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Base Catalysis of Imidazole Catalysis of Ester Hydrolysis[1]

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The nucleophilic reactions of imidazole with phenyl acetate, trifluoroethyl acetate, acetoxime acetate, and *p*-nitrophenyl toluate are catalyzed by hydroxide ion. The nucleophilic catalysis of the hydrolysis of *p*-methylphenyl acetate and *p*-methoxyphenyl acetate by imidazole is itself subject to general base catalysis by imidazole. No base-catalyzed reaction of imidazole with *p*-nitrophenyl acetate or ethyl acetate could be detected.

The hydrolysis and transfer of the acyl groups of esters and related compounds is catalyzed by imidazole by two different mechanistic pathways: through nucleophilic catalysis, with the intermediate formation of an acylimidazole,[2-7] and through general base catalysis, in which imidazole acts solely as a catalyst for proton transfer.[5,8] It has been shown that the attack of imidazole or certain substituted imidazoles on acyl groups is itself subject to base catalysis. Bruice and co-workers have shown that the anions of weakly basic imidazoles, which are substituted with strongly electron-withdrawing groups, may be the reactive species in reactions with *p*-nitrophenyl acetate,[9] and it has been shown that the reactions of imidazole itself with certain substituted *p*-nitrophenyl benzoates contain a term in the rate law which is second-order in respect to imidazole and corresponds to general base catalysis by imidazole of the nucleophilic attack of imidazole on these esters.[10a,b] On the other hand, it has been suggested that the concentration of the anion of imidazoie would be so low near neutral pH that reactions of this species would not be significant.[11] The experiments on base-catalyzed reactions of imidazole reported here, which provide further evidence for this "catalysis of catalysis," form part of a more extensive examination of the effect of substrate structure on the mechanism of catalysis and susceptibility to catalysis of ester hydrolysis by imidazole.

Experimental

Materials.—Ethyl and phenyl acetates were commercial products redistilled before use. *p*-Nitrophenyl acetate was prepared by the method of Chattaway[12] and recrystallized from ether. Trifluoroethyl acetate was synthesized according to Bruice, *et al.*[13]; $n^{25}D$ 1.3185, reported $n^{25}D$ 1.3190. Acetoxime acetate was made by the method of Zinner[14]; b.p. 84° (22 mm.), reported 70–72° (10 mm.). *p*-Nitrophenyl toluate was kindly supplied by Dr. Bruce Anderson. Imidazole was recrystallized before use. N-Methylimidazole was prepared by the method of Häring[15] or obtained commercially and was redistilled before use. Triethylamine was redistilled from KOH and stored as a 3.0 *M* solution of the hydrochloride in water. Trifluoroethanol was purchased from Columbia Organic Chemicals Co., Inc. Water was glass distilled twice, boiled, and stored in a carbon dioxide-free atmosphere.

Rate Measurements.—The reactions in which phenol or *p*-nitrophenol was released were followed spectrophotometrically as described previously.[16] The temperature was controlled with a thermostated brass block inserted in the cell compartment of a Zeiss PMQII spectrophotometer. The reactions of other esters were followed by the following modifications of the hydroxylamine assay.[17,18] Reactions of acetoxime acetate were studied in glass-stoppered test tubes, containing an initial volume of 17.9 ml., which were equilibrated in a 25 ± 0.05° water bath. The reactions were initiated by the addition of 0.1 ml. of 0.07 *M* ester in water and 2.0-ml. aliquots were taken at appropriate time intervals. The aliquots were pipetted into 2 ml. of a mixture containing 1 volume of 4 *M* $NH_2OH \cdot HCl$, 2 volumes of 3.5 *M* NaOH, and 1 volume of water. To this mixture was added 8.0 ml. of 10% $FeCl_3 \cdot 6H_2O$ in 0.7 *N* HCl after incubation periods varying from 2 to 10 min. Optical density was measured in 5.0-cm. cells at 540 mμ after an average time of 15 min., but never less than 5 min. after the addition of ferric chloride. Reactions of trifluoroethyl acetate and ethyl acetate were studied in glass test tubes sealed with rubber serum stoppers. The runs were initiated by the addition of a small amount of a concentrated solution of the ester in water and the serum stoppers were immediately placed over the tubes. Aliquots were withdrawn through the stopper with a calibrated syringe. This procedure minimized the evaporation loss of these volatile esters. Reaction rates determined in triethylamine buffers were shown to be independent of buffer concentration in the range employed in experiments in which the buffer was varied over a twofold range of concentration at constant pH and ionic strength.

All reactions were run under pseudo-first-order conditions and followed first-order kinetics for at least two half-times, unless otherwise noted. Ionic strength was maintained at 1.0 with KCl. Rate constants were obtained as described previously.[16] Third-order rate constants for the hydroxide ion-catalyzed reactions of imidazole with esters were obtained by one of two methods. In the first method the observed pseudo-first-order rate constants in the presence of imidazole were corrected for the rate of alkaline hydrolysis and were then plotted against hydroxide ion concentration. The slope of the resulting line, when divided by the imidazole concentration, gave the desired third-order rate constant. Alternatively, the observed rate constants were plotted against the concentration of imidazole at constant pH. For the reactions of trifluoroethyl acetate and acetoxime acetate no correction was necessary for the very slow uncatalyzed reaction of imidazole free base. The slope of the resulting line was divided by the hydroxide ion concentration to give the third-order rate constant.

Measurements of pH were made with the Radiometer PHM 4b pH meter employing a G 200B glass electrode. The activity coefficient of hydroxide ion at ionic strength 1.0 was found to be 0.67 from triplicate measurements of the pH of 0.01, 0.012, and 0.015 *M* solutions of KOH brought to ionic strength 1.0 with potassium chloride, taking $K_w = 10^{-14}$ at 25°.

(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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(10) (a) M. Caplow and W. P. Jencks, *Biochem.*, **1**, 883 (1962). (b) T. C. Bruice and S. J. Benkovic (personal communication) have recently carried out an investigation of the reaction of imidazole with phenyl acetates and have independently found a term in the rate law proportional to [imidazole]^2 for the reactions with *p*-methoxyphenyl and *p*-methylphenyl acetates. The observed large negative entropy of activation (−51 e.u.) and the solvent deuterium isotope effect of 2.2 are in accord with a mechanism involving general base catalysis for the reaction with *p*-methylphenyl acetate. The values of the rate constants for the catalyzed reactions at 34° reported by these workers are smaller than those observed at 25° in the experiments reported here (see footnote 20 for a possible explanation for low values of this rate constant).

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TABLE I

RATES OF THE HYDROXIDE ION-CATALYZED REACTIONS OF IMIDAZOLE WITH ESTERS AT 25° AND IONIC STRENGTH 1.0

Ester	Initial ester, $M \times 10^4$	Imidazole, M	Hydroxide ion,[a] $M \times 10^3$	No. of detn.	k_3, M^{-2} min.$^{-1}$	Method
p-Nitrophenyl acetate	0.3	0–0.2	1.49×10^{-3} [b]	3	<4700[c]	O.D. 400 mμ
Phenyl acetate	0.2	.2–0.6	0.36–2.1[d]	12	210	O.D. 287 mμ
Acetoxime acetate	4.0	.25–0.5	1.72[d]	3	280	Alk. NH_2OH
Trifluoroethyl acetate	5.2	.167–0.5	1.24[d]	4	350	Alk. NH_2OH
Ethyl acetate	30.0	1.0	24–50[e]	3	<10[c]	Alk. NH_2OH
p-Nitrophenyl toluate[f]	0.3	0.03–0.5	40–100[e]	8	610	O.D. 400 mμ

[a] Determined from measured pH and activity coefficient 0.67, except where noted. [b] In 0.05 M triethylamine buffers. [c] No reaction detected; see text. [d] In 0.15 M triethylamine buffers. [e] Unbuffered solutions; $[OH^-]$ = amount of added KOH. [f] In 30% acetonitrile; ionic strength 0.01–0.02.

Analysis of Products.—The products of the base-catalyzed hydrolysis of acetoxime acetate in D_2O were shown to be acetoxime and acetate by comparison with authentic samples in a Perkin–Elmer Model 21 double beam infrared spectrophotometer equipped with CaF_2 cells. No carbonyl absorption characteristic of acetone or N-methylacetamide was observed.

Results

The rate of the reaction of imidazole with *p*-nitrophenyl toluate in alkaline solution increases linearly with the concentration of hydroxide ion (Fig. 1). Under these experimental conditions the rate of the uncatalyzed reaction of imidazole as the free base is negligible.[10] This establishes that the reaction of this ester with imidazole is subject to catalysis by hydroxide ion and that the k_3 term in the over-all rate law for imidazole-catalyzed reactions with esters (eq. 1) is significant. The value of k_3 for this compound is

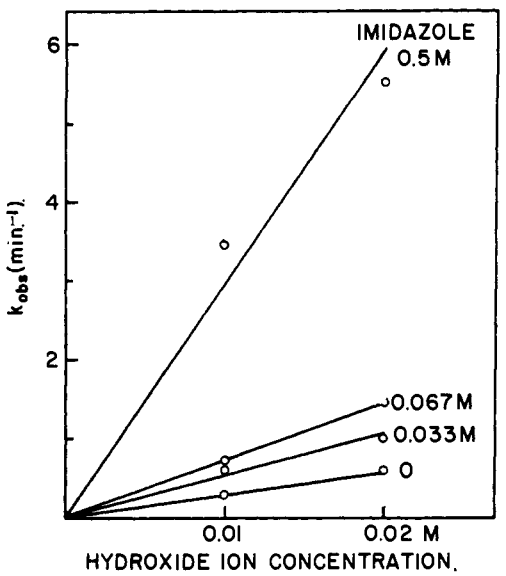

Fig. 1.—Imidazole-catalyzed hydrolysis of *p*-nitrophenyl toluate in alkaline solution in 30% acetonitrile at 25°.

$$\text{rate} = k_1[\text{RCOOR}][\text{Im}] + k_2[\text{RCOOR}][\text{Im}]^2 + k_3[\text{RCOOR}][\text{Im}][OH^-] + k_{OH^-}[\text{RCOOR}][OH^-] \quad (1)$$

610 M^{-2} min.$^{-1}$ (Table I); this may be compared to the value of k_1 of 0.067 M^{-1} min.$^{-1}$ for the uncatalyzed reaction.[10] Since the acylimidazole product of these reactions itself undergoes hydrolysis readily, the over-all reaction results in hydrolysis of the ester.

The reaction of imidazole with phenyl acetate is also subject to catalysis by hydroxide ion (Fig. 2). In this reaction the intercepts at zero hydroxide ion concentration, which represent the k_1 terms for the uncatalyzed reaction of imidazole, are appreciable. N-Methylimidazole does not exhibit the hydroxide ion-catalyzed reaction, as would be expected because of the absence of a proton on the nitrogen atoms of this compound. The absence of catalysis by N-methylimidazole shows that the observed base catalysis with imidazole is not some unusual medium effect of imidazole on ester saponification. The value of k_1 for N-methylimidazole is 0.15 M^{-1} min.$^{-1}$ at 25° and ionic strength 1.0; this is significantly smaller than the value of 0.52 for the corresponding reaction with imidazole.[19]

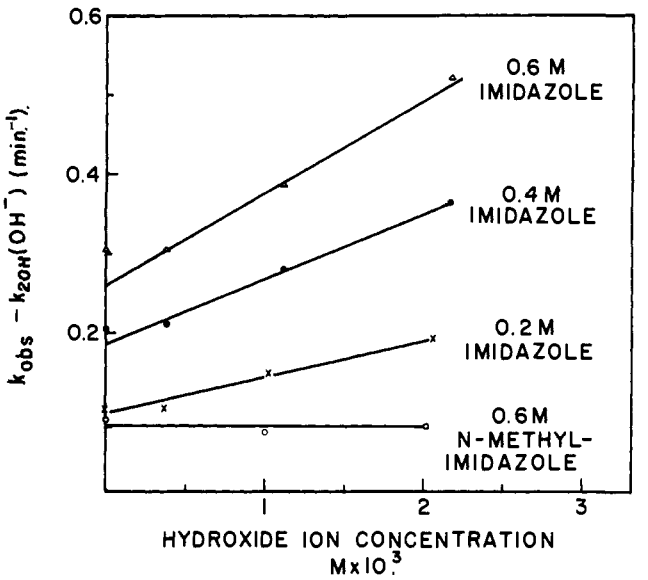

Fig. 2.—Imidazole-catalyzed hydrolysis of phenyl acetate, $k_{obsd} - k_{2OH^-}[OH^-]$, in 0.15 M triethylamine buffers at 25°, ionic strength 1.0. The points on the ordinate are calculated from values of k_1 of 0.52 M^{-1} min.$^{-1}$ for imidazole[19] and 0.15 M^{-1} min.$^{-1}$ for N-methylimidazole; k_{OH^-} = 76 M^{-1} min.$^{-1}$.

No hydroxide ion-catalyzed reaction of imidazole with *p*-nitrophenyl acetate could be detected. At pH 11.0 the rate of hydrolysis of this compound in the presence of 0.2 M imidazole was completely accounted for by the rate of the uncatalyzed reaction of imidazole and the rate of alkaline hydrolysis. If it is assumed that a 10% increase in rate due to a hydroxide ion-catalyzed reaction of imidazole could have been detected, an upper limit of 4700 M^{-2} min.$^{-1}$ may be placed on the rate constant for this reaction. Since the rate constant, k_1, for the uncatalyzed reaction of imidazole with *p*-nitrophenyl acetate[19] is 35 M^{-1} min.$^{-1}$, the ratio k_3/k_1 for this ester is less than 135. The corresponding ratio for phenyl acetate is 405.

Hydroxide ion catalysis of the reaction of imidazole with trifluoroethyl acetate and acetoxime acetate is shown in Fig. 3. Under the conditions of these experiments, near pH 11, the rate of the uncatalyzed reaction of imidazole with these esters is very small in comparison to the observed reaction rates[19] and may be neglected. These experiments were carried out at an ester concentration of 5×10^{-4} M. At higher concentrations of ester or in the presence of added alcohol

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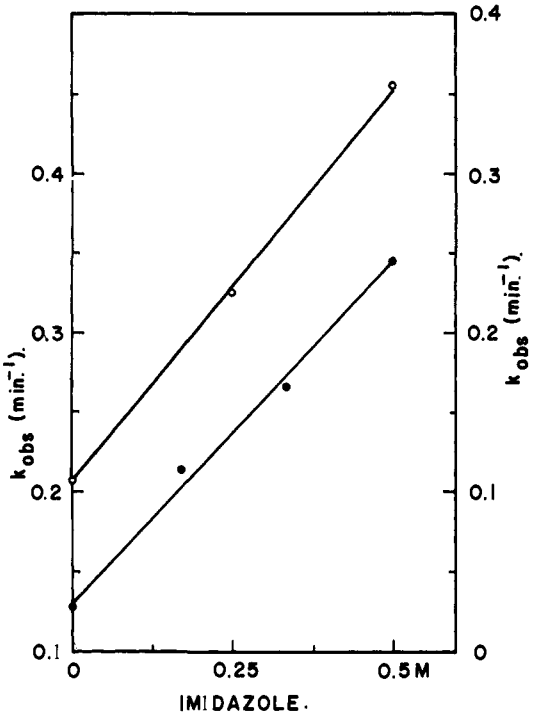


Fig. 3.—Observed rates of hydrolysis of trifluoroethyl acetate (●, and left scale; pH 10.92 ± 0.01) and acetoxime acetate (○, and right scale; pH 11.07 ± 0.02) as a function of imidazole concentration; triethylamine buffer, 0.15 M, ionic strength 1.0. The imidazole free base hydrolysis[19] would give a k_{obsd} of approximately 10^{-3} min.$^{-1}$ at 0.5 M imidazole for both of these esters and is therefore negligible under these conditions.

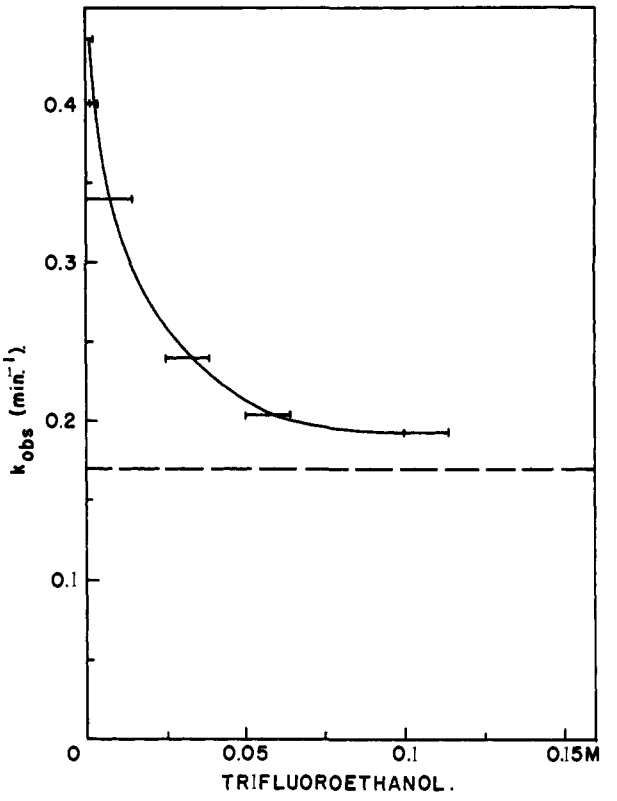


Fig. 4.—Observed pseudo-first-order rate constants for the hydrolysis of trifluoroethyl acetate in 0.75 M imidazole at pH 11.00 ± 0.02, determined by automatic titration. The horizontal lines represent the range of trifluoroethanol concentration produced by hydrolysis of the ester during the experiment. The dashed line is the uncatalyzed alkaline hydrolysis rate at pH 11.00.[19]

the reactions were slower. As shown in Fig. 4, the addition of trifluoroethanol to the reaction mixtures results in a progressive decrease in the reaction rate until, at 0.05–0.1 M trifluoroethanol, the observed rate of ester disappearance approaches the rate of alkaline hydrolysis asymptotically and no catalysis by imidazole is observed. All of these reactions were found to follow (pseudo) first-order kinetics. No formation of trifluoroethyl acetate was observed upon the reaction of 5×10^{-4} M acetylimidazole with 5×10^{-4} M trifluoroethanol at pH 10. This experiment and the data shown in Fig. 4 indicate that the reverse reaction is not significant under the experimental conditions used for the determination of the rate constant for the base-catalyzed reaction of imidazole with trifluoroethyl acetate (Table I; see Discussion).

The rate of alkaline hydrolysis of ethyl acetate in 0.024–0.050 M KOH was not increased by 1.0 M imidazole. Since the k_3 term could easily have been observed if $k_3 = 1.5k_{OH^-}$, k_3 must be less than 10 M^{-2} min.$^{-1}$. For phenyl acetate, $k_3 = 2.8k_{OH^-}$.

The pseudo-first-order rate constants for the reaction of imidazole with p-methylphenyl acetate are proportional to more than the first power of the imidazole concentration (Fig. 5). This is not a nonspecific solvent effect, because the addition of relatively nonpolar materials to water decreases the rate of this type of reaction.[10] This behavior indicates that the reaction contains a term more than first order in respect to imidazole; *i.e.*, k_2 is significant for this reaction, as has been shown previously for substituted p-nitrophenyl benzoates.[10] The value of k_2 (eq. 1) for this reaction, from a plot of k'_{obsd}/[Im] against [Im] (Fig. 5) is 0.17 M^{-2} min.$^{-1}$. Similar behavior was found for the reaction of p-methoxyphenyl acetate, which has a k_2 value of approximately 0.19 M^{-2} min.$^{-1}$.

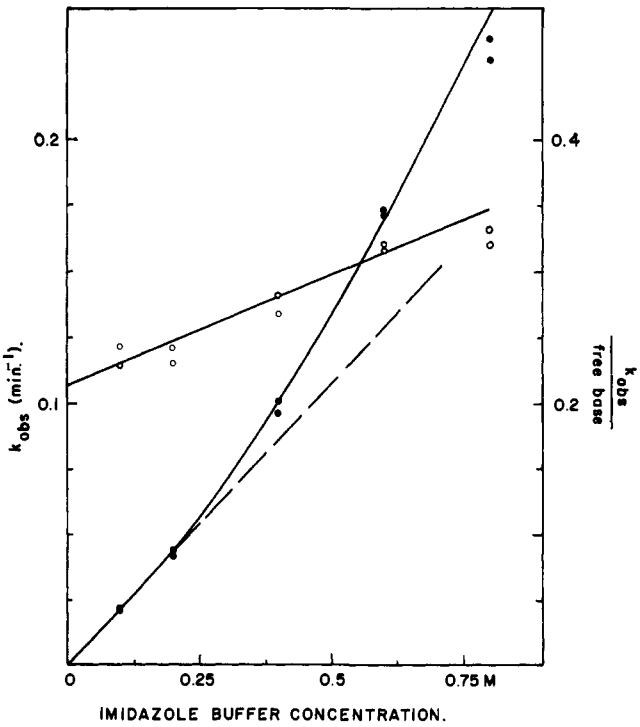


Fig. 5.—Catalysis of p-methylphenyl acetate hydrolysis by imidazole buffer, 90% free base, pH 8.25, at 25°, ionic strength 1.0, 0.1 M sodium arsenate; left scale is for lower lines; dashed line calculated for rate law dependent upon first-order term in imidazole only; upper line and right scale, k_{obsd}/[free amine].

The values of k_1 for these two compounds are 0.21 and 0.20 M^{-1} min.$^{-1}$, respectively.[20]

Discussion

The relative importance of the different terms in the rate law for imidazole catalysis of ester hydrolysis (eq. 1) varies with the structure of the ester and the experimental conditions. The k_1 term, which represents relatively uncomplicated catalysis by imidazole through either nucleophilic or general base catalysis, is of relatively small importance for most of the esters and experimental conditions examined here. The k_2 term represents general base catalysis by imidazole of the nucleophilic reaction of imidazole. This type of reaction has been more extensively examined previously and was shown to exhibit a deuterium isotope effect and to be absent in catalysis by N-methylimidazole.[10] It is possible that water also aids the attack of imidazole by acting as a general base catalyst; this reaction would, of course, not be detectable from a study of the kinetics of the reaction. The possible existence of such catalysis by water is suggested by the fact that the rate of the reaction of imidazole with phenyl acetate is some threefold larger than that of N-methylimidazole, which cannot lose a proton to water. Esters with leaving groups which are relatively easy to displace, such as *p*-nitrophenyl acetate and acetyl phenyl phosphate, show similar reactivities with imidazole and N-methylimidazole.[3-5]

The k_3 term represents hydroxide ion catalysis of the nucleophilic reaction of imidazole with esters. The data do not permit a decision as to whether this reaction represents general base catalysis of the reaction of imidazole or a reaction of the imidazole anion, formed in a pre-equilibrium ionization. The pK_a of imidazole as an acid is 14.5.[21] The fact that imidazole reactions are subject to general base catalysis by imidazole provides a precedent for the possibility that hydroxide ion may catalyze the reaction in a similar manner. The kinetics of the reaction and the absence of such catalysis by N-methylimidazole establish that this reaction involves the loss of a proton by imidazole at some point in the reaction. For esters with relatively poor leaving groups, for which the k_1 term is small, the hydroxide ion-catalyzed reaction with imidazole is the predominant pathway for hydrolysis of the ester over a wide range of pH. The large contribution of this reaction made it technically difficult to measure the k_1 term for the imidazole-catalyzed hydrolysis of trifluoroethyl acetate even at pH values near neutrality, and it was therefore necessary to estimate the rate of this reaction from the rate of catalysis by N-methylimidazole, which cannot undergo the hydroxide ion-catalyzed reaction.[19]

The hydroxide ion-catalyzed reaction of imidazole with trifluoroethyl acetate is readily reversible (Fig. 4). Unless the concentration of ester is kept very low, even the small amount of alcohol released during the reaction is sufficient to cause a significant back reaction, and at 0.05 M trifluoroethanol the back reaction becomes so large that the steady-state concentration of acetylimidazole becomes vanishingly small and the imidazole-catalyzed hydrolysis becomes insignificant. The steady state rate equation for this reaction (2 and 3) is given in eq. 4. When the back reaction, k_{-3}[HOR], is small

$$CH_3COR + Im + OH^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} CH_3C(=O)-Im + HOR + OH^- \quad (2)$$

$$CH_3C(=O)-Im + OH^- \xrightarrow{k_4} CH_3CO^- + Im \quad (3)$$

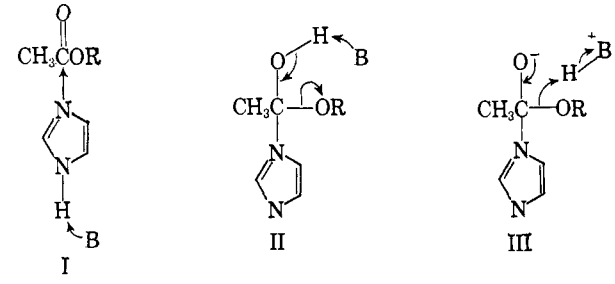
$$\frac{d[CH_3COOR]}{dt} = \frac{k_3k_4[CH_3COOR][Im]}{k_{-3}[HOR] + k_4}[OH^-] \quad (4)$$

this reduces to eq. 5, which is the same as the k_2 term

$$\text{rate} = k_3[CH_3COOR][Im][OH^-] \quad (5)$$

of eq. 1. It was shown that the back reaction was insignificant under the conditions ordinarily used for rate determinations by calculation from the data shown in Fig. 4 and by showing directly that no ester is formed from the reaction of acetylimidazole with 5×10^{-4} M trifluoroethanol. From Fig. 4 it is seen that the hydroxide ion-catalyzed reaction of imidazole with trifluoroethyl acetate is reduced by one-half at a trifluoroethanol concentration of 0.015 M. At this concentration, k_{-3}[ROH] and k_4 must be equal and from the known values for k_2[5] and the dissociation constant for trifluoroethanol,[22] the rate constant for the reaction of acetylimidazole with trifluoroethoxide may be calculated to be approximately 29,000 M^{-1} min.$^{-1}$. This is larger than the rate constant of 19,000 M^{-1} min.$^{-1}$ for the reaction of hydroxide ion with acetylimidazole, as is found also for the corresponding reactions with *p*-nitrophenyl acetate,[13,23] in spite of the considerably lower basicity of trifluoroethoxide compared to hydroxide ion. The existence of this back reaction proves that the hydroxide ion-catalyzed reaction of imidazole with trifluoroethyl acetate is a nucleophilic reaction, because a general base-catalyzed reaction involving the imidazole anion would not be subject to inhibition by trifluoroethanol.

Structures I, II, and III represent three possible mechanisms for the general base-catalyzed reaction of imidazole with esters. I involves abstraction of a proton from an attacking imidazole molecule to make it a more effective nucleophilic reagent. In II and III the departure of the alcohol is facilitated by removal of a proton from a tetrahedral intermediate or by addition of a proton to the leaving alcohol, respectively. Three related mechanisms have the same



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arrangement of atoms but differ in the relative amounts of bond making and breaking in the transition state.[8] All of these mechanisms are kinetically indistinguishable, because they have the same stoichiometric com-

(20) At low imidazole concentrations these reactions exhibit significant deviations from pseudo-first-order kinetics in the latter part of the reaction because of a significant back reaction of the substituted phenol with acetylimidazole. The equilibrium constant, $K \approx$ [*p*-methoxyphenyl acetate][imidazole]/[*p*-methoxyphenol][acetylimidazole], is approximately 130 (J. Gerstein, unpublished experiments) so that in an experiment starting with 5×10^{-4} M ester the reaction proceeds only 78% toward completion at equilibrium in 0.2 M imidazole, but proceeds 96% toward completion with 1.0 M imidazole. Satisfactory first-order kinetics were obtained when the reactions were carried out in the presence of 0.1 M arsenate which acts as a trap for acetylimidazole[5] and pulls the reaction to completion. Arsenate was shown in control experiments not to react directly with the ester at a significant rate. The presence of a large fraction of imidazole hydrochloride in the imidazole buffers tends to mask the third-order term in these reactions because of salting in of the ester by imidazole hydrochloride (Table III, ref. 19). Thus, the most accurate rate constants are obtained in imidazole buffers which are predominantly in the basic form and even these values are not of high precision because of these activity coefficient effects. The experimental conditions which were used for the determination of the rate constants reported in the text are given in Table II of ref. 19.

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

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.

(24) E. R. Stadtman in "The Mechanism of Enzyme Action," W. D. McElroy and B. Glass, Ed., The Johns Hopkins Press, Baltimore, Md., 1954, p. 581.

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

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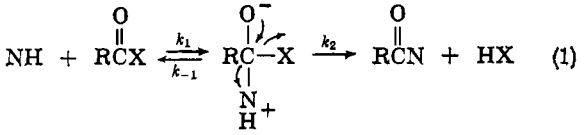
The rates of imidazole-catalyzed and alkaline hydrolysis of a series of acetates with leaving groups of pK_a 4 to 16 have been determined under standard reaction conditions. The rates of the imidazole-catalyzed reactions vary over a range of 10^9 and show two breaks, accompanied by a change in the mechanism 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*-

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