position of the transition state. The existence of general base catalysis does not prove the existence of a tetrahedral addition intermediate in the reaction. In these mechanisms the proton transfers to and from the catalyst are concerted with bond making and breaking to carbon. Other mechanisms in which the proton transfer occurs in a separate rate-determining step may be written, but appear less likely because they require that proton transfer to or from nitrogen or oxygen, which is usually diffusion-controlled, be slower than at least one step involving bond making or breaking with carbon.

The relative importance of the different pathways for base catalysis of imidazole-catalyzed hydrolysis varies in a regular manner as the leaving group is varied in the series of acetate esters. With very good leaving groups, such as *p*-nitrophenolate, uncomplicated nucleophilic catalysis is the only observed mechanism. As the leaving group becomes worse, simple nucleophilic attack becomes less important and the two types of base catalysis of imidazole catalysis emerge as the important reaction mechanisms. With a still worse leaving group, in ethyl acetate, even the base-catalyzed mechanism becomes insignificant and no nucleophilic reaction with imidazole is observed. The significance of these changes in mechanism will be discussed further in the following paper.[19]

It has frequently been suggested that the imidazole group of a histidine residue in the active site of chymotrypsin acts as a nucleophilic reagent in the catalytic action of chymotrypsin and it might be thought that the existence of a base-catalyzed reaction of imidazole would make such a reaction possible for the relatively unreactive esters and amides which are hydrolyzed by chymotrypsin. While such a mechanism is possible in principle, it seems unlikely in practice because of the very unfavorable equilibrium constant for the formation of acylimidazoles from such substrates[24,25] and the fact that ethyl acetate does not undergo a base-catalyzed reaction with imidazole. Furthermore, such a pathway is made more difficult by the free energy requirement for the removal of a proton from imidazole, which is nearly as large as that required for the removal of a proton from water to form hydroxide ion. Complete removal of a proton from imidazole at pH 7 requires some 10 kcal.; partial removal in the transition state would require a smaller, but still significant, expenditure of energy which would add to the over-all energy barrier for the catalytic reaction.

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[CONTRIBUTION NO. 269 FROM THE GRADUATE DEPARTMENT OF BIOCHEMISTRY, BRANDEIS UNIVERSITY, WALTHAM 54, MASS.]

Nonlinear Structure–Reactivity Correlations. The Imidazole-Catalyzed Hydrolysis of Esters[1]

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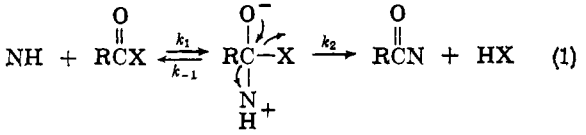
RECEIVED OCTOBER 2, 1963

The rates of imidazole-catalyzed and alkaline hydrolysis of a series of acetates with leaving groups of pK_a 4 to 16 have been determined under standard reaction conditions. The rates of the imidazole-catalyzed reactions vary over a range of 10^9 and show two breaks, accompanied by a change in the mechanism of catalysis, when plotted against the rates of the corresponding hydroxide ion reactions. The results are interpreted in terms of a change in the shape of the transition state diagram with changing leaving group for the imidazole-catalyzed reactions.

It is well known that a weak nucleophilic reagent cannot displace a poor leaving group in either a one-step or a two-step reaction. Wiberg and others[2-4] have discussed this phenomenon for acyl group reactions on the assumption that such reactions occur in two steps with the intermediate formation of a tetrahedral addition compound (eq. 1). If the attacking nucleophilic reagent is a much better leaving group



(1)

than X, the intermediate addition compound will revert to starting materials and no reaction will occur unless proton transfer takes place to make the nucleophile a poorer leaving group or X a better leaving group. It has been shown that there is a change in the mechanism of imidazole catalysis of ester hydrolysis as the structure of the ester is varied, such that esters which are activated in the acyl group but have a poor leaving group are subject to classical general base catalysis by imidazole, while esters with a good leaving group are subject to nucleophilic catalysis by imidazole.[5] It was concluded that a structure–reactivity correlation in which the rate constants for imidazole-catalyzed hydrolysis are plotted against the rate constants for alkaline hydrolysis of a series of esters with the same acyl group, but with progressively worse leaving groups, would show a break corresponding to a change in the rate-determining step of the nucleophilic reaction, followed by a second break corresponding to a change in the mechanism of the reaction from nucleophilic catalysis to general base catalysis. Although evidence was obtained that at least the first of these breaks must exist, the break itself was not directly demonstrated. The experiments reported here were carried out to obtain more information on the reasons for a change in the mechanism of imidazole catalysis of ester hydrolysis as a function of the change in structure of the ester and to attempt a more complete description of the behavior of structure–reactivity correlations of acyl group reactions as the attacking and leaving groups are varied.

Experimental

Materials.—Acetic anhydride, acetonitrile, and *p*-methylphenyl acetate were redistilled commercial products. *p*-

(1) Supported by grants from the National Cancer Institute of the National Institutes of Health (CA-03975) and the National Science Foundation. Carried out by J. F. K. during the tenure of a postdoctoral fellowship from the Jane Coffin Childs Memorial Fund.

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TABLE I

RATES OF ALKALINE HYDROLYSIS OF ESTERS AT 25° AND IONIC STRENGTH 1.0

Ester	pK_a of alcohol moiety	Init. ester concn., $M \times 10^4$	Hydroxide ion, $M \times 10^4$ [a]	No. of detn.	k_w,[b] $min.^{-1}$	k_2,[c] M^{-1} $min.^{-1}$	Method
Acetic anhydride	4.76	1.7	0.015–0.076[d,e]	4	0.17	58,000[e]	Auto. titrator
		8.3	0.023–0.119[f]	9	.15	68,400[g]	Auto. titrator
2,4-Dinitrophenyl acetate	4.02	0.3	2.8–13.6[h]	9	< .01	3,220	O.D. 400 mμ
p-Nitrophenyl acetate	7.14	0.4	3–18[i]	9	< .01	570	O.D. 400 mμ
m-Nitrophenyl acetate	8.35	4	4.5–18[f]	10	< .001	412	O.D. 390 mμ
p-Chlorophenyl acetate	9.38	2.5	40–120[j]	9	< .01	132	O.D. 300 mμ
Phenyl acetate	9.95	3	50–150[j]	9	< .002	76	O.D. 287 mμ
p-Methylphenyl acetate	10.19	2.5	50–150[j]	9	< .001	59	O.D. 295 mμ
p-Methoxyphenyl acetate	10.20	3	50–150[j]	9	< .001	63	O.D. 295 mμ
N,O-Diacetyl-N-methylhydroxylamin	8.85[k]	21	3.5–10.5[l]	14	< .002	850	$FeCl_3$ color
Trifluoroethyl acetate	12.37[m]	33	23–96[n]	11	< .005	109	Alk. NH_2OH
		140	15–38	5	< .002	115	Auto. titrator
		29	6.8–21.4[e,o]	9	< .002	184[e,o]	Alk. NH_2OH
		140	9.1–25.7[e,p]	5	< .002	191[e,p]	Auto. titrator
Acetoxime acetate	12.42[q]	29	16–99[n]	11	< .002	58	Alk. NH_2OH
Ethyl acetate	16.0[m]	30	300–500[j]	3	< .001	6.8	Alk. NH_2OH

[a] Calculated from measured pH, activity coefficient 0.67, and $K_w = 10^{-14}$ except where noted (see Experimental). [b] Rate extrapolated to zero hydroxide ion concentration. [c] $(k_{obsd} - k_w)/C_{OH^-}$. [d] In water with 0.2% acetonitrile, ionic strength *ca.* zero. [e] Rates calculated from measured pH assuming OH^- activity coefficient of 1.0. [f] Ionic strength 1.0 and 0.8% acetonitrile. [g] This rate constant was divided by 2 for insertion into Fig. 6–8, for comparison with esters having only one site for nucleophilic attack. [h] In 0.05 *M* triethylamine buffers and 0.4% acetonitrile. [i] In 0.05 *M* triethylamine buffers. [j] Unbuffered solutions; OH^- concentration determined from the known amount of added KOH. [k] This work. [l] In 0.50 *M* triethylamine buffers. Halving the triethylamine concentration while maintaining constant ionic strength produced no change in pH and had no effect on the rate constant within experimental error (*ca.* 3%). [m] Ref. 20. [n] In 0.15 *M* triethylamine buffers. [o] In 0.09 *M* triethylamine buffers, ionic strength 0.09. [p] In water; ionic strength *ca.* zero. [q] Ref. 21.

Methoxyphenyl acetate, m.p. 32.5–33.5°, reported[6] 31–32°, was prepared by the method of Bergmann[7] by Mr. David Rhoads. *p*-Chloro- and *m*-nitrophenyl acetates were prepared by Chattaway's procedure.[8] 2,4-Dinitrophenyl acetate, m.p. 70–71°, reported 72°, was prepared according to Blanksma,[9] and N,O-diacetyl-N-methylhydroxylamine, $n^{20}D$ 1.4350, reported $n^{20}D$ 1.4340, was prepared according to Exner.[10] Other materials were as described in the preceding paper.[11]

Rate Measurements.—Reactions were followed, usually in a 5-ml. volume, as described previously.[11,12] If the half-time of the reaction was less than about 1 min., 2.7 ml. of the reaction mixture was temperature-equilibrated in the thermostated brass block of a Zeiss PMQII spectrophotometer and the reaction was initiated by the rapid addition with stirring of a small amount (<0.1 ml.) of a concentrated solution of the ester in water or acetonitrile. In this manner the first reading could be obtained 5 sec. after the addition of ester. Reactions of substituted phenyl acetates were followed by observing the rates of appearance of the corresponding phenol or phenolate anion at the wave lengths given in Tables I and II. The rates of the reactions of acetic anhydride and N,O-diacetyl-N-methylhydroxylamine with imidazole were obtained from the rates of appearance of acetylimidazole, determined spectrophotometrically at 245 mμ. Since the rate of acetylimidazole hydrolysis is not negligible under these conditions, it was necessary to correct each experimental point for this hydrolysis. The pseudo-first-order rate constant for the hydrolysis of acetylimidazole was determined either directly in each reaction mixture, after the disappearance of ester was complete, or by calculation from the known catalyzed and uncatalyzed rate constants for acetylimidazole hydrolysis[13]; the rate constants obtained by these two methods agreed within 10%. The amount of acetylimidazole hydrolysis between each pair of readings was obtained from the average acetylimidazole concentration in the (short) time interval and the rate constant for acetylimidazole hydrolysis, and the cumulative correction was added to the observed readings. For short-time intervals and a relatively small amount of acetylimidazole hydrolysis, this procedure does not introduce an uncertainty greater than the estimated error of the rate measurements from other sources. At high imidazole concentrations the maximum correction amounted to approximately 3% of the readings, while at lower imidazole concentrations it amounted to 6 to 12% of the readings.

The reactions with imidazole of all esters except acetic anhydride were studied in imidazole buffers at ionic strength 1.0 maintained with potassium chloride. The high reactivity of acetic anhydride made it necessary to study its reaction with imidazole at low imidazole free base concentrations in acetate buffers. The concentration of imidazole as the free base was calculated in these experiments from the measured pH and the pK_a of imidazole, which was found to be 7.20 ± 0.03 at ionic strength 1.0 and 25°. The observed second-order rate constants for reactions of acetic anhydride with hydroxide ion and with imidazole, which are given in Tables I and II, were divided by 2 for comparison with other esters in Fig. 6–8, because acetic anhydride has two acyl groups susceptible to nucleophilic attack. The reactions of some esters did not proceed to completion at low imidazole concentrations because of an unfavorable equilibrium (see ref. 11). These reactions were studied at high imidazole concentrations in the presence of 0.1 *M* arsenate, which acts as a trap for acetylimidazole, and were shown to proceed to completion under these conditions.

The imidazole-catalyzed hydrolyses of acetoxime acetate, trifluoroethyl acetate, and ethyl acetate were followed by the alkaline hydroxylamine method.[11] The volatile esters, trifluoroethyl and ethyl acetate, were incubated in separate sealed ampoules for each experimental point and were analyzed in duplicate after removal of aliquots with a calibrated Luer-Lok syringe.

The alkaline hydrolysis of N,O-diacetyl-N-methylhydroxylamine could be conveniently measured by the rate of appearance of N-methylacetohydroxamic acid, assayed as its colored $FeCl_3$ complex. To 1.0-ml. aliquots were added 1.0 ml. of water and 4.0 ml. of 10% $FeCl_3 \cdot 6H_2O$ in 0.7 *M* HCl. The absorbance was read at 540 mμ 5 to 10 min. later. Within this time interval there is no appreciable acid-catalyzed hydrolysis of the remaining ester.

Saponification rates of acetoxime acetate, trifluoroethyl acetate, and ethyl acetate were followed by analysis of 1.0-ml. aliquots, withdrawn through serum stoppers.[11] In addition, the saponification rate of trifluoroethyl acetate was determined with a Radiometer TTTlc titrator equipped with an SBR2c recorder and SBUIc syringe buret. The GK 2021B combined electrode was standardized with pH 10.00 buffer (Fisher Scientific Co.) and at pH 11.94 with 0.01 *N* KOH before and after hydrolysis of the ester. If the standardization changed by more than 0.02 pH unit during the course of the experiment the data were discarded. Reaction mixtures of 14-ml. volume and a magnetic stirring bar were placed in cylindrical 15-ml. polyethylene containers, which were inserted in a circulating water bath at 25°. The top of the cylinder was covered with a rubber stopper through which the electrode and a capillary tube from the microburet were inserted making a tight seal. The reaction mixture was brought to the desired pH by the addition of KOH and, after temperature equilibration, the experiment was initiated by the addition of ester from a micropipet. The pH was maintained constant by the addition of KOH at a concentration such that a total volume of <0.2 ml. was added over the course of the re-

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TABLE II

RATES OF REACTIONS OF ESTERS WITH IMIDAZOLE BUFFERS AT 25° AND IONIC STRENGTH 1.0

Ester	Initial ester concn., $M \times 10^4$	Total imidazole, M	Buffer ratio $\frac{[Im]}{[Im] + [ImH^+]}$	No. of detn.	k_0,[a] min.$^{-1}$	k_2,[b] M^{-1} min.$^{-1}$	k_2,[c] M^{-1} min.$^{-1}$	Method
Acetic anhydride[d]	2.2	0.016–0.032	0.021	5	~0.15	182	8850	O.D. 245 mμ
	2.2	.008– .012	.044	6	~ .15	386	8780	O.D. 245
2,4-Dinitrophenyl acetate[e]	0.3	.05 – .20	.12	5	< .03	40.0	333	O.D. 400
	0.3	.04 – .12	.17	5	< .03	61.8	364	O.D. 400
p-Nitrophenyl acetate	0.6	.02 – .06	.50	5	< .01	17.6	34.6	O.D. 400
	1.1	.02 – .08	.25	5	< .01	8.68	35.2	O.D. 400
m-Nitrophenyl acetate	3	.025– .20	.40	5	< .01	5.35	14.1	O.D. 335
	3	.025– .20	.70	5	< .01	9.85	13.4	O.D. 335
p-Chlorophenyl acetate	4	.10 – .80	.40	5	< .01	0.637	1.62	O.D. 280
	4	.10 – .80	.70	5	< .01	1.14	1.59	O.D. 280
Phenyl acetate	4.5	.10 – .80	.40	5	< .001	0.206	0.534	O.D. 275
	4.5	.10 – .80	.70	5	< .001	0.374	.515	O.D. 275
p-Methylphenyl acetate	4	.10 – .80[f]	.40	5	< .001	[g]	.218[h]	O.D. 280
	4	.10 – .80[f]	.70	5	< .001	[g]	.206[h]	O.D. 280
	3	.10 – .80[f]	.90	10	< .001	[g]	.214[h]	O.D. 280
p-Methoxyphenyl acetate	3	.10 – .80[f]	.40	5	$<5 \times 10^{-4}$	[g]	.195[h]	O.D. 295
	3	.10 – .80[f]	.70	5	$<5 \times 10^{-4}$	[g]	.196[h]	O.D. 295
	3	.40 – .80	.70	6	$<5 \times 10^{-4}$	[g]	.194[h]	O.D. 295
	2	.10 – .80	.90	10	$<5 \times 10^{-4}$	[g]	.184[h]	O.D. 295
N,O-Diacetyl-N-methyl-hydroxylamine	2.3	.80 –1.00	.70	4	<0.02	2.94	4.20	O.D. 245[i]
	2.3	.60 –1.00	.90	6	<0.02	3.92	4.35	O.D. 245[i]
Trifluoroethyl acetate	30	.20 –1.0[j]	.40	5	3.5×10^{-5}	9.05×10^{-5}	2.26×10^{-4}[j]	Alk. NH_2OH
	30	.20 –1.0[j]	.70	5	7.4×10^{-5}	1.76×10^{-4}	2.51×10^{-4}[j]	Alk. NH_2OH
	30	.40 –1.0[j,k]	.70	4	6.6×10^{-5}	4.60×10^{-5}	6.6×10^{-5}[j,k]	Alk. NH_2OH
Acetoxime acetate	30	.20 –0.80[l]	.40	5	4.2×10^{-5}[m]	2.44×10^{-4}[n]	5.8×10^{-4}	Alk. NH_2OH
	30	.20 –0.40[l]	.70	3	8.6×10^{-5}[m]	5.64×10^{-4}[o]	6.9×10^{-4}	Alk. NH_2OH
	30	.25 –1.00	.70	4	4.2×10^{-5}	4.89×10^{-4}[p]	6.96×10^{-4}	Alk. NH_2OH
	30	.25 –1.00[k]	.70	4	2.3×10^{-5}	2.59×10^{-4}	3.57×10^{-4}	Alk. NH_2OH
Ethyl acetate	30	.50 –1.50	.65	5	4.5×10^{-6}	4.9×10^{-6}	7.5×10^{-6}	Alk. NH_2OH
	30	.50 –1.50	.85	5	9.2×10^{-6}	6.4×10^{-6}	7.5×10^{-6}	Alk. NH_2OH

[a] Rate extrapolated to zero imidazole concentration. [b] $(k_{obsd} - k_0)$/(total imidazole concentration). [c] For the reactive (free base) species of imidazole. [d] Rates determined in 0.05 M sodium acetate buffers in 2% acetonitrile; ionic strength 1.0 (see Experimental). [e] In 0.4% acetonitrile. [f] In 0.1 M sodium arsenate. [g] Not determined directly; k_{obsd} is dependent on both [Im] and [Im]^2. [h] Rate determined from extrapolation to zero imidazole concentration of a plot of $(k_{obsd} - k_0)$/[Im] against [Im]. [i] Experimental points corrected for acetylimidazole hydrolysis (see Experimental). [j] N-Methylimidazole. [k] In D_2O. [l] In 0.09 M sodium arsenate. [m] Includes a contribution to k_0 dependent on $[Ars^{-2}]$. [n] Includes a contribution of approximately 5% from catalysis proportional to [Im] $[OH^-]$; this was corrected for in the calculation of the free base rate. [o] Includes a contribution of approximately 16% from catalysis proportional to [Im]$[OH^-]$, which was corrected for as in footnote *n*. [p] Uncorrected for a 16% contribution for catalysis proportional to [Im]$[OH^-]$, in order to permit comparison with the uncorrected rate constant in D_2O.

action. Pseudo-first-order rate constants were obtained from plots of log $(m_\infty - m_t)$ against time or by the Guggenheim method.[14] The hydrolysis rate of acetic anhydride was followed by essentially the same procedure, except that the pH meter was standardized at pH 7.00 and 10.00 and the acetic anhydride was added in a small volume of acetonitrile. The rate of acetic anhydride disappearance was also followed spectrophotometrically at 240 mμ in 0.06–0.18 M phosphate buffer, pH 7.70, using 5.0-cm. path length silica cells. All alkaline hydrolysis reactions were studied in the presence of at least three different concentrations of hydroxide ion. Second- and third-order rate constants were determined as described previously.[12,15]

The pK_a' of N-methylacetohydroxamic acid at 25° was found by titration to be 8.79 ± 0.02 in 1.0 M KCl, and 8.85 ± 0.02 at ionic strength 0.01.

Product Analysis.—A difference spectrum of the products of the reaction of 1.6×10^{-4} M N,O-diacetyl-N-methylhydroxylamine with 0.8 M imidazole against the products of the alkaline hydrolysis of the same amount of ester in 0.8 M imidazole showed an absorption maximum at 245 mμ, characteristic of acetylimidazole.[16]

Results

Alkaline Hydrolysis.—The second-order rate constant for the alkaline hydrolysis of acetic anhydride was determined with an automatic titrator and found to be 68,400 M^{-1} min.$^{-1}$ at 25° and ionic strength 1.0 (Table I). This reaction has been studied previously by Skrabal,[17] who gives $k_2 \leq 4.4 \times 10^6$ M^{-1} min.$^{-1}$ in 2.5% acetone–water at 25°, and by Koskikallio,[18] who reports $k_2 = 1.2 \times 10^6$ M^{-1} min.$^{-1}$ in water at 15°, determined by a flow method. An Arrhenius plot can be constructed from Koskikallio's data at three lower temperatures to give an extrapolated value at 25° of approximately 1.5×10^6 M^{-1} min.$^{-1}$.

In an attempt to resolve this large discrepancy, the rate constant was redetermined in water at 25° (Fig. 1), and a slightly smaller value of $k_2 = 58{,}000$ M^{-1} min.$^{-1}$ was obtained, in good agreement with the value at ionic strength 1.0, but 30-fold smaller than that reported by Koskikallio. The rate constant for the neutral hydrolysis (water reaction), obtained from the intercept, is $k_w = 0.17$ min.$^{-1}$, which is in satisfactory agreement with reported[18,19] values of 0.16 and 0.15 min.$^{-1}$.

The disappearance of acetic anhydride was also studied spectrophotometrically in dilute phosphate buffer (Fig. 2). The effect of ionic strength on the rate of hydrolysis of acetic anhydride is small, as shown by the experiments described above and by Kilpatrick.[22] Extrapolation to zero phosphate buffer concentration

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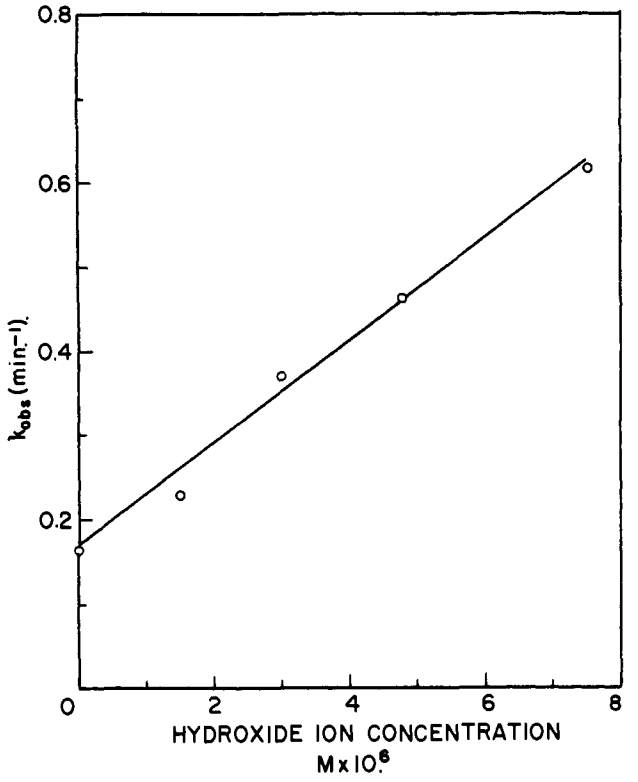


Fig. 1.—The rates of reaction of acetic anhydride with hydroxide ion in water (0.2% acetonitrile) at 25°, determined with an automatic titrator.

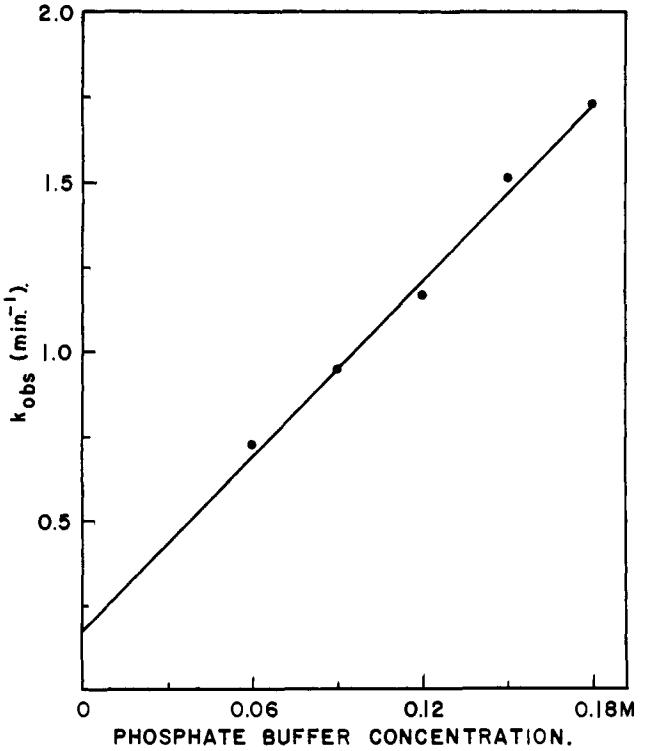


Fig. 2.—Rates of disappearance of 10^{-3} M acetic anhydride in potassium phosphate buffers at pH 7.70 ± 0.02 and 25°; ionic strength, 0.12–0.51; followed at 240 mμ in 5-cm. cells.

gives $k_{OH}\cdot[OH^-] + k_w$. The rate constant for the reaction of hydroxide ion with acetic anhydride reported by Koskikallio gives a calculated intercept at this pH value of k_{obsd} = 0.97 min.$^{-1}$, for an activity coefficient of OH^- near 1.0. This value is much larger than the observed intercept and is even larger than the

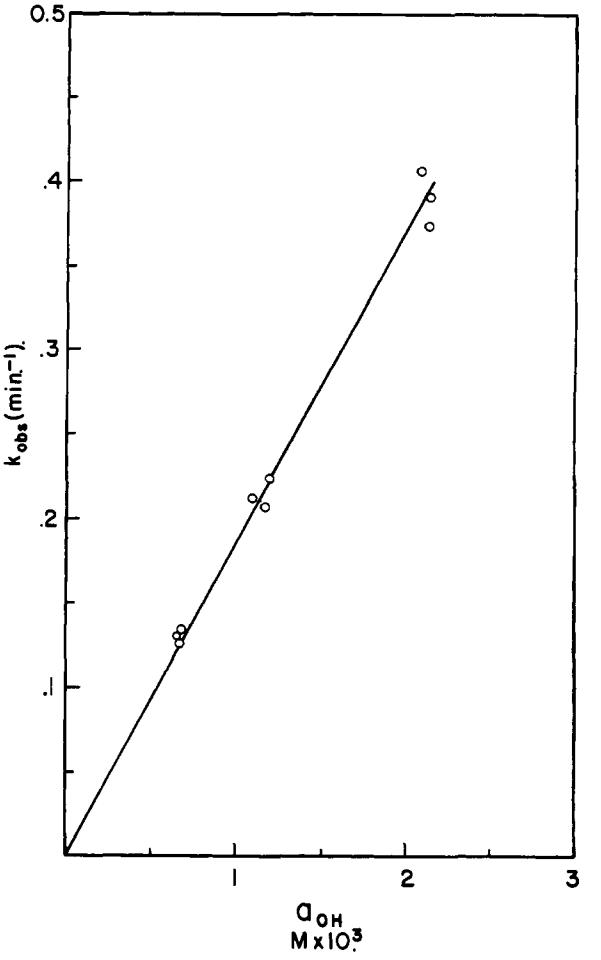


Fig. 3.—The observed first-order rate constants for the hydrolysis of trifluoroethyl acetate in 0.09 M triethylamine buffers as a function of hydroxide ion activity at ionic strength 0.08, determined by the hydroxamate method.

observed rates of acetic anhydride disappearance in the presence of phosphate. The observed intercept of 0.18 min.$^{-1}$ agrees within experimental error with the value of 0.20 min.$^{-1}$, calculated from k_2 and k_w values of 58,000 M^{-1} min.$^{-1}$ and 0.16 min.$^{-1}$, respectively. The second-order rate constant calculated from these data for the reaction of acetic anhydride with phosphate dianion is 8.9 M^{-1} min.$^{-1}$.

The rate constants for the alkaline hydrolysis of a series of substituted phenyl acetates in aqueous solution at 25° and ionic strength 1.0 are reported in Table I. These values are about 30% smaller than those recently reported by Bruice and Mayahi[23] for a number of substituted phenyl acetates at 30° in 1% dioxane at ionic strength 1.0, if the latter values are expressed in terms of hydroxide ion concentration, rather than activity.

The rate constants for the alkaline hydrolysis of the acetate esters of N-methylacetohydroxamic acid, acetoxime, trifluoroethanol, and ethanol are also reported in Table I. The values of 109 and 115 M^{-1} min.$^{-1}$ for the hydrolysis of trifluoroethyl acetate at ionic strength 1.0, obtained by two independent methods, are considerably larger than the value of 41 M^{-1} min.$^{-1}$ reported by Bruice, *et al.*[24] Accordingly, the value was redetermined by two methods at low ionic strength, under conditions similar to those used by these workers. The rate constants under these conditions (Fig. 3)

(23) T. C. Bruice and M. F. Mayahi, *J. Am. Chem. Soc.*, **82**, 3067 (1960).
(24) T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochem.*, 1, 7 (1962).

were found to be 184 and 191 M^{-1} min.$^{-1}$, which are in even poorer agreement with the previously reported value. The reason for this discrepancy is not known. The rate constant of 6.8 M^{-1} min.$^{-1}$ for the alkaline hydrolysis of ethyl acetate in water, ionic strength 1.0 at 25°, may be compared to that of 7.69 M^{-1} min.$^{-1}$ in 5.6% acetone–water, ionic strength 0.30 at 26.1°, reported by Amis and Siegel.[25]

Imidazole Reactions.—The rate constants for the reactions with imidazole are given in Table II. The value of 4400 M^{-1} min.$^{-1}$ for the reaction with acetic anhydride at 25° and ionic strength 1.0 may be compared to the value of 1200 M^{-1} min.$^{-1}$ obtained by Brouwer, *et al.*, at 0°, in water.[26] The rate constants for the reactions with 2,4-dinitrophenyl acetate and *p*-nitrophenyl acetate are very similar to those obtained previously under slightly different conditions.[27,28] The values for the reactions with substituted phenyl acetates are generally about three times larger than those reported by Bruice and Schmir for the corresponding reactions in 28.5% ethanol.[4]

The reactions of imidazole with N,O-diacetyl-N-methylhydroxylamine and the phenyl acetates were found to be reversible and did not proceed to completion at low concentrations of imidazole. Accordingly, these reactions were studied in concentrated imidazole solutions, in which it was shown that they proceeded essentially to completion (see Experimental section and footnote 20 of ref. 11). A further experimental difficulty in the measurement of the rates of certain of these reactions results from appreciable activity coefficient effects of potassium chloride and imidazole hydrochloride on the esters (Table III).

TABLE III

APPROXIMATE ACTIVITY COEFFICIENTS OF ESTERS IN 1.0 *M* SOLUTIONS OF VARIOUS REAGENTS AT 25°[a]

Acetate	1.0 *M* KCl	1.0 *M* imidazole hydrochloride	1.0 *M*[b] imidazole	1.0 *M* tetraethylammonium bromide
p-Methylphenyl	1.64	0.66	..	0.44
Trifluoroethyl	1.42	1.22	0.89	..
Ethyl	1.50	1.20	0.73	..

[a] Determined from the solubility of the ester in the indicated solution and in water and the relation $S_{H_2O}/S_x = f_x/f_{H_2O}$; solubility determinations were carried out by the alkaline hydroxylamine procedure or by absorbance measurements. [b] 95% free base.

Because of these effects, the most accurate rate constants are obtained at relatively high buffer ratios, in which the concentration of imidazole hydrochloride is low and the concentration of potassium chloride is high and nearly constant. These effects cause a considerably greater uncertainty in the third-order constants for imidazole catalysis[11] than they do for the second-order constants, which are obtained by extrapolation to zero imidazole–imidazolium ion concentration. The second-order constants obtained at different buffer ratios show good agreement for a given ester (Table II), which suggests that the uncertainty from this effect is not large for these rate constants.[29]

(25) E. S. Amis and S. Siegel, *J. Am. Chem. Soc.*, **72**, 674 (1950).

(26) D. M. Brouwer, M. J. van der Vlugt, and E. Havinga, *Proc. Koninkl. Ned. Akad. Wetenschap.*, **B61**, 141 (1958).

(27) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1656 (1957).

(28) W. P. Jencks, *ibid.*, **80**, 4585 (1958).

(29) The rate constants for the reaction of N,O-diacetyl-N-methylhydroxylamine were determined at high imidazole concentration in order to avoid large corrections for acetylimidazole hydrolysis, as described in the Experimental section. Therefore, the observed rate constants for this compound may include an undetected contribution of a reaction second-order in respect to imidazole.[11] Preliminary experiments in which the rate of the reverse reaction and the equilibrium constant of this reaction were determined (J. Gerstein, unpublished experiments) suggest that the value of k_2 given in Table II may be somewhat too large for this reason.

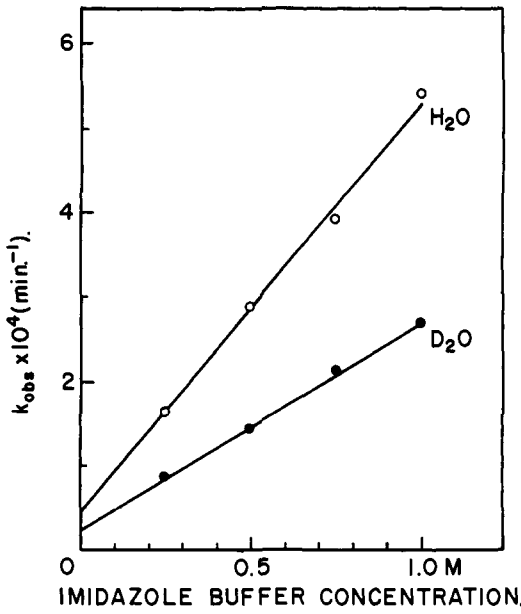


Fig. 4.—Catalysis of acetoxime acetate hydrolysis by imidazole buffer (70% free base) at 25° and ionic strength 1.0: O, in water; ●, in deuterium oxide.

The rate of imidazole-catalyzed hydrolysis of acetoxime acetate is twofold slower in D_2O than in H_2O (Fig. 4 and Table II). The rate constant for this reaction is not affected, within experimental error, by the addition of 0.09 *M* sodium arsenate (Table II). It was necessary to make a small correction of the observed rate constants for this reaction for the contribution of the hydroxide ion-catalyzed reaction of imidazole,[11] which is significant even at pH values below 8.0.

In the case of the reaction with trifluoroethyl acetate, the hydroxide ion catalyzed reaction of imidazole is so large that evaluation of the rate constants for the reaction of imidazole as the free base requires a very large correction for the former reaction even at pH values near neutrality.[11] Consequently, the rate constants for this reaction were estimated from measurements of the rate of the corresponding reaction with N-methylimidazole, which is not subject to hydroxide ion catalysis (Table II). The values so obtained were similar to those estimated for the imidazole reaction, after correction for the hydroxide ion catalyzed reaction, but an exact comparison was not possible for the reasons given. The reaction with N-methylimidazole exhibits a k_{H_2O}/k_{D_2O} ratio of 3.8.

Catalysis by imidazole of the hydrolysis of ethyl acetate was demonstrated by prolonged incubation of the reactants in sealed ampoules at 25° (Fig. 5). Although complete concentration–rate curves were not carried out in deuterium oxide, the rates are clearly decreased in this solvent and the decrease is too large to be accounted for by an effect on the rate of alkaline hydrolysis.

Neutral Hydrolysis of 2,4-Dinitrophenyl Acetate.—The rate of hydrolysis of 2,4-dinitrophenyl acetate was followed in duplicate in 0.001 and 0.002 *M* HCl, at 25°, ionic strength 1.0, by measurement of the release of 2,4-dinitrophenol at 330 mμ. Identical first-order rate constants of (6.5 ± 0.2) × 10^{-4} min.$^{-1}$ were obtained at both concentrations.

Discussion

Alkaline Hydrolysis.—The rate constant for the alkaline hydrolysis of acetic anhydride (Table I) is

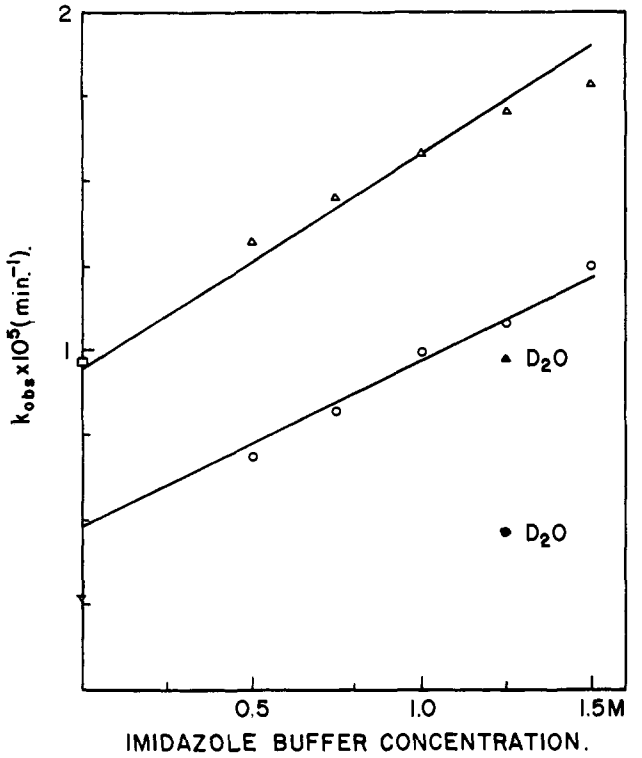


Fig. 5.—Catalysis of ethyl acetate hydrolysis by imidazole buffers at 25° and ionic strength 1.0: Δ, 85% free base; O, 65% free base; ▲, 85% free base in D_2O; ●, 65% free base in D_2O; □, ▽, calculated alkaline hydrolysis rates. The solid lines are calculated for $k_2 = 7.53 \times 10^{-6}$ M^{-1} min.$^{-1}$.

considerably smaller than that previously reported[18] and indicates that the alkaline hydrolysis of this compound is of little significance, compared to the water reaction, at pH values below neutrality. The hydrolysis of aspirin anhydride also does not show a significant hydroxide ion reaction at pH values below neutrality.[30] Johnson has recently concluded that the alkaline hydrolysis of benzoic anhydride is significant at pH values below neutrality,[31] but the evidence for this conclusion rests on a long extrapolation of the experimental data and should be supplemented by more direct evidence. It has been suggested, because of the observed formation of acetanilide in the reaction of acetic anhydride with aniline at alkaline pH values and the reported rate constants for the reaction of acetic anhydride with aniline and hydroxide ion, that there must be a base-catalyzed reaction of aniline with acetic anhydride[32]; the revised values for the rate of the reaction with hydroxide ion suggest that it may not be necessary to postulate such a reaction to account for acetanilide formation at alkaline pH.

The alkaline hydrolysis of trifluoroethyl acetate exhibits an unusually large negative salt effect for ester hydrolysis, with a 40% smaller rate constant in 1 M potassium chloride than at an ionic strength near zero. However, the decrease in rate is in the expected direction for the reaction of an ion with a neutral molecule. The rate of alkaline hydrolysis of ethyl acetate in 5.6% acetone is decreased only 5% by 0.3 M sodium nitrate.[25] Ethyl acetate and trifluoroethyl acetate are salted out to approximately the same extent by 1.0 M potassium chloride (Table III). Abadi and Wilcox have reported that the rate of alkaline hydrolysis of N-acetyl-DL-homocysteine thiolactone is reduced by one-third in 0.1 M potassium chloride.[33]

(30) E. R. Garrett, *J. Am. Chem. Soc.*, **82**, 711 (1960).
(31) S. L. Johnson, *ibid.*, **84**, 1729 (1962).
(32) J. Koskikallio, *Suomen Kemistilehti*, **32B**, 133 (1959).

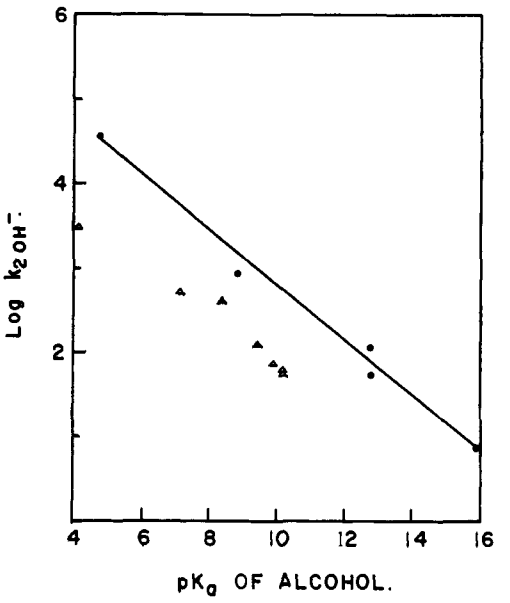
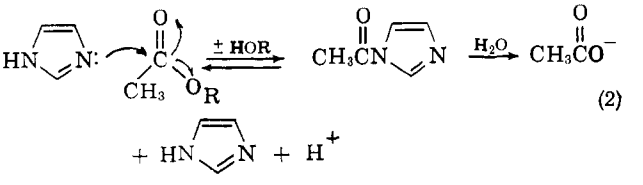


Fig. 6.—Rates of alkaline hydrolysis of acetate esters as a function of the pK_a of the alcohol moiety at 25°, ionic strength 1.0: Δ, substituted phenyl acetates; ●, other acetate esters.

The logarithms of the rates of alkaline hydrolysis of acetate esters of aliphatic alcohols at ionic strength 1.0 at 25° show a linear relationship with the pK_a of the alcohol over the range pK_a 4 to 16 (Fig. 6). The slope of the line is 0.32. This suggests that these reactions are well-behaved and occur by a similar or identical mechanism, since there is no break in the curve that might suggest a change in mechanism or rate-determining step. The points for the phenolic esters also fall on a straight line, but this line is almost an order of magnitude below that for the aliphatic esters. This presumably reflects principally the steric hindrance of the bulky benzene ring in these compounds. Bruice, *et al.*,[24] have previously reported a somewhat more limited correlation, similar to that of Fig. 6, in which phenyl esters were reported to fall on the same line as other esters. This result is probably due to the fact that the experimental data used by these authors were obtained under a number of different reaction conditions and are, therefore, not directly comparable.

Mechanism of Catalysis of Ester Hydrolysis by Imidazole.—The reactions of acetic anhydride[34] and N,O-diacetyl-N-methylhydroxylamine with imidazole lead to the quantitative formation of acetylimidazole and are, therefore, examples of nucleophilic reactions of imidazole (eq. 2). The reactions of *p*-nitrophenyl acetate and phenyl acetate with imidazole also form



(2)

acetylimidazole[34,35] and there is evidence that the imidazole-catalyzed hydrolysis of other phenyl esters also represents nucleophilic catalysis by imidazole.[36]

(33) D. M. Abadi and P. E. Wilcox, *J. Biol. Chem.*, **235**, 396 (1960).
(34) D. M. Brouwer, M. J. van der Vlugt, and E. Havinga, *Proc. Koninkl. Ned. Akad. Wetenschap.*, **B60**, 275 (1957).
(35) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652 (1957).
(36) J. Gerstein (unpublished experiments) has shown spectrophotometrically that acetylimidazole is formed from *p*-methoxyphenyl acetate and has measured the equilibrium constant for this reaction.

Solvent deuterium isotope effects are small or absent for this type of reaction under conditions in which the formation of acetylimidazole is not reversible.[31,37,38,41]

The much slower imidazole catalysis of the hydrolysis of esters with a poorer leaving group than a substituted phenolate ion represents classical general base catalysis; *i.e.*, imidazole is acting as a catalyst for proton transfer. Reactions of this class show a solvent deuterium isotope effect of 2.0 or more.[5,38,41,42] Such isotope effects were observed for the imidazole-catalyzed hydrolysis of acetoxime acetate and the N-methylimidazole-catalyzed hydrolysis of trifluoroethyl acetate. Other evidence for general base catalysis of the hydrolysis of esters with poor leaving groups has been reported previously.[5]

Bunton and Shiner have calculated the expected solvent deuterium isotope effects from a model for the transition state of acyl solvolysis reactions and obtained values of the correct magnitude, which reflect differences in hydrogen bonding in the initial and transition states and which are classified as secondary isotope effects.[43,44] It is not quite clear whether this is necessarily entirely different from an explanation based on the expectation of a deuterium isotope effect for a reaction which involves general base catalysis,[5] since general base catalysis must certainly involve hydrogen bonding. In any case, since general base catalysis has been demonstrated for these reactions and since water falls on the same Brönsted plot as other general base catalysts,[5] it seems clear that the deuterium isotope effect reflects general base catalysis, at least in part. As discussed below, this does not mean that proton transfer *alone* is rate-determining.

Imidazole catalysis of the hydrolysis of ethyl acetate has not been observed previously, because of the slow rate of the reaction at 25°. The evidence that this is classical general base catalysis, rather than nucleophilic catalysis, is: (a) The rate is markedly reduced in deuterium oxide (Fig. 5). (b) The rate constant of 7.5×10^{-5} M^{-1} min.$^{-1}$ for imidazole catalysis of the hydrolysis of ethyl acetate at 25° is very similar to the value of 3.0×10^{-5} M^{-1} min.$^{-1}$ for phosphate catalysis of ethyl acetate hydrolysis at 30°, obtained by Holland and Miller.[45] For nucleophilic catalysis the rates of imidazole and phosphate attack on an ester vary by 10^3, but for general base catalysis they are very similar.[5] (c) The rate of imidazole-catalyzed hydrolysis of ethyl acetate is almost exactly that predicted from an extrapolation of a logarithmic plot (Fig. 7) of the rate of alkaline hydrolysis against the rate of imidazole-catalyzed hydrolysis of a series of ethyl and methyl esters which have been shown to be

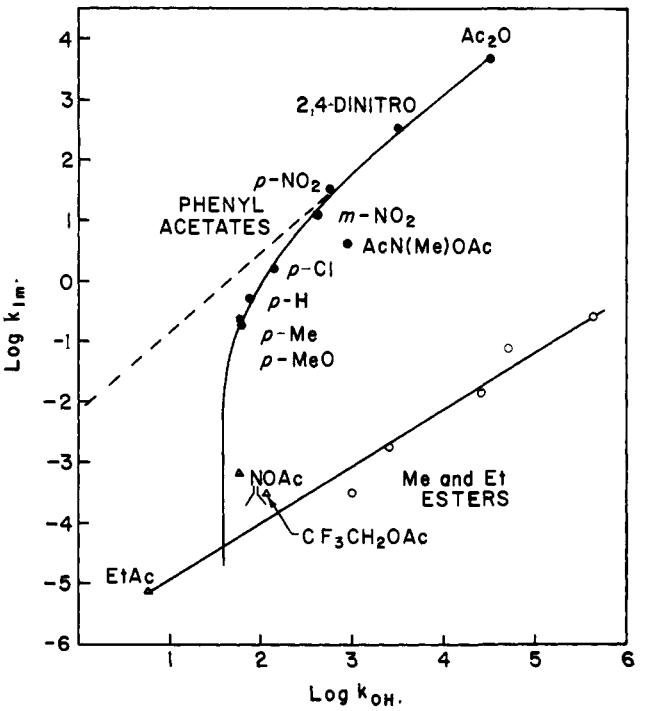
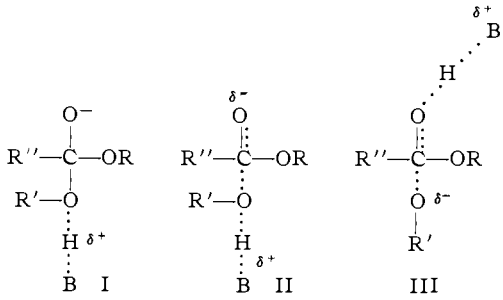


Fig. 7.—Rates of imidazole-catalyzed ester hydrolysis as a function of the rate of alkaline hydrolysis: nucleophilic reactions of acetates, ●; general base catalysis of acetates, Δ; general base catalysis of methyl and ethyl esters,[5] O (ionic strength 1.0; 25°). Trifluoroethyl acetate rate measured with N-methylimidazole.

subject to general base-catalyzed hydrolysis by imidazole.[5] The point for phosphate catalysis falls near the same line, which is further evidence that this catalysis also represents general base catalysis, rather than nucleophilic catalysis with the intermediate formation of acetyl phosphate.[45]

The mechanism of general base catalysis of the hydrolysis of esters and related compounds could involve either (A) proton transfer only (*e.g.*, ref. 46) or (B) proton transfer concerted with bond making or breaking involving other atoms in the rate-determining step. Mechanism A would involve the generalized transition state I, in which R and R′ refer to a proton and the



organic moiety of the leaving group, depending on whether the catalysis involves the rate-determining removal of a proton from water or addition of a proton to the leaving group, after the pre-equilibrium addition of the nucleophile to the ester. Arguments against mechanism A have been summarized by Johnson.[31] In particular, it is difficult to see how it would be possible to have a pre-equilibrium addition of hydroxide ion[46] to compounds with a good leaving group, such as phenolate or acetate. Furthermore, proton transfers between nitrogen and oxygen atoms are generally diffusion controlled in the direction that is favored by

(37) B. M. Anderson, E. H. Cordes, and W. P. Jencks, *J. Biol. Chem.*, **236**, 455 (1961).

(38) Nucleophilic catalysis of ester hydrolysis by tertiary amines (eq. 2) can show a solvent deuterium isotope effect if the decomposition of the acylated amine is rate determining,[39,40] but this is not the case under the reaction conditions used in the experiments reported here. If the hydrolysis of acetylimidazole or acetyl-N-methylimidazolium ion were rate determining the rate should show a dependence on the concentration of arsenate and a second-order dependence on the concentration of imidazole (or N-methylimidazole), since both imidazole (or N-methylimidazole) and arsenate catalyze the hydrolysis of acetylimidazole (and acetyl-N-methylimidazolium ion); no such dependence was observed.

(39) A. R. Butler and V. Gold, *J. Chem. Soc.*, 4362 (1961).

(40) C. A. Bunton, N. A. Fuller, and S. G. Perry, *Tetrahedron Letters*, **14**, 458 (1961).

(41) M. L. Bender, E. J. Pollock, and M. C. Neveu, *J. Am. Chem. Soc.*, **84**, 595 (1962).

(42) T. C. Bruice, T. H. Fife, J. J. Bruno, and P. Benkovic, *ibid.*, **84**, 3012 (1962).

(43) C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner, Jr., *J. Chem. Soc.*, 2918 (1963).

(44) C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **83**, 3207 (1961).

(45) J. M. Holland and J. G. Miller, *J. Phys. Chem.*, **65**, 463 (1961).

(46) A. R. Butler and V. Gold, *J. Chem. Soc.*, 976, 1334, 2212 (1962).

the equilibrium of the proton transfer reaction.[47] If the rate-determining step of mechanism A were diffusion-controlled, the rate of the reaction should be independent of the basicity of the catalyst, at least for some catalysts, but this is not the case.[5]

Mechanism B could involve transition states II or III, in which R and R′ are as defined above, and the degree of bond making or breaking between the different atoms is not specified. Symmetry considerations suggest that if there is a tetrahedral addition intermediate, a similar mechanism of catalysis will obtain for both the addition and elimination steps.[5] As pointed out by Kresge and Chiang, the rate of such a reaction is first order in respect to catalyst concentration, even if both steps are subject to catalysis.[48] On the other hand, if there is no intermediate and the reaction is symmetrical, the reaction should be second order in respect to catalyst, because catalysis of both addition and leaving should be occurring at the same time. Mechanisms II and III differ in that in mechanism II the catalysis involves proton transfer to and from the entering and leaving groups, while in mechanism III it involves proton transfer to and from the carbonyl group. It should be noted that although proton transfer is occurring at the same time as the making and breaking of bonds with carbon, proton transfer is itself a much faster process than the latter process and the proton may, in fact, move back and forth several times between the substrate and the catalyst as addition to the carbonyl group occurs. If this is indeed the case, the observed deuterium isotope effect will reflect the different relative affinities of the catalyst and substrate for hydrogen and deuterium, *i.e.*, a different average location of the proton and deuteron between the catalyst and substrate.

Although no rigorous choice can be made between mechanisms II and III at the present time, mechanism II is preferred, by analogy with the mechanism of simple addition reactions to the carbonyl group and on the ground that the reaction path is generally to be preferred which involves the fewest unstable intermediates. Mechanism III requires the pre-equilibrium formation of hydroxide ion, which then adds to the carbonyl group in a reaction catalyzed by the general acid, HB^+. Mechanism II involves only the formation of the (solvated) anion of the addition compound or transition state, which is presumably more stable than hydroxide ion, accompanied by proton removal from the attacking nucleophile by the catalyzing base. Furthermore, in accordance with the principle that catalysis occurs at the point at which it is most needed, there is evidence that the addition of strong bases to the carbonyl group is not subject to general acid catalysis, while the addition of weak nucleophiles is subject to general base catalysis.[49]

The mechanistic utility of general base catalysis arises from the fact that several proton transfers, as well as the formation and breaking of C–O bonds, are required in the course of these reactions. Such proton transfers can occur by a lower energy pathway if they are carried out concurrently with the rest of the reaction, by general base catalysis, than if they are carried out in pre-equilibria or after the rate-determining step. Proton transfer is also required for the oxygen exchange between ester and solvent which is observed during the hydrolysis of many esters, and Bender and co-workers have recently presented convincing evidence that such proton exchange is kinetically significant in the alkaline hydrolysis of substituted benzoate esters.[50] It would be of considerable interest to determine whether this exchange is subject to general acid–base catalysis.

Selectivity and Reactivity.—It would be expected that decreased reactivity in a series of acyl compounds would be paralleled by an increased selectivity toward nucleophilic reagents.[49,51] The rates of the water reactions are plotted logarithmically against the rates of alkaline hydrolysis for two series of acyl compounds in Fig. 8. The upper line is for a series

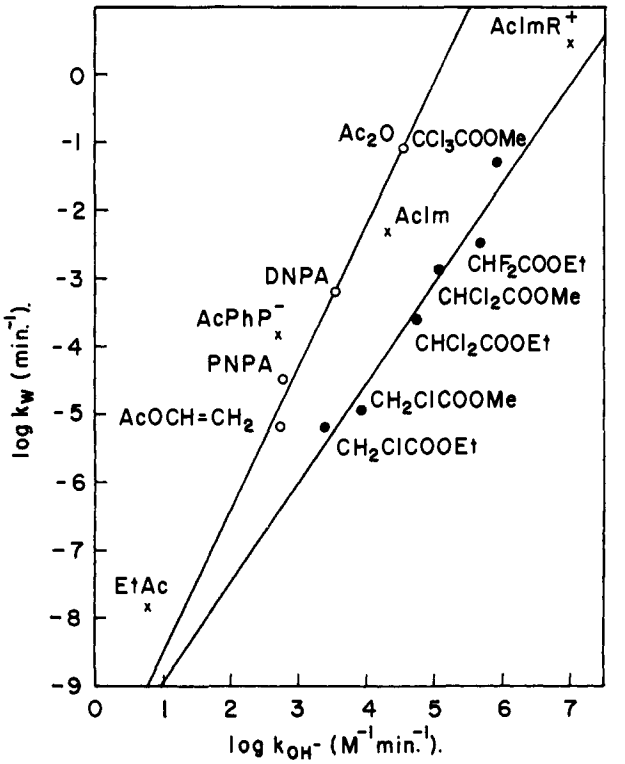


Fig. 8.—Logarithmic plot of the rates of water hydrolysis against the rates of alkaline hydrolysis for a series of esters and related compounds at 25° in water: O, acetate esters, this work and ref. 52; ●, methyl and ethyl esters[5,52]; X, other compounds[53,54] and ethyl acetate.[55]

of acetates with varying leaving groups. Acetyl phenyl phosphate anion and acetyl-N-methylimidazolium cation show deviations from the line in the expected directions, because of the effect of their charge on the reaction with hydroxide ion. Surprisingly, acetylimidazole does not fall far from the line for oxygen esters. The lower line is for a series of ethyl and methyl esters with varying acyl groups. The point for ethyl acetate is based on the known rate of alkaline hydrolysis and the rate constant for the water reaction reported by Skrabal[55]; in view of the experimental difficulties involved in obtaining the latter value, which corresponds to a half-time of 89 years and represents only 36% of the observed hydrolysis rate even under the most favorable conditions, this should probably be regarded as only an upper limit for this rate constant. The slope of the upper line is 2.1 and that of the lower line is 1.4. The following conclusions may be drawn from this figure: (1) The water reaction shows a greater

(47) M. Eigen, *Pure Appl. Chem.*, **6**, 97 (1963).
(48) A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **83**, 2877 (1961).
(49) W. P. Jencks in "Progress in Physical Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., in press.
(50) (a) M. L. Bender and R. J. Thomas, *J. Am. Chem. Soc.*, **83**, 4189 (1961); (b) M. L. Bender and R. D. Ginger, *Suomen Kemistilehti*, **33B**, 25 (1960).
(51) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
(52) R. Skrabal, *Monatsh.*, **71**, 298 (1938).
(53) R. Wolfenden and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4390 (1961).
(54) G. Di Sabato and W. P. Jencks, *ibid.*, **83**, 4400 (1961).
(55) R. Skrabal and Z. Zahorka, *Monatsh.*, **53**, 562 (9192).

sensitivity to the structure of the ester than does the hydroxide ion reaction, as shown by the fact that the slopes of both lines are greater than 1.0. (2) Conversely, the selectivity of both series of compounds decreases as the reactivity increases. This is best shown by the ratio k_{OH^-}/k_w, which decreases from $10^{7.24}$ to $10^{6.70}$ to $10^{5.60}$ in the series *p*-nitrophenyl acetate, 2,4-dinitrophenyl acetate, and acetic anhydride, and decreases from $10^{8.83}$ to $10^{7.97}$ to $10^{7.16}$ in the series methyl chloroacetate, methyl dichloroacetate, and methyl trichloroacetate.[52] (3) The different slopes of the two lines can be accounted for by a greater sensitivity of the water reaction than the hydroxide reaction to changes in the nature of the leaving group or, conversely, a relatively large sensitivity of the hydroxide ion reaction to changes in the nature of the acyl group.

It should be kept in mind that the mechanisms of the water reaction and the hydroxide reaction are somewhat different. In the hydroxide ion reaction the rate is largely or entirely dependent on the rate of attack of the nucleophilic reagent on the carbonyl group, while in the water reaction proton transfer is required and the nature of the leaving group would be expected to be of greater importance.[3,5] The high sensitivity of the rates of the water reactions of these compounds to the nature of the leaving group may be contrasted with the low sensitivity recently reported by Bunton, *et al.*, for a limited series of anhydrides,[43] but is similar to the high sensitivity reported by Morawetz for the intramolecular attack of the weak nucleophile, carboxylate ion, on a series of phenyl esters.[56] In this series, also, there appears to be appreciable bond breaking by the leaving group in the transition state.

The rate of the water reaction of ethyl acetate may be estimated by two independent methods. Ethyl acetate should be common to the two series of compounds in Fig. 8 and an extrapolation of the two lines to the known rate constant for ethyl acetate saponification gives a value of k_w slightly below 10^{-9} min.$^{-1}$. The rate constants for the general base-catalyzed hydrolysis of ethyl dichloroacetate fall on a Brönsted plot of slope 0.47 and the point for water falls on the same line as for other bases.[5] If a similar slope is assumed for the reaction of ethyl acetate and the line is drawn through the point for the imidazole-catalyzed hydrolysis, k_w may be estimated to be 3×10^{-8} min.$^{-1}$. These estimates may be compared with Skrabal's value of 1.5×10^{-8} min.$^{-1}$.

Nonlinear Structure–Reactivity Correlations.—In Fig. 7 the rate constants for imidazole-catalyzed hydrolysis are plotted logarithmically against the rate constants for alkaline hydrolysis of a number of esters. It is assumed that the mechanism of alkaline hydrolysis is the same for the different esters studied and the rate of alkaline hydrolysis is used as an empirical measure of the effects of structural change, rather than σ^* or a related parameter, in an attempt partially to cancel out differences in steric effects in the different esters and to permit comparison on a common scale of the effects of variations in both the acyl and alcohol portions of the ester. The lower line is drawn through the points for the imidazole-catalyzed hydrolysis of a series of methyl and ethyl esters with varying acyl groups; in these reactions imidazole acts as a classical general base catalyst.[5] The upper line is drawn through the points for a series of acetates with varying leaving groups. With the exception of N,O-diacetyl-N-methylhydroxylamine, the points for the acetate compounds which have a good leaving group fall on a line which is straight for the compounds with the best leaving groups, but shows a downward curvature for the acetates of less acidic phenols.[57] As the leaving groups become still worse there is a sharp downward curvature and the points for acetoxime acetate, trifluoroethyl acetate, and ethyl acetate are several orders of magnitude below those for the more reactive esters. The points for these compounds approach the line for the general base-catalyzed hydrolysis of methyl and ethyl esters. Thus, the over-all curve for the imidazole-catalyzed hydrolysis of acetates with leaving groups which have pK_a values in the range 4 to 16 is sigmoid, with upper and lower portions corresponding to nucleophilic and general base catalysis, respectively, and a sharp break between, corresponding to a change in the mechanism of catalysis. The rate constants for the nucleophilic reactions of imidazole with acetoxime acetate, trifluoroethyl acetate, and ethyl acetate are even lower than those for the general base-catalyzed reactions of imidazole with these esters, since no such nucleophilic reaction is observed.

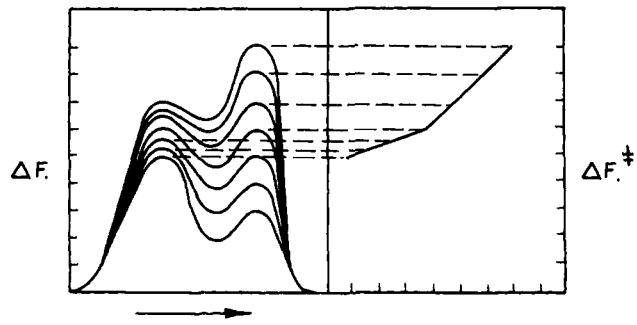


Fig. 9.—Transition state diagram for a two-step reaction showing how changes in structure which affect principally the second step result in a nonlinear structure reactivity correlation.

The downward curvature in this structure–reactivity correlation could be explained qualitatively by the statement that as the leaving group becomes so poor that it can no longer be displaced by imidazole, a nucleophilic reaction is no longer observed. If the mechanism involves a tetrahedral addition intermediate, this could be expanded to the conclusion that, with a poor leaving group, the intermediate expels imidazole rather than alcoholate ion and thus returns to starting materials rather than going on to products (eq. 1).[2-5] The situation may be visualized more clearly with the help of transition state diagrams for the nucleophilic reaction (Fig. 9). We will assume that with a good leaving group, such as acetate ion in the case of acetic anhydride, the attack of imidazole on the ester is rate determining and almost every molecule of addition intermediate that is formed goes on to products (lower curve). As the leaving group is made worse, the energy barrier to the second step of the reaction will increase, but the rate will be decreased only to the extent that the change in structure of the leaving group affects the energy barrier for the first step. Thus, in this region, the reaction rate will have a relatively small sensitivity to changes in the structure of the leaving group and, in fact, the slope of the plot of log k_{OH^-}

(56) E. Gaetjens and H. Morawetz, *J. Am. Chem. Soc.*, **82**, 5328 (1960).

(57) A more exact description would take more explicit account of steric effects. While the use of the rate of the hydroxide reaction as a standard for comparison is partially successful in compensating for steric effects, as shown by the fact that plots against this parameter show considerably less scatter than plots against the pK_a of the leaving group, σ, or σ^*, some ambiguity which it is not presently possible to avoid, remains. Presumably, if it were possible to allow quantitatively for steric effects the points for the phenyl acetates would be shifted upward and to the right, and the curvature in the line would be shifted correspondingly. This would have the desirable effect of putting the points for the general base-catalyzed reactions of trifluoroethyl acetate and acetoxime acetate above and to the left of the line for nucleophilic reactions and might also result in a better fit to the line of the point for N,O-diacetyl-N-methylhydroxylamine.

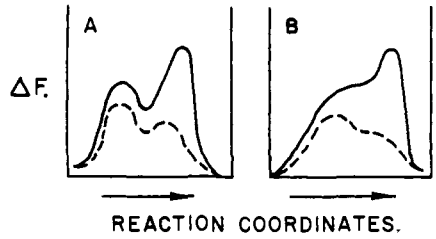


Fig. 10.—Transition state diagrams (A) for reactions with an unstable intermediate and (B) for reactions with no intermediate.

vs. log k_{Im} (Fig. 7) for esters with good leaving groups is near 1.2, as might be expected if attack of the nucleophile were rate determining in both reactions. As the leaving group is made progressively worse (Fig. 9), the energy barrier for the second step will become larger than that for the first step; *i.e.*, the second step becomes rate determining. A given increment of structural change will now be *directly* reflected in the observed rate, which will accordingly become much more sensitive to the nature of the leaving group. This accounts for the downward curvature in the structure–reactivity plot. As the leaving group becomes still worse, the rate of the nucleophilic reaction becomes so slow that it is not observed, and another reaction, the general base-catalyzed hydrolysis which has less sensitivity to the nature of the leaving group, becomes the observed reaction path.

This description has been in terms of a tetrahedral addition intermediate with some stability, but such an intermediate is not required for the argument. The same situation obtains if there is no metastable intermediate, but only a skewed transition state, the nature of which changes as the leaving group becomes less favorable (Fig. 10).

It should be noted that it is not a requirement for general base catalysis that the pK_a of the leaving alcohol be less than pK_w.[42] General base catalysis by imidazole of the hydrolysis of a series of ethyl esters has been reported previously.[5] In fact, as shown in this study, the requirement that general base catalysis be detectable is that the leaving group be several pK units more basic than the catalyst; otherwise nucleophilic reaction takes place and general base catalysis is not ordinarily detectable.

There are several other examples of changes in the mechanism of carbonyl group reactions as the structure of the reactants is varied. A change in the predominant mechanism of the *nucleophilic* reaction of imidazole with a series of acetates with varying leaving groups has been described in the preceding paper.[11] With a good leaving group, as in acetic anhydride and *p*-nitrophenyl acetate, the uncatalyzed reaction of imidazole is of overwhelming importance and no other reaction paths are detected. With the acetates of less acidic phenols, expulsion of the leaving group is more difficult and a general base-catalyzed nucleophilic reaction of imidazole becomes significant. With still worse leaving groups, in the reactions with acetoxime acetate and trifluoroethyl acetate, the uncatalyzed nucleophilic reaction is no longer detectable and the nucleophilic attack of imidazole proceeds only through a hydroxide ion-catalyzed reaction. Finally, with ethyl acetate, the leaving group is so unfavorable that no nucleophilic reaction of imidazole can be detected.

The same situation is presumably reflected in the facts that (a) the nucleophilic reaction of acetate (measured by isotope exchange for acetic anhydride[40]) is faster than the general base-catalyzed hydrolysis by acetate in the case of acetic anhydride but is slower in the case of *p*-nitrophenyl acetate, with its poorer leaving group[46]; (b) nitrite ion (pK_a 3.4) is an unusually effective nucleophile toward acetic anhydride,[58] but is not unusually reactive toward *p*-nitrophenyl acetate[4,8]; and (c) hydroxylamine (pK_a 6.0) reacts readily as the free base with thiol esters,[59] but reacts with ordinary oxygen esters only in a base-catalyzed reaction,[60] in spite of the fact that the rates of alkaline hydrolysis of oxygen and thiol esters are very similar.[61]

A break in a structure–reactivity plot may also be observed if the nucleophile, rather than the leaving group, is varied. The hydrolysis of ethyl dichloroacetate is subject to general base catalysis by a number of weak bases, which follow a Brönsted relationship with a slope of $\beta = 0.47$.[5] With stronger bases, such as ammonia, tris-(hydroxymethyl)-aminomethane, and hydroxide ion, a nucleophilic reaction with ethyl chloroacetate and ethyl dichloroacetate is observed and the rate constants for the nucleophilic reactions are larger than those predicted by the Brönsted plot for general base catalysis. This results in a break in a plot of log k against pK_a, in which weak bases follow a Brönsted relationship with a slope of approximately 0.5 and strong bases fall on a series of intersecting lines for different types of nucleophiles, with slopes of approximately 0.8.[5,62,63] The relative rates of reaction of a series of nucleophilic reagents toward *p*-nitrophenyl acetate and δ-thiolvalerolactone have recently been interpreted in similar terms.[64]

A somewhat analogous situation is seen in semicarbazone formation from substituted benzaldehydes in 25% ethanol at pH 3.9. In this reaction there is a change in rate-determining step with changing substituents on benzaldehyde, which results in a sharp break in the $\sigma-\rho$ plot.[65]

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