[CONTRIBUTION FROM THE GRADUATE DEPARTMENT OF BIOCHEMISTRY, BRANDEIS UNIVERSITY]

General Base Catalysis of the Aminolysis of Phenyl Acetate[1]

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Rates of aminolysis and ammonolysis of phenyl acetate have been determined under conditions of controlled *p*H and ionic strength in aqueous solution. In addition to the uncatalyzed reaction of free amine, the reactions of all amines examined except imidazole are subject to catalysis: glycine, ammonia, glycylglycine and glycine ethyl ester to general base catalysis by a second molecule of amine, piperidine and morpholine to hydroxide ion catalysis, dimethylamine and *n*-butylamine to both general base and hydroxide ion catalysis, methoxyamine to general acid catalysis by methoxyammonium ion and hydroxylamine to both general base and general acid catalysis. General base catalysis by glycine and by ammonia is only slightly decreased in deuterium oxide. Possible structures of the transition states for the catalyzed reactions are considered in the light of these results.

The classical experiments of Betts and Hammett established that the ammonolysis of methyl phenylacetate in methanol is base-catalyzed, as shown experimentally by a more than first-order dependence on the concentration of free amine in unbuffered solution.[2] As pointed out in their paper, this base catalysis could involve a pre-equilibrium to form the highly reactive amide ion

$$RNH_2 + \text{base} \overset{\text{fast}}{\rightleftharpoons} RNH^- + \text{base } H^+ \quad (1a)$$

$$RNH^- + \text{ester} \xrightarrow{\text{slow}} \text{products} \quad (1b)$$

or the formation of a ternary complex which could decompose to give products

$$RNH_2 + \text{base} + \text{ester} \rightleftharpoons [\text{complex}] \longrightarrow \text{products} \quad (2)$$

These two mechanisms differ by the absence or presence of the molecule of catalyzing base in the activated complex and correspond to specific and general base catalysis, respectively. More recent experiments[3-7] have confirmed these findings and demonstrated a number of catalytic effects of hydroxylic reagents in non-aqueous solvents,[4] but have not resulted in a clear conclusion as to the relative importance of specific and general base catalysis in these reactions.

A number of acyl transfer reactions from acetylimidazole to nucleophilic reagents with a replaceable hydrogen atom have recently been shown to be general base catalyzed, and it has been suggested that this catalysis occurs through removal of a proton from the attacking reagent in the transition state.[8] Further, clear cut evidence for general base catalysis is available for reactions involving attack of amines on thiol esters[9] and activated aromatic compounds,[10] although interpretations as to the mechanism of the catalysis differ. Since it seemed likely that a reaction mechanism which would avoid the formation of the highly unstable amide ion would provide a facile path for ester aminolysis, the present study was undertaken to evaluate the importance of general base catalysis in these reactions in aqueous solution at 25° under conditions of controlled *p*H, ionic strength and base concentration. Phenyl acetate was chosen for study because it has a convenient reaction rate under these conditions, it is possible to study aminolysis by amines of both greater and lesser basicity than the leaving group and the reaction course may be conveniently followed spectrophotometrically by measuring the release of phenol or phenolate ion.

Bunnett and Davis have independently obtained evidence for general base catalysis in the aminolysis of formate esters in alcohol solution.[11]

Experimental

Materials.—Amines, with the exception of reagent grade dimethylamine, were redistilled from KOH or recrystallized shortly before use and stored in aqueous solution as the hydrochlorides at 5°. Amine buffers were prepared just before use by addition of KOH to concentrated solutions of the amine hydrochloride or zwitterion. Neutralization of glycine ethyl ester hydrochloride was carried out carefully at 0° just before use to avoid hydrolysis and rate constants for reactions with phenyl acetate were calculated from runs in concentrated solutions (0.4 to 1.0 *M*) at *p*H 7.6, which were complete before appreciable decomposition had taken place. *p*-Nitrophenyl acetate (PNPA) and redistilled phenyl acetate were dissolved in water and used after less than a week of storage at 5°; during this time there was no appreciable hydrolysis of either compound. KOH (Baker) contained less than 1% carbonate. Water for reagents and reaction mixtures was boiled to remove dissolved CO_2. Deuterium oxide, 99.8%, was obtained from the Atomic Energy Commission through the courtesy of the Department of Chemistry, Harvard University. Water and deuterium oxide were glass distilled before use. Reagents which contained readily exchangeable hydrogen were dissolved in D_2O, evaporated to dryness, and redissolved in D_2O before use in experiments in D_2O solution.

Rate Measurements.—Reaction mixtures were prepared, generally in a 5-ml. volume (1–2 ml. for deuterium oxide experiments), and temperature equilibrated in a thermostat at 25.0 ± 0.1°. The reaction was started by addition of ester and the reaction mixture was transferred to a 3- or 1-ml. quartz cuvette and placed in the thermostated cell compartment of a Zeiss PMQ II or Beckman DU spectrophotometer. Phenol or phenolate release was followed at 270 mμ using 5×10^{-4} *M* phenyl acetate in the reaction mixtures; occasional experiments in alkaline solution were followed at 280–300 mμ with more dilute phenyl acetate. *p*-Nitrophenolate and *p*-nitrophenol release were followed at 400 and 330 mμ, respectively, using 5×10^{-5} *M* PNPA. For slow reactions the sample was kept in the water-bath between readings; the temperature of samples in the thermostated cell compart-

(1) Publication No. 40 of the Graduate Department of Biochemistry, Brandeis University, Waltham, Mass.

(2) R. L. Betts and L. P. Hammett, THIS JOURNAL, **59**, 1568 (1937).

(3) J. H. Gorvin, *J. Chem. Soc.*, 732 (1945).

(4) J. G. Miller, A. R. Day and co-workers, THIS JOURNAL, (a) **70**, 1946 (1948); (b) **71**, 1245 (1949); **72**, 5635 (1950); (d) **73**, 5393 (1951); (e) **75**, 953 (1953); (f) **75**, 1150 (1953); (g) **75**, 4664 (1953); (h) **78**, 4372 (1956); (i) **80**, 5963 (1958).

(5) R. Baltzly, I. M. Berger and A. A. Rothstein, *ibid.*, **72**, 4149 (1950).

(6) P. J. Hawkins and I. Piscalnikow, *ibid.*, **77**, 2771 (1955).

(7) W. H. Watanabe and L. R. DeFonso, *ibid.*, **78**, 4542 (1956).

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

(9) J. Th. G. Overbeek and V. V. Koningsberger, *Koninkl. Nederl. Akad.*, **B57**, 464 (1954).

(10) J. F. Bunnett and J. J. Randall, THIS JOURNAL, **80**, 6020 (1958), and references quoted therein,

(11) J. F. Bunnett and G. T. Davis, *ibid.*, **82**, 655 (1960).

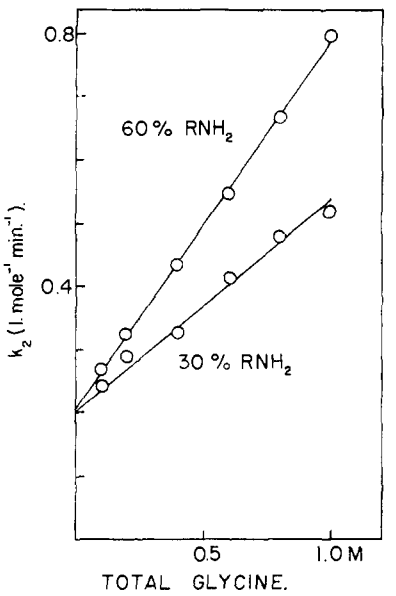


Fig. 1.—The observed second-order rate constants for the reactions of phenyl acetate with glycine buffers in deuterium oxide at 25° as a function of glycine concentration.

ments was shown to vary less than 0.1° in an hour. Samples were stoppered or covered with polyethylene film; the runs with ammonia were carried out in glass-stoppered cuvettes. Phenol, phenolate and *p*-nitrophenolate were shown to follow Beer's law up to absorbancies higher than those used in these experiments. Reactions were generally followed to 60–90% completion with at least 8–10 readings as well as a final reading. For very slow reactions at low concentrations of methoxyamine and glycine ethyl ester the final readings obtained with high amine concentrations were used. Reactions which were followed to completion showed the same final readings at all concentrations of amine, indicating that the reverse reaction is not significant under these conditions. All experiments were carried out with a large excess of amine or hydroxide ion and followed pseudo first order kinetics. Rate constants were obtained by plotting the extent of the reaction, $x_\infty - x_t$, against time on semi-logarithmic graph paper and calculating the pseudo first order constants from the equation $k_1 = 0.693/t_{1/2}$. Second order rate constants were obtained by dividing each observed first order rate constant by the concentration of free amine and were plotted against the concentration of amine, hydroxide ion or ammonium ion. The slope of the resulting straight line gave the third order catalytic constant for amine, hydroxide ion or ammonium ion, respectively, and the intercept gave the second order rate constant for the uncatalyzed reaction; an example is shown in Fig. 1. For hydroxylamine, *n*-butylamine and dimethylamine, which showed more than a single type of catalysis, such plots were made at several *p*H values and the relative contributions of the various forms of catalysis evaluated from the catalytic constants at each *p*H. For these reactions the rate constants and conclusions were checked with experiments at constant total amine concentration and varying *p*H over the range of amine dissociation. KCl was added to all reaction mixtures to maintain a constant ionic strength of 1.0. The contribution of zwitterions to the ionic strength was neglected, but, at an ionic strength of 1.0, this introduces no serious error since identical rate constants for the uncatalyzed and glycinate catalyzed reactions of glycine with phenyl acetate were obtained at two-fold different relative concentrations of glycine zwitterion (*cf.* Fig. 2). In order to avoid sodium ion effects on the glass electrode, no sodium salts were used. Ethylenediamine tetraacetic acid (EDTA, 10^{-4} *M*) was added to reaction mixtures containing hydroxylamine or methoxyamine to avoid occasional erratic results apparently due to a heavy metal-catalyzed decomposition. The *p*H of each reaction mixture was determined at the end of the experiment with a Beckman model G *p*H meter using general purpose or type E-2 glass electrodes standardized with *p*H 7 buffer and also with 0.01 *N* KOH at *p*H 11.94 for alkaline solutions. The rate constants for hydroxide ion catalyzed reactions were calculated for hydroxide ion activity using the observed *p*H and $K_W = 10^{-14}$; the rate constants given in Table II would accordingly require correction by a constant factor to obtain rate constants based on hydroxide ion concentration.

Hydrolysis Rates.—The rate of alkaline hydrolysis of phenyl acetate at 25.0° in 1 *M* KCl was determined in quadruplicate in 0.005 and 0.01 *M* KOH and KOD in water and deuterium oxide. Second order rate constants, based on OH^- and OD^- concentrations, of 69 l. mole^{-1} min.$^{-1}$ and 93 l. mole^{-1} min.$^{-1}$ for the reactions with OH^- and OD^-, respectively, were obtained. The k_{OD^-}/k_{OH^-} ratio for this reaction is accordingly 1.35, which is close to the ratio of 1.33 for ethyl acetate hydrolysis.[12] In order to avoid corrections for activity coefficients in 1 *M* KCl, the apparent *p*H and *p*D of these solutions were measured and the rates of hydrolysis expressed as log $k_{hyd} = pH - C$ with $C = 12.01$ and 12.20 for water and deuterium oxide solutions, respectively; these expressions were used to correct the observed rate constants in the aminolysis experiments for hydrolysis. The results agreed well with the observed rates extrapolated to zero amine concentration. Because of uncertainties as to the significance and measurement of *p*D with the glass electrode, measurement of the deuteroxide-catalyzed piperidine aminolysis, which requires appreciable correction for hydrolysis at high *p*H, was not considered reliable and is not reported; in the glycine aminolysis the corrections were small and a large uncertainty in *p*D would not affect the results. To further ensure that this procedure gave correct hydrolysis rates at less alkaline *p*H and that there was not a significant neutral hydrolysis, the rates of phenyl acetate disappearance at *p*H 9.86 and 10.55 were measured in phenol buffer by a slight modification of Lipmann and Tuttle's method for determination of active acetyl groups as hydroxamic acid[13]; the average value of *C* was found to be 12.03. Similar experiments were carried out in a series of phosphate and borate buffers of varying concentration from *p*H 5.9 to 9.7. Specific rate accelerations at constant *p*H with increasing concentrations of both of these buffers were observed, and while a careful study of the rates under these conditions was not made, the rates extrapolated to zero buffer concentration agreed with the above equation within experimental error at all *p*H values examined and ruled out the presence of an appreciable uncatalyzed neutral hydrolysis.

Analysis of Products.—Aminolysis of phenyl acetate with a number of amines was allowed to proceed under conditions in which the amine or hydroxide ion catalyzed reaction accounted for a large fraction of the total reaction. The reaction mixture then was analyzed for amides by a slight modification of the procedure of Katz, Lieberman and Barker[8] and the result compared with authentic amide, prepared from acetyl chloride and the appropriate amine in ether. The results (Table I) show that amides are the major product of

TABLE I

RECOVERY OF AMIDES FROM THE AMINOLYSIS OF PHENYL ACETATE

Aminolysis carried out for 2 hours at 25°. Reaction mixtures and standard solutions of the appropriate amide were then boiled for 90 minutes with hydroxylamine to form hydroxamic acid which was determined as the ferric chloride complex.[8]

Amine	R_2NH, *M*	$R_2N^+H_2$, *M*	Klett reading: Reaction mixture	Klett reading: Amide control	Recovery, %
Ammonia	0.6	0.4	252	270	94
Glycine	.6	.4	200	215	93
Morpholine	.3	.2	165	167	99
Piperidine	.5	.5	131	135	97
Butylamine	.5	.5	128	153	84
Dimethylamine	.1	.1	96	138	70

the reactions and rule out the possibility that an appreciable part of the catalyzed reaction represents a base-catalyzed hydrolysis. Brouwer, *et al.*,[14] have shown that acetylimida-

(12) W. F. K. Wynne-Jones, *Chem. Revs.*, **17**, 115 (1935).

(13) W. P. Jencks, THIS JOURNAL, **80**, 4581, 4585 (1958).

(14) D. M. Brouwer, M. J. v. d. Vlugt and E. Havinga, *Koninkl. Nederl. Akad.*, **B60**, 275 (1957).

TABLE II

RATE CONSTANTS FOR THE AMINOLYSIS OF PHENYL ACETATE AT 25° AND IONIC STRENGTH 1.0 ACCORDING TO THE RATE LAW $v = k_1(\text{ester})(\text{amine}) + k_{RNH_2}(\text{ester})(\text{amine})^2 + k_{OH}(\text{ester})(\text{amine})(OH^-) + k_{RNH_3^+}(\text{ester})(\text{amine})(RNH_3^+)$

Amine	pK_a[a]	k_1, l. mole^{-1} min.$^{-1}$	k_{RNH_2}, l.^{2} mole^{-2} min.$^{-1}$	k_{OH^-}, l.^{2} mole^{-2} min.$^{-1}$	$k_{RNH_3^+}$, l.^{2} mole^{-2} min.$^{-1}$
Glycine	9.78	0.26	1.16	..	..
in D_2O		0.21	1.06	..	..
with PNPA		155	..	..	..
Ammonia	9.21	0.14	0.85	..	..
in D_2O		.14	.58	..	..
Glycylglycine	8.25	.0090	.044	..	..
Glycine ethyl ester	7.75	.0054	.022	..	..
with PNPA		4.0	..	..	..
Piperidine	11.22	4.3	..	400	..
in D_2O		3.6	..	[c]	..
Dimethylamine	10.64	4.5	14.0	2430	..
n-Butylamine	10.59	4.5	5.0	1900	..
Morpholine	8.36	0.0315	..	1030	..
Imidazole	6.95	.520	..	..	..
Hydroxylamine	5.97	.70	6.0	..	1.7
with PNPA[b]		110	..	..	..
Methoxyamine	4.60	0.0015	..	..	0.087
with PNPA		0.20	..	..	0.32
Hydroxide ion[d]	15.8	69			

[a] Of the conjugate acid; ref. 19 and J. T. Edsall and J. Wyman, "Biophysical Chemistry," Academic Press, Inc., New York, N. Y., 1958. [b] Ref. 13. [c] Not determined. [d] Included for comparison.

zole is formed in the reaction of phenyl acetate with imidazole. The reaction of hydroxylamine with phenyl acetate, like that with PNPA,[13] gives predominantly O-acetylhydroxylamine and only a small fraction of the expected amount of hydroxamic acid concurrently with phenol release. Hydroxamic acid formation was found to follow strict first-order kinetics at rates corresponding to the rates of hydroxamic acid formation from O-acetylhydroxylamine[13] and about one-fifth as fast as the rates of phenol release. Extrapolation of hydroxamic acid formation gave $x_\infty - x_t$ values at zero time corresponding to 94 ± 2% of the x_∞ value at 0.1, 0.2, 0.5 and 1.0 *M* hydroxylamine concentrations, showing that the immediate product of the reaction is over 90% O-acetylhydroxylamine in both the catalyzed and uncatalyzed reactions.

Acid Dissociation Constants in Water and 99% Deuterium Oxide.—The K'_{HA}/K'_{DA} ratios of anilinium ion and glycine were measured by comparison with acetic acid and phenol, essentially by the method of Martin and Butler.[15] To 5×10^{-4} *M* solutions of aniline in H_2O and D_2O were added 0.01 volume aliquots of a series of 2 *M* aqueous acetate buffers. The absorbance of free aniline was determined at 280 mμ. A similar procedure likewise was employed with 5×10^{-4} *M* phenol, using 0.01 volume of 1.82 *M* glycine buffers and measuring phenolate absorption at 300 mμ; in each case at least seven different buffers were employed over the range of dissociation of the reference acid. The average K'_{HA}/K'_{DA}: K'_{HB}/K'_{DB} ratios for anilinium–acetic acid and for phenol–glycine were found to be 1.08 and 1.17, respectively. Assuming that these *ratios* are independent of the ionic strength[16] and taking the K_{HA}/K_{DA} ratios for acetic acid to be 3.3[17] and for phenol, by comparison with other phenolic acids[15,17] to be 4.1, this gives the similar ratios 3.6 and 3.5 for anilinium ion and glycine, respectively. These may be compared to the values 3.1 and 3.4 obtained by Schwarzenbach[18]; these results were criticized by Rule and La Mer, however, because of uncertainties regarding the liquid junctions used in the determinations.

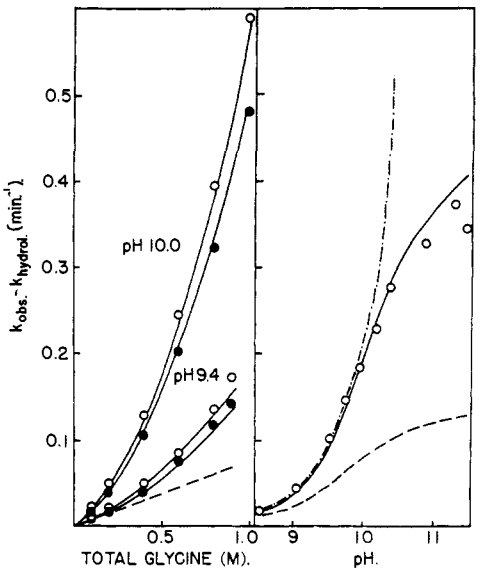


Fig. 2.—The rates of reaction of glycine with phenyl acetate at 25° in water (open circles) and deuterium oxide (closed circles) as a function of glycine concentration and *p*H; the *p*H values refer to the aqueous solutions. KCl was added to all reaction mixtures to give a constant K^+ concentration of 1.0 *M*; ——, calculated from the rate constants given in Table II; — — — —, calculated for no glycine catalysis; —·—·—·, calculated on the assumption that the increase in rate at *p*H 9.75 is due to hydroxide ion catalysis.

Results and Discussion

The rate of aminolysis of phenyl acetate by glycine at 25° increases with more than the first power of the glycine concentration in a series of glycine buffers of increasing concentration and constant *p*H (Fig. 2). From the variation in the observed second-order rate constant with glycine concentration (Fig. 1), the rate constants for both the uncatalyzed and the glycine-catalyzed reactions with glycine were calculated (Table II). The possibility of catalysis by hydroxide ion was evaluated by studying the rate as a function of glycine concentration at two different *p*H values and at a constant total glycine concentration over a wide range of *p*H (Fig. 2). The calculated rates for the sum of the uncatalyzed and glycine-catalyzed reactions are shown as solid lines in the figure; the calculated rates for a reaction without glycine catalysis and for a hypothetical hydroxide ion catalyzed reaction are shown as dashed lines. Although there is some scatter of the points at high *p*H owing to the large hydrolysis correction, the results serve to rule out a significant contribution of a hydroxide ion catalyzed reaction and agree satisfactorily with the calculated rates for glycine catalysis. In moderately concentrated glycine solutions the catalyzed reaction accounts for the major part of the total observed rate; in 0.6 *M* glycine, for example, 73% of the total rate is due to the glycine-catalyzed reaction. In deuterium oxide solution the rates of both the uncatalyzed and the glycine catalyzed reactions are only slightly lower

(15) D. C. Martin and J. A. V. Butler, *J. Chem. Soc.*, 1366 (1939).

(16) Although K'_{HA} and K'_{DA} are, of course, dependent on ionic strength, this dependence may be expected to be similar in H_2O and D_2O so that the K'_{HA}/K'_{DA} *ratios* given should be a reasonable first approximation to the thermodynamic ratios; *cf.* ref. 15.

(17) C. K. Rule and V. K. LaMer, THIS JOURNAL, **60**, 1974 (1938).

(18) G. Schwarzenbach, *Z. Elektrochem.*, **44**, 46 (1938).

(19) H. K. Hall, Jr., THIS JOURNAL, **79**, 5441 (1957).

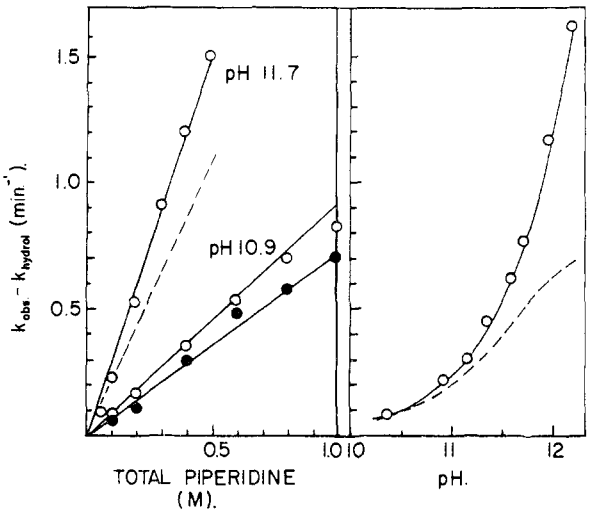


Fig. 3.—The rates of reaction of piperidine with phenyl acetate at 25° and ionic strength 1.0 in water (open circles) and deuterium oxide (closed circles) as a function of piperidine concentration and pH; pH values refer to the aqueous solutions: solid lines, calculated from the rate constants in Table II; dashed lines, calculated for no base catalysis.

than in water solution at the same buffer compositions (solid circles, Fig. 2).

High concentrations of KCl increase the reaction rate in both 0.1 and 0.8 M glycine (Table III). Both the catalyzed and uncatalyzed reactions are therefore favored by increasing ionic strength and presumably proceed through activated complexes with more ionic character than the starting materials; the increases in rate, however, are small compared to the magnitude of the catalyzed reaction.

TABLE III

EFFECT OF IONIC STRENGTH ON THE AMINOLYSIS OF PHENYL ACETATE BY GLYCINE AT 25.0°

Added KCl, M	$k_{obsd.}$, min.$^{-1}$ 0.1 M glycine[a]	$k_{obsd.}$, min.$^{-1}$ 0.8 M glycine[a]
0	0.024	0.36
0.24	.025	
.48	.027	0.40
.96	.025	0.43
1.92	.034	
3.2	.043	

[a] Glycine buffer, 60% potassium glycinate.

The reaction of phenyl acetate with piperidine, in marked contrast to that with glycine, shows no evidence of more than first-order dependence on amine concentration at constant pH, but increases in rate with increasing pH faster than the concentration of free piperidine (solid line, Fig. 3) and thus shows specific hydroxide ion catalysis.

Rate constants for the uncatalyzed, general base catalyzed and hydroxide ion catalyzed reactions of phenyl acetate with a number of other amines are shown in Table II. With the exception of glycine ethyl ester, each reaction was studied at five or more different concentrations of amine buffer at each of two different pH values as shown in Table IV. Although space does not permit presentation of the complete data, the agreement of the experimental points with the calculated rates was, in

TABLE IV

EXPERIMENTAL CONDITIONS FOR THE DETERMINATION OF RATE CONSTANTS AT 25.0 ± 0.1° AND IONIC STRENGTH 1.0

Amine	Fraction as free base	Apparent pH	Concn. range, M	Number of terminations
Glycine	0.3	9.4	0.1–0.9	6
	.6	10.0	.1–1.0	6
	.1–0.98	8.5–11.4	.5	10
In D_2O	.3		.1–0.9	6
	.6		.1–1.0	6
With PNPA	.3	9.4	.008–0.04	5
	.6	9.9	.002–0.020	6
Ammonia	.3	9.1	.1–1.0	6
	.6	9.7	.1–1.0	6
In D_2O	.6		.1–1.0	6
Glycylglycine	.4	8.2	.1–1.0	6
	.7	8.8	.1–1.0	6
Glycine ethyl ester	.4	7.6	.1–1.0	6
With PNPA	.4	7.6	.1–1.0	6
	.7	8.2	.1–1.0	6
Piperidine	.2	10.9	.1–1.0	6
	.5	11.7	.05–0.5	6
	.1–0.8	10.4–12.2	.2	8
In D_2O	.2		.1–1.0	6
Dimethylamine	.2	10.4	.1–1.0	6
	.5	11.1	.05–0.5	6
	.1–0.7	10.1–11.5	.2	12
n-Butylamine	.2	10.4	.1–1.0	6
	.5	11.1	.05–0.5	6
	.1–0.7	10.0–11.4	.2	7
Morpholine	.3	8.4	.1–0.6	6
	.6	9.0	.1– .6	6
Imidazole	.4	7.0	.1– .8	5
	.7	7.6	.1– .8	5
Hydroxylamine	.3	5.7	.1–1.0	6
	.7	6.5	.1–1.0	6
	.10–0.96	5.1–7.6	.2	10
Methoxyamine	.1	3.6	.2–1.0	3
	.3	4.2	.2–1.0	3
	.6	4.8	.2–1.0	3
	.9	5.9	.2–1.0	3
With PNPA	.3	4.2	.1–1.0	6
	.6	4.9	.1–1.0	6

all cases, as good or better than shown in Figs. 1–3 for the reactions of glycine and piperidine. The reactions of ammonia, glycylglycine, glycine ethyl ester and hydroxylamine show general base catalysis by a second molecule of amine, but do not show detectable catalysis by hydroxide ion. The reaction with hydroxylamine proceeds predominantly to give O-acetylhydroxylamine; the attack of oxygen is, therefore, also subject to general base catalysis. Morpholine, like piperidine, reacts with hydroxide ion catalysis, but no general base catalysis. Dimethylamine and n-butylamine represent intermediate cases with both general base catalysis, shown by a more than first-order dependence on amine concentration at constant pH, and hydroxide ion catalysis, shown by an increase in reaction rate with increasing pH which is greater than can be accounted for by the uncatalyzed and general base catalyzed reactions alone. Good agreement of observed with calculated rates was

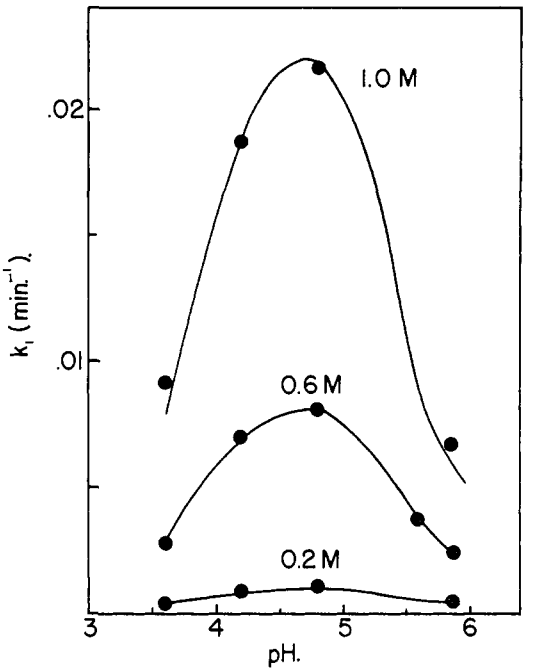


Fig. 4.—The reaction of methoxyamine with phenyl acetate as a function of pH and total methoxyamine concentration at ionic strength 1.0 and 25°.

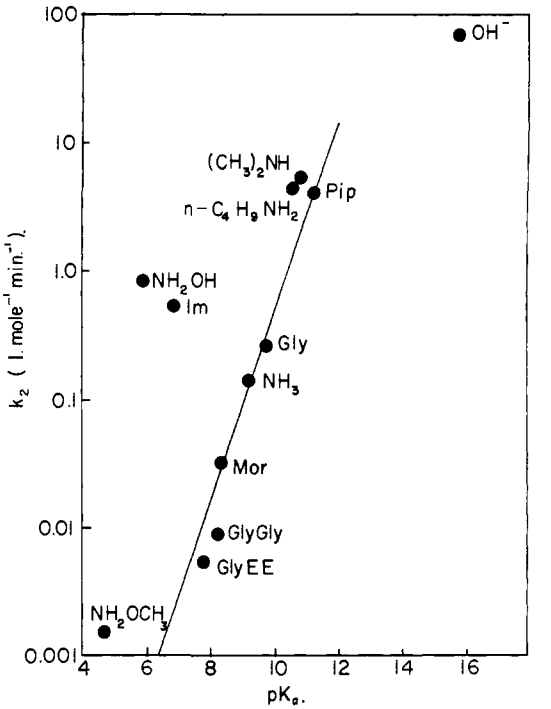


Fig. 5.—Rates of the uncatalyzed reactions of phenyl acetate as a function of the basicity of the attacking reagent.

found at 7–12 different pH values with a constant total concentration of amine plus ammonium ion.

No general or specific base catalysis was found of the reactions of imidazole with phenyl acetate at two different pH values, confirming the results obtained by Bender and Turnquest at a single pH,[20a] nor of the reactions of glycine and glycine ethyl ester with p-nitrophenyl acetate, a more reactive compound with a better leaving group than phenyl acetate.

Hawkins and Piscalnikow have interpreted their data on the reaction of butylamine with α-naphthyl acetate in aqueous solution on the basis of simultaneous acid and specific base catalyzed reactions.[6] The results shown in Figs. 1–3 and Table II rule out the presence of a significant acid catalyzed reaction for the reactions of phenyl acetate with strong bases. However, the reaction of the weak base, methoxyamine, with phenyl acetate in relatively acidic solution shows a rate maximum at the pK_a of methoxyamine and a more than first order dependence on methoxyamine concentration (Fig. 4). The agreement of the observed rates with those calculated from the rate law

$$v = k(\mathrm{RNH_2})(\mathrm{ester}) + k_{\mathrm{RNH_3^+}}(\mathrm{RNH_2})(\mathrm{RNH_3^+})(\mathrm{ester})$$

(solid lines, Fig. 4) establish general acid catalysis for this reaction. Smaller contributions of general acid catalyzed reactions are found in the reactions of PNPA with methoxyamine, of phenyl acetate with hydroxylamine (Table II) and of O-acetylhydroxylamine with hydroxylamine.[13] Previously demonstrated catalytic effects of ammonium salts on aminolysis in relatively non-polar solvents have been interpreted as acid catalysis[4g,21] but have not been clearly differentiated from salt effects.[7,22]

The reactivities of the amines examined generally increase with increasing basicity and the logarithms of the rate constants for the uncatalyzed reactions fall near a line of slope 0.73 when plotted against the pK_a of the conjugate acid of the amine (Fig. 5). Considerably greater scatter was found in plots against the σ^*-values recently collected by Hall.[19] The agreement is probably more apparent than real since it is likely that primary and secondary amines fall near the same line because the greater steric requirements of the latter are approximately offset by the abnormally high ratio of basicity to nucleophilic reactivity (due to specific solvation of primary ammonium ions in water) of the former.[18,23] The remarkably high reactivity of imidazole, which reacts as a tertiary amine[8,20] but is only slightly hindered, is in agreement with this interpretation. The abnormally high reactivity of hydroxylamine, which attacks with the ordinarily only weakly nucleophilic oxygen atom, is discussed elsewhere.[13] No reaction could be observed, over the hydrolysis blank, with the sterically hindered molecule, t-butylamine. If it is assumed that lone pair electrons must be equatorial for nucleophilic attack, the normal reactivities of piperidine and morpholine are consistent with, and provide some further support for, the recent conclusion of Aroney and Le Fèvre that the free electron pair on these molecules is predominantly

(20) (a) M. L. Bender and B. W. Turnquest, THIS JOURNAL, **79**, 1656 (1957); (b) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957).

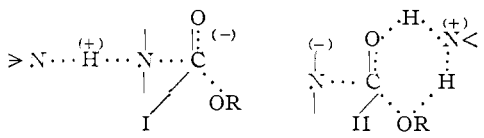
(21) P. K. Glasoe, J. Kleinberg and L. F. Audrieth, *ibid.*, **61**, 2387 (1939).

(22) P. K. Glasoe, L. D. Scott and L. F. Audrieth, *ibid.*, **63**, 2965 (1941).

(23) A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1293 (1949); R. G. Pearson and D. C. Vogelsong, THIS JOURNAL, **80**, 1038, 1048 (1958).

equatorial.[24] It may be noted that there is no evidence of a sharp break in the curve, suggestive of a fundamental change in reaction mechanism, as the basicity of the attacking amine becomes less than that of the leaving phenolate ion. For those amines which show only general base catalysis, the rate constants for the base catalyzed reaction also increase with increasing basicity and are numerically generally about five times larger than the constant for the uncatalyzed reaction with the same amine.

The observed general base catalysis could proceed either by removal of a proton from a molecule of attacking amine by a second molecule of amine (I) or by a kinetically indistinguishable specific base–general acid catalyzed reaction in which a proton is removed from the reacting amine in a pre-equilibrium (either before or after addition to the carbonyl group) and the second amine molecule acts as a general acid catalyst in its ammonium form (II); two mechanisms involving



I II

addition of an amine molecule to the carbonyl group followed by displacement by a second amine molecule are ruled out for reasons which are considered elsewhere.[8] Mechanism I is favored for the aminolysis of phenyl acetate for the following reasons: (1) With a Brönsted coefficient of less than 1, a reaction will proceed most readily by a path which does not involve the formation of unstable intermediates such as the amide anion. General base catalysis avoids the formation of such an intermediate by removing a proton in the transition state (which may be preceded by weakly-bonded intermediates) as the relatively stable phenoxide ion is being expelled.

(2) General acid catalyzed addition of a proton to aid phenol expulsion in the forward reaction (II) requires general base catalyzed removal of a proton from attacking free phenol in the reverse reaction. At *p*H 10, catalysis by glycine causes a fourfold increase in the rate of the forward reaction and, in the absence of an effect on the equilibrium constant, must cause a similar increase in the rate of the reverse reaction. But since phenol is already half converted to phenolate anion at *p*H 10, such catalysis could cause, at most, a twofold increase in rate.

(3) The absence of catalysis in the reactions of imidazole with phenyl acetate and PNPA[20] and of pyridine with PNPA[20] is difficult to explain by mechanism II, but is reasonable for mechanism I since these compounds react as tertiary amines[8,20] and do not require the removal of a proton in the transition state.[25]

Mechanism I implies that the attack of oxygen anions on amides, as in alcoholysis or hydrolysis, should be general acid catalyzed. Although direct evidence for this is lacking, Laidler has interpreted the volume change, entropy and solvation of the activated complex in amide hydrolysis as evidence for bonding of water through hydrogen to the departing nitrogen[26] and such bonding is, in fact, general acid catalysis by water.

The presence of general base catalysis in ester aminolysis (or nucleophilic aromatic substitution[10,27]) does not in itself distinguish between a direct displacement mechanism and one involving a tetrahedral addition intermediate[28] since the transition states for these mechanisms (*e.g.*, I) have the same stoichiometric composition and differ only in the extent to which various bonds have been formed or broken. Thus, while it can be argued that general base catalysis can influence the direction of breakdown of an addition intermediate to give products rather than starting materials, it can equally well be argued that, in a simple displacement reaction, general base catalysis increases the nucleophilic reactivity of the attacking base by removing a proton in the transition state. In the catalyzed reactions of piperidine, dimethylamine and *n*-butylamine, it is unlikely that an addition intermediate is of kinetic significance, since such an intermediate, if formed, should nearly always break down[29] to expel the more weakly basic phenolate anion. Since it would then not be in equilibrium with starting materials, it would exist only after the rate-limiting step of the reaction and catalysis of its breakdown could not affect the rate.

Molecular models of the transition states for aminolysis by piperidine, morpholine, dimethylamine and *n*-butylamine reveal that catalysis by a second amine molecule would be sterically hindered. The observed hydroxide ion catalysis in these reactions may therefore be general base catalysis which is only evident with the relatively smaller hydroxide molecule.

Proton transfer in the catalyzed reactions may proceed through an intermediate water molecule rather than directly; there is evidence that this is the predominant pathway for proton transfer between an amine and its conjugate acid in aqueous solution.[30]

Although other possibilities are not excluded, a transition state similar to that for the base-catalyzed reactions is proposed for the general acid-catalyzed aminolyses (III); the bond from nitrogen to carbon may be partly or fully formed, depending on whether or not a tetrahedral addition compound is an intermediate.

(24) M. Aroney and R. J. W. LeFèvre, *Proc. Chem. Soc.*, 82 (1958).

(25) Since the preparation of this manuscript, the "cage" tertiary amine, triethylenediamine (pK_a' 8.8), has been shown to react with phenyl acetate at *p*H 8.7 and 9.3 with a rate constant of 0.0090 l. mole^{-1} min.$^{-1}$ without specific or general base catalysis; this provides further support for this argument.

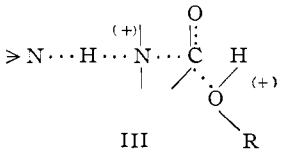
(26) K. J. Laidler and P. A. Landskroener, *Trans. Faraday Soc.*, **52**, 200 (1956); K. J. Laidler and D. Chen, *ibid.*, **54**, 1026 (1958).

(27) The possibility does not appear to have been excluded that the apparent decrease in the catalytic constant for hydroxide catalysis with increasing hydroxide concentration in these reactions might be due to formation of charge transfer complexes with the nitroaromatic compound (J. B. Ainscough and E. F. Caldin, *J. Chem. Soc.*, 2528 (1956)).

(28) (a) M. L. Bender, THIS JOURNAL, **73**, 1626 (1951); (b) M. L. Bender and R. D. Ginger, *ibid.*, **77**, 348 (1955); (c) M. L. Bender, R. D. Ginger and J. P. Unik, *ibid.*, **80**, 1044 (1958).

(29) K. B. Wiberg, *ibid.*, **77**, 2519 (1955).

(30) E. Grunwald, A. Loewenstein and S. Meiboom, *J. Chem. Phys.*, **27**, 630 (1957); A. Loewenstein and S. Meiboom, *ibid.*, **27**, 1067 (1957).



III

The rates of the general base catalyzed reactions of phenyl acetate with glycine and with ammonia are 1.1 and 1.5 times faster in water than in deuterium oxide (Table II). Rate differences of this magnitude may be expected simply from the solvent properties of deuterium oxide.[31] The absence of a significant deuterium isotope effect in these reactions is unexpected, since they must almost certainly involve a proton transfer in the rate-limiting step.[32] One possible explanation is that "bond-making" of hydrogen or deuterium to the catalyzing amine molecule is as important as "bond-breaking" from the positively charged nitrogen atom in the activated complex; a similar explanation has been proposed by Wiberg[33] to explain the absence of a deuterium isotope effect in the transfer of a proton from -OH to C^-. Similarly, there is no significant difference between the rates of proton transfer from H_3O^+ and from D_3O^+ in the ketonization of methylacetylacetone enol[31] and in the general acid catalyzed mutarotation of glucose,[34] for which there is evidence that proton transfer occurs in the rate-limiting step. This may be the result of an anomalously small difference in the zero point vibrational energies of H_3O^+ and D_3O^+, which is reflected in the greater tendency of D_3O^+ to donate a deuteron to bases of both greater and lesser basicity than water.[15,17,35] This does not seem to be the explanation for the lack of an isotope effect with $H_2N^+<$ and $D_2N^+<$, however, since anilinium ion and glycine were found to have approximately the same K'_{HA}/K'_{DA} ratios as acetic acid and phenol (see Experimental and ref. 17). In any case, the results serve to emphasize the necessity of interpreting the absence of a deuterium isotope effect in a proton transfer reaction with caution.

Acknowledgment.—The authors wish to express their appreciation to the National Science Foundation, the National Cancer Institute of the National Institutes of Health (Grant #C-3975) and to the Lilly Research Laboratories, for financial support.

(31) F. A. Long and D. Watson, *J. Chem. Soc.*, 2019 (1958).

(32) If the reaction were specific base and general acid-catalyzed it would involve, in addition to breaking a N^+–H bond, the equilibria for formation of amide ion and of ammonium ion; from the known effects of deuterium oxide on acid–base equilibria[15,17] the isotope effect for such a reaction should be larger than for a general base catalyzed reaction.

(33) K. B. Wiberg, THIS JOURNAL, **77**, 5987 (1955).

(34) E. L. Purlee, *ibid.*, **81**, 263 (1959).

(35) J. G. Pritchard and F. A. Long, *ibid.*, **80**, 4162 (1958).

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Hydroboration. III. The Reduction of Organic Compounds by Diborane, an Acid-type Reducing Agent

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Diborane is a powerful reducing agent for organic compounds, rapidly reducing at room temperatures aldehydes, ketones, epoxides, lactones, carboxylic acids, nitriles, azo compounds and *t*-amides. Esters are reduced more slowly, and acid chlorides, nitro compounds and sulfones do not react under these conditions. These reductions can be carried out either by passing diborane, generated externally, into a solution of the organic compound in a suitable solvent, such as diglyme or tetrahydrofuran, or by adding boron trifluoride etherate to a solution of sodium borohydride and the compound in diglyme. These procedures make possible a number of selective reductions, such as the reduction of a carboxylic acid group or a nitrile group in the presence of the nitro group. The marked difference in the relative sensitivity of various groups to reduction by sodium borohydride and by diborane is attributed to the acid–base characteristics of these reducing agents. Sodium borohydride is essentially a base, reaction occurring through nucleophilic attack of the borohydride ion on an electron deficient center of the reacting groups. On the other hand, diborane is a Lewis acid, and preferentially attacks the group at a position of high electron density. By a judicious use of diborane and alkali metal borohydrides, it becomes possible to reduce many groups in the presence of other groups, and to reverse the process at will.

Some time ago it was demonstrated that diborane reacts rapidly with simple aldehydes and ketones, such as acetaldehyde and acetone, to produce the corresponding dialkoxyboranes.[2] Since these substances are readily hydrolyzed to form boric acid and the corresponding alcohol, it was evident that the procedure offered a promising route for the reduction of carbonyl groups.

However, at the time diborane was a rarity, prepared only with difficulty in relatively minor amounts.[3] Consequently, this synthetic route appeared to be of theoretical interest only, and it was not examined further.

The discovery of the alkali metal borohydrides[4] and aluminohydrides[5] made possible an alternate route for such reductions.[6] Although a number of simple, practical synthetic routes to diborane are now available,[7,8] there appeared, at first, little

(1) Post-doctorate research assistant, 1955–1957, on grants provided by the Upjohn Co., Parke, Davis and Co., and Merck and Co.

(2) H. C. Brown, H. I. Schlesinger and A. B. Burg, THIS JOURNAL, **61**, 673 (1939).

(3) H. I. Schlesinger and A. B. Burg, *ibid.*, **53**, 4311 (1931).

(4) H. I. Schlesinger and H. C. Brown, *ibid.*, **62**, 3429 (1940); H. I. Schlesinger, H. C. Brown, H. R. Hockstra and L. R. Rapp, *ibid.*, **75**, 199 (1953).

(5) A. F. Finholt, A. C. Bond, Jr., and H. I. Schlesinger, *ibid.*, **69**, 1199 (1947).

(6) R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 1197, 2548 (1947); **70**, 3738 (1948); S. W. Chaikin and W. G. Brown, *ibid.*, **71**, 122 (1949).

(7) H. I. Schlesinger, H. C. Brown, J. R. Gilbreath and J. J. Katz, *ibid.*, **75**, 195 (1953).

(8) H. C. Brown and P. A. Tierney, *ibid.*, **80**, 1552 (1958).