrolysis assay unless otherwise noted. [b] Based on a % ester max of 70% and the acidic form of the buffer. [c] Based on a % ester max of 100% and the acidic form of the buffer. [d] Estimated by partial neutralization of a 0.10 *M* solution. [e] Buffered with 0.07 *M* methoxyacetic acid (50% base). [f] The data refer to the conjugate acid. [g] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968). [h] The yield of ester was determined with both the alkaline hydrolysis and the hydroxamic acid assays. [i] Determined by titration of a 0.10 *M* solution. [j] Buffered with 0.10 *M* chloroacetic acid (50% base). [k] M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 8828 (1972). [l] Buffered with 0.10 *M* methoxyacetic acid (50% base). [m] The yield of ester was determined with the hydroxamic acid assay. [n] Small corrections were made for the increase in the base line buffer-independent ester yield resulting from decreasing pH with increasing buffer concentrations. [o] Determined by titration of a 0.01 *M* solution of the base. [p] A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5432 (1970). [q] G. D. Oakenfull and W. P. Jencks, *ibid.*, **93**, 178 (1971). [r] J. M. Sayer and W. P. Jencks, *ibid.*, **91**, 6353 (1969). [s] Buffered with 0.10 *M* acetic acid (50% base). [t] Buffered with 0.10 *M* methoxyacetic acid (80% base).

Phosphate buffers cause a *decrease* in ester yield from II, presumably because of a nucleophilic reaction of phosphate dianion with the imidate; no such decrease was observed at pH 4.0. The effects of salts and cosolvents on the yield of ester from II are small (Table V), which shows that the observed catalysis by buffers does not represent a nonspecific salt or solvent effect.

Dependence on pH of the Reactions of *p*-Tolyl Acetate with Methylamine and Dimethylamine. The rate constants for the aminolysis and dimethylaminolysis of *p*-tolyl acetate were compared at pH values above and below the break points in Figures 1 and 2 to determine whether these reactions undergo a partial change in rate-determining step, as might be predicted from the change in products upon imidate hydrolysis.[6,12] Since the decrease in rate caused by such a change in rate-determining step is small, 12.5% for methylamine and 17.5% for dimethylamine, the experiments were run in pairs at the two pH values and were normalized by reference to a standard to correct for differences in the rate constants resulting from differences in pH standardization. Under the conditions of the experiments, the term k_2 in the rate law of eq 2 (in which

$$k_{obsd} = k_0 + k_1[N] + k_2[N]^2 + k_3[N][NH^+] + k_4[buffer] \quad (2)$$

N refers to the free amine) is insignificant, and small corrections for hydrolysis (k_0) were necessary only for the dimethylaminolysis experiments at low pH. The results were evaluated in terms of experimental second-order rate constants at zero buffer concentration,

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Table IV. General Acid Catalysis of Ester Yield from the Tetrahedral Addition Intermediates Generated from I at Low and High pH at 25°, Ionic Strength 1.0 (KCl)

Acid	pK_a	pH	k_{cat}[a] predicted	k_{cat}[b] observed
Hexafluoroacetone	6.45	3.90[c]	1.9	1.9
		6.60–6.71	0.95	1.5[d]
		7.02–7.34	0.16	1.6[d]
Tetrafluoroacetone hydrate	8.90	5.50[e]	0.16	0.16 ± 0.02
		7.65–7.39[f]	0.02	0.20 ± 0.02[d]
N-Allylmorpholine	7.40	3.90[g]	0.22	0.22
		6.93–6.85	0.08	0.16
N-Propargylmorpholine	5.55	4.00[g]	1.2	1.2
		5.14–5.04	1.2	1.0
2,4-Lutidine	7.00	4.00[g]	1.30	1.30 ± 0.10
		4.00[h]	1.30	1.30 ± 0.10[i]
		7.52–7.38	0.11	1.25 ± 0.10
		7.52–7.38	0.11	1.30 ± 0.10
		7.51–7.44	0.11	1.28 ± 0.12[i]

[a] Predicted k_{cat} values for Mechanisms 1 and 2 (see Discussion). [b] Based on the acidic form of the buffer. The yield of *p*-tolyl acetate was determined with the alkaline hydrolysis method unless otherwise noted. [c] Buffered with 0.05 *M* acetate (20% base). [d] Small corrections were made for the increase in the base-line buffer-independent ester yield resulting from decreasing pH with decreasing buffer concentration. [e] Buffered with *N*-propargylmorpholine (50% base). [f] Buffered with 0.10 *M* *N*-methylmorpholine (30% base). [g] Buffered with 0.10 *M* acetate (20% base). [h] Buffered with 0.02 *M* acetate (20% base). [i] The yield of *p*-tolyl acetate was determined using both the alkaline hydrolysis and hydroxamic acid methods.

Table V. Salt and Solvent Effects on the Ester Yield from the Tetrahedral Intermediates Generated from II at 25°, Ionic Strength Maintained at 1.0 (KCl)

Salts, solvents	Concn, *M* or % (v/v)	pH[a]	% ester
Potassium dichloroacetate	0.00 *M*	3.4	20
	0.85	3.7	19
Lithium chloride	0.0 *M*	4.1	15
	0.5	3.9	17
	1.0	3.8	16
Methylamine hydrochloride	0.0 *M*	2.8[b]	18
	1.0	2.8[b]	21
	0.0	3.4[b]	15
	1.0	3.3	15
Tetramethylammonium chloride	0.1 *M*	4.0	10
	0.3	4.0	10
	0.5	4.1	10
	0.7	4.1	9
	0.9	4.1	9
Acetonitrile	0%	4.1	17
	5	4.2	16
	15	4.4	14
	30	4.6	14
Dioxane	0%	4.1	17
	5	4.2	16
	15	4.4	13
	30	4.8	12
Methyl acetate	0%	1.3[c]	54
	10	1.3[c]	50
	0%	1.3[d]	60
	10	1.3[d]	54

[a] Buffered with 0.05 *M* *N*-allylmorpholine (pH 7.0–7.9), 0.1–0.3 *M* acetate (pH 3.4–4.8), or 0.1–0.13 *M* methoxyacetate (pH 2.8–4.1) buffers. [b] Ionic strength 1.0 to 2.0. [c] In 0.06 *M* hydrochloric acid. [d] Buffered with 0.5 *M* cyanoacetic acid (9% base).

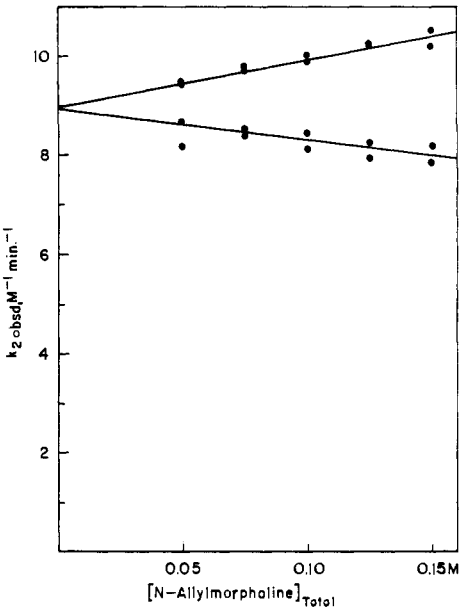


Figure 5. Plot of $k_{2,obsd}$ values for the reaction of methylamine with *p*-tolyl acetate as a function of *N*-allylmorpholine buffer concentrations at pH 6.64 (upper line, 10% base) and pH 8.20 (lower line, 85% base).

k'_2. Since the values of k_3 for general acid catalysis were shown in separate experiments to be small relative to k'_2, the values of k'_2 are essentially equal to k_1 ($k_3 \leq 1$ M^{-2} min^{-1} for methylamine[13] and ≤ 0.5 M^{-2} min^{-1} for dimethylamine, compared with values for k'_2 of 8.8 M^{-1} min^{-1} and 4.5 M^{-1} min^{-1} at 25° for the same two amines, respectively; the value of k'_2 for dimethylamine at 50° is 7.2 M^{-1} min^{-1}). A small contribution of the k_3 term would not affect the conclusions in any case, since both k_3 and k_1 would be decreased by a change in rate-determining step. The observed second-order rate constants, $k_{2\,obsd}$, were extrapolated to zero buffer concentration in each pair of experiments, as shown for an experiment with methylamine in *N*-allylmorpholine buffers in Figure 5. In most experiments, the rate was increased by the presence of buffer; the decrease shown in Figure 5 at high pH is presumably caused by complexation of the basic form of the buffer with the ester.

The results of three pairs of experiments for each amine are summarized in Figure 6. In no case is there any indication of the decrease in the rate constant with decreasing pH that might be expected from the imidate partitioning experiments, shown as the dashed lines in the same figure.

(13) (a) A value of $k_3 = 5.16$ M^{-2} min^{-1} at 30° has been reported;[13b] however, this value was determined under conditions in which general base catalysis, with a 20-fold larger third-order rate constant, is the predominant mechanism of catalysis. (b) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, 89, 2106 (1967).

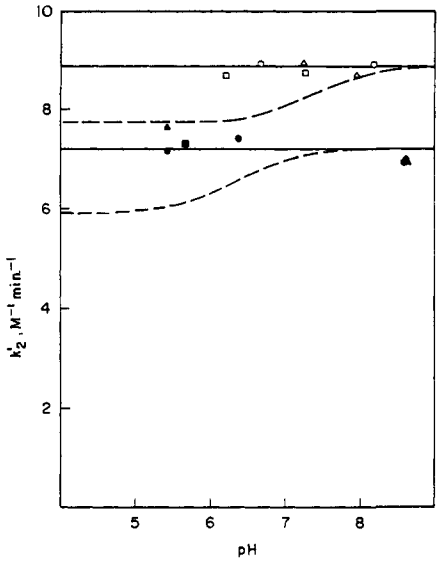
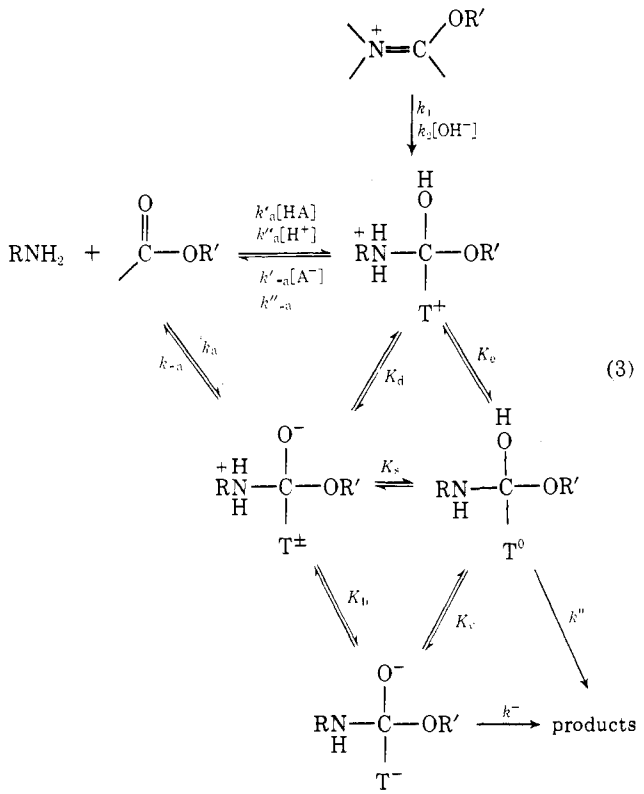


Figure 6. The dependence on pH of normalized k_2' values for the reaction of *p*-tolyl acetate with methylamine at 25° (upper line) and with dimethylamine at 50° (lower line), ionic strength 2.0. The three experiments for each amine are identified by separate symbols. The buffers were 0.02–0.15 *M* *N*-allylmorpholine, *N*-methylmorpholine, and *N*-propargylmorpholine for methylamine and 0.04–0.15 *M* acetate, 0.01–0.08 *M* cacodylate, and 0.04–0.20 *M* borate for dimethylamine. The dashed lines indicate the position and magnitude of the change in rate-determining step predicted from the pH-product profile for the hydrolysis of the corresponding imidates.

Discussion

Ester Aminolysis and the Predicted Change in Rate-Determining Step. The generally accepted scheme for ester aminolysis and imidate hydrolysis is shown in Mechanism 1 (eq 3).[3,5,6,13b,14] According to this mechanism the various ionic forms of the tetrahedral addition intermediate T that is formed in the course of ester aminolysis and imidate hydrolysis are in protonic equilibrium with each other and with the solvent, so that their relative concentrations are determined by the pH and the equilibrium constants K_b, K_c, K_d, K_e, and K_s for their interconversion. Since they are in equilibrium, the same forms of the intermediate will be generated during ester aminolysis and upon hydrolysis of the imidate by the attack of either water or hydroxide ion, and these forms will decompose in the same manner to ester or to amide with the rate constants k_{-a}, k'_{-a}, and k''_{-a} or k^0 and k^-, respectively. A change in the ratio of ester to amide formation upon imidate hydrolysis with changing pH or buffer concentration corresponds to a change in the lowest energy pathway for the breakdown of the addition intermediate and, hence, to a change in the rate-determining step of ester aminolysis. This change in rate-determining step will also be observed in the kinetics of ester aminolysis as the pH or buffer concentration is changed in a corresponding manner.[6,12]

Mechanism 1



(3)

The fact that the partitioning to products can be varied independently of the rate of imidate hydrolysis shows that an intermediate is formed during the hydrolysis of I, in agreement with the behavior of other imidates, including the closely related phenyl *N*-methylacetimidate.[5,6,11,14,15] This is evident in the decrease in ester yield from 50 to 19%, as the pH is increased from 2.3 to 5.0 over a range in which the rate of hydrolysis of I is independent of pH (Figure 1) and in the catalysis of ester formation from I by the uncharged species of hexafluoroacetone hydrate, which has no effect on the rate of hydrolysis of I (Table II). The same intermediate(s) must be formed in ester aminolysis if the ionic forms of the intermediates are in equilibrium with each other.

According to Mechanism 1, the increase in ester yield upon the hydrolysis of I and II as the pH is changed from above to slightly below neutrality (Figures 1 and 2) corresponds to a partial change in rate-determining step that should give a 12 to 17% decrease in the rate of the corresponding ester aminolysis reactions, as the pH is lowered over the same range. According to this mechanism, the intermediate breaks down rapidly to amide through T^-, and formation of the intermediate is rate determining in ester aminolysis at high pH; whereas at lower pH, the intermediate breaks down to both ester and amide through k_{-a}, k''_{-a}, and k^0, so that breakdown to amide becomes partly rate determining in ester aminolysis (any breakdown of $T^{\pm}$ directly to amide is included in k^0 since the intermediates are in equilibrium, and $T^{\pm}$ has no net charge). The predicted decrease in rate with decreasing pH is not observed for either reaction (Figure 6). This result is inconsistent with Mechanism 1 and means that the same intermediate is not formed during the ester aminolysis and imidate hydrolysis reactions. Therefore, the observed product yields from imidate hydrolysis do not *necessarily* determine the rate-determining step of ester aminolysis. However, the result is consistent with, and in fact is required by the conclusions regarding the mechanism of ester aminolysis that were presented in the preceding paper.[2]

(14) T. C. Pletcher, S. Koehler, and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 7072 (1968).
(15) B. A. Cunningham and G. L. Schmir, *J. Amer. Chem. Soc.*, **88**, 551 (1966).

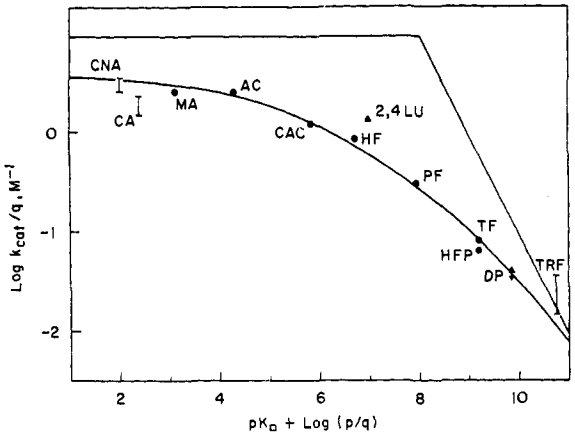


Figure 7. Brønsted plot for general acid catalysis of *p*-tolyl acetate formation from the tetrahedral intermediates generated from I at 25°, ionic strength 1.0 (KCl), by oxygen acids (●) and substituted pyridinium ions (▲) (Table II). The curved line is characteristic of the Brønsted plots observed by Eigen and coworkers for simple proton-transfer reactions.[16]

General Acid Catalysis of Ester Formation in Imidate Hydrolysis. Brønsted plots for catalysis by general acids of ester formation from the intermediates formed during the hydrolysis of I and II are shown in Figures 7–9. These Brønsted plots are inconsistent with a linear dependence of log k upon pK, but are consistent with the curvature that is expected for a simple proton-transfer reaction that is diffusion controlled when proton transfer is strongly favored thermodynamically. Limiting slopes of 0 and 1.0 and curves of the shape that has been observed for simple proton transfer reactions[16] are shown in each figure. This result suggests that the breakdown to ester of the intermediate formed upon the hydrolysis of I and II is determined by a simple proton transfer in the product-determining step.

The values of k_{cat} and pK_a in Figures 7–9 have been statistically corrected,[17] but the only significant difference in the results, if statistical corrections are not made, is a decrease from 0.13 to 0.07 in the Brønsted α value for oxygen acids of pK_a = 2.3–6.5. Values of k_{cat}, rather than k'_{cat}, have been plotted in Figures 8 and 9. If the plots are arbitrarily divided into segments corresponding to catalysts of low and high pK, plots based on k'_{cat} give the same Brønsted slopes for oxygen acids and for substituted pyridinium ions as those based on k_{cat}, but the break in the k'_{cat} plots is slightly sharper, from an α value of 0.12 to 0.40, instead of to 0.33 for N-substituted morpholinium ions, and to α = 0.42 instead of 0.36 for the substituted imidazolium ions. In each case, the data require an increase of at least three- to fourfold in the value of α, as the strength of the catalyzing acid decreases.

The value of k_{cat} for the solvated proton is 25-fold larger than that for cyanoacetic acid and 10–12 times larger than those for acidic pyridinium ions in the reactions of II; it is 33- to 35-fold larger than that for cyanoacetic acid in the hydrolysis of I. An enhanced rate of protonation by the solvated proton has been observed in simple proton transfer reactions and is presumably caused by the enhanced rate of diffusion and

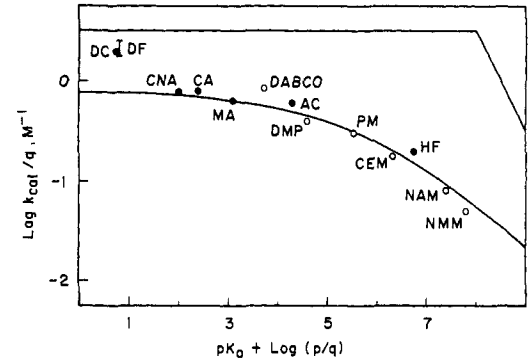


Figure 8. Brønsted plot for general acid catalysis of *p*-tolyl acetate formation from the tetrahedral intermediates generated from II at 25°, ionic strength 1.0 (KCl), by oxygen acids (●) and protonated cyclic tertiary amines (○) (Table III). The curved line is for simple proton transfer, as in Figure 7.

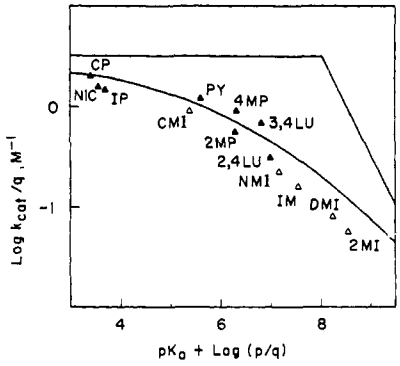


Figure 9. Brønsted plot for general acid catalysis of *p*-tolyl acetate formation from the tetrahedral intermediates generated from II at 25°, ionic strength 1.0 (KCl), by substituted pyridinium ions (▲) and substituted imidazolium ions (△) (Table III). The curved line is for simple proton transfer, as in Figure 7.

proton transfer that is made possible by a "proton jump" mechanism in water.[16] Dichloroacetic and difluoroacetic acids exhibit larger values of k_{cat} than might be expected from their acidity (Figure 8). We believe that this represents a faster rate of proton transfer from these relatively strong acids that is somewhat analogous to the enhanced rate of transfer from the solvated proton, even though these reactions are close to diffusion controlled. Support for this hypothesis comes from the finding that the rate of proton transfer to acetate ion from dichloroacetic acid is slower by only a factor of 4 compared with the solvated proton, rather than the factor of 15–35 that is observed for most other catalysts.[16,18] It is noteworthy that the Brønsted plot for proton transfer from carboxylic acids to acetate ion gives no indication of a leveling off at ΔpK = 0 and appears to be still rising at the point for dichloroacetic acid.[18]

The limiting values of k_{cat} for the substituted pyridinium and imidazolium ions are 2.6 times larger than those for carboxylic acids and cyclic tertiary amines. Differences of this magnitude are not unexpected for simple proton-transfer reactions between different classes of acids and bases, and it has been reported, in a closely related case, that the rate of proton transfer from $CH_3OH_2^+$ to 4-methylpyridine in methanol is

(16) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964).
(17) R. P. Bell and P. G. Evans, *Proc. Roy. Soc., Ser. A*, 291, 297 (1966).
(18) M.-L. Ahrens and G. Maass, *Angew. Chem., Int. Ed. Engl.*, 7, 818 (1968).

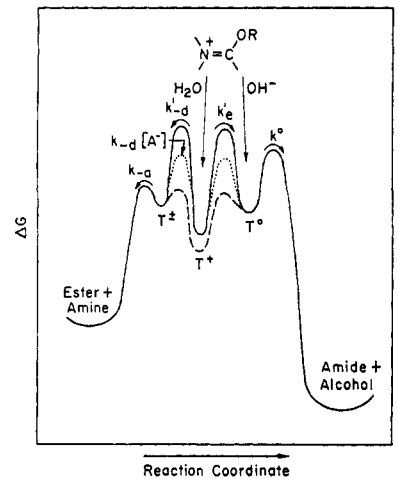
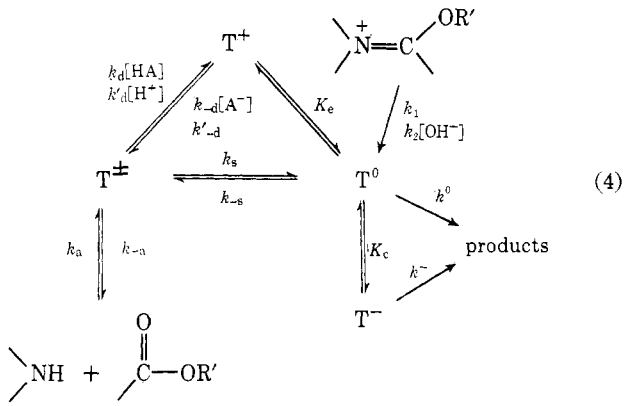


Figure 10. Free-energy reaction coordinate diagram for the hydrolysis of I according to Mechanism 3. The free energies refer to a given pH value. Thus, T^+ becomes relatively more stable at a lower pH, for example.

2.0 times larger than from $CH_3OH_2^+$ to trimethylamine.[19]

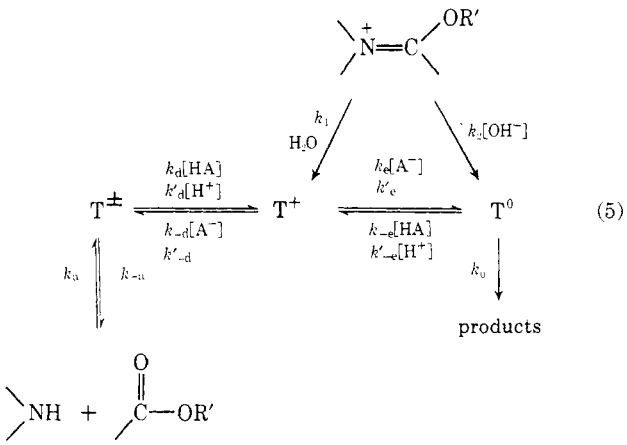
Mechanisms 2 and 3. Two mechanisms for imidate hydrolysis that incorporate product-determining proton-transfer steps are shown in eq 4 and 5. The mechanisms differ principally with respect to the products that are formed initially by the attack of water or hydroxide ion on the cationic imidate and the mechanism for the decrease in ester yield at high pH. According to Mechanism 2 (eq 4), the same uncharged intermediate, T^0, is formed with water and hydroxide ion; in the case of water attack, the initially formed oxonium ion rapidly loses a proton to the bulk solvent (eq 6, path A). According to Mechanism 3, the excess proton that is formed upon water attack is transferred to the basic nitrogen atom to form T^+ before it diffuses into the solvent (eq 6, path B). This interpretation is consistent with the usual diffusion-controlled mechanism for thermodynamically favorable proton transfer, in which proton transfer within an encounter complex is faster than the separation of the complex.[16] According to this mechanism, the attack of hydroxide ion gives a different initial product, T^0.

Mechanism 2

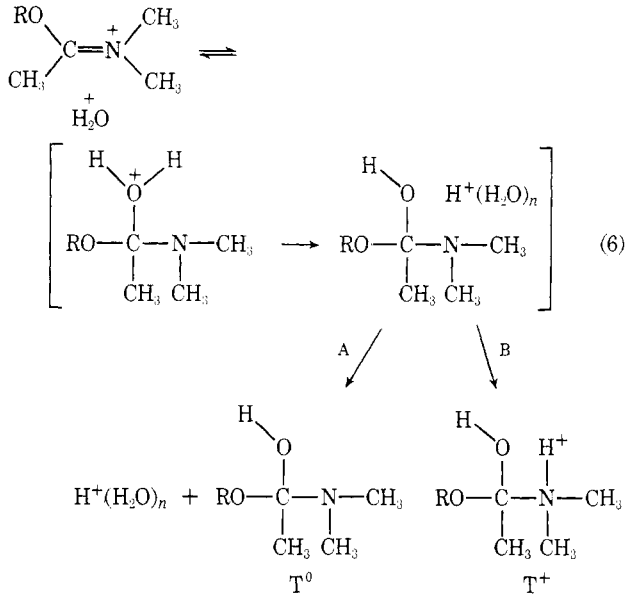


(4)

Mechanism 3



(5)



(6)

In Mechanism 2, which is similar to that proposed for thiazoline hydrolysis,[7] the proton-transfer steps that become product determining in imidate hydrolysis are an intramolecular proton switch, k_{-s}, that converts T^0 directly to $T^{\pm}$, and the deprotonation of the hydroxyl group of T^+ by a base A^- to form $T^{\pm}$ through k_{-d}. In both cases, the intermediate $T^{\pm}$ breaks down rapidly to ester. The buffer- and pH-independent product ratio at slightly acidic pH is given by the ratio k_{-s}/k^0. Catalysis of ester formation from T^0 by general acids or the proton represents the kinetically equivalent abstraction of a proton from T^+ by A^- or solvent and competes with k^0 to increase the yield of ester. In ester aminolysis, the reverse proton transfers through k_d, k'_d and k_s serve to trap the initially formed $T^{\pm}$ and prevent its rapid reversion to starting materials.

A description of Mechanism 3 (eq 5) may be aided by reference to the free energy *vs.* reaction coordinate diagram of Figure 10. According to this mechanism, the pH-independent product ratio at low buffer concentration is determined by the relative rates of proton abstraction by solvent from the oxygen and nitrogen atoms of the initially formed intermediate T^+ (k'_{-d} and k'_e, respectively), followed by the rapid breakdown of $T^{\pm}$ to ester and T^0 to amide. Since these proton transfers are thermodynamically unfavorable, the product

(19) M. Cocivera, *J. Phys. Chem.*, 72, 2515, 2520 (1968).

ratio will depend on the relative acidities of the protonated oxygen and nitrogen atoms.[16] Attack on the imidate by hydroxide ion generates T^0 directly, which breaks down rapidly to amide. This accounts for the formation of amide at high pH and low buffer concentration. The addition of buffers serves to lower the barrier for the proton-transfer steps between T^0 and $T^{\pm}$, as shown by the dotted line in Figure 10. When this barrier is lowered sufficiently, some of the T^0 that would otherwise break down to give amide is converted to $T^{\pm}$ and gives ester. Catalysis of ester formation by buffer acids and the proton may be regarded as a diversion of T^0 from amide to ester formation, regardless of whether T^0 is formed from T^+ or directly from the addition of hydroxide ion to the imidate. At sufficiently low pH (dashed line, Figure 10), the proton-transfer steps become fast, and the formation of ester becomes dependent on the rate of amine expulsion from $T^{\pm}$, k_{-a}, so that the product ratio approaches a constant value that is independent of acid concentration, as observed (Figures 2 and 3).

The following predictions provide a means of distinguishing between Mechanisms 2 and 3 and were tested experimentally.

(1) According to Mechanisms 1 and 2, the formation of amide in the region of pH-independent product yield depends on the expulsion of phenolate ion and should increase with increasing acidity of the phenol, whereas according to Mechanism 3, the product ratio depends on the relative rates of proton removal from the nitrogen and oxygen atoms of T^+, which should be independent of substituents on the leaving phenol.

(2) For Mechanism 3, the fraction of imidate that gives amide at high pH depends directly on the fraction that reacts with hydroxide ion to give T^0, whereas no such relationship is expected for Mechanisms 1 or 2.

(3) For Mechanisms 1 and 2, the decrease in ester yield with increasing pH is caused by an increase in base-catalyzed breakdown of the intermediate to amide through T^-, and this competition will result in a decrease in the effectiveness of general acids in catalyzing ester formation, whereas according to Mechanism 3, the decrease in ester yield is a consequence of the attack of hydroxide ion on the imidate to form T^0, and general acids can still facilitate ester formation by catalyzing the formation of $T^{\pm}$ from T^0. In other words, the observed catalytic constants for acids should decrease sharply with increasing pH in the region in which the yield of ester decreases according to Mechanisms 1 and 2, but not for Mechanism 3.

1. Effect of Leaving Group Variation on the pH-Independent Yield of Ester. In a series of experiments carried out in collaboration with Haggerty and Suva, it was shown that the yield of ester in the pH-independent region remains constant at 10–12% as the leaving group is varied from *p*-cresol (pK_a = 10.2) to *m*-nitrophenol (pK_a 8.35) in the series II, III, and IV (Figures 2 and 3, Table I). This result is consistent with product-determining proton transfer (Mechanism 3) but is inconsistent with product-determining phenolate expulsion, which is expected to increase greatly with increasing acidity of the phenol.

The expected effect of substituents in the phenol on the pH-independent % ester/% amide ratio may be analyzed in more detail as follows. For Mechanism 1, this ratio is equal to k_{-a}/K_sk^0 (eq 10, Experimental Section). Electron-withdrawing substituents should slightly decrease k_{-a}, will have little effect on K_s since there is no net change in charge in the $T^0 \rightleftarrows T^{\pm}$ equilibrium, and should markedly increase k^0. For Mechanism 2, the product ratio is equal to k_{-s}/k^0 (eq 12, Experimental Section). Electron-withdrawing substituents are expected to have no effect or to decrease k_{-s}, depending on whether there is positive-charge development on the intermediate in the transition state for this proton switch,[2] and will increase k^0 as before. For Mechanism 3, the product ratio is equal to k'_{-d}/k'_e (eq 14, Experimental Section). The rate constants for these thermodynamically unfavorable proton transfers to water are expected[16] to be directly proportional to the ionization constants of the protonated oxygen and nitrogen atoms of T^+, and since both of these ionizations should be altered to nearly the same extent by substituents on the phenol,[20] the ratio is expected to be substituent independent.

Related observations with these imidates are also consistent with Mechanism 3. When the leaving group is changed from *p*-cresol to *m*-nitrophenol, the limiting yield of ester at high acid concentration decreases from ~69 to 14%. At sufficiently high acid concentration, the proton-transfer steps become fast and the product ratio is given by k_{-a}/K_sk^0. The observed decrease in the limiting yield of ester is accounted for by the expected decrease in the ratio k_{-a}/K_sk^0 with electron-withdrawing substituents.

There is little or no detectable general acid catalysis of ester formation from the *p*-chlorophenyl and *m*-nitrophenyl imidates, and catalysis by the proton becomes significant at a lower pH value for IV than for II (Figures 2 and 3). According to Mechanism 3, acid catalysis of ester formation represents a diversion of T^0 to $T^{\pm}$ that competes with its breakdown to amide through k^0. Since k^0 is larger for the intermediates with the more acidic leaving groups, acid catalysis competes less effectively with breakdown to amide for these compounds, in agreement with experiment.

2. Correlation of the Rates of Water and Hydroxide Ion Attack on I with the Product Yield. According to Mechanism 3, the buffer-independent yield of ester decreases above pH 5 because the attack of hydroxide ion on the imidate gives T^0 directly, which then breaks down rapidly to amide. Consequently, the change in ester yield should be correlated with the fraction of I that reacts with hydroxide ion, *i.e.*, with the ratio $k_2a_{OH^-}/k_{obsd}$. Such a correlation is observed for the hydrolysis of I at both 25 and 50° (Figure 11). This correlation would be an improbable coincidence for Mechanisms 1 or 2, in view of the several rate and equilibrium constants that are involved in determining the product ratio and the fact that an increase from 25 to 50° increases the rate of the reaction of I with water 9-fold and with hydroxide ion 20-fold.

3. The Effect of pH on the Values of k_{cat}. According to Mechanisms 1 and 2, the increasing formation of amide through T^- with increasing pH will compete with both the pH-independent and the acid-catalyzed paths to ester formation so that the yields of ester through both of these paths will decrease proportionally (eq 9, 10, and 12, Experimental Section). This will be

(20) J. P. Fox and W. P. Jencks, *J. Amer. Chem. Soc.*, **96**, 1436 (1974).

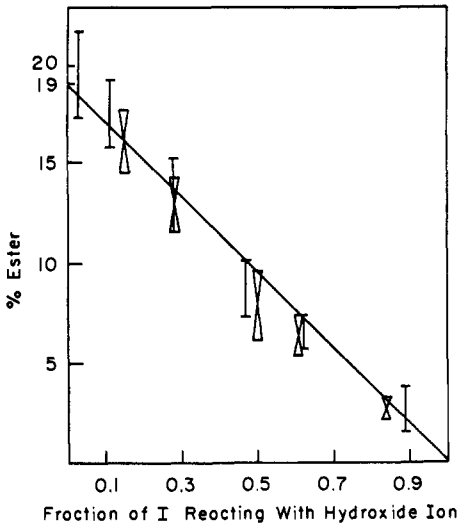


Figure 11. Correlation of the decrease in % ester yield from I as the pH is increased from 5 to 8 with the fraction of I reacting with hydroxide ion at 25° (I) and 50° (X).

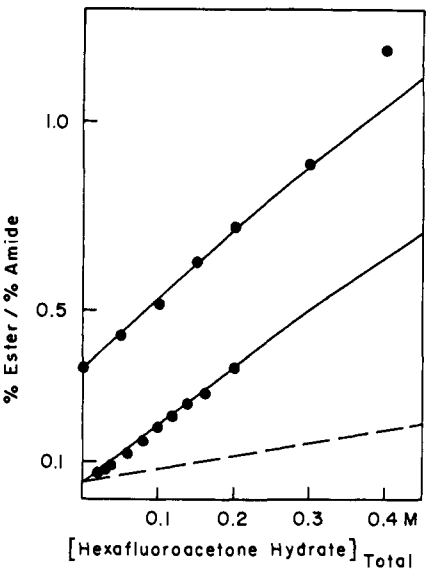


Figure 12. The % ester/% amide ratio from I as a function of hexafluoroacetone hydrate concentrations at pH 3.90 (upper curve) and pH 7.34 (lower curve). The solid lines are calculated from the partition equation for Mechanism 3 and the rate constants in Table VI. The dashed line is a theoretical line for Mechanisms 1 and 2 at pH 7.34.

apparent as a decrease in the observed value of k_{cat}, as the yield of ester decreases above pH 5. According to Mechanism 3, the value of k_{cat} will decrease from $k_{-d}K_a/k^0K_e$ to $k_{-d}K_a/[k^0K_e(1 + c)]$ as the pH is increased, and the buffer-independent yield of ester decreases to zero (eq 14, Experimental Section). Since c is equal to the buffer-independent % ester/% amide ratio, the value of k_{cat} for I should be decreased by 20% as the buffer-independent yield of ester is reduced to zero.

Experimentally, the values of k_{cat} for two oxygen acids and two nitrogen acids in the hydrolysis of I show no change or decrease slightly as the pH is increased to *ca.* 7.0 (Table IV). As shown in the table, the calculated decrease in k_{cat} for Mechanisms 1 and 2 over this pH range is large, on the order of tenfold. The data for hexafluoroacetone hydrate are plotted in Figure 12. They show good agreement with the calculated solid lines for Mechanism 3 and are inconsistent with the calculated dashed line for Mechanisms 1 and 2.

It is unlikely that hexafluoroacetone hydrate acts as a nucleophile toward I at high pH, because the value of k_B for this compound is not significantly larger than that for acetate, which acts as a general base catalyst. The small decrease in k_{cat} for *N*-allylmorpholinium ion with increasing pH may represent complexation with the basic form of the buffer, since a similar decrease is observed with *N*-propargylmorpholinium ion in a pH range in which there is no change in the buffer-independent yield of ester (Table IV).

Quantitative Treatment of Mechanism 3. The assigned rate and equilibrium constants that describe the effects of pH and catalyst concentration on the partitioning of the tetrahedral intermediates formed in the hydrolysis of I and II are summarized in Table VI. The absolute values of these constants are approximate, and some variation in the assigned values is permissible without significantly altering the fit to the experimental data, as long as the appropriate ratios are maintained constant. The calculated lines for the buffer-independent partitioning ratio in the hydrolysis of I and II at 25° as a function of pH are shown in Figures 1 and 2. The calculated lines for the effects of methoxyacetate at two buffer ratios and hexafluoroacetone hydrate buffers at low and high pH on the partitioning ratio are shown in Figures 4 and 12. The calculated lines based on the rate constants of Table VI and the equations in the Experimental Section and Appendix provide a satisfactory and self-consistent quantitative description of the experimental results.

Table VI. Rate and Equilibrium Constants According to Mechanism 3 for the Buffer-Independent Ester Yield from I and II at 25°, Ionic Strength 1.0 (KCl)

Rate and equilibrium constants[a]	I	II
k_{-a}, sec^{-1}	$\geq 4 \times 10^9$	3×10^9
k'_{-d}, sec^{-1}	5×10^2	5×10^2
k'_d, M^{-1} sec^{-1}	5×10^{10}	5×10^{10}
k'_e, sec^{-1}	2.2×10^3	3.5×10^3
k'_{-e}, M^{-1} sec^{-1}	5×10^{10}	5×10^{10}
k^0, sec^{-1}	8.5×10^7	1.9×10^8
K_s[b]	4.4	7.1
pK_d[c]	8.00	8.00
pK_e[d]	7.37	7.15

Buffer Catalysis (for I and II)

	Methoxyacetic acid	Hexafluoroacetone hydrate
k_{-d}, M^{-1} sec^{-1}	2.8×10^4	1.9×10^7
k_d, M^{-1} sec^{-1}	1.1×10^9	6.9×10^8
k_e, M^{-1} sec^{-1}	1.9×10^5	8.3×10^7
k_{-e}, M^{-1} sec^{-1}	1.1×10^9	6.9×10^8

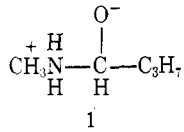
[a] Rate constants are defined in eq 5. [b] $K_s = [T^0]/[T^\pm]$. [c] $pK_d = -\log [T^\pm][a_{H^+}]/[T^+]$. [d] $pK_e = -\log [T^0][a_{H^+}]/[T^+]$.

The rate and equilibrium constants in Table VI were estimated as follows. The rate constants k'_d and k'_{-e} for the diffusion-controlled addition of a proton[16] to $T^\pm$ and T_0 were taken as 5×10^{10} M^{-1} sec^{-1}. The break in the Brønsted plot of Figure 7 was taken as the point at which $\Delta pK = 0$ for the catalyst and T^+,[16] so that $pK_d = 8.0$. The value of k'_{-d} is then equal to $k'_dK_d = 5 \times 10^2$ M^{-1} sec^{-1}. According to Mechanism 3, the pH-independent product ratio is given by

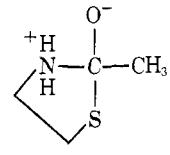
k'_{-d}/k'_e, so that $k'_e = 2.2 \times 10^3$ and $pK_e = 7.35$. Values of $k_{-a} = 4 \times 10^9$ sec^{-1} and $k^0 = 8.5 \times 10^7$ sec^{-1} then provide a satisfactory fit to the experimental data shown in Figure 1. The rate constants for II were estimated similarly. Values of k_{-e} for buffer catalysis were assigned from the proportionality $k_{-e}/k'_{-e} = [k_{cat}(HA)]/[k_{cat}(H^+)]$. The values of k_{-d}, k_e, and k_d may then be obtained from K_e, K_d, and $k_{-d}/k_e = k'_{-d}/k'_e = c$, where c is the pH-independent product ratio (see Experimental Section).

The values of pK_b, pK_e, pK_d, and pK_e (defined in eq 3) were estimated to be 10.8, 11.8, 7.0, and 5.6–6.3, respectively, according to the procedure described previously[20] and based on values of $\sigma_I = 0.39$ and 0.10 for C_6H_5O– and $(CH_3)_2N$–, respectively.[21] At ionic strength 1.0, the values of the dissociation constants for ROH and R_3NH^+ groups are expected to be increased and decreased, respectively, by approximately 0.2 pK unit. These estimates are in reasonable agreement with the values in Table VI, allowing for the uncertainty of both estimations.

The value of $k_{-a} = 3 \times 10^9$ sec^{-1} for the breakdown of T± to ester and amine may be compared with the experimental value of $k = 4.9 \times 10^6$ sec^{-1} for the analogous breakdown of **1**.[22] The additional oxygen



1



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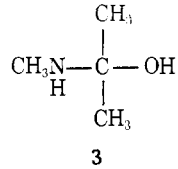
atom of T± may be expected to provide nonbonding interactions and electron donation that increase the rate of amine expulsion and stabilize the ester product. A value of $k = 6.6 \times 10^8$ sec^{-1} has been estimated for the breakdown of **2**, and rate constants of $>10^8$ and $\geq 10^9$ sec^{-1} have been estimated for the expulsion of protonated amines from analogous addition compounds formed from acetylimidazole and acetyltriazole.[7,20,23]

The rate constant k^0 for expulsion of the phenolate ion from T⁰ is approximately 10^7 times larger than that for the expulsion of hydroxide ion from **3**.[24] Although



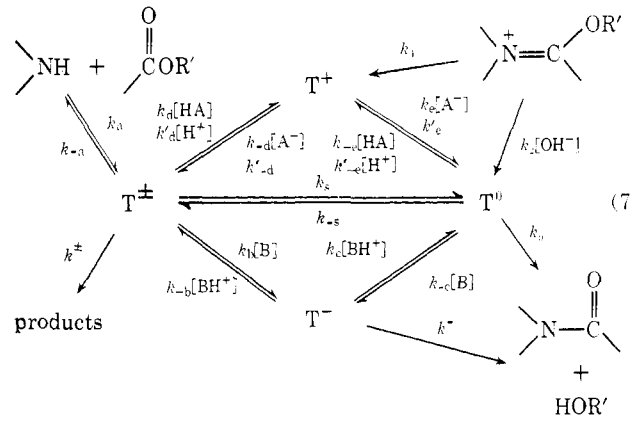
3

a quantitative estimation is not possible, this difference appears to be reasonable in view of the $10^{5.6}$ times greater acidity of phenol than of water and the additional electron donation from the HO– group in T⁰ that facilitates phenolate expulsion and provides resonance stabilization to the product.

The equilibrium constant for the addition of methylamine to *p*-tolyl acetate to form T± may be estimated to be 1.9×10^{-11} M^{-1} from the ratios of the rate constants for the formation and breakdown of T±. The overall equilibrium constant for the formation of T⁰ from methylamine is then 1.9×10^{-10} M^{-1}, from the estimated ionization constants of the intermediate. This value may be compared to a value of 9.3×10^{-11} M^{-1} for the formation of T⁰ from dimethylamine and methyl acetate that has been estimated by Guthrie from the free energies of formation of amide dimethyl acetals.[25]

Relationship to Ester Aminolysis. The demonstration that the ratio of products formed upon imidate hydrolysis does not necessarily indicate which step is rate determining in the corresponding ester aminolysis reaction, *i.e.*, that a common intermediate is not formed in the two reactions, resolves several of the problems in interpreting the mechanism of ester aminolysis. Mechanism 3, for which only the essential steps for imidate hydrolysis are given in eq 5, is consistent with the mechanism proposed for ester aminolysis in the preceding paper.[2] The complete Mechanism 3a is shown in eq 7. According to Mechanism 3a, the

Mechanism 3a



(7)

dipolar intermediate T± breaks down rapidly with amine expulsion *via* k_{-a} rather than with phenolate expulsion to give amide. When the same intermediate T± is formed by the attack of amine on a phenyl ester, it will also break down preferentially to ester so that phenolate expulsion from T± with the rate constant $k^\pm$ becomes the rate-determining step in the aminolysis reaction. This avoids the necessity of postulating that phenolate ($pK = 10$) be expelled more rapidly from T± than both methylamine and nicotinamide ($pK = 3.6$), as is required if amine attack is rate determining.[5] The intermediate T± does not equilibrate with other ionic forms of the intermediate in the absence of buffers; *i.e.*, $k^\pm > k_s$. Consequently, the aminolysis of phenyl esters does not undergo a change in rate-determining step with changing pH. The addition of buffer catalysts makes possible the formation of these different ionic species of the intermediate and thereby opens new pathways to the amide product. This is consistent with Mechanism 3 and with the observed characteristics of the ester aminolysis reactions.

In principle, a change in rate-determining step to amine attack, k_a, should occur at sufficiently high con-

(21) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964); C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 334 (1964).
(22) J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *J. Amer. Chem. Soc.*, **92**, 5194 (1970).
(23) M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 8828 (1972).
(24) J. Hine and F. A. Via, *J. Amer. Chem. Soc.*, **94**, 190 (1972).
(25) J. P. Guthrie, *J. Amer. Chem. Soc.*, **96**, 3608 (1974). We are grateful to Dr. Guthrie for communicating this result to us before publication.

centrations of catalysts when the proton-transfer steps become fast; but it is not possible to demonstrate this experimentally for the reactions described here. For esters of highly acidic phenols and basic amines, a change to rate-determining amine attack is observed for ester aminolysis so that an imidate formed from these components should break down to amide from both T^0 and $T^{\pm}$. For alkyl esters, the intermediate $T^{\pm}$ expels alcoholate ion to give amide relatively slowly so that a proton switch mechanism to equilibrate $T^{\pm}$ with T^0 and T^- becomes significant and a new mechanism of pH-independent amide formation *via* k_s is observed.[2]

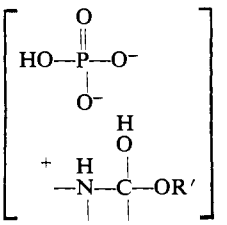
Hydrolysis of Other Imidates. The available data for the product distribution in the hydrolysis of other class II imidates with moderately acidic alcohol leaving groups are consistent with Mechanism 3.[5,14] The behavior of class III imidates with weakly acidic alcohol leaving groups may be explained by the expanded Mechanism 3a (eq 7). Since the alcohol in the intermediate T^0 is a relatively poor leaving group for these imidates, k^0 will be small. Consequently, T^0 has a sufficient lifetime to undergo a proton switch (k_{-s}) to form $T^{\pm}$ which rapidly gives ester. The rate of the proton-switch step is expected to be less sensitive than alcohol expulsion, k^0, to decreasing acidity of the alcohol. At high pH the base-catalyzed breakdown of the intermediate to give amide through T^- and k^- becomes the predominant reaction path [in principle, the formation of T^- from T^0 may become product (or rate) determining in some reactions, but there is no evidence for this possibility at this time]. The higher energy pathways for breakdown of the intermediate in imidate hydrolysis correspond to the rate-determining steps in ester aminolysis so that these assignments are consistent with a rate-determining proton switch at high pH and rate-determining alkoxide expulsion from T^- at lower pH in the aminolysis of esters with poor leaving groups.[2]

The pH–product profile for these imidates may be described by its inflection point, pK', which is equal to $-\log (k^-K_c/k_{-s})$ according to Mechanism 3a. Both the formation (K_c) and the breakdown (k^-) of T^- will be favored relative to k_{-s} by electron-withdrawing substituents in the leaving alcohol so that the value of pK' is expected to decrease with increasing alcohol acidity, as observed;[14] the dependence of pK' on alcohol acidity exhibits a value of $\beta \sim 1.0$.

Decreasing basicity of the *amine* will cause a large decrease in k_{-s}, as the equilibrium for proton transfer in the conversion of T^0 to $T^{\pm}$ becomes progressively more unfavorable, and will cause smaller decreases in K_c and k^-, which involve processes 2 atoms further away from the substituent. Since the effects on k_{-s} and K_c are expected to be larger than on k^-, the value of pK' should decrease with decreasing amine basicity. There is some experimental support for this in imidate hydrolysis,[6,26] but more data are available from the change in rate-determining step in ester aminolysis, in which the value of pK' increases with increasing basicity of aliphatic amines with a value of $\beta \sim 0.9$.[6] With amines of still lower basicity, such as nitroanilines, the proton-switch mechanism becomes still more unfavorable and other mechanisms for decomposition of the intermediate become predominant.[26]

According to Mechanisms 3 and 3a, catalysis of ester formation by general acids involves the product-determining conversion of T^0 to $T^{\pm}$ through T^+, which competes with decomposition to amide. The decomposition to amide is also weakly subject to buffer catalysis in reactions involving relatively basic aliphatic alcohols, such as the aminolysis of methyl formate, so that both steps of the reaction become subject to buffer catalysis.[6,27]

Mechanism 3a provides an explanation for the high activity of bifunctional acid–base catalysts in promoting ester formation from imidates of weakly basic amines and their smaller effectiveness with imidates formed from basic amines. As the pK_a of the resident amines is increased from 4.6 to 10.6, the ratio of the rate constant for bifunctional catalysis by phosphate to that for monofunctional catalysis by imidazolium ion decreases from >200 to ~12.[15,26] The Brønsted plot for general acid catalysis of the formation of $T^{\pm}$ from T^0 is expected to be curved, like those in Figures 7–9. Proton transfer from imidazolium ion to a basic nitrogen atom in T^0 will be thermodynamically favorable and imidazolium ion will exhibit a near-maximal rate of catalysis, but proton transfer to the nitrogen atom of intermediates formed from weakly basic amines will be thermodynamically unfavorable so that the break in the Brønsted plot will occur at a lower pK and imidazolium ion will be a less effective catalyst for proton transfer. A bifunctional catalyst, such as phosphate, will be less sensitive to substituent effects, because it can catalyze a proton switch in a concerted manner or can protonate the nitrogen atom and then remove a proton rapidly from the hydroxyl group of T^+ without diffusing out of the encounter complex, **4**, so that it will be relatively



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more effective as a catalyst for ester formation with the less basic amines. Analogous mechanisms are possible for basic bifunctional catalysts, with proton abstraction preceding proton donation. A similar situation has been observed in the intramolecular aminolysis of a thiol ester, in which bifunctional catalysts show an enhanced activity only in comparison with catalysts for which proton transfer is thermodynamically unfavorable.[7]

Deslongchamps, *et al.*, have reported evidence that conformational effects can be significant in the breakdown of tetrahedral intermediates formed from imidates and amides.[28] There is no indication that such effects become significant for the breakdown of phenyl imidates, which have a relatively good oxyanion leaving group.

(26) R. K. Chaturvedi and G. L. Schmir, *J. Amer. Chem. Soc.*, **90**, 4413 (1968); T. Okuyama, T. C. Pletcher, D. J. Sahn, and G. L. Schmir, *ibid.*, **95**, 1253 (1973); T. Okuyama, D. J. Sahn, and G. L. Schmir, *ibid.*, **95**, 2345 (1973).

(27) T. Okuyama and G. L. Schmir, *J. Amer. Chem. Soc.*, **94**, 8805 (1972).

(28) P. Deslongchamps, C. Lebreux, and R. Taillefer, *Can. J. Chem.*, **51**, 1665 (1973).

chloride and at an ionic strength brought to 2.0 with potassium chloride (methylamine) or tetramethylammonium chloride (dimethylamine).

Since it was desired to measure possible changes in rate constants rather than absolute rate constants, the experiments were run in pairs at two pH values, and the observed rate constants were normalized by comparison with a standard kinetic run at a standard pH value that was carried out with each experiment. The pH measurements are critical and the Radiometer 26 pH meter with a Radiometer GK 2321 C combined electrode was standardized with Fisher Standard buffers at pH 4.00 and 7.00 at 25° and at 4.06 and 6.95 at 50° (the value 6.95 was obtained by standardization of the standard with Radiometer Type S1500 precision buffer). Measurements of pH were carried out at the temperature of the kinetic experiments. The error in the second-order rate constants due to inaccuracies in the pH measurements was estimated to be $\leq 2\%$.

At low pH values, the pseudo-first-order rate constants for the dimethylamine reaction were corrected (by $<5\%$) for hydrolysis of the ester. A series of rate constants was determined in the presence of 1 *M* dimethylammonium hydrochloride and three concentrations of cyanoacetate or methoxyacetate buffers at seven pH values between pH 2.0 and 4.6 at 50°. A value of $k_0 = 4.1 \times 10^{-6}$ min^{-1} for pH-independent hydrolysis was obtained after correcting for acid-catalyzed hydrolysis and the reaction with the amine at the higher pH values.

Quantitative Evaluation of the Acetimidate Product Data. The yields of ester and amide from the hydrolysis were evaluated according to the simplified scheme of eq 8 to obtain the relative

$$\begin{array}{ccc} & \text{acetimidate} & \\ & \downarrow \text{slow} & \\ & \overset{k_{-a} + k_{HA}[HA]}{\longleftarrow} \quad T \quad \overset{k_{am}}{\longrightarrow} & \\ \text{ester} & & \text{amide} \end{array} \qquad (8)$$

rate constants k_{HA} for general acid catalysis of ester formation from the tetrahedral intermediate, T, and by a more complex scheme based on Mechanisms 2 and 3 to obtain relative catalytic constants k'_{HA} for reactions in which the maximum yield of ester is $<100\%$. The ratio of ester to amide product is equal to the ratio of the sums of the pseudo-first-order rate constants for the formation of each product from T under the conditions of the experiment and is given by eq 9 for the scheme of eq 8. The relative values of k_{HA}

$$\frac{\%\ \text{ester}}{\%\ \text{amide}} = \frac{k_{-a}}{k_{am}} + \frac{k_{HA}[HA]}{k_{am}} \qquad (9)$$

were obtained from the slopes of plots of % ester/% amide against [HA] at constant pH, which give $k_{cat} = k_{HA}/k_{am}$.

The product ratio for Mechanism 1 (eq 3) is given by eq 10, in

$$\frac{\%\ \text{ester}}{\%\ \text{amide}} = \frac{k''_{-a}a_{H^+}/K_e}{k^0 + k^-K_c/a_{H^+}} + \frac{k_{-a}/K_s}{k^0 + k^-K_c/a_{H^+}} + \frac{k'_{-a}K_{HA}[HA]/K_e}{k^0 + k^-K_c/a_{H^+}} \qquad (10)$$

which K_{HA} is the dissociation constant of HA. The pseudo-first-order rate constants for the paths to product formation are expressed in terms of T^0 which, according to this mechanism, is at equilibrium with the other ionic forms of the addition intermediates as described by the equilibrium constants of eq 3.

The corresponding equations for mechanisms 2 and 3 were derived by the steady state treatment as described in the Appendix.[33] When the rate constants are such that the yield of ester at high concentrations of acid approaches 100%, the equations reduce to the form of eq 9, and the experimental values of k_{cat} are proportional to k_{HA}. When the rate constants are such that the yield of ester at infinite acid concentration (% ester, max) is significantly less than 100%, the modified eq 11 must be used. The reduction of the

$$\frac{\%\ \text{ester obsd}}{\%\ \text{ester max} - \%\ \text{ester, obsd}} = R = \frac{\%\ \text{ester, } H_2O}{\%\ \text{ester max} - \%\ \text{ester, } H_2O + k'_{cat}[HA]} \qquad (11)$$

(33) See paragraph at end of paper regarding supplementary material.

partition equations for Mechanism 3 to a tractable form that gives a linear dependence of the partition ratio on acid concentration requires the assumption that $c = k'_{-d}/k'_e = k_{-d}/k_e$. This amounts to the assumption that the relative rates for the removal of a proton from the oxygen and nitrogen atoms of T^+ are the same for water and A^-. This assumption is reasonable as a first approximation, and its validity, within the limits of the experimental error of our measurements, is supported by the observed linearity of the plots of product ratio against buffer concentration. The yields for Mechanism 2 (eq 4) may be described by eq 12 and 13 and those for Mechanism 3 (eq 5) by eq 14 and 15. These equations are simplified forms of the general equation and hold only under restricted conditions. Equations 12 and 14 hold when the maximum yield of ester at infinite [HA] is 100%, and eq 13 and 15 hold at a given pH value in the plateau region of the pH–product curves when the maximum yield of ester is $<100\%$. Equations 13 and 15 show that values of k'_{cat} provide a measure of the relative values of the rate constants for proton transfer. For both mechanisms, the observed general acid catalysis of ester formation actually represents the kinetically equivalent removal of a proton from T^+ by a base so that the rate constants for general acid catalysis are proportional to $k_{-d}K_a$. The theoretical lines in the figures were calculated from the complete expression for Mechanism 3, eq 36 in the Appendix. This treatment for the derivation of eq 11 gives essentially the same result as that obtained by Schmir and Cunningham by a different approach;[3,15] however, the derivation does not assume the formation of a complex between the catalyst and the tetrahedral intermediate.

$$\frac{\%\ \text{ester}}{\%\ \text{amide}} = \frac{k'_{-d}a_{H^+}/K_e}{k^0 + k^-K_c/a_{H^+}} + \frac{k_{-s}}{k^0 + k^-K_c/a_{H^+}} + \frac{k_{-d}K_{HA}[HA]/K_e}{k^0 + k^-K_c/a_{H^+}} \qquad (12)$$

$$R = \frac{k_{-s}(k_{-a}K_d + k^0K_e)}{k^0(k_{-a}K_d - k_{-s}K_e)} + \frac{k_{-d}K_a[HA](k_{-a}K_d + k^0K_e)}{K_ek^0(k_{-d}K_d - k_{-s}K_e)} \qquad (13)$$

$$= \frac{\%\ \text{ester, } H_2O}{\%\ \text{ester max} - \%\ \text{ester, } H_2O} + k_{-d}K_a[HA](\text{constant})$$

$$\frac{\%\ \text{ester}}{\%\ \text{amide}} = \frac{k_1}{k_{obsd}}\left[\frac{k'_{-d}a_{H^+}}{k^0K_e} + \frac{k'_{-d}}{k'_e} + \frac{k_{-d}K_a[HA]}{k^0K_e}\right] + \frac{k_2a_{OH^-}}{k_{obsd}}\left[\frac{k'_{-d}a_{H^+} + k_{-d}K_a[HA]}{k^0K_e(1 + c)}\right] \qquad (14)$$

$$R = \frac{k_{-a} + k^0K_s}{k_{-a}/c - k^0K_s} + \frac{k_{-d}K_a[HA](k_{-a} + k^0K_s)}{cK_ek^0k_{-a}/c - k^0K_s}$$

$$= \frac{\%\ \text{ester, } H_2O}{\%\ \text{ester max} - \%\ \text{ester, } H_2O} + k_{-d}K_a[HA](\text{constant}) \qquad (15)$$

Acknowledgment. We are grateful to Robert Suva and Dennis Haggerty for the experiments with compounds III and IV.

Supplementary Material Available. The Appendix will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-7031.