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THE COPPER(II)–2,2′-DIPYRIDYLAMINE PROMOTED HYDROLYSIS OF GLYCINE ETHYL ESTER. KINETIC EVIDENCE FOR INTRAMOLECULAR ATTACK BY COORDINATED HYDROXIDE

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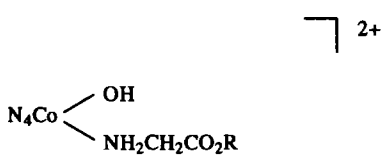
Abstract—The hydrolysis of glycine ethyl ester (EtGly) is catalysed by the copper(II) complex $[Cu(DPA)]^{2+}$ (DPA = 2,2′-dipyridylamine). The reaction has been studied by pH-stat over the pH range 5.8–7.0 at 25°C and $I = 0.1$ mol dm^{-3} (KNO_3). The kinetic and equilibrium results can be interpreted in terms of the kinetic scheme

$$[Cu(DPA)(EtGly)(OH_2)]^{2+} + OH^- \overset{K}{\rightleftharpoons} [Cu(DPA)(EtGly)(OH)]^+ + H_2O$$

$$[Cu(DPA)(EtGly)(OH)]^+ \xrightarrow{k} [Cu(DPA)(Gly)]^+ + EtOH.$$

Hydrolysis takes place by reaction of coordinated hydroxide with the nitrogen-bonded amino acid ester. The pK for ionization of the coordinated water molecule is 6.78 and $K = 1.70 \times 10^7$ dm^3 mol^{-1} determined from the kinetic results. The pK determined by direct potentiometric titration of the complex $[Cu(DPA)(OH_2)_2]^{2+}$ is 6.74. The rate constant k for intramolecular attack of coordinated hydroxide on the ester is 4.9×10^{-4} s^{-1}. At pH 7.7, where the hydroxo complex is completely formed, hydrolysis of the complexed ester is *ca* 60 times faster than that of the uncomplexed ester. The rate enhancement compared with the free unprotonated ester is *ca* 10^3 fold. In this system it has been possible, for the first time, to define the involvement of coordinated hydroxide ion in the copper(II)-catalysed hydrolysis of amino acid esters.

Since the initial discovery by Kroll[1] there have been extensive studies of the metal-ion-promoted hydrolysis of α-amino acid esters.[2] In the kinetically inert cobalt(III) complexes it has been possible to establish that an important reaction pathway for the hydrolysis of complexes of type **1** involves intramolecular attack of coordinated hydroxide on the nitrogen-coordinated ester.[3] In kinetically labile copper(II) complexes, it is difficult to define the



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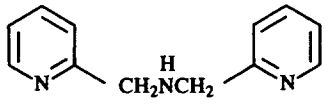

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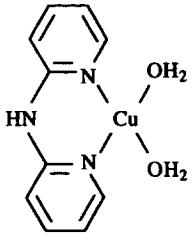

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role, if any, of coordinated hydroxide in the hydrolysis. Nakon *et al.*[4] have studied the hydrolysis of glycine methyl ester catalysed by the complex $[Cu(PMA)]^{2+}$, where PMA is bis(2-pyridylmethyl)amine (**2**) and additional studies have dealt with the catalytic effects of the copper(II) complexes of IMDA (iminodiacetate),[5] NTA (nitrilotriacetate)[6] and dien (diethylenetriamine)[7] on the reaction. It has recently been found that the copper(II) complex of 2,2′-dipyridylamine (**3**) catalyses the hydrolysis of methyl acetate,[8] simple amides[9] and triesters of phosphoric acid.[10] For this reason we have studied the effects of the copper(II) complex on the hydrolysis of ethyl glycinate. The presence of the amino group is expected to lead to quite strong binding to the metal ion. In previous studies of the effects of metal complexes on the hydrolysis of glycine esters it has proved impossible to distinguish between the two possible mechanisms: (a) attack of external hydroxide on the chelated ester species (**4**) and (b) intramolecular attack by coordinated hydroxide on the nitrogen-bonded ester of the type shown in **1**.

EXPERIMENTAL

Reagents

The amine 2,2′-dipyridylamine (DPA) was purchased from Aldrich and was recrystallized twice from toluene. Ethyl glycinate hydrochloride was prepared by standard methods.[11] Solutions of the ester were standardized by potentiometric titration against standard base. Metal ion solutions of $Cu(NO_3)_2 \cdot 3H_2O$ were standardized by passing them through a Dowex 50W-X8 strongly acidic cation exchange resin and titrating the acidic effluent solutions with standard NaOH.

Kinetic measurements

Rates of glycine ethyl ester (EtGly) hydrolysis in the presence of $Cu(DPA)^{2+}$ were determined by pH-stat techniques using a Radiometer Titralab system. Hydrolysis of ethyl glycinate (5×10^{-4} mol dm^{-3}) in the presence of $[Cu(DPA)(H_2O)_2]^{2+}$ (5.26×10^{-3} mol dm^{-3}) was studied at 25°C and $I = 0.1$ mol dm^{-3} (KNO_3) over the pH range 5.8–7.0. A 10% excess of DPA over copper(II) was used to ensure coordination of all copper(II), which is itself an excellent catalyst.[1] A 20% excess of DPA gave the same rates as with a 10% excess, indicating that free copper(II) was not involved in the catalysis.

After equilibrating $Cu(DPA)^{2+}$ solutions at 25°C under a nitrogen flow, a solution of EtGly·HCl was added and the pH brought to the desired value by the addition of 0.02 mol dm^{-3} NaOH. The hydrolysis was then followed by the automatic addition of 0.02 mol dm^{-3} NaOH. The observed first order rate constants k_{obs} were obtained from the slopes of plots of $\ln (V_\infty - V_t)$ vs time, where V_∞ is the final volume of base consummed and V_t is the volume consumed at time t. Excellent first order kinetics were observed at constant pH. Variations of both the $[Cu(DPA)(OH_2)_2]^{2+}$ and ethyl glycinate concentrations at constant pH confirmed that the reaction was first order in both the total complex concentration and the total ethyl glycinate concentration (Table 1).

Values of the hydroxide ion concentration were estimated from the pH using $pK_W = 14.0467$[12] and an activity coefficient of 0.772 determined from the Davies equation.[13] Potentiometric titrations were carried out at 25°C using the Radiometer Titralab system at an ionic strength of 0.1 mol dm^{-3} (KNO_3).

RESULTS AND DISCUSSION

Potentiometric titration of ethyl glycinate in aqueous solution gave a $pK = 7.7$ for the equilibrium $EH^+ \rightleftharpoons E + H^+$, where EH^+ is the nitrogen-protonated ester and E is the free base form. We have shown previously[14] that for base hydrolysis of EH^+, $k_{OH} = 22.9$ dm^3 mol^{-1} s^{-1}, while for E, the rate constant for base hydrolysis is 0.64 dm^3 mol^{-1} s^{-1} at 25°C and $I = 0.1$ mol dm^{-3}.

Hydrolysis of ethyl glycinate (5×10^{-4} mol dm^{-3}) was studied in the presence of a 10-fold excess of $[Cu(DPA)]^{2+}$ so that essentially all of the ester was bound to the complex. Equilibrium studies indicated that at least 85% or more of the EtGly is bound to the complex as $[Cu(DPA)(EtGly)]^{2+}$, and after hydrolysis the Gly^- product remains coordinated as $[Cu(DPA)(Gly)]^+$. The predominant reaction occurring in the hydrolysis studies is

$$Cu(DPA)(MeGly)^{2+} + OH^- \longrightarrow Cu(DPA)(Gly)^+ + EtOH. \quad (1)$$

The total amount of NaOH consumed in the reaction was always within 4% of the value expected from eq. (1). The observed first order rate constants obtained over the pH range 5.8–7.0 are summarized in Table 1. In the pH range of the studies, the rate of hydrolysis of EtGly is neglible in the absence of $Cu(DPA)^{2+}$.

Table 1. Dependence of the reaction rate on the ethyl glycinate concentration at pH 6.40 and $I = 0.1$ mol dm^{-3} (KNO_3)

10^4[EtGly] (mol dm^{-3})	$10^4 k_{obs}$ (s^{-1})	$10^1 k_{obs}$/[EtGly] (dm^3 mol^{-1} s^{-1})
2.00	0.72	3.60
3.00	1.07	3.57
4.00	1.36	3.40
5.00	1.74	3.48

The concentration of $[Cu(DPA)]^{2+}$ used in the measurements was 5.36×10^{-3} mol dm^{-3}. Measurements at 25°C.

The overall $Cu(DPA)^{2+}$ promoted hydrolysis of EtGly proceeds by the two steps

$$CuL^{2+} + EtGly \overset{K_L}{\rightleftharpoons} CuL(EtGly)^{2+} \xrightarrow{OH^-} CuL(Gly)^{2+} + EtOH.$$

Under the conditions used in the present study (where L = DPA), the ester EtGly is bound almost entirely as $[Cu(DPA)(EtGly)]^{2+}$. Thus, the observed rate law represents the second step only. A plot of k_{obs} vs the hydroxide ion concentration is not linear as is normally observed in reactions of this type,[4-7] but shows pronounced curvature (Fig. 1). If the reaction takes place by the scheme

$$[Cu(DPA)(EtGly)(OH_2)]^{2+} + OH^- \overset{K}{\rightleftharpoons} [Cu(DPA)(EtGly)(OH)]^+ + H_2O$$

$$\downarrow k$$

$$[Cu(DPA)(Gly)]^+ + EtOH,$$

in which hydrolysis occurs by intramolecular attack of the coordinated hydroxide ion on the ester carbonyl group, it can be readily shown that

$$k_{obs} = kK[OH^-]/(1 + K[OH^-]). \quad (2)$$

Rearrangement of eq. (2) gives the expression

$$1/k_{obs} = 1/kK[OH^-] + 1/k.$$

A plot of $1/k_{obs}$ vs $1/[OH^-]$ should be linear of slope $1/kK$ and intercept $1/k$. Such a plot is indeed linear (Fig. 2). Least squares analysis gives $k = 4.90 \times 10^{-4}$ s^{-1} and $K = 1.7 \times 10^7$ dm^3 mol^{-1} at 25°C and $I = 0.1$ mol dm^{-3}. The rate constant $k = 4.90 \times 10^{-4}$ s^{-1} is the rate constant for intramolecular hydrolysis by coordinated hydroxide in the nitrogen-bonded ethyl glycinate complex, and K is the formation constant for formation of the hydroxo complex (log $K = 7.25$). The pK for the ionization of the aqua complex can readily be calculated as pK = pK_w − log K = 6.78.

Potentiometric titration of $[Cu(DPA)(OH_2)_2]^{2+}$ with sodium hydroxide gave the titration curve shown in Fig. 3. There is a well defined end point after addition of one equivalent of sodium hydroxide

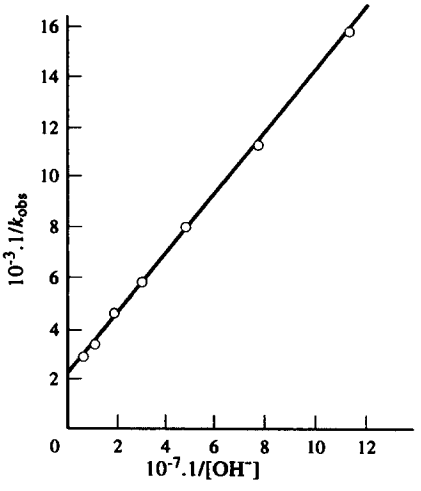


Fig. 2. Double reciprocal plot for the $Cu(DPA)^{2+}$ promoted hydrolysis of EtGly at 25°C and $I = 0.1$ mol dm^{-3}.

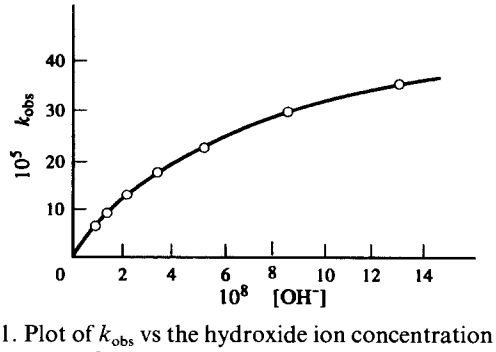


Fig. 1. Plot of k_{obs} vs the hydroxide ion concentration for the $Cu(DPA)^{2+}$ promoted hydrolysis of EtGly at 25°C and $I = 0.1$ mol dm^{-3}.

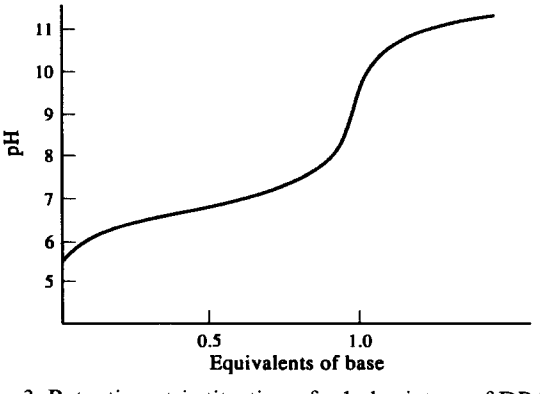


Fig. 3. Potentiometric titration of a 1 : 1 mixture of DPA and copper(II) nitrate (both 5×10^{-3} mol dm^{-3}) at 25°C.

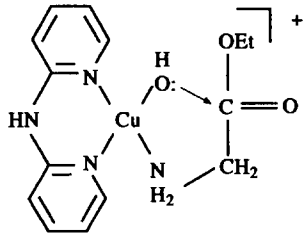
Table 2. The copper(II)–dipyridylamine promoted hydrolysis of ethyl glycinate at 25°C and $I = 0.1$ mol dm^{-3} (KNO_3)

pH	$10^8[OH^-]$ (mol dm^{-3})	$10^5 k_{obs}$ (s^{-1})	α	$10^4 k_{obs}/\alpha$ (s^{-1})
5.83	0.89	6.33	0.11	5.75
6.00	1.31	8.85	0.15	5.90
6.20	2.06	12.4	0.22	5.64
6.40	3.29	17.4	0.31	5.61
6.60	5.20	21.8	0.41	5.32
6.80	8.25	29.7	0.53	5.60
7.00	13.10	35.3	0.65	5.43

Rate constants obtained using $[Cu(DPA)]^{2+} = 5.36 \times 10^{-3}$ mol dm^{-3} and an ethyl glycinate concentration $= 5.0 \times 10^{-4}$ mol dm^{-3}. Values of α were calculated using a pK of 6.74.

which can be attributed to ionization of one of the coordinated water molecules. The pK determined from the titration results is 6.74 at 25°C and $I = 0.1$ mol dm^{-3}, in almost exact agreement with the kinetically determined pK. Using this pK the fraction (α) of the complex ionized to the hydroxo complex was calculated at the pH values used in the kinetic measurements. Values of k_{obs}/α are constant, giving the limiting rate constant 5.6×10^{-4} s^{-1} (Table 2), which agrees quite well with the constant determined from the double reciprocal plot.

The kinetic measurements support the view that hydrolysis occurs by intramolecular attack of coordinated hydroxide in the complex **4**. Complete formation of the active hydroxo complex will occur at a pH of *ca* 7.7 with a limiting value of k_{obs} *ca* 5×10^{-4} s^{-1}. At this pH, an approximate value of k_{obs} for the hydrolysis of glycine ethyl ester can be



(4)

calculated from the expression $k_{obs} = k_{OH}[E][OH^-] + k_{OH}[EH^+][OH^-]$, where k_{OH} for the unprotonated ethyl glycinate (E) is 0.64 dm^3 mol^{-1} s^{-1} and k_{OH} for the nitrogen-protonated species (EH^+) is 22.9 dm^3 mol^{-1} s^{-1} at 25°C and $I = 0.1$ mol dm^{-3}.[14] As the pK for the equilibrium $EH^+ \rightleftharpoons E + H^+$ is 7.7, there is a *ca* 50 : 50 mixture of the protonated and unprotonated ester in solution at pH 7.7 and $k_{obs}/[OH^-] = 11.8$ dm^3 mol^{-1} s^{-1}. As the hydroxide ion concentration is 6.5×10^{-7} mol dm^{-3}, the calculated value of k_{obs} for hydrolysis of ethyl glycinate at this pH is 7.6×10^{-6} s^{-1}. The direct rate enhancement for the reaction is *ca* 60-fold. This rather low value occurs because base hydrolysis of protonated ethyl glycinate is quite rapid due to electrostatic facilitation of the reaction. A more valid comparison can be made with the base hydrolysis of the unprotonated form of the ester. To give a value of $k_{obs} = 4.9 \times 10^{-4}$ s^{-1}, the hydroxide ion concentration would be $k_{obs}/k_{OH} = 4.9 \times 10^{-4}/0.64 = 7.6 \times 10^{-4}$ mol dm^{-4}, giving a pH of *ca* 11. On this basis the rate enhancement is roughly 10^3-fold.

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