electronic destabilization of the acetylpyridinium ion, *i.e.*, an internal energy effect rather than a solvation effect, in the two following ways.

(a) The positive charge on the nitrogen atom destabilizes the partial positive charge on the sp^2 carbonyl carbon atom. The very large sensitivity of the thermodynamic and kinetic stability of the acylpyridinium ions to the polar character of this atom, as measured by the basicity of the parent pyridine, supports this assertion.

(b) In spite of the existence of some resonance stabilization by conjugation with the aromatic ring, the loss of the normal resonance stabilization of amides by electron donation from the amide nitrogen atom (I) causes a marked destabilization of acetylpyridinium ions. It has been estimated that the resonance structure Ib contributes about 40% to the structure and some 20 kcal/mol of resonance stabilization to simple aliphatic amides.[37] Solvent structure effects are unlikely to give rise to large free-energy changes because of the tendency for mutual compensation of entropy and enthalpy changes upon solvent rearrangement.[38]

Acknowledgment. We are indebted to Mrs. Karin Salvesen for carrying out the activity coefficient measurements.

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(37) P. Haake, W. B. Miller, and D. A. Tyssee, *J. Amer. Chem. Soc.*, 86, 3577 (1964);
L. C. Pauling, "Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 197.

(38) See, for example, L. G. Hepler, *J. Amer. Chem. Soc.*, 85, 3089 (1963).

Reactions of Nucleophilic Reagents with Acylating Agents of Extreme Reactivity and Unreactivity. Correlation of β Values for Attacking and Leaving Group Variation[1]

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Received December 31, 1969

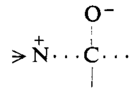
Abstract: Rate constants are reported for the reactions of a series of nucleophilic reagents with substituted N-acetylpyridinium ions. Logarithmic plots of reaction rate against the pK of the nucleophile for oxygen nucleophiles are curved and for nitrogen nucleophiles show an initial slope of ~0.9, followed by a leveling off. Nevertheless, a high degree of selectivity with respect to factors other than basicity is maintained for reactions with rate constants of up to $3.3 \times 10^8\ M^{-1}\ \text{sec}^{-1}$. Rate constants for nucleophilic reactions with methyl acetate, trifluoroethyl acetate, and acetic acid, calculated from the equilibrium constants and the rate constants for the reverse reaction, show a large dependence on basicity with β values of ~1.5, compared to 1.7 for the complete reaction. A similar β value is obtained for leaving group variation in the reactions of unreactive esters with 4-methylpyridine and p-nitrophenolate ion. Acyl transfer reactions exhibit a rough correlation of β values for the nucleophile with the (negative) β values for the leaving group. Proton transfer from the nucleophile has a large effect on the rate for reactions with acetate esters less reactive than phenyl acetate.

We report here a study of structure–reactivity relationships for the reactions of a series of substituted N-acylpyridinium ions with nitrogen and oxygen nucleophilic reagents. These and other results have made possible the correlation of rate constants for reactions of nucleophiles with acyl compounds over a wide range of reaction rates, from 10^{-20} to 10^8 M^{-1} sec^{-1}. The experiments were carried out for the following three reasons.

(1) We wished to determine whether such extremely reactive *acylating agents* as the acetylpyridinium ions display a selectivity toward nucleophiles similar to that exhibited by less reactive acyl compounds; *i.e.*, to what extent do the transition states for reactions of these compounds occur early along the reaction coordinate (a "Hammond postulate"[2] type of effect) and what is the nature of any resulting change in the nature of the transition state?

(2) We wished to determine whether these compounds exhibit a sharp leveling off in their sensitivity toward the basicity of the *nucleophile* with strongly basic nucleophiles, as is observed with oxygen esters with good leaving groups.[3]

(3) We hoped to obtain further information about the nature of transition states and structure–reactivity correlations for acyl transfer reactions in general by examining a series of symmetrical reactions with the same entering and leaving atom. If proton transfer does not occur, the reactions of nitrogen bases with acylpyridinium ions have a symmetry, analogous to that in the reactions of esters with alkoxide ions,[3] such that with attacking and leaving groups of similar pK the transition state should be almost symmetrical.



$$>\overset{+}{N}\cdots\overset{O^-}{\underset{|}{C}}\cdots N<$$

Although there is no question but that tetrahedral ad-

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(1) Supported by grants from the National Science Foundation (GB 5648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD 01247).

(2) G. S. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955); J. E. Leffler, *Science*, 117, 340 (1953).

(3) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 90, 2622 (1968).

Table I. Experimental Conditions for Determination of the Rates of Reactions of Nucleophilic Reagents with Acetyl-4-methylpyridinium at 25°, Ionic Strength 1.0

Compd	Concn, *M*	Fraction base	Concn of 4-methylpyridine, *M*	Concn of 4-methylpyridinium, *M*	No. of runs
Propylamine	0–0.7	2.56×10^{-5}	0.05	0.05	5
	0–0.007	2.6×10^{-4}	0.10	0.01	4
Glycine ethyl ester	$0–2.5 \times 10^{-3}$	1.2×10^{-2}	0.05	0.10	4
Trifluoroethylamine	$0–1.2 \times 10^{-3}$	0.775	0.055	0.045	5
	$0–1.2 \times 10^{-3}$	0.97	0.10	0.01	4
Hydrazine	$0–10^{-3}$	5.25×10^{-3}	0.10	0.20	5
Semicarbazide	$0–2 \times 10^{-3}$	0.99	0.05	0.10	5
Piperidine	0–0.075	7.8×10^{-6}	0.05	0.05	6
	0–0.15	3.7×10^{-6}	0.05	0.10	4
Piperazine[a]	$0–1.5 \times 10^{-3}$	$7 \times 10^{-5}, - 9.6 \times 10^{-4}$	0.10	0.02, 0.2	12
Morpholine	$0–2.5 \times 10^{-3}$	1.26×10^{-3}	0.05	0.10	5
Piperazine-H^+[a]	$0–1.5 \times 10^{-3}$	0.46–0.92	0.10	0.02, 0.2	12
Anion of water[b]		$(0.04 - 1.35) \times 10^{-9}$	0.05	*b*	7
Methanol[c]	0–1.6	7×10^{-10}	0.055	0.045	5
	0–1.8	6.3×10^{-9}	0.05	0.005	6
Trifluoroethanol	0–0.035	9.95×10^{-6}	0.10	0.01	5
Hydrogen peroxide	$0–4.8 \times 10^{-3}$	2.5×10^{-6}	0.05	0.10	7
	$0–2.9 \times 10^{-3}$	2×10^{-6}	0.10	0.10	4
p-Nitrophenol[d]			0.225	0.0225	3

[a] Based on observed rate constants of 4.85×10^3 and 16.9×10^3 M^{-1} sec^{-1} at pH 5.96 and 7.09, respectively (based on total amine concentration). [b] 4-Methylpyridine component of buffer held constant, 4-methylpyridinium varied. [c] Based on observed rate constants of 0.40 and 0.98 M^{-1} sec^{-1} at pH 6.34 and 7.30, respectively. The 15–20% rate increase caused by methanol itself may be interpreted as a solvent effect or as a nucleophilic reaction with a rate constant of 0.32 M^{-1} sec^{-1}. [d] The rate constant was calculated from the ratio of phenoxide nucleophilic attack to hydrolysis rate for the acylpyridinium[3] and the hydrolysis rate (this study).

dition compounds with an appreciable lifetime are formed as intermediates in a number of acyl transfer reactions, the structure–reactivity relationships reported here are, in fact, most easily interpreted without invoking such intermediates or by assuming that the transition states for formation and breakdown of the intermediate closely resemble the intermediate and each other over a wide range of structural variation.

The interpretation of structure–reactivity relationships for reaction rates, *i.e.*, for the partial reaction that takes place upon transformation of starting materials to the transition state, is greatly facilitated by comparison with the effects of structure on the free energy of the overall reaction, which is known from the effects of substituents on the equilibria for acyl transfer from acylated pyridines and alcohols.[4,5]

Experimental Section

Pyridines were purified as described previously.[4] Propylamine, glycine ethyl ester, trifluoroethylamine, hydrazine, semicarbazide, and piperidine were purified by recrystallization of the hydrochlorides and morpholine as its perchlorate. Piperazine was sublimed. Trifluoroethanol was redistilled. Hydrogen peroxide was standardized against sodium thiosulfate.

Kinetic measurements were carried out with a stopped-flow apparatus as described in the previous paper.[4] A solution containing the pyridine buffer and nucleophilic reagent made up to ionic strength 1.0 with potassium chloride was placed in one syringe and a solution of acetic anhydride in 1 *M* potassium chloride in the other. After mixing and initiating the reaction, readings were taken after 8–10 half-lives of the formation reaction of the acetylpyridinium ion so that the decay was experimentally first order. Second-order rate constants were obtained by the usual method of plotting k_{obsd} against the concentration of the nucleophile. In most experiments the acetic anhydride concentration was 1–2 $\times$ 10^{-4} *M*. In the case of some reactive, weakly basic amines, it was possible to use only a 5–10-fold excess of amine over the lowest initial concentration of acetic anhydride that gave adequate absorbance changes (5×10^{-6} *M*). However, since rate constants for these reactions were obtained after the initial 2 half-lives for the disappearance of the acetylpyridinium ion, there is no more than a 1–2% change in amine concentration in the course of the measured pseudo-first-order reaction. All runs were carried out at 25.0 ± 0.1° and ionic strength 1.0 (added potassium chloride) and all pH measurements were made under the same conditions.[4] The concentrations of the basic species of the more reactive nucleophiles were calculated from the measured pH and p*K* values for the same experimental conditions.[3] In the case of weakly acidic alcohols it was necessary to use ionization constants obtained at low ionic strengths, but the error introduced by this approximation does not appear to be large, presumably because the salt effect on the ionization is largely compensated by an opposite effect on the reaction rate.[6] The experimental conditions for the determination of rate constants are summarized in Tables I–III.

The rate constant for the attack of the 4-nitrophenolate ion on acetyl-4-methylpyridinium ion (AMeP$^+$) was calculated from its previously determined ratio[3] to that of the rate constant for hydrolysis of AMeP$^+$ at 25°, ionic strength 1.0, with 0.225 *M* 4-methylpyridine and 0.0225 *M* 4-methylpyridinium. This ratio was found to be 1.84×10^4. The hydrolysis rate of AMeP$^+$ was determined in this study to be 4.84 sec^{-1} under the same conditions, and hence gives the required rate constants.

The "calculated" rate constants for the reactions of nucleophiles with esters and acetic acid were calculated from the measured rate constant for the reaction in one direction and the equilibrium constant, based upon the known free energies of hydrolysis.[5] For example, the equilibrium constant for the reaction of trifluoroethyl acetate and 4-methylpyridine was calculated from the difference in the free energies of hydrolysis of the ester and acetyl-4-methylpyridinium ion; the rate constant was calculated from the equilibrium constant, the measured rate constant for attack of trifluoroethoxide ion on acetyl-4-methylpyridinium ion, and the appropriate ionization constants.

Results

Rate constants for the reactions of nucleophilic reagents with substituted acetylpyridinium ions are summarized in Table IV. The acetylpyridinium ions were generated *in situ* by the addition of the pyridine to acetic anhydride, under conditions such that the rate constant for their formation was much larger than

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(4) A. R. Fersht and W. P. Jencks, *ibid.*, **92**, 5432 (1969).

(5) J. Gerstein and W. P. Jencks, *ibid.*, **86**, 4655 (1964).

(6) W. P. Jencks and M. Gilchrist, *ibid.*, **84**, 2910 (1962).

Table II. Experimental Conditions for Determination of the Rates of Reactions of Nucleophilic Reagents with Acetyl-3,4-lutidinium at 25°, Ionic Strength 1.0

Compd	Concn, *M*	Fraction base	Concn of lutidine, *M*	Concn of lutidinium, *M*	No. of runs
Propylamine	0–0.05	7.6×10^{-5}	0.025	0.025	9
Glycine ethyl ester	$0–1.75 \times 10^{-3}$	0.034	0.025	0.050	13
Trifluoroethylamine	$0–3 \times 10^{-3}$	0.89	0.025	0.025	9
Piperidine	0–0.05	2.24×10^{-5}	0.025	0.025	9
Piperazine[a]	$0–1.5 \times 10^{-3}$	$(2.2–9.8) \times 10^{-4}$	0.025	0.0025, 0.05	14
Morpholine	$0–1.75 \times 10^{-3}$	3.8×10^{-3}	0.025	0.050	8
Piperazine-H$^+$ [a]	$0–1.5 \times 10^{-3}$	0.73–0.92	0.025	0.0025, 0.05	14
Anion of water		$10^{-9}–10^{-8}$	0.025	*b*	9
Methanol[c]	0–1.2	1.78×10^{-8}	0.025	0.0025	6
	0–1.5	7.6×10^{-10}	0.025	0.050	8
Trifluoroethanol	0–0.02	2.5×10^{-5}	0.025	0.0025	6

[a] Based on observed rate constants of 4.35×10^3 and 9.43×10^3 M^{-1} sec^{-1} at pH 6.45 and 7.09, respectively (based on total amine concentration). [b] Performed in lutidine buffers of varying lutidinium or total amine concentration, but constant lutidine concentration. [c] The observed second-order rate constants are 0.37 and 1.06 M^{-1} sec^{-1} at pH 5.38 and 7.75, respectively. The rate constant for methanol itself is 0.29 M^{-1} sec^{-1}, corresponding to about a 20% increase in spontaneous rate in the region examined.

Table III. Experimental Conditions for Determination of the Rates of Reactions of Nucleophilic Reagents with Acetyl-4-methoxypyridinium at 25°, Ionic Strength 1.0

Compd	Concn, *M*	Fraction base	Concn of 4-methoxy-pyridine, *M*	Concn of 4-methoxy-pyridinium, *M*	No. of runs
Propylamine	0–0.125	8.93×10^{-5}	0.025	0.025	10
Glycine ethyl ester	$0–3 \times 10^{-3}$	8.5×10^{-2}	0.025	0.025	9
Trifluoroethylamine	$0–1.75 \times 10^{-2}$	*a*	*a*	*a*	12
Piperidine	0–0.10	2.64×10^{-5}	0.025	0.025	9
	0–0.10	2.57×10^{-5}	0.050	0.050	5
Morpholine	$0–3.5 \times 10^{-3}$	9.1×10^{-3}	0.025	0.025	7
Hydroxide ion	$(0.3 - 6.6) \times 10^{-7}$		0.05	*b*	6

[a] These runs were performed at a series of pH values between pH 6.89 and 6.45. [b] 4-Methoxypyridine component of buffers held constant, 4-methoxypyridinium varied.

Table IV. Summary of Rate Constants for the Reactions of Nucleophilic and General Base Reagents with Acetylpyridinium (AP$^+$), Acetyl-4-methylpyridinium (AMeP$^+$), Acetyl-3,4-lutidinium (AL$^+$), and Acetyl-4-methoxypyridinium (AMeOP$^+$) at 25°, Ionic Strength 1.0[a]

			k_2, M^{-1} sec^{-1}		
Compd	pK[a,b]	AP$^+$	AMeP$^+$	AL$^+$	AMeOP$^+$
Nucleophilic Reagent					
Propylamine	10.89		1.54×10^6	1.31×10^6	5.02×10^5
Glycine ethyl ester	7.90		1.74×10^5	1.22×10^5	3.29×10^4
Trifluoroethylamine	5.84		4.3×10^3	2.19×10^3	3.50×10^2
Hydrazine	8.20[c]		3.3×10^6		
Semicarbazide	3.86		2.24×10^3		
Piperidine	11.42		4.76×10^6	4.36×10^6	2.24×10^6
Piperazine	10.10		9.1×10^6 [d]	5.7×10^6 [d]	
Morpholine	8.87		1.6×10^6	1.06×10^6	2.46×10^5
Piperazine-H$^+$	6.01		9.0×10^3	4.2×10^3	
Water[e]	−1.75	1.25×10^{-1}	4.15×10^{-2}	2.7×10^{-2}	7.2×10^{-3}
Anion of					
Water[f]	15.75		1.60×10^6	1.48×10^6	5.33×10^5
Methanol	15.5[g]		1.09×10^8	1.06×10^8	
Trifluoroethanol	12.37[g]		1.2×10^7	9.3×10^6	
Hydrogen peroxide	11.60[h]		3.3×10^8		
Phenol	9.86	1.7×10^7 [i]	6.0×10^6 [i]		
p-Nitrophenol	7.02[j]	2.9×10^5 [i]	9.1×10^4		
Acetic acid[e]	4.61	9.1×10^2	2.62×10^2	1.2×10^2	30

[a] Ionic strength maintained with potassium chloride unless otherwise noted. [b] Taken from ref 3 unless otherwise noted. [c] T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, **86,** 418 (1964). [d] Approximate value. [e] Ref 4. [f] Based on $K_w = 10^{-14}$ and an activity coefficient of 0.67 for the hydroxide ion (J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, **86,** 833, 837 (1964)). Without this correction, the rate constants are 1.5 times larger than in the table. [g] At low ionic strength; P. Ballinger and F. A. Long, *ibid.*, **82,** 795 (1960). [h] At low ionic strength; A. J. Everett and G J. Minkoff, *Trans. Faraday Soc.*, **49**, 410 (1953). [i] Calculated from the equilibrium constant and rate constant for attack of the pyridine on the appropriate ester. [j] Reference 5.

that for the subsequent hydrolytic and acetylation reactions. By this method it was possible to study compounds considerably more reactive than previously examined in this class. Only a limited number of rate constants were determined for reactions of acetylpyridinium ion itself, because of the similar values of

Table V. Summary of Rate Constants for the Reactions of Nucleophiles with Methyl Acetate (MA), 2,2,2-Trifluoroethyl Acetate (TFEA), and Acetic Acid (AcOH) at 25°

		k_2, M^{-1} sec^{-1} [b]		
Nucleophile	pK_a[a]	AcOH	MA[c]	TFEA
Acetate	4.76	3.6×10^{-20}		
4-Methylpyridine	6.02	7.1×10^{-17}	1.3×10^{-13}	5.4×10^{-9}
3,4-Lutidine	6.52	3.5×10^{-16}	5.6×10^{-13}	2.7×10^{-8}
4-Methoxypyridine	6.62	3.8×10^{-16}		
Imidazole	7.05	2.2×10^{-14}		1.4×10^{-6}
p-Nitrophenolate	7.14	3×10^{-15}	5.3×10^{-12}	2.0×10^{-7}
m-Nitrophenolate	8.35	1.4×10^{-13}		
p-Chlorophenolate	9.38	2.7×10^{-12}		
Phenolate	9.95	7.5×10^{-12}	1.5×10^{-8}	4.6×10^{-4}
p-Methylphenolate	10.19	2×10^{-11}		
p-Methoxyphenolate	10.20	3.5×10^{-11}		
Trifluoroethoxide	12.37	2.5×10^{-7}		
2-Chloroethoxide	14.31	8.6×10^{-5}		
2-Methoxyethoxide	14.82	4.4×10^{-4}		
Methoxide	15.5	3.3×10^{-3}		
Ethoxide	15.9	1.2×10^{-2}		

[a] Thermodynamic value for the conjugate acid from H. A. Sober, Ed., "Handbook of Biochemistry," Chemical Rubber Publishing Co., Cleveland, Ohio, 1968. [b] Rate constants calculated from free energies of hydrolysis[5] and rate constants for the reverse reactions; from this study, ref 3, and J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 833, 837 (1964); J. Barthell, G. Bader, and G. Schmeer, *Z. Phys. Chem. (Frankfurt am Main)*, **62**, 63 (1968), and A. Satterthwait, unpublished results, for OH^-; ref 3 for MeO^-; ref 3 and D. G. Oakenfull and W. P. Jencks, in preparation, for trifluoroethoxide. [c] Free energy of hydrolysis of methyl acetate used is −1.7 kcal, from interpolation in ref 5.

Table VI. Summary of Rate Constants for the Reactions of the *p*-Nitrophenolate Ion and 4-Methylpyridine with Acetate Derivatives at 25° [a]

		k_2, M^{-1} sec^{-1}	
Ester or amide	pK_a[b] leaving group	*p*-Nitrophenolate	4-Methylpyridine
Acetyl-4-methylpyridinium	6.02	9.1×10^{4} [c]	
N-Acetoxy-4-methoxypyridinium	2.05	1.15×10^{2}	3.3×10^{3} [c]
Acetic anhydride	4.76	15[d,e]	2.33×10^{2} [d]
2,4-Dinitrophenyl acetate	4.11		13
p-Nitrophenyl acetate	7.14		2.7×10^{-2} [c]
p-Chlorophenyl acetate	9.38	1.75×10^{-4}	
Phenyl acetate	9.95	4.5×10^{-5}	5.3×10^{-5} [c]
p-Methylphenyl acetate	10.19	2.3×10^{-5}	
Trifluoroethyl acetate	12.37	2.1×10^{-7}	5.4×10^{-9}
Acetylcholine	13.90	3.9×10^{-10}	
2-Chloroethyl acetate	14.31	9.3×10^{-11}	
2-Methoxyethyl acetate	14.82	9.5×10^{-12}	
Methyl acetate[f]	15.54	5.3×10^{-12}	1.3×10^{-13}
Ethyl acetate	15.9	7.0×10^{-13}	

[a] Calculated from equilibrium constants and rate constants for the reverse reaction unless noted otherwise. [b] Thermodynamic value for 25° unless otherwise noted. Rate and equilibrium data from this study and ref 3 and 6. [c] Measured directly.[3] [d] Rate constant divided by a factor of 2 to allow for two carbonyl groups. [e] The observed rate constant for acetate ion catalysis of *p*-nitrophenyl acetate hydrolysis was assumed to be 50% nucleophilic (V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc. B*, 515 (1968)). [f] Free energy of hydrolysis interpolated from the results of ref 5.

the rate constants for the formation and hydrolysis of this compound and the resulting complexity of the kinetics.[4]

Spot checks revealed no catalysis of the nucleophilic reactions by the pyridine buffers in which the reactions were carried out. The rate constants for the reactions of propylamine, trifluoroethylamine, and hydrogen peroxide with acetyl-4-methylpyridinium ion were found to show no significant dependence upon pyridine buffer concentration in the range 0.05–0.10 *M* 4-methylpyridine and no catalysis of the reaction of piperidine with acetyl-4-methoxypyridinium ion was observed with 0.025–0.05 *M* 4-methoxypyridine. The second-order rate constants for the reactions of propylamine, trifluoroethylamine, and piperidine with acetyl-4-methylpyridinium ion, based upon the concentration of the basic form of the nucleophile, were shown to be unchanged upon variation of the pH by 0.3 unit (see Table I).

The reactions of acetyl-4-methylpyridinium and acetyl-3,4-lutidinium ions with methanol show a pH-independent component as well as the expected reaction with methoxide ion (Tables I and II). Although this may represent a nucleophilic reaction[7] with a second-order rate constant 6–9 times larger than that for water, the possibility is not ruled out that it is simply a solvent effect in view of the small observed rate increase (15–20%).

Rate constants for a series of nucleophilic reactions with trifluoroethyl acetate, methyl acetate, and acetic acid were calculated from the equilibrium constants and the observed rate constants of the reverse reactions (Table V). Most of these rate constants are inaccessible to direct measurement because of their small magnitude, the intervention of general base catalyzed hydrolysis, and, in the case of acetic acid, ionization to

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(7) E. R. Garrett, *J. Amer. Chem. Soc.*, **79**, 3401 (1957); A. R. Fersht and A. J. Kirby, *ibid.*, **89**, 4857 (1967).

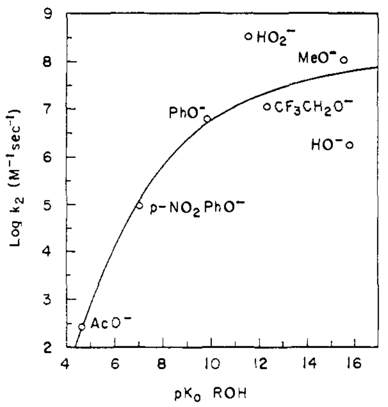

Figure 1. Dependence of the rate constants for the reactions of oxyanions with acetyl-4-methylpyridinium ion on the basicity of the nucleophile at 25°.

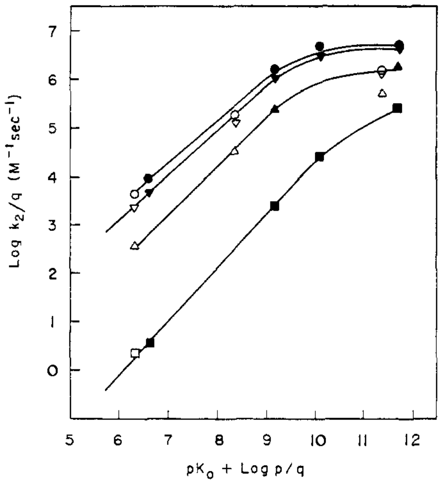

Figure 2. Dependence of the reaction rate on the basicity of the nucleophile for the reactions of amines with acetyl-4-methylpyridinium, ○; acetyl-3,4-lutidinium, ▽; acetyl-4-methoxypyridinium, △, and acetylimidazolium (ref 9 and W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272, 1280 (1959); W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *J. Amer. Chem. Soc.*, **88**, 4464 (1966)), □, at 25°, corrected for statistical factors. Solid symbols, secondary amines; open symbols, primary amines.

the unreactive acetate ion. The absolute values of these rate constants may be inaccurate by a factor of 2, in view of the several measurements on which they depend, but this error is not significant over the range of 10^{18} under consideration and the relative values, upon which structure–reactivity correlations depend, are more accurate than the absolute values. Rate constants, calculated in the same way, for nucleophilic reactions of p-nitrophenolate ion and 4-methylpyridine with a series of acetate derivatives with leaving groups of pK 2–16 are shown in Table VI.

Discussion

The rate constants for reactions of a series of oxygen anions and amine nucleophiles with acetyl-4-methylpyridinium ion are plotted as a function of the basicity of the nucleophile in Figures 1 and 2, respectively. Both plots are similar to those observed for nucleophilic reactions with the highly reactive ester AMPP (1-acetoxy-4-methoxypyridinium perchlorate, pK of leaving group = 2.0)[3] and, in fact, there is a surprisingly close correlation of these rate constants with each other, as shown in the correlation line of Figure 3 with a slope of 1.03. A similar correlation has been observed for the reactions of nucleophiles with p-nitrophenyl acetate and dimethylcarbamoylpyridinium ion, but the data are not sufficiently extensive to determine whether these two compounds show similar structure–reactivity behavior in plots of nucleophile reactivity against basicity.[8]

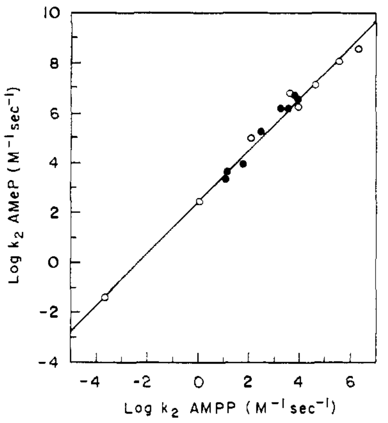

Figure 3. Proportionality of the rate constants for the reactions of amine (●) and oxygen nucleophiles (○) with acetyl-4-methylpyridinium and 1-acetoxy-4-methoxypyridinium[3] ions at 25°. The line has a slope of 1.03.

The data for oxygen anions (Figure 1), while not as extensive as those for AMPP, are sufficient to show that the plot exhibits a similar curvature, with a large dependence on the basicity of the nucleophile for reactions of weak bases, such as acetate, and a much smaller dependence for strongly basic alkoxide ions. Hydroxide ion shows its characteristic negative deviation and the hydroperoxide ion, which may be an "α effect" compound, shows its typical enhanced reactivity. The Bronsted slopes, β, for the nucleophile decrease from approximately 0.9 for acetate to 0.2 for strongly basic alkoxides.

The corresponding plot for amines (Figure 2) shows a large dependence on amine basicity (β = 0.9) for less basic amines, followed by a leveling off to little or no dependence on amine basicity for the most basic amines. Similar but slightly less marked behavior is seen for acetylated 3,4-lutidine and 4-methoxypyridine, whereas there is only a small tendency toward leveling off for the less reactive acetylimidazolium ion (lower line). This behavior for amine nucleophiles is closely similar to that observed with esters, which show linear plots of slope 0.8–1.0 for phenyl acetate and p-nitrophenyl acetate and an increasing amount of leveling off for 2,4-dinitrophenyl acetate and AMPP.[3]

This leveling off of the reaction rate with respect to the basicity of strongly basic oxyanion and amine nucleophiles means that the transition state occurs early along the reaction coordinate at a point at which there is little or no change in the charge on the attacking nucleophilic reagent. It might be regarded as an extreme example of a "Hammond postulate" type of effect, but several facts suggest that it is not an ordinary effect of this kind. These reactive acylating agents

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(8) S. L. Johnson and K. A. Rumon, *J. Amer. Chem. Soc.*, **87**, 4782 (1965).

maintain an extraordinarily large selectivity with respect to the nucleophile up to very high reaction rates. This is manifested in the large β values of approximately 0.9 for amines of moderate basicity in reactions with acetylpyridinium ions and with esters[3] over a total range of some 10^{13} in reaction rate, which is followed by a rather sharp development of insensitivity to basicity. However, there is no absolute limitation to the rate in this range. The plateau for reactions of acetylpyridinium ions with amines occurs at an absolute rate of about 5×10^6 M^{-1} sec^{-1}, whereas that for AMPP occurs at about 5×10^3 M^{-1} sec^{-1} for the same amines. Furthermore, the close correlation of the rate constants for AMPP and acetyl-4-methylpyridinium ions (Figure 3) in spite of the large difference in reaction rates is not in accord with a "Hammond postulate" effect which depends on absolute reaction rates. The strongest indication of the absence of any overall decrease in selectivity is the reaction of hydroperoxide ion with acetyl-4-methylpyridinium ion, which occurs with a rate constant of 3.3×10^8 M^{-1} sec^{-1}. Although this rate constant is approaching the diffusion-controlled limit and is much larger than the rate constants for reactions of other, more basic oxyanions, it does not show a significant negative deviation in the correlation with the much slower reaction rates of AMPP and also shows a rate enhancement of the same magnitude, compared to other oxyanions, as is observed with the much less reactive acetylimidazolium ion.[9]

Finally, a selectivity with respect to the acylating agent is maintained even for the very fast reactions in the plateau region. Acetyl-4-methoxypyridinium ion reacts more slowly than the corresponding 4-methyl compound because of resonance stabilization from the methoxy group,[4] and this rate difference is maintained in the plateau region (Figure 2). The rate decrease caused by this resonance stabilization amounts to 400–600 cal/mol in the free energy of activation for the reaction with basic amines, compared to an estimated 700 cal/mol stabilization of the starting material by resonance,[4] indicating that there is a considerable loss of resonance stabilization when the transition state of these reactions is reached, even when there is very little sensitivity to the basicity of the nucleophile.

Thus, the leveling off of reaction rate reflects a decrease in the sensitivity of the reaction rate to the basicity of the nucleophile and, as will be shown later, to the basicity of the leaving group, that is accompanied by a maintenance of sensitivity toward other factors affecting the rate, such as the special qualities which are reflected in the high reactivity of hydroperoxide ion and the degree of resonance stabilization of the acylating agent. In this sense these reactions resemble S$_N$2 displacements on saturated carbon, in which bond formation occurs at a distance and the reaction rate has little or no sensitivity to the basicity of the nucleophile. It is thought that the large sensitivity of these reactions to the polarizability and related properties of the nucleophile is a consequence of this bond formation at a distance in the transition state because of the unavailability of unoccupied orbitals for bond formation and the increased steric demands of pentavalent transition states involving saturated carbon.[10] It is understandable, therefore, that the hydroperoxide ion, which is derived from the abnormally polarizable hydrogen peroxide molecule,[11] maintains its enhanced reactivity toward acyl compounds at very high reaction rates.

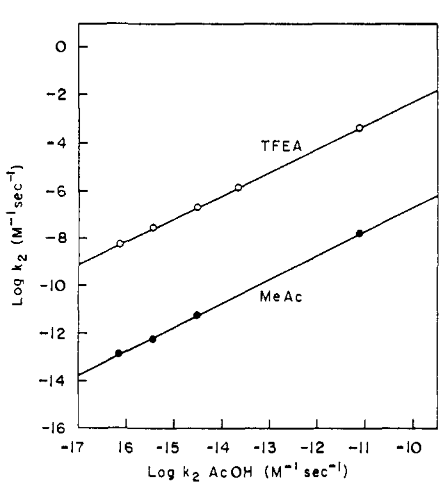

Figure 4. Plot of log k_2 (nucleophilic attack on ester) against log k_2 (nucleophilic attack on acetic acid) at 25° for 2,2,2-trifluoroethyl acetate (○), slope = 0.97, and methyl acetate (●), slope = 1.00.

Some support for this interpretation comes from a comparison of oxygen and sulfur anions as general base catalysts for elimination reactions. When the value of β is large, so that there is a large amount of bond formation to the base, oxygen and sulfur bases have a similar effectiveness for a given basicity. When β is small and bond formation to hydrogen occurs at a distance in the transition state, the decreased sensitivity to basicity is accompanied by an increased sensitivity to polarizability, so that a sulfur anion is considerably more effective than an oxygen anion of comparable basicity.[12] The reactions of amines with phosphate ester dianions are similar to the acyl group reactions in that the sensitivity to basicity of the nucleophile becomes small or zero as the leaving group becomes better, but differ in that there is a very large amount of bond breaking of the leaving group in the phosphate reactions, manifested in the large sensitivity of the rate to the basicity of the leaving group ($\beta = -1.2$).[13]

The opposite extreme of behavior is seen in the rate constants for the reactions of nucleophilic reagents with methyl acetate, trifluoroethyl acetate, and acetic acid (Table V), which were calculated from the equilibrium constants and the observed rate constants for the reverse reactions. The widest range of data available is for nucleophilic displacement on acetic acid to form an ester and hydroxide ion. Lest this reaction seem improbable and unreal we have calculated also rate constants for methyl acetate and trifluoroethyl acetate. Plots of these rate constants against those for acetic acid give excellent straight lines of slope approximately 1.0 (Figure 4), showing that acetic acid is behaving as a typical ester with a poor leaving group. It has been pointed out before that the "equivalent" pK_a of the

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[9] D. G. Oakenfull and W. P. Jencks, in preparation.

[10] W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 85.

[11] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 1778 (1960).

[12] P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.*, 41 (1956); D. J. McLennan, *ibid.*, *B*, 705 (1966); J. F. Bunnett and E. Bacciochi, *J. Org. Chem.*, **32**, 11 (1967).

[13] A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3209 (1965); A. J. Kirby and A. G. Varvoglis, *J. Chem. Soc. B*, 135 (1968).

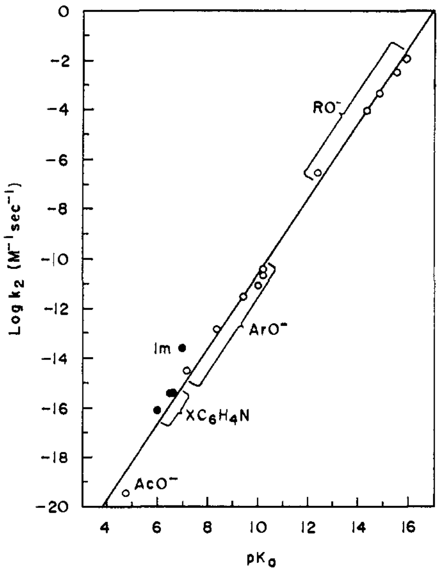


Figure 5. Brønsted plot for the attack of nucleophiles on acetic acid at 25°: AcO^- = acetate; XC_6H_4N (●) = pyridines; Im (●) = imidazole; ArO^- = phenoxide ions; and RO^- = alkoxide ions.

hydroxide[14] group in acetic acid is about 17 when compared with other esters by extrapolation of equilibrium measurements of free energies of hydrolysis. The "best" value is 17.4 Estimates made for the value of the pK_a of hydroxide as a typical alcoholate leaving group from extrapolation of the rate constants of 4-methylpyridine and *p*-nitrophenolate with other esters are 17.2 and 17.5, respectively. Acetic acid is seen on both equilibrium and kinetic grounds to be equivalent to an ester of an alcohol of pK_a 17.4.

The Brønsted plot for reactions of nucleophiles with acetic acid gives a good straight line of slope 1.52 (Figure 5). There is the possibility, however, of slight curvature, with a line of slope 1.3 going through the alkoxide ions and another of slope 1.6 at the other extreme. For simplicity we shall say that the Brønsted plot for nucleophilic attack on acetic acid is characterized by a β value of 1.5. The β value for complete acetyl transfer is 1.7 for oxygen esters[5] and 1.6 for acetylpyridinium ions.[4] Thus, the value of 1.5 corresponds to almost complete reaction and the range of values of 0–1.5 encompasses nearly the entire possible range of values.

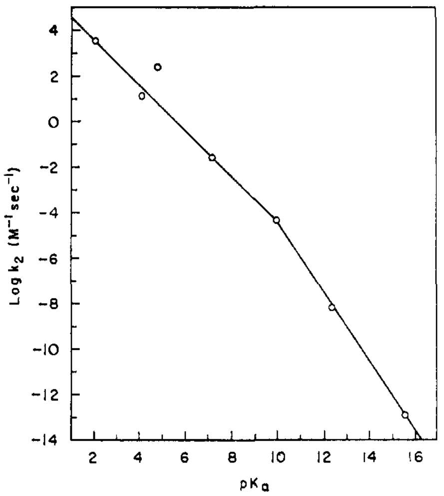
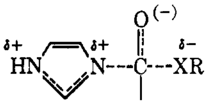


Figure 6. The rate constants for the reactions of 4-methylpyridine with acetates at 25° as a function of the basicity of the oxyanion leaving group (Table VI). The rate constant for acetic anhydride has been corrected by a statistical factor of 2.

The reactivity of the alkoxide ions is strongly dependent on their pK_a's, unlike the reactions with the phenyl acetates. The relative insensitivity of alkoxide ion reactivity with respect to pK_a in the phenyl acetate reactions is not just a peculiarity of the nucleophiles, such as solvation (which may account for the low reactivity of the hydroxide ion), but is clearly a function of the whole reaction, as these compounds are well behaved here. The reactivity of pyridines is similar to that of oxyanions of similar p*K*, but imidazole exhibits a positive deviation of more than an order of magnitude. A similar enhanced reactivity is seen with both imidazole and N-methylimidazole for reaction with phenyl acetate (which indicates that the increased reactivity is not accounted for by proton transfer from the attacking imidazole to water in the transition state).[3,15] This rate enhancement is the converse of the increased thermodynamic stability and decreased reactivity of the acetylimidazolium ion which has been attributed to resonance stabilization,[4] suggesting that the increased nucleophilic reactivity of imidazole is a consequence of resonance stabilization of the transition state involving electron donation from the second nitrogen atom to the carbonyl group and, possibly, the leaving group. With highly reactive acyl compounds, such as acetic anhydride[4,16] and AMPP,[3] the transition state may be reached earlier so that less bond formation and resonance stabilization are developed and the enhanced reactivity of imidazole disappears. The faster reaction of imidazole compared to other amines with positively charged esters has also been attributed to delocalization of positive charge in the transition state.[17]



Values of β for the leaving group may be calculated over this extended range in a few cases.[18] As shown in Figure 6, the reactions of 4-methylpyridine with acetate esters that have leaving groups of p*K* 2–16 show an increase in sensitivity to the nature of the leaving group as the leaving group becomes worse, with an increase in β from the value of ~1.0 characteristic of phenyl esters[3] to 1.5 for alkyl acetates (the positive deviation of the point for acetic anhydride is presumably a consequence of the smaller steric requirement of this compound, compared to phenyl acetates). The *p*-nitrophenolate ion, for which there are more data available in the high p*K* region (Table VI), also has a β value of 1.5 for reaction with the alkyl acetates.

The effect of variation in the basicity of the leaving group in the acetylpyridinium series can best be seen by

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[14] S. A. Shain and J. F. Kirsch, *J. Amer. Chem. Soc.*, **90**, 5848 (1968); S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

[15] J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 833, 837 (1964).

[16] D. M. Brouwer, M. J. Vlugt, and E. Havinga, *Proc. Kon. Ned. Akad. Wetensch., Ser. B*, **60**, 275 (1957).

[17] B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 2982, 2985 (1969).

[18] For simplicity the negative sign of the β values for leaving group variation will be omitted in the following discussion.

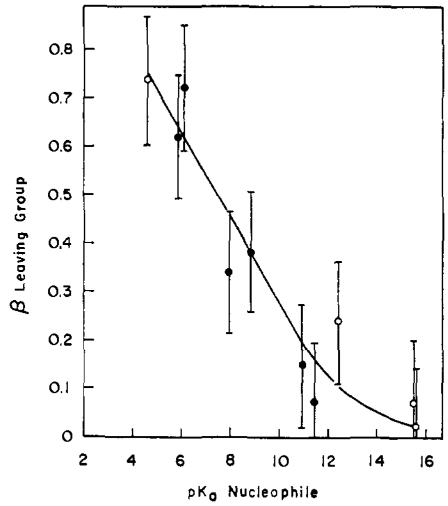

Figure 7. The sensitivity of acyl transfer reactions to the basicity of the leaving group as a function of the basicity of the attacking group. The value of β (leaving group) is plotted against the pK_a of amine (●) and oxyanion (○) nucleophiles for reactions with acetylpyridinium ions. Uncertainty limits for β of ±0.13 are shown.

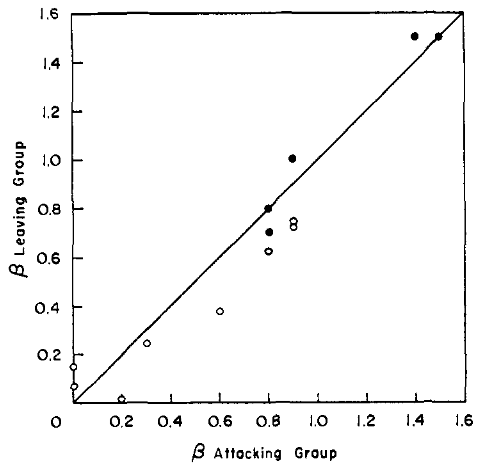

Figure 8. Correlation of the sensitivity of acyl transfer reactions to the basicity of the attacking and of the leaving groups (β values). Reactions of aryl and alkyl acetates, ●; reactions of acylpyridinium ions, ○.

a comparison of the rate constants for reaction with acetyl-4-methylpyridinium and acetyl-3,4-lutidinium ions, in order to avoid perturbations caused by resonance stabilization. Values of β for the leaving group calculated from these rate constants are not of high precision because of the small difference in basicity of the leaving group (ΔpK = 0.46), but they do serve to indicate trends.[19] They are summarized, along with some β values for other reactions and for the attack of nucleophiles on acetylpyridinium ions, in Table VII. As the basicity of the nucleophile increases, the β value for the leaving group decreases for both oxygen and nitrogen nucleophiles (Figure 7). In the series of amine nucleophiles, the decrease in the sensitivity of the reaction to nucleophile basicity that occurs with strongly basic amines is paralleled by a decrease in the sensitivity to the pK of the leaving group, with β values decreasing from 0.7 to 0.1. A similar trend is seen in the oxygen anion series, with a decrease in β for the leaving group from 0.7 to 0 going from acetate to hydroxide, accompanying a decrease in β for the attacking group from 0.9 to 0.2. Again, the sensitivity to factors other than basicity is maintained as β becomes small—resonance stabilization leads to a threefold decrease in the rate constants for the reaction of hydroxide ion with acetyl-4-methoxypyridinium ion, compared to those for acetyl-4-methylpyridinium and acetyl-3,4-lutidinium ions, in spite of the almost identical basicities of 4-methoxypyridine and 3,4-lutidine.

These results for the acetylpyridinium series are paralleled in other acyl transfer reactions for which β values are available for both the attacking and leaving groups, as shown in the upper part of Table VII. Although the correlation is by no means perfect, there is a definite trend for these two values to change in a parallel manner, as shown graphically in Figure 8. It may be concluded that these reactions are coupled in such a way that a given degree of bond formation is accompanied by a similar amount of bond cleavage. This is the behavior expected for a simple S_N2 displacement reaction.[20] There is no indication of a tendency for a large amount of bond formation to be accompanied by much less bond breaking, as might be expected if only the addition step to form a tetrahedral intermediate were important in the reaction, nor for bond breaking to be

Table VII. Correlation of β Values for Variation of Attacking and Leaving Groups in Nucleophilic Displacement Reactions at the Carbonyl Group

Reaction	β Variation of nucleophile	−β Variation of leaving group	Ref
Alkyl and Aryl Acetates			
Imidazoles and phenyl acetates	0.8	0.8[a]	*b*, *c*, *d*
Acetates and nitrophenyl acetates	0.8[a]	0.7[a]	*c*, *e*, *f*
Amines and phenyl acetates	0.9	1.0	*c*, *g*, *h*
Oxyanions on alkyl acetates	1.5	1.5	*i*
Pyridines on alkyl acetates	1.4	1.5	*i*
Nucleophiles on Acetylpyridiniums[j]			
Nucleophile			
Propylamine	0	0.15	*i*
Trifluoroethylamine	0.8	0.62	*i*
Piperidine	0	0.07	*i*
Morpholine	0.6	0.38	*i*
Piperazine-H$^+$	0.9	0.72	*i*
Hydroxide		0.07	*i*
Methoxide	0.2	0.02	*i*
2,2,2-Trifluoroethoxide	0.3	0.24	*i*
Acetate	0.9	0.74	*i*

[a] Approximate values. [b] T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, **80**, 148 (1958); T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964). [c] Reference 3. [d] Reference 15. [e] V Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc.*, 515 (1968B). [f] Reference 7. [g] Reference 5. [h] T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, **89**, 2106 (1967). [i] This study. [j] The leaving group variation β is calculated from the ratio of rate constants for acetyl-4-methyl- and acetyl-3,4-dimethylpyridinium ions and has an estimated error of ±0.13. The β values for nucleophile variation are approximate values, calculated from the tangent at the particular nucleophile on the Brønsted plot for acetyl-4-methylpyridinium reactions.

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(19) Allowing a generous error of ±10% in the rate constants, the error in the β values is ±0.13; this range is shown in the data plotted in Figure 7.

(20) J. C. Harris and J. L. Kurz, *J. Amer. Chem. Soc.*, **92**, 349 (1970).

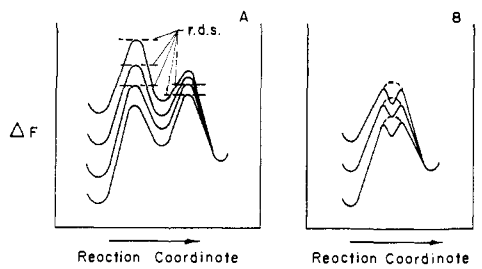


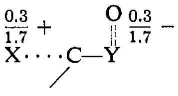
Figure 9. Schematic transition state diagrams for acyl transfer reactions: A, effect of a change in the reactivity of the nucleophile or acyl compound with a relatively stable tetrahedral intermediate and well-separated steps for the attack and breakdown of the intermediate; B, same, for a reaction with no intermediate or an unstable intermediate.

more important than bond making, as might be expected if the reactions approached a monomolecular mechanism of oxocarbonium ion formation. Because of this correlation it is generally more meaningful to consider acyl transfer reactions in terms of "early" or "late" transition states (see below) than in terms of the *relative* amounts of bond formation and cleavage.[21] It is noteworthy that this rough correlation holds also for the acetylpyridinium ions, in which resonance donation from the leaving nitrogen atom to the carbonyl group is not important, indicating that the large sensitivity to the basicity of the leaving group is not necessarily a consequence of inhibition of this type of resonance in the transition state as bond formation to the carbonyl group takes place. A similar correlation of β values for attacking and leaving groups with changing reactivity has been observed by Khan and Kirby for reactions with substituted phenyl dialkyl phosphate triesters[22] (in contrast to the behavior of phosphate monoester dianions).

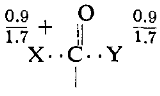
This discussion may be summarized by a division of these reactions into three classes (Table VIII). There is, of course, a continuum of types of reaction with no sharp dividing line between classes, but such a division is useful for purposes of discussion. Typical transition states for the three classes are shown as I, II, and III, in

Table VIII. Classification of Acyl-Transfer Reactions

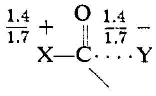
Class		β nucleophile	$-\beta$ leaving group
I	Basic alkoxide (hydroxide) and most esters Basic amines–reactive esters (pK of leaving group <5) Basic amines–acetylpyridinium ions Basic alkoxide–acetyl-$N^+ \lessdot$	0–0.4	0–0.4
II	RO^- and esters (similar pK's of attacking and leaving groups) Most amines–phenyl esters Most amines–acetyl-$N^+ \lessdot$ RO^-–acetyl-$N^+ \lessdot$ (intermediate and low basicity)	0.7–1.0	0.7–1.0
III	Weakly basic RO^-–alkyl esters Most amines–alkyl esters (general base catalysis excepted) Weakly basic RO^- (acetate)–acetylimidazolium ion	1.2–1.6	1.2–1.6



I



II



III

which the numbers represent a typical amount of change in the charge on an attacking or leaving atom, compared to the change in charge for complete reaction. The classification is for reactions in which the transition state has the same net charge as the starting acyl compound and the reactive species of the nucleophile and in which the β values are not altered by general base catalysis. The first class consists of reactions of strongly basic nucleophiles with acyl compounds having good leaving groups, such as basic amines and alkoxide ions with acetylpyridinium ions or AMPP. These reactions have an asymmetric transition state with little bond formation to the attacking group and bond breaking of the leaving group. There is little sensitivity to the basicity of the attacking or leaving groups (β = 0–0.4 for both), but there remains a sensitivity to other properties of both the nucleophile and the acyl group, as manifested by the differences in the reaction rates of AMPP, acetyl-3,4-lutidinium, and acetyl-4-methoxypyridinium ions and of hydroperoxide compared to other oxygen anions. If there is a tetrahedral addition intermediate, this is a transition state for formation of the intermediate. The third class is the converse of the first and involves weakly basic nucleophiles and poor leaving groups. It has an asymmetric transition state with almost complete bond formation to the attacking group and bond breaking of the leaving group (β = 1.2–1.6 for both). If there is a tetrahedral addition intermediate, this transition state involves rate-determining breakdown of the intermediate.

The second category comprises the large number of reactions in which the transition state appears to be more or less symmetrical with respect to the entering and leaving groups; the β values for both are generally in the range of 0.7–1.0 out of a possible 0–1.7. The symmetry of this class is apparent in the reactions of oxyanions with esters and in the reactions of amines with acylpyridinium ions when the entering and leaving groups have similar pK's. It is less obvious when the entering and leaving groups are different, as in the reactions of amines with esters and the reactions of oxyanions with acylpyridinium ions, but the characteristics of these reactions appear to be very similar to those of the former group. In the reactions of amine nucleophiles with phenyl esters of widely varying reactivity[3] and with acetylimidazolium[9,11] and acetylpyridinium ions there is a wide range of reaction rates in which the β value for the attacking amine is 0.9 ± 0.1 before a rather sharp break occurs to the class I reactions; the change appears to be more gradual for the reactions of oxygen anions with both types of acyl compounds. This behavior is difficult to explain in terms of rate-determining formation or breakdown of a moderately stable tetrahedral addition intermediate—either the attack step or the breakdown step should be completely rate determining for most reactions and the sensitivity to the basicity of the attacking and leaving groups should be characteristic of that step (Figure 9A, eq 1).

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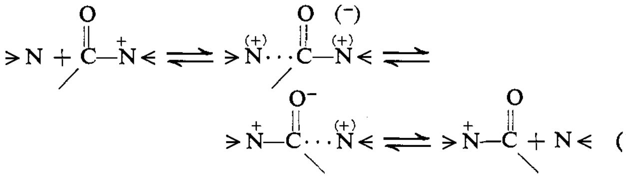
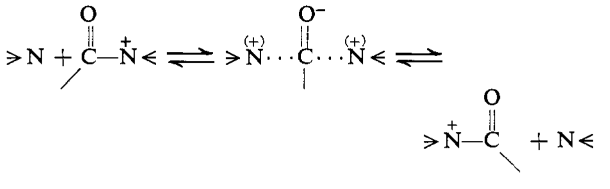
[21] See, for example, J. Hipkin and D. P. N. Satchell, *J. Chem. Soc. B*, 345 (1966).

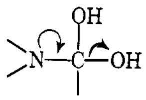
[22] S. A. Khan and A. J. Kirby, personal communication.


(1)

The intermediate, symmetrical region in which both steps are partially rate determining should be small. Instead, the transition between classes I and III appears either to be gradual, as in the oxyanion reactions, or to consist of a very large class II transition region, in the amine reactions. If bond formation and cleavage are rate determining, this suggests either that there is no addition intermediate (eq 2) or that there is such an intermediate, but it is so unstable that the transition states for its formation and breakdown resemble it and are very similar in structure to each other (Figure 9B). It is possible that a rotation (or pseudorotation) of the groups attached to the central carbon atom contributes a significant part of the energy barrier in the transition state. The transition state might then closely resemble a tetrahedral intermediate with almost fully formed bonds to both the entering and leaving groups, and be nearly symmetrical with respect to its electronic properties. If the attacking and leaving groups are very good or very poor the transition state would occur early or late, as in class I or III reactions, respectively, with little or no such movement in the transition state. Pseudorotation of a bipyramidal intermediate is known to be rate determining in certain phosphate reactions.[23]


(2)

The Role of Proton Transfer in Aminolysis. Although general base catalysis is observed for the aminolysis of phenyl acetates, the fact that there is no large difference between the rates of reactions of primary, secondary, and tertiary amines and that all three classes of amines follow similar structure–reactivity correlations[3] suggests that proton transfer plays a relatively small role energetically in the ordinary, second-order reactions of these compounds, which are generally class II reactions. The situation is very different with alkyl acetates. The reaction of pyridines with these esters is a class III reaction with a value of β for the nucleophile of 1.4, much larger than the value of approximately 0.7 for the attack of primary amines on methyl formate.[24] Furthermore, the absolute rate constants for the reactions of primary amines with alkyl esters are some 10^5 larger than those for tertiary amines of comparable basicity,[25] rather than almost equal as in the phenyl acetate series. These differences provide a striking illustration of the importance of proton transfer when the leaving group becomes too poor to be easily expelled by the attacking nucleophile, so that the uncatalyzed reaction falls into class III with a transition state far along the reaction coordinate. The primary and secondary amine reactions take place at a reasonable rate because a proton can be removed to give an anionic tetrahedral intermediate which breaks down by a reaction path not available to tertiary amines.[24] The observed β value of 0.7 for these reactions is for the *formation* of the tetrahedral intermediate and is about midway along the range 0–1.6, in the same region as for class II reactions. The existence of the base-catalyzed pathway for breakdown of the tetrahedral intermediate means that class III reactions are generally not observed for primary and secondary amines; however, the pH-independent region of rate-determining intermediate breakdown that is observed at low pH in these reactions presumably represents either a transition state similar to that of a class III reaction or a breakdown of the uncharged form of the intermediate (*e.g.*, IV).


IV

The "Element Effect." 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 trifluoroethyl thiolacetate are directly proportional to those for the reactions of the same nucleophiles with *p*-nitrophenyl acetate.[26] Based on the reasonable assumptions (1) that the reactions of hydroxide and trifluoroethoxide ions on these esters with weakly basic leaving groups represent rate-determining attack and (2) that the substitution of sulfur for oxygen should cause large differences in relative rate if cleavage of the sulfur or oxygen bond occurred in the transition state of some of the reactions, but not others, these workers postulate that the direct proportionality of the rate constants for the two esters with different nucleophiles means that the transition states for the two reactions are similar and that leaving group bond cleavage is not important in the transition state; *i.e.*, attack of the nucleophile is rate determining in all cases.

Now there is an excellent correlation between the rate constants for the reactions of a series of nucleophiles with AMPP and with acetyl-4-methylpyridinium ion (Figure 3). Since AMPP is an ester with an even better leaving group than *p*-nitrophenyl acetate (pK = 2.0) it is certain that attack of the nucleophile is rate determining in the reactions with hydroxide and trifluoroethoxide ions. Following the above line of reasoning it can be concluded that the attack of phenoxide, *p*-nitrophenoxide, and acetate ions on acetyl-4-methylpyridinium ion involves rate-determining attack. Therefore, from the principle of microscopic reversibility, it follows that in the reaction of pyridine with phenyl acetate, *p*-nitrophenyl acetate, and acetic anhydride the expulsion of the oxygen leaving group is rate determining. This is in direct contradiction to the conclusion reached by Gregory and Bruice for the reactions of a series of amines of widely varying reactivity and, since tertiary

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(23) R. Kluger and F. H. Westheimer, *J. Amer. Chem. Soc.*, **91**, 4143 (1969).

(24) G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968).

(25) A factor of 5 × 10^5 was calculated from the Brønsted plot for reaction of amines with methyl formate,[24] the rate constant for the reaction of 4-methylpyridine with methyl acetate (Table VI), and a factor of 200 for the greater reactivity of methyl formate than methyl acetate, based upon the difference in the rate constants for alkaline hydrolysis (R. A. Fairclough and C. N. Hinshelwood, *J. Chem. Soc.*, 538 (1937); R. Leimu, R. Korte, E. Laaksonen, and U. Lehmuskoski, *Suom. Kemistilehti B*, **19**, 93 (1946); H. M. Humphreys and L. P. Hammett, *J. Amer. Chem. Soc.*, **78**, 521 (1956)).

(26) M. J. Gregory and T. C. Bruice, *ibid.*, **89**, 2121 (1967).

amines show the same behavior as primary and secondary amines with *p*-nitrophenyl acetate,[3] suggests that the application of the "element effect" to these reactions in this way is not valid. Such a correlation shows only that the two compounds being compared have similar transition states for each individual reaction under consideration; if there is a change in the nature of the transition state with changing nucleophile (as there is in the reactions of oxyanions with *p*-nitrophenyl acetate), the correlation shows that this change takes place in a similar manner for both compounds.

It has been pointed out previously that the argument for rate-determining attack of strongly basic amines on phenyl acetate based on the observed products of the hydrolysis of phenyl N-methylacetimidate depends on the uncertain assumption that any tetrahedral intermediate be at equilibrium with respect to proton transfer steps and raises difficulties of interpretation for reactions of weakly basic tertiary amines.[3] The argument for rate-determining amine attack in reactions of phenyl acetates is, therefore, not conclusive, although we believe it is likely that such attack is involved in the rate-determining step of most such reactions. As noted above, this attack may be interpreted in terms of a more or less concerted mechanism, in which bond breaking is in some way coupled to bond making.

Intramolecular Nucleophilic Participation. VIII. Acetolysis of *o*- and *p*-Nitro- and *o*- and *p*-Carbophenoxybenzhydryl Bromides

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Received January 22, 1970

Abstract: In acetic acid, in the presence of sufficient sodium acetate to prevent accumulation of hydrogen bromide in the medium, *o*-nitrobenzhydryl bromide solvolyzes to form *o*-nitrosobenzophenone. When hydrogen bromide is present at moderate concentration, the solvolysis product is exclusively 5-bromo-3-phenyl-2,1-benzisoxazole. Solvolysis rate constants evaluated from the results of runs in which either hydrogen bromide or sodium acetate is initially present are in good agreement. This suggests that the alternate products are derived from a common intermediate formed in the slow step of the reaction. The reactions are considered to proceed with participation of the *o*-nitro group as an internal nucleophile, and this supposition is greatly strengthened by the observation that at 45° the acetolysis rate constant for the bromide in question is of the order of 1500 times that for its *para* isomer. At 45° the acetolysis rate constant for *o*-carbophenoxybenzhydryl bromide is *ca.* 150 times larger than that for its *para* isomer, and this is considered as indicative of the capacity of *o*-$COOC_6H_5$ to participate. The *k*(*ortho*)/*k*(*para*) rate constant ratio for the acetolysis of *o*- and *p*-bromobenzhydryl bromides is of the order of 0.05–0.06 at 45°. This ratio may be used as a rough estimate of the magnitude of steric retardation to acetolysis of benzhydryl bromide as produced by a nonparticipating *ortho* substituent (Br).

The *o*-nitro- and *o*-carbophenoxybenzhydryl bromides hydrolyze significantly more rapidly than do their *para* isomers.[1,2] This is considered to be illustrative of the capacity of the *ortho* substituents in question to participate as internal nucleophiles in reactions at aromatic side chains. In the case of the reaction of *o*-nitrobenzhydryl bromide this explanation is strengthened by the observation that the organic hydrolysis product is *o*-nitrosobenzophenone. Also pertinent in this connection are the facts that *o*-nitrobenzhydrol is converted to the nitroso ketone by *p*-toluenesulfonyl chloride in pyridine and to 5-chloro-3-phenyl-2,1-benzisoxazole by thionyl chloride in chloroform.[3] Furthermore the bromine analog of this isoxazole derivative has been obtained as a product of reaction of *o*-nitrodiphenylmethane and N-bromosuccinimide.[2]

A study of the acetolysis of the nitro- and carbophenoxybenzhydryl bromides has been undertaken with two objectives in mind. First, the substances generated in the reaction of *o*-nitrobenzhydryl bromide have been investigated to determine whether or not the identity of the solvolysis product of this halide is affected by changes in acidity of the medium. It has, in fact, been found that the conditions can be altered so that either *o*-nitrosobenzophenone or 5-bromo-3-phenyl-2,1-benzisoxazole are obtained as the exclusive organic product of the reaction in acetic acid. Second, a comparison of the relative reactivities of each pair of the *ortho*- and *para*-substituted benzhydryl bromides has been made to test the premise that the solvolytic rate influence of a participating *ortho* substituent should become more obvious when an aqueous medium is replaced by one less favorably constituted to provide for nucleophilic solvation of carbon at the reaction center.

Experimental Section

Materials. The *o*- and *p*-nitrobenzhydryl bromides[2,4] and the *o*- and *p*-carbophenoxybenzhydryl bromides[1] were prepared as described previously. The method of preparation of *o*- and *p*-bromodiphenylmethanes has also been described elsewhere.[5] The *o*- and *p*-

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