A Highly Efficient Copper(II) Complex catalysed Hydrolysis of Methyl Acetate at pH 7.0 and 25 °C

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The turnover time for [(2,2′-dipyridylamine)$Cu(OH_2)_2$]$^{2+}$ (1 mM) catalysed hydrolysis of methyl acetate (1 M) is 23 min at pH 7, 25 °C.

Successful catalysed hydrolysis of activated esters is no guarantee that the same catalyst will hydrolyse unactivated esters.[1] We recently reported that a 10 mM solution of (**1**) gives a six-fold rate enhancement for methyl trifluoroacetate hydrolysis but no rate enhancement for methyl acetate hydrolysis.[2] Indeed, true catalytic hydrolysis of unactivated esters under mild conditions has only been obtained with real enzymes despite enormous efforts to design efficient artificial esterases.[3,4] Here we report on efficient catalytic hydrolysis of methyl acetate using a simple Cu^{II} complex (**2**).

A solution of (**2**) was standardised by titration with standard NaOH solution. The pK_a of the copper co-ordinated water molecule is 7.2 at 25 °C. Catalysed hydrolysis of methyl acetate (1 M) with (**2**) (0.3 to 1 mM) was monitored by the pH stat method.† The pH of the reaction solution was maintained with a Radiometer PHM63 pH meter equipped with a Radiometer RTS 822 automatic titrator. The catalytic turnover‡ time is 23 min at pH 7.0, 25 °C (Figure 1).

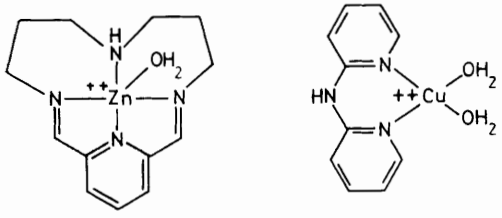
Based on the pK_a of the copper co-ordinated water molecule and the pH–rate profile (Figure 2), we propose that the mechanism of catalysed hydrolysis of methyl acetate using (**2**) involves co-ordination of the ester to the copper followed by intramolecular metal hydroxide attack on the co-ordinated ester (Scheme 1).[5] Since Cu^{II} is substitutionally labile, either formation or breakdown of the tetrahedral intermediate is the rate-determining step (k_2). The rate of acetic acid production is given by $k_{obs}[(2)]_T$[ester] where $[(2)]_T$ is the total catalyst concentration and k_{obs} is given by equation (1). The pH–rate profile (Figure 2) was fitted according to equation (1) (Scheme 1).§ Under our experimental conditions, mono-aquo complexes such as (**1**) or (**3**) do not catalyse the hydrolysis of methyl acetate to any observable extent.

$$k_{obs} = k_2K_1[K_a/(K_a + [H^+])] \quad (1)$$

We chose to use 2,2′-dipyridylamine for its strong affinity towards Cu^{II}. The ligand binds Cu^{II} more tightly (K = 1.15 × 10^8 mol^{-1} dm^3)[6] than it binds H^+ (K = 1.38 × 10^7 mol^{-1} dm^3).[6] Consequently, the metal ion does not dissociate from 2,2′-dipyridylamine over a wide range of the solution pH, including the pK_a region for the copper-bound water molecule.

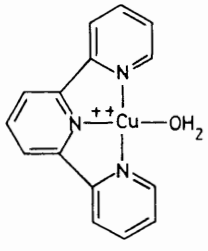
The second order rate constants§ (k_{obs}) for catalysed hydrolysis of methyl acetate and *p*-nitrophenyl acetate using (**2**) are 7.2 × 10^{-4} and 1.6 × 10^{-1} mol^{-1} dm^3 s^{-1} respectively (pH 7.0, 25 °C). The rates for methyl acetate[7] and *p*-nitrophenyl acetate[8] hydrolyses with water are 3 × 10^{-10} and 6 × 10^{-7} s^{-1} respectively. Therefore, (**2**) gives a greater rate acceleration for methyl acetate hydrolysis than for *p*-nitrophenyl acetate hydrolysis. Simple catalysts that are highly efficient at hydrolysing activated esters are not necessarily efficient at hydrolysing unactivated esters. For example, (**1**), (**3**) or imidazole gives a much greater rate acceleration for *p*-nitrophenyl acetate hydrolysis than for methyl acetate hydrolysis.[1]

The equilibrium constant (K_1, Scheme 1) for complexation of methyl acetate to the copper complex cannot be measured directly. However K_1 can be approximated as follows. There is a linear free energy relationship between the basicity of the ligands (L) and the equilibrium constant for complexation of L to aqueous Cu^{II} [equation (2)],[9] where $K = [(H_2O)_5(Cu)L]^{2+}/[(Cu)(H_2O)_6]^{2+}[L]$ and pK_a is the acid dissociation constant for the conjugate acid of L. The pK_a of protonated methyl acetate is about −6.0.[10] Therefore, the equilibrium constant for binding methyl acetate to aqueous Cu^{II} should be about 2.6 × 10^{-3} mol^{-1} dm^3 [equation (2)]. This is an extended extrapolation considering that equation (2) is based on a series of substituted pyridines. However, log K for L = H_2O calculated from equation (2) [log K = 0.45 (−1.72 − 7) + 3.26 = −0.66] is in excellent agreement with what it should be [log K = log (6/55) = −0.96]. Assuming that the affinity of methyl

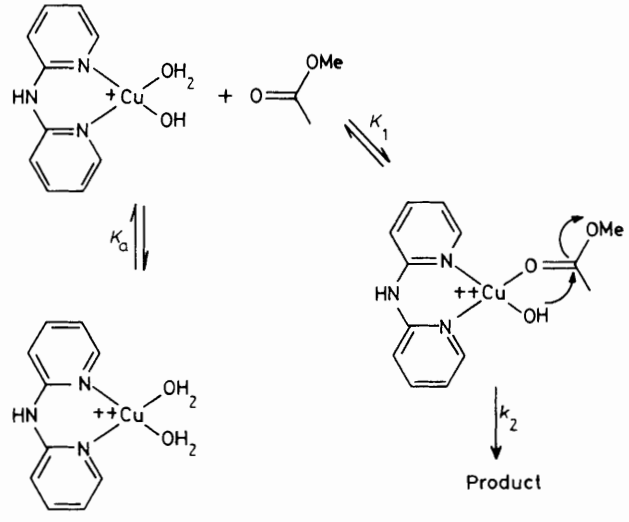


(**1**)

(**2**)



(**3**)



Scheme 1

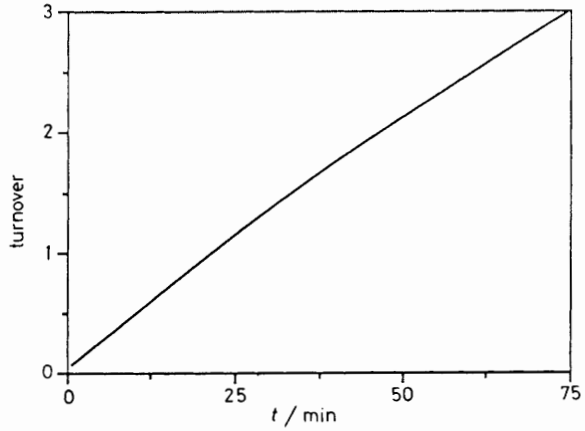


Figure 1. Catalysed hydrolysis of methyl acetate (1 M) using (**2**) (1 mM) at pH 7.0, 25 °C.

† Methanol production was confirmed by ^1H n.m.r.

‡ At 1 mM catalyst concentration, one catalytic turnover every 23 min translates to a reaction rate of 7.2 × 10^{-7} mol^{-1} dm^3 acetic acid produced per second [10^{-3}/(23 × 60)]. The rate constants were reproducible to within 3%.

§ A non-linear least square curve fitting program was used to fit the data (K_a = 2.8 × 10^{-7}, K_1k_2 = 1.0 × 10^{-3} mol^{-1} dm^3 s^{-1}). The K_a value obtained through potentiometric titration (6.3 × 10^{-8}) is more reliable than the one obtained kinetically.

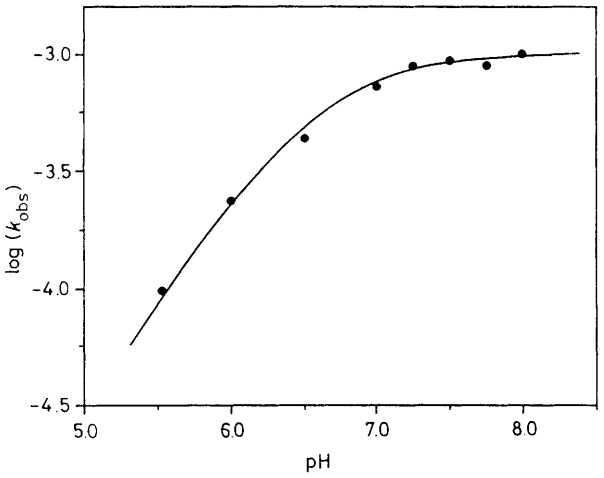


Figure 2. pH–Rate profile for (**2**) (1 mM) catalysed hydrolysis of methyl acetate (1 M) at 25 °C.

acetate for aqueous copper and for (**2**) are comparable, k_2 (3.8×10^{-1} s^{-1}, half-life = 2 s) is 10^9 times greater than the water rate for free methyl acetate hydrolysis.[7] This is a spectacular rate acceleration for such a simple catalyst. Indeed, the k_2 value is comparable to the k_{cat} values for chymotrypsin catalysed hydrolysis of esters[11] (5×10^{-1} s^{-1}). However, nature's most efficient esterase that hydrolyses the neurotransmitter, acetyl choline, is in a league by itself (acetyl choline esterase: $k_{cat} = 3 \times 10^4$ s^{-1}).[12]

$$\log K = 0.45\ (pK_a - 7) + 3.26 \qquad (2)$$

In conclusion, we have shown for the first time that Cu^{II} can be rationally activated to catalyse the hydrolysis of a simple, unactivated ester with great efficiency.¶

¶ Detailed mechanistic analysis will be reported later in a full paper.

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