determined for the four buffers. The scatter of those values implies an uncertainty of about ±2% in the value of $[OH^-]$. Each set of four observed first-order rate constants was plotted as a function of total buffer concentration, and the rate constant for zero buffer concentration (assumed to be $k_0 + k_{OH}[OH^-]$ for the corresponding average value of $[OH^-]$) obtained by linear extrapolation. The values of k_0 and k_{OH} for each temperature were then calculated from the two corresponding extrapolated rate constants.

2,4,6-Trimethylpyridinium perchlorate was prepared from Matheson Coleman and Bell *s*-collidine and perchloric acid, and recrystallized from absolute ethanol to obtain white needles; neutralization equivalent (by titration to the potentiometric inflection point with 0.1 *N* sodium hydroxide): 221.2, 221.6 (calcd: 221.6). Buffers were prepared from weighed quantities of this salt and the calculated amount of standard 0.1 *N* sodium hydroxide.

The values of k_0 and k_{OH} obtained and the corresponding values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are shown in Tables I and II along with comparable values from the literature. The values obtained for k_0 from the measured hydration rates in these collidine buffers are in good agreement with those from reactions run in dilute perchloric acid.[38] The new values obtained for k_{OH} give $\Delta S^\ddagger = -7$ eu, which is in better agreement with expectation than the old value of +8 eu.

Acknowledgment. The authors gratefully acknowledge financial support by the National Science Foundation (Grant GP-4422). The authors also wish to express their appreciation for the work of Mr. L. Motlow, without which this paper might not have been written.

General Acid and General Base Catalysis for the Methoxyaminolysis of Phenyl Acetates[1]

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Abstract: Investigation of the dependence of second-order rate constants for the reaction of a series of substituted phenyl acetates with methoxyamine in aqueous solution at 25° on the concentration of methoxyamine and on pH reveals these reactions to be subject to both general base catalysis, by a second molecule of amine, and general acid catalysis, by a molecule of the conjugate acid of the amine. In addition, these reactions have been found to be subject to general base catalysis by carboxylate anions and to general acid catalysis by carboxylic acids and by other ammonium ions. The following values of ρ have been measured: for the uncatalyzed (or water-catalyzed) methoxyaminolysis, 1.6; for general base catalysis by methoxyamine and acetate, 1.0 and 0.8, respectively; for general acid catalysis by methoxyammonium ion and acetic acid, 0.45 and 0.8, respectively. Thus, general acid and general base catalysis becomes of increasing importance as the reactivity of the substrate decreases, a conclusion consistent with earlier results. The third-order rate constants for general base catalysis of the methoxyaminolysis of *p*-nitrophenyl acetate by a series of carboxylate anions are correlated by a straight line in a Brønsted plot with a slope, β, of 0.45. Third-order rate constants for general acid catalysis of this reaction fall into two categories. In the case of catalysis by carboxylic acids, the rate constants are substantially independent of the acidity of the catalyst ($\alpha = 0$), a result interpreted tentatively in terms of bifunctional catalysis by these species, while in the case of catalysis by ammonium ions, the rate constants decrease with decreasing acidity of the catalyst. The reaction of *p*-nitrophenyl acetate with N,O-dimethylhydroxylamine is also subject to both general acid and general base catalysis. Values of ρ for the reaction of substituted phenyl acetates with piperidine (2.1), ethylenediamine (1.9), morpholine (2.6), and glycine ethyl ester (2.2) were determined.

General acid–base catalysis for nucleophilic reactions at the acyl carbon atom is a well-established phenomenon. The earliest such example is provided by the observation of Kilpatrick in 1928 that acetate ion functions as a general base catalyst for hydrolysis of acetic anhydride.[3] General base catalysis has subsequently been established for hydrolysis of acyl-activated esters,[4] nonactivated esters,[5,6] acetylimidazolium ion,[7] and ethyl trifluorothiolacetate.[8] General acid–base catalysis for those reactions at acyl carbon involving nitrogen nucleophilic reagents is particularly well studied. Seminal studies include the observation of general acid and general base catalysis for phenyl acetate aminolysis in water,[9] general base catalysis for ammonolysis of phenyl acetates in water,[10] and general base catalysis for *n*-butylaminolysis of ethyl formate in ethanol.[11] Subsequently, such catalysis has been established for a variety of esters,[12–15] lactones,[16] thiol esters,[17–20] and thiolactones.[21] A detailed summary

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(1) Supported by Grant AM 08232 from the National Institutes of Health.

(2) Career Development Awardee of the National Institutes of Health.

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(6) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, **86**, 837 (1964).

(7) W. P. Jencks, and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272, 1280 (1959).

(8) L. R. Fedor and T. C. Bruice, *J. Am. Chem. Soc.*, **87**, 4138 (1965).

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

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

(11) J. F. Bunnett and G. T. Davis, *ibid.*, **82**, 665 (1960).

(12) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 833 (1964).

(13) R. B. Martin, A. Parcell, and R. I. Hedrick, *ibid.*, **86**, 2406 (1964).

(14) T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964).

(15) W. P. Jencks and M. Gilchrist, *ibid.*, **88**, 104 (1966).

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(17) T. C. Bruice and L. R. Fedor, *ibid.*, **86**, 738 (1964).

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of this work has been prepared by Bruice and Benkovic.[22]

Substituted phenyl acetates have been widely employed as substrates for study of general acid–base catalysis involving amines as nucleophilic reagents. From certain of the studies cited above, the following tentative generalizations may be drawn. First, general acid and general base catalysis becomes more important as the reactivity of the phenyl acetate decreases. This was first clearly demonstrated for phenyl acetate ammonolysis by Bruice and Mayahi who observed that the term in the rate law second order in ammonia became progressively less important as the electron-withdrawing power of the polar substituent increased.[10] Later experiments have supported this finding.[9,12,14,23] Second, such catalysis is dependent on the nucleophilic reagent possessing a dissociable proton. A particularly nice example of this behavior is provided by general base catalysis for reactions of imidazole with phenyl acetates and related esters.[14,23] Though imidazole reacts as a tertiary amine, its reactions may be promoted by removal of the proton on the secondary nitrogen. Imidazole is the only tertiary amine for whose reactions general base catalysis has been detected. Third, the pattern of general acid–base catalysis for aminolysis of phenyl acetates is complex. Thus, for certain nucleophilic reagents only general base catalysis is observed, while for others both general base and general acid catalysis is found.[22] Reactions of some amines exhibit catalysis by hydroxide ion as well as by the amine itself while others do not.[9,12,24] Specific acid catalysis for these reactions, though reported,[25] could not be confirmed.[26] The currently known pattern of general acid–base catalysis seems likely to undergo several additional changes since it is clear that detection of such catalysis is a sensitive function of reaction conditions including temperature, ionic strength, and nature of the salt required to maintain the ionic strength constant.[15] It is probably best to assume that both tetrahedral intermediate formation and decomposition are subject to general acid–base and specific acid–base catalysis. Thus, rate laws will, in general, take the form

$$k_{\text{obsd}} = k_0 + k_{\text{OH}}(\text{OH}^-) + k_{\text{H}}(\text{H}^+) + \sum_i k_{\text{B}_i}(\text{B}_i) + \sum_j k_{\text{A}_j}(\text{A}_j) \quad (1)$$

Despite this impressive body of experimental information, there exist several uncertainties concerning nucleophilic reactions of phenyl acetates. Indeed, the uncertainties lie at the heart of these reactions. For example, neither the nature of the rate-determining step nor the mechanisms for the observed catalytic pathways nor reactivity–susceptibility to catalysis correlations are well understood. In an effort to provide additional insight into these matters, we have studied the methoxyaminolysis of phenyl acetates in some detail. The results of these and some ancillary investigations are reported herein.

Experimental Section

Materials. Substituted phenyl acetates were synthesized from acetic anhydride and the appropriate phenol according to the method described by Bender and Nakamura.[27] Methoxyamine hydrochloride was obtained from Eastman Organic Chemicals and was recrystallized at least twice prior to use. N,O-Dimethylhydroxylamine hydrochloride was prepared by a known procedure.[28] Other amines were obtained commercially and were recrystallized or redistilled prior to use. Acids and their salts, employed as catalysts and buffers, were also obtained commercially and purified prior to use. Inorganic salts were used without additional purification. Distilled water was employed throughout.

Kinetic measurements were carried out spectrophotometrically with the aid of a Zeiss PMQ II spectrophotometer equipped with a cell holder thermostated at 25°. All esterolytic reactions were followed by observing the appearance of the phenol or phenolate anion as a function of time. In all cases, a sufficient excess of nucleophilic reagent was employed so that pseudo-first-order rate behavior was observed. First-order rate constants were evaluated from the slopes of plots of log $(A_\infty - A_t)$ against time in the usual manner. Second-order rate constants were obtained by dividing the first-order constants by the concentration of nucleophilic reagent in the reactive, free-base, form. The reactions of methoxyamine and N,O-dimethylhydroxylamine with phenyl acetates in the absence of additional buffers exhibited rate laws of the following form.

$$k_2 = k_{\text{obsd}}/(\text{RNH}_2) = k_0 + k_{\text{N}}(\text{RNH}_2) + k_{\text{NH}}(\text{RNH}_3^+) \quad (2)$$

Employing the dissociation constant for the conjugate acid of the nucleophilic reagent, $K = (\text{RNH}_2)(\text{H}^+)/(\text{RNH}_3^+)$, eq 2 may be rewritten as

$$k_2 = k_0 + (\text{RNH}_2)[k_{\text{N}} + k_{\text{NH}}(\text{H}^+)/\text{K}] \quad (3)$$

or

$$k_2 = k_0 + (\text{RNH}_3^+)[k_{\text{NH}} + k_{\text{N}}K/(\text{H}^+)] \quad (4)$$

Employing, for example, eq 3, plots of second-order rate constants against the concentration of nucleophilic reagent in the free-base form (primary plots) yield straight lines from whose intercepts k_0 was evaluated. The slopes of the primary plots are given by $k_{\text{N}} + k_{\text{NH}}(\text{H}^+)/K$ and were measured at several values of (H^+). Secondary plots of these slopes against $(\text{H}^+)/K$ again yielded straight lines from which k_{N} (intercept) and k_{NH}(slope) were evaluated. Alternatively, one may employ eq 4 in the same fashion. Typical secondary plots derived from both eq 3 and 4 are indicated in Figure 2.

The reaction of methoxyamine with phenyl acetates in the presence of added buffers exhibited rate laws of the form

$$k_2 = k_0 + k_{\text{N}}(\text{RNH}_2) + k_{\text{NH}}(\text{RNH}_3^+) + k_{\text{HB}}(\text{HB}) + k_{\text{B}}(\text{B}) \quad (5)$$

in which HB and B refer to the acidic and basic forms of the added buffer system, respectively, and k_{HB} and k_{B} to the associated third-order rate constants. Employing the dissociation constant for HB, eq 5 may be written in a fashion analogous to either eq 3 or 4, and the appropriate rate constants may be derived as outlined above. The intercepts of the primary plots are given by $k_0 + k_{\text{N}}(\text{RNH}_2) + k_{\text{NH}}(\text{RNH}_3^+)$. Since the necessary rate constants and concentrations were known from previous experiments and from experimental conditions, such intercepts were regularly checked for compliance with previously determined quantities. For those reactions in which only general acid or general base catalysis was important, catalytic constants were obtained directly from plots of second-order rate constants against the concentration of the catalytically active species.

All reactions were carried out in aqueous solution containing 3% ethanol or acetonitrile. Ionic strength was maintained at 1.0 throughout with KCl unless noted otherwise. Values of pH were recorded with a Radiometer PHM 4c pH meter equipped with a glass electrode.

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[22] T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1966.

[23] M. Caplow and W. P. Jencks, *Biochemistry*, **1**, 883 (1962).

[24] T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, **80**, 148 (1958).

[25] P. J. Hawkins and I. Piscalnikow, *ibid.*, **77**, 2771 (1955).

[26] T. C. Bruice and R. W. Huffman, cited in ref 22, p 71.

[27] M. L. Bender and K. Nakamura, *J. Am. Chem. Soc.*, **84**, 2577 (1962).

[28] R. T. Major and E. E. Fleck, *ibid.*, **50**, 1479 (1928).

Values of pK_a for certain of the amines employed in this study were evaluated from the measured values of pH of samples of the purified amines carefully neutralized to various extents with hydrochloric acid and from the Henderson–Hasselbach equation.

Results

Second-order rate constants have been determined for the reaction of methoxyamine with *p*-chloro-, *m*-nitro-, *p*-nitro-, 2-chloro-4-nitro-, and unsubstituted phenyl acetates at several concentrations of methoxyamine and at several values of pH. Representative results are collected in Table I. All reactions were carried out in aqueous solution at 25° and ionic strength 1.0. With the single exception of the data for 2-chloro-4-nitrophenyl acetate, the second-order rate constants increase with increasing concentration of methoxyamine for all of the substrates and at all of the values of pH studied. These data indicate that the reaction of methoxyamine with *p*-nitro-, *m*-nitro-, *p*-chloro-, and phenyl acetate is subject to catalysis by a second molecule of methoxyamine, by a molecule of methoxyammonium ion, or by both.

Table I. Second-Order Rate Constants for Reaction of *p*-Chlorophenyl Acetate with Methoxyamine in Aqueous Solution at 25° and Ionic Strength 1.0

pH	$(CH_3ONH_2)_{total}$, *M*	$k_2{}^a$, M^{-1} min^{-1}
3.14	0.2	0.10
	0.4	0.11
	0.6	0.05
	0.8	0.09
	1.0	0.11
4.35	0.2	0.015
	0.4	0.029
	0.6	0.039
	1.0	0.062
4.79	0.2	0.012
	0.4	0.020
	0.6	0.027
	0.8	0.039
	1.0	0.052
5.12	0.2	0.0095
	0.4	0.016
	0.6	0.022
	0.8	0.028
	1.0	0.036
5.60	0.2	0.0064
	0.4	0.0091
	0.6	0.011
	0.8	0.016
	1.0	0.020

[a] $k_2 = k_{obsd}/(CH_3ONH_2)_{free\ base}$.

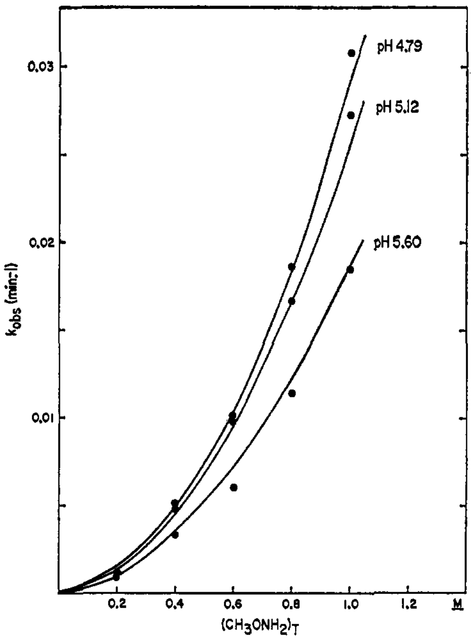


Figure 1. First-order rate constants for the methoxyaminolysis of *p*-chlorophenyl acetate at several values of pH plotted against the total concentration of methoxyamine. Reactions conducted at 25° and an ionic strength of 1.0.

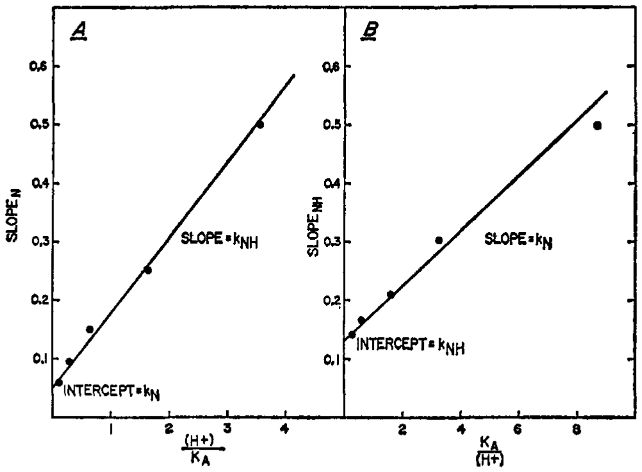


Figure 2. Secondary plots of data for the methoxyaminolysis of *m*-nitrophenyl acetate illustrating the method of arriving at rate constants for the general acid and general base catalyzed terms. k_N and k_{NH} refer, respectively, to the catalytic constants for methoxyamine and methoxyammonium ion. Slope$_N$ and slope$_{NH}$ refer, respectively, to the slopes of plots of second-order rate constants against the concentration of methoxyamine and methoxyammonium ion.

In Figure 1, first-order rate constants for reaction of methoxyamine with *p*-chlorophenyl acetate at three values of pH are plotted as a function of total methoxyamine concentration. As required by the dependence of the second-order rate constants on methoxyamine concentration (Table I), the first-order constants increase more rapidly than the concentration of methoxyamine. The fact that the catalysis becomes more marked as the pH is lowered certainly requires general acid catalysis by methoxyammonium ion but does not exclude general base catalysis by methoxyamine as well. The data for this and the remaining esters studied have been analyzed by the method described in the Experimental Section. In Figure 2, typical secondary plots are presented; in this case, those for *m*-nitrophenyl acetate. Each of the plots in Figure 2 have finite slopes and intercepts; thus the reaction involves both general acid and general base catalysis. Similar analysis of the rate data for the remaining esters reveals that both types of catalysis are again present. The second- and third-order rate constants for methoxyaminolysis of four phenyl acetates are collected in Table II. The solid lines in Figure 1 are calculated lines based on the rate constants for *p*-chlorophenyl acetate given in this table. Thus the indicated rate constants provide a satisfactory description of the reaction kinetics.

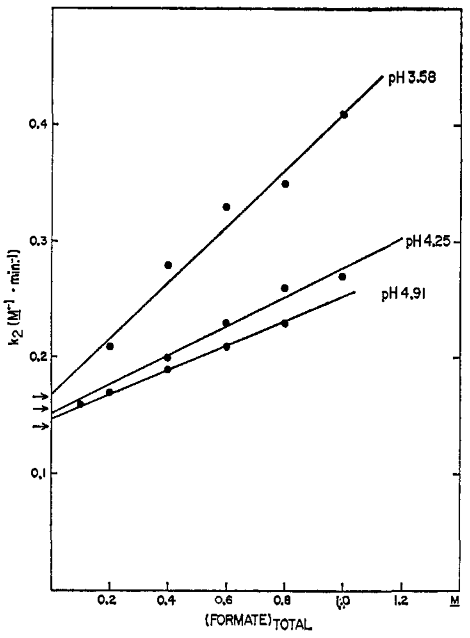


Figure 3. Plot of the second-order rate constants for methoxyaminolysis of *p*-nitrophenyl acetate against the total concentration of a formate buffer at three values of pH. The arrows on the ordinate indicate the calculated intercepts based on the rate constants collected in Table II.

The methoxyaminolysis of phenyl and *p*-nitrophenyl acetates has been previously studied by Jencks and Carriuolo under conditions similar to those employed in this study.[9] The values reported here for the uncatalyzed (or solvent-catalyzed) and general acid catalyzed reactions are in reasonable agreement with those obtained earlier. However, these workers did not observe the relatively minor contribution to these reactions due to general base catalysis.

Table II. Catalytic Constants for General Acid and General Base Catalysis of the Methoxyaminolysis of Substituted Phenyl Acetates in Aqueous Solution at 25° and Ionic Strength 1.0[a]

Subst	k_0, M^{-1} min^{-1}	k_N, M^{-2} min^{-1}	k_{NH}, M^{-2} min^{-1}	k_{Ac}, M^{-2} min^{-1}	k_{HAc}, M^{-2} min^{-1}
H	0.0018	0.005	0.064	0.028	0.062
p-Cl	0.0030	0.0096	0.096	0.030	0.15
m-NO_2	0.013	0.054	0.13	0.10	0.28
p-NO_2	0.12	0.10	0.25	0.18	0.42

[a] The rate constants of this table have the following meanings: k_0, the rate constant for the uncatalyzed or water-catalyzed reaction; k_N and k_{Ac}, those for general base catalysis by methoxyamine and acetate, respectively; k_{NH} and k_{HAc}, those for general acid catalysis by methoxyammonium and acetic acid, respectively.

The methoxyaminolysis of phenyl acetates is subject to general acid–base catalysis by species other than those derived from the nucleophilic reagent itself. For example, second-order rate constants for the methoxyaminolysis of *p*-nitrophenyl acetate are presented as a function of the concentration of formate buffers at three values of pH in Figure 3. At each value of pH, the rate constants increase with increasing buffer concentration. Control experiments reveal that the reaction of formate with this substrate occurs at a negligible rate under the conditions of this experiment; thus the observed rate increases must reflect general acid–base catalysis and not nucleophilic catalysis. Analysis of the data by the methods indicated above reveals that both formic acid and formate anion are effective catalysts, the former species being somewhat the more efficient.

Having established the phenomenon of general acid–base catalysis by carboxylate buffers for methoxyaminolysis reactions, acetate buffers were chosen for more detailed study. In Table III, representative second-order rate constants for catalysis of the methoxyaminolysis of *m*-nitrophenyl acetate by acetate buffers in aqueous solution are collected. For each ester, rate constants were measured at five concentrations of acetate buffer at each of three values of pH. Third-order rate constants for acetic acid and acetate ion were evaluated as described in the Experimental Section. These are collected in Table II.

Table III. Second-Order Rate Constants for Catalysis of Methoxyaminolysis of *m*-Nitrophenyl Acetate by Acetate Buffers in Aqueous Solution at 25° and Ionic Strength 1.0[a]

(Acetate)$_{total}$,	pH		
M	3.73	4.83	5.13
0.1			0.040
0.2	0.12	0.058	0.052
0.4	0.17	0.086	0.085
0.6	0.22	0.13	0.12
0.8	0.28	0.17	0.15
1.0	0.33	0.20	

[a] Rate constants in units of M^{-1} min^{-1}. All reactions were carried out with 0.2 M total methoxyamine.

Second-order rate constants for the uncatalyzed (or solvent-catalyzed) and third-order rate constants for the methoxyamine-, methoxyammonium-, acetate-, and acetic acid catalyzed methoxyaminolyses of phenyl acetates are reasonably well correlated by the σ^- substituent constants. The derived values of ρ, together with several from the literature and several indicated below, are collected in Table IV. In constructing the linear free energy plots, we have adopted the value of σ^- for the *p*-nitro substituent of 1.0 in accord with the

Table IV. Values of ρ for Reactions of Various Nucleophiles with a Series of Substituted Phenyl Acetates

Nucleophilic	Catalyst	ρ	Ref
CH_3ONH_2		1.6	This work
CH_3ONH_2	CH_3ONH_2	1.0	This work
CH_3ONH_2	$CH_3ONH_3^+$	0.45	This work
CH_3ONH_2	CH_3COO^-	0.80	This work
CH_3ONH_2	CH_3COOH	0.8	This work
NH_2NH_2	NH_2NH_2	0.55	14
NH_2NH_2	$NH_2NH_3^+$	0.65	14
Imidazole	Imidazole	0.5	14
Imidazole		1.8	14
NH_3	NH_3	0.55	10
NH_3		2.1	10
$(CH_3)_3N$		2.6	30
Tris(hydroxymethyl)-aminomethane		0.71	*a*
Piperidine		2.1	This work
Ethylenediamine		1.9	This work
Morpholine		2.6	This work
Glycine ethyl ester		2.2	This work

[a] T. C. Bruice and J. L. York, *J. Am. Chem. Soc.*, **83**, 1382 (1961).

Table V. Second-Order Rate Constants for the Methoxyaminolysis of *p*-Nitrophenyl Acetate as a Function of the Concentration of Several Acidic and Basic Species in Aqueous Solution at 25° and Ionic Strength 1.0[a]

Catalyst	Concn, M	pH		
Formic–formate		3.58	4.25	4.91
	0.1	...	...	0.16
	0.2	0.21	0.17	0.17
	0.4	0.28	0.20	0.19
	0.6	0.33	0.23	0.21
	0.8	0.35	0.26	0.23
	1.0	0.41	0.27	
Methoxyacetic–methoxyacetate		3.50	4.32	4.88
	0.1	...	...	0.17
	0.2	0.20	0.15	0.18
	0.4	0.26	...	0.19
	0.6	0.31	0.17	0.19
	0.8	0.34	...	0.20
	1.0	0.38	0.21	
β-Chloropropionate–β-chloropropionic		3.62	4.33	5.23
	0.1	...	...	0.17
	0.2	0.28	0.21	0.19
	0.4	0.35	0.25	0.20
	0.6	0.44	0.31	0.21
	0.8	0.49	0.35	0.24
	1.0	0.54	0.39	
Chloroacetic acid		2.72		
	0.2	0.27		
	0.4	0.36		
	0.6	0.40		
	0.8	0.45		
	1.0	0.50		
Propionic acid		3.75		
	0.2	0.23		
	0.4	0.34		
	0.6	0.40		
	1.0	0.55		
Pyridinium[b]		4.38		
	0.0	0.17		
	0.1	0.20		
	0.3	0.23		
	0.5	0.25		
	0.7	0.26		
Glycine ethyl ester·HCl		4.50		
	0.0	0.12		
	0.2	0.14		
	0.4	0.12		
	0.6	0.15		
	0.8	0.11		
Ammonium ion		4.40		
	0.0	0.15		
	0.2	0.15		
	0.4	0.14		
	0.6	0.15		
	0.8	0.15		

[a] Rate constants in units of M^{-1} min^{-1}. Methoxyamine concentration 0.20 M except in those experiments involving glycine ethyl ester and ammonium ion in which the concentration was 0.15 M. [b] Second-order rate constants corrected for reaction of the catalyst as a nucleophilic reagent, *i.e.*, $k_2 = (k_{\text{obsd}} - k_N)/(\text{CH}_3\text{ONH}_2)$.

suggestion of Bruice and Benkovic.[14] With the exception of the apparent uncatalyzed reaction, all the data is correlated more satisfactorily by this value than by the usual value of 1.27. In the case of the rate constants for the uncatalyzed reaction, use of 1.0 accentuates the tendency of the values to show an upward curvature in the Hammett plot as the substrates become more reactive. At any event, the values of ρ calculated from these plots are not to be considered to have a high degree of accuracy. In the first place, the rate constants themselves are derived by the indirect means outlined previously and are not particularly reliable and, in the second place, only four substrates have been examined. We do believe that the values of ρ are approximately correct and that the differences in the various values are real.

p-Nitrophenyl acetate was chosen as substrate for investigation of the effects of catalyst structure on catalytic efficiency in the methoxyaminolysis reaction. In Table V, second-order rate constants for this reaction are presented as a function of the concentration of several potential catalysts. Catalysis is observed for formate, chloroacetate, propionate, methoxyacetate, β-chloropropionate, and pyridine buffers but not with the conjugate acids of glycine ethyl ester and ammonia. For the latter cases, maximum catalytic constants have been calculated assuming that a 50% increase in second-order rate constant has been overlooked. Data for the formate, methoxyacetate, and β-chloropropionate buffers were analyzed as previously indicated. Buffers derived from chloroacetic and propionic acids were studied at a single value of pH only. Under the conditions of these experiments, the observed catalysis is largely due to the carboxylic acids since (a) at the indicated values of pH the acids, rather than the carboxylate anions, are the predominant species in solution, and (b) the catalytic constants from the acids are larger than those for the anions. Thus, catalytic constants for propionic acid and chloroacetic acid were derived directly from plots of second-order rate constants against the concentration of the acid in solution. A similar procedure was adopted for the case of the pyridine-catalyzed reaction. In this case, however, it was necessary to apply a small correction to account for the direct nucleophilic reaction of pyridine with the *p*-nitrophenyl acetate. In no other case was this correction necessary. Catalytic constants for methoxyaminolysis of *p*-nitrophenyl acetate are collected in Table VI.

Table VI. Catalytic Constants for General Acid and General Base Catalysis of the Methoxyaminolysis of *p*-Nitrophenyl Acetate

Catalyst	pK_a[a]	k_3, M^{-2} min^{-1}
Acetic acid	4.76	0.42
Acetate	4.76	0.18
Formic acid	3.75	0.38
Formate	3.75	0.085
Methoxyacetic acid	3.53	0.36
Methoxyacetate	3.53	0.046
β-Chloropropionic acid	3.98	0.46
β-Chloropropionate	3.98	0.10
Propionic acid	4.87	0.45
Chloroacetic acid	2.86	0.52
Methoxyammonium ion	4.60	0.25
Methoxyamine	4.60	0.10
Pyridinium ion	5.14	0.13
Glycine ethyl ester cation	7.75	0.0075[b]
Ammonium ion	9.21	0.009[b]
Water	15.74	0.0022

[a] Of the catalyst or the conjugate acid of the catalyst, as the case may be. [b] Maximum rate constants; see text.

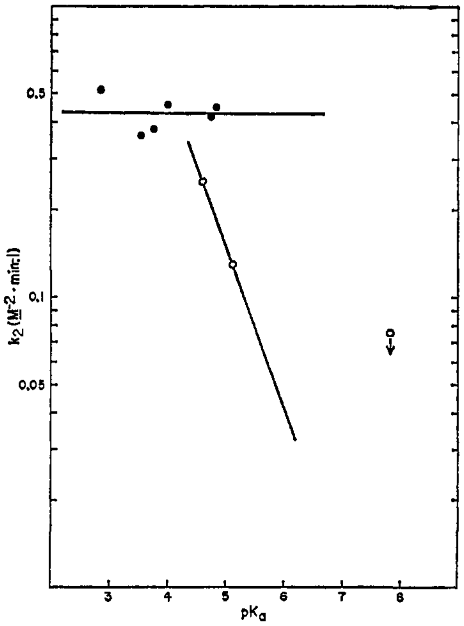


Figure 4. The catalytic constants for several acids as catalysts for the methoxyaminolysis of *p*-nitrophenyl acetate plotted against their respective values of pK_a: ●, carboxylic acids; ○, ammonium ions (see Table V).

In Figure 4, catalytic constants for general acid catalysis of *p*-nitrophenyl acetate methoxyaminolysis are plotted against the appropriate values of pK_a. The acids fall into two groups. For the carboxylic acids, the catalytic constants are largely independent of acid strength ($\alpha = 0$) while for the ammonium ions a marked dependence is observed.

In Figure 5, catalytic constants for general base catalysis of the methoxyaminolysis of *p*-nitrophenyl acetate are plotted against the values of pK_a for their conjugate acids. The rate constants are reasonably well correlated by a single line with a slope near 0.45.

In Table VII, second-order rate constants for reaction of *p*-nitrophenyl acetate with N,O-dimethylhydroxylamine are presented as a function of the total concentration of the latter species. At each value of pH studied, the second-order rate constants increase with increasing concentration of the nucleophilic reagent.

Table VII. Second-Order Rate Constants for Reaction of *p*-Nitrophenyl Acetate with N,O-Dimethylhydroxylamine in Aqueous Solution at 25° and Ionic Strength 1.0

pH	$(CH_3ONHCH_3)_{total}$, M	k_2, M^{-1} min^{-1}
3.84	0.2	0.035
	0.6	0.041
	0.8	0.045
	0.9	0.058
4.82	0.2	0.035
	0.4	0.037
	0.6	0.041
	0.8	0.046
	0.88	0.047
5.73	0.2	0.035
	0.4	0.037
	0.6	0.041
	0.8	0.042
	0.88	0.043

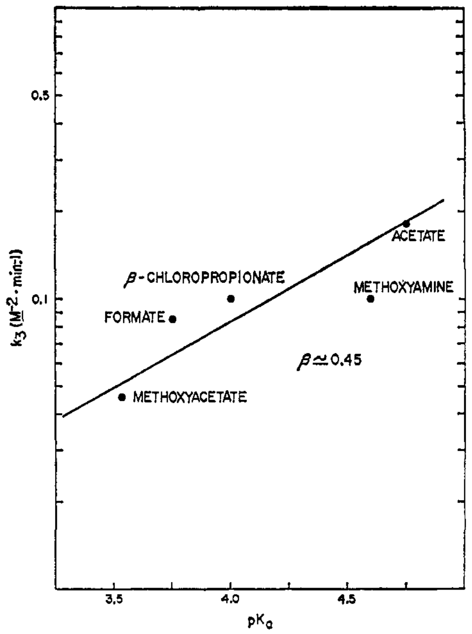


Figure 5. Catalytic constants for several bases as catalysts for the methoxyaminolysis of *p*-nitrophenyl acetate plotted against the values of pK_a of their respective conjugate acids (see Table V).

Analysis of these data according to the procedures outlined earlier reveals that both N,O-dimethylhydroxylamine and its conjugate acid are catalysts. Thus the reaction of this species is also subject to general acid and general base catalysis. The derived rate law is $k_{obsd} = 0.032(N) + 0.01(N)^2 + 0.02(N)(NH)$ in which N and NH refer to the nucleophilic reagent and its conjugate acid, respectively.

Second-order rate constants for reaction of a series of substituted phenyl acetates with piperidine, ethylenediamine, morpholine, and glycine ethyl ester were determined in aqueous solution at 25° and an ionic strength of 0.50; the results are compiled in Table VIII. In arriving at the second-order rate constants, the following values of pK_a for the conjugate acids of the nucleophilic reagents were employed: morpholine, 8.62, piperidine, 11.24, glycine ethyl ester, 7.76, and ethylenediamine, 9.98. Each of these values was determined at ionic strength 0.50 and 25° in this study and are in reasonable agreement with literature values. In accord with the results of Jencks and Carriuolo,[9] the reaction of piperidine with phenyl acetate was observed to be subject to catalysis by hydroxide ion and the reactions of glycine ethyl ester with phenyl acetate and with *p*-methoxyphenyl acetate were observed to be subject to catalysis by a second molecule of amine. The second-order rate constants for the uncatalyzed reactions were obtained by extrapolation to zero hydroxide ion and zero amine concentration, respectively, as previously described.[9] The rate constant for reaction of piperidine with phenyl acetate is in excellent agreement with that previously obtained at ionic strength 1.0; our values for rate constants for reaction of glycine ethyl ester with phenyl and *p*-nitrophenyl acetates are somewhat larger than those obtained at the higher ionic strength.[9] The second-order rate constants are well correlated by the σ^- substituent constants, as indicated in Figure 6. The derived values of ρ are included in Table IV. These data are appreciably

Table VIII. Second-Order Rate Constants for the Reaction of a Series of Substituted Phenyl Acetates with Several Nucleophilic Reagents in Aqueous Solution at 25° and Ionic Strength 1.0

Subst	Nucleophilic reagent	pH	Concn range, M	k_2, M^{-1} min^{-1}
H	Piperidine	10.93	0.1–0.5	4.9 } 4.1[a]
		11.55	0.015–0.075	7.2
	Ethylenediamine	10.04	0.05–0.25	1.6
		10.52	0.05–0.25	1.6
	Morpholine			0.031[b]
	Glycine ethyl ester	8.55	0.1–0.5	0.011[c]
p-Cl	Piperidine	10.94	0.05–0.25	23
		11.55	0.015–0.075	22
	Ethylenediamine	10.04	0.05–0.25	5.1
		9.67	0.03–0.15	4.9
	Morpholine	8.53	0.2–0.8	0.11
	Glycine ethyl ester	8.96	0.1–0.5	0.047
p-CH$_3$CO	Piperidine	10.68	0.02–0.10	310
	Morpholine	8.20	0.05–0.04	2.5
		9.22	0.05–0.25	2.6
	Glycine ethyl ester	8.82	0.1–0.5	0.84
m-NO$_2$	Ethylenediamine	8.80	0.01–0.05	28
p-OCH$_3$	Glycine ethyl ester	8.55	0.1–0.5	0.0047[c]
p-NO$_2$	Piperidine	10.06	0.005–0.025	1700
	Ethylenediamine			420[b]
	Morpholine	8.20	0.05–0.4	25
		9.22	0.05–0.25	26
	Glycine ethyl ester	7.90	0.1–0.5	5.4

[a] Rate constant extrapolated to zero hydroxide ion concentration (see text). [b] Reference 9. [c] Rate constants obtained by extrapolation to zero amine concentration (see text).

better correlated by σ^- for *p*-nitro of 1.27 than by a value of 1.0, and the former value is employed.[29]

Discussion

Data presented above indicate that the rate laws for reaction of methoxyamine with substituted phenyl acetates have the form indicated in eq 1 in which general acid catalysts include ammonium ions and carboxylic acids and general base catalysts include amines and carboxylate anions. That term in the rate law which is second order in the concentration of methoxyamine clearly indicates general base catalysis of the reaction of methoxyamine by a second such molecule and that which is first order in both methoxyamine and its conjugate acid clearly indicates general acid catalysis of this reaction by the methoxyammonium ion. Other terms are not necessarily so uncomplicated. Thus the term which is first order in both methoxyamine and a carboxylate anion might represent general base catalysis of the methoxyamine reaction by carboxylate or of the carboxylate reaction by methoxyamine. The second alternative is exceptionally unlikely since (a) the reactions of carboxylate ions with phenyl acetates actually involve general base catalysis of the reaction of water and not the direct nucleophilic attack of carboxylate,[30,31] and (b) reaction of carboxylate ions with phenyl acetates under the conditions employed here are so slow that they were not detectable with respect to the rate of the methoxyamine reaction, and (c) it is difficult to write a mechanism for such a reaction. Points a and b apply with equal force to the terms in the rate law which are first order in both methoxyamine and carboxylic acid. Thus these reactions are certainly the catalyzed attack of methoxyamine acting as nucleophilic reagent. This is apparently the first example of general acid–base catalysis for ester aminolysis which involves catalysts other than the amine or its conjugate acid.

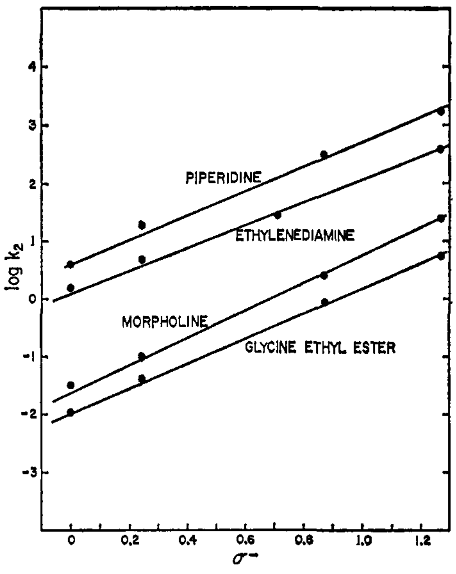
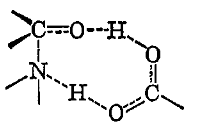


Figure 6. The logarithm of second-order rate constants for reaction of a series of nucleophilic reagents with a series of substituted phenyl acetates plotted against the σ^- substituent constants.

The Brønsted plot for general acid catalysis of the methoxyaminolysis of *p*-nitrophenyl acetate is most interesting (Figure 4). Catalytic constants for the carboxylic acids are, within the error of the experimental measurements, independent of the acid strength of the catalyst; that is, α is near or equal to zero. In contrast, the catalytic constants for the two ammonium ions for which catalysis could be detected are markedly sensitive to the acid strength of the catalyst although the data do not permit evaluation of an α value. A reasonable explanation for this behavior is that carboxylic acids function as bifunctional catalysts for the methoxyaminolysis reactions. One possible visualization of such catalysis is depicted below as formula I.



I

In this formulation, the carbonyl oxygen acts as a general base catalyst by withdrawing a proton from the attacking nucleophilic reagent in the transition state. At the same time, the hydroxyl component acts as a general acid catalyst by partially protonating the carbonyl oxygen atom of the substrate. Since a polar

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[29] On the basis of an extended collection of data for reactions of the type of interest here, Dr. J. F. Kirsch has concluded that the best σ value for the *p*-nitro function is 0.89. If one employs this value for the *p*-nitro substituent and 0.58 for the *p*-acetyl substituent, a value arrived at by allowing the same fractional mixing of the ordinary σ and σ^- values as employed to obtain the above value for *p*-nitro, the data are correlated just as well as with the values employed here. We are indebted to Dr. Kirsch for providing us with these data prior to publication and for performing a least-squares regression analysis on our data.

[30] T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, 85, 1 (1963).

[31] A. R. Butler, and V. Gold, *J. Chem. Soc.*, 1334 (1962).

substituent in the carboxylic acid catalyst will affect the proton-donating powers of the hydroxyl function and the proton-withdrawing powers of the carbonyl oxygen atom in opposite fashion, the independence of the catalytic constants of the nature of such substituents receives a natural explanation. Since such a transition state is impossible for monofunctional general acid catalysts such as ammonium ions, the appreciable value of α for these catalysts is also in accord with this suggestion. A similar proposal has been made for carboxylic acid catalysis of methyl orthobenzoate hydrolysis[32] although the basis on which the suggestion rests has been challenged.[33,34]

The value of β, 0.45, for general base catalysis of the methoxyaminolysis of *p*-nitrophenyl acetate is similar to those previously obtained for such catalyses of the hydrolysis of ethyl dichloroacetate, 0.47,[4] and of the hydrolysis of ethyl trifluorothiolacetate, 0.33.[8] The position of the point for methoxyamine in the Brønsted plot (Figure 5) is interesting in light of previous results. In the present case, this species is seen not to be an abnormally effective catalyst. In contrast, it is abnormally efficient as a catalyst for hydrolysis of ethyl trifluorothiolacetate.[8] Fedor and Bruice have observed that the α effect[35] is more important for general acid–base catalyzed hydrazinolysis of thiol esters than for the uncatalyzed reaction.[36] Thus, the importance of an unshared pair of electrons adjacent to the nucleophilic center in the determination of catalytic efficiencies is an apparent function of the nature of the reaction.

Values of ρ for the methoxyamine-, methoxyammonium-, acetate-, and acetic acid catalyzed methoxyaminolysis of phenyl acetates are appreciably smaller than that for the unassisted or solvent-assisted reaction (Table IV). This corroborates previous findings on general acid and base catalysis for reactions of hydrazine,[14] general base catalysis for reactions of ammonia,[10] and general base catalysis for reactions of imidazole[14,23] (Table IV). The decreased sensitivity of the catalyzed reactions to the nature of the polar substituents presumably reflects the tendency of these reactions to reach the transition state rather earlier along the reaction coordinate compared to the uncatalyzed reactions.[37,38]

The reaction of the secondary amine, N,O-dimethylhydroxylamine, with *p*-nitrophenyl acetate is also subject to general acid and general base catalysis (Table VII). Reactions of secondary amines with phenyl acetates have previously been reported to be subject to catalysis by hydroxide ion[9] and the reactions of imidazole are known to be subject to general base catalysis.[14,23] Reactions of secondary amines with thiol esters are subject to general acid and general base catalysis.[36] Although the reaction of this amine is somewhat less susceptible to catalysis than is that of methoxyamine, presumably reflecting the more stringent steric requirements for the incorporation of two molecules of the secondary amine into the transition state, general acid and general base catalysis seem to be about equally affected. Thus, the ratio k_{NH}/k_H for the reaction of methoxyamine with *p*-nitrophenyl acetate is 2.5 while that for the reaction of N,O-dimethylhydroxylamine is 2.0. This finding is in accord with the conclusion of Fedor and Bruice that general acid and general base catalysis for nucleophilic reactions at the thiol ester bond are about equally sensitive to steric hindrance.[36]

The correlation of these data into meaningful transition states for general acid and general base catalysis of ester aminolysis is a formidable task. Difficulties stem from several sources. In the first place, there exist a large number of kinetically indistinguishable alternatives. Thus, one can write nine kinetically equivalent alternatives for general acid catalysis and seven kinetically equivalent alternatives for general base catalysis of ester aminolysis depending on which step in the reaction sequence is rate determining, the precise type of catalysis, how the catalytic groups are disposed, and so forth. These 16 possibilities include only those for which proton transfer is concerted with covalent bond formation to carbon, only those which conform to the "anthropomorphic rule,"[39] and only those for which no specific role for solvent is envisaged. The actual total number of possibilities must be at least 50. A reasonable number of these have been supported as correct formulations at one time or another.

In the second place, the nature of the rate-determining step for aminolysis of phenyl acetates is uncertain. These reactions must proceed *via* the formation and subsequent decomposition of a tetrahedral intermediate but the relative rates of the steps are unclear. It is certainly likely that as the nature of the leaving group is varied or as the nature of the nucleophilic reagent is varied, a transition in rate-determining step might occur. Such behavior has been demonstrated for the reaction of imidazole with a series of acetyl esters by Kirsch and Jencks.[6] These workers find a transition from rate-determining attack of imidazole on esters with good leaving groups to rate-determining decomposition of the tetrahedral intermediate with esters with poorer leaving groups. The phenyl acetates fall largely into the former class. There exists no substantial evidence for change of rate-determining step with any phenyl acetate as the nucleophilic reagent is varied nor with any single nucleophilic reagent as the phenyl acetate is varied. Even if the rate-determining step were known in the absence of catalysts, the situation might not be entirely clear since the catalysts themselves might strongly affect the partitioning of the tetrahedral intermediate. An example of such behavior has been discovered by Cunningham and Schmir.[40]

In the third place, catalysis may be either symmetric, in the sense that catalytic mechanisms for the formation and decomposition of the tetrahedral intermediate are similar, or asymmetric, in which case they are not. For example, the hydroxylaminolysis of several thiol esters occurs with symmetrical general acid–base catalysis[17,18,41] but the hydrolysis of ethyl trifluorothiolacetate occurs with unsymmetrical general base catalysis.[42] In view of the generality of acid–base catalysis for ester aminolysis, it seems likely that both

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[33] R. H. DeWolfe and J. L. Jensen, *ibid.*, **85**, 3264 (1963).

[34] E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).

[35] J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

[36] L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 4117 (1964).

[37] G. S. Hammond, *ibid.*, 77, 334 (1955).

[38] J. E. Leffler, *Science*, **117**, 340 (1953).

[39] J. E. Reimann and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3973 (1966).

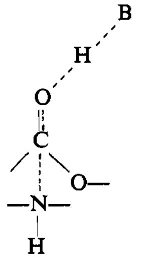
[40] B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

[41] T. C. Bruice and L. R. Fedor, *ibid.*, **86**, 739 (1964).

[42] L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 5697 (1964).

formation and decomposition of the tetrahedral intermediate are subject to such catalysis.

In view of the above considerations, a detailed analysis of all the existing data in terms of possible transition states for the general acid–base catalyzed reactions seems premature. However, it is possible that the apparent bifunctional catalysis by carboxylic acids (I) provides an important clue as to the correct transition states. If we assume, for the moment, that the monofunctional catalytic pathways partake of the individual aspects of the bifunctional transition state indicated in I, then we are led to the following transition states for general acid (II) and general base catalysis (III). Transition state III, which involves true general base catalysis, has previously been suggested by Jencks and Carriuolo[9] who have presented several arguments in its favor. Transition state II is similar to that proposed for general acid catalyzed attack of nucleophilic reagents on carbonyl substrates.[39,43–47] Concerning these transition states, two points are of interest. First, each of them is consistent with known data, much of which has been summarized above. Second, the failure to observe general acid catalysis for reactions involving tertiary amines (see the introductory section) does not provide a strong argument against transition state II, which might well occur with such amines, since such catalysis has never really been searched for with weakly basic tertiary amines whose conjugate acids, therefore, are reasonably strong acids and would be expected to be efficient catalysts.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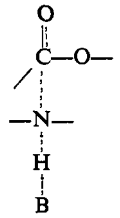
III

Previous considerations regarding structure–reactivity relationships suggest that the value of ρ for reaction of a series of structurally related amines with substituted phenyl acetates might be a linear function of the pK_a of the nucleophilic reagent.[43,44,48] With this in mind, values of ρ for piperidine, morpholine, ethylenediamine, and glycine ethyl ester reactions with phenyl acetates were determined (Table IV). These values do not, in fact, vary in any systematic fashion with basicity of the nucleophilic reagent. Examination of these data in reference to more comprehensive collections (see ref 14 and 22) suggest that basicity *per se* is not the most important factor in the determination of ρ for these reactions.

[43] E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 4319 (1962).

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Solvolysis of Bicyclo[2.1.0]pentane-1-methyl *p*-Nitrobenzoate[1]

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Received February 13, 1967

Abstract: Bicyclo[2.1.0]pentane-1-methanol (**1a**) was synthesized in a five-step reaction sequence from cyclobutanecarboxylic acid *via* 1-cyclobutenecarboxylic acid (**7**), the pyrazoline ester **8**, and the bicyclo[2.1.0]pentanecarboxylic acid ester **11**. The *p*-nitrobenzoate ester of **1a** was solvolyzed in 60% aqueous acetone at 50° to yield 3-methylenecyclopentanol (**12a**), and the rate of the reaction was 400,000 times faster than that of cyclopropylmethyl *p*-nitrobenzoate. Possible reasons for the large rate enhancement are discussed.

The remarkable facility of cyclopropane rings to stabilize carbonium ions has been demonstrated repeatedly. Cyclopropylcarbinyl cations are exceptionally stable, and the rates of reactions leading to them from cyclopropylcarbinyl, cyclobutyl, and allycarbinyl derivatives are greatly accelerated in comparison to related lesser strained, saturated systems. Considerable interest attends the nature of these rearrangements, and the structures of the intermediate carbonium ions have been the object of a large number of experimental studies and theoretical calculations.[3–5]

As part of a program to investigate the effects of conformation and strain on the reactivity of carbinyl derivatives attached to angular positions of a bicyclic fused ring system,[6] bicyclo[2.1.0]pentane-1-methanol (**1a**) has been prepared and the solvolytic rearrangement of its *p*-nitrobenzoate ester **1b** studied. The alcohol **1a** is a member of a homologous series, which in-

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[1] This work was supported in part by Grant GP-3890, National Science Foundation.

[2] National Science Foundation Postdoctoral Fellow, 1964–1965.

[3] For recent reviews see: (a) N. C. Deno, *Progr. Phys. Org. Chem.*, **2**, 129 (1964); (b) R. Breslow, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., Chapter 4; (c) M. J. S. Dewar and A. P. Marchand, *Ann. Rev. Phys. Chem.*, **16**, 321 (1965).

[4] For a thorough bibliography of recent work, see P. von R. Schleyer and G. W. Van Dine, *J. Am. Chem. Soc.*, **88**, 2321 (1966).

[5] (a) L. Birladeanu, T. Hanafusa, B. Johnson, and S. Winstein, *ibid.*, **88**, 3217 (1966); (b) M. Vogel and J. D. Roberts, *ibid.*, **88**, 2262 (1966).

[6] For the previous paper in this series, see W. G. Dauben and P. Laug, *Tetrahedron*, **20**, 1259 (1964).