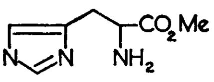
The Copper(II)-catalysed Hydrolysis of Histidine Methyl Ester

By R. W. HAY and P. J. MORRIS

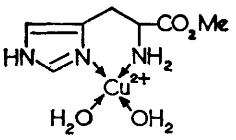
(*Department of Chemistry, Victoria University of Wellington, Wellington, New Zealand*)

A NUMBER of kinetic investigations have been made of the transition-metal ion catalysed hydrolysis of histidine methyl ester.[1–3] Interpretation of the results has been complicated by the uncertain nature of the labile metal complexes in solution. Conley and Martin[2] followed the hydrolysis by a pH-stat method and determined reaction rates from the initial slope of the pH-stat trace of base added against time (the "initial rate method"). The results obtained by Kelly[3] indicated that under certain conditions consecutive reactions could occur which would invalidate Conley and Martin's analysis. We have therefore re-investigated the reaction and have confirmed Kelly's findings.

The thermodynamic acid ionisation constants of histidine methyl ester (I), determined potentiometrically at 25° are $pK_1 = 5{\cdot}01$ and $pK_2 = 7{\cdot}23$.



(I)



(II)

The formation constants for the copper(II) complexes, where $K_3 = [CuE^{2+}]/[Cu^{2+}][E]$ and $K_4 = [CuE_2^{2+}]/[CuE^{2+}][E]$ and E is the free ester, are $\log_{10}K_3 = 8{\cdot}55$ and $\log_{10}K_4 = 5{\cdot}97$ at $I = 0{\cdot}1$M and 25°.

In solutions containing copper(II) and histidine methyl ester in a 1 : 2 metal–ligand ratio, the formation constants show that the concentration of free copper(II), CuE^{2+} (II) and free ester (E) are small compared with CuE_2^{2+}. The kinetics of alkaline hydrolysis of this system in the pH range 7·5—8·6 followed by a pH-stat are consistent with a kinetic scheme involving two consecutive second order processes (*pseudo*-first order at constant pH),

$$CuE_2^{2+} + OH^- \xrightarrow{k_1} CuEA^+ + MeOH$$

$$CuEA^+ + OH^- \xrightarrow{k_2} CuA_2 + MeOH$$

where E is histidine methyl ester and A^- is the carboxylate anion of histidine. The rate constants k_1 and k_2 are readily evaluated by the time ratio method[4] (see Table).

In solutions containing a 1 : 1 metal to ester ratio, hydrolysis occurs with *pseudo*-first-order kinetics at constant pH. In contrast to the 1 : 2 case, $k_{obs}/[OH^-]$ is pH-dependant. Potentiometric measurements show that this effect is due to the presence of two hydrolytically active species, the 1 : 1 complex CuE^{2+} and the monohydroxy-complex $CuEOH^+$. For such a system a plot of $(k_{obs}/[OH^-])([H^+]/K_a + 1)$ against $[H^+]/K_a$ will be linear of slope $k(\mathrm{CuE}^{2+})$ and intercept $k(\mathrm{CuEOH}^{+})$ where $\mathrm{p}K_a = 6{\cdot}91$ is the ionisation constant for the equilibrium $\mathrm{CuE(OH_2)_2}^{2+} \rightleftharpoons \mathrm{CuE(OH)(OH_2)}^{+} + \mathrm{H}^{+}$ Values of the two rate constants were obtained from such a plot which showed excellent linearity (see Table). The monoprotonated form of the ester hydrolyses *ca.* 100 times faster than the free ester and the bis-complex $\mathrm{CuE_2}^{2+}$ *ca.* 500 times faster than the free ester. The ratio $k(\mathrm{CuE_2}^{2+})/k(\mathrm{CuE}^{2+})$ is close to the expected statistical value of 2. The species $\mathrm{CuE_2}^{2+}$ and CuE^{2+} carrying dipositive charges hydrolyse faster than the species CuEA^{+} and CuEOH^{+} carrying unit positive charges. Similar observations on the effect of charge on the basic hydrolysis of esters have been previously noted. For example the betaine $\mathrm{Et_3\overset{+}{N}CH_2{\cdot}CO_2Et}$ hydrolyses 200 times faster than ethyl acetate[5] and 38 times faster than ethyl glycinate.[6]

We conclude, as did Conley and Martin, that in the case of the metal-ion catalysed hydrolysis of esters in which there is no interaction between the metal ion and the labile ester group that catalysis is mainly due to electrostatic effects.

TABLE

Reaction	k(M^{-1} min.$^{-1}$)*
$\mathrm{E + OH^- \rightarrow A^- + CH_3OH}$	$3{\cdot}7 \times 10^{1}$
$\mathrm{EH^+ + OH^- \rightarrow A^- + CH_3OH}$	$4{\cdot}0 \times 10^{3}$
$\mathrm{CuE_2}^{2+} + \mathrm{OH^- \rightarrow CuEA^+ + CH_3OH}$	$1{\cdot}97 \times 10^{4}$
$\mathrm{CuEA^+ + OH^- \rightarrow CuA_2 + CH_3OH}$	$2{\cdot}56 \times 10^{3}$
$\mathrm{CuE^{2+} + OH^- \rightarrow CuA^+ + CH_3OH}$	$1{\cdot}06 \times 10^{4}$
$\mathrm{CuEOH^+ + OH^- \rightarrow CuAOH + CH_3OH}$	$2{\cdot}02 \times 10^{3}$

* At 25° and $I = 0{\cdot}1$ M.

(*Received, November* 15*th*, 1966; *Com.* 896.)

[1] N. C. Li, B. E. Doody, and J. M. White, *J. Amer. Chem. Soc.*, 1957, **79**, 5859.
[2] H. L. Conley and R. B. Martin, *J. Phys. Chem.*, 1965, **69**, 2923.
[3] T. R. Kelly, Ph.D. Thesis, University of Glasgow, 1962.
[4] C. G. Swain, *J. Amer. Chem. Soc.*, 1944, **66**, 1696.
[5] R. P. Bell and F. J. Lindars, *J. Chem. Soc.*, 1954, 4601.
[6] R. W. Hay, L. J. Porter and P. J. Morris, *Austral. J. Chem.*, 1966, **19**, 1197.