The Very Rapid Zinc(II)- and Copper(II)-promoted Hydrolysis of 8-Acetoxyquinoline-2-carboxylic Acid. A Model for the Rate of Catalysis by Carboxypeptidase A

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In the range pH 5—12 the hydrolysis of 8-acetoxyquinoline-2-carboxylic acid (EH) follows the rate law, rate = $k_0[E^-] + k_{OH}[E^-][OH^-]$ with $k_0 = 1.67 \times 10^{-4}$ s^{-1} and $k_{OH} = 0.84$ dm^3 mol^{-1} s^{-1} at 25°C and $I = 0.1$ mol dm^{-3}. Activation parameters for the 'spontaneous' reaction ($\Delta H^{\ddagger} = 57.3$ kJ mol^{-1}, $\Delta S^{\ddagger} = -159$ J K^{-1} mol^{-1}) and the solvent deuterium-isotope effect ($k_{H_2O}/k_{D_2O} = 2.5$) support a mechanism involving intramolecular general-base catalysis by the quinoline nitrogen. The 1 : 1 metal complexes of the ester, $[ME]^+$ (M = Zn^{II} and Cu^{II}), undergo base hydrolysis *ca.* 2×10^8 times faster than the deprotonated ligand (E^-). The metal-promoted reactions involve intramolecular attack by co-ordinated hydroxide ion and this effect in conjunction with a perturbation of 6 pK_a units in the acidity of the conjugate acid of the leaving group leads to rates of hydrolysis (k 5 $\times 10^1$—5 $\times 10^3$ s^{-1}) comparable to the reported values of k_{cat} for the hydrolysis of a good ester substrate by the zinc metalloenzyme carboxypeptidase A (k_{cat} *ca.* 2.3 $\times 10^2$ s^{-1}).

THE metal-ion-promoted hydrolysis of esters continues to attract considerable attention.[1] Recent studies [2-5] have demonstrated the importance of metal–carbonyl-oxygen bonding in activating the ester towards nucleophilic attack; less attention, however, has been paid to metal-ion activation of the leaving group. As part of a general study of the metal-ion-promoted hydrolysis of esters we have examined the hydrolysis of 8-acetoxyquinoline-2-carboxylic acid (EH), both in the presence and absence of Cu^{II} and Zn^{II}. Molecular models show that

[1] For a recent review, see R. W. Hay and P. J. Morris in 'Metal Ions in Biological Systems,' vol. 5, ed. H. Sigel, Marcel Dekker, New York, 1976.

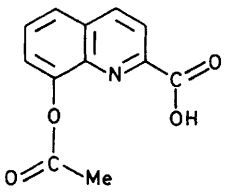
[2] R. J. Angelici and B. E. Leach, *J. Amer. Chem. Soc.*, 1968, **90**, 2499.

[3] D. A. Buckingham, D. M. Foster, and A. M. Sargeson, *J. Amer. Chem. Soc.*, 1968, **90**, 6032.

[4] R. W. Hay and C. R. Clark, *J.C.S. Dalton*, 1977, 1866.

[5] D. A. Buckingham, D. M. Foster, and A. M. Sargeson, *J. Amer. Chem. Soc.*, 1970, **92**, 5701.

when metal complex formation occurs (*via* the quinoline nitrogen and the carboxylate groups) a direct interaction between the metal ion and the carbonyl oxygen of the ester group cannot occur. As the donor atoms are situated on the phenolic moiety of the ester, metal-ion activation could arise primarily as a leaving-group effect.



(EH)

Metal-ion promotion of the hydrolysis of 8-acetoxyquinoline has been studied previously;[6] however, the substrate binds rather weakly to metal ions and as a result the system is not amenable to a detailed kinetic analysis.

EXPERIMENTAL

8-Acetoxyquinoline-2-carboxylic acid monohydrate was prepared as follows. To a solution of 8-hydroxyquinoline-2-carboxylic acid [4] (0.5 g, 0.027 mol) in sodium hydroxide (5 cm^3, 10% w/v) was added ice (6 g) and acetic anhydride (0.75 g). The mixture was stirred for 1 min and acidified to pH *ca.* 3 with hydrochloric acid (3 mol dm^{-3}). The precipitated ester was immediately filtered off, washed with ice-cold water, and dried. Recrystallisation from ethanol–water (2 : 1) gave light tan crystals which decomposed on heating or on exposure to air for appreciable periods. Infrared spectrum (Nujol mull) : ν(CO) at 1 770 (ester) and 1 700 cm^{-1} (carboxylic acid) (Found: C, 57.8; H, 4.65; N, 5.70. Calc. for $C_{12}H_9NO_4 \cdot H_2O$: C, 57.8; H, 4.45; N, 5.75%). Piperazine-*NN'*-bis(ethane-2-sulphonic acid) (pipes) and *N*-(2-hydroxyethyl)piperazine-*N'*-ethane-2-sulphonic acid (hepes) were supplied by B.D.H., and deuterium oxide (99.8%) by Fluorochem. All the other materials were of AnalaR grade.

Kinetic Measurements.—In most cases kinetic measurements were made using either a Unicam SP 500 spectrophotometer fitted with a Gilford 222 modification or a Gilford 2400S instrument. Those reactions too fast to be monitored by conventional procedures were studied using a Canterbury SF3A stopped-flow instrument coupled to a Cossor CDU 110c oscilloscope.

All the measurements were made at an ionic strength of 0.1 mol dm^{-3} ($Na[ClO_4]$). Solutions of the ester (10^{-2} mol dm^{-3}) were prepared in dry acetonitrile and stored at −10 °C until required. Runs monitored by conventional spectrophotometry were initiated by the addition of the ester stock solution (10 μl) to the appropriate thermostatted buffer solution (3.0 cm^3) contained in a 1-cm cell. Under these conditions, pseudo-first-order kinetics were observed in each case. Reactions were monitored for at least 4 half-lives. Base hydrolysis was followed at 268 nm ($\lambda_{max.}$ for 8-hydroxyquinoline-2-carboxylate dianion), and the pH-independent hydrolysis at 254 nm.

The copper(II)-, nickel(II)-, and zinc(II)-promoted reactions were monitored at 256, 268, and 268 nm respectively.

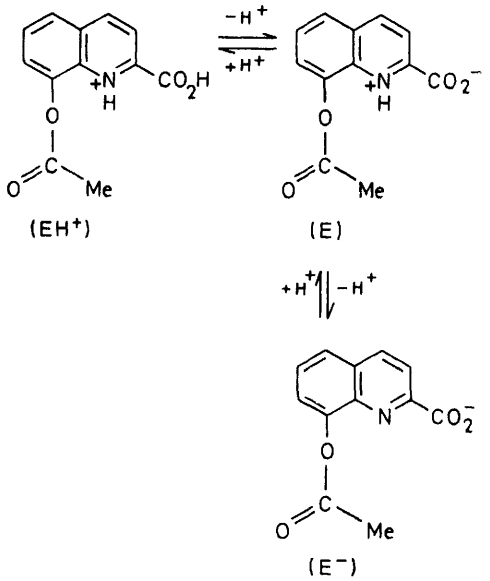
[6] R. H. Barca and H. Frieser, *J. Amer. Chem. Soc.*, 1966, **88**, 3744.

[7] T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, 1961, **65**, 1079.

Acetate and formate buffers were used for the copper(II)-promoted reaction and pipes for the zinc(II)- and nickel(II)-promoted reactions. Buffer concentrations were in the range 5×10^{-3}—1.5×10^{-2} mol dm^{-3}. Catalysis by buffer species was not observed. The u.v. spectra of solutions from kinetic runs recorded after 10 half-lives were identical to those obtained from buffered solutions of the metal salts to which the requisite quantity of 8-hydroxyquinoline-2-carboxylic acid had been added. Measurements of pH and pD were made using a Radiometer 26 pH meter. Values of pD were taken as the pH meter reading plus the appropriate correction.[7] Hydroxide-ion concentrations at 25 °C were obtained from the pH using a value of 0.772 for the mean molar activity coefficient at $I = 0.1$ mol dm^{-3} and pK_w 13.997. Hydroxide-ion concentrations at other temperatures were obtained using the pK_w values listed by Robinson and Stokes [8] and molar activity coefficients obtained from the Davies equation.[9]

RESULTS AND DISCUSSION

The protonation equilibria of 8-acetoxyquinoline-2-carboxylic acid can be represented as in Scheme 1. The protonation constants were not determined owing to the



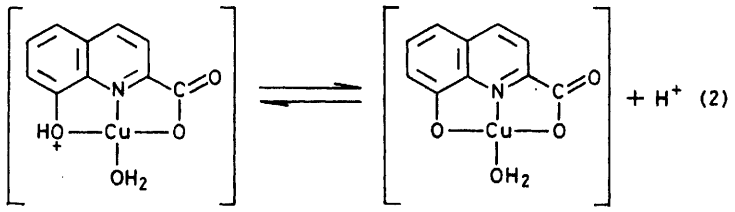
SCHEME 1

lability of the ester and the complexity of the equilibria at low pH. A consideration of the p*K* values of 8-acetoxyquinoline (3,08 for the pyridine nitrogen) and quinoline-2-carboxylic acid (1.9 for the carboxyl group) suggests that the ester exists exclusively as the anion (E^-) at pH > 5. The pK_a of the phenolic group of the 8-hydroxyquinoline-2-carboxylate anion was determined spectrophotometrically (λ 383 nm, using morpholine and triethylamine buffers) as 9.80 ± 0.05 at 25 °C and I = 0.1 mol dm^{-3} ($Na[ClO_4]$). The pK_a for the ionisation process (2) was determined by spectrophotometric titration ($\lambda_{max.}$ 268 nm) of a solution 4×10^{-3} mol dm^{-3} in copper(II)

[8] R. A. Robinson and R. H. Stokes, 'Electrolyte Solutions,' 2nd edn., Butterworths, London, 1969.

[9] C. W. Davies, *J. Chem. Soc.*, 1938, 2093.

chloride and 2.8×10^{-5} mol dm^{-3} in 8-hydroxyquinoline-2-carboxylic acid at 25 °C and $I = 0.1$ mol dm^{-3} (Na[ClO_4]). Under these conditions the ligand is fully bound at pH >2.4. The observation of a single protonation



(1) (2)

step (pK_a 3.93 ± 0.04) on lowering the pH of a neutral solution of Cu^{II} and the ligand is consistent with the protonation of (2) to give (1). The protonated species (1) has $\lambda_{max.}$ 254 nm (ε 4.7×10^4 dm^3 mol^{-1} cm^{-1}) while the deprotonated species (2) has $\lambda_{max.}$ 268 nm ($\varepsilon = 3.5 \times 10^4$ dm^3 mol^{-1} cm^{-1}).

Kinetics.—Values of $k_{obs.}$ obtained for the hydrolysis of 8-acetoxyquinoline-2-carboxylic acid (EH) in the range pH 5—12 are listed in Table 1. The pH–rate profile

TABLE 1

Rate constants for the ' spontaneous ' and base hydrolysis of 8-acetoxyquinoline-2-carboxylic acid at $I = 0.1$ mol dm^{-3} (Na[ClO_4])[a]

(*i*) Spontaneous hydrolysis

pH	$10^4 k_{obs.}$/s^{-1}
5.24	1.73 [b]
6.29	1.37 [c] (35 °C, D_2O)
6.84	1.63 [c]
6.84	3.41 [c] (35 °C)
6.84	7.45 [c] (45 °C)
6.87	1.62 [c]
6.88	1.34 [c] (35 °C, D_2O)
7.96	1.60 [d]
8.45	1.70 [d]
9.12	1.77 [e]

$k_0^{25} = 1.67 \times 10^{-4}$ s^{-1}

(*ii*) Base hydrolysis [f]

10^2[OH$^-$]/mol dm^{-3}	$10^3 k_{obs.}$/s^{-1}	$k_{OH} = (k_{obs.} - k_0)$/[OH$^-$]/dm^3 mol^{-1} s^{-1}
1.0	4.60 (15 °C)	0.450
1.0	8.48	0.831
1.0	8.66	0.849
1.0	15.4 (35 °C)	1.51
2.0	16.9	0.835
3.0	25.4	0.840

[a] At 25 °C unless otherwise stated. Buffer concentrations in the range 5×10^{-3}—10^{-2} mol dm^{-3}. Buffer effects were not observed. [b] Acetate buffer. [c] pipes buffer. [d] hepes buffer. [e] Borate buffer; the rate constant includes a small contribution (*ca.* 5%) from the base-catalysed reaction. [f] Sodium hydroxide solutions.

(Figure 1) indicates that the rate expression takes the form (3). The first term of equation (3) represents the

$$\text{Rate} = k_0[E^-] + k_{OH}[E^-][OH^-] \quad (3)$$

' spontaneous ' hydrolysis, which could be due to nucleophilic attack by water, while the second term is due to base hydrolysis of the anion. At 25 °C and $I = 0.1$ mol dm^{-3}, $k_0 = 1.67 \times 10^{-4}$ s^{-1} (*i.e.* k_{H_2O} 3.0×10^{-6} dm^3 mol^{-1} s^{-1}) and $k_{OH} = 0.84$ dm^3 mol^{-1} s^{-1}. The ratio $k_{OH} : k_{H_2O} = 2.8 \times 10^5 : 1$ is considerably lower than the normal values (10^7—$10^9 : 1$) usually observed in ester hydrolysis

This effect can be attributed to intramolecular general-base catalysis (see later). For the ' spontaneous ' hydrolysis $\Delta H^\ddagger = 57.3$ kJ mol^{-1} and $\Delta S^\ddagger = -159$ J K^{-1} mol^{-1} at 298 K, and for base hydrolysis $\Delta H^\ddagger = 41.8$ kJ

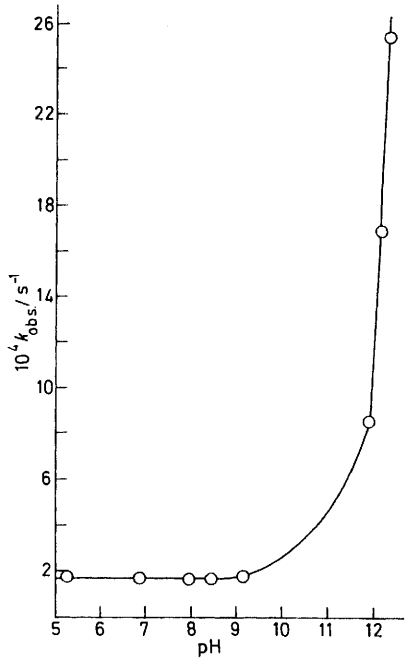


FIGURE 1 pH–Rate profile for the hydrolysis of 8-acetoxyquinoline-2-carboxylic acid at 25 °C and $I = 0.1$ mol dm^{-3}

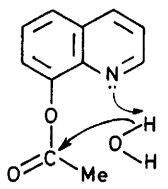
mol^{-1} and $\Delta S^\ddagger = -105$ J K^{-1} mol^{-1} at 298 K. A significant solvent deuterium-isotope effect $k_{H_2O}/k_{D_2O} = 2.5$ at 35 °C is observed for the ' spontaneous ' hydrolysis.

Possible mechanisms for intramolecular catalysis in the 8-acetoxyquinoline system have been discussed.[6,10,11] Nucleophilic catalysis by the quinoline nitrogen to give an *N*-acyl intermediate has been excluded by the results of Felton and Bruice [10] and the accepted mechanism [11] involves intramolecular general-base catalysis by the quinoline nitrogen as in (3). A similar intramolecular general-base mechanism also applies to the hydrolysis of 8-acetoxyquinoline-2-carboxylic acid and this view is supported by the solvent deuterium-isotope effect of 2.5

[10] S. M. Felton and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969, **91**, 6721.

[11] A. J. Kirby and A. R. Fersht, *Progr. Bio-org. Chem.*, 1971, **1**, 1.

and the large negative entropy of activation. The carboxylate group in the 2 position does not greatly effect



(3)

the reaction rate since $k_{2\text{-}CO_2}/k_{2\text{-}H} = 3.5$ so that anchimeric assistance by this group does not occur. The more rapid reaction of the carboxylate derivative is expected since electron donation by CO_2^- ($\rho = -0.03$) [12] should increase the basicity of the pyridine nitrogen.

Metal-promoted Reactions.—Hydrolysis of 8-acetoxyquinoline-2-carboxylic acid as a function of pH and metal-ion concentration was studied using Zn^{II} and Cu^{II} (Table 2). With Zn^{II} at pH 6.18, values of $k_{obs.}$ exhibit an initial linear dependence on $[Zn^{II}]$, but at higher metal concentrations $k_{obs.}$ approaches a limiting value of 2.7 s^{-1} (Figure 2). Increases in $[Zn^{II}]$ beyond 2×10^{-2} mol

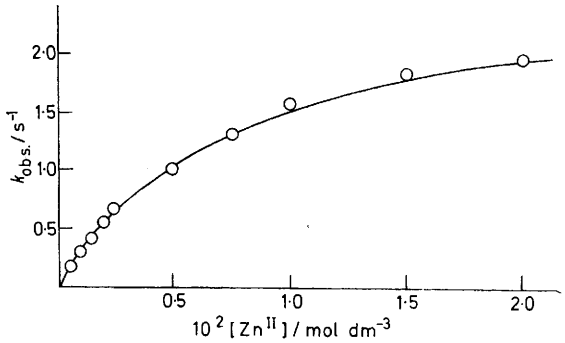


FIGURE 2 Zinc(II)-promoted hydrolysis at pH 6.18, 25 °C, and $I = 0.1$ mol dm^{-3}

dm^{-3} were not possible owing to the precipitation of zinc(II) hydroxide. In the pH 6.18—7.24 region, values of $k_{obs.}$ are given by equation (4) where $[Zn^{2+}]$ may be

$$k_{obs.} = \frac{k_{OH}K_{ZnE}[Zn^{2+}][OH^-]}{K_{ZnE}[Zn^{2+}] + 1} \quad (4)$$

equated to the total zinc(II) concentration ($[Zn^{2+}]_T \gg [E^-]$) and K_{ZnE^+} is the kinetically determined formation constant for the 1 : 1 complex of the ester anion with Zn^{II}. $K_{ZnE^+} = [ZnE^+]/[Zn^{2+}][E^-] = 130$ dm^3 mol^{-1} and $k_{OH} = (1.4 \pm 0.2) \times 10^8$ dm^3 mol^{-1} s^{-1} at 25 °C and $I = 0.1$ mol dm^{-3}. The pH dependence of the zinc(II)-promoted reaction (pH 6.18—7.24) at $[Zn^{II}] = 2.5 \times 10^{-3}$ mol dm^{-3} confirms a first-order dependence on the hydroxide-ion concentration with $k_{obs.}/[OH^-] = k_{OH} = 1.4 \times 10^8$ dm^3 mol^{-1} s^{-1}.

In the case of the copper(II)-promoted reaction, constant values of $k_{obs.}$ were obtained at pH 3.40 when $[Cu^{II}]$ was varied from 1×10^{-3} to 5×10^{-3} mol dm^{-3}. Full complexation of the substrate as the 1 : 1 complex $[CuE]^+$ occurs under these conditions. Hydrolysis of $[CuE]^+$ in the range pH 3.32—4.52 is first order in $[OH^-]$ (Table 2) with $k_{OH} = (1.42 \pm 0.06) \times 10^8$ dm^3 mol^{-1} s^{-1}. Activation parameters for base hydrolysis were calculated from the temperature dependence of k_{OH} (Table 3) giving $\Delta H^\ddagger = 33.9$ kJ mol^{-1} and $\Delta S^\ddagger = 25$ J K^{-1} mol^{-1} at 298 K.

Nickel(II) also promotes the hydrolysis of the ester at pH 6.88 (Table 2). Values of $(k_{obs.} - k_0)$ increase linearly with the nickel(II) concentration over the range $[Ni^{II}] = 2.5 \times 10^{-3}$—$12.5 \times 10^{-3}$ mol dm^{-3}. This result indicates that only a small percentage (<20%) of the ester substrate is present as the 1 : 1 complex under these conditions. The somewhat rigid geometry of the metal bind-

TABLE 2

Rate constants for the copper(II)- and zinc(II)-promoted hydrolysis of 8-acetoxyquinoline-2-carboxylic acid at 25 °C and $I = 0.1$ mol dm^{-3} ($Na[ClO_4]$) [a]

(*i*) Copper(II) dependence, pH 3.40

$10^3[Cu^{II}]$/mol dm^{-3}	$10^3k_{obs.}/s^{-1}$
0.0	<0.2
1.0	4.61
2.0	4.67
3.0	4.67
5.0	4.67

(*ii*) pH dependence using $[Cu^{II}] = 5 \times 10^{-3}$ mol dm^{-3}

pH	$10^3k_{obs.}$ / s^{-1}	$10^{11}[OH^-]$ / mol dm^{-3}	$10^{-8}k_{OH}$ / dm^3 mol^{-1} s^{-1}
3.320	4.01	2.71	1.48
3.400	4.67	3.25	1.44
3.745	10.1	7.20	1.40
3.980	16.8	12.4	1.36
4.195	28.4	20.3	1.40
4.430	51.9	35.0	1.48
4.520	61.0	42.9	1.42

(*iii*) Zinc(II) dependence, pH 6.18

$10^3[Zn^{II}]$ / mol dm^{-3}	$k_{obs.}$ / s^{-1}	$k_{calc.}$ [b] / s^{-1}
0.50	0.165	0.167
1.00	0.281	0.314
1.50	0.386	0.445
2.00	0.573	0.563
2.50	0.685	0.670
5.00	0.983	1.11
7.50	1.34	1.35
10.00	1.63	1.54
15.00	1.88	1.80
20.00	2.01	1.97

(*iv*) pH Dependence using $[Zn^{II}] = 2.5 \times 10^{-3}$ mol dm^{-3}

pH	$k_{obs.}$ / s^{-1}	$10^8[OH^-]$ / mol dm^{-3}	$10^{-8}k_{OH}$ / dm^3 mol^{-1} s^{-1}
6.18	0.685	1.95	1.43
6.42	1.19	3.41	1.42
6.62	1.97	5.40	1.49
6.78	2.77	7.81	1.45
6.87	3.85	9.60	1.64
7.04	5.37	14.9	1.47
7.24	8.01	23.6	1.38

(*v*) Nickel(II) dependence, pH 6.88

$10^3[Ni^{II}]$ / mol dm^{-3}	$10^2k_{obs.}$ / s^{-1}	$(k_{calc.} - k_0)/[Ni^{2+}]$ / dm^3 mol^{-1} s^{-1}
2.50	1.67	6.60
5.00	3.30	6.56
7.50	4.79	6.36
10.0	6.22	6.20
12.5	7.82	6.24

[a] Substrate concentration *ca.* 3×10^{-5} mol dm^{-3}. [b] Obtained from equation (4) using the values of the constants given in the text.

[12] J. Clark and D. D. Perrin, *Quart. Rev.*, 1964, **18**, 295.

ing site appears to impose a degree of selectivity on complex formation ($K_{ZnE^+} > K_{NiE^+}$). Normally this stability order is reversed in substituted quinolines.[13]

Very large rate enhancements are observed in the metal-ion-promoted reactions; thus $[CuE^+]$ undergoes

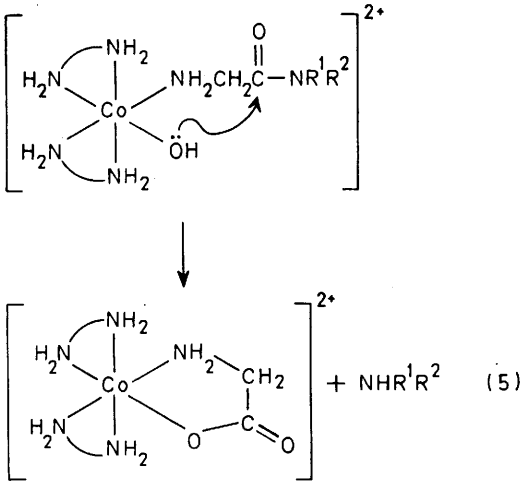
TABLE 3

Temperature dependence of the copper(II)-promoted hydrolysis of 8-acetoxyquinoline-2-carboxylic acid at $I = 0.1$ mol dm^{-3} ($Na[ClO_4]$) *

θ_c / °C	pH	$10^3 k_{obs.}$ / s^{-1}	$10^{11}[OH^-]$ / mol dm^{-3}	$10^{-8} k_{OH}$ / dm^3 mol^{-1} s^{-1}
15.0	3.590	1.91	2.258	0.846
25.0	3.580	6.83	4.922	1.39
35.0	3.590	22.8	10.58	2.16

* Substrate concentration *ca.* 3×10^{-5} mol dm^{-3}; reaction medium 4×10^{-3} mol dm^{-3} in $Cu[ClO_4]_2$ and 8×10^{-3} mol dm^{-3} in formate buffer. Values of $[OH^-]$ were calculated from the measured pH values using $pK_w = 14.35$ (15), 14.00 (25), and 13.68 (35 °C), and activity coefficients for $[OH^-]$ of 0.775 (15), 0.772 (25), and 0.768 (35 °C).

base hydrolysis 1.7×10^8 times faster than E^- and a similar enhancement is observed with $[ZnE]^+$. These rate accelerations appear to be the largest yet reported for ester hydrolysis. Direct metal-ion polarisation of a carbonyl group leads to rate accelerations of *ca.* 10^6 in bound-substrate–free-nucleophile reactions,[1] however, intramolecular hydrolysis in a metal hydroxo-species (bound substrate–bound nucleophile) can lead to much higher rate accelerations. Thus intramolecular hydrolysis in the *cis*-$[Co(OH)(en)_2L]^{2+}$ ion (en = ethylenediamine, L = *NN*-disubstituted glycine) is at least 10^7 and possibly 10^{11} times faster than base hydrolysis of unco-ordinated glycine amide [equation (5)].[14]

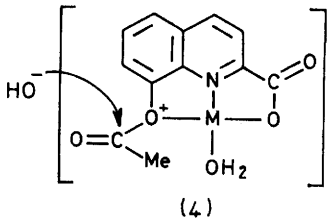


+ NHR^1R^2 (5)

Two possible mechanisms can be considered for the present reactions. Mechanism (A) involves rate-determining hydroxide-ion attack on the metal complex (4), while mechanism (B) involves rapid pre-equilibrium ionisation of the aqua- to give the hydroxo-complex

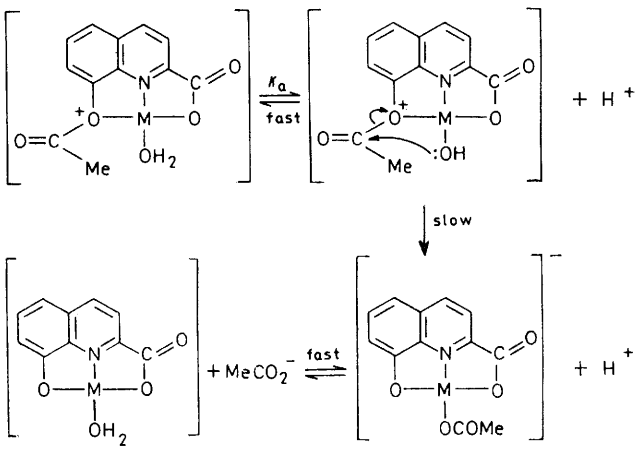
[13] See, for example, 'Stability Constants of Metal–Ion Complexes,' eds. L. G. Sillén and A. E. Martell, *Special Publ.*, The Chemical Society, London, 1964, no. 17.

followed by rate-determining intramolecular attack by co-ordinated hydroxide (Scheme 2). Since the pK_a values are probably *ca.* 7.5 for $[CuE]^+$ and >9 for $[ZnE]^+$, the



(4)

concentration of the active hydroxo-species is directly proportional to $[OH^-]$ under the reaction conditions. At



SCHEME 2 Mechanism (B) for the metal-promoted reactions (tetrahedral intermediates are assumed)

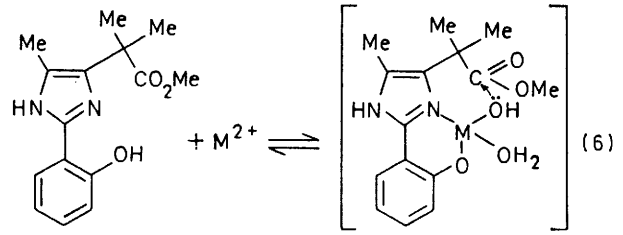
low pH values [*i.e.* $pH < (pK_a - 1)$] the two mechanisms are kinetically indistinguishable. Mechanisms involving carbonyl-bonded ester intermediates seem unlikely since their formation would require the involvement of a thermodynamically improbable seven-membered chelate ring. Mechanism (B) is favoured by the available evidence. Polarisation of the ester linkage as in (A) would be expected to lead to more rapid hydrolysis of $[CuE]^+$ than $[ZnE]^+$. In addition, nucleophilic or general-base catalysis by buffer species is not observed, consistent with an intramolecular process. We were also unable to detect a water reaction, *i.e.* $[CuE]^+ + H_2O \longrightarrow$ products, implying that there is an abnormally large nucleophilic ratio $k_{OH} : k_{H_2O}$ for a carbonyl substrate possessing a leaving group of pK_a 3.93. On the assumption that the water reaction could make a 5% contribution to the hydrolysis at pH 3.32 and remain undetected, then $k_{H_2O} < 3.6 \times 10^{-6}$ dm^3 mol^{-1} s^{-1} for $[CuE]^+$ and $k_{OH} : k_{H_2O} > 4 \times 10^{13} : 1$. This ratio is very much higher than that observed for a variety of activated carbonyl substrates, *e.g.* 1-acetyl-3-methylimidazolium cation [15] (1.7×10^8),

[14] D. A. Buckingham, D. M. Foster, and A. M. Sargeson, *J. Amer. Chem. Soc.*, 1970, **92**, 6151.

[15] R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, 1961, **83**, 4390.

4-nitrophenyl acetate [16] (3.1×10^9), propionic anhydride [17] (2.8×10^7), and 2,4-dinitrophenyl acetate [18] (2.8×10^8), indicating that a simple bimolecular process, $[CuE]^+ + [OH]^-$, does not occur.

Metal-bound hydroxide has recently been found to promote the hydration of carbon dioxide [19] and to promote the hydrolysis of a variety of carbonyl derivatives.[17,20-22] A recent communication [22] has dealt with the intramolecular hydrolysis of the methyl ester (5) by metal-bound hydroxide (M = Co^{II} and Ni^{II}). In this



(5) (6)

case it was possible to show a zero-order dependence on $[OH^-]$ at pH values beyond the pK_a of M–OH_2 due to complete conversion into M–OH.

Ionisation of an aqua-ligand on Zn^{II} is normally associated with a pK_a of *ca.* 9.5,[23] while aquacopper(II) complexes are somewhat more acidic (pK_a *ca.* 7.5).[24] Using these approximate values, the rate constants for intramolecular hydroxide-ion attack in the $[ME]^+$ complexes are *ca.* 5×10^3 s^{-1} (Zn) and *ca.* 5×10^1 s^{-1} (Cu). These values were calculated from the expression $k = k_{obs.}/\alpha$ where $k_{obs.}$ is the observed first-order rate constant under saturation conditions (full complex formation) and α is the degree of ionisation to the hydroxo-complex at the pH of the measurement. One notable feature of the intramolecular reactions is that catalysis by Zn^{II} is considerably more effective than by Cu^{II}. Somewhat similar results have been obtained by Bruice and his co-workers [22] for intramolecular attack by $[OH]^-$ on the ester (5). In this case the rate constants for intramolecular catalysis by M–OH are 0.245 and 0.02 s^{-1} for Co^{II} and Ni^{II} respectively. [Nickel(II) normally gives somewhat more thermodynamically stable complexes than Co^{II}.] On the basis of the limited evidence available, it appears that metal ions with high Lewis acidity {as measured by the pK values of the $[M(OH_2)_6]^{2+} \rightleftharpoons [M(OH)(OH_2)_5]^+ + H^+$ equilibrium} give rise to $[M–OH]^+$ species which are poorer nucleophiles. Such an inverse relation is not unexpected since metal ions of high Lewis acidity would be expected to hold the electron pairs on oxygen more tightly. The recent results of Buckingham and Engelhardt [17] on the reaction of a variety of kinetically inert hydroxo-complexes with propionic anhydride also support this conclusion. The Brønsted plot (including the points for $[OH]^-$ and OH_2) gives a smooth curve confirming that the rate constant k_{MOH} is related to the pK_a of the aqua-complex, the most acidic complexes being the least effective nucleophiles.

The measured activation parameters for the hydrolysis of $[CuE]^+$ are not definitive for the mechanism since they include contributions from both the proton-ionisation step and the intramolecular process; however, it is clear that the observed rate enhancements for the metal-promoted reaction are due primarily to an entropy effect. For base hydrolysis of E^-, $\Delta H^\ddagger = 41.8$ kJ mol^{-1} and $\Delta S^\ddagger = -105$ J K^{-1} mol^{-1} at 298 K ($\Delta G^\ddagger = 83.0$ kJ mol^{-1}). A substantial negative entropy of activation is expected for a bimolecular reaction of this type. For the copper-promoted reaction, $\Delta H^\ddagger = 33.9$ kJ mol^{-1} and $\Delta S^\ddagger = 25$ J K^{-1} mol^{-1} at 298 K ($\Delta G^\ddagger$ 26.4 kJ mol^{-1}). An intramolecular process is expected to have a $\Delta S^\ddagger$ of *ca.* 0.

The rate constant for the intramolecular hydrolysis of the zinc complex is similar to the reported values [25] of $k_{obs.}$ for the hydrolysis of a good ester substrate by the zinc metalloenzyme carboxypeptidase (2.3×10^2 s^{-1}). Metal complexes of 8-acetoxyquinoline-2-carboxylic acid exhibit a number of features favouring a ready hydrolytic reaction. As a consequence of ligand geometry the metal ion can bind to the ether oxygen of the ester and provide a better leaving group (the conjugate acid of the leaving group is a stronger acid by *ca.* 6 pK units) while simultaneously providing a high concentration of nucleophile close to the carbonyl carbon atom.

Intramolecular hydroxide-ion attack does not require rupture of the M–OH bond and probably involves acyl transfer with concomitant deprotonation to give the metal–acetate species. Subsequent loss of acetate from the co-ordination sphere of the metal ions used here is expected to be rapid ($k > 10^4$ s^{-1}).[26] A somewhat similar mechanism has been considered to account for the rapid zinc(II)-promoted hydrolysis of an anhydride.[21]

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