

achieved uneventfully by a multiresolution weighted tangent formula approach.²⁵ Hydrogen atoms were located on a ΔF synthesis following partial refinement of the heavy atoms. Block-diagonal least-squares refinements with anisotropic heavy atoms and isotropic hydrogens have converged to a conventional crystallographic residual of 0.043 for the observed reflections. Additional crystallographic details are available and are described in the supplementary material.

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Registry No. 1(enamine), 90941-38-1; 1-Li, 90941-39-2; 2(enamine), 90941-40-5; 2-Li, 90941-41-6; 2-Na, 90941-42-7; 2-K, 90941-43-8; 3a, 90941-44-9; 3b, 15839-54-0; 4a, 90941-45-0; 4b, 15839-55-1; 5a, 90941-46-1; 5b, 22249-31-6; 6a, 90941-47-2; 6b, 22249-30-5; 7a, 90941-48-3; 7b, 90941-49-4; 8a, 90941-50-7; 8b, 90941-51-8; 9a, 90941-52-9; 9b, 90941-53-0; 10a, 90941-54-1; 10b, 90941-55-2; 11a, 90941-56-3; 11b, 90941-57-4; 12a, 90941-58-5; 12b, 90941-59-6; 13, 5758-08-7; 14, 90941-60-9; 15, 90941-61-0; 16, 90941-62-1; 17a, 58911-79-8; 17b, 766-43-8; 18a, 66930-26-5; 18b, 766-42-7; 19a, 90941-63-2; 19b, 90941-64-3; 20a, 90941-65-4; 20b, 90941-66-5; 21a, 90941-67-6; 21b, 60774-42-7; 22a, 90941-68-7; 22b, 60774-43-8; 23a, 90941-69-8; 23b, 73751-60-7; 24a, 90941-70-1; 24b, 73751-61-8; 25, 66930-59-4.

Supplementary Material Available: Procedures for the characterization, alkylation, and stereochemical analysis of substituted cyclohexanone dimethylhydrazones and tables of fractional coordinates, bond distances, bond angles, and observed and calculated structure factors for lithiated hydrazone 25 (24 pages). Ordering information is given on any current masthead page.

(25) All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN78 and -80, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. DeClercq, and M. M. Woolfson, University of York, England, 1978; BLS78A, an anisotropic block-diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge, Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University.

Nucleophilic Reactivity toward Acetyl Chloride in Water¹

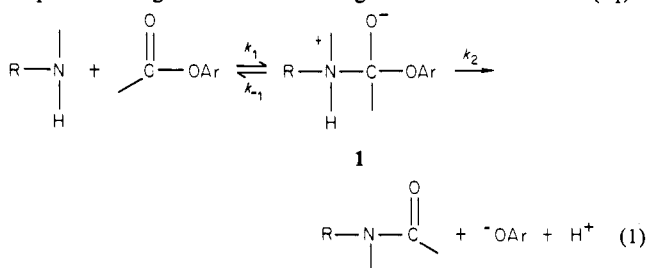
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Abstract: Rate constant ratios for the reactions of acetyl chloride with nucleophilic reagents in water containing 2.5% (v/v) dioxane were determined by product analysis. The rate constants show a small dependence on the basicity of primary amines, with $\beta_{\text{nuc}} = 0.25$, and are assigned to rate-limiting attack of the nucleophile. Pyridines with $\text{p}K_{\text{a}} > 5$ behave similarly, with $\beta_{\text{nuc}} = 0.24$, but less basic pyridines react more slowly. Several "α-effect" amines and anionic oxygen nucleophiles show small rate enhancements that are attributed to increases in the rate of nucleophilic attack. The rate constants do not fit the N_{a} correlation equation, and it is concluded that the reactions of nucleophilic reagents with acyl compounds are not satisfactorily correlated by simple modifications of this equation.

Rate constants for the uncatalyzed reactions of amines with acetate esters follow a biphasic dependence on amine basicity, with a slope of $\beta_{\text{nuc}} = 0.9 \pm 0.1$ that levels off sharply to a much smaller slope in plots of $\log k$ against $\text{p}K_{\text{a}}$ for the aminolysis of a series of substituted phenyl acetates.² The change in slope occurs when the attacking amine is ~ 5 pK units more basic than the leaving phenolate anion. After an initial incorrect assignment, because it was not appreciated that proton-transfer steps could control the direction of breakdown of the tetrahedral addition intermediate,² the reactions with $\beta_{\text{nuc}} = 0.9$ were assigned to rate-limiting breakdown of the addition intermediate (k_2 , eq 1), and the smaller slope was assigned to rate-limiting attack of the amine (k_1).³



The experiments reported here were carried out to determine the value of β_{nuc} for rate-limiting attack of amines on acetate derivatives. The value of $\beta_{\text{nuc}} = 0.9 \pm 0.1$ for rate-limiting breakdown of the intermediate is well established and is consistent with the expected amount of charge development on the nitrogen atom in the transition state for cleavage of the tetrahedral addition intermediate, 1, but the range in which amine attack is rate limiting is too small to establish a reliable value of β_{nuc} for the attack of amines on acetate esters.² A value of $\beta_{\text{nuc}} = 0.2-0.4$ was estimated from the data for phenyl acetates,³ and values in this range have been reported for reactions of basic amines with acetic anhydride,^{4,5} methyl chloroformate,⁶ diphenyl carbonates,⁷ and penicillins.⁸

However, a computer-assisted analysis of rate constants for the aminolysis of phenyl acetates, based on the N_{a} scale of nucleophilic reactivity for reactions with carbocations, led to the conclusion that the attack of amines on esters follows N_{a} and has a larger

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value of β_{nuc} .⁹ This analysis also led to assignments of rate-limiting steps that were different from previous assignments.

We have examined the reactions of a series of amines with acetyl chloride because we expected that chloride ion would be a sufficiently good leaving group¹⁰ that amine attack would be rate limiting for most amines ($k_2 > k_{-1}$, eq 1). The results are consistent with our original estimate of β_{nuc} for rate-limiting amine attack. Rate constants for reactions of several "α-effect" and oxygen anion nucleophiles with acetyl chloride are also reported.

Experimental Section

Acetyl chloride was refluxed with phosphorus pentachloride, distilled after addition of *N,N*-dimethylaniline, and stored over molecular sieves. 4-Nitropyridine was prepared by reduction of the *N*-oxide.¹¹ Dioxane was distilled from sodium and stored over molecular sieves. Other organic reagents and hydroxylammonium chloride were recrystallized or distilled before use. Reagent grade inorganic salts were used without further purification. Glass-distilled water was used throughout.

Solutions of reagents were prepared on the day of use. Solutions of acetyl chloride in dioxane were kept stoppered and used within <30 min. These solutions were shown to be free of acetic anhydride on a number of occasions by quenching with water and immediately adding concentrated hydroxylamine, as described below.

Pseudo-first-order rate constants for reactions of acetyl chloride with a large excess of nucleophilic reagents were obtained from product analysis and the rate constant for hydrolysis of acetyl chloride. Reactions were carried out by rapid mixing of acetyl chloride in 0.1 mL of dioxane with 4.0 mL of an aqueous solution containing the nucleophilic reagent. The solutions were added to a 10-mL glass syringe and a 0.25-mL Hamilton syringe using three-way valves and were mixed by rapid injection of the two solutions into a mixing chamber, using a common bar and manual driving of the syringes. The mixing chamber was connected to the syringes through a Delrin block containing holes of 2.2 and 0.41 mm diameter. These two holes connected with the two ends of a double diamond mixing chamber. The mixing chamber consisted of 0.41 × 1 mm and 2 × 2.77 mm channels that were cut into a 6 × 60 × 25 mm block of Delrin. Mixing and exit occurred in a 2.2 mm diameter hole in the center. These two blocks were tightly clamped together. The exit from the mixing chamber was connected to a short length of plastic tubing that carried the mixed solution to a collection tube. In some experiments the collection tube contained a quenching solution. Some preliminary experiments were carried out by rapid injection of 0.15 mL of acetyl chloride in dioxane, using a Hamilton CR-700-200 spring-loaded syringe, into 5 mL of an aqueous solution of the nucleophilic reagent that was being rapidly stirred.

All experiments were carried out at 22 ± 2 °C. Second-order rate constants were obtained from the slopes of plots of five or more observed pseudo-first-order rate constants against the concentration of nucleophile unless otherwise indicated. The pseudo-first-order rate constants were obtained from duplicate or, usually, triplicate measurements. The products of the reactions with different nucleophilic reagents were analyzed as follows.

Hydroxylamine. Acetyl chloride acylates hydroxylamine at both the N and O atoms. The *N*-acetylated product was analyzed spectrophotometrically at 540 nm as the acetohydroxamic acid–ferric chloride complex,¹² and the sum of the products was determined by conversion of the *O*-acyl to *N*-acyl product by incubation with hydroxylamine. Acetohydroxamic acid formation was measured by quenching the reaction mixture in 4 mL of 1 M hydrochloric acid in the collection tube. This solution was mixed with an equal volume of 10% FeCl₃ in 2 M HCl and the absorbance was read at 540 nm against a blank prepared in the same way but with dioxane instead of the acetyl chloride solution. An identical run was quenched with 2 M hydroxylamine (85% free base) instead of hydrochloric acid in the collection tube. The solution was allowed to stand for 10 min to convert *O*-acetylhydroxylamine to acetohydroxamic acid and was then assayed with ferric chloride. The yield of *O*-acetylhydroxylamine was obtained by subtraction of the concentration of acetohydroxamic acid formed initially from the total acetohydroxamic acid after this incubation. The total acetyl chloride concentration was obtained by mixing acetyl chloride with 2 M hydroxylamine (85% free base) directly, which gives a quantitative yield of the hydroxamic acid. The difference between the yield of hydroxamic acid and the total acetyl chloride concentration in a particular experiment gives the yield of acetic

acid and hence the product ratio and first-order rate constant. These reactions were carried out in phosphate buffers and the results were corrected for the formation of acetyl phosphate (<5%), measured in separate experiments.

Aniline. The reaction of aniline with acetyl chloride was studied by measuring the yield of acetanilide spectrophotometrically or by competition with hydroxylamine, by measurement of acetohydroxamic acid formation. Acetanilide formation was determined spectrophotometrically at 236 nm, using extinction coefficients of 9800 for acetanilide and 60 for aniline in 1 M hydrochloric acid under the conditions of the experiments. The acetyl chloride concentration was determined by adding an aliquot of the acetyl chloride solution to 1% aniline in 5:95 water:dioxane (v/v), which gave complete conversion to acetanilide. One set of experiments was carried out with the Hamilton spring-loaded syringe in 50% aqueous dioxane (v/v) at several concentrations of acetyl chloride. The rate constant was calculated from the product ratios and a value of 17 s⁻¹ for hydrolysis in this solvent at 23 °C.¹³⁻¹⁵

Competition between aniline and hydroxylamine was carried out at a series of aniline concentrations with quenching of the reaction mixtures into 2 M hydroxylamine, 85% free base, followed by incubation for 10 min and analysis for hydroxamic acid as described above. Rate constants were obtained from the product ratios and the rate constant for reaction with hydroxylamine, 37 000 M⁻¹ s⁻¹ (see below), as described in eq 2.

$$\frac{[\text{CH}_3\text{CONHOH}]}{[\text{CH}_3\text{COOH}] + [\text{CH}_3\text{CONHPh}]} = \frac{k_{\text{NH}_2\text{OH}}[\text{NH}_2\text{OH}]}{k_{\text{h}} + k_{\text{An}}[\text{PhNH}_2]} \quad (2)$$

The total concentration of acetyl chloride was measured in a similar experiment by mixing with 2 M hydroxylamine, 85% free base.

Primary Aliphatic Amines, Hydrazine, Methoxyamine, and Semicarbazide. The reactions of these compounds with acetyl chloride were studied by the hydroxylamine competition method described for aniline. Above pH 8, the hydroxylamine reaction is faster because of base catalysis. The second-order rate constants for reaction with hydroxylamine were determined at a series of pH values between pH 8 and 11 in borate buffers. The observed rate constant was found to be independent of the concentration of borate buffer.

The assay of hydroxamic acid formation in the presence of glycineamide was limited to exactly 5 min incubation with 2 M hydroxylamine (85% free base) and was corrected for the small amount of reaction of hydroxylamine with glycineamide under these conditions. No hydroxamic acid was formed from glycineamide and 0.05 M hydroxylamine in the reaction mixtures in the absence of acetyl chloride. Care was taken to avoid evaporation of trifluoroethylamine from reaction solutions.

Pyridines. The reactions of acetyl chloride with pyridines were followed by trapping the acetylpyridinium ion with inorganic phosphate to give acetyl phosphate, which was analyzed as the hydroxamic acid. A solution of the pyridine in phosphate buffer was mixed with a solution of acetyl chloride in dioxane as described above. After 30 s an equal volume of 2 M hydroxylamine (85% free base) was added to the collection tube to form the hydroxamic acid, which was analyzed with ferric chloride after 10 min as described above. The incubation was reduced to exactly 5 min for nicotinamide. The concentration of phosphate was varied to give a concentration that trapped all of the acetylpyridinium ion. In one experiment with pyridine the acetylpyridinium ion was trapped with dilute hydroxylamine in the reaction mixture. The yields were corrected for direct acylation of phosphate (or hydroxylamine) by acetyl chloride (≤5% of total products).

Phosphate was not an effective trapping agent above pH 9 for the reaction with 4-(dimethylamino)pyridine and the *N*₁-acetyl-4-(dimethylamino)pyridinium ion was trapped directly with an equal volume of 2 M hydroxylamine (85% free base) in the collection tube after mixing of the reaction solutions, followed by assay of hydroxamic acid formation as described above.

The quenching time of ≤50 ms was estimated by reacting acetyl chloride with 3,4-dimethylpyridine (in the absence of phosphate) and quenching with 2 M hydroxylamine (85% free base) in the collection tube. The yield of hydroxamic acid from the reaction with *N*-acetyl-3,4-dimethylpyridinium ion was found to be 90% of that expected from the rate constant for reaction of 3,4-dimethylpyridine with acetyl chloride. This shows that quenching captures approximately 90% of the acetyl-3,4-dimethylpyridinium ion before hydrolysis and gives a quenching time of ≤50 ms from the known rate of hydrolysis of this ion.¹⁶

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No hydroxamic acid was obtained from acetyl chloride in the absence of the pyridine.

Imidazole. The reaction of acetyl chloride with imidazole was examined by trapping acetylimidazole with 2 M hydroxylamine (85% free base) in the collection tube and assaying the acetohydroxamic acid as described above.

Hydroxide, Trifluoroethoxide, Acetohydroxamate, and Hydrogen Peroxide Anions. Rate constants for the reactions of these anions with acetyl chloride were measured by competition with aniline at pH ≥ 12.7 with hydroxide ion as the buffering species. The rate constants were obtained from the yields of acetanilide according to eq 3. The rate

$$\frac{[\text{CH}_3\text{COCl}] - [\text{CH}_3\text{CONHPh}]}{[\text{CH}_3\text{CONHPh}]} = \frac{k_h + k_{\text{OH}^-}[\text{OH}^-] + k_{\text{RO}^-}[\text{RO}^-]}{k_{\text{An}}} \quad (3)$$

constant for the reaction of acetyl chloride with aniline was measured at the pH of every experiment and found to be the same as that obtained at neutral pH; i.e., there is no significant base catalysis of this reaction. The reactions were quenched with excess hydrochloric acid in the collection tube. Hydrogen peroxide solutions were prepared immediately before use and were titrated with permanganate.¹⁷ It was shown that the acylated peroxide anion did not react with aniline, by varying the interval between reaction and quenching.

Acetate and Phosphate. The reactions of acetyl chloride with acetate and phosphate anions were measured by injecting 150 μL of a solution of acetyl chloride in dioxane from a Hamilton spring-loaded syringe into 5 mL of reaction solution, which was rapidly stirred. This was followed immediately by quenching with 5 mL of 2 M hydroxylamine (85% free base), which was followed by incubation for 10 min and determination of hydroxamic acid as described above. Delays of 5 s and 1 min before quenching gave decreases in the yield of acetohydroxamic acid from acetic anhydride of 0 and 9%, respectively. The concentration of acetyl chloride was determined by injection of the acetyl chloride solution directly into 2 M hydroxylamine (85% free base). The color yield of acetohydroxamic acid was shown to be independent of the concentration of chloride ion and the acidity over the range used in the experiments.

Results

Determination of Rate Constants. Pseudo-first-order rate constants for reactions of acetyl chloride with nucleophilic reagents were measured by product analysis under conditions in which reaction with the nucleophile is competitive with hydrolysis. Rate constants were calculated from product ratios and a value of $k_h = 1100 \text{ s}^{-1}$ for the hydrolysis of acetyl chloride in water. A rate constant of $k_h = 1500 \text{ s}^{-1}$ at 27 °C was obtained from extrapolation of a linear correlation of $\log k_h$ in a series of dioxane-water mixtures against Y values,¹⁸ with a slope of $m = 0.81$; the observed values of k_h are in the range 0.31–292 s^{-1} .¹³ This value was corrected to 22 °C using a value of $\Delta H^\ddagger = 14 \text{ kcal mol}^{-1}$ that is based on values of $\Delta H^\ddagger = 13.2, 14.1, \text{ and } 14.3 \text{ kcal mol}^{-1}$ in 12.3, 14.1, and 29.7% dioxane, respectively.¹⁵ Rate constant ratios $k_h/k_{\text{nuc}}[\text{nuc}]$ were obtained from measured product ratios $[\text{AcOH}]/[\text{Ac-nuc}]$ as described in the Experimental Section. Reactions of amines and basis oxygen anions were measured by competition with the reactions of hydroxylamine or aniline. The experimental conditions and results are summarized in Table I.

The most difficult experimental problem in the measurement of these rate constants is to obtain adequate mixing of the solution of acetyl chloride in dioxane with the aqueous reaction mixture. The following evidence shows that the rate constants obtained with the rapid-mixing apparatus are not determined by the rate of mixing.

(1) The rate constants are self-consistent, reproducible, and independent of the rate of flow through the mixing chamber.

(2) The rate constants are independent of the concentration of acetyl chloride over a twofold range and increase linearly with the concentration of added nucleophilic reagents in all cases, except for the reaction with imidazole.

(3) The rate constants are independent of the concentration of added buffer.

(4) The pattern of nucleophilic reactivity follows the expected nucleophilic order for reactions with acyl compounds; in particular, “ α -effect” compounds show increased reaction rates.

(5) The same rate constant was obtained for the reaction of phosphate dianion with the rapid mixing apparatus and with the spring-loaded syringe, which gives less efficient mixing.

(6) The observed second-order rate constants differ over a range of 7000-fold.

We conclude that the rate constants are reliable, but not precise; they appear to be satisfactory for structure–reactivity correlations. Uncertainties in the absolute values of the rate constants arise from the extrapolation of $\log k_h$, correction of k_h from 27 to 22 °C with a value of ΔH^\ddagger determined in aqueous dioxane, and the possibility that some reaction occurs before the concentration of dioxane is uniform throughout the solution. The largest uncertainty presumably holds for the largest rate constants, for the reactions of hydrogen peroxide and acetohydroxamate anions; however, these rate constants are only slightly larger than those for basic pyridines, which show no downward deviation from a structure–reactivity correlation.

Initial experiments in which acetyl chloride in dioxane was injected from a spring-loaded syringe into a stirred solution of nucleophilic reagent in water gave inadequate mixing and low rate constants. The product ratios were found to be independent of the stirring rate and the volume of added acetyl chloride solution. However, the product ratios and calculated second-order rate constants were found to increase as the concentration of acetyl chloride was decreased and as the concentrations of nucleophile and of buffer were increased. This resulted in upward curvature in plots of k_{obsd} against nucleophile concentration and increases in k_{obsd} with increasing buffer concentration that could be mistaken for general base catalysis of the nucleophilic reaction. These results can be explained by release of acid from the hydrolysis of acetyl chloride that protonates the nucleophilic reagent and inhibits its reaction; it is less important at lower concentrations of acetyl chloride and at higher concentrations of buffer or nucleophile.

A rate constant of 950 $\text{M}^{-1} \text{ s}^{-1}$ was obtained for the reaction of acetyl chloride with aniline in 50% dioxane (v/v) at 23 °C using the spring-loaded syringe. This is in reasonable agreement with a reported value of 1490 $\text{M}^{-1} \text{ s}^{-1}$ at 26 °C in the same solvent.¹³ The slower rate of hydrolysis in this solvent presumably allows better mixing before reaction occurs.

Hydroxylamine. Acetyl chloride reacts with both the nitrogen and oxygen atoms of hydroxylamine, as do other acylating agents.¹⁹ The rate constants for N- and O-acylation are 28 000 and 8900 $\text{M}^{-1} \text{ s}^{-1}$, respectively.

Figure 1A shows the nonlinear increase in k_{obsd} with increasing hydroxylamine concentration for reaction of 0.01 M acetyl chloride that is caused by inadequate buffering and mixing with the rapid-injection syringe technique. Figure 1B shows the linear increase in rate with 0.0012 M acetyl chloride in the presence of 0.12 M phosphate buffer, using the rapid mixing apparatus.

The rate constant for the reaction of hydroxylamine with acetyl chloride was found to show an increase at pH values above 8. The results are consistent with a rate constant on the order of $2 \times 10^8 \text{ M}^{-2} \text{ s}^{-1}$ for a reaction catalyzed by hydroxide ion, or $10^8 \text{ M}^{-1} \text{ s}^{-1}$ for hydroxylamine anion ($\text{p}K_a = 13.7$),²⁰ but quantitative determination of this rate constant was not attempted. The reaction presumably represents acylation of the hydroxylamine anion; no buffer catalysis was observed.

Other Amines. The rate constant for the reaction of acetyl chloride with aniline was determined by measurement of the yield of acetanilide and by competition with the formation of acetohydroxamic acid in the presence of hydroxylamine. The two methods gave rate constants of 9500 and 9600 $\text{M}^{-1} \text{ s}^{-1}$ that agree well (Table I).

Rate constants for the reactions of primary aliphatic amines and of the “ α -effect” compounds hydrazine, methoxyamine, and

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Table I. Rate Constants for Reactions of Nucleophilic Reagents with Acetyl Chloride^a

	nucleophile	[nuc], ^b M	pH	[AcCl], M	pK _a ^c	k ₂ , M ⁻¹ s ⁻¹	conditions
1	hydroxylamine	0.0074– 0.0378	7.26	1.20 × 10 ⁻³	6.17 ^d	37 000 ^e	0.12 M phosphate
2	aniline	0.035– 0.175	7.44	9.08 × 10 ⁻⁴	4.85 ^d	9 600 ^f	0.05 M NH ₂ OH 0.3 M phosphate
		0.025– 0.165	6.87	1.02 × 10 ⁻³		9 500 ^g	0.08 M phosphate
		0.0087		2.64 × 10 ⁻⁴ – 1.22 × 10 ⁻³		690 ^{g,h}	
3	imidazole	0.048– 0.502	7.45	8.34 × 10 ⁻⁴	7.21 ^d		0.12 M phosphate
		0.064– 0.805	7.83	1.16 × 10 ⁻³		1 300 ⁱ	
4	ethylamine	0.0035– 0.0486	11.07	6.92 × 10 ⁻⁴	10.97 ^d	83 000	0.06 NH ₂ OH 0.2 M phosphate
5	ethylenediamine	0.010– 0.107	10.29	1.01 × 10 ⁻³	10.18 ^d	73 000	0.06 M NH ₂ OH
6	ethanolamine	0.030– 0.196	9.57	1.10 × 10 ⁻³	9.87 ^j	44 000	0.16 M NH ₂ OH
7	methoxyethylamine	0.033– 0.275	9.60	9.49 × 10 ⁻⁴	9.72 ^d	45 000	0.16 M NH ₂ OH
		0.040– 0.240	9.70	1.04 × 10 ⁻³		43 000	0.04–0.24 M NH ₂ OH ^k
8	glycinamide	0.0083– 0.0845	9.03	7.70 × 10 ⁻⁴	8.32 ^j	23 000	0.025 M NH ₂ OH 0.048 M borax ^l
9	ethylenediamine H ⁺	0.037– 0.245	7.84	7.79 × 10 ⁻⁴	7.42 ^d	13 000 ^m	0.04 M NH ₂ OH
10	trifluoroethylamine	0.0186– 0.171	5.75	9.75 × 10 ⁻⁴	5.84 ^d	4 800	0.028 M NH ₂ OH
11	methoxyamine	0.064– 0.664	5.98	7.95 × 10 ⁻⁴	4.72 ⁿ	2 300	0.07 M NH ₂ OH ^o 0.07 M phosphate
12	hydrazine	0.0013– 0.016	7.48	1.04 × 10 ⁻³	8.20 ^d	153 000	0.02 M NH ₂ OH 0.15 M phosphate
13	semicarbazide	0.073– 0.545	6.42	1.28 × 10 ⁻³	3.86 ^d	1 400	0.04 M NH ₂ OH ^o 0.15 M phosphate
14	4-nitropyridine	0.05– 0.20	6.64	3.83 × 10 ⁻³	1.75 ^p	310	0.2 M phosphate
15	3-chloropyridine	0.03– 0.15	6.51	2.61 × 10 ⁻³	3.30 ^q	1 750	0.2 M phosphate
16	nicotinamide	0.02– 0.20	7.15	1.28 × 10 ⁻³	3.55 ^q	2 600	0.077 M phosphate
17	pyridine	0.024– 0.143	6.01	6.04 × 10 ⁻⁴	5.51 ^d	14 100	2.05 × 10 ⁻³ M NH ₂ OH ^o
		0.024– 0.143	7.63	3.75 × 10 ⁻⁴		13 900	0.071 M phosphate
18	4-methylpyridine	0.0198– 0.0966	6.31	8.95 × 10 ⁻⁴	6.33 ^r	21 700	0.28 M phosphate
19	3,4-dimethylpyridine	0.0032– 0.0384	7.88	8.20 × 10 ⁻⁴	6.79 ^r	25 000	0.069 M phosphate
20	4-(dimethylamino)pyridine	0.0643– 0.096	9.13– 9.92	4.74 × 10 ⁻⁴ – 1.09 × 10 ⁻³	10.07 ^s	160 000	t
21	hydroxide ion	0.08– 0.64	>12.8	3.59 × 10 ⁻³	15.74	6 250	0.08 M aniline
22	hydrogen peroxide anion	0.00091– 0.00638	12.7	1.18 × 10 ⁻³	11.6 ^d	528 000	0.12 M aniline 0.08 M OH ⁻
23	trifluoroethoxide anion	0.0036– 0.0467	12.8	9.83 × 10 ⁻⁴	12.4 ^d	89 000	0.09 M aniline 0.08 M OH ⁻
24	acetohydroxamate anion	0.0032– 0.032	12.8	1.51 × 10 ⁻³	9.37 ^d	217 000	0.16 M aniline 0.08 M OH ⁻
25	acetate	0.86 ^u	4.63	4.00 × 10 ⁻³ – 2.54 × 10 ⁻²	4.61 ^d	153 ^v	
	phosphate	0.50 ^{u,w}	5.8– 7.3	4 × 10 ⁻²			
26	monoanion				1.72 ⁿ	77	
27	dianion				6.49 ⁿ	128	
	water				-1.74	20 ^x	

^a In water containing 2.5 vol % dioxane at 22 ± 2 °C and ionic strength maintained at 1.0 with potassium chloride. ^b Concentration of the reactive ionic species of the nucleophilic reagent. ^c At ionic strength 1.0, except for basic oxygen anions. ^d Reference 2. ^e The ratio of N-acylation to O-acylation was found to be 3:1; therefore $k_{2(N)} = 28\,000$, $k_{2(O)} = 8900$. ^f Obtained by competition with hydroxylamine. ^g Obtained by direct measurement of acetanilide. ^h Solvent: 50% aq dioxane (v/v). ⁱ There is also an apparent third-order term with $k_3 = 1540\text{ M}^{-2}\text{ s}^{-1}$. ^j Determined from the pH of partially neutralized solutions. ^k Equal concentrations of free NH₂OH and CH₃OEtNH₂ in each run. ^l In a control experiment it was shown that this concentration of borax does not reduce the yield of acetohydroxamic acid formed by reaction of acetyl chloride with 0.025 M hydroxylamine at pH 9.03. ^m The observed rate constant was corrected by 4% for reaction of the free base. ⁿ Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436–1449. ^o [NH₂OH] + [NH₃OH⁺]. ^p Determined in dilute hydrochloric acid solutions by measurement of acid–base ratios at 280 nm. ^q Reference 3. ^r Reference 16. ^s Determined in carbonate buffers by measurement of acid–base ratios at 281 nm. ^t Reactions were carried out in 0.05–0.30 M carbonate buffers at pH 9.1, 9.5, 9.6, and 9.9, with hydroxylamine (2 M, 85% base) present in the collection tube; see text. ^u Measured with the spring-loaded syringe at ionic strength = 2.0 (KCl). ^v An experiment with 0.4–2.0 M [AcOH + AcO⁻] and 0.036 M [AcCl] at pH 3.8 showed more scatter in the data and gave $k_2 = 120\text{ M}^{-1}\text{ s}^{-1}$. ^w Total phosphate concentration; the pH was varied. ^x Extrapolated from the data of Hudson and Moss,¹³ corrected to 22 °C with $\Delta H^\ddagger = 14\text{ kcal mol}^{-1}$,¹⁴ and divided by 55.5 M.

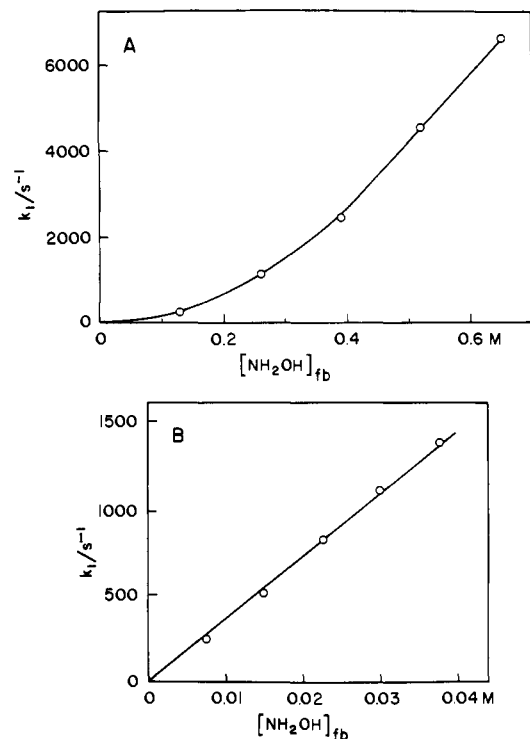


Figure 1. The dependence of first-order rate constants for the reaction of acetyl chloride with hydroxylamine on the concentration of hydroxylamine base at ionic strength 1.0 (KCl). The rate constants are for the sum of N- and O-acylation. (A) At pH 6.35 with 0.01 M acetyl chloride, using the rapid-injection syringe. The line is curved because of inadequate buffering. (B) At pH 7.26 with 0.12 M potassium phosphate buffer and 0.0012 M acetyl chloride, using the rapid-mixing apparatus.

semicarbazide were determined by the competition method with hydroxylamine (Table I). Results for the reaction with methoxyethylamine are shown in Figure 2A.

Rate constants for the reactions of acetyl chloride with pyridines were determined by trapping the acetylpyridinium ion intermediate with phosphate and analyzing acetyl phosphate as the hydroxamic acid. Trapping with phosphate is possible because the selectivity of the acetylpyridinium ions toward phosphate compared with water is much larger than that of acetyl chloride. Results for the reaction with 3-chloropyridine are illustrated in Figure 2B and the rate constants are summarized in Table I. Linear plots of k_{obsd} against pyridine concentration were obtained in every case, without correction for self-association or activity coefficient changes of the pyridines.¹⁶ A rate constant of $14\,100\ M^{-1}\ s^{-1}$ was obtained for the reaction with pyridine using hydroxylamine as a trapping reagent, which agrees well with the value of $13\,900\ M^{-1}\ s^{-1}$ that was obtained by trapping with phosphate.

The reaction with the basic 4-(dimethylamino)pyridine could not be followed satisfactorily by this method. An approximate rate constant of $1.6 \times 10^5\ M^{-1}\ s^{-1}$ was obtained by analyzing the acetylpyridinium ion directly as the hydroxamic acid after reaction in a series of carbonate buffers. The rate constant was obtained by extrapolation of the apparent rate constants to zero buffer concentration in order to correct for reaction with the carbonate buffer, which gives hydrolysis. There is a negative deviation of the points at low buffer concentration that arises from inadequate buffering and protonation of the nucleophile, as described above, and a smaller rate constant was obtained at pH 9.9, which probably arises from hydrolysis of the N_1 -acetyl-4-(dimethylamino)pyridinium ion at this pH in the period of ~ 50 ms between its formation and its quenching with hydroxylamine buffer in the collection tube. Approximate rates of hydrolysis, estimated from the data of Guibe-Jampel and Wakselman²¹ ($k \sim 0.05\ s^{-1}$ at pH

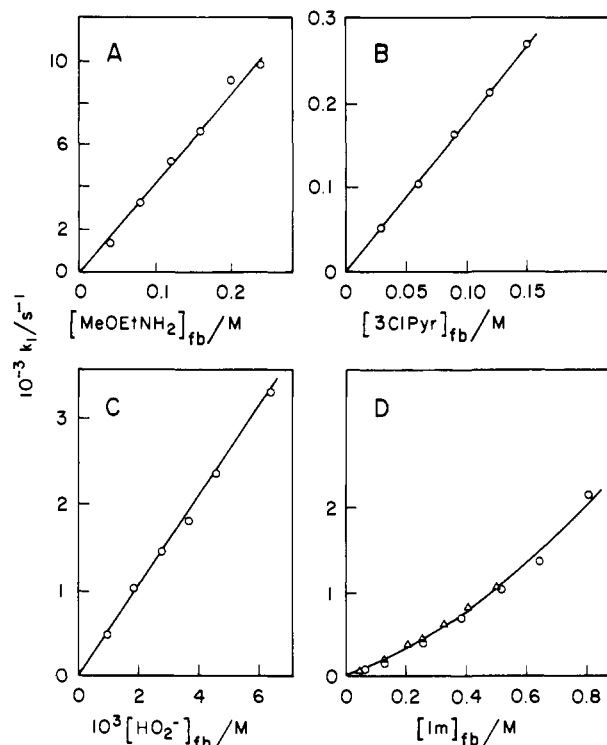


Figure 2. The dependence of first-order rate constants for reactions of acetyl chloride on the concentration of nucleophilic reagents at ionic strength 1.0 (KCl). (A) Methoxyethylamine at pH 9.60 with $9.5 \times 10^{-4}\ M$ acetyl chloride and 0.16 M hydroxylamine. (B) 3-Chloropyridine at pH 6.51 with $2.6 \times 10^{-3}\ M$ acetyl chloride and 0.2 M phosphate buffer. (C) Hydrogen peroxide anion at pH 12.7 with $1.2 \times 10^{-3}\ M$ acetyl chloride, 0.12 M aniline, and 0.08 M potassium hydroxide. (D) Imidazole in the presence of 0.12 M phosphate at pH 7.45 with $8.3 \times 10^{-4}\ M$ acetyl chloride (Δ) or pH 7.83 with $1.2 \times 10^{-3}\ M$ acetyl chloride (\circ). The line was calculated from the rate constants in Table I.

8), are consistent with this explanation.

The reaction with imidazole was followed by determination of the acetylimidazole product as the hydroxamic acid. The first-order rate constants for this reaction exhibit upward curvature at high concentrations of imidazole base, as shown in Figure 2D. The reason for this is not known. It probably does not represent inadequate buffering or mixing because the solutions were well buffered and linear plots were obtained at comparable or lower buffer concentrations with several other nucleophiles. The pseudo-first-order rate constants for the reactions with methoxyamine and semicarbazide showed no upward curvature at concentrations up to 0.7 and 0.6 M, respectively. A second-order rate constant of $1300\ M^{-1}\ s^{-1}$ for imidazole was obtained by extrapolation of $k_{obsd}/[imidazole]$ to zero imidazole concentration. The curvature could be described by a third-order term in the rate law with $k_3 = k_{obsd}/[imidazole]^2 = 1540\ M^{-2}\ s^{-1}$.

Oxygen Anions. Rate constants for the reactions of acetyl chloride with hydroxide, trifluoroethoxide, hydrogen peroxide, and acetohydroxamate anions were obtained in the presence of excess hydroxide ion, which acted as a buffer, by competition with aniline. A value of $k_2 = 8800\ M^{-1}\ s^{-1}$ that was obtained for the reaction with aniline in the presence of hydroxide ion at pH 12.85 does not differ significantly from the value of $9500\ M^{-1}\ s^{-1}$ measured at pH 6.87. This result and the constant value of k_2 for hydroxide ion in the range 0.08–0.64 M $[HO^-]$ in the presence of 0.08 M aniline (Table I) show that there is no significant catalysis of the reaction with aniline by hydroxide ion. The results with hydrogen

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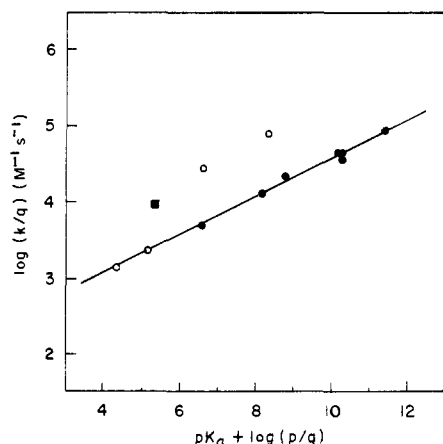


Figure 3. Dependence on amine basicity of the rate constants for reactions of acetyl chloride with primary amines in water containing 2.5% dioxane, ionic strength 1.0, 22 °C: primary aliphatic amines, ●; semicarbazide, methoxyamine, hydroxylamine, and hydrazine, ○; aniline, ■.

peroxide anion are illustrated in Figure 2C and the rate constants are given in Table I.

Rate constants for reactions with acetate ion and with phosphate monoanion and dianion were determined by injection of acetyl chloride in dioxane from a spring-loaded syringe into concentrated acetate or phosphate buffer solutions, followed immediately by addition of hydroxylamine to convert acetic anhydride or acetyl phosphate into the hydroxamic acid. Rate constants obtained by this method were found to be independent of the concentration of acetyl chloride and gave linear plots against the concentrations of acetate and phosphate anions, because of the low reactivity and high buffering capacity of the concentrated solutions. The same rate constant was obtained for phosphate using the rapid mixing apparatus. The rate constants for phosphate monoanion and dianion were obtained from the ordinate intercepts of a plot of the observed second-order rate constants obtained with a series of different buffer ratios against the fraction of phosphate dianion in the buffer.

Discussion

The reactions of acetyl chloride with nucleophilic reagents show the behavior that is expected for straightforward bimolecular substitution reactions of a reactive acylating agent. The reaction with aniline has been shown directly to be second order in 50% dioxane-water,¹³ and there is strong evidence supporting a bimolecular mechanism for substitution reactions of methyl chloroformate and related compounds.^{6,22} Bimolecular reactions through ion-pair intermediates with nucleophiles of widely varying reactivity are inconsistent with the low stability and short lifetime for diffusional separation of ion pairs in aqueous solution.²³

The Brønsted-type plot for the reactions of primary amines with acetyl chloride, Figure 3, shows the expected pattern for the reactions of an active acetyl compound with a good leaving group. The slope of $\beta_{\text{nuc}} = 0.25$ fits the rate constants for aliphatic amines (solid circles) and for methoxyamine and semicarbazide. The "α-effect" compounds hydrazine and hydroxylamine react five times faster and aniline reacts four times faster than ordinary amines.

The value of $\beta_{\text{nuc}} = 0.25$ agrees with the value of 0.2 ± 0.2 proposed by Satterthwait and Jencks for the reactions of amines with acyl compounds when nucleophilic attack is rate limiting (class I reactions).³ It means that the change in "effective charge" that is seen by polar substituents on the attacking amine upon reaching the transition state for nucleophilic attack is one-quarter

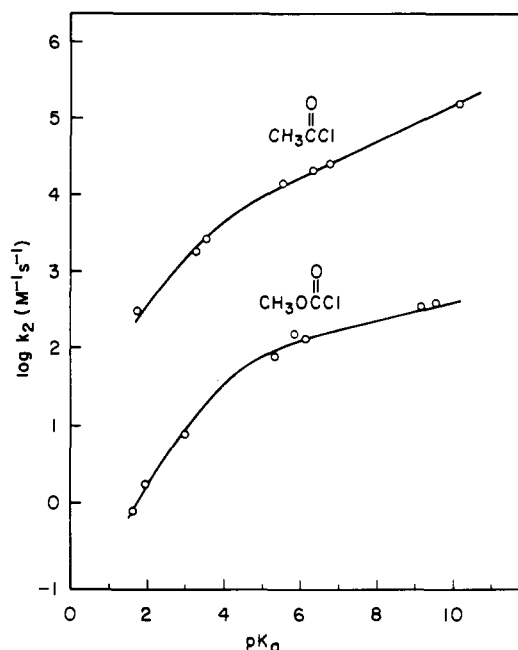


Figure 4. Dependence on basicity of the rate constants for the reactions of substituted pyridines with acetyl chloride and with methyl chloroformate⁶ in aqueous solution. The solid lines were calculated for a change in rate-limiting step with increasing basicity of the pyridine, as described in the text.

as large as the change in charge in the reference protonation reaction. It is consistent with the small dependence on basicity of the rate constants for reactions of basic primary, secondary, and tertiary amines with AMPP (1-acetoxy-4-methoxypyridinium perchlorate),² and with well-defined values of $\beta_{\text{nuc}} = 0.3$ for rate-limiting attack and 1.0 for rate-limiting breakdown in the aminolysis of substituted diphenyl carbonates.⁷ The assignments of rate-limiting steps for the reactions of diaryl carbonates have been confirmed by determination of the products formed when the addition intermediates are generated by a different route.²⁴ It also agrees with the value of $\beta_{\text{nuc}} = 0.3$ for rate-limiting attack in the aminolysis of benzylpenicillin and 6-aminopenicillanic acid.⁸

The reaction of methyl chloroformate with basic pyridines gives a similar value of $\beta_{\text{nuc}} = 0.12-0.16$,⁶ but the Brønsted plot for the reactions of primary amines is curved.²⁵ The plots for reactions of pyridines with acetic anhydride⁴ and for the aminolysis of succinic and phthalic anhydride⁵ show clearcut biphasic behavior with breaks at $pK_a = 6.1$ and 8.5 , respectively. The two parts of the curves may be assigned to rate-limiting attack with $\beta_{\text{nuc}} = 0.2$ (based on limited data) and rate-limiting breakdown with $\beta_{\text{nuc}} = 0.8-1.0$. Other data are consistent with values of $\beta_{\text{nuc}} = 0.46$ for acetic anhydride,²⁶ $0.2-0.3$ for basic amines and acetic anhydride,²⁷ 0.4 for diethyl pyrocarbonate,²⁸ and 0.6 for Leuchs' anhydride,²⁹ but these values probably represent rate constants in the region in which a single step is not rate limiting.

The rate constants for the reactions of *N*-acetylpyridinium ions with amines of pK_a up to 9 are in the same range as those for acetyl chloride, but show a value of $\beta_{\text{nuc}} = 0.9$, while the rate constants for more basic amines show a sharp break in the curve to a small dependence on the basicity of the nucleophile.¹⁶ These reactions may be assigned to rate-limiting breakdown of the intermediate for weakly basic amines with a change to rate-limiting attack for

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basic amines. Rate-limiting breakdown is presumably favored by the *push* for expulsion of the attacking amine that is provided by electron donation by resonance from the remaining pyridine.

Pyridines of $pK_a > 5$ react with acetyl chloride four times faster than primary amines and show a similar value of $\beta_{\text{nuc}} = 0.24$, as shown in the upper line of Figure 4. However, less basic pyridines react more slowly and give a downward curvature in the correlation. Very similar behavior was observed by Bond, Castro, and Moodie for the reactions of pyridines with methyl chloroformate, as shown in the lower line of Figure 4, and was ascribed to a change in rate-limiting step from nucleophilic attack with basic pyridines to expulsion of the leaving chloride ion with weakly basic pyridines.⁶ The rate constants for the reactions of acetyl chloride are consistent with the upper solid line in the figure, which was calculated for a two-step reaction with values of $\beta_{\text{nuc}} = 0.24$ and 0.8 according to eq 4–6.⁷ The rate constant k_b is the observed

$$\log k_1 = 0.24pK + 2.94 \quad (4)$$

$$\log k_b = 0.80pK + 1.2 \quad (5)$$

$$k_{\text{obsd}} = k_1 k_b / (k_1 + k_b) \quad (6)$$

rate constant when breakdown of the intermediate is rate limiting. The data for methyl chloroformate can be fit with the same value of $\beta_{\text{nuc}} = 0.8$ and a smaller value of $\beta_{\text{nuc}} = 0.12$ for rate-limiting attack (lower line); they are also consistent with the values of $\beta_{\text{nuc}} = 0.93$ and 0.15 reported previously.⁶

The break in both curves, which corresponds to the change in rate-limiting step, occurs with pyridines of $pK_a = 3.6$. This means that chloride ion and a pyridine of $pK_a \sim 3.6$ are expelled from the tetrahedral addition intermediate at equal rates; i.e., they have the same leaving group ability in this system in spite of the much greater basicity of the pyridine, according to this model. This conclusion is somewhat less surprising in view of the facts that acetyl chloride and *N*-acetylpyridinium ions have similar reactivities¹⁶ and chloride has a significant ability to donate electrons by resonance. Relative leaving abilities from addition intermediates are determined by the *push* from remaining groups as well as the *pull* of the leaving group. The quantity $\sigma^+ - \sigma^n$ provides a measure of the ability of an atom or group to donate electrons by resonance and the value of $\sigma^+ - \sigma^n = 0.15$ for chloride is one-quarter of that for PhO, 0.59;³⁰ substitution of PhO for H increases the rate of expulsion of methylamine from a tetrahedral addition intermediate by $\sim 10^3$.²⁴ Thus, chloride can provide a small but significant *push* for the expulsion of pyridine from the addition intermediate. However, it should be kept in mind that a nonlinear Brønsted plot does not prove that the reaction proceeds through an intermediate. Changes in transition state structure that give nonlinear Brønsted plots are also possible when there is no addition intermediate with a significant lifetime and the reaction is concerted.³¹

The similar values of β_{nuc} , the similar absolute values of the rate constants for the reactions of pyridines and primary amines, and the absence of general base catalysis show that proton removal from the tetrahedral addition intermediate is not significant for the reactions of primary amines.

The values of β_{nuc} for the reactions of pyridines with acetyl chloride and methyl chloroformate provide no indication of a decrease in β_{nuc} with increasing reactivity of the acyl compound.

Imidazole is a relatively poor nucleophile toward acetyl chloride, with a rate constant smaller by a factor of ~ 25 than that of pyridine of the same pK_a . Relatively low nucleophilicity of imidazole for rate-limiting attack has been observed previously for reactions with methyl chloroformate, AMPP, acetic anhydride, and a phthalimidium cation.^{2,6,16,32} Considerably faster reactions of imidazole compared with other amines are observed when leaving group expulsion is rate limiting, presumably because of the additional *push* provided by electron donation by resonance from imidazole and its poor leaving ability.^{2,24,32}

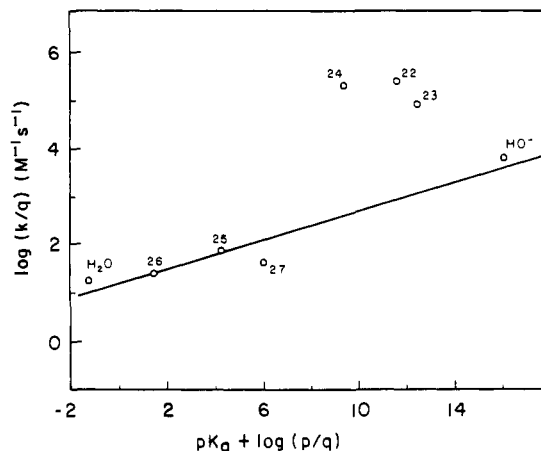


Figure 5. Dependence on basicity of the rate constants for reactions of anionic oxygen nucleophiles and water with acetyl chloride in water containing 2.5% dioxane, ionic strength 1.0, 22 °C. The numbers refer to the nucleophiles in Table I.

Rate constants for the reactions of acetyl chloride with hydroxide ion, water, acetate, and phosphate mono- and dianions fall near the line with a slope of $\beta_{\text{nuc}} = 0.15$ in Figure 5. However, little or no significance should be attached to this slope because it is determined largely by the rate constant for hydroxide ion, which is characteristically low; a line through the rate constants for acetate and trifluoroethoxide anions has a slope of 0.37 and the rate constants for the reactions of acetate and phenolate anions with methyl chloroformate give a slope of 0.7.⁶ Anionic oxygen nucleophiles react with esters with a value of $\beta_{\text{nuc}} = 0.7$ for rate-limiting attack.^{33,34} The reason why this value is larger than that for nitrogen nucleophiles is not known.

Reactivity of α -Effect Nucleophiles. The small rate increases for the reactions of acetyl chloride with hydrazine and hydroxylamine, compared with other primary amines of comparable pK_a , and the absence of significant rate increases with methoxyamine and semicarbazide show that the α -effect for nitrogen nucleophiles does not cause a large rate increase when nucleophilic attack is rate limiting. (It is possible that normal primary amines of $pK_a < 5$ would show a downward deviation, similar to that of pyridines, so that methoxyamine and semicarbazide would also show a small rate increase.) The same conclusion may be drawn from the rate constants for the reactions of hydrazine and hydroxylamine with AMPP, which are similar to those for the moderately basic primary amines that are assigned to rate-limiting nucleophilic attack.²

In contrast, the (statistically corrected) rate constants for the reactions of hydrazine and hydroxylamine with phenyl acetate and *p*-nitrophenyl acetate are larger than those for primary amines of comparable basicity by factors of 30–2500 and methoxyamine shows a similar rate increase of 100-fold.² These reactions involve rate-limiting breakdown of the intermediate or proton transfer, so that the larger carbon basicity of these nucleophiles can contribute to the observed rate increase by increasing the equilibrium concentration of the tetrahedral intermediate.^{35,36} Morris and Page have shown that in the hydrazinolysis of benzylpenicillin the α -effect is manifested in a 15-fold increase in the rate constant and a 350-fold increase in the equilibrium constant for formation of the addition intermediate.³⁷ Thus, the thermodynamic α -effect, which remains unexplained, is more important than the kinetic α -effect for reactions of nitrogen nucleophiles.

Anionic oxygen nucleophiles that exhibit the α -effect, such as acetohydroxamate and hydrogen peroxide anions, show rate in-

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creases of $\sim 10^2$ relative to other nucleophiles of comparable pK_a in the reactions of acetate esters containing leaving groups in the range $pK_a = 2-10$.² Nucleophilic attack is rate limiting for most of these reactions, but there is a change to a transition state corresponding to predominant rate-limiting bond cleavage for the reaction of acetoxyacetate with phenyl acetate.³⁴ This indicates that these α -effect nucleophiles show different behavior, with similar stabilization of transition states that involve predominant bond formation or bond cleavage. The enhanced reactivity of these oxygen nucleophiles is also accompanied by an enhanced thermodynamic stability of their addition compounds, although the correlation is not as close as for the nitrogen nucleophiles.^{35,36}

Rate constants for the reactions of acetyl chloride with acetoxyacetate and hydrogen peroxide anions fall above the line in Figure 5 by factors of 10^3-10^4 , but are only slightly larger than that for trifluoroethoxide anion.

Correlation with the N_+ Scale. The rate constants for the reactions of a number of nucleophiles with carbocations and related electrophiles have been found to follow the N_+ scale of nucleophilic reactivity according to eq 7 with varying degrees of precision.³⁸⁻⁴¹

$$\log k = \log k_0 + N_+ \quad (7)$$

It has been suggested that the same equation could be used to correlate rate constants for nucleophilic attack on acyl compounds and could be extended to reactions of acyl compounds with rate-limiting leaving group expulsion if appropriate corrections are made for partitioning of the intermediate between reactants and products.⁹ An iterative data-fitting procedure was found to give a satisfactory correlation of the rate constants for a number of reactions of acetate esters according to eq 8, in which k_{-x} and

$$\log k_{\text{obsd}} = \log k_0 + N_+ - \log(1 + k_{-x}/k_{-y}) \quad (8)$$

k_{-y} are the rate constants for breakdown of the addition intermediate to reactants and products, respectively. It was assumed that the relative values of k_{-x} and k_{-y} are characteristic of the leaving groups involved and independent of the nature of other groups in the intermediate (i.e., independent of the *push* from the remaining group that might affect the rate of leaving group expulsion).²⁴

This correlation led to several conclusions and assignments of rate-limiting steps that differ from those reported from this laboratory.

(1) According to the N_+ correlation, the value of β_{nuc} for rate-limiting attack on esters is 0.56 for amines and 0.49 for primary amines,⁹ rather than 0.2 ± 0.2 .³

(2) According to the N_+ correlation the reactions of AMPP and 2,4-dinitrophenyl acetate with trifluoroethylamine, ethylenediamine monocation, and glycine ethyl ester occur with rate-limiting attack.⁹ However, the rate constants for these reactions fall close to lines of slope $\beta_{\text{nuc}} = 0.8$ and have been assigned to predominantly rate-limiting breakdown of the intermediate.^{2,3} The differences in these assignments involve differences in relative rate constants by factors of up 10^3 .

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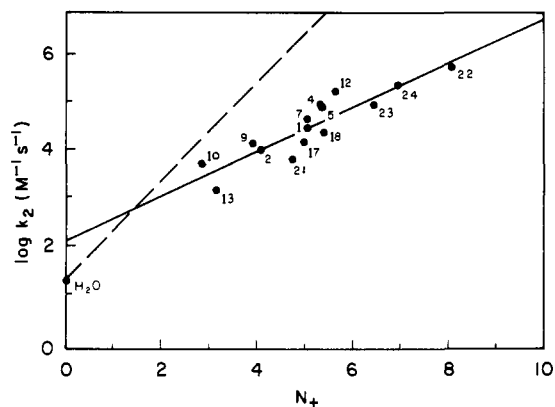


Figure 6. Correlation with the N_+ scale of rate constants for the reactions of nitrogen and oxygen nucleophiles with acetyl chloride. The dashed line has a slope of 1.0, and the solid line of slope 0.47 is based on a least-squares correlation of the data. The numbers refer to the nucleophiles in Table I.

(3) According to the N_+ correlation the reactions of *p*-nitrophenyl acetate with ethylenediamine, ethylamine, propylamine, and piperidine occur with rate-limiting attack.⁹ However, these rate constants show no significant deviation from the line of slope $\beta_{\text{nuc}} = 0.8$ that has been assigned to rate-limiting breakdown of the intermediate.^{2,3}

The value of $\beta_{\text{nuc}} = 0.25$ for reactions of amines with acetyl chloride and similar values for other reactions of amines with acyl compounds with good leaving groups support the assignment of rate-limiting attack to values of $\beta_{\text{nuc}} = 0.2 \pm 0.2$ and rate-limiting breakdown of the intermediate to larger values that are usually in the range 0.8-1.0. They are inconsistent with the assignment of rate constants that follow $\beta_{\text{nuc}} \geq 0.8$ to rate-limiting nucleophilic attack.

The rationale for the application of the N_+ scale to reactions involving nucleophilic attack at carbonyl carbon implies that the observed second-order rate constants for reactions of acetyl chloride (except for pyridines of $pK_a < 5$) should be correlated by the N_+ scale, with a gradient of 1.0. Figure 6 shows the poor correlation actually obtained. The best fit to the data is a line of gradient 0.47 (correlation coefficient = 0.91).

We conclude that the reactions of nucleophilic reagents with acyl compounds are not satisfactorily correlated by the N_+ scale according to eq 7 or 8. Values of N_+ that were obtained from reactions of esters should not be used for structure-reactivity correlations of reactions that do follow the N_+ scale without verification.

The reason for the different sensitivity to amine basicity of the rate constants for attack on esters, $\beta_{\text{nuc}} \sim 0.2$, and on carbocations, $\beta_{\text{nuc}} \sim 0.5$, is not known.

Registry No. $\text{CH}_3\text{C}(\text{O})\text{Cl}$, 75-36-5; NH_2OH , 7803-49-8; PhNH_2 , 62-53-3; EtNH_2 , 75-04-7; $\text{NH}_2(\text{CH}_2)_2\text{NH}_2$, 107-15-3; $\text{NH}_2(\text{CH}_2)_2\text{OH}$, 141-43-5; $\text{MeO}(\text{CH}_2)_2\text{NH}_2$, 109-85-3; MeONH_2 , 67-62-9; H_2NNH_2 , 302-01-2; HO_2^- , 14691-59-9; H_2PO_4^- , 14066-20-7; HPO_4^{2-} , 14066-19-4; imidazole, 288-32-4; glycylamide, 598-41-4; trifluoroethylamine, 753-90-2; semicarbazide, 57-56-7; 4-nitropyridine, 1122-61-8; 3-chloropyridine, 626-60-8; nicotinamide, 98-92-0; pyridine, 110-86-1; 4-methylpyridine, 108-89-4; 3,4-dimethylpyridine, 583-58-4; 4-(dimethylamino)pyridine, 1122-58-3; trifluoroethoxide anion, 24265-37-0; acetoxyacetate anion, 41879-86-1.