Catalysis by Carbonyl Compounds of the Hydrolysis of the *p*-Nitrophenyl Ester of Leucine

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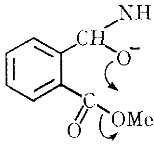
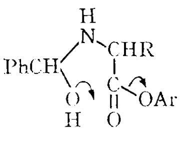
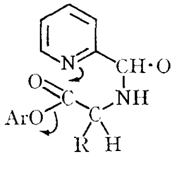
CATALYSIS of the hydrolysis of methyl phthalaldehydate by morpholine has been shown by Bender and Silver[1] to involve nucleophilic attack by the morpholine on the aldehyde group followed by an intramolecular nucleophilic attack by the hydroxyl group of the resulting carbinolamine (see I). Catalysis involving an analogous interaction in which the catalyst is an aldehyde and the substrate the ester of an amino-acid has not previously been demonstrated but we now report an example. Benzaldehyde (concentration = 10^{-3}—10^{-4}M) is an efficient and specific catalyst for the hydrolysis of the *p*-nitrophenyl ester of leucine with a catalytic constant of 8·5 l. mole^{-1} sec.$^{-1}$ at pH 6·83 and 25°, more than six times that for catalysis by imidazole despite the latter being the stronger base by fourteen powers of ten.[2] Since benzaldehyde at a concentration of 10^{-2} M is without effect on the rate of hydrolysis of *p*-nitrophenyl acetate, it is suggested that the catalysis of the hydrolysis of the leucine ester involves the formation of a carbinolamine (II) whose ester group then undergoes hydrolysis with intramolecular nucleophilic participation by the hydroxyl group. Neighbouring-group participation by an hydroxyl group in a γ-position to an amide function is well established[3] and it would not be unreasonable to expect similar participation in the hydrolysis of an ester.



(I)



(II)



(III)

Under the reaction conditions used ([ester] = 10^{-4}M, [aldehyde] = 10^{-5}—10^{-4}M) no carbinolamine nor Schiff base could be detected spectrophotometrically. However the presence of a small concentration of a Schiff base would be expected since Cordes and Jencks[4] have shown that in dilute aqueous solution these are formed rapidly but that the equilibrium constants for their formation are unfavourable. Since at neutral pH the rate-determining step in the formation of Schiff bases is thought to be the dehydration of the carbinolamine intermediate, the formation of the latter should be even more rapid than that of the Schiff base.

Pyridine-2-carboxyaldehyde is about fifteen times more efficient as a catalyst for the hydrolysis of the leucine ester than benzaldehyde but pyridine (concentration = 10^{-3}M) is without catalytic effect. The catalytic effect of pyridine-2-carboxyaldehyde was investigated since it was thought that the ester group of the carbinolamine might undergo hydrolysis with participation by the tertiary amino-group (see III). However the enhanced catalytic activity

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[1] M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, 1962, **84**, 4589.

[2] See E. M. Arnett, *Progr. Phys. Org. Chem.*, 1963, **1**, 324.

[3] For a review see B. Capon, *Quart. Rev.*, 1964, **18**, 45.

[4] E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 1962, **84**, 832; see also W. P. Jencks, *J. Amer. Chem. Soc.*, 1959, **81**, 475; D. E. Metzler, *J. Amer. Chem. Soc.*, 1957, **79**, 485; P. Zuman, *Coll. Czech. Chem. Comm.* 1951, **15**, 839; O. Bloch-Chaude, *Compt. rend.*, 1954, **239**, 804; R. W. Green and P. W. Alexander, *Austral. J. Chem.*, 1965, **18**, 329.

cannot be ascribed to this since pyridine-4-carboxyaldehyde ($k_{\text{cat}} = 130$ l. mole^{-1} sec.$^{-1}$) is almost as effective a catalyst as pyridine-2-carboxyaldehyde ($k_{\text{cat}} = 140$ l.mole^{-1} sec.$^{-1}$) and it probably arises from the increased ease of formation of the carbinolamine. Indeed the failure of pyridine-2-carboxyaldehyde to be a much more effective catalyst than pyridine-4-carboxyaldehyde suggests that the formation of the carbinolamine may be the rate-determining step, since the anchimeric assistance provided by a tertiary base would be expected to be much more effective than that provided by an hydroxyl group.[3]

To our knowledge the only previous example of catalysis of the hydrolysis of an ester of an amino-acid in which the catalyst interacts first with the amino-group is the catalysis by bicarbonate which was postulated by Wieland and his co-workers to involve the formation of carbamate.[5]

(*Received, September 7th,* 1965; *Com.* 564.)

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[5] T. Wieland, R. Lambert, H. U. Lang, and G. Schramm, *Annalen*, 1955, **597**, 181; T. Wieland and F. Jaenicke, *ibid*, 1956, **599**, 125.