two runs were made with 0.8 M n-propylamine and the same temperature, the average of their rate constants was used. Observed rate constants were used for runs in which the base concentrations at two temperatures differed by less than 0.010 M; otherwise pseudo-first-order constants were calculated from base concentrations and second- or third-order rate constants, whichever was appropriate. Standard deviations were calculated by the method of total differentials.

Nonlinear Structure–Reactivity Correlations. The Reactivity of Nucleophilic Reagents toward Esters[1]

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Abstract: Rate constants are reported for the reactions of water and of nucleophiles of pK = 3.1–15.8 with a series of acetate esters with leaving groups of pK = 10–2. The reactions with oxygen anions exhibit a small sensitivity to the basicity of both the attacking group and the leaving group when the former is more basic than the latter and a large sensitivity to the basicity of both groups in the converse case. Logarithmic plots of rate constants against the pK of the attacking and leaving groups are nonlinear with limiting slopes, β, approaching 0.3 and 1.0 in both cases. The behavior of nucleophiles with "abnormal" reactivity in such plots is governed by their basicity rather than their absolute nucleophilic reactivity, so that inversions of relative reactivities may occur as the leaving group is varied. The reactions of "normal" nitrogen nucleophiles show β values for the nucleophile close to 0.8 over a range of 10^8 in reaction rate and then level off to a much smaller sensitivity to basicity in the reactions of strongly basic amines with the most reactive esters. Values of β for varying leaving groups are close to 1.0 for most reactions, indicating a large change in the charge on the leaving group in the transition state, and decrease to 0.4 for the rapid reactions. It is argued that no tetrahedral addition intermediate is formed before the transition state is reached in any of the aminolysis reactions. The similarity in the behavior of primary, secondary, and tertiary amines means that proton transfer is not required in these reactions and that amine attack and leaving-group expulsion can occur through transition state(s) of zero net charge. The results do not discriminate unequivocally between a concerted mechanism and one involving a metastable tetrahedral intermediate for these reactions.

The Brønsted slopes, β, of logarithmic plots of the rate constants for the reactions of nucleophilic reagents with phenyl acetates against the pK_a of the nucleophile are generally thought to be close to 0.8, indicating a large sensitivity of these reactions to the basicity of the nucleophile.[2-5] Hammett $\sigma\rho$ plots for reactions of substituted phenyl acetates with a given amine generally exhibit values of ρ near 2, indicating that these reactions also have a large sensitivity to the nature of the leaving group, while reactions with basic oxygen nucleophiles exhibit smaller ρ values.[6-9] A few exceptions to these generalizations are known. The reactions of strongly basic oxygen anions with p-nitrophenyl acetate exhibit very little sensitivity to the basicity of the nucleophile[10] and the reactions of thiol anions with p-nitrophenyl acetate[11] and of amino acids with acetic anhydride[12] and Leuchs anhydrides[1] exhibit Brønsted slopes of only approximately 0.4, 0.5, and 0.6, respectively. The rates of the nucleophilic reactions of imidazole with a series of acetate esters in which the pK of the leaving group varies from 16 to 4 exhibit a transition from a relatively small sensitivity to a large sensitivity with respect to the nature of the leaving group as the leaving ability of the alcohol is decreased.[14] This change was attributed to a change in the nature of the transition state from one resembling that expected for rate-determining attack of the amine on the ester to one resembling that expected for rate-determining breakdown of a tetrahedral addition intermediate; the results may be described equally well in terms of a tetrahedral intermediate or in terms of an asymmetrical energy barrier along the reaction coordinate with no addition intermediate. The change from a nucleophilic to a general base catalyzed mechanism as the leaving group becomes more basic in the reactions of esters with imidazole[14] and with acetate ion[15] may be interpreted in the same manner.

In spite of the large amount of experimental work on the problem, the mechanism of this class of reactions is

(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) M. L. Bender, *Chem. Rev.*, 60, 53 (1960).

(3) T. C. Bruice and R. Lapinski, *J. Am. Chem. Soc.*, 80, 2265 (1958).

(4) W. P. Jencks and J. Carriuolo, *ibid.*, 82, 1778 (1960).

(5) No distinction will be made in this paper between positive and negative values of β, in order to simplify the discussion; it should be understood that the reaction rates increase with increasing basicity of the nucleophile and with decreasing basicity of the leaving group.

(6) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, 86, 418 (1964).

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(12) D. M. Brouwer, M. J. van der Vlugt, and E. Havinga, *Koninkl. Ned. Akad. Wetenschap. Proc. Ser. B*, 61, 141 (1958).

(13) P. D. Bartlett and R. H. Jones, *J. Am. Chem. Soc.*, 79, 2153 (1957).

(14) J. F. Kirsch and W. P. Jencks, *ibid.*, 86, 837 (1964).

(15) D. G. Oakenfull, T. Riley, and V. Gold, *Chem. Commun.*, 385 (1966).

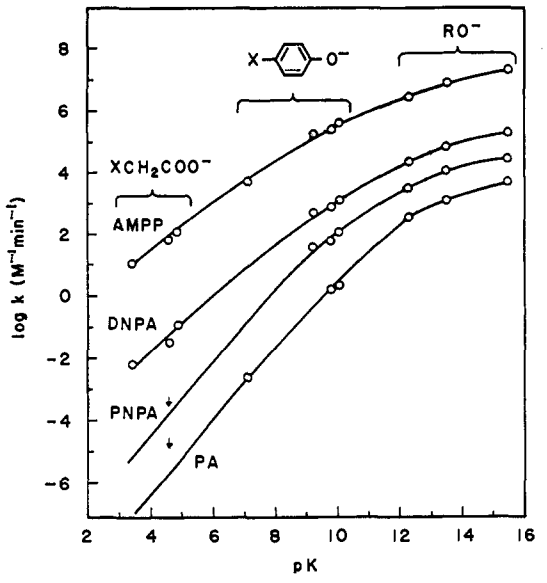


Figure 1. Logarithmic plot of rate constants for the reactions of anionic oxygen nucleophiles with esters against the basicity of the nucleophile at 25°.

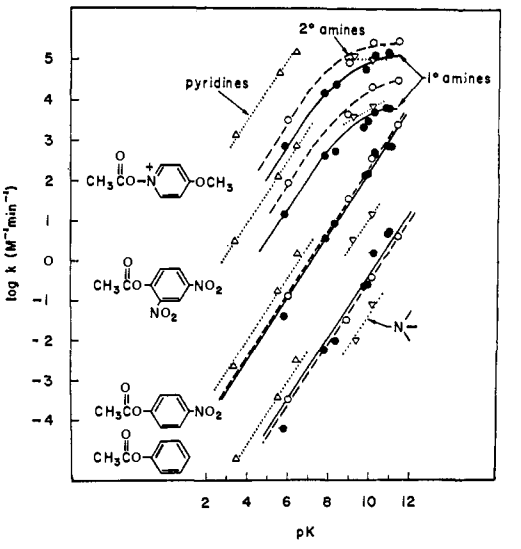
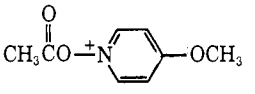


Figure 2. Logarithmic plot of the rate constants for reactions of phenyl acetate, *p*-nitrophenyl acetate, 2,4-dinitrophenyl acetate, and 1-acetoxy-4-methoxypyridinium cation with structurally similar primary, secondary, and tertiary amines as a function of amine basicity at 25°.

not well understood. The experiments reported here were carried out in an attempt to define more clearly the nature of the transition state for ester aminolysis by determining its sensitivity to the basicity of the amine in a series of acetate esters ranging from phenyl acetate through *p*-nitrophenyl acetate (PNPA), 2,4-dinitrophenyl acetate (DNPA), and 1-acetoxy-4-methoxypyridinium perchlorate (AMPP), which includes leaving groups with pK values[16] from 10 to 2. The study was



AMPP

extended to an examination of the reactions of the same esters with a series of oxygen anions, in which the nature of the transition state can be predicted with some assurance because of the symmetrical nature of the reaction. Although a large number of rate constants have been determined for reactions of this kind, it appeared desirable to obtain a series of rate constants measured under a single set of experimental conditions.

Results

Second-order rate constants, k_2, for the reactions of a series of nucleophilic reagents with a series of acetate esters are summarized in Table I. The results for some structurally similar nucleophiles are plotted logarithmically as a function of the basicity of the nucleophile for oxygen anions in Figure 1 and for amines in Figure 2. Third-order rate constants for the amine-catalyzed and hydroxide ion catalyzed reactions of amines (eq 1)

$$\frac{\text{rate}}{[\text{ester}]} = k_2[\text{RNH}_2] + k_3[\text{RNH}_2][\text{RNH}_2] + k_{3\text{OH}}[\text{RNH}_2][\text{OH}^-] \quad (1)$$

were determined for a few of the reactions and are given in the footnotes of Tables VII–X in the Experimental Section. In general the rate constants are in agreement with previous results from this and other laboratories which have been obtained under similar experimental conditions; a few discrepancies are noted in the footnotes to the tables. The rate constant for the reaction of PNPA with hydroperoxide anion is based on a different dissociation constant for hydrogen peroxide and is slightly lower than a previously reported value[17] and that for methyl hydroperoxide anion is lowered because of an incomplete reaction in the analytical method used previously to determine methyl hydroperoxide concentration;[4] however, the relative rates of the reactions of these two compounds with PNPA and with the other esters examined (Table I) confirm our earlier conclusion that the hydrogen atom of the hydroperoxide anion does not cause a large rate enhancement by hydrogen bonding to the substrate; some of the observed rate difference may be attributed to the presence of two potentially reactive oxygen atoms in the unsubstituted hydrogen peroxide molecule.

Approximate thermodynamic activation parameters for the reactions of phenyl acetate, PNPA, and DNPA with ethylamine, morpholine, and piperidine are summarized in Table II. The results are based on only a single set of rate measurements for each compound at 5 and 25° and are, therefore, not of high precision, but they do serve to illustrate trends. The results are similar to those for other reactions of amines with phenyl esters.[6,11] The levelling off of the rate as a function of amine basicity which is observed for the reaction of strongly basic amines with DNPA (Figure 2) is accompanied by a similar levelling of $\Delta H^{\pm}$ at a value of 7 to 8 kcal/mol.

Back reaction of the liberated phenolate ion with unstable acylated intermediates, as shown for the reaction with pyridine in eq 2, was found to present an unexpectedly severe experimental problem in several of the reactions. Inhibition of the 4-methylpyridine-catalyzed hydrolysis of PNPA by low concentrations of

(16) J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.*, 4375 (1957).

(17) W. P. Jencks, *J. Am. Chem. Soc.*, 80, 4581, 4585 (1958).

Table I. Summary of Rate Constants for the Reactions of Nucleophilic Reagents with Phenyl Acetate (PA), *p*-Nitrophenyl Acetate (PNPA), 2,4-Dinitrophenyl Acetate (DNPA), and 1-Acetoxy-4-methoxypyridinium Perchlorate (AMPP) at 25°, Ionic Strength 1.0 M[a]

Compound	pK_a[a,b]	k_2, M^{-1} min^{-1} PA	PNPA	DNPA	AMPP
Ethylamine	10.97	6.4	960	7,100	1.67×10^5
at 5°	11.62	2.1[c]	330	2,640	
Propylamine	10.89	4.9	960	7,100	2.02×10^5
Ethylenediamine	10.18	1.68[d]	536	6,600	1.7×10^5
Methoxyethylamine	9.72	0.25	160	2,530	7×10^4
Glycine	9.76	0.26[e]	155[e]	3,370	
Glycylglycine	8.25	0.009[e]	10.3	550	2.9×10^4
Glycine ethyl ester	7.90	0.0054[e,f]	4.0[e]	470[f]	1.7×10^4
Ethylenediamine-H$^+$	7.42	0.022[d]	5.6	325	8800
Trifluoroethylamine	5.84	6.3×10^{-5}	0.042	15.3	840
Aniline	4.85	2.1×10^{-5} [g]	0.011[h]	14.2[f]	3600
Hydrazine	8.20[i]	0.47[i]	450[i]	18,000	4.9×10^5
Hydroxylamine	6.17	0.7[e]	110[e]	2,800	2.9×10^5
Semicarbazide	3.86	4.3×10^{-5}	0.0115	6.6	760
Piperidine	11.42	4.3[e]	2,900	38,000	3.9×10^5
at 5°	12.07	1.34	1,100	15,000	
Piperazine	10.10	0.37	430	25,000	3.2×10^5
Morpholine	8.87	0.032	38	4,800[f]	1.01×10^5
at 5°	9.33	0.0053	9.8	1,480	
Piperazine-H$^+$	6.01	3.3×10^{-4}	0.125	96	3600
Quinuclidinol	10.07	0.076	15	7,900	1.20×10^5
Triethylenediamine	9.20	0.0090[e]	3.06	4,300	1.40×10^5
Triethylenediamine-H$^+$	3.47	1.9×10^{-5}	1.19×10^{-4}	0.090	22
Imidazole	7.21	0.52[j]	35[j]	350[f,j]	4.9×10^4
4-Methylpyridine	6.33	3.2×10^{-3}	1.6	780	2.0×10^5
Pyridine	5.52	4.4×10^{-4}	0.17	148[f]	5.4×10^4
Nicotinamide	3.55	1.2×10^{-5}	2.4×10^{-3}	3.2	1540
Water	−1.75	2×10^{-8}	4.7×10^{-7}	1.2×10^{-5}	0.013
Anion of					
Water	15.75	76[j]	570[j]	3,220[f,j]	5.7×10^5
Methanol	15.5[k]	5,200	2.9×10^4 [l]	1.92×10^5	2.2×10^7
2-Propyn-1-ol	13.55[k]	1,410[g]	10,800[g]	6.8×10^4 [g]	8.3×10^6
Trifluoroethanol	12.37[k]	410[g]	3,850[l,m]	2.4×10^4 [g]	2.75×10^6
Hydrogen peroxide	11.6[n]	32,000	2.2×10^5 [g]	9.75×10^5 [g]	1.4×10^8
Methyl hydroperoxide	11.5[n]	6,300[g]	60,000[g]	3.6×10^5 [g]	4.0×10^7
p-Cresol	10.07	2.4	113	1,240	3.5×10^5
Phenol	9.86	1.7[o]	58[l]	730	2.35×10^5
Acetohydroxamic acid	9.37	190	7,000	6.2×10^4	1.34×10^7
p-Chlorophenol	9.28		41	570	1.8×10^5
p-Nitrophenol	7.14	2.4×10^{-3} [p]			6.9×10^3
Trimethylacetic acid	4.86			0.107	115
Acetic acid	4.61	2.1×10^{-5} [q]	3.8×10^{-4} [q]	0.034[q]	66
Methoxyacetic acid	3.43			0.0068	12.1
Cyanide	9.3[r]	1.27	10.8[s]	33	4400
Azide	4.0[m]	0.014	1.82	57	2.3×10^4
Fluoride	3.1[t]	1.5×10^{-5}	1.37×10^{-3}	0.19	220
Nitrite	3.4[r]		1.37×10^{-3}	0.53	510

[a] Ionic strength maintained with potassium chloride unless noted otherwise. [b] The pK_a of the conjugate acid was determined from measurements of the pH of partially neutralized solutions or from titration curves under the conditions of the kinetic experiments, unless noted otherwise. [c] Reference 18. [d] T. C. Bruice and R. G. Willis, *J. Am. Chem. Soc.*, **87**, 531 (1965). [e] W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 675 (1960). [f] These values are significantly larger than a series of recently reported values (ref 8 and K. Koehler, R. Skora, and E. H. Cordes, *J. Am. Chem. Soc.*, **88**, 3577 (1966)), except for hydroxide ion and glycine ethyl ester–phenyl acetate which are smaller. [g] No added salt. [h] At ionic strength 1.0. A previously reported value of 0.015 is incorrect because of neglect of catalysis by phosphate buffer. The catalytic constant for catalysis by phosphate buffer, 75% dianion, is 0.13 M^{-2} min^{-1}. [i] Reference 6. [j] Reference 14. [k] P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **82**, 795 (1960). [l] Reference 10. [m] R. P. Bell and W. C. E. Higginson, *Proc. Roy. Soc.* (London), **A197**, 141 (1949). [n] A. J. Everett and G. J. Minkoff, *Trans. Faraday Soc.*, **49**, 410 (1953). [o] M. Bender and W. Glasson, *J. Am. Chem. Soc.*, **81**, 1590 (1959). [p] Calculated from the equilibrium constants for the reactions of *p*-nitrophenolate and phenolate ions with acetylimidazolium ion [J. Gerstein and W. P. Jencks, *ibid.*, **86**, 4651 (1964)] and the rate constant for the reaction of phenolate ion with PNPA. [q] These values agree closely with those recently obtained at the same temperature in the presence of 0.5 M sodium chloride.[15] [r] N. V. Sidgewick, "Chemical Elements and Their Compounds," Oxford Press, London, 1950. [s] Reference 4. [t] H. H. Broene and T. DeVries, *J. Am. Chem. Soc.*, **69**, 1644 (1947)

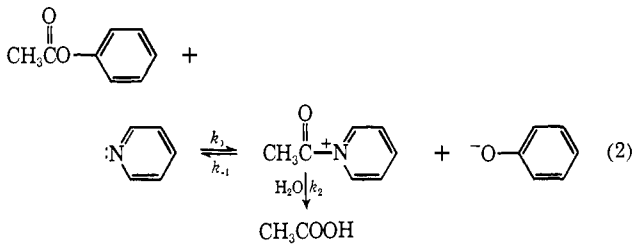
added *p*-nitrophenol, caused by this back reaction, is shown in Figure 3. In order to avoid the determination of erroneously low rate constants because of this back reaction it was necessary to carry out some experiments with very dilute solutions of ester in cuvettes with a 5-cm path length. Although the back reaction causes deviations from first-order kinetics, these may not be obvious, and the rate constants for reactions with tertiary amines and other nucleophiles which might give reactive acylated intermediates were often checked by the addition of a second aliquot of ester to a reaction mixture in which phenol had already been liberated in

Table II. Approximate Thermodynamic Activation Parameters for Reactions of Amines with Substituted Phenyl Acetates[a]

Ester	Ethylamine			Morpholine			Piperidine		
	$\Delta F^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta F^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta F^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Phenyl acetate	18,720	8600	−34	21,400	14,300	−25	18,960	9100	−33
p-Nitrophenyl acetate	15,800	8200	−25	17,660	10,700	−23	15,100	7400	−26
2,4-Dinitrophenyl acetate	14,600	7600	−24	14,800	9,100	−19	13,600	7100	−22

[a] From measurements at 5 and 25°, ionic strength 1.0 *M*. See Tables I and VII–X for experimental conditions and rate constants. $\Delta F^{\ddagger}$ and $\Delta H^{\ddagger}$ are in units of kilocalories/mole; $\Delta S^{\ddagger}$ is in entropy units. $\Delta H^{\ddagger} = E_a - RT$; $\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta F^{\ddagger})/T$.

the initial reaction. Steady-state treatment of eq 2



(2)

gives eq 3 and the solid line in Figure 3 was calculated from eq 3, based on a ratio, k_{-1}/k_2, of 1.84×10^4. On a

$$k_{obsd} = \frac{k_1 k_2}{k_2 + k_{-1}[RO^-]} \quad (3)$$

molar basis this corresponds to a relative reactivity of *p*-nitrophenolate ion and water toward N-acetyl-4-methylpyridinium ion of 10^6 and gives a Brønsted slope of approximately 0.7 for the latter compound, based on these two points. A more extensive study by this technique should make possible the construction of a scale of relative nucleophilic reactivities toward N-acylpyridinium ions and related compounds by this technique. In the reaction of phenyl acetate with 4-methylpyridine the back reaction of phenol was found to proceed at a rate equal to the rate of hydrolysis of the intermediate in the presence of 0.004 *M* phenol at pH 7.2. The occurrence of these back reactions proves that the forward reaction represents nucleophilic attack; no inhibition by this mechanism would occur in a general base catalyzed hydrolysis. The low concentrations of phenolate ion required for inhibition and the fact that inhibition is not observed in reactions with nucleophiles which give an unreactive product indicate that inhibition is not caused by complex formation between ester and phenolate.

In early experiments an increase in the rate of the reaction of pyridine with AMPP was observed in the presence of increasing concentrations of phosphate buffer. Experiments at lower concentrations of AMPP revealed that the reaction of pyridine with AMPP is not subject to catalysis by phosphate buffer. The rate acceleration at higher AMPP concentrations is presumably caused by phosphate catalysis of the decomposition of the N-acetylpyridinium ion intermediate; this decreases the inhibition of AMPP disappearance which is caused by the back reaction with *p*-methoxypyridine N-oxide and, therefore, causes an acceleration of the observed rate of AMPP disappearance.

A number of spot checks for the occurrence of buffer catalysis were carried out as indicated in Tables VII–X. The observations that the reaction of aniline with PNPA is catalyzed by phosphate buffer and that the reaction of aniline with phenyl acetate is catalyzed by a second mole of aniline suggest that these reactions are nucleophilic, because no such third-order terms would be expected for general base catalyzed hydrolysis. The reaction of DNPA with ethylamine, which is in the levelled off region of Figure 2, was found to show no catalysis by phosphate or tris(hydroxymethyl)aminomethane buffers at concentrations up to 0.25 *M* and the reactions of AMPP with piperidine and quinuclidinol were found to show no catalysis by borate or phosphate buffers up to 0.05 *M*.

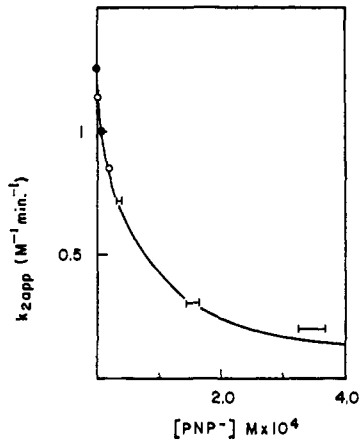


Figure 3. Inhibition of the 4-methylpyridine-catalyzed hydrolysis of *p*-nitrophenyl acetate by added *p*-nitrophenolate ion at 25°, ionic strength 1.0 *M*: ○, 50% free base; ●, 90% free base amine. The bars show the range over which the concentration of *p*-nitrophenolate varied during the experiment. The solid line is calculated from eq 3. The initial concentration of PNPA was varied from 2×10^{-6} to 7×10^{-5} *M* and the wavelength from 330 to 452 mμ in order to obtain convenient absorbance changes during the reaction; some cuvettes were read against blanks containing *p*-nitrophenolate ion.

Salt and Solvent Effects. The reactions of AMPP with glycine ethyl ester and ethylamine, compounds which fall above and below the point at which the log *k*–p*K* curve of Figure 2 levels off, show an acceleration with 1 *M* potassium chloride, similar to that observed for related reactions with phenyl acetates,[7,18] and show little change or a small inhibition in the presence of 1 *M* sodium perchlorate or 4.5% *t*-butyl alcohol, compounds which are thought to have "structure-breaking" and "structure-making" influences on water, respectively (Table III).

The reactions of substituted pyridines and phenyl acetates become nonlinear with respect to pyridine concentration at high concentrations of the pyridine. A similar result was obtained previously for nucleophilic reactions of pyridines with several different types of substrate and was attributed to an aggregation or self-interaction effect of the amine.[19] A 1 *M* solution of

(18) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **88**, 104 (1966).

(19) A. J. Kirby and W. P. Jencks, *ibid.*, **87**, 3209 (1965).

Table III. Effects of Salts and *t*-Butyl Alcohol on the Reaction of Glycine Ethyl Ester and Ethylamine with AMPP[a]

Addition	$k_2 \times 10^4$, M^{-1} min^{-1} Glycine ethyl ester[b]	Ethylamine[c]
None	1.38	12.5
1 *M* $NaClO_4$	1.35	9.0
4.5% *t*-butyl alcohol (v/v)	1.18	12.7
1 *M* KCl	1.80	15.0

[a] At 25°. Apparent p*K* values for the amine and the rate of AMPP hydrolysis in the absence of amine were determined under the same experimental conditions used for each run. [b] In 0.02 *M* phosphate buffer, pH 6.1 in water. [c] In 0.02 *M* borate buffer, pH 8.7 in water.

nicotinamide increases the solubilities of phenyl acetate and PNPA, 2.6- and 3.8-fold, respectively, whereas a higher concentration of dioxane causes a considerably smaller effect (Table IV). This suggests that differences in the effects of concentrated solutions of substituted pyridines on the activity coefficients of the ester and the transition state may also influence observed rate constants, possibly through the formation of an ester–pyridine complex.

Table IV. Effects of Nicotinamide and Dioxane on the Solubility of Phenyl Acetate and *p*-Nitrophenyl Acetate in 1 *M* Potassium Chloride at 25° [a]

Solvent	Phenyl acetate Solubility, *M*	S/S_0	*p*-Nitrophenyl acetate Solubility, *M*	S/S_0
1 *M* KCl	0.027		0.0024	
+ 1 *M* nicotinamide (9%, v/v)	0.070	2.6	0.0090	3.8
+ 12% dioxane (v/v)	0.039	1.4	0.0037	1.6

[a] Measured by the hydroxamic acid method after shaking for 10 and 20 min with excess phenyl acetate or rotating in a water bath for at least 2 hr with excess *p*-nitrophenyl acetate until equilibrium was reached.

The rates of the reactions of AMPP with triethylenediamine and quinuclidinol are the same or slightly faster in deuterium oxide compared to water (Table V).

The rate constant for the hydrolysis of AMPP in 10^{-3} *M* hydrochloric acid is decreased from 1.0 to 0.29 min^{-1} by the addition of 3.6 *M* hydrochloric acid and to 0.0026 min^{-1} by the addition of 7.2 *M* sodium perchlorate. These salt effects are very similar to those observed for the hydrolysis of acetylimidazole[20] and are qualitatively similar to those for the hydrolysis of ethyl difluoroacetate and acetic anhydride.[21]

Products of the Hydrolysis of Phenyl Acetimidates. The amount of phenyl acetate formed upon the hydrolysis of phenyl N-methylacetimidate was determined by the hydroxamic acid method and by measuring the increase in phenol absorption at 270 mμ after alkaline hydrolysis and reacidification of aliquots of the reaction mixture. Above neutrality no phenyl acetate is formed, confirming the results of Kandel and Cordes.[22] Between pH 3 and 5 there is a yield of approximately 10% phenyl acetate and at more acid pH the yield increases

(20) S. Marburg and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 232 (1962).
(21) W. P. Jencks and J. Carriuolo, *ibid.*, **83**, 1743 (1961); C. A. Bunton, N. A. Fuller, S. G. Perry, and I. H. Pitman, *J. Chem. Soc.*, 4478 (1962).
(22) M. Kandel and E. H. Cordes, *J. Org. Chem.*, **32**, 3061 (1967).

Table V. Solvent Deuterium Isotope Effect on the Reaction of AMPP with Triethylenediamine and Quinuclidinol in 0.01 *M* Borate Buffer at 25°, Ionic Strength 1.0 *M*

Concn, *M*	Solvent	No. of runs	pH (pD)[a]	p*K*[b]	$k_2 \times 10^5$, M^{-1} min^{-1}	k_H/k_D
			Triethylenediamine[c]			
$1.7\text{–}5 \times 10^{-4}$	H_2O	6	8.47	9.20	1.60	0.94
	D_2O	6	9.10	9.89	1.70	
			Quinuclidinol[c]			
$1.7\text{–}5 \times 10^{-3}$	H_2O	6	8.42	10.12	1.29	0.98
	D_2O	6	9.07	10.78	1.32	

[a] pD = measured pH + 0.40 [P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960)]. [b] Determined by adding 0.050 ml of amine buffer of known composition in water to 1.95 ml of 1 *M* potassium chloride in H_2O or D_2O and measuring the pH (pD). [c] Prepared by adding 0.050 ml of the same concentrated solution of amine in water to 10.0 ml of H_2O or D_2O.

Table VI. Products from the Hydrolysis of Phenyl N-Methylacetimidate as a Function of pH[a]

pH	% phenyl acetate product I[f]	II[f]
0.4		
30 min	37[b]	
60 min	42	
90 min	42	
120 min	40	48
1.1	42	50
1.7	28	31
1.7	29[c]	31[c]
1.9	23	27
2.2	15	18
3.5	9	11
4.0	9	11
4.8	9	
4.8	9[d]	
5.9	7	7
8.8–7.6[e]	1	2

[a] The experiments were carried out at 25° with 0.007–0.014 *M* imidate in the presence of hydrochloric acid, 0.03 *M* acetate buffer, or no added buffer. Ester formation was measured at the time indicated or after 2–5 hr by the hydroxamic acid method and by measuring the absorbance of a diluted aliquot of the reaction mixture at 270 mμ in dilute acid before and after hydrolysis in 0.1 *M* potassium hydroxide for 10 min. The imidate does not react directly with hydroxylamine to give a ferric chloride reactive product. [b] The reaction had proceeded approximately half way to completion at this time. [c] 0.1 *M* acetic acid added. [d] 0.14 *M* acetate buffer. [e] Added phenyl acetate was recovered in 95% yield from a duplicate experiment carried out under these conditions. [f] I = hydroxamic acid method, II = alkaline hydrolysis method.

to 40–50% (Table VI). The limiting yield in acid solution could not be determined because of acid-catalyzed hydrolysis of phenyl acetate, but in one experiment at pH 0.4 a 37% yield of phenyl acetate was obtained when the reaction had proceeded approximately 50% to completion, which shows that phenyl acetate is the predominant product under these conditions. The yield of phenyl acetate is not significantly affected by the addition of acetic acid or acetate buffer at pH 1.7 or 4.8. The rate constant for the formation of phenyl acetate was found to be 0.054 min^{-1}, measured by the hydroxamic acid method, which agrees with the rate constant for imidate hydrolysis of 0.052 min^{-1} in the same reaction mixture at pH 5.0. The product was shown to react with a hydroxylamine buffer with the same rate constant as authentic phenyl acetate.

The phenyl acetimidate of glycine ethyl ester was prepared in solution from glycine ethyl ester and phenyl N-methylacetimidate at a pH of approximately 3 (see Experimental Section) in order to examine the products of decomposition of an imidate with a less basic leaving group. This compound was not examined in as much detail as the methylamine compound, but it was shown to behave in a qualitatively similar manner in that hydrolysis between pH 3 and 5 gave yields of phenyl acetate of 10% or less, whereas the yield increased in acid, to 18% at pH 1.07. Since the material was not isolated as a pure compound we do not wish to draw any conclusion about the products of the decomposition reaction between pH 3 and 5 except that there is little or no phenyl acetate formed.

Discussion

Anionic Nucleophiles. The reactions of oxygen anions with esters may be analyzed most straightforwardly and are discussed first. Suppose a tetrahedral addition intermediate is formed from an anion, RO^-, and an ester, CH_3COOR' (eq 4). If OR and

$$RO^- + CH_3\overset{\overset{O}{\|}}{C}OR' \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RO\overset{\overset{O^-}{|}}{\underset{\underset{CH_3}{|}}{C}}OR' \xrightarrow{k_2} CH_3\overset{\overset{O}{\|}}{C}OR + {}^-OR' \quad (4)$$

OR′ are identical, the intermediate will break down at equal rates to starting materials and products in this symmetrical reaction. If $R'O^-$ has the more electron-withdrawing substituent it will be less basic and a better leaving group; in this case $k_{-1} < k_2$, almost every molecule of intermediate that is formed will go on to products rather than back to starting materials, and the first step, k_1, will be rate determining. If RO^- is the better leaving group, $k_{-1} > k_2$, the intermediate will go back to starting materials more often than it goes on to products, the first step will be a rapid preequilibrium, and the second step will be rate determining. If no addition intermediate is formed, a similar situation will obtain in that the transition state will resemble that for the (hypothetical) k_1 step in the first case, with relatively little bond formation and breaking, and that for the k_2 step, with a larger amount of bond formation and breaking, in the second case. These reactions have the further advantage that there is no kinetically significant proton-transfer step.

The logarithmic plots of reaction rate against the basicity of the oxygen anion nucleophile which are shown in Figure 1 cover a range of basicity of the nucleophile of 10^{12}, a range of basicity of the leaving group of 10^8, and a range of reaction rates of 10^{12}. The observed reactions of acetate with PNPA and PA are partly or entirely general base catalysis,[15] so that the rate constants of the nucleophilic reactions are smaller than the observed rate constants; this is indicated by arrows in the figures. None of the curves is linear,[23] but there does not appear to be a sharp break at the pK of the leaving group in any case. The most significant result is that the slopes of the lines for nucleophiles with pK values which are less than the pK of the leaving group, *i.e.*, for reactions in which the transition state is expected to resemble that for breakdown of a tetrahedral intermediate, are steeper than those for nucleophiles with pK values larger than the pK of the leaving group, for which the transition state is expected to resemble that for attack on the ester. This is the behavior expected for such reactions, as described in the preceding paragraph. The large sensitivity to the basicity of weakly basic nucleophiles may be explained either in terms of a large sensitivity of the equilibrium addition step to basicity, if there is an addition intermediate, or in terms of a large amount of bond formation in the transition state, if there is no discrete addition intermediate. The latter explanation might be regarded as a rather extreme expression of the considerations discussed by Hammond and others.[2,25]

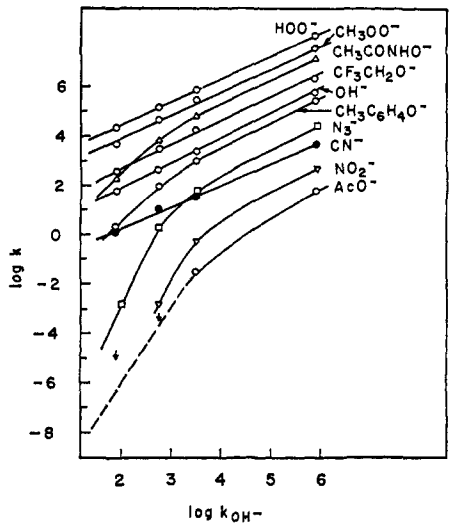


Figure 4. Logarithmic plot of the rate constants for reactions of esters with selected anionic nucleophiles compared to the rate constants for their reactions with hydroxide ion at 25°.

The situation is illustrated more clearly by the logarithmic plot of observed reaction rate against log k_{OH^-} for the different esters, shown in Figure 4. Some oxygen nucleophiles of unusual reactivity which deviate from plots of rate against basicity, such as hydroperoxide and acetohydroxamate anions, and the carbon and nitrogen nucleophiles, cyanide and azide anions, are included in this plot. All oxygen nucleophiles with pK values greater than the pK of the leaving group are well behaved and show a linear correlation with the rate of the hydroxide ion reaction with a slope very nearly equal to 1.0. As the pK of the nucleophile becomes less than that of the leaving group there is a negative deviation from this correlation and the lines approach a new, steeper slope. It is particularly noteworthy that this behavior is a function of the pK of the nucleophile and not of the absolute rate or nucleophilicity; acetohydroxamate (pK = 9.4) shows such a deviation, although its reaction rate is more than an order of magnitude greater than that of hydroxide ion toward AMPP and DNPA. Cyanide is known to have an affinity for the carbonyl group many orders of magni-

(23) A previously reported[24] linear logarithmic correlation of reaction rate with the pK of the oxygen nucleophile includes data obtained in 28.5% alcohol as well as in water.

(24) T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochemistry*, **1**, 7 (1962).

(25) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955); J. E. Leffler, *Science*, **117**, 340 (1953); E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 4319 (1962).

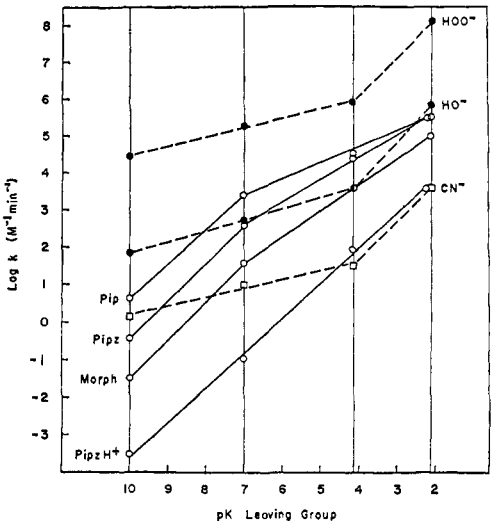
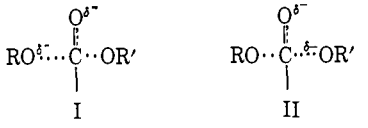


Figure 5. Logarithmic plot of the rate constants for the reactions of three anionic nucleophiles (dashed lines) and four secondary amines (solid lines) with esters at 25° as a function of the pK of the leaving group. The upward deviations for the anionic nucleophiles are for the reactions with the cationic ester AMPP.

tude greater than that of oxygen nucleophiles of comparable basicity, so that it would not be expected to leave readily once bond formation has taken place, and cyanide ion shows no deviation, although its rate of reaction is two orders of magnitude less than that of hydroxide ion. Azide ion shows an exceptionally rapid rate of reaction with AMPP and DNPA, but then undergoes a break and reacts much more slowly with PNPA and PA; fluoride (not shown) and nitrite behave similarly.

Two important practical consequences of these results are, first, that no single value of the Brønsted coefficient, β, describes the relationship of the basicity of oxygen and other anionic nucleophiles to their nucleophilicity toward esters over a large range of variation in the structure of either the nucleophile or the ester and, second, that compounds which have an "abnormally" high reactivity toward one ester may have a normal or low reactivity toward others. Thus, cyanide ion reacts an order of magnitude more rapidly than amines of comparable basicity toward phenyl acetate, but more than an order of magnitude more slowly than amines of comparable basicity toward AMPP (in spite of the electrostatic facilitation of the reaction of cyanide anion with this cationic ester). The reactivity of azide ion toward AMPP and DNPA is larger than that of the much more basic cyanide ion, but is three orders of magnitude smaller than that of cyanide toward phenyl acetate, because of the break in the curve of Figure 4 for azide ion. The same situation is found with acetohydroxamate ion compared to the more basic trifluoroethoxide ion and similar changes in relative reactivities occur with other anionic and nitrogen nucleophiles.

It is concluded that the transition states for reactions of oxygen nucleophiles with esters resemble I or II,



depending on whether the attacking group is more or less basic than the leaving group, respectively. The slopes, β, of logarithmic plots of reaction rate against the basicity of the nucleophile approach 0.3 (Figure 1) and against the basicity of the leaving group approach 0.25–0.30 for type I reactions (some representative examples are shown as the dashed lines in Figure 5). The slopes of both types of plots approach 1.0 for type II reactions. This indicates that the attacking group has lost little charge and there has been little change in the charge of the leaving group in type I reactions, whereas the attacking group has lost a considerable amount of charge and there has been a large change in the charge of the leaving group in type II reactions.

The results do not provide conclusive evidence as to whether a metastable tetrahedral addition intermediate is formed on the reaction path. However, they do show that there is a correlation between the bond-making and bond-breaking steps such that substituents in the attacking or leaving anion have roughly the same effect on the rate of the reaction. One might have expected that if a stable tetrahedral intermediate were formed the rate of the attack step would be more sensitive to substituents on the attacking reagent than on the leaving alcohol, because the leaving group is not directly involved in this step. This is not the case. This point may be clarified by a more concrete description in terms of the values of β for a series of calibrating equilibrium processes. Starting with an alcoholate ion, the β value for the addition of a proton with complete loss of the negative charge is, by definition, 1.0. The equilibrium for the addition of an acyl group from a constant acyl donor (*e.g.*, acetylimidazolium ion) has a β value of 1.7, reflecting the greater destabilization by electron-withdrawing substituents of an ester than an acid; *i.e.*, the electron-withdrawing acyl group with its polarized carbonyl group is more electropositive than even a proton.[26,27a] Thus, one might say roughly that a β value of 0.3 for the nucleophile means that the reaction behaves as if the attacking anion had lost some 0.3 of its charge in the transition state and had proceeded less than 0.3 of the way along the reaction coordinate for the complete reaction, which corresponds to a β value of 1.7. Similarly, a β value of 0.3 for the leaving group indicates a small decrease in the electropositivity of the ethereal oxygen atom and suggests that in terms of change in the charge of the leaving group the reaction has proceeded only some 0.3/1.7 of the way toward completion. The β values of 1.0 for the attacking and leaving groups which are observed for poor nucleophiles and poor leaving groups may be interpreted in an

(26) J. Gerstein and W. P. Jencks, *J. Am. Chem. Soc.*, **86**, 4655 (1964).

(27) (a) It should perhaps be pointed out that the fact that this equilibrium was measured with acetylimidazolium ion as a constant, reference compound has no bearing on this statement. The β value of 1.7 reflects only the *differences* in free energy for the transfer of an acetyl group from a constant donor to alcoholate ions of different basicity. (b) These correlations are not precise. For the purpose of these comparisons the extent to which bond making or breaking or changes in charge distribution have taken place are defined in terms of the effects of polar substituents on the free energies of transition states and equilibria. In the starting ester there is presumably partial double-bond character to the alcohol oxygen atom and electron-withdrawing substituents will increase the observed rate by interfering with this partial double-bond character and destabilizing the electrophilic carbonyl center, as well as by stabilizing the leaving alcoholate ion. "Bond breaking" and "change in charge of the leaving group" include all of these effects and the notation C · · · · OR means that there has been a large change from the character of the starting ester, not that the bond order of the C–O bond is very much less than 1.0.

analogous manner and suggest that changes in the charge of the attacking and leaving groups have proceeded somewhat more than halfway to completion.[27b] Since these reactions are symmetrical, the values of β for the forward and reverse reactions should be complementary, so that the reverse of the reaction with β values of 0.3 should exhibit β values of $1.7 - 0.3 = 1.4$ for the attacking and leaving groups. This situation has not been attained experimentally, because of the unfavorable rates and equilibria of such reactions and the incursion of other reaction mechanisms, such as general base catalysis; however, it is approached in the reactions with an observed β value of 1.0. Values of β near 0.3 have been observed previously for the reactions of acetate esters with hydroxide ion[14,24] and the value of σ required for the *p*-nitro group in $\rho\sigma$ correlations of the alkaline hydrolysis of phenyl esters suggests that little bond breaking has occurred in the transition state,[9,28] in agreement with the present conclusion; however, the present results do not support the additional conclusion[9] that bond formation has proceeded more than bond breaking in these reactions. The intramolecular nucleophilic reactions of carboxylate anion with substituted phenyl succinates, glutarates,[29] and phthalates,[30] which show β values for the leaving group of 0.8 to 1.0, undergo a larger change in the charge of the leaving group and may be interpreted in terms of a concerted reaction,[29] although such an interpretation is not unique.

An incidental point of some interest is that the reactions of the cationic ester AMPP with all of the anions examined are increased approximately 30-fold by an electrostatic effect corresponding to a decrease of some 2000 cal/mol in the free energy of activation. This acceleration is evident as a positive deviation for such reactions in logarithmic plots of reaction rate against the pK of the leaving group (Figure 5, dashed lines). No such deviation is observed for the reaction of AMPP with amines (Figure 5, solid lines). A similar electrostatic rate acceleration occurs in the reactions of acetylimidazolium cation with anions,[4,26] also at ionic strength 1.0. There is no significant effect of the charge of ethylenediamine and piperazine monocations on the rate constants for the reactions of these compounds with AMPP and there is no significant electrostatic effect in the reaction of anions with *p*-nitrophenyl oxalate monoanion;[31a] in these reactions the charges are further removed from the reaction center. Surprisingly, there appears to be little electrostatic effect on the rate of the reaction of nucleophiles with N,N-dimethylcarbamoylpyridinium cation.[31b]

Nitrogen Nucleophiles. The dependence of the reactivity of structurally related amines on their basicity, covering a range of reaction rates of over 10^{10}, is different from that observed with anionic nucleophiles (Figure 2). The linear portions of the lines in the figure are drawn with an arbitrary slope of 0.8. The following facts and interpretations follow rather directly from the data summarized in Figure 2 and Table I.

(1) The rate constants which fall near the *linear* portions of these lines follow a Brønsted slope, β, close to 0.8 and do not show a large difference in this slope for the different esters. This suggests (a) that there is no significant difference in mechanism or rate-determining step for the reactions which follow this slope, *i.e.*, there is no change in rate-determining step for the reactions of phenyl acetate (with a pK of the leaving group = 10) with amines of pK as low as 3.5, and (b) an increase in reaction rate *per se* has only a small effect on the sensitivity of these reactions to the basicity of the nucleophile. There is a small decrease in β with increasing reactivity of the ester—the data for reactions of primary amines with phenyl acetate are fitted better by a line of slope 1.0 than 0.8 (see also ref 7) and for the reaction with AMPP the corresponding slope may be slightly less than 0.8. These differences are consistent with the small decrease in selectivity with increasing reactivity which might be expected over a range of reaction rates of 10^8 from the considerations discussed by Hammond and others.[2,25] These reactions will be designated as "normal" in the following discussion.

(2) There is a rather sharp levelling off of the rate with increasing basicity of the amine in the reactions with DNPA and AMPP. Part of this levelling may be the result of a statistical effect for the diamines, but there is no question but that there is such a levelling and that these reactions behave differently from those of PA and PNPA. Note that the levelling occurs with tertiary amines, which cannot lose a proton, as well as with primary and secondary amines. This levelling means that the nature of the transition state is different for these reactions compared to those which follow a line of slope 0.8.

(3) The tendency of tertiary amines in the pyridine series to react more rapidly than other amines becomes larger as the substrate becomes more reactive; for AMPP these amines react two orders of magnitude faster than primary amines of comparable basicity. This fact, the nonlinear dependence of the rates of many of these reactions on the concentration of amine, and the fact that nicotinamide increases the solubility and decreases the activity coefficient of phenyl acetate and PNPA (Table IV) suggest that some sort of complex formation between the nucleophile and the substrate, possibly of the donor–acceptor type, may facilitate these reactions. However, any such complex formation does not perturb the reactivity–basicity correlation for these amines. Aniline also shows an enhanced reactivity with AMPP and DNPA. The more hindered and more basic tertiary amines, triethylenediamine and quinuclidinol, react more slowly than other amines of comparable basicity, but show a similar relationship of basicity to reactivity for their reactions with phenyl acetate and PNPA.

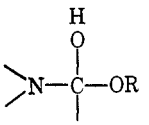
(4) Hydroxylamine and hydrazine, which exhibit an abnormally high reactivity with the less reactive esters, are subject to the same limit in absolute reaction rate as are other amines in their reactions with AMPP and, to a lesser extent, with DNPA. Unusually reactive oxygen anions show no such limit or levelling of their rate of reaction with these esters. Imidazole reacts abnormally fast by about two orders of magnitude with phenyl acetate (this is not a function of the dissociable hydrogen on imidazole, because N-methyl-

(28) J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, **33**, 127 (1968).
(29) E. Gaetjens and H. Morawetz, *J. Am. Chem. Soc.*, **82**, 5328 (1960).
(30) J. W. Thanassi and T. C. Bruice, *ibid.*, **88**, 747 (1966).
(31) (a) T. C. Bruice and B. Holmquist, *ibid.*, **89**, 4028 (1967); (b) S. L. Johnson and K. A. Rumon, *ibid.*, **87**, 4782 (1965).

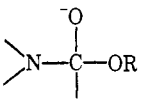
imidazole reacts only some three times slower than imidazole[32]) but this unusual reactivity disappears with the more reactive esters and imidazole reacts with AMPP and DNPA more slowly than the less basic 4-methylpyridine.

(5) Logarithmic plots of reaction rate against the pK of the leaving group for the "normal" reactions exhibit a slope of 1.0 ± 0.1; this slope decreases to approximately 0.4 for the reactions of strongly basic amines with AMPP and DNPA. This is illustrated for the reactions of secondary amines by the *solid lines* in Figure 5.

(6) The fact that the reactions of tertiary amines display similar characteristics to those of primary and secondary amines, in particular a similar sensitivity to amine basicity, means that proton transfer to the solvent or within the reacting complex is not necessary in any step of the reaction in order that these reactions may proceed at the observed rates. Thus, there is no necessity in these reactions to implicate intermediates or transition states such as III and IV, which could be



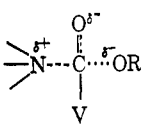
III



IV

formed from primary and secondary amines and might have been expected to provide a more rapid reaction pathway than is available to tertiary amines. Furthermore, it strongly suggests that both steps of the reaction, if there are two steps, can proceed through transition states with no net charge.

The β values of 0.8 for the amine nucleophile and approximately 1.0 for the leaving group show that there is a large amount of bond formation and a large amount of bond breaking in the transition state of the "normal" reactions. Based on the calibrating values of β discussed in the previous section one might say that the reactions behave as if there is some 0.8 of a positive charge developed on the attacking nitrogen atom in the transition state and an equal or somewhat larger change in the electron density of the leaving oxygen atom; based on a β value of 1.7 for the complete loss of an oxygen anion from an ester, the leaving group appears to be somewhat more than halfway toward the product.[27a] Thus, the transition state for these reactions may be illustrated by V, taking no position for the

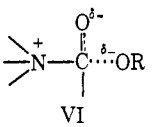


V

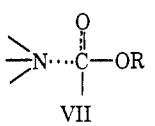
moment as to whether a metastable tetrahedral addition intermediate is formed in the course of the reaction. Changes in the nature of the leaving group have a remarkably small effect on the sensitivity of this transition state to changes in the basicity of the attacking group and *vice versa*.

A difference between the behavior of nitrogen and anionic nucleophiles is also evident in the greater increase in reaction rates with anionic than with nitrogen nucleophiles upon the addition of electron-withdrawing substituents to the *acyl* portion of the ester.[33] The larger amount of bond formation in the transition state with nitrogen than with oxygen nucleophiles would make this difficult to understand if only bond formation were important in the transition state; the complementary changes in the amount of charge on the leaving group make this result reasonable, because a transition state with an over-all negative charge should be stabilized more than one with no net charge by electron-withdrawing substituents in this position.[33]

The reason for the rather sudden break in the structure–reactivity correlation and in the nature of the transition state for the reactions of strongly basic amines with reactive esters cannot be described with certainty. Our first hypothesis was that this represents a change from a transition state resembling that expected for rate-determining breakdown of a tetrahedral intermediate in the reactions with β values of 0.8–1.0 (VII) to a transition state resembling that expected for rate-determining amine attack (VII), with much smaller values of β in the reactions of strongly basic amines



VI



VII

with reactive esters. This is the behavior which is observed for the reactions of oxygen anions as the nature of the attacking and leaving groups is changed and, in fact, the latter reactions were examined after most of the experiments with amines were completed, in order to provide information on the sensitivity of the transition state to changes in the attacking and leaving groups in a reaction in which the nature of the rate-determining step was known. However, this hypothesis is opposed to the prevailing opinion that the rate-determining step of the aminolysis of PNPA is amine attack, and the following reasons indicate that it is almost certainly incorrect.

(a) Kandel and Cordes have shown,[22] and we have confirmed, that the predominant products of the breakdown of phenyl N-methylacetimidate near neutral pH are phenol and N-methylacetamide. The tetrahedral intermediate which is formed in the course of the hydrolysis of this compound is the same as that which may be formed in the aminolysis of phenyl acetate by methylamine, *provided* that proton transfers are fast and can reach equilibrium during the lifetime of this intermediate or transition state (Figure 6). Even if a mestastable tetrahedral intermediate is not formed in the aminolysis reaction, the mode of breakdown of the imidate provides an indication of the expected direction of breakdown of the species along the reaction path which most closely resembles the tetrahedral intermediate (Figure 6, dashed line). The fact that this intermediate breaks down to expel phenol rather than amine under the conditions of the aminolysis experiments means that phenol expulsion is the lowest energy path from such an intermediate and that attack of amine on the ester is rate determining (Figure 6). If the attack of methylamine on phenyl acetate is rate determining, the attack of similar alkylamines on PNPA

(32) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, **86**, 833 (1964).

(33) K. Koehler, R. Skora, and E. H. Cordes, *ibid.*, **88**, 3577 (1966).

and on esters with still better leaving groups must certainly be rate determining.

(b) The value of β for the attack step of the aminolysis of methyl formate, in which the attack and decomposition steps have been separated kinetically, is approximately 0.7.[34] This means that in rate-determining amine attack there is a much larger change in the charge of the nucleophile in the transition state than in the attack of an oxygen anion, which has a β value of approximately 0.3. The fact that the value of β for this step in aminolysis is essentially the same as that in the "normal" aminolysis of the esters described here means that the large value of β in the latter reactions cannot be taken as evidence that the breakdown of a tetrahedral intermediate is rate determining and suggests that the transition state for these reactions resembles that for rate-determining amine attack.

(c) Gregory and Bruice have shown that the rate constants for the reactions of a series of nucleophiles, including amines and hydroxide and trifluoroethoxide ions, with 2,2,2-trifluoroethyl thiolacetate are directly proportional to those for the reactions of the same nucleophiles with PNPA.[35] This suggests that the transition states are similar for the reactions of a given nucleophile with these two esters. The transition states for the reactions of PNPA with strongly basic oxygen anions certainly resemble those expected for rate-determining attack and the fact that the amine reactions follow the same correlation for both esters suggests that the transition state for these reactions also resembles that expected for rate-determining attack, if it is assumed that substitution of sulfur for oxygen will have different effects on attack and breakdown steps (the "element" effect).

(d) The curves relating reaction rate to basicity of the nucleophile for oxygen anions (Figure 1) do not resemble those for nitrogen nucleophiles (Figure 2), suggesting that a different type of transition in the nature of the rate-determining step is taking place in the two reaction series.

It is concluded that the transition state for the "normal" reactions of amines does not represent the breakdown of a metastable tetrahedral addition intermediate and that it either represents rate-determining formation of such an intermediate or a concerted reaction with properties similar to those expected for rate-determining attack. It is a corollary of this conclusion that amine attack is occurring in the transition state even with amines with pK values 6.5 units below that of the leaving phenoxide ion, whereas with oxygen nucleophiles the transition state changes to that expected for rate-determining leaving group expulsion when the pK of the attacking group is less than that of the leaving group. The reaction of imidazole appears to undergo a change from predominantly rate-determining attack to rate-determining leaving group expulsion with leaving groups of pK above 10;[14] this may be a reflection of the unusually rapid rate of the attack step with imidazole, which results in the second step becoming rate determining at an earlier point as the leaving group is varied.

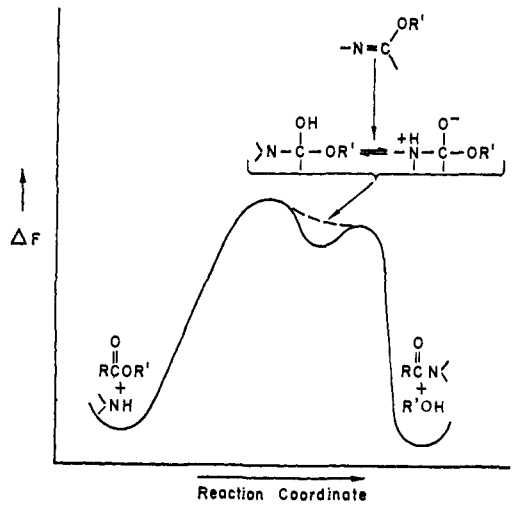


Figure 6. Transition-state diagram to indicate how the mode of decomposition of the tetrahedral intermediate formed during imidate hydrolysis may indicate which step is rate determining in ester aminolysis, if there is an intermediate in the latter reaction (solid line), or the mode of breakdown of the species along the reaction coordinate which most resembles such an intermediate if no metastable intermediate is formed (dashed line).

Thus, the transition state for amine attack in aminolysis is asymmetrical and resembles products, in contrast to that for attack of oxygen anions of equal basicity, which resembles starting materials. Evidently, both more bond formation and more bond breaking are required to reach the transition state for amine compared to oxygen attack, but once it is reached in the amine reactions, expulsion of the leaving group follows rapidly. In the very fast reactions of basic amines with the most reactive esters the sensitivity to amine and leaving group basicity decreases sharply, to more closely resemble that for oxygen anion attack. This change in sensitivity to substituents means that there is a change in the nature of the transition state for amine attack, but this change can hardly represent a transition from rate-determining attack to rate-determining breakdown of an addition intermediate, because if attack is rate determining for the reaction of a tertiary amine with phenyl acetate and PNPA, it must certainly be rate determining with the better leaving groups of DNPA and AMPP. The reaction behaves as if that portion of the energy barrier which is rate determining and is well behaved for the "normal" reactions has decreased to an insignificant level and some earlier stage along the reaction coordinate has rather suddenly become rate determining. The occurrence of linear free energy relationships may be regarded as a consequence of the approximate linearity of the energy surfaces which constitute a reaction coordinate over a limited range of structural variation;[36] the nonlinear relationships observed in these ester aminolyses may reflect a curvature in these surfaces which becomes significant as the activation energy decreases. The reaction of an amine with an ester requires (a) the diffusion of the reactants into a solvent "cage," (b) the energetically unfavorable loss of solvating water from the amine and the ester, (c) the development of properly oriented solvation at the carbonyl oxygen atom and the leaving alkoxide ion,

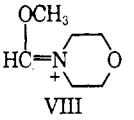
(34) M. Blackburn and W. P. Jencks, *J. Am. Chem. Soc.*, 90, 2638 (1968).

(35) M. J. Gregory and T. C. Bruice, *J. Am. Chem. Soc.*, 89, 2121 (1967).

(36) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 169.

and (d) rotation of the leaving phenoxide group out of the plane of the ester and rotation of the entering amine into the plane of the product amide, as well as (e) bond formation, bond breaking, and partial rehybridization of nitrogen, carbon, and oxygen atoms. Some of these requirements are manifested in the well-known large negative entropies of activation for these reactions. The reaction of basic amines with the most reactive esters is certainly not a simple diffusion-controlled reaction, but the change in the character of the transition state suggests that one or more of the steps a–d may be contributing to the energy barrier of the observed reaction. It may be noted that the removal of a water molecule from between two reactants, while much faster than the aminolysis reaction, may slow the rate of a reaction which would otherwise be diffusion controlled by up to several orders of magnitude; this is the case for the formation of an intimate ion pair from divalent cations and anions[37] and for the *direct* transfer of a proton from a tertiary ammonium ion to an amine or ammonia.[38]

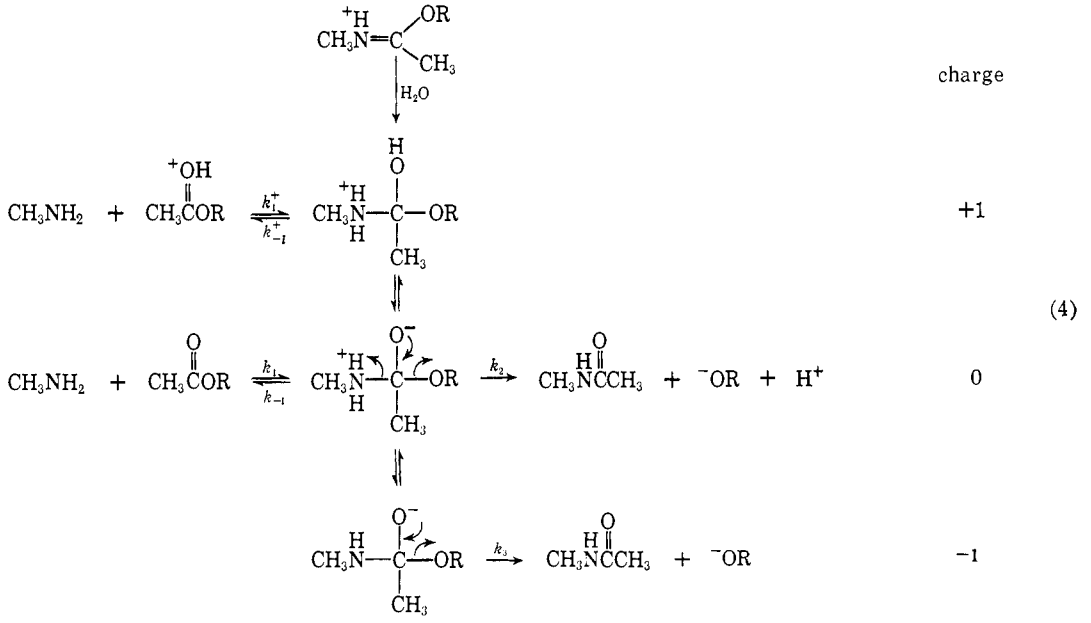
Pathways of Ester Aminolysis. Phenyl N-methylacetimidate undergoes hydrolysis at neutrality exclusively with phenol expulsion,[22] but hydrolysis in acid solution occurs with methylamine expulsion to give phenyl acetate as the primary product, with a transition at pH 1–2. The corresponding imidate with the less basic glycine ethyl ester as the leaving group also decomposes predominantly with phenol expulsion at pH 3–5 and with a larger amount of amine expulsion, to give phenyl acetate, in more acidic solution. This behavior is similar to that observed with thioimidates[39] and is also analogous to that of 2-phenyliminotetrahydrofuran[40] and the cationic imidate derived from



VIII

sion with these compounds occurs near neutral pH. The *yield* of phenyl acetate from the hydrolysis of phenyl N-methylacetimidate increases with increasing acidity under conditions in which there is no change in the *rate* of hydrolysis; for example, there is a twofold increase in phenyl acetate yield as the pH is decreased from 4 to 2 (Table VI), although there is no change in the rate of hydrolysis in this pH range.[22] Such a change in product distribution without a change in rate is evidence for the existence of an intermediate in the reaction, which is formed in a rate-determining step and breaks down to different products at different pH values.[40]

These results show that the transition state for amine expulsion from the addition intermediate has a charge one unit more positive than that for phenolate expulsion, but they do not establish whether the two charges are +1 and zero or zero and −1 for these two modes of breakdown.[40] These two possibilities correspond to breakdown *via* the k_{-1}^{+} and k_2 steps and *via* the k_{-1} and k_3 steps in the scheme of eq 4, respectively. We know that the k_1–k_{-1} pathway is an efficient mode of breakdown and of amine attack near neutral pH, because the aminolysis of phenyl esters proceeds through such a mechanism of amine attack with zero net charge near neutrality. The fact that tertiary amines react with phenyl esters with very much the same reaction characteristics as primary and secondary amines means that phenolate expulsion can also occur efficiently through a



methyl formate and morpholine (VIII)[34] except that the transition from alcohol expulsion to amine expul-

transition state with no net charge near neutrality (k_2). However, these two transition states of identical charge do not account for the fact that there must be transition states of different charge for the predominant mode of breakdown of the phenyl imidate at neutral and acidic pH. The k_3 pathway, with an anionic transition state, is the predominant mechanism for the breakdown of the intermediate formed in the aminolysis of methyl formate,[34] and this pathway must also be available to

(37) M. Eigen, *Discussions Faraday Soc.*, **24**, 25 (1957); G. Atkinson and S. K. Kor, *J. Phys. Chem.*, **71**, 673 (1967).
(38) A. Lowenstein and S. Meiboom, *J. Chem. Phys.*, 27, 1067 (1957); E. Grunwald and A. Y. Ku, *J. Am. Chem. Soc.*, 90, 29 (1968).
(39) R. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *ibid.*, **89**, 6984 (1967).
(40) G. L. Schmir and B. A. Cunningham, *ibid.*, **87**, 5692 (1965).

Table VII. Experimental Conditions for Determination of the Rates of Reactions of Nucleophilic Reagents with Phenyl Acetate at 25°, Ionic Strength 1.0 M

Compound	Concn, M	Fraction base	No. of runs	Compound	Concn, M	Fraction base	No. of runs
Ethylamine[a]	0.05–0.30	0.4	4	Pyridine[n]	0.18–0.72	0.9	4
Propylamine[a]	0.05–0.30	0.4	4		0.4	0.2–0.8	4
Methoxyethylamine[a]	0.05–0.2	0.3	4	Nicotinamide[o]	0.2–1.0	0.98	5
	0.05–0.2	0.5	4	Water[b,p]			
Trifluoroethylamine[b–d]	0.12–0.77	0.95	6	Anion of			
Aniline[b,e]	0.05–0.22	0.98	5	Methanol[q]	0.4–1.6	3.6×10^{-5}	8
Semicarbazide[b,f]	0.1–0.4	0.99	4	2-Propyn-1-ol[r]	0.1–0.5	1.4×10^{-3}	5
Piperidine at 5°[g,h]	0.1–1.0	0.2	6	Trifluoroethanol[r]	0.1–0.25	0.02	5
	0.05–0.5	0.5	6	Hydrogen peroxide[s]	0.06–0.18	3.2×10^{-4}	4
Piperazine[g,i]	0.025–0.20	0.4	5	Methyl hydroperoxide	0.22–0.39	5×10^{-5}[t]	3
	0.17	0.2–0.6	4		0.11–0.33	3.8×10^{-4}[s]	3
Morpholine[c]	0.2–1.0	0.3	5	p-Cresol[u]	0.05	0.8	1
	0.2–1.0	0.7	5		0.05–0.1	0.6	3
At 5°[c,j]	0.2–1.0	0.3	5		0.05	0.4	1
	0.2–1.0	0.7	5	Acetohydroxamic acid	0.002–0.010	0.6	5
Piperazine-H^+[k]	0.1–0.5	0.6	5	Acetic acid[b]	0.25–1.0	0.95	4
	0.5	0.4–0.7	4	Cyanide	0.1–0.4	0.9	4
Quinuclidinol[l,m]	0.067–1.0	0.5	15	Azide[v]	0.2–0.6	1.0	5
Triethylenediamine-H^+[b]		0.7	5	Fluoride[b]	0.2–1.0	0.95	5
4-Methylpyridine[n]	0.1–0.4	0.5	4				
	0.2	0.2–0.6	3				

[a] The observed second-order rate constants, $k_{2\text{-app}} = (k_{obsd} - k_{hyd})/[RNH_2]$, were extrapolated to zero amine concentration and corrected for a contribution (about 10%) from the hydroxide ion catalyzed reaction (see ref 18). [b] By measurement of the initial rate of phenol release at 275 mμ in reaction mixtures containing 0.01–0.02 M phenyl acetate. [c] The values of k_2 and k_3 were obtained from the intercept and slope, respectively, of a plot of $k_{2\text{-app}} = (k_{obsd} - k_{hyd})/[RNH_2]$ against $[RNH_2]$. [d] k_3 is approximately 1.2×10^{-4} M^{-2} min^{-1}. [e] Aliquots of the reaction mixture were quenched in 0.13 M HCl and read at 275 mμ. Carried out in the presence of 10^{-4} M ethylenediaminetetraacetic acid and no added salt. The value of k_3 is 11×10^{-4} M^{-2} min^{-1}. [f] In 0.01 M trimethylacetate buffer, 90% anion. The observed second-order rate constants were extrapolated to zero amine concentration to correct for a third-order catalytic term. The resulting rate constant was corrected by 20% for catalysis by buffer, which was determined in a separate experiment in 0.005–0.020 M buffer, 0.3 M semicarbazide. Catalysis by semicarbazide cation accounts for most of the observed reaction at lower pH values. [g] The value of k_2 was obtained from the intercept of a plot of $k_{2\text{-app}} = (k_{obsd} - k_{hyd})/[R_2NH]$ against (OH^-). [h] The value of k_{3OH^-} is 660 M^{-2} min^{-1}. [i] The value of k_{3OH^-} is approximately 400 M^{-2} min^{-1}. [j] The value of k_3 is 0.011 M^{-2} min^{-1}. [k] Corrected for the contribution of the free base reaction at each pH. [l] The value of k_2 was obtained from the initial slope of a plot of k_{obsd} against [amine]; the value of k_2 decreases at high concentrations because of solvent effects or association of the reactants. [m] A second addition of phenyl acetate to the reaction mixture gave the same rate constant, showing that a back reaction of liberated phenol with an intermediate is not significant under the conditions of the experiment. [n] Followed by the hydroxamic acid method with 10^{-3} M phenyl acetate. The first-order rate constants were obtained from plots which were linear for one-half time; 10^{-3} M phenol causes an 8–18% inhibition by back reaction with an intermediate. The second-order rate constants were extrapolated to zero amine concentration to correct for solvent or association effects of pyridine and picoline solutions.[19] [o] Followed by measurements of the initial rate of phenol release from 0.015 M phenyl acetate by diazotization. The second-order rate constants were extrapolated to zero amine concentration to correct for a solvent or association effect at high amine concentration.[19] [p] Extrapolated to zero buffer concentration from runs in 0.01–0.03 M potassium acetate buffer, pH 4.60. The observed pseudo-first-order rate constant, after corrections of 3 and 11% for base- and acid-catalyzed hydrolysis, respectively, is 1.10×10^{-6} min^{-1}. [q] In 0.1 M triethylamine buffer. [r] In 0.1 M t-butylamine buffer with no added salt. The runs with 2-propyn-1-ol were followed at 295 mμ; the readings were corrected for the change in absorption of a blank containing no phenyl acetate. [s] In 0.1 M Tris buffer, no added salt. [t] In 0.1 M phosphate buffer, no added salt. [u] Followed by measuring the rate of disappearance of 7.5×10^{-3} M phenyl acetate by gas chromatography (see text). [v] In 0.05 M phosphate buffer, pH 6.7.

phenyl esters. Finally, the k_1^+–k_{-1}^+ pathway is well known in acid-catalyzed reactions of esters with weakly basic amines, and acid catalysis has recently been reported to be significant for more basic amines.[7,41]

The hydrolysis of phenyl N-methylacetimidate in the pH range 3–5 gives a small, but apparently significant, yield of approximately 10% phenyl acetate, which is formed with the same rate constant as that for hydrolysis of the imidate. This and the preceding observations could be explained by the following scheme. In the pH range 3–5, the tetrahedral intermediate breaks down through transition states with no net charge, according to the k_2 and k_{-1} pathways, with $k_2 = 10k_{-1}$. At higher pH values, the base-catalyzed expulsion of phenolate, k_3, becomes significant, and the intermediate breaks down exclusively with phenolate expulsion. At pH 1, the cationic transition state for amine expulsion by the k_{-1}^+ pathway becomes significant and phenyl acetate is the predominant product.

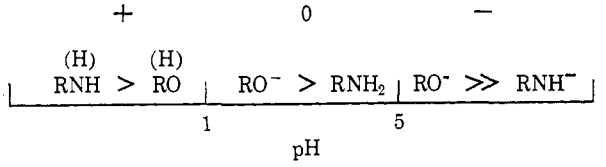
(41) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 82, 675 (1960).

There are two consequences of this hypothesis. First, the postulation of a significant k_1^+–k_{-1}^+ pathway at acid pH requires that the decrease in the rate of the hydrolysis of phenyl N-methylacetimidate in acid solution[22] cannot represent a complete change in rate-determining step to breakdown of the intermediate through a neutral transition state. It must represent either an activity coefficient effect or only a partial change in rate-determining step. Second, it might be expected that the comparable dipolar addition intermediate formed from weakly basic tertiary amines would decompose predominantly by the k_{-1} pathway, so that the k_2 step would be rate determining for the aminolysis of phenyl acetate by these amines. The absence of any evidence for a change from rate-determining formation to breakdown of an intermediate in the aminolysis of phenyl acetate by amines of differing basicity suggests that the k_2 step does not become rate determining. Perhaps the intermediate in the aminolysis reaction, if it exists at all, does not have a sufficient lifetime to reach equilibrium with respect to proton transfer; *i.e.*, it is possible that the same inter-

mediate is not formed in phenyl acetate aminolysis and in the hydrolysis of phenyl N-methylacetimidate. The scheme is consistent with the expected decrease of several pH units in the pH for the transition from predominant base catalyzed to predominant neutral breakdown of the intermediate as the leaving group is changed from aliphatic alkoxide[34,40] to phenolate; both the k_2 and k_3 steps should be favored relative to the k_{-1} step by such a change in the oxygen leaving group. In order to explain the predominant breakdown of the phenyl imidate of glycine ethyl ester with phenol expulsion, it is necessary to take into account the equilibria between the dipolar, uncharged, and anionic forms of the intermediate as well as the reactivities of these species; we do not wish to draw any detailed conclusions from this result at this time.

The proposed mechanism for the breakdown of the tetrahedral intermediate formed in the hydrolysis of phenyl N-methylacetimidate may be summarized schematically by Scheme I, which illustrates the preferred

Scheme I



mode of leaving group expulsion from the intermediate and the charge of the transition state for this expulsion as a function of pH. To the extent that a species resembling this intermediate is formed in the course of phenyl acetate aminolysis, this diagram also describes the mode of breakdown of such a species. In this diagram the parentheses indicate that the proton must be added in an equilibrium step, so that the observed rate is a function of the basicity of the leaving group as well as the leaving ability of the protonated leaving group. If similar diagrams could be constructed for other acyl group reactions the mechanisms of these reactions would be largely understood; it appears probable that this will be accomplished within the next few years.

Experimental Section

Materials and methods have been described previously.[4,10,14,18,41] Organic reagents were redistilled or recrystallized, and water was glass distilled before use. It was necessary to recrystallize piperidine as its hydrochloride (mp 245–246°) from absolute ethanol to remove traces of pyridine (approximately 0.1%) which caused a major fraction of the observed reaction in experiments carried out between pH 5 and 6. 1-Acetoxy-4-methoxypyridinium perchlorate (AMPP) was synthesized from 4-methoxypryidine N-oxide[42] and acetic anhydride by the method of Traynelis and Pacini.[43] Preparations of phenyl acetate were found to be contaminated with a significant amount of phenol, which could not be removed by several attempted purification procedures. A pure product for use in initial rate experiments was prepared by shaking phenyl acetate with one volume of 0.2 *M* 1:1 sodium bicarbonate–sodium carbonate for 4 min immediately after the addition of $^1/_{20}$ volume of acetic anhydride. After this procedure was repeated, the phenyl acetate was separated, dried over sodium sulfate, and fractionally distilled under vacuum (bp 75° (10 mm)). Phenyl N-methylacetimidate (bp 63–64° (0.55 mm)) was prepared by the method of Oxley and Short[44] and was found to undergo hydrolysis at pH 3–3.7, ionic strength 0.5 *M*, with a rate constant of 0.063 min^{-1}; this may be compared to the product obtained by Kandel and Cordes (bp 79° (5 mm)), which

(42) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).
(43) V. J. Traynelis and P. L. Pacini, *J. Am. Chem. Soc.*, **86**, 4917 (1964).
(44) P. Oxley and W. F. Short, *J. Chem. Soc.*, 1514 (1948).

Table VIII. Experimental Conditions for Determination of the Rates of Reactions of Nucleophilic Reagents with *p*-Nitrophenyl Acetate at 25°, Ionic Strength 1.0 *M*

Compound	Concn, *M*	Fraction base	No. of runs
Ethylamine[a]	0.05–0.3	2.4×10^{-3}	4
at 5°	0.05–0.5	1.8×10^{-3}	6
Propylamine[a]	0.05–0.3	2.8×10^{-3}	4
Ethylenediamine[b]	0.05	$1\text{–}41 \times 10^{-3}$	7
Methoxyethylamine	0.01–0.04	0.3	4
Glycylglycine	0.05–0.2	0.5	4
Glycine ethyl ester			
Ethylenediamine-H^+ [b]	0.05	0.2–1.0	5
Trifluoroethylamine	0.1–0.4	0.8	4
Aniline[c]	0.06–0.18	0.9	3
Semicarbazide[d]	0.075–0.3	0.8	4
		0.6	1
Piperidine[a]	0.05–0.3	7.6×10^{-4}	4
at 5°	0.05–0.5	6.3×10^{-4}	6
Piperazine[b]	0.1	$1\text{–}16 \times 10^{-4}$	6
Morpholine	0.025–0.10	0.5	4
at 5°	0.025–0.20	0.5	6
Piperazine-H^+[b]	0.1	0.2–1.0	5
Quinuclidinol	0.013–0.067	0.1	4
Triethylenediamine[e]	0.025–0.10	0.5	4
Triethylenediamine-H^+[f]	0.15–0.6	0.7	4
4-Methylpyridine [g,h]	0.05–0.15	0.5	3
Pyridine[g,h]	0.05–0.15	0.5	3
Nicotinamide[h,i]	0.1–0.5	0.9	5
Water[i,j]			
Anion of			
2-Propyn-1-ol[k]	0.02–0.06	5.25×10^{-4}	3
	0.02–0.06	1.05×10^{-3}	3
	0.013–0.027	3.24×10^{-3}	2
Hydrogen peroxide[l,m]	0.09–0.26	1.4×10^{-5}	3
	0.09–0.26	4.1×10^{-5}	3
Methyl hydro-	0.1–0.3	1.5×10^{-5}	3
peroxide[l]	0.1–0.3	4.1×10^{-5}	3
p-Cresol	0.017–0.067	0.3	5
p-Chlorophenol	0.02–0.08	0.3	4
Acetohydroxamic	0.01–0.04	1.2×10^{-3}	4
acid[n]	0.02	3.6×10^{-3}	1
Acetic acid[i]	0.01–0.60	0.5	4
Azide[n]	0.05–0.2	1.0	4
Fluoride	0.2–1.0	0.95	3
Nitrite[n]	0.3–1.0	1.0	4

[a] In 0.05 *M* tris(hydroxymethyl)aminomethane buffer. [b] The values of k_2 for the free base and the monocation were obtained from the slope and intercept, respectively, of a plot of k_{obsd}/[amine-H^+] against *fraction* free amine. [c] Aliquots were removed and added to phosphate buffer, pH 7.5, to measure the rate of *p*-nitrophenol release. [d] A small extrapolation of the observed second-order rate constants to zero amine concentration was made to correct for a third-order term caused by catalysis by the amine buffer. [e] The same rate constant was obtained in a second run in which additional ester was added; *i.e.*, a back reaction of the liberated RO^- with the acylated tertiary amine does not affect the rate. [f] Measured by the initial rate of *p*-nitrophenol release from 5×10^{-4} *M* PNPA. The second-order rate constant was corrected by 10% for the contribution of the reaction with the free base at this pH. [g] Determined with 5×10^{-6} *M* ester in 5-cm path length cells to avoid back reaction with liberated RO^-. [h] A small extrapolation of the observed second-order rate constants to zero amine concentration was made to correct for a solvent or association effect at high amine concentrations.[19] [i] Measured from the (linear) initial rate of release of *p*-nitrophenol from 5×10^{-4} *M* PNPA. [j] From an extrapolation to zero buffer concentration of rate constants obtained in 0.01–0.03 *M* acetate buffer, pH 4.6, to give a value of $k_w = 2.6 \times 10^{-6}$ min^{-1}. Because of the small extrapolation, the value of k_2 of 4.7×10^{-7} is more accurate than the previously reported[4] value of 6×10^{-7} M^{-1} min^{-1}. [k] In 0.05 *M* *t*-butylamine buffer with no added salt. The same result was obtained with three preparations of 2-propynl-1-ol. We believe our previous result[10] to be in error. [l] In 0.1 *M* potassium phosphate buffer with no added salt. [m] The second-order rate constant of 220,000 is smaller than that of 275,000 M^{-1} min^{-1} reported previously[4] which was based on a p*K* of 11.7; the observed rates in the two series of experiments agree closely. [n] In 0.05 *M* phosphate buffer.

Table IX. Experimental Conditions for Determination of the Rates of Reactions of Nucleophilic Reagents with 2,4-Dinitrophenyl Acetate at 25°, Ionic Strength 1.0 *M*

Compound	Concn, *M*	Fraction base	No. of runs	Compound	Concn, *M*	Fraction base	No. of runs
Ethylamine[a]	0.025–0.10	0.0028	4	Triethylenediamine-H$^+$	0.1–0.4	0.9[h]	4
	0.025–0.15	0.0018	5		0.1–0.4	0.6[h]	4
Propylamine[a]	0.025–0.10	0.0028	4	4-Methylpyridine[i]	0.005–0.02	0.25	8
Ethylenediamine[b]	0.01	0.001–0.028	8	Pyridine[i]	0.01–0.025	0.5	4
Methoxyethylamine[c]	0.033–0.10	0.0013	4	Nicotinamide[i]	0.025–0.1	0.9	4
Glycine[c]	0.025–0.10	0.0012	6	Water[j]			
Glycylglycine	0.01–0.05	0.1	4	Anion of			
Glycine ethyl ester	0.01–0.05	0.1	4	Methanol[k]	0.2–0.8	1.38×10^{-5}	12
Ethylenediamine-H$^+$ [b]	0.01	0.2–1.0	5	2-Propyn-1-ol[l]	0.02–0.06	4.5×10^{-4}	5
Trifluoroethylamine	0.005–0.02	0.5	4	Trifluoroethanol[l]	0.007–0.02	6.9×10^{-3}	5
Aniline	0.025–0.10	0.5	4	Hydrogen peroxide[m]	0.01–0.02	1.6×10^{-5}	2
Hydrazine[d]	0.025–0.10	8×10^{-4}	5		0.005–0.01	4.8×10^{-5}	2
	0.05	3.6×10^{-4}	1	Methyl hydro-	0.01–0.02	2×10^{-5}	2
Hydroxylamine[d]	$5–20 \times 10^{-3}$	6.6×10^{-3}	5	peroxide[m]	0.01	6×10^{-5}	1
	0.01	0.017	1	*p*-Cresol	0.005–0.02	0.1	8
Semicarbazide	0.02–0.08	0.8	4	Phenol	0.005–0.02	0.1	8
	0.04	0.5	1	*p*-Chlorophenol	0.01–0.08	0.1	8
Piperidine[a]	0.025–0.10	7.4×10^{-4}	8	Acetohydroxamic	0.003–0.012	1.3×10^{-3}	4
at 5°	0.025–0.10	6.6×10^{-4}	8	acid[c]	0.006	3.6×10^{-3}	1
Piperazine[e]	0.01	2×10^{-4}	8	Trimethylacetic acid	0.15–0.53	0.9	4
		4.3×10^{-3}		Acetic acid	0.1–0.3	0.5	4
Morpholine[c]	0.025–0.10	9.4×10^{-3}	8	Methoxyacetic acid	0.15–0.60	0.95	4
at 5°	0.025–0.10	4.3×10^{-3}	8	Cyanide	0.005–0.1	0.1	5
Piperazine-H$^+$ [e]	0.01	0.2–1.0	8	Azide[c]	0.0025–0.01	1.0	4
Quinuclidinol[f]	0.007–0.027	0.046	4	Fluoride[n]	0.1–0.5	1.0	5
Triethylenediamine[g]	0.0005–0.002	0.16	7	Nitrite[c]	0.05–0.2	1.0	4

[a] In 0.05 *M* tris(hydroxymethyl)aminomethane buffer. Doubling the buffer concentration did not affect the rate of the piperidine reaction. [b] The values of $k_{obsd}/[H_2NCH_2CH_2NH_3^+]$, from a series of experiments at pH 6.8–8.6, were plotted against $fraction_{H_2NCH_2CH_2NH_2}$. The second-order rate constants for the monocation and free base were obtained from the intercept and slope, respectively, of the resulting straight line. [c] In 0.05 *M* potassium phosphate buffer. Doubling the buffer concentration did not affect the rate of the morpholine reaction. [d] In 0.017 *M* acetate buffer. Doubling the buffer concentration did not affect the rate constant. [e] The values of $k_{obsd}/[Pip \cdot H^+]$, from a series of experiments in 0.033 *M* tris(hydroxymethyl)aminomethane buffer, pH 6.3–7.7, were plotted against $fraction_{Pip}$ (free base). The second-order rate constants for the monocation and free base were obtained from the intercept and slope, respectively, of the resulting straight line. [f] In 0.02 *M* borate buffer. [g] In 0.01 *M* borate buffer. [h] Corrected for contribution of the free-base reaction of 40 and 12% of the observed rates, respectively. [i] With 3×10^{-5} *M* DNPA. Spot checks with 6×10^{-6} *M* DNPA in 5-cm cuvettes gave the same rate constants, which shows that the back reaction with dinitrophenolate ion is not significant under these conditions. [j] Extrapolated to zero buffer concentration from experiments in 0.01–0.03 *M* acetate buffer, pH 4.6, to give $k_{obsd} = 6.6 \times 10^{-4}$ min^{-1}. [k] In 0.1 *M* triethylamine buffer. Above 0.5 *M* methanol there is a decrease in the second-order rate constants, which is attributed to a solvent effect. The rate constant was calculated from the more dilute solutions. [l] In 0.05 *M* *t*-butylamine buffer. Doubling the concentration of buffer did not increase the rate constant for trifluoroethanol. No added salt. [m] In 0.1 *M* phosphate buffer, no added salt. [n] In 0.1 *M* phosphate buffer, pH 6.2.

underwent hydrolysis with a rate constant of 0.065 min^{-1} under the same conditions.[22]

The phenyl imidate of glycine ethyl ester, $CH_3C(OC_6H_5)=N-CH_2COOC_2H_5$, was prepared in weakly acidic solution by the amine exchange reaction of glycine ethyl esters for the methylamine moiety of phenyl N-methylacetimidate.[22,45] Phenyl N-methylacetimidate was added to a final concentration of 0.4 *M* to a solution containing 3.6 *M* glycine ethyl ester hydrochloride and 0.4 *M* acetic acid. After 3 min at 25°, the solution was cooled in an ice bath and was extracted twice with ether to remove hydrolysis products. Aliquots of the aqueous phase were immediately removed and diluted 30- to 300-fold into reaction mixtures for further examination. The product was found to undergo hydrolysis, measured by the rate of release of 270-mμ absorbing material in dilute hydrochloric acid or acetate buffers, according to satisfactory first-order kinetics with rate constants of 0.015, 0.019, and 0.018 min^{-1} at pH 1.09, 4.58, and 5.18, respectively. These rate constants are about three times smaller than those for the hydrolysis of phenyl N-methylacetimidate under the same conditions. At higher pH values the rate of hydrolysis could not be measured because of interference caused by reaction with the remaining glycine ethyl ester. The product was obtained in approximately 30% yield, based on the maximum release of phenol absorption at 270 mμ upon hydrolysis.

An aqueous solution of methyl hydroperoxide[46] was purified by two distillations and assayed by titration with iodide–thiosulfate.[46] The concentration obtained by this method agreed within 10% with that obtained by measurement of the absorbance at 250 mμ, based on an extinction coefficient which was read from a published spectrum.[47] It was shown to contain less than 0.01% hydrogen peroxide by assay with titanium sulfate.[48] The absorbance at 406 mμ which is developed upon the addition of 1/5 volume of saturated titanium sulfate in 1 *M* sulfuric acid was shown to be proportional to the concentration of hydrogen peroxide in the sample to be assayed and is not affected by the presence of methyl hydroperoxide.[49]

Kinetic Methods. Pseudo-first-order rate constants were generally obtained as previously described[4,10,14,18,41] by spectrophotometric measurement of the release of the alcohol moiety of the ester in the presence of a large excess of the nucleophilic reagent. Phenol and phenolate release were generally followed at 275 mμ, *p*-nitrophenolate and 2,4-dinitrophenolate at 400 mμ, *p*-nitrophenol at 330 mμ, and *p*-methoxypyridine N-oxide at 275 mμ; different wavelengths were occasionally used to avoid interference caused by absorption of the nucleophilic reagent. The initial concentrations of ester were generally between 1.5×10^{-5} and 10^{-4} *M*. The reactions of PNPA with pyridine and 4-methylpyridine were carried out with 5×10^{-6} *M* ester in 5-cm path-length cuvettes, and the reactions of AMPP with pyridines were carried out with 1.7×10^{-5} *M* ester in order to avoid interference caused by a back reaction of the liberated alcohol with the intermediate acylpyridinium ion. The reactions of 10^{-3} *M* phenyl acetate with pyridine and 4-methylpyridine were followed by measuring the disappearance of ester by the hydroxamic acid method.[17] The measurements were carried

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(49) We are grateful to Dr. E. Sander for the preparation and assay of this compound.

Table X. Experimental Conditions for Determination of the Rates of Reactions of Nucleophilic Reagents with 1-Acetoxy-4-Methoxypyridinium Perchlorate at 25°, Ionic Strength 1.0 *M*

Compound	Concn, *M*	Fraction base	No. of runs	Compound	Concn, *M*	Fraction base	No. of runs
Ethylamine[a]	$5\text{–}25 \times 10^{-3}$	0.003	6	4-Methylpyridine[e,k]	$2\text{–}3 \times 10^{-4}$	0.14	7
	$2.5\text{–}15 \times 10^{-3}$	0.0065	6	Pyridine[e,k]	$2\text{–}3 \times 10^{-4}$	0.52	6
Propylamine[a]	$5\text{–}25 \times 10^{-3}$	0.0035	6	Nicotinamide[e,k]	$0.5\text{–}2 \times 10^{-3}$	1.0	10
	$5\text{–}18 \times 10^{-3}$	0.0071	6	Water[l]			
Ethylenediamine[b–d]	5×10^{-4}	0.023–0.077	8	Anion of			
Methoxyethylamine[b]	$0.5\text{–}2.0 \times 10^{-3}$	0.047	6	Water[m,n]		$1\text{–}12 \times 10^{-6}$	8
	$0.5\text{–}1.0 \times 10^{-3}$	0.10	4	Methanol[b]	0.05–1.8	8×10^{-8}	6
Glycylglycine[e]	$6\text{–}20 \times 10^{-3}$	0.0014	3		0.6–1.2	1.8×10^{-7}	4
	$6\text{–}12 \times 10^{-3}$	0.0033	2	2-Propyn-1-ol[b]	0.03–0.10	7×10^{-6}	6
Glycine ethyl ester[e]	$1.7\text{–}5.0 \times 10^{-3}$	0.0035	6		0.03–0.06	1.5×10^{-5}	4
	$1.7\text{–}3.4 \times 10^{-3}$	0.0083	4	Trifluoroethanol[b,c]	0.013–0.050	1.1×10^{-4}	8
Ethylenediamine-H^+	$1.3\text{–}5 \times 10^{-3}$	0.2	8		0.013	2.4×10^{-4}	2
Trifluoroethylamine	$2.5\text{–}10 \times 10^{-3}$	0.2	7	Hydrogen peroxide[e]	0.005–0.015	7.6×10^{-7}	6
	$2.5\text{–}5 \times 10^{-3}$	0.5	4			1.7×10^{-6}	4
Aniline[e]	$2\text{–}4 \times 10^{-4}$	0.82	6	Methyl hydroperoxide[e]	0.02–0.08	8.5×10^{-7}	6
Hydrazine[c,e]	$2.5\text{–}10 \times 10^{-3}$	1.6×10^{-3}	3		0.02–0.05	2×10^{-6}	4
	5×10^{-3}	3.6×10^{-3}	1	*p*-Cresol[b]	$0.25\text{–}0.75 \times 10^{-4}$	0.024	6
Hydroxylamine[c,f]	$1.5\text{–}10 \times 10^{-4}$	7×10^{-3}	5		$0.25\text{–}0.5 \times 10^{-4}$	0.048	4
Semicarbazide[c,e]	$5\text{–}1.5 \times 10^{-4}$	1.0	5	Phenol[b]	$0.5\text{–}2.0 \times 10^{-3}$	0.033	6
Piperidine[b,g]	$6.5\text{–}20 \times 10^{-3}$	1×10^{-3}	6		$0.5\text{–}1.5 \times 10^{-3}$	0.066	6
	$6.5\text{–}13 \times 10^{-3}$	2.1×10^{-3}	4	*p*-Chlorophenol[b]	$1.3\text{–}3.8 \times 10^{-4}$	0.12	6
Piperazine[b,d]	5×10^{-4}	0.042–0.089	6		$1.3\text{–}2.5 \times 10^{-4}$	0.22	4
Morpholine[e]	0.025–0.10	3.7×10^{-4}	8	Acetohydroxamic acid[e]	$1\text{–}3 \times 10^{-3}$	1.4×10^{-4}	3
	0.05	1.5×10^{-3}	2		$1\text{–}2 \times 10^{-3}$	3.1×10^{-4}	2
Piperazine-H^+ [e]	$0.2\text{–}1.2 \times 10^{-3}$	0.33	8	Trimethylacetic acid	0.005–0.02	0.5	8
Quinuclidinol[b,h,i]	$1\text{–}3 \times 10^{-3}$	0.022	6				
	$1\text{–}2 \times 10^{-3}$	0.046	4	Acetic acid	0.015–0.06	0.5	10
Triethylenediamine[b,h]	$1.25\text{–}5.0 \times 10^{-4}$	0.15	6			0.25	2
	$1.25\text{–}2.5 \times 10^{-4}$	0.26	4	Methoxyacetic acid	0.05–0.2	0.8	8
Triethylenediamine-H^+ [h,i]	0.01–0.07	0.4	7	Cyanide	0.005–0.020	0.17	10
				Azide[e,h]	$1.3\text{–}10 \times 10^{-4}$	1.0	8
	0.01–0.05	0.6	6	Fluoride[h]	0.0025–0.02	0.95	14
Imidazole[e]	$0.5\text{–}1.5 \times 10^{-3}$	0.018	6	Nitrite[e,h]	0.003–0.010	1.0	6
	$2.5\text{–}5 \times 10^{-4}$	0.04	4	*p*-Nitrophenol[o]	$1\text{–}3 \times 10^{-3}$	0.4	6

[a] In 0.02 *M* borate buffer. [b] In 0.01 *M* borate buffer. [c] Doubling the buffer concentration was shown not to affect the rate. [d] The value of k_2 was obtained from the slope of a plot of $k_{obsd}/[amine]_{tot}$ against *fraction* free amine. [e] In 0.02 *M* phosphate buffer. [f] In 0.01 *M* acetate buffer. [g] No buffer catalysis was observed at borate concentrations up to 0.05 *M*. [h] The same rate constant was obtained in a second run in which additional ester was added; *i.e.*, a back reaction of the liberated RO^- with the acylated tertiary amine does not affect the rate. [i] No catalysis of this reaction by 0.05 *M* borate buffer, pH 8.5, or 0.04 *M* phosphate buffer, pH 6.4, was observed. [j] A 2–3% correction was made for the contribution of the free base reaction. [k] With 1.7×10^{-5} *M* AMPP; higher concentrations give inhibition by reaction of *p*-methoxypyridine N-oxide with the intermediate. See text. [l] By extrapolation to zero buffer concentration in a series of 0.01–0.04 *M* phosphate buffers, pH 5.5 and 6.5, to give $k_{obsd} = 0.72$ min^{-1}. [m] From a series of experiments in 0.005–0.010 *M* borate buffers. This concentration of buffer does not have an appreciable effect on the rate. [n] From $k_2 = 8.5 \times 10^5$, based on a_{OH^-}, and $f_{OH^-} = 0.67$. [o] With $0.5\text{–}1.0 \times 10^{-4}$ *M* AMPP. Followed at 275 mμ with a 0.2-cm path length.

out at an ionic strength maintained at 1.0 *M* with potassium chloride unless noted otherwise. Some experiments with alcohols were carried out at lower ionic strength to permit calculation of the rate of reaction of the anion from pK_a values which had been measured at low ionic strength; this has been shown not to have a large effect on the rate constants.[10]

Slow reactions were followed by measuring the initial rate of phenol release spectrophotometrically. In order to avoid possible errors from uncertainty as to the exact concentration of ester, the absorbance of the liberated phenol was measured after alkaline hydrolysis of the solution of phenyl acetate used in each experiment. The observed rate of change of absorbance was divided by the extinction coefficient of phenol minus that of phenyl acetate and by the concentration of ester to give the pseudo-first-order rate constant for each run. The reaction of nicotinamide with PNPA was followed by the determination of both initial rates and pseudo-first-order rate constants with identical results.

The rate of the reaction of *p*-cresol with phenyl acetate was determined by measuring the disappearance of phenyl acetate by gas chromatography of benzene extracts of aliquots of the reaction mixture. Chromatography was carried out on a column of 10% diethylene glycol succinate and 2% phosphoric acid on 60–80 mesh Diatoport S with an F & M dual-column programmed-temperature chromatograph. The peak heights were found to be proportional to the concentration of phenyl acetate and satisfactory pseudo-first-order kinetics were observed in the rate determinations.

The initial rate of phenol release in the reaction with nicotinamide was measured colorimetrically.[50] Diazotized *p*-nitroaniline was freshly prepared from 0.03% *p*-nitroaniline in 0.1 *M* hydrochloric acid and 0.1% sodium nitrite. A 0.2-ml aliquot of the reaction mixture, which contained 0.015 *M* phenyl acetate initially, was added to 1.0 ml of this solution. The absorbance was read at 470 mμ 2 min after the addition of 5 ml of a solution prepared from one volume of 0.5 *M* sodium carbonate and two volumes of 0.5 *M* sodium bicarbonate.

The concentrations of activated esters and of amides were determined by slight modifications of the neutral hydroxylamine methods of Lipmann and Tuttle and of Katz, Lieberman, and Barker, respectively.[17]

Experiments which were carried out in dilute buffer solutions were prepared with water which had been boiled to remove dissolved carbon dioxide. Experiments with concentrated fluoride salts were carried out in plastic tubes; aliquots were removed for spectrophotometric determination of the extent of reaction. Solutions of AMPP were prepared in acetonitrile and solutions of DNPA were prepared in 20% acetonitrile; the final concentration of acetonitrile in the reaction mixtures was less than 1%. The dilute solutions of borate buffers used in the kinetic experiments would not be expected to undergo an appreciable amount of complex formation with nucleophilic reagents which contain hydroxyl groups, because the equilibrium constants for the formation of such complexes are in the range of 2 to 100 M^{-1};[51] in addition, a number of control ex-

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periments showed that the rates are independent of buffer concentration or composition. Experiments lasting more than a few minutes were carried out in stoppered reaction tubes or cuvettes. Particular care was taken to avoid loss of trifluoroethylamine and of phenyl acetate in long-term experiments.

Rate measurements were carried out in temperature-controlled cell compartments after temperature equilibration of the reactants, with a Zeiss PMQ II or a Gilford 2000 spectrophotometer. Reproducible pseudo-first-order rate constants of up to 20 min^{-1} were obtained with the latter instrument. Experiments with AMPP were generally carried out in duplicate at each concentration of the nucleophilic reagent and a hydrolysis control, in the absence of added nucleophile, was carried out as a part of each experiment.

Measurements of pH in alkaline solutions were carried out with type B Radiometer glass or combined electrodes on solutions immediately after they had been removed from a 25° water bath. The pK values and concentrations of strongly basic amines were corrected for hydrolysis at high pH values if necessary. Determinations of pH and pK for experiments at 5° were carried out at 5.5°.

The experimental conditions for the rate determinations are summarized in Tables VII–X. The reactions of strongly basic amines with the more reactive esters were generally carried out in buffer solutions at pH values well below the pK of the amine. In order to be certain that some unexpected kinetic phenomenon was not perturbing these results, the rate constants for the reaction of AMPP with three concentrations of half-neutralized quinuclidinol and triethylenediamine solutions were measured directly in a stopped-flow apparatus. The rate constants, for the reaction of the free base form, were found to agree within 10% with those calculated from the experiments carried out at lower pH. In these experiments, 0.01 ml of a solution of 0.03 M AMPP in acetonitrile was placed in a 10-ml beaker, dissolved rapidly in 3 ml of 1 M potassium chloride added from a syringe, taken up in the same syringe, transferred to the syringe of the stopped-flow apparatus, and finally mixed with the amine.

Products. The products of the reactions of AMPP with a series of oxygen and nitrogen nucleophiles, measured by the hydroxamic acid method, are shown in Table XI. Good yields of the expected ester or amide are formed in each case; the 72% yield of acetic anhydride found from the reaction with acetate ion is in the expected range, taking account of the expected losses caused by hydrolysis of the starting material and product. *p*-Methoxypyridine N-oxide (λ_{max} 260 mμ, lit.[16] 261 mμ) was shown to be the product of the neutral hydrolysis and of the reaction with cyanide of AMPP, indicating that these reactions do not involve opening of the pyridine ring. The product of the reaction of 2,4-dinitrophenyl acetate with ethylamine was identified spectrophotometrically as 2,4-dinitrophenol; no residual color indicative of the formation of dinitroaniline remained upon acidification of a solution of the reaction products.

Table XI. Products from the Reaction of 1-Acetoxy-4-methoxypyridinium Perchlorate with Nucleophilic Reagents at 25°

Oxygen nucleophile	Reacn time, min	% ester or anhydride product[a]
Acetate, 0.1 M[b]	1	72
Phosphate, 0.05 M[c]	1	91
Phenol, 0.01 M[d]	1	95
Nitrogen nucleophile	**Reacn time, min**	**% amide product[e]**
Aniline, 0.05 M[f]	10	98
Ethylamine, 0.1 M[g]	10	86
Piperidine, 0.1 M[g]	10	100

[a] Analyzed by the hydroxamic method with neutral hydroxylamine, 10-min incubation. [b] 90% anion. [c] 50% dianion. [d] In 0.01 M borate buffer, 40% base. [e] Analyzed by the hydroxylamine method with neutral hydroxylamine for 90 min at 100°; standardized with controls of the appropriate amide. [f] 10% hydrochloride. [g] A solution of the hydrochloride in 0.1 M borate buffer, 40% base.

The yield of phenyl acetate upon hydrolysis of the phenyl acetimidate of glycine ethyl ester was measured by the hydroxamic acid method, by incubation of aliquots of the reaction mixture for 10 min at room temperature with the acidic hydroxylamine buffer used for amide determinations;[17] under these conditions, there is no significant reaction of the glycine ester group.

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