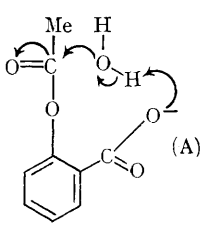
Mechanism of the Solvolysis of 4-(2′-Acetoxyphenyl)imidazole

By STEPHEN M. FELTON and THOMAS C. BRUICE*

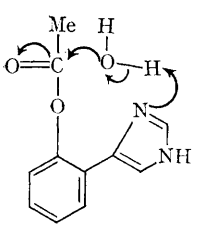
(*Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California* 93106)

THE mechanism of imidazole catalysis of ester hydrolysis continues to be of considerable importance,[1a] due to the fact that an imidazolyl group of a single histidine residue is directly involved in the mechanism of action of the serine esterases.[1b] Our re-investigation of the solvolysis of 4-(2′-acetoxyphenyl)imidazole (I) has been promoted by the finding[2] that the solvolysis of aspirin occurs *via* a general-base mechanism (A). It appeared probable to us that (I), the first model system involving anchimeric participation by an imidazolyl group, also hydrolyzes *via* the same mechanism (B) rather than by nucleophilic catalysis as previously suggested[3] (C).

Three pieces of experimental data support (B) in preference to (C). These are: (a) a deuterium



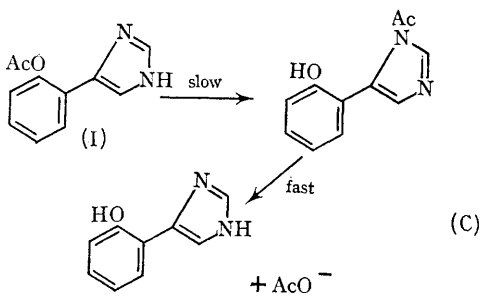
(A)



(B)

solvent kinetic isotope effect (k^{H_2O}/k^{D_2O}) of 3·23 determined at pH = pD for the hydrolysis of the

neutral base form of (I) [based on six rate determinations in H_2O and five in D_2O employing both pH-stat and spectrophotometric techniques]; (b) a determined value of $T\Delta S^{\ddagger} = -10{\cdot}8$ kcal. mole^{-1} in 28·5% (v/v) aqueous ethanol (approximately $-8{\cdot}90$ kcal. mole^{-1} in water); and (c) a larger than anticipated rate of reaction of (I) with hydrazine, with a significant absence of a second-order term in hydrazine.



(C)

The nucleophilic attack of imidazole on phenyl acetate exhibits a deuterium solvent isotope effect of between 1·07 and 1·8 depending on ionic strength.[4] General base-catalyzed hydrolysis of esters is associated with isotope effects of 1·9 to 4·3.[5] The value of 3·24 is clearly in agreement with (2).

Intramolecular nucleophilic catalyses by carboxyl anion in simple monophenyl hydrogen glutarate[6a] and phthalate[6b] esters are associated with $T\Delta S^{\ddagger}$ values of $-3{\cdot}1$ kcal.mole^{-1} and $-2{\cdot}1$ kcal.mole^{-1} respectively. These values are considerably larger than the $-6{\cdot}7$ kcal. mole^{-1} for the intramolecular general base catalysis of aspirin hydrolysis.[2] Similarly, the value of $T\Delta S^{\ddagger}$ for the solvolysis of the neutral base form of (I) is considerably smaller than anticipated for intramolecular nucleophilic catalysis and approaches that for the bimolecular nucleophilic attack of imidazole on *m*- and *p*-substituted phenyl acetates (*i.e.* $T\Delta S^{\ddagger} = -11$ to -14).[4] The smaller values of $T\Delta S^{\ddagger}$ for the intramolecular general base-catalyzed reactions are indicative of the striction of water as a reactant in the transition state.

The reaction of hydrazine with phenyl acetate in aqueous solution in the pH range 7·5 to 9·2 follows the rate law of (4), whereas the reaction of (I) with

$$v = (0{\cdot}49 + 14{\cdot}1\ [N_2H_4] + 4{\cdot}88\ [N_2H_5^+])\ [N_2H_4][PhOAc] \quad (4)$$

hydrazine follows the approximate rate law of (5)

$$v = (12{\cdot}9 + 1{\cdot}6\ [N_2H_5^+])\ [N_2H_4]\ [I] \quad (5)$$

[units in moles and minutes]. The termolecular general-base catalyzed path of hydrazinolysis for phenyl acetate is not detectable for (I), whereas the nucleophilic second order term for (I) is *ca.* 25-fold greater than that for phenyl acetate. Since the second-order rate constants for alkaline hydrolysis of (I) and phenyl acetate are comparable,[7] the hydrazinolysis data finds explanation in the inability of hydrazine to compete with the imidazolyl group as a general base catalyst for nucleophilic attack [*i.e.* $H_2N{\cdot}NH_2$ replaces H_2O in mechanism (2)].

The energetically-preferred general-base mechanism for the solvolysis of (I) (compared to the nucleophilic mechanism for the reaction of imidazole with phenyl acetate[8]) finds interpretation based on the three following factors: (a) the pK_{app} of the imidazolyl group[3] of (I) is 5·5 compared to 7·0 for imidazole, thus the imidazolyl nitrogen is a poorer nucleophile in (I) than in imidazole; (b) the acetyl group once transferred to the nitrogen of (I), can be recaptured by the phenolic hydroxyl group in competition with water molecules; and (c) the formation of a tetrahedral intermediate during an $O \rightarrow N$-acyl shift involves the formation of a tricyclic system involving fusion of two 5-membered rings.

Compound (I) appears ideal as a model for the serine esterases since the imidazolyl group can act as a general base to promote the attack of nucleophiles possessing a proton attached to the nucleophilic atom.

(*Received, May 30th,* 1968; *Com.* 707.)

[1] (a) T. C. Bruice and S. J. Benkovic, "Bio-organic Mechanisms", vol. I, W. A. Benjamin, New York, 1966, (a) ch. 2; (b) ch. 1.
[2] A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 1967, **89**, 4853.
[3] G. L. Schmir and T. C. Bruice, *J. Amer. Chem. Soc.*, 1958, **80**, 1173.
[4] T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, 1964, **86**, 418.
[5] T. C. Bruice, T. H. Fife, J. J. Brunl, and P. Benkovic, *J. Amer. Chem. Soc.*, 1962, **84**, 3012.
[6] (a) T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, in the press; (b) A. M. Turner and T. C. Bruice, unpublished results.
[7] S. M. Felton and T. C. Bruice, unpublished results.
[8] J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, 1964, **86**, 837.