Imidazole Catalysis

II. ACYL TRANSFER AND THE REACTIONS OF ACETYL IMIDAZOLE WITH WATER AND OXYGEN ANIONS*

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Catalysis of p nitrophenyl acetate hydrolysis by imidazole and its derivatives has been described in a number of investigations, of which the most extensive are those by Bruice and Schmir and by Bender and Turnquest (2-9). Imidazole catalysis of the transfer of activated acyl groups from acyl phosphates to a number of acceptor molecules, which is a model for carboxyl-activating enzymes and transacytalsase, appears to be an analogous reaction except that molecules other than water act as the acyl acceptor (1). The imidazole group of a histidine residue has been implicated as a necessary part of the catalytically active center of a large number of enzymes, although the evidence is often indirect and its exact role has not been established (10). The studies reported here were carried out to define more fully the properties and mechanisms of reaction of imidazole and acyl imidazoles in nonenzymatic reactions in order to provide a more complete background for consideration of their possible role in enzymatic catalysis.

EXPERIMENTAL

Materials—Acetyl imidazole was prepared by the method of Boyer (11). Acetyl phosphate derivatives were prepared by pyridine-catalyzed acetylation with acetic anhydride as described by Avison (12). Acetyl-AMP was prepared by Moyed and Lipmann's modification of this procedure (13). For the preparation of acetyl phenyl phosphate 1.08 gm. of disodium phenyl phosphate were dissolved in 10 ml. of 40 per cent pyridine at 0° and 2.5 ml. of acetic anhydride were added with stirring over 5 minutes. The mixture was immediately extracted three times with ether and chilled in an alcohol-ice bath. The product (yield, 536 mg.) was recrystallized twice for analysis by adding

\[
\text{C}_8\text{H}_8\text{O}_3\text{PNa}
\]

Calculated: C 40.3, H 3.4, P 13.0

Found: C 39.2, H 3.7, P 13.4

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1 Analysis by S. M. Nagy, Massachusetts Institute of Technology.

Acetyl ethyl phosphate was prepared similarly. Attempts to purify this compound were unsuccessful and it was used as the crude product. Dimethyl phosphate was precipitated as the barium salt from 80 to 85 per cent acetone after removal of contaminating materials in the commercial product by addition of hot 1 N barium hydroxide to a concentrated aqueous solution; it was recrystallized from acetone-water. Deuterium oxide, 99.8 per cent, was prepared by the Atomic Energy Commission and obtained through the courtesy of the Department of Chemistry, Harvard University. Water and deuterium oxide were glass-distilled before use.

Methods—Reactions were followed spectrophotometrically by measurement of the change in acetyl imidazole absorption at 254 mµ or of thiol ester absorption at 232 or 235 mµ with a Zeiss PMQ II or Beckman DU spectrophotometer equipped with a thermostatted cell compartment. Reactants were brought to temperature equilibrium in a water bath before mixing and then transferred to a cuvette with a 1.0-cm. path length unless otherwise noted; shorter path lengths were obtained by the use of quartz inserts. Kinetic experiments were carried out with one reactant in great excess so that pseudo first order kinetics was followed. Rate constants were obtained by plotting the extent of the reaction, \( x, - x_0 \), against time on semilogarithmic graph paper and calculating the first order constants from the equation \( k_1 = 0.693/t_1 \). Approximately 10 points were obtained for each reaction, and the rates were found to follow first order kinetics closely in all cases. The pseudo first order rate constants obtained at each of a number of different concentrations of the reactant present in large excess were plotted against the concentration of this reactant. The slope of this line gave the second order rate constant for the reaction.

Acetyl imidazole concentration was also measured by conversion to hydroxamic acid by a slight modification of the Lipmann and Tuttle procedure (14). Free sulphydryl group concentration was measured by the nitroprusside reaction (15). The pH was measured at the end of each experiment with a Beckman model G pH meter.

RESULTS

Imidazole Catalysis of Acyl Transfer—In earlier experiments on imidazole catalysis of acyl transfer (1), naturally occurring substrates or their derivatives were used in order to imitate the action of known enzymes. In order to facilitate spectrophotometric studies, mercaptoethanol and mercaptoacetic acid were used as acyl acceptors in these experiments instead of coenzyme

\[
\text{C}_8\text{H}_8\text{O}_3\text{PNa} \quad \text{Found:} \quad \text{C 39.2, H 3.7, P 13.4}
\]
Fig. 1. A, imidazole catalyzed acyl transfer from acetyl phenyl phosphate to mercaptoethanol at 25.0°, 0.2-cm. path length. The composition of the standard reaction mixture (Curve 1) was as follows: 0.02 M imidazole, pH 7.0; 0.005 M mercaptoethanol; 0.001 M acetyl phenyl phosphate; 0.01 M triethanolamine buffer, pH 7.0; 5 X 10^-4 M ethylenediaminetetraacetic acid.

The other reaction mixtures were the same except for the following: Curve 2, 0.01 M mercaptoethanol; Curve 3, 0.04 M imidazole; Curve 4, 0.002 M acetyl phenyl phosphate; Curve 5, no imidazole; and Curve 6, no mercaptoethanol (acetyl imidazole formation followed at 245 mJ).

B, Curve 1, spectra of the products from the imidazole (0.05 %)-catalyzed reaction of acetyl ethyl phosphate (approximately 0.001 M) with mercaptoethanol (0.01 M) in triethanolamine buffer (0.01 M, pH 7.0) at 25.0°. Curve 2, mercaptoethanol omitted. Spectra taken from 20 to 40 minutes after the start of the reaction, during which time there was little change in the absorption. Path length, 0.2 cm.

Fig. 2. A, catalysis of acyl transfer by imidazole and N-methyl imidazole (0.002 M) from acetyl phenyl phosphate (0.003 M) to mercaptacetic acid (0.002 M) in triethanolamine buffer (0.01 M, pH 7.6) at 25.0°. Free sulfhydryl disappearance measured by the nitroprusside reaction.

B, formation and arsenolysis of acetyl imidazole from acetyl-AMP. The reaction mixtures contained 0.001 M acetyl-AMP and 0.1 M imidazole, pH 7.0. At the time indicated by the arrow arsenate to 0.028 M was added. The reaction was followed at 245 mJ, 0.2-cm. path length, against a control cuvette containing AMP instead of acetyl-AMP. The difference spectrum of the reaction product showed an absorption maximum at approximately 243 mJ.
creasing the concentration of acetyl phenyl phosphate increases the rate of the reaction when measured by thiol ester absorption at 232 m.

Acetyl phenyl phosphate was present in limiting concentration, and the reaction follows first order kinetics in respect to thiol ester absorption at 232 m. Doubling the concentration of mercaptoethanol has no effect on the rate. In the presence of mercaptoethanol, the reaction rate is negligible under these conditions. Doubling the concentration of mercaptoethanol has no effect on the rate, whereas a similar reaction in which acetyl ethyl phosphate was used as the acyl donor is shown in Fig. 1.B. In the presence of a thiol acceptor the spectrum has a maximum at 233 m typical of thiol esters; in the absence of acceptor the absorption maximum at 245 m indicates the formation of acetyl imidazole (16).

The enzyme acetyl imidazole hydrolysis as a function of pH, obtained by determining the rate at each pH at several different buffer concentrations and extrapolating to zero buffer concentration. This procedure was necessary because the rate was found to increase with increasing buffer concentration with all buffers tested. Between pH 5 and 8, the rates are similar to, but slightly lower than, those reported by Stadtman (16). Below pH 4 the rate approaches a plateau and remains almost constant up to a hydrochloric acid concentration of 1 M. This suggests that in this pH range, acetyl imidazole becomes completely converted to its conjugate acid so that a further increase in acid concentration does not increase the concentration of the reactive acetyl imidazolium cation; a similar phenomenon is well known, at lower pH, in the hydrolysis of aliphatic amides (17). From these data the pK'a of acetyl imidazole was estimated to be 3.6 and the rate law for acetyl imidazole hydrolysis may be formulated as

\[
v = 2.8[\text{AcImH}^+] + 0.005[\text{AcIm}] + 19,000[\text{AcIm}]^2
\]

The calculated rate of hydrolysis from this equation is shown in Fig. 3 as the solid line. The rates of hydrolysis in deuterium oxide at neutrality and in 0.02 M DC1 are slower than in water with k(H2O) : k(D2O) ratios of 2.7 and 2.5, respectively.

The molar heats and entropies of activation for the hydrolysis of the acetyl imidazolium cation in 0.1 M HCl were determined from rate measurements at 35.0°, 19.4°, and 8.5° as 10,260 calories and -30.2 calories per degree, respectively (Table I). The former value may be compared to 10,200 to 11,600 calories per mole found for E in the mixed reaction at pH 7.6 by Atkinson and Green (18). In concentrated acid or salt solutions the rate falls off markedly. In 4.8 M perchloric acid the rate was found to be 0.257
min.\(^{-1}\) compared to 2.88 min.\(^{-1}\) in 0.1 M HCl, and in 0.8 M perchloric acid and 4.0 M sodium perchlorate it was 0.173 min.\(^{-1}\).

In 0.1 M HCl the decrease in the logarithm of the rate is proportional to the concentration of added sodium chloride (Fig. 4).

**Reaction of Acetyl Imidazole with Carboxylic Acids, Arsenate, and Phosphate**—The rates of the reactions of acetyl imidazole with formic, acetic, and succinic acids [HA] were obtained by measuring the increase in the rate of acetyl imidazole disappearance with increasing buffer concentration at constant pH and ionic strength. The increase in rate is proportional to the concentration of added acetate or succinate buffer and is greater at lower pH (Fig. 5). Similar data were obtained with formic acid. The principal term in the rate law for these reactions is thus

\[ v = k[\text{AcIm}][\text{HA}] \]

or the kinetically indistinguishable term

\[ v = k[\text{AcImH}^+][\text{A}^-] \]

and not

\[ v = k[\text{AcIm}][\text{A}^-] \]

The reaction of acetyl imidazole with arsenate is faster than with carboxylic acids and also increases with decreasing pH (Fig. 6). The predominant reaction is thus proportional to the concentration of the \(H_2\text{AsO}_4^-\) ion, although a plot of the rate against the concentration of this ion present at each pH (broken line, Fig. 6) intercepts the ordinate above zero, indicating that there is also a small contribution from the \(H\text{AsO}_4^{2-}\) ion. Stadtman has shown that the reaction with phosphate, although slower, has similar characteristics (16). Varying the concentration of imidazole buffer at constant pH has no effect on the rate of these reactions (Fig. 6,B).

If the reactive species of phosphate and arsenate were in fact the monoanion, one might expect that the monoanion of dimethyl phosphate would react with acetyl imidazole at a similar rate. No reaction could be detected, however, in a 0.4 M solution of this compound.

The calculated rate constants for the reactions of acetyl imidazole with the different ionic species of these compounds are summarized in Table II.

### Table I

<table>
<thead>
<tr>
<th>Temperature</th>
<th>(k_1)</th>
<th>(\Delta H^\circ)</th>
<th>(\Delta S^\circ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.0°</td>
<td>2.88</td>
<td>10,086</td>
<td></td>
</tr>
<tr>
<td>12.4°</td>
<td>1.30</td>
<td>10,438</td>
<td></td>
</tr>
<tr>
<td>1.5°</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\Delta S_{av} = 10,290\) calories

\(\Delta S^\circ = -30.2\) calories per degree

* Calculated from the relations: \(\Delta H^\circ = E_a - RT\); \(\Delta S^\circ = -RT\ln k_B k_B T\); \(\Delta S^\circ = (\Delta H^\circ - \Delta F^\circ)/T\) where \(E_a\) is the Arrhenius energy of activation, \(k_B\) is Planck's constant, and \(k_B\) is Boltzmann's constant.

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**Fig. 4.** The effect of sodium chloride concentration on the rate of hydrolysis of acetyl imidazole in 0.1 M HCl at 25.0°.
Fig. 5. A, the reaction of acetyl imidazole with acetate buffers at 25.0°C. Ionic strength maintained at 0.2 with sodium chloride. B, the reaction of acetyl imidazole with succinate buffers at 25.0°C. Ionic strength maintained at 0.6 with sodium chloride.

Fig. 6. A, the reaction of acetyl imidazole with arsenate at 25.0°C. ---, rate as a function of the concentration of $\text{H}_2\text{AsO}_4^-$. Ionic strength maintained at 0.3 with sodium chloride. B, effect of imidazole on the rate of reaction of acetyl imidazole with arsenate, phosphate, and succinate at 25.0°C. Ionic strength maintained at 0.3 (arsenate and phosphate) or 0.6 (succinate) with sodium chloride.
TABLE II
Rate constants for reactions of acetyl imidazole at 25°

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Ionic strength</th>
<th>k₁ (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O (AcIm)</td>
<td>0.2</td>
<td>0.005</td>
</tr>
<tr>
<td>H₂O (AcImH⁺)</td>
<td>0.2</td>
<td>2.8</td>
</tr>
<tr>
<td>OH⁻</td>
<td>0.2</td>
<td>19.000</td>
</tr>
<tr>
<td>CH₃COOH</td>
<td>0.2</td>
<td>1.3</td>
</tr>
<tr>
<td>-OOCCH₂CH₂COOH</td>
<td>0.6</td>
<td>1.4</td>
</tr>
<tr>
<td>H₃COOH</td>
<td>0.2</td>
<td>~9</td>
</tr>
<tr>
<td>H₂AsO₄⁻</td>
<td>0.3</td>
<td>6.2</td>
</tr>
<tr>
<td>H₃AsO₄⁺</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>H₂PO₄⁻</td>
<td>1.2*</td>
<td></td>
</tr>
<tr>
<td>HPO₄⁻</td>
<td>0.34*</td>
<td></td>
</tr>
<tr>
<td>(CH₂O)₂PO₄−</td>
<td>0.2</td>
<td>&lt;0.01†</td>
</tr>
</tbody>
</table>

* Calculated from Stadtman’s data at 26° (16) which agree closely with our results.
† Calculated for a 50 per cent increase in rate over the control; in fact, no significant reaction was observed with this compound.

DISCUSSION

Imidazole catalysis of the acyl transfer reactions described here appears to proceed according to the reaction scheme:

\[
\text{AcOPO}_4^− + \text{N} \xrightleftharpoons[k_1]{X^-} \text{AcX} + \text{N} \xrightleftharpoons[k_2]{+} \text{NH}^+ + \text{H}^+
\]

where X⁻ is the acceptor thiol, phosphate or arsenate anion. For the reactions with thiol acceptors, which were investigated most thoroughly, the reverse reactions of Steps 1 and 3 do not appear to be of kinetic significance, since the reaction proceeds to completion and is not affected by the concentration of acceptor thiol. The rate-limiting step is the initial attack of imidazole on the acyl donor molecule, since the rate is proportional to the concentration of both these molecules and not to that of the acceptor; furthermore, no accumulation of acetyl imidazole was observed. This interpretation is consistent with the similar reaction rates observed for imidazole and N-methyl imidazole, which are of similar basicity. If k₃ were rate-limiting it would be expected that the N-methyl imidazole reaction would be much faster, because loss of a proton (k₂) is impossible for the acetyl N-methyl imidazolium cation, and this species would be expected to react with the acceptor much faster than an equilibrium mixture of acetyl imidazole and acetyl imidazolium cation. Finally, the rate of the over-all reaction is the same as the rate of the reaction of the acyl donor with imidazole in the absence of acceptor. Brouwer et al. (7), in a study of the imidazole-catalyzed hydrolysis of p-nitrophenyl acetate, have found that the formation of acetyl imidazole and the release of p-nitrophenol proceed at the same rate, which indicates that acetyl imidazolium is not hydrolyzed before it can attain equilibrium with acetyl imidazole and that the equilibrium mixture of acetyl imidazole and acetyl imidazolium is an intermediate in this reaction.

The choice of the acetyl imidazolium cation rather than neutral acetyl imidazole as the species which reacts with the acyl acceptor is based on the pH dependence of the reaction of acetyl imidazole with thiol and other acceptors which is described in this and the following paper. It may be noted here that the directly measured rate of this reaction is fast in comparison to the rate of the initial acylation of imidazole and is therefore consistent with a low steady state concentration of intermediate in the overall reaction.

The finding that N-methyl imidazole is an active catalyst for acyl transfer as well as hydrolysis (3, 4) indicates that the acetyl imidazolium cation is sufficiently stable to react with acceptors other than water. The high reactivity of thiols as acyl acceptors is strikingly illustrated here by the fact that the acyl group of this reactive intermediate is transferred to 0.002 M mercaptoacetic acid in preference to 55 m water. Koshland (19) has shown that the acetyl pyridinium cation behaves similarly and, in spite of an exceedingly fast rate of hydrolysis, will react with hydroxylamine in preference to water.

The hydrolysis of acetyl imidazole was shown by Stadtman to consist of acid-catalyzed, neutral, and base-catalyzed reactions. The results in Fig. 3, which have been corrected for buffer catalysis, indicate that at pH 7 the observed rate of hydrolysis has contributions from all of these reactions: about 14 per cent from the acid-catalyzed, 62 per cent from the neutral and 24 per cent from the base-catalyzed hydrolyses. In dilute acid all of the imidazole is converted to the acetyl imidazolium cation and the rate becomes independent of pH.

Although the alkaline reaction undoubtedly proceeds through an attack of hydroxide ion, it is not possible from these data alone to decide whether the neutral and acid-catalyzed reactions proceed by an attack of water on acetyl imidazole or acetyl imidazolium, respectively (Sx2, Equation 1), or by a preliminary dissociation to form the acetylium cation followed by a rapid reaction with water (Sx1, Equations 2a and b)
Reaction 2 has been suggested by Staab (20) as the normal path of hydrolysis of acetyl imidazole.

That the hydrolysis of acetyl imidazolium follows the bimolecular route, Equation 1, is strongly suggested by the following evidence.

1. The rate of the reaction is strongly depressed by one component trated acid or salt. Edward and Meacock (21) have shown that the rates of hydrolysis of a series of amides at an acid concentration such that the amide is completely converted to its conjugate acid, follow the equation \( k_{obs} = k_{2}K(\left[\text{H}^{+}\right]/h_{c}) \), where \( k_{2} \) and \( K \) refer to the rate constant for hydrolysis of the conjugate acid by attack of water and to the equilibrium constant for its formation, respectively, and \( h_{c} \) is the acidity function. As the concentration of a strong mineral acid or neutral salt is increased, \( h_{c} \) increases much faster than \( [\text{H}^{+}] \) (22) which results in a decrease of the observed rate. This phenomenon may be regarded as the result of a decrease in the availability of water in these concentrated solutions and its presence in the case of acetyl imidazole supports the bimolecular mechanism. Formation of an acetyl cation (Equation 2), on the contrary, should be favored by increasing salt concentration since the transition state for this reaction should resemble the product in having a more localized charge distribution than the starting material.

2. The rate of acetyl imidazolium hydrolysis is 2.5 times faster in water than in deuterium oxide. This is consistent with mechanism 1, in which stretching of the O-H bonds of water occurs in the transition state but not with Reaction 2, which does not involve proton shifts.

3. The entropy of activation for the hydrolysis of acetyl imidazolium is \(-30.2\) calories per degree. Lang et al. (23) have shown that the entropies of activation of a series of acid-catalyzed reactions, which are known from other criteria to occur by an S_n1 mechanism, fall in the range of \(+9\) to \(-6.1\) calories per degree, compared to \(-20.9\) to \(-24.6\) for a group of \(S_{n2}\) reactions. This difference is presumably due to the higher degree of orientation required of an attacking water molecule in the latter case than of a group of solvating water molecules in the former. These values cannot be directly compared to that obtained for acetyl imidazolium hydrolysis, since they include the entropy associated with the preliminary proton transfer to the substrate. Although the entropy for the dissociation of acetyl imidazolium is unknown, it may be predicted with considerable certainty that it will be small and probably close to the range of \(-4\) to \(-7\) calories per degree for the dissociation of other imidazolium derivatives (24). Even with such a correction, the over-all entropy of acid-catalyzed acetyl imidazolium hydrolysis is among the largest in this series and strongly supports the bimolecular mechanism.

If it is accepted that the hydrolysis of acetyl imidazolium occurs through an attack of water, it follows that the neutral hydrolysis of acetyl imidazole is almost certainly not monomolecular (20). Such a monomolecular reaction would require a dissociation of neutral acetyl imidazole into acetylium cation and imidazole anion, both highly unstable species, and would be even more unfavorable than the corresponding dissociation of acetyl imidazolium into acetylium cation and neutral imidazole.

The further distinction as to whether the neutral reaction represents an attack by water or an acid-catalyzed attack of hydroxide ion

\[ \text{AcImH}^{+} + \text{OH}^{-} \rightarrow \text{AcOH} + \text{Im} \]

cannot be answered with certainty from the available data.

Acetyl imidazolium reacts 5,600 and 4,800 times faster than acetyl imidazole with phosphate and arsenate dianions (see below). The corresponding ratio of reactivities required to account for the neutral hydrolysis as an attack of hydroxide ion on the acetyl imidazolium ion is 6,600 \((k = h_{c}\over K_{\text{AcImH}^{+}/\text{K}})\) which suggests that this is a reasonable mechanism; the ratio for attack of water on the two species would be 500.

The rate of reaction of acetyl imidazole with phosphate was shown by Stadtman (16) to be in largest part proportional to the concentration of the phosphate monoanion, \(\text{HPO}_{4}^{-}\). The data reported here show that the rates of reaction of acetyl imidazole with formic, acetic, succinic, and arsenic acids are also proportional in greatest part to the concentration of undisassociated formic and acetic acids and of the half-dissociated species of succinic and arsenic acids. In each of these cases, then, the reaction rate is proportional to a molecular species which is present in lower concentration and is a weaker base and nucleophilic reagent than its conjugate base, the mono- or dianion. Furthermore, if the monoanion of phosphate were the reacting species, the dimethyl phosphate anion should have similar reactivity, but no reaction could be detected with this reagent. It therefore appears likely that these reactions do not involve an attack of the acid, but rather represent an acid-catalyzed attack of the conjugate base. Such a reaction is kinetically indistinguishable, since the concentrations of the various species are related by the equilibrium constant for acid dissociation

\[ [\text{acid}]K_{a} = [\text{H}^{+}]\over [\text{base}]^{2} \]

The reaction of acetyl imidazole with phosphate, for example, is then interpreted as an attack of the phosphate dianion, \(\text{HPO}_{4}^{2-}\) on the acetyl imidazolium cation. Evidence that a number of other reactions of acetyl imidazole also proceed by a mechanism of this kind is presented in the following paper (25).

**SUMMARY**

Imidazole catalyzes the transfer of activated acyl groups from acyl phosphates to sulfhydryl and other acceptor compounds. These reactions are formulated as proceeding through a slow formation of acetyl imidazole and acetyl imidazolium cation followed by a fast acylation of the acyl acceptor.

\(N\)-methyl imidazole catalyzes acyl group transfer at a similar rate to imidazole. This indicates that the acetyl imidazolium cation reacts with very dilute sulfhydryl acceptors in preference to water.

The rate of hydrolysis of acetyl imidazole increases above and below neutrality and levels off at acid pH. The \(pK_{a}\) of the acetyl imidazolium cation is calculated to be 3.6, and the rate law for acetyl imidazolium hydrolysis is described.

The acid-catalyzed hydrolysis of acetyl imidazole is strongly inhibited by concentrated acid and salt, is 2.5 times slower in deuterium oxide than in water, and shows a \(\Delta H^{\circ}\) of 10,260 calories and a \(\Delta S^{\circ}\) of \(-30.2\) calories per degree. These results strongly favor a rate-limiting bimolecular attack of water on the acetyl imidazolium cation rather than a monomolecular formation of acetylium cation.

The rates of the reactions of acetyl imidazole with acetate, succinate, formate, phosphate and arsenate increase with decreasing pH and are in largest part proportional to the concentration of acetic and formic acids and the monoanions of the other compounds. These reactions are not affected by imid-
azole buffer. The rate of reaction with dimethyl phosphate is negligible.

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