A STUDY OF SOME METAL ION CATALYSED REACTIONS

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To Pamela, Jonathan, Geoffrey
and Gerard for a long trip.
Not forgetting Meredith.

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ABSTRACT

A study has been made of the reactivity of certain complexed and uncomplexed carboxylic acid derivatives of 8-quinolinol toward nucleophilic attack by hydroxide ion.

Binding of 2-cyano-8-quinolinol to 1st row transition metal ions markedly increases the rate of base hydrolysis to the corresponding carboxamide. Similarly large rate enhancements (10^3 - 10^6) have been observed for the metal ion promoted base hydrolysis of 2-carbomethoxy-8-quinolinol (M = Zn, Cu, Ni, Co and Mn). Base hydrolysis of the 1:1 complex of 8-acetoxy-2-carboxyquinoline with zinc(II) or copper(II) proceeds 1.7×10^8 times faster than base hydrolysis of the deprotonated ligand. Arrhenius parameters for the hydrolytic processes have been determined and possible mechanisms for the reactions are considered.

The iodination of the metal ion complexes (M = Zn, Cu and Ni) of 2-acetyl-8-quinolinol has been investigated. The reactions exhibit substantial kinetic deuterium isotope effects (acetyl-d_3) and are general base catalysed, indicating that the rate determining step involves ionization of the active H atom in the methyl group. Comparative studies, using 2-acetylpyridine as a reference substrate, suggest that electrostatic facilitation of ionization may be of importance in the metal ion promoted reactions.

A number of transition metal complexes of 2-carbethoxypyridine have been prepared and characterised. Data for mono- and bis-ligand complexes are reported.

Complex formation between copper(II) and the macrocyclic ligand 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane (tet $\underline{a}$) has been studied using spectrophotometric and pH-stat techniques. Under the conditions of measurements the product is a blue complex Cu(tet $\underline{a}$)(blue)$^{2+}$. The rate law for the reaction in the presence of acetate ion has been established as:

$$\text{rate} = k_1'[Cu^{2+}][\text{tet } \underline{a}\ H^+] + k_2'[CuOAc^+][\text{tet } \underline{a}\ H^+] + k_3'[CuOAc^+][\text{tet } \underline{a}\ H_2^{2+}]$$

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ABBREVIATIONS

Pipes	Piperazine-NN'-bis-2-ethanesulphonic acid
Hepes	N-2-Hydroxyethylpiperazine-N'-2-ethanesulphonic acid

1. INTRODUCTION

Metal ions have been observed to catalyse a large number of organic reactions including decarboxylation and carboxylation reactions, Redox processes, nucleophilic displacements, hydrogenation and hydration of unsaturated systems, polymerization reactions and hydrolytic processes.

Metal ion catalysed reactions have been studied intensively only over the last two decades. As yet many processes are not fully understood and opinions concerning mechanisms often differ widely. Among the more recent publications dealing with general aspects of the field are those by Jones[1], Bender[2], Martell[3], Candlin, Taylor and Thompson[4] and Ochai[5].

Metal ion catalysis is usually considered to arise from specific complexation or chelation of the metal ion with the substrate molecule. One result to be anticipated from such coordination is that a distortion of electron density toward the positively charged metal centre would occur. In the absence of any other effect this should facilitate nucleophilic attack and lead to a retardation in the rate of attack by electrophiles. Factors other than ligand polarization, however, may also influence substrate reactivity.

(i) Many reactions require the presence of an "electron sink" to absorb electron density produced in the reaction. A suitably positioned metal ion may provide such an electron deficient region.

(ii) Stabilization of leaving groups will often facilitate reaction. Metal ion stabilization of mercaptide, halide, phosphate and other anions facilitate reactions involving these as leaving groups.

(iii) In a bimolecular process a metal ion may complex with both the substrate molecule and the incoming nucleophile. In this manner the metal ion acts as a collection point for the reaction components and assists reaction by making the entropy of activation more positive.

(iv) A suitably positioned metal ion within the substrate may interact specifically with a reactive group. This effect may polarize a susceptible bond, facilitating nucleophilic attack or leading directly to bond cleavage.

(v) In a bimolecular process involving attack by an anionic species on a metal-substrate complex the coordinated metal ion may "solvate" the localized negative charge developed in the transition state. The solvation requirements of the transition state are therefore minimal and the entropy of activation more positive than would be expected on the basis of reaction molecularity alone. This effect may lead to substantial rate accelerations.

Protons may similarly bring about certain of these electronic changes which promote organic reactions. Metal ion catalysis, however, has a number of advantages over hydrogen ion catalysis. Firstly, a metal ion can introduce a multiple positive charge into the substrate. Di- and tri-positive metal ions have been termed "super-acid" catalysts[6], however the polarizing ability (as defined by the charge to radius ratio) of a given metal ion is less than that of the proton. For a great many reactions charge density is more important than net charge. Secondly, a metal ion may coordinate with a number of donor points on the ligand whereas a proton may interact strongly with only one. Finally, and of particular importance in biological systems, metal ion catalysis can occur in neutral and weakly basic media whereas specific acid catalysis cannot.

The participation of metal ions in the structure and catalytic function of enzymes has prompted many studies of metal ion catalysed reactions in aqueous solution as models for the much more complex enzymatic systems.

The catalytic metal centres fall into one of two general categories.

(i) Non-labile centres such as cobalt(III) which are characterized by very slow rates of ligand substitution.

(ii) Labile centres (e.g. copper(II), nickel(II), zinc(II), etc.) where extremely fast rates (10^4-10^7 s^{-1}) of ligand substitution are observed[7].

The kinetic analysis of reactions catalysed by metal ions in the second category is often greatly complicated by the problem of ligand lability. Thus, in a solution of metal ions (M^{2+}) a ligand substrate (E) with, for example, 2 donor groups may be distributed among the complexed and uncomplexed forms, ME_3^{2+}, ME_2^{2+}, ME^{2+} and E. Furthermore, if E, or a complex of E reacts to produce a product, A^-, then a number of mixed complexes, ME_2A^+, MEA^+, etc., may also be generated as the reaction proceeds. The successful interpretation of kinetic data obtained from such a system then requires a detailed knowledge of the equilibria linking the various reactive species.

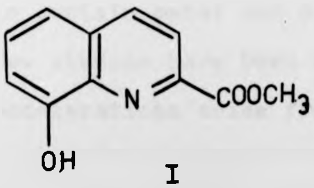
In the present study it was decided that these difficulties could be overcome, at least in part, by choosing reaction systems that fulfilled a number of conditions:

(i) That the ligand substrates should form thermodynamically stable complexes with a number of divalent metal ions.

(ii) That for a particular reaction, conditions could be arranged such that the metal ion was always in considerable excess over the substrate. Given this condition only the 1:1 complexes should be of kinetic significance since both substrate and product should coordinate with free M^{2+} in solution rather than form bis, tris or mixed ligand complexes.

(iii) That the thermodynamic stability of a given complex should be sufficiently high to allow full complexation of the substrate at reasonable concentrations (i.e. $< 10^{-1}$M) of metal ion.

The ligand that was chosen to form the basis of the study was 8-hydroxyquinoline. Primary interest was centred on the areas of ester and nitrile hydrolysis and it was therefore decided to study the metal ion catalysed hydrolysis of 2-carbomethoxy-8-quinolinol (I) and 2-cyano-8-quinolinol (II).



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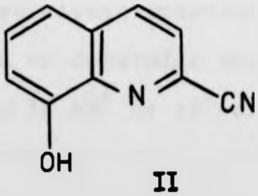
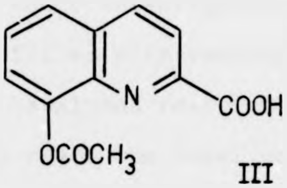
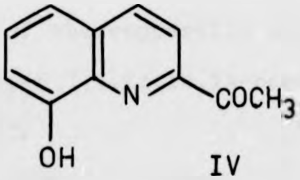


II

Both substrates are bidentate ligands and have the hydrolysable group situated adjacent to the metal ion binding site. In addition, a study was also made of the hydrolysis of the related ester 8-acetoxy-2-carboxyquinoline (III). The metal ion catalysed hydrolysis of this substrate was of particular interest as the donor atoms are situated on the leaving group.


III

The rate of halogenation of ketones has been shown to be a measure of the rate of enolization or ionization of the active C-H bond adjacent to the carbonyl group except under conditions of low halogen concentration, in which case halogenation of the enol or enolate ions may become rate determining[8]. The final kinetic study involving a derivative of 8-hydroxyquinoline dealt with the effect of copper(II) and nickel(II) on the iodination of 2-acetyl-8-quinolinol (IV).

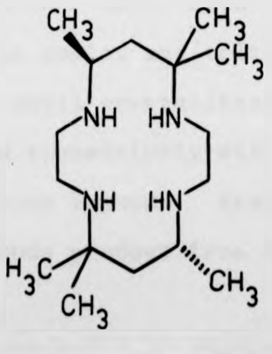

IV

Although very large rate enhancements have been observed in certain metal ion promoted hydrolytic reactions relatively few studies have been undertaken to determine whether the accelerations arise from changes in $\Delta H^{\ddagger}$ or $\Delta S^{\ddagger}$ or both.

Throughout the course of the present investigations particular emphasis was placed on the evaluation of these kinetic parameters in order to provide insight into the manner by which a given metal ion may influence reaction rates.

For each system under investigation the three conditions listed above were fulfilled with varying degrees of success. As all the metal ion catalysed reactions were carried out in buffered solutions where the total concentration of buffer species was comparable with the concentrations of the divalent metal ions, particular care was taken to choose buffers which did not interact strongly with the catalytically active species. Three buffers in particular, Pipes ($pK_1^M = 6.73$, 25°, $I = 0.1M$), Hepes ($pK_1^M = 7.48$, 25°, $I = 0.1M$) and morpholine ($pK = 8.70$, 25°)[9] proved satisfactory in this respect and had the added advantage, when used in spectrophotometric studies, of u.v. transparency to below 260 nm.

In addition to these investigations two other studies were also undertaken. The first involved the preparation and characterization of transition metal complexes of ethyl-2-picolinate. The second was concerned with the kinetics of formation of the copper(II) complex of the macrocyclic ligand meso-5,7,7,12,14,14-hexamethyl-1,4,8,11-tetra azacyclotetradecane (V).



V

2. EXPERIMENTAL

2.1 Synthesis

An overall scheme for the preparation of derivatives of 8-quinolinol is shown in Scheme 1. The reaction procedures are essentially analogous to these developed for the synthesis of quinoline[10] and 1,10-phenanthroline[11] derivatives.

8-Quinolinol-N-oxide

The N-oxide was prepared by the method of Murase and Demura[12].

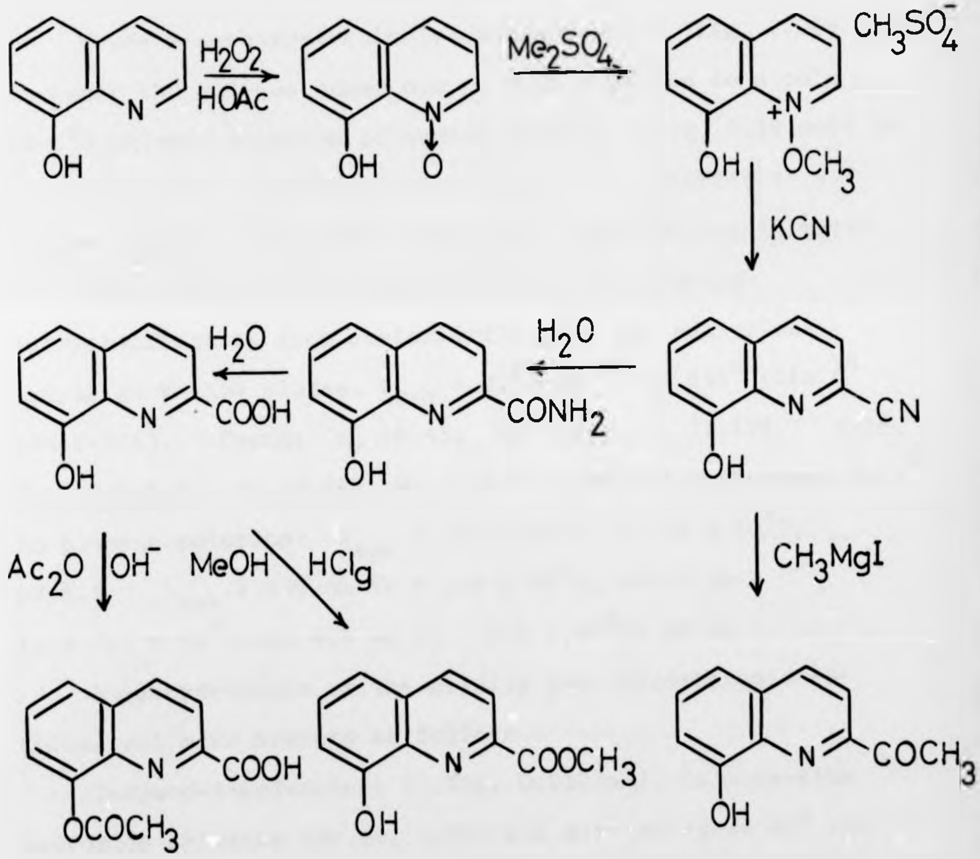
8-Quinolinol (50g, 0.33 mol) in glacial acetic acid (70 ml) and water (150 ml) was refluxed for 3 hours with hydrogen peroxide (80g, 30% w/v). The resultant dark red solution was cooled to room temperature and extracted with chloroform (6 x 70 ml). The combined chloroform extracts were washed, first with hydrochloric acid (5%, 2 x 200 ml), then with water (2 x 200 ml) and dried over anhydrous sodium sulphate. Removal of the chloroform by rotary evaporator gave the crude product which crystallized from ethanol-water as fine yellow needles, mp 138° (Lit.[12,13] 137-138°).

N-Methoxy-8-quinolinol methosulphate[14]

A mixture of finely powdered 8-quinolinol-N-oxide (20g, 0.124 mol) and freshly distilled dimethyl sulphate (15.7g, 0.124 mol) was heated on a water bath for 2 hours under reflux. The resultant mass was cooled and triturated with sodium dried ether (100 ml) until crystallization occurred. The solid was then washed successively with three 100 ml portions of ether and dried under vacuum. Krasavin et al[14] have recrystallized the crude product from ethanol-diethyl ether,

SCHEME 1.

8-QUINOLINOL DERIVATIVES.



mp, 143-4.5°. The impure material is, however, quite satisfactory for the subsequent preparation.

2-Cyano-8-quinolinol and 2-Carboxamido-8-quinolinol monohydrate

2-Cyano-8-quinolinol was prepared in 80% yield using a modification of the procedure given by Krasavin[15].

Crude N-methoxy-8-quinolyl methosulphate (18g, 0.066 mol) in water (40 ml) was added over a 2 hour period to a cold (0-5°) stirred solution of sodium cyanide (9.2g, 0.19 mol) in water (40 ml). The pH of the mixture was adjusted to 4.5 by the addition of glacial acetic acid and the precipitated nitrile filtered off, washed with water, and dried. Recrystallization from acetonitrile gave the analytical sample as yellow plates, $\nu_{C\equiv N}$ = 2250 cm^{-1}, mp 135° (Lit.[15] 134.5-5.5). Found: C, 70.45; H, 3.68; N, 16.62%. Calc. for $C_{10}H_6N_2O$: C, 70.56; H, 3.55; N, 16.46%. Spectral data* in aqueous solution: λ_{max} = 253.5 nm (ε = 5.4 x 10^4), pH 6.3. λ_{max} = 270 nm (ε = 3.9 x 10^4), 347.5 nm (ε = 2.7 x 10^3) and 414 nm (ε = 3.5 x 10^3), pH 12.

Base hydrolysis of the nitrile gave 2-carboxamido-8-quinolinol mono hydrate as follows.

2-Cyano-8-quinolinol (1.70g, 0.010 mol) in potassium hydroxide solution (30 ml, 1.0M) was maintained at 80° for 5 mins. The reaction was quenched by immediately cooling the mixture to ca. 10°, and the chilled solution neutralized to pH 6.5 with acetic acid. Recrystallization of the precipitated product from acetone-water (1:1) yielded the amide as irridescent brown plates mp 212° (Lit.[15] 214-215°).

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* Units of ε dm^3 mol^{-1} cm^{-1}

2-Carboxy-8-quinolinol

2-Cyano-8-quinolinol (3.40g, 0.02 mol) in water (50 ml) was refluxed with sodium hydroxide (6.0g) until ammonia was no longer evolved (4-5 hours). The solution was cooled to room temperature and hydrochloric acid (5M) added until yellow acid was completely precipitated (pH 4). The crude product was recrystallized from aqueous dimethylformamide giving large yellow-brown crystals, mp 217-18°. Found: C, 63.22; H, 3.94; N, 7.52%. Calc. for $C_{10}H_7NO_3$: C, 63.48; H, 3.73; N, 7.40%. Irving and Pinnington[16] have previously prepared 2-carboxy-8-quinolinol (mp 211°) by catalytic demethylation of 8-methoxyquinaldic acid. A subsequent report[17], where the same preparative procedure was employed, gives the melting point as 216-17°.

2-Acetyl-8-quinolinol

A powdered suspension of 2-cyano-8-quinolinol (5.0g, 0.029 mol) in sodium dried ether (150 ml) and under an atmosphere of dry nitrogen was cooled to 10°C. The mixture was stirred continuously and methyl magnesium iodide (0.066 mol in 100 ml Et_2O) added over a 2 hour period. Hydrolysis of the complex was accomplished by cautious addition of hydrochloric acid (5M) and the ethereal layer removed by decantation. Neutralization of the aqueous phase to pH 6 with sodium hydroxide resulted in precipitation of the product which was washed with water and dried. The crude ketone was extracted into acetonitrile (100 ml) and filtered hot to remove magnesium hydroxide. Evaporation of the filtrate gave a yellow residue which recrystallized readily from ethanol-water (2:1). Yield 3.4g (62%), mp 103.5-4.5°. Found: C, 70.25; H, 4.91; N, 7.50%. Calc. for $C_{11}H_9NO_2$: C, 70.57; H, 4.85; N, 7.48%, $\nu_{C=O}$ 1695 cm^{-1}. Spectral data* in aqueous solution, λ_{max} 260 nm (ε = 4.0 x 10^4), pH 6.0; λ_{max} 280.5 (ε = 3.3 x 10^4), pH 12.5. $\delta(CD_3COCD_3)$ 2.90 (3H, s, CH_3) 7.1-7.8 (3H, m, H-5,6,7) 8.07 (1H, d, J = 9Hz, H-3) 8.45 (1H, d, J = 9 Hz, H-4) 8.95 (1H, s, OH).

2-Acetyl-5,7-diodo-8-quinolinol

To a solution of 2-acetyl-8-quinolinol (0.187g, 0.001 mol) in methanol (20 ml) was added potassium iodide (1g) in water (5 ml) and 20 ml of 0.10M iodine solution (0.002 mol). The solution was stirred continuously and 0.1M sodium hydroxide (20 ml, 0.002 mol) added dropwise over a period of 5 min. Stirring was continued for a further 5 min. before the precipitated pale yellow iodination product was filtered off, washed with water and dried. Recrystallization from dimethylformamide gave yellow crystals, mp > 200° (sealed tube, decomp.). Found: C, 30.46; H, 1.90; N, 3.13%. Calc. for $C_{11}H_7NO_2I_2$: C, 30.09; H, 1.61; N, 3.19%, $\nu_{C=O}$ 1680 cm^{-1}. $\delta(C_5D_5N)$ 2.42 (3H, s, CH_3), 8.08 (1H, d, J = 9 Hz, H-3) 8.35 (1H, d, J = 9 Hz, H-4) 8.60 (1H, s, H-6).

2-Acetyl-d_3-8-quinolinol

2-Acetyl-8-quinolinol (0.20g) was added to a solution of NaOH (0.20g) in D_2O (30 ml). The bright orange solution was maintained at 40° for 4 hours, rapidly neutralized to pH 5 by the dropwise addition of conc. H_2SO_4 and the precipitated product filtered off, washed with water and dried.

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* Units of ε dm^3 mol^{-1} cm^{-1}

Recrystallization was effected from methanol-water (1:1). The absence of an n.m.r. signal at δ 2.90 showed deuteration of the methyl group was complete, $\nu_{C=O}$ 1690 cm^{-1}. $\delta(CD_3COCD_3)$ 7.1-7.75 (3H, m, H-5,6,7) 8.00 (1H, d, J = 9 Hz, H-3) 8.38 (1H, d, J = 9 Hz, H-4) 8.90 (1H, s, OH). Deuteration of the ring system did not occur.

8-Acetoxy-2-carboxyquinoline monohydrate

To a solution of 2-carboxy-8-quinolinol (0.50g, 0.027 mol) in sodium hydroxide (5 ml, 10% w/v) was added ice (6g) and acetic anhydride (0.75g). The mixture was stirred for 1 min. and brought to pH 3 with the addition of hydrochloric acid (3M). The crude acetate was immediately filtered off, washed with ice cold water and dried. Purification was effected by recrystallization from ethanol-water (2:1) giving light tan crystals that decomposed rapidly on heating, or on exposure to air for appreciable periods. $\nu_{C=O}$ (carboxyl) 1700 cm^{-1}, $\nu_{C=O}$ (ester) 1770 cm^{-1}. Found: C, 57.79; H, 4.67; N, 5.68%. Calc. for $C_{12}H_9NO_4.H_2O$: C, 57.82; H, 4.45; N, 5.75%. The i.r. and n.m.r. spectra both indicated the presence of water.

2-Carbomethoxy-8-quinolinol hemihydrate

Dry hydrogen chloride was bubbled continuously through a suspension of powdered 2-carboxy-8-quinolinol (2.5g, 0.137 mol) in anhydrous methanol (35 ml) until all the solid had dissolved. The resultant solution was then poured into dry ether (500 ml) and the precipitated yellow ester hydrochloride filtered off, washed with ether, and dried under vacuum. A suspension of the product in water (100 ml) was titrated to pH 6 with 2,6-lutidine and the free base form of ester recovered by filtration. After treatment with decolourising charcoal the ester was recrystallized from methanol-water yielding fine golden needles, mp 105-6°, $\nu_{C=O}$ 1715 cm^{-1}. Found: C, 62.16; H, 4.86; N, 6.63%. Calc. for $C_{11}H_9NO_3.\frac{1}{2}H_2O$: C, 62.23; H, 4.75; N, 6.60%. The i.r. and n.m.r. spectra both indicated the presence of water.

2.2 pH Measurements

pH measurements were made with a Radiometer 26 pH meter equipped with a G202B high alkalinity glass electrode and a K401 calomel electrode. The scale expansion mode allowed the meter to be standardized to ±0.005 pH units. The electrode assembly was standardized with both M/100 borax and M/20 oven dried (110°) potassium hydrogen phthalate. Normally, calibration was carried out daily when the meter was in use. The glass electrode was replaced at ca. 3 month intervals or when its condition otherwise warranted replacement. Poor meter response was noted when aged glass electrodes were used in obtaining the pH of solutions at temperatures below ~20°. The saturated calomel electrode was replaced less frequently and was found to perform satisfactorily for up to 12 months or more.

Borax and phthalate buffers were prepared regularly using deionized water of specific conductance ~1×10^{-6} ohm^{-1}. The former buffer readily absorbs carbon dioxide from the atmosphere and particular care was taken during its preparation and subsequent use to prevent carbon dioxide absorption.

The N.B.S. values[18] of the pH of the two buffers are given below.

Buffer	15.0°C	25.0°C	35.0°C	45.0°C
M/20 KHphthalate	3.999	4.008	4.024	4.047
M/100 Borax	9.276	9.180	9.102	9.038

Mean molar activity coefficients, y_1, were calculated from the Davie's equation[19].

$$-\log y_1 = A.z^2\left[\frac{I^{\frac{1}{2}}}{1 + I^{\frac{1}{2}}} - 0.2I\right] \qquad .....(1)$$

$$\text{where } I = \tfrac{1}{2}\,\Sigma\, c_i.z_i^{\,2} \qquad .....(2)$$

Hydroxide ion concentrations were obtained from measured pH values according to the relation

$$[OH^-] = K_w/a_{H^+}.y_1 \qquad .....(3)$$

Accepted values of pK_w[20], of the Debye-Huckel parameter A[21], and the calculated values of y_1 for a univalent ion at an ionic strength of 0.1M at a number of temperatures are given below

Temp/°C	A	y_1(0.1M)	pK_w
15.0	0.5028	0.775	14.346
25.0	0.5115	0.772	13.997
35.0	0.5211	0.768	13.680
45.0	0.5317	0.764	13.396

2.3 Proton Ionization Constants

Where possible (i.e. when solubilities permitted) the pK_a values of selected compounds were determined by the potentiometric procedures outlined by Albert and Serjeant[22]. Acid-base titrations were performed under conditions of constant ionic strength. In general, substrate concentrations were checked by direct estimation of titration end points.

Proton ionization constants of compounds of low solubility were determined by a spectrophotometric method. The low ionic strength buffers described by Perrin[23], which are nearly transparent in the ultraviolet region were employed for spectrophotometric measurements on organic substrates. The method depends on the direct determination of the ratio of molecular species to ionized species. Provided the same total concentration of the substance is used for all measurements and the cell pathlength is invariant equation (4) is applicable for monobasic neutral acids.

$$pK_a^M = pH \pm \log \frac{OD_I - OD}{OD - OD_M} \qquad \ldots\ldots(4)$$

Here OD_I and OD_M are the optical densities of the ionized and molecular species respectively, and OD is the observed optical density at a given pH. The complete derivation of (4) has been given and an analogous relatio. holds if the functional group to be determined is a base. At a particular ionic strength K_a^M is defined as:

$$K_a^M = \frac{a_{H^+}.[A^-]}{[HA]}$$

$$\text{i.e. } pK_a^M = pH + \log[HA] - \log[A^-]$$

Both the potentiometric and spectrophotometric procedures furnish the concentration ratio of the molecular to ionized species. The measured pK_a's are therefore mixed constants. Thermodynamic constants reported in this work have been calculated from the mixed constants by use of the appropriate activity coefficients calculated from Davie's equation[19].

$$K_a^T = \frac{a_{H^+} \cdot a_{A^-}}{[HA]} \qquad \text{(assuming an activity coefficient of unity for HA)}$$

$$= \frac{a_{H^+} \cdot [A^-] \cdot \gamma_1}{[HA]}$$

$$\text{i.e. } pK_a^T = pH + \log[HA] - \log[A^-] - \log \gamma_1$$

2.4 Apparatus

Electronic solution and solid state spectra were respectively recorded on Perkin-Elmer 402 and Unicam SP700a instruments. The diffuse reflectance spectra were obtained against a magnesium oxide reference.

Spectrophotometric pK_a measurements were carried out using either a Gilford 2400S instrument or a Unicam SP500 fitted with Gilford 222 attachments. The cell compartments of both instruments were thermostatted to within ±0.2° of the desired temperature by water circulated from a Heto constant temperature water bath. Both spectrophotometers were employed for kinetic studies.

A Radiometer 26 pH meter, used in conjunction with a Titrator 11 titration unit, a Radiometer magnetic valve type MNV1 and a conventional titration assembly was used for pH-stat rate measurements. Electrode standardization was carried out by the procedure given in Section 2.2. All reactions were carried out under an atmosphere of oxygen free nitrogen.

Infra red spectra of solid compounds were run as mulls in nujol or hexachlorobutadiene on a Perkin-Elmer 457 instrument. Wavelength calibration was effected by recording the spectra of thin film polystyrene.

A Newport variable temperature Gouy balance was employed for magnetic measurements. Field calibration was accomplished using $HgCo(CNS)_4$ ($\chi g = 16.44 \times 10^{-6}$ c.g.s. units, 20^{o})[24]. Measured susceptibilities of metal complexes were corrected for diamagnetism of the component atoms by use of the appropriate Pascal constants[25].

^{1}H N.m.r. spectra were recorded on a Hitachi Perkin-Elmer R24 spectrophotometer. Tetramethylsilane or 3-(trimethylsilyl) propanesulphonate were employed as internal standards for solutions in deuterated solvents.

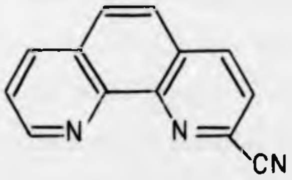
Conductivity studies were performed with a Portland direct reading conductivity bridge.

3. THE METAL ION CATALYSED HYDROLYSIS OF 2-CYANO-8-QUINOLINOL

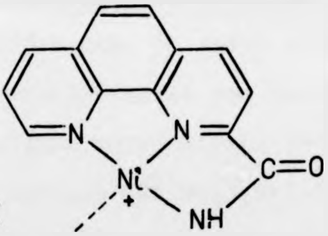
3.1 Introduction

Recently a number of investigators have noted that coordination to cationic metal centres markedly enhances the rates of base hydrolysis of organonitriles to the corresponding carboxamides.

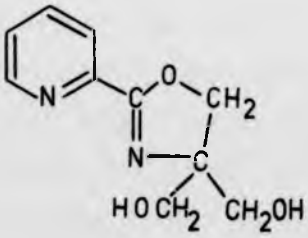
Breslow, Fairweather and Keana[26] found that the 1:1 complex of nickel(II) and 2-cyano-1,10-phenanthroline is hydrolysed 10^7 faster than the uncomplexed ligand (VI). The bound carboxamide product (VII) is not markedly susceptible to subsequent hydrolysis. Even larger rate accelerations ($> 10^9$) occur with the transition metal complexes of 2-cyanopyridine[27]. However, in the presence of 'tris' (tris(hydroxymethyl) aminomethane) and nickel(II) or copper(II) 2-cyanopyridine yields 2-(2'-pyridyl)-4,4'-di(hydroxymethyl)-Δ^2-isoxazoline (VIII) rather than the expected amide[28]. The product



VI



VII



VIII

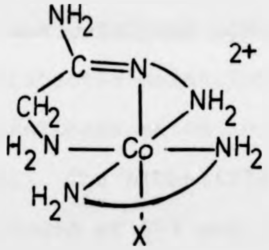
presumably arises as a result of the formation of a ternary complex involving 'tris', metal ion and nitrile.

Coordinated nitriles of the type $[Co(NH_3)_5N{\equiv}C\text{-}Ar]^{3+}$ are hydrolysed rapidly in base to give the corresponding nitrogen bonded carboxamido complexes[29,30]. The rate accelerations of ca. 2×10^6 observed in these systems are similar with that reported for the base hydrolysis of the acetonitrile complex $[Co(NH_3)_5N{\equiv}C\text{-}CH_3]^{3+}$[31].

Coordination of benzonitrile or acetonitrile to the $[Ru(NH_3)_5]^{3+}$ centre results in even greater reactivity toward base hydrolysis[32]. Rate enhancements of 10^8 have been reported for these systems. Homologous Ru(III), Rh(III) and Ru(II) complexes show marked differences in their rates of base hydrolysis which has been attributed to the metal ion electronic configuration and related metal-ligand interactions. Thus the reactivity of the $4d^6$ complex $[Rh(NH_3)_5N{\equiv}C\text{-}CH_3]^{3+}$ ($k_{OH} = 1.0\ dm^3\ mol^{-1}\ s^{-1}$, 25°) is similar to that of the $3d^6$ complex $[Co(NH_3)_5N{\equiv}C\text{-}CH_3]^{3+}$ ($k_{OH} = 3.4\ dm^3\ mol^{-1}\ s^{-1}$, 25°)[31]. The greater reactivity of the analogous $4d^5$ complex $[Ru(NH_3)_5N{\equiv}C\text{-}CH_3]^{3+}$ ($k_{OH} = 2.2 \times 10^2\ dm^3\ mol^{-1}\ s^{-1}$, 25°) has been attributed to the increased ability of ruthenium(III) to act as a π acceptor thus allowing greater stabilization of developing negative charge resulting from rate determining hydroxide ion attack on the nitrile unit. In contrast to these results the lack of reactivity of the complex cation $[Ru(NH_3)_5N{\equiv}C\text{-}CH_3]^{2+}$ ($k_{OH} < 6 \times 10^{-5}\ dm^3\ mol^{-1}\ s^{-1}$, 25°) represents an enhancement at most by a factor of 38 over the free ligand value ($k_{OH} = 1.6 \times 10^{-6}\ dm^3\ mol^{-1}\ s^{-1}$, 25°)[32].

The slow rate of hydrolysis of $4d^6$ ruthenium(II) complex has been interpreted as arising from stabilization of the nitrile unit as a consequence of π-backbonding from the metal centre.

In the system $[Co(en)_2X(NH_2-CH_2-C\equiv N)]^{2+}$ (en = ethylenediamine, X = Cl or Br) a different reaction occurs under basic conditions and the tridentate amidine complex (IX) is formed following attack of a coordinated amide ion (produced by deprotonation of an amine proton of en) on the nitrile carbon atom[33,34].



IX

A number of papers dealing with the synthetic aspects of the metal ion catalysed hydrolysis of nitriles[35], and with the formation of complexed nitriles[36-38] have also been published.

The present kinetic study is concerned with the metal ion promoted hydrolysis of 2-cyano-8-quinolinol to 2-carboxamido-8-quinolinol.

3.2 Experimental

3.2.1 Kinetic Measurements

The hydrolysis of the nitrile and its nickel(II) and cobalt(II) complexes was studied spectrophotometrically using a Gilford 2400S instrument.

A solution of the appropriate reaction mixture (3.0 cm^3) in a 1 cm pathlength silica cell was equilibrated in the spectrophotometer cell compartment for 25 min. The reaction was then initiated by injecting into the cell contents 10 µl of a solution of 2-cyano-8-quinolinol in ethanol.

All reactions were carried out under pseudo first order conditions. The base catalysed hydrolysis was monitored at 398.5 nm; an isosbestic point for the conversion of the 2-carboxamido-8-quinolinate anion to the corresponding carboxylate dianion. The nickel(II) and cobalt(II) promoted hydrolyses were followed at 347 and 274 nm respectively. In the latter reaction particular care was taken to exclude oxygen from the system. Buffered solutions of cobalt(II) were thoroughly flushed with nitrogen and transferred to the spectrophotometer cells under a nitrogen atmosphere. Hydrolysis of the cobalt(II)-nitrile complex (λ_{max} 275 nm, $\varepsilon = 4.9 \times 10^4$ dm^3 mol^{-1} cm^{-1}) gave initially the cobalt(II)-amide complex (λ_{max} 276 nm, $\varepsilon = 3.2 \times 10^4$ dm^3 mol^{-1} cm^{-1}) which subsequently underwent a further slow reaction (presumably hydrolysis to the carboxylate complex). Because of this stable values of OD_∞ were not observed and as a consequence rate constants were evaluated from computer extrapolated infinity plots using data collected over the first two reaction half lives. The computer program used was of the generalized least squares type based on the Letagrop programs of Sillén[39].

First order rate constants for the unpromoted and nickel(II) promoted reactions were obtained from plots of $\log[OD_t - OD_\infty]$ versus time.

No evidence for general base catalysis by buffer species was observed in the metal ion promoted reactions. Two fold variations in the concentrations of Hepes (cobalt(II) promoted hydrolysis) and 2,6-dimethylpyridine (nickel(II) promoted hydrolysis) had no effect on reaction rates.

All pH measurements were made at the temperature of the kinetic studies using a Radiometer 26 pH meter. Hydroxide ion concentrations were calculated from the measured pH values using the appropriate molar activity coefficients and values of pK_w listed in Section 2.2.

Hepes was a B.D.H. biochemical and 2,6-dimethylpyridine was purified by distillation (b.p. 143-45°). All other chemicals were of analytical reagent grade and were used without further purification.

3.2.2 Product Isolation

A 1:1 molar ratio of 2-cyano-8-quinolinol and nickel(II) chloride was dissolved in dioxan-water at 45° and the pH adjusted to 8.0 (pH meter) with added sodium hydroxide (2.0 ± 0.1 mole per mole of nitrile). The i.r. spectrum of the yellow nickel(II) complex which precipitated showed the absence of $\nu_{C\equiv N}$. The product was insoluble in both water and common organic solvents and could not be readily purified.

Careful acidification of an aqueous suspension of the complex resulted in the liberation of 2-carboxamido-8-quinolinol monohydrate, identical (m.p. and i.r. spectrum) with an authentic sample[15].

3.3 Results

3.3.1 Base Hydrolysis

The proton ionization constant (phenolic hydroxyl group) was determined spectrophotometrically at 414 nm by the method of Albert and Serjeant[22]. Introduction of the strongly electron withdrawing cyano group into the 2-position of 8-quinolinol results in a significant increase in the acidity of the phenolic group. The pK_a^T of 2-cyano-8-quinolinol is 8.78 ± 0.03 at 25^o (Appendix 3.1) while the corresponding value for the parent compound is 9.81 under the same conditions[40].

In basic solution the 2-cyano-8-quinolinate anion is hydrolysed initially to the 2-carboxamido-8-quinolinate anion which is subsequently hydrolysed to the corresponding carboxylate dianion. Base hydrolysis of the nitrile may be studied in isolation by following the reaction at 398.5 nm, an isosbestic point for the conversion of the amide to the carboxylic acid. In 1.0M sodium hydroxide at 45^o the value of k_{obs} is 4.80×10^{-3} s^{-1} ($k_{OH} = 4.85 \times 10^{-3} dm^3 mol^{-1} s^{-1}$) corrected for volume expansion of the reaction medium. The base hydrolysis of the carboxamide was studied separately under the same conditions by monitoring the increase in absorbance at 360 nm. Base hydrolysis of the carboxamide ($k_{obs} = 2.02 \times 10^{-4}$ s^{-1} in 1.0M sodium hydroxide at 45^o) is some 24 times slower than that of the nitrile.

Rate data obtained from a study of the temperature dependence of the nitrile hydrolysis is summarized in Table 1.

Table 1

Rate Data for the Hydrolysis of 2-Cyano-8-quinolinol[a]. Temperature Dependence.

Temp/°C	$10^3\ k_{obs}{}^{b}/s^{-1}$	$10^3\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
25.0	1.11	1.11
35.0	2.48	2.48
45.0	4.80	4.85[c]

$\Delta H^{\ddagger} = 13.4 \pm 0.5$ kcal mol^{-1}

$\Delta S^{\ddagger}_{308} = -27 \pm 2$ cal K^{-1} mol^{-1}

[a] In 1.0M sodium hydroxide solution. Monitoring wavelength 398.5 nm. Substrate concentration 3.2×10^{-4}M

[b] Average of duplicate determinations.

[c] Rate constant corrected for volume expansion.

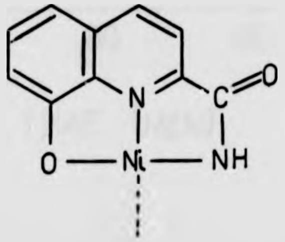
The large negative entropy of activation is expected for a reaction of this type where two anions come together in the transition state.

3.3.2 Metal Ion Catalysed Hydrolysis

At a given pH rate measurements as a function of the nickel(II) concentration of the reaction medium demonstrated that full complexation of the ligand was achieved. Thus at pH 6.86 and a nitrile concentration of 1.7×10^{-4}M constant values of k_{obs} were obtained when the concentration of nickel(II) was varied from 5.24×10^{-4}M to 2.63×10^{-3}M at 45° and I = 0.1M (Table 2). Included in the table are the results obtained from a similar study using cobalt(II) as a catalyst. In both cases the zero order dependence of the observed rates on the metal ion concentration at metal:ligand ratios in excess of 3:1 (nickel(II) catalysed hydrolysis) and 15:1 (cobalt(II) catalysed hydrolysis indicates that the substrate is present entirely as the 1:1 complex, ML^+ (L^- = 2-cyano-8-quinolinate anion). Typical pseudo first order plots for the hydrolyses are given in Figure 1.

In the pH region 6.2 to 8.0 at 45° both metal ion promoted reactions are first order in hydroxide ion concentration with $k_{obs} = k_{OH}[OH^-]$, Table 3. For reaction of NiL^+ $k_{OH} = (9.2 \pm 0.4) \times 10^2$ dm^3 mol^{-1} s^{-1} while the corresponding value for the reaction of CoL^+ is $(2.6 \pm 0.2) \times 10^2$ dm^3 mol^{-1} s^{-1}. Base hydrolysis of the 1:1 nickel complex is thus 2×10^5 times faster than base hydrolysis of the deprotonated ligand ($k_{OH} = 4.85 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}, 45°, I = 1.0M) and some 3.5 times faster than base hydrolysis of the analogous cobalt(II) complex at 45°.

It is probable that the carboxamide complex with nickel(II) is present as the charge neutral deprotonated species (X) at the pH values of kinetic measurements. N-bonded amide



X

Fig 1 PSEUDO FIRST ORDER KINETIC PLOTS FOR THE METAL ION CATALYSED HYDROLYSIS OF 2-CYANO-8-QUINOLINOL, 45°, $I = 0.1$ M.

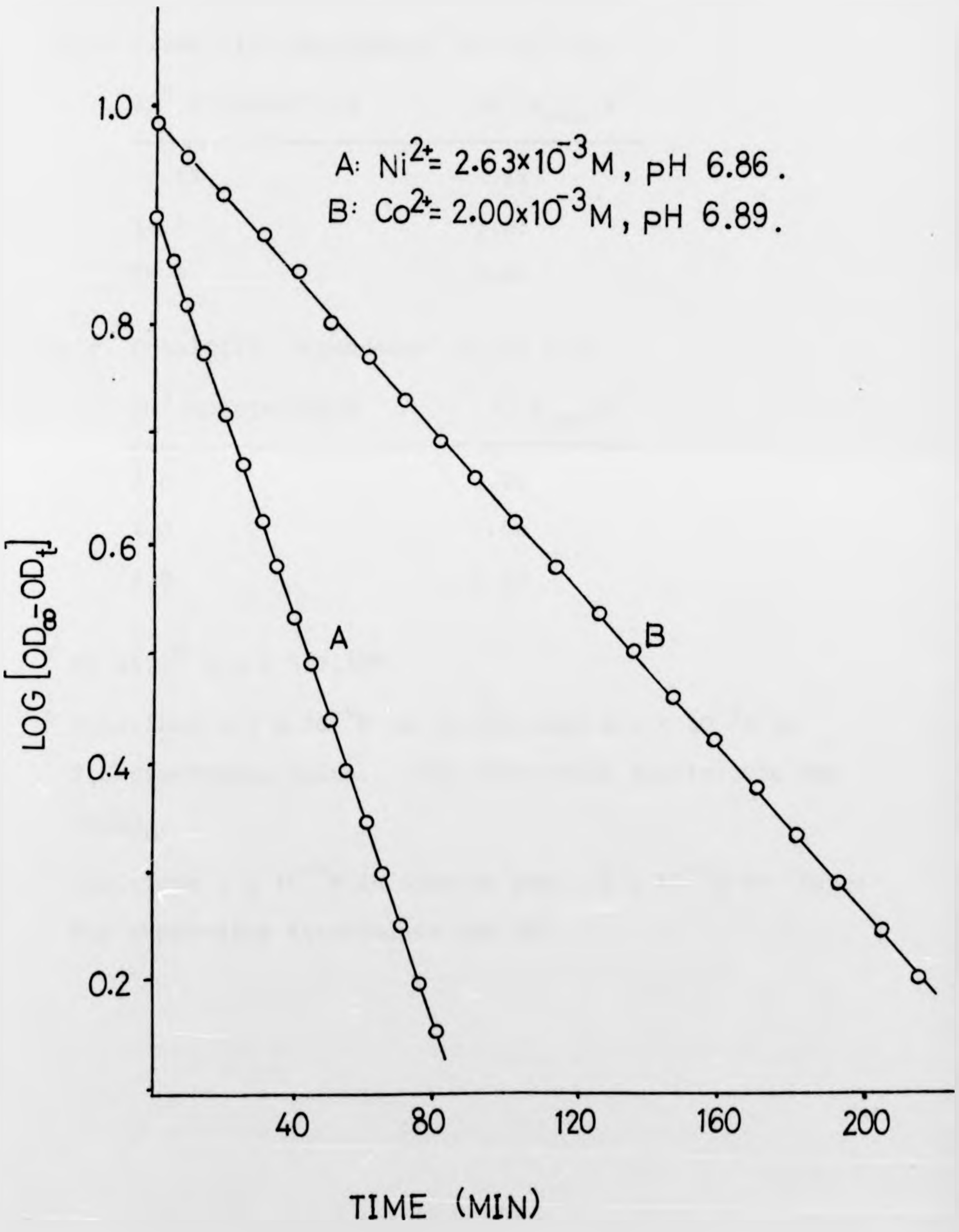


Table 2

The Nickel(II) and Cobalt(II) Catalysed Hydrolysis of 2-Cyano-8-quinolinol, Metal Ion Dependence[a].

(i) Nickel(II) dependence[b] at pH 6.86

10^4 Nickel(II)/M	10^4 k_{obs}/s^{-1}
5.25	3.25
13.1	3.33
26.3	3.45

(ii) Cobalt(II) dependence[c] at pH 6.89

10^3 Cobalt(II)/M	10^4 k_{obs}/s^{-1}
2.0	1.05
4.0	1.03
8.0	1.10

[a] At 45.0° and I = 0.10M

[b] Solutions 1.7×10^{-4}M in nitrile and 2.0×10^{-2}M in 2,6-dimethylpyridine. The supporting electrolyte was $NaClO_4$.

[c] Solutions 4×10^{-5}M in nitrile and 1.0×10^{-2}M in 'Hepes'. The supporting electrolyte was KCl.

Table 3

The Nickel(II) and Cobalt(II) Catalysed Hydrolysis of 2-Cyano-8-quinolinol, pH Dependence[a].

(i) Nickel(II) promoted reaction[b].

pH	$10^4\ k_{obs}/s^{-1}$	$10^7[OH^-]/M$	$10^{-2}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
6.27	0.872	0.971	8.98
6.54	1.77	1.81	9.78
6.86	3.45	3.78	9.13
7.18	6.97	7.89	8.83
7.60	19.4	20.8	9.33

(ii) Cobalt(II) promoted reaction[c].

pH	$10^4\ k_{obs}/s^{-1}$	$10^6[OH^-]/M$	$10^{-2}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
6.89	1.05	0.404	2.50
7.08	1.72	0.627	2.74
7.44	3.95	1.44	2.74
7.69	6.30	2.55	2.47
8.02	13.1	5.46	2.40

[a] At 45° and I = 0.10M.

[b] Solutions 2.63×10^{-3}M in $Ni(ClO_4)_2$, 2.0×10^{-2}M in 2,6-dimethylpyridine and 1.7×10^{-4}M in nitrile.

[c] Solutions 2.0×10^{-3}M in $Co(NO_3)_2$, 10^{-2}M in Hepes and 4.1×10^{-5}M in nitrile.

complexes of this type are unreactive toward base hydrolysis[41]. Deprotonation of the cobalt(II)-carboxamide complex presumably occurs at higher pH and subsequent slow hydrolysis to the carboxylate derivative prevents the observation of stable values of OD_∞.

The results obtained from a study of the temperature dependence of the nickel(II) and cobalt(II) promoted hydrolysis of the nitrile are listed in Table 4.

Table 4

The Metal Ion Promoted Hydrolysis of 2-Cyano-8-quinolinol, Temperature Dependence.

(i) Nickel(II) at I = 0.108M[a].

Temp/$^\circ$C	pH	$10^4\ k_{obs}/s^{-1}$	$10^6[OH^-]/M$	$10^{-2}\ k_{OH}/dm^3\,mol^{-1}\,s^{-1}$
25.0	7.97	1.97	1.20	1.64
35.0	7.82	6.61	1.80	3.67
45.0	7.66	19.0	2.39	7.97

(ii) Cobalt(II) at I = 0.108M[b].

Temp/$^\circ$C	pH	$10^4\ k_{obs}/s^{-1}$	$10^6[OH^-]/M$	$10^{-2}\ k_{OH}/dm^3\,mol^{-1}\,s^{-1}$
25.0	8.00	0.697	1.30	0.536
35.0	7.87	2.32	2.02	1.15
45.0	7.77	8.40	3.07	2.74

[a] Solutions 2.63×10^{-4}M in $Ni(ClO_4)_2$, 4×10^{-2}M in 2,6-dimethylpyridine and 2.1×10^{-4}M in nitrile. Supporting electrolyte, $NaClO_4$.

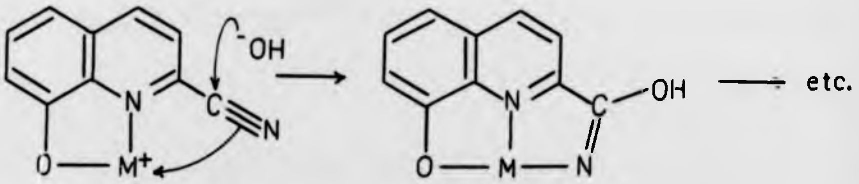
[b] Solutions 1.6×10^{-3}M in $Co(NO_3)_2$, 10^{-2}M in Hepes and 4.1×10^{-5}M in nitrile. Supporting electrolyte, KCl.

The reaction was also catalysed by both zinc(II) and copper(II). In the former case the formation constant of the zinc-nitrile complex was appreciably lower than that of the nickel(II) derivative. Attempts to increase the zinc(II):nitrile ratio to achieve full complexation of the substrate were frustrated due to precipitation of zinc(II) hydroxide. However, zinc(II) was at least as effective as nickel(II) in promoting the reaction. The low solubilities of both the copper(II)-amide and -nitrile complexes in water prevented a detailed investigation of the effect of copper(II) on the reaction. A limited study using NN-dimethylformamide (5% v/v) in water as a solvent indicated a rate acceleration in this system of between 10^7 and 10^8.

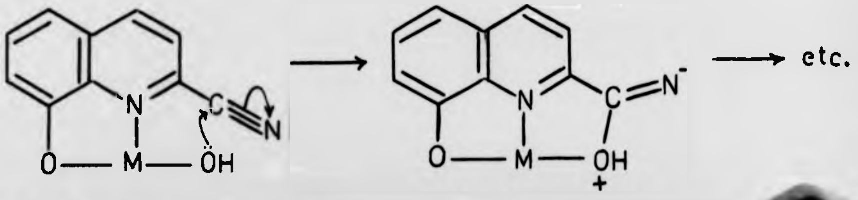
3.4 Discussion

Two general mechanisms may be considered to account for the fact that the metal ion promoted hydrolyses of 2-cyano-8-quinolinol are first order in hydroxide ion concentration and are not susceptible to general base catalysis. Mechanism 1, attack by external hydroxide ion on the metal complex; or mechanism 2, attack by coordinated hydroxide ion from within a ternary complex.

(1)



(2)



Here the problem of mechanism arises as a consequence of ligand lability and cannot be resolved by rate studies over an extended pH range. Two cases may be considered.

(i) External attack by hydroxide ion on the aquo complex coupled with external attack on the hydroxo complex at high pH.

$$\begin{tikzcd}
ML^{+}\text{-}OH_2 \arrow[r, shift left, "K_a"] \arrow[d, "OH^{-}"', "k'"] & ML\text{-}OH \arrow[l, shift left] \arrow[d, "OH^{-}"', "k'_{OH}"] & + \; H^{+} \\
\text{product} & \text{product} &
\end{tikzcd}$$

$$K_a = \frac{[ML\text{-}OH][H^{+}]}{[ML^{+}\text{-}OH_2]} \qquad \text{.....(5)}$$

$$[ML^{+}\text{-}OH_2] = \frac{K_w[ML\text{-}OH]}{K_a[OH^{-}]} \qquad \text{.....(6)}$$

$$\text{rate} = k_{obs}([ML^{+}\text{-}OH_2] + [ML\text{-}OH]) \qquad \text{.....(7)}$$

$$= k'[ML^{+}\text{-}OH_2][OH^{-}] + k'_{OH}[ML\text{-}OH][OH^{-}] \qquad \text{.....(8)}$$

Equating (7) with (8) after substituting for $[ML^{+}\text{-}OH_2]$ from (6) gives

$$k_{obs} = \frac{K_w k' + K_a k'_{OH}[OH^{-}]}{[H^{+}] + K_a} \qquad \text{.....(9)}$$

(ii) Intramolecular reaction (bound hydroxide) coupled with nucleophilic attack by hydroxide ion on the hydroxo complex at high pH.

$$\begin{tikzcd}
\text{ML-OH} \arrow[r, "k_i"] \arrow[d, "\text{OH}^-"', "k'_{OH}"] & \text{product} \\
\text{product} &
\end{tikzcd}$$

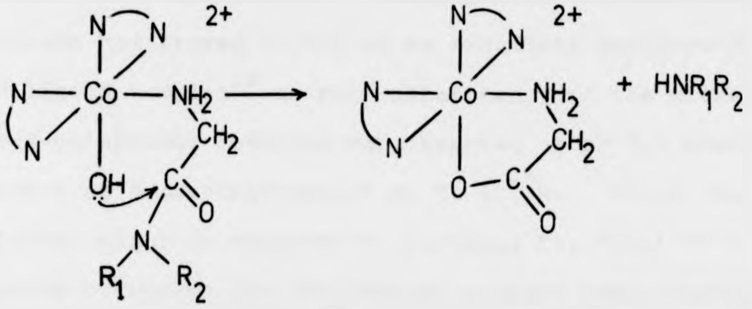
$$\text{rate} = k_i[\text{ML-OH}] + k'_{OH}[\text{ML-OH}] \qquad \text{.....(10)}$$

Equating (7) with (10) after substituting for $[\overset{+}{\text{ML}}\text{-OH}_2]$ yields in this case

$$k_{obs} = \frac{K_a k_i + K_a k'_{OH}[\text{OH}^-]}{[\text{H}^+] + K_a} \qquad \text{.....(11)}$$

Equations (9) and (11) predict that the pH-rate profile will be sigmoid in form ($k' > k'_{OH}$) irrespective of which pathway is followed. The observation of a plateau in the pH-rate profile would not be confirmation of the intramolecular process.

Buckingham et al. have demonstrated that the hydrolysis of certain carboxylic acid derivatives of cobalt(III) involves attack by hydroxide ion coordinated to the metal ion[42,43]. Here the mechanism may be resolved by ^{18}O tracer studies. It has been found[43] that the pathway is particularly effective in the hydrolysis of coordinated glycinamides of the type cis-$[\text{Co(en)}_2(\text{OH})(\text{glyNR}_1\text{R}_2)]^{2+}$ (XI). On the other hand extremely large rate enhancements (10^6 to 10^8) have been observed in nitrile hydrolyses where a mechanism of this type may be definitely excluded. Thus base hydrolysis of



XI

$[Co(NH_3)_5N{\equiv}C\text{-}Ar]^{3+}$ ions to give the corresponding benzamido complexes proceeds 2 x 10^6 times more rapidly than base hydrolysis of uncoordinated benzonitrile[29]. Even larger rate enhancements (10^8) are observed when the cobalt(III) centre is replaced by ruthenium(III)[32].

P.m.r. studies[31] have indicated that the hydrolysis of the $[Co(NH_3)_5N{\equiv}C\text{-}CH_3]^{3+}$ cation is concurrent with methyl proton exchange. The exchange rate is such that slightly more than one exchange occurs for every hydrolysis act. Exchange of the phenyl protons does not occur during the hydrolysis of the benzonitrile analogue. The similarity in the rates of base hydrolysis of the $[Co(NH_3)_5N{\equiv}C\text{-}CH_3]^{3+}$ ion (k_{OH} = 3.5 $dm^3\ mol^{-1}\ s^{-1}$) and the $[Co(NH_3)_5N{\equiv}C\text{-}C_6H_5]^{3+}$ ion (k_{OH} = 18 $dm^3\ mol^{-1}\ s^{-1}$) at 25° suggests some identity in the reaction mechanisms. Hydrolysis of both complexes is presumed to occur by direct hydroxide ion attack with exchange in the acetonitrile complex being an independent process.

It has been suggested[26] that mechanism 1 applies in the case of the nickel(II) promoted hydrolysis of 2-cyano-1,10-phenanthroline. In this system attempts to demonstrate that the presence of second nucleophilic ligand, such as 2-aminoethanol of β-hydroxyethylethylenediamine, in the coordination sphere of the metal ion would lead to enhanced reactivity were unsuccessful. Although tris(hydroxymethyl) aminomethane has proved to act as an excellent nucleophile in a mixed ligand complex[28] no rate enhancement of the nickel(II)-2-cyano-8-quinolinol reaction was observed at pH 7.5 when tris was present at concentrations of up to 10^{-2}M. Since the aminoalcohol might be expected to parallel the function of coordinated hydroxide ion this result appears more consistent with mechanism 1. The pK_a values for the acid dissociation of the aqua-ions $[Co(H_2O)_6]^{2+}$ and $[Ni(H_2O)_6]^{2+}$ are 8.9 and 10.6 respectively at 25°[44]. The cobalt(II) and nickel(II) complexes of 2-cyano-8-quinolinol carry a single positive charge and it would therefore be expected that proton ionization would occur at somewhat higher pH than for the dipositive ions. It could be argued that since the ionization constants of the cobalt(II) and nickel(II) complexes probably differ by 1.5 to 2.0 pK units, hydrolysis by mechanism 2 does not occur as similar catalytic effects are observed with both metal ions.

Rate data for the hydrolysis of a number of coordinated and uncoordinated nitriles are listed in Table 5. Base hydrolysis of the 2-cyano-8-quinolinate anion has $\Delta H^{\ddagger} = 13.4$ kcal mol^{-1} and $\Delta S^{\ddagger} = -27$ cal K^{-1} mol^{-1} at 308°K. These kinetic parameters are comparable with those obtained for the base hydrolysis of 2-cyano-1,10-phenanthroline ($\Delta H^{\ddagger} = 15.1$ kcal mol^{-1}, $\Delta S^{\ddagger} = -20$ cal K^{-1} mol^{-1})[26]. Reference to Table 5 clearly demonstrates that the catalytic effect of metal ions in both these reactions is due to a more positive $\Delta S^{\ddagger}$. A similar general conclusion may be drawn concerning

Table 5

Rate Data and Kinetic Parameters for the Hydrolysis of Nitriles

Substrate^a	k_{OH}^{25} /dm^{3}mol^{-1} s^{-1}	$\Delta H^{\ddagger}$ /kcal mol^{-1}	$\Delta S^{\ddagger}$ /cal K^{-1} mol^{-1}	Reference
$[Co(NH_3)_5$(benzonitrile)$]^{3+}$	18	16.5	+2.7	29
Benzonitrile	8×10^{-6}	19.9	-15.2	46
Ni(2-cyano-1,10-phenanthroline)$^{2+}$	2.4×10^{4}	15.7	+14.0	26
2-Cyano-1,10-phenanthroline	2.6×10^{-3}	15.1	-20	26
Ni(2-cyano-8-quinolinate)$^{+}$	1.6×10^{2}	14.2	-1.0	this work
Co(2-cyano-8-quinolinate)$^{+}$	50	14.3	-3.0	"
2-Cyano-8-quinolinate anion	1.1×10^{-3}	13.4	-27	"
$[Co(NH_3)_5$(1,4-dicyanobenzene)$]^{3+}$	3.69×10^{2}	13.3	-2	30
$[Co(NH_3)_5$(4-cyanophenoxide)$]^{2+}$	0.18	16.3	-7.4	29

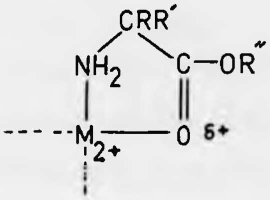
the catalytic effect of the kinetically non-labile cobalt(III) centres.

In the present case steric factors prevent bonding of the 2-cyano group to the metal ion in the initial state of the reaction. Breslow et al.[26] have proposed that the transition state for the nickel(II) promoted hydrolysis of 2-cyano-1,10-phenanthroline involves bonding of the developing imino group to the metal centre possibly producing the displacement of a coordinated water molecule. Coordination of the group undergoing reaction is gained in the transition state. Bimolecular reactions are characterised by $\Delta S^{\ddagger}$ values in the range -5 to -15 cal K^{-1} mol^{-1}[45]. The results of the present investigation, where $\Delta S^{\ddagger}$ values of -3 and -1 cal K^{-1} mol^{-1} were observed for the metal ion promoted reactions, are consistent with the view of Breslow however, since the transition state for hydrolysis is effectively solvated by the metal ion. This effect should give rise to more positive entropies of activation than would be expected on the basis of reaction molecularity alone and would thus account for the observed results. In addition, electrostatic effects may be of some importance. Base hydrolysis of the singly positively charged nickel(II)-2-cyano-8-quinolinate complex at 25 is slower by a factor of ca. 10^2 than base hydrolysis of the nickel(II)-2-cyano-1,10-phenanthroline complex which carries a dipositive charge. This observation appears consistent with the proposed pathway; rate differences of 10^2 would not be unexpected in reactions involving negatively charged nucleophiles. Alternatively, a metal centre of reduced charged density should be less effective in stabilizing the developing negative charge in the transition state.

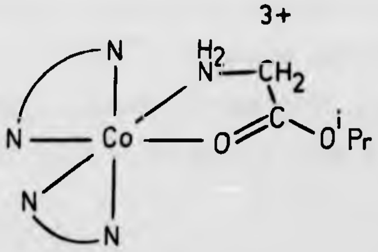
4. THE HYDROLYSIS OF 2-CARBOMETHOXY-8-QUINOLINOL

4.1 Introduction

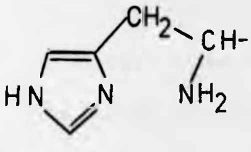
A number of mechanisms have been proposed to account for the catalytic effects of labile metal ions on the hydrolysis of esters[47-55]. In most of these it has been assumed that nucleophilic attack at the carbonyl carbon atom is enhanced by direct activation of the carbonyl group by the metal ion in the initial state of the reaction:



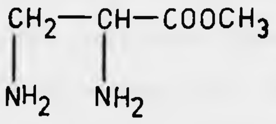
Early kinetic investigations were concerned primarily with the hydrolysis of α-amino acid esters[47,48,56]. The low formation constants of the metal ion-ester complexes has complicated the interpretation of results, and studies of these systems have provided rate constants which show only order of magnitude agreement. It has been established that the predominant nucleophile is hydroxide ion and evidence for attack by water has been obtained[49,57,58]. The rate enhancements observed (ca. 10^5 in the case of the copper(II)-glycine ester systems) are consistent with a pathway involving metal-carbonyl bonding, since similar rate accelerations (ca. 10^6) have been observed for the hydrolysis of the $[Co(en)_2(glyO^iPr)]^{3+}$ ion[59,60].



Rate constants have been reported for the base hydrolysis of certain complexes of methyl-histidinate (XII)[61] of methyl-2,3-diaminopropionate (XIII)[55,62,63] and of cysteinate esters (XIV)[47,64-67].

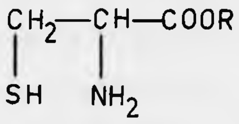


XII



$\underset{NH_2}{CH_2}-\underset{NH_2}{CH}-COOCH_3$

XIII



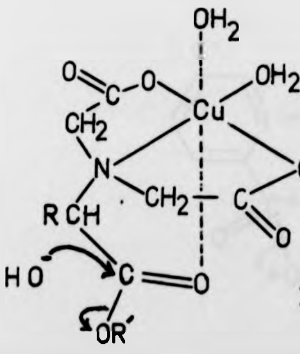
$\underset{SH}{CH_2}-\underset{NH_2}{CH}-COOR$

XIV

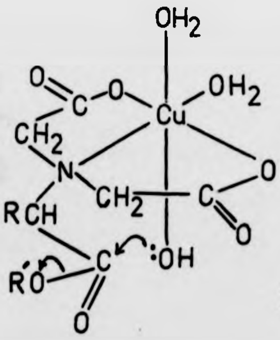
The rate accelerations observed in these systems are much lower than that found for the hydrolysis of ethylglycinate. The ligands are bidentate and metal-ester carbonyl bonding appears unimportant. Kinetic data has been obtained for the base hydrolysis of mono- and bis-ligand complexes with a number of divalent metal ions. The main factor in determining the rates of hydrolysis in these systems is the charge carried on the substrate. A species carrying a double positive charge is usually more reactive than a species carrying a single positive charge which in turn is more reactive than an uncharged complex. Angelici et al.[54] have studied the hydrolysis of glycine methyl ester (glyOMe) catalysed by the copper(II) complex Cu(DPA)$^{2+}$, where DPA is bis(2-pyridylmethyl) amine. Equilibrium constant determinations for the formation of Cu(DPA)$^{2+}$ (K_L) and for its binding to glyOMe (K_x) indicated that Cu(DPA)(glyOMe)$^{2+}$ was the predominant species in solution prior to rate determining attack by hydroxide ion. An examination of several Cu(L)$^{2+}$ complexes suggested that strongly coordinating L ligands (those with large K_L values) reduce the ability of Cu(L)$^{2+}$ to bind glyOMe (low K_x values) and reduce the rate of base hydrolysis of the ester in the $Cu(L)(glyOMe)^{2+}$ substrates. The trends in reactivity have been interpreted in terms of the Lewis acidity of the $Cu(L)^{2+}$ complexes and previous results[55] reinterpreted in the light of these findings.

The difficulties associated with low formation constants of metal ion-ester complexes have been overcome by incorporating the ester species into the structure of a larger polydentate ligand. The 1:1 complexes of ethyl valinate-N,N-diacetic acid with copper(II), cobalt(II), nickel(II), lead(II) and samarium(III) are large and there is little tendency to add a second ligand[52].

Base hydrolysis of the ester function occurs rapidly in the pH range 7 to 9. Similar studies have been carried out for ligands of this type involving a number of amino acid esters[51,52,68]. Hydrolysis of the copper(II) valinate complex is subject to general nucleophilic catalysis by nitrite ion, pyridine, 4-methylpyridine, acetate ion and phosphate dianion. It has been concluded[52] that ester hydrolysis occurs via hydroxide ion attack on the ester carbonyl group which is transiently bonded to the metal ion (XVa), rather than by the kinetically equivalent pathway involving attack by bound hydroxide (XVb).



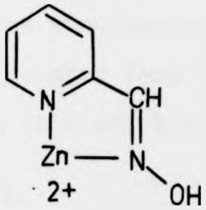
XVa

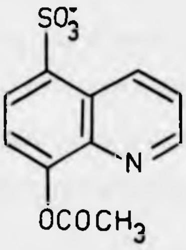


XVb

It has been reported[69] that the zinc complex of pyridine-2-carboxaldoxime (XVI) is a particularly effective nucleophilic catalyst in the hydrolysis 8-acetoxyquinoline-5-sulphonate (XVII).

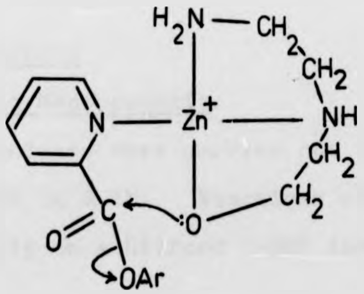
XVI





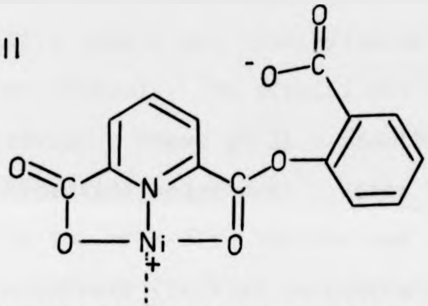
XVII

The reaction involves acyl transfer within the catalyst-substrate complex and the intermediate, pyridine-2-carboxaldoxime acetate, has been isolated. The zinc complex (XVI) is an extraordinary nucleophile, comparable in reactivity with hydroxide ion, although its pK_a is only 6.5. Sigman and Jorgensen[70] have found that zinc(II) catalyses a fascile transesterification between N-(β-hydroxyethyl)ethylenediamine and p-nitrophenyl picolinate. The reaction, which is many ways analogous to that outlined above, is considered to involve a reactive ternary complex in which the metal ion perturbs the pK_a of the hydroxyethyl group of the ligand, and provides a high local concentration of the nucleophile near to the carbonyl carbon atom.



Breslow and McAllister[71] have studied the hydrolysis of the salicylic acid and phenyl esters of pyridine-2,6-dicarboxylic acid in the presence of nickel(II) over the pH range 3 to 7. The enhanced reactivity of the carboxylate ionized species (XVIII) towards attack by H_2O has been attributed to a reaction involving simultaneous catalysis by metal and carboxylate ion. The protonated form of the complex is less reactive than the ionized form which in the opposite direction expected for the reactivity of salicylate as a leaving group. The overall effect of the bifunctional catalysis is relatively modest, and the carboxylate group is presumed to act as a general base rather than as a nucleophile (c.f. the hydrolysis of aspirin derivatives[72].)

XVIII



A recent thorough discussion of the metal ion catalysed hydrolysis of amino acid esters has been given[73]. Earlier work has been reviewed in detail by Bruice and Benkovic[74].

The following section is concerned with the metal ion catalysed hydrolysis of 2-carbomethoxy-8-quinolinol.

4.2 Experimental

4.2.1 Kinetic Measurements

All hydrolyses were carried out in aqueous media at an ionic strength of 0.1M. Reactions were followed spectrophotometrically on a Gilford 2400S instrument by use of the following method. A methanolic solution of the ester (5 to 10 μl) was injected into the appropriate temperature pre-equilibrated reaction mixture (3.0 cm^3) contained in a 1 cm pathlength cell. The cell contents were then mixed by rapidly inverting the stoppered cell 3 or 4 times before measurements were begun.

The base catalysed hydrolysis was monitored by following the decrease in absorbance at 420 nm. In the pH range 9.2 to 11.5 borate and triethylamine buffers were used to effect pH control. No significant catalysis by buffer species was observed. Above pH 11.5 reactions were carried out in sodium hydroxide solutions. Since the concentration of hydroxide ion or buffer species was at least 70 times that of the substrate (initial concentration = 1.33×10^{-4}M) the reaction followed pseudo first order kinetics.

The metal ion catalysed hydrolyses were studied using solutions of metal perchlorate salts with the exception of the manganese(II) catalysed hydrolysis where manganese chloride was employed. In all cases the appearance of the product acid (or the metal ion-acid complex) was monitored in the region 257-280 nm, at the wavelength where the absorbance change was greatest for the particular conditions employed. The initial concentration of ester in these reactions lay in the range 10^{-5} to 5×10^{-5}M.

Pseudo first order rate constants for the hydrolyses in both the presence and absence of metal ions were obtained from plots of log $[OD_t - OD_\infty]$ (or log $[OD_\infty - OD_t]$) against time. Kinetic data giving rise to plots which were not linear over at least 3 reaction half lives were rejected. Normally, the cell compartment temperature was monitored periodically during the course of a kinetic run. A temperature deviation of greater than $\pm 0.2^{\circ}$ was considered unacceptable.

The pH of kinetic solutions was determined prior to, and in some cases on completion of, reaction. Pronounced but reversible poisoning of the glass electrode occurred with certain solutions of manganese(II) which ultimately precipitated manganese hydroxide on storage. In these cases the pH measurements were made on solutions not containing the metal ion, but which were identical with the reaction media in all other respects. The general technique of pH measurement has been described in section 2.2. Estimations of the pD of deuterium oxide solutions were made in the same manner. The pD values were taken as the pH meter readings plus the appropriate correction factor for the liquid junction potential given by Fife and Bruice[75].

$$\mathrm{pD} = \mathrm{pH}_{\text{meter reading}} + \frac{14.29 \times 10^{2}}{{}^{\circ}\mathrm{K}} - 1.04$$

At 25° $\mathrm{pD} = \mathrm{pH}_{\text{meter reading}} + 0.40$

Values of pOD at 25° were calculated from pD using a value of $\mathrm{p}K_{D_2O} = 14.81$[76,77]. Deuteroxide concentrations were obtained from pOD using a value of 0.772 for the mean molar activity coefficient at 25° and $I = 0.1M$. A recent study has confirmed that at low ionic strengths the activity coefficients of alkali metal deuteroxides in D_2O are closely comparable with those of the corresponding alkali metal hydroxides in H_2O[78].

Deuterium oxide (99.8%) was supplied by Fluorochem Ltd. Pipes and Hepes were B.D.H. biochemical reagents.

Morpholine (b.p. 128°) and triethylamine (b.p. 89°) were redistilled prior to use.

Zinc(II) perchlorate hexahydrate was prepared by reaction of perchloric acid with basic zinc carbonate and its solutions were standardized by E.D.T.A. titration. All other metal salts were AnalaR grade.

4.2.2 pK_a Measurements

The pK_a (phenolic group ionization) of 2-carbomethoxy-8-quinolinol was determined spectrophotometrically at 25° and I = 0.1M by the method of Albert and Serjeant[22].

Measurements were made by mixing a solution of the ester with an equal volume of the appropriate buffer and recording the absorbance of the resultant solution at 399 nm. Hydrolysis of the substrate was negligible in the time scale (~20 seconds) of the measurement except in the case where the solution pH was sufficiently high (>11.5) to fully generate the ester anion. Here the hydrolysis problem was overcome by the choice of the analytical wavelength; an isosbestic point for the conversion of the ester anion to the corresponding carboxylate dianion.

Relevant experimental data is tabulated in Appendix 3.2. The mean value of the pK_a^M was 9.25 ± 0.03.

The proton ionization constant for dissociation of the conjugate base (NH^+ ionization) was not determined with precision. Spectroscopic measurements indicated ca. 50% protonation of the quinolyl nitrogen in 0.3M hydrochloric acid at 25°.

4.2.3 Formation Constants

Values of K_{ME^+} for the formation of the metal ion ester complexes (M = Mn, Zn and Ni) in aqueous solution were obtained by spectrophotometric titration of solutions 3.0×10^{-5}M in 2-carbomethoxy-8-quinolinol and $2-8 \times 10^{-3}$M in metal ion over the pH range 3.4 to 6.5 at 25 ± 0.5° and I = 0.1M ($NaClO_4$). Under these conditions only the 1:1 complexes (ME^+) are formed and any uncomplexed ester is present as the neutral form, EH(λ_{max} 254 nm, $\varepsilon = 4.2 \times 10^4$ dm^3 mol^{-1} cm^{-1}). The 1:1 complexes with manganese(II), zinc(II) and nickel(II) all have λ_{max} 275 ± 1 nm and extinction coefficients, ε_{max}, of 3.3×10^4, 3.1×10^4 and 3.2×10^4 dm^3 mol^{-1} cm^{-1} respectively.

The stability constants, K_{ME^+} refer to the equilibrium

$$M^{2+} + E^- \rightleftharpoons ME^+$$

where $$K_{ME^+} = \frac{[ME^+]}{[M^{2+}][E^-]} \quad .....(12)$$

$$= \frac{[ME^+] . a_{H^+}}{K_a^M [EH][M^{2+}]} \quad .....(13)$$

and K_a^M is the proton ionization constant for the ionization of the phenolic proton. The concentration ratios, $[ME^+]/[EH]$ were obtained from measurements at 275 nm with the use of the measured extinction coefficients of the metal ion-ester complexes and the extinction coefficient of EH ($\varepsilon = 3.2 \times 10^3$ dm^3 mol^{-1} dm^{-1}) at this wavelength. Hydrolysis of NiE^+ was troublesome above pH 6. In this case the concentration ratios were estimated from spectra extrapolated to zero time and were related to K_{NiE^+} through equation (13).

The constants K_{NiE^+} and K_{CoE^+} were also obtained at 25^o and I = 0.1M by the use of a kinetic method of which details are given in the following section. The formation constants obtained in these investigations are given below.

Complex	K_{ME^+}/dm^3 mol^{-1}	
MnE$^+$	$(4.9 \pm 0.4) \times 10^4$	
ZnE$^+$	$(3.8 \pm 0.4) \times 10^6$	
NiE$^+$	$(5.3 \pm 0.4) \times 10^{5*}$	$(5.9 \pm 0.5) \times 10^5$
CoE$^+$	$(3.4 \pm 0.2) \times 10^{5*}$	

* Kinetically determined. All other values determined spectrophotometrically.

No attempt was made to accurately determine the constant for formation of CuE$^+$ since this species underwent hydrolysis rapidly even below pH 5. Kinetic measurements made at pH 5.6 suggested that in the presence of 4.0×10^{-4}M copper(II) at 25^o and I = 0.1M the fraction of ester (initial concentration 3.3×10^{-5}M) present as the complexed form (CuE$^+$) was at least 0.95. From these data the value of K_{CuE^+} can be calculated as being greater than 2×10^8 dm^3 mol^{-1}.

4.3 Results

4.3.1 Base Hydrolysis

In the pH range 9.2 to 12.2 the rate law for the hydrolysis of 2-carbomethoxy-8-quinolinol takes the form:

$$\text{rate} = k_{obs}[\text{Total Ester}] \qquad .....(14)$$

$$= k_{obs}([EH] + [E^-]) \qquad .....(15)$$

$$= k_{EH}[EH][OH^-] + k_{E^-}[E^-][OH^-] \qquad .....(16)$$

where EH and E^- represent the un-ionized and phenolic group ionized forms of the ester respectively. The concentration of E^- may be expressed as:

$$[E^-] = K_a^M.[EH]/a_{H+} \qquad .....(17)$$

Substitution for the concentration of E^- in both (15) and (16) by use of equation (17), and equating the resultant expressions gives (18).

$$k_{obs}/[OH^-].(a_{H+} + K_a^M) = k_{EH}.a_{H+} + k_{E^-}.K_a^M \qquad .....(18)$$

Equation (18) is of the form y = ax + b. Hence a plot of a_{H+} against $k_{obs}[OH^-].(a_{H+} + K_a^M)$ will be linear, of slope k_{EH} and intercept $k_{E^-}.K_a^M$. The kinetic data obtained at 25° and I = 0.1M (Table 6) was plotted out according to equation (18) and yielded $k_{EH} = 4.0$ dm^3 mol^{-1} s^{-1} and $k_{E^-} = 0.485$ dm^3 mol^{-1} s^{-1}. The tabulated data include both the observed first order rate constants and those calculated by use of equation (16).

The second term in the right hand side of equation (16) can only be interpreted as arising from a specific base catalysed reaction on E^-. The term involving k_{EH} is assigned to a specific base catalysed reaction on EH rather than the kinetically equivalent, pH independent reaction of E^-. In the latter case the ionized phenolic group appears too far

Table 6

Rate Constants for the Base Catalysed Hydrolysis of 2-Carbomethoxy-8-hydroxyquinoline at 25.0 and I = 0.1M (KCl)

pH	$10^4\ k_{obs}/s^{-1}$	$10^4\ k_{calc}^{a}/s^{-1}$
9.185[b]	0.447	0.447
9.610[b]	0.753	0.787
9.980	1.27	1.27
10.360	2.10	2.22
10.715	4.20	4.00
11.095	8.78	8.33
11.490	18.3	19.8
11.895[c]	48.7	49.2
12.195[c]	97.2	97.3

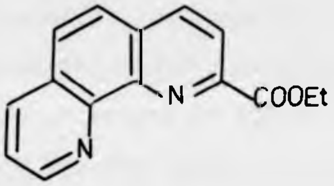
[a] Calculated according to equation (6). Reaction media 10^{-2}M in triethylamine buffer unless otherwise stated

[b] Reaction media 10^{-2}M in borate buffer

[c] Sodium hydroxide solution

removed from the reaction centre to influence the reaction rate by any reasonable mechanism featuring intramolecular catalysis.

Consistent with the proposed scheme is the observation that k_{EH} is 1.9 times larger than the second order rate constant obtained for the base catalysed hydrolysis of 2-carbethoxy-1,10-phenanthroline (k_{OH} = 2.1 $dm^3\ mol^{-1}\ s^{-1}$, 25°)[79]. Steric and electronic effects at carbonyl carbon should be similar for the 2-carbalkoxy derivatives of both



8-hydroxyquinoline and 1,10-phenanthroline. The observed rate ratio is expected on the basis of the increased +I effect of the $-CH_3$ group relative to the $-CH_2CH_3$[80]. Methyl esters are normally found to undergo base hydrolysis ca. twice as fast as the corresponding ethyl esters[81].

Pathways for the base hydrolysis of 2-carbomethoxy-8-quinolinol at 25° are summarized in Scheme 2.

Scheme 2

$$\begin{tikzcd}
EH_2^{+} \arrow[d, leftrightharpoons, "pK_a\ \sim 0.3"'] & & \\
EH \arrow[d, leftrightharpoons, "pK_a\ = 9.36"'] \arrow[rr, "k_{OH} = 4.0", "OH^-"'] & & AH^- + CH_3OH \arrow[d, leftrightharpoons] \\
E^- \arrow[rr, "k_{OH} = 0.485", "OH^-"'] & & A^{2-} + CH_3OH
\end{tikzcd}$$

(A^{2-} = The dianion of 2-carboxy-8-quinolinol)

4.3.2 Metal Ion Catalysed Hydrolysis

In the presence of divalent metal ions 2-carbomethoxy-8-quinolinol is hydrolysed rapidly to the corresponding acid in near neutral solution. The dependence of the reaction rate on the concentrations of cobalt(II) and nickel(II) has been studied spectrophotometrically at 25° and I = 0.1M ($NaClO_4$) using Hepes as a buffering medium. At a constant pH the hydrolysis rate of the ester increased with increasing metal ion concentration of the reaction medium, ultimately reaching a plateau. The limiting rate, where the kinetics become zero order in the metal ion concentration, represents the hydrolysis rate of the fully complexed substrate, ME^+ (metal ion:ligand ratios in excess of 500:1). Typical pseudo first order plots for the hydrolyses are given in Figure 2.

Generally, the total concentration of Hepes was comparable with that of the metal ions. However, even when relatively large buffer:metal ion ratios were employed (for example, up to 50:1 in certain of the nickel(II) catalysed reactions) no detectable buffer effects were observed. This finding implies negligible binding between the buffer base and both cobalt(II) and nickel(II) under the conditions of the kinetic measurements. Removal of free M^{2+} in solution through complexation with buffer species should significantly decrease the observed hydrolysis rate of the ester since the equilibrium $M^{2+} + E^- \rightleftharpoons ME^+$ would be perturbed. Goode et al.[82] have investigated complex formation between various metal ions with both Pipes and Hepes. A potentiometric study indicated that neither copper(II), manganese(II), calcium(II) or magnesium(II) were significantly bound by either of the buffer base species under the conditions of measurements.

In the present investigation the metal ion catalysed reactions were studied using Hepes (nickel(II), cobalt(II) and manganese(II) catalysed hydrolyses) and Pipes (copper(II) and zinc(II) catalysed hydrolyses) as buffering agents. Buffer effects were absent in all cases.

Below pH 7.25 all of the uncomplexed ester ($pK_a^M = 9.25$) is present as EH which is hydrolysed negligibly slowly in neutral or slightly acidic solution. On the assumption that 1:1 complexes only are formed, the rate law for the metal ion catalysed hydrolyses may be written as

$$\text{rate} = k_{obs}([ME^+] + [EH]) \qquad .....(19)$$

$$= k_{lim}[ME^+] \qquad .....(20)$$

where k_{lim} is the pseudo first order rate constant for the reaction of the fully complexed substrate at a particular pH. Equating (19) with (20) gives on rearrangement the concentration ratio, $[ME^+]/[EH]$.

$$\frac{[ME^+]}{[EH]} = \frac{k_{obs}}{k_{lim} - k_{obs}} \qquad .....(21)$$

An expression for the kinetically determined formation constant may then be obtained by substitution for the concentration ratio into equation (13), i.e.

$$K_{ME^+} = \frac{k_{obs}}{(k_{lim} - k_{obs})} \cdot \frac{a_{H^+}}{K_a^M[M^{2+}]} \qquad .....(22)$$

Kinetic analysis of the data obtained for the cobalt(II) and nickel(II) catalysed hydrolyses according to equation (22) gives the respective values of K_{CoE^+} and K_{NiE^+} as $(3.4 \pm 0.2) \times 10^5$ and $(5.3 \pm 0.4) \times 10^5$ dm^3 mol^{-1} at 25° and I = 0.1M, Table 7.

Similar attempts to equate rate with equilibrium data in the case of the copper(II) catalysed hydrolysis were unsuccessful. Full complexation of the ester was achieved at pH 5.62 and 25° when relatively low copper(II) to ligand ratios were employed (i.e. the observed hydrolysis rates were independent of the copper(II) concentration of the reaction medium when the metal ion was present in greater than a 12 fold excess over the substrate), Table 8. When even lower metal ion to ligand ratios were used plots of $\log[OD_\infty - OD_t]$ against time deviated from linearity. This feature of the reaction is most likely attributable to one of two effects.

(i) CuEAH is generated in appreciable concentration as the reaction proceeds (AH^- = 8-hydroxyquinolin-2-carboxylate anion).

or

(ii) The copper(II)-ester equilibrium is increasingly perturbed when copper(II) is bound as $CuAH^+$ or CuA.

The manganese(II) catalysed reaction was studied at pH 7.88 (25°, I = 0.1M) using an initial ester concentration of 3.3×10^{-5}M. Increases in the metal ion concentration of the reaction media from 5×10^{-3}M to 3.0×10^{-2}M increased the fraction of ester present as MnE^+ from 0.92 to 0.984. Here the fractions have been calculated by use of the spectrophotometrically determined value of $K_{MnE^+} = (4.9 \pm 0.4) \times 10^4$ dm^3 mol^{-1} at 25° and I = 0.1M. The first order rate constants observed as a function of the concentration of

Fig 2 PSEUDO FIRST ORDER KINETIC PLOTS FOR THE METAL ION CATALYSED HYDROLYSIS OF 2-CARBOMETHOXY-8-QUINOLINOL, 25°, I=0.1M.

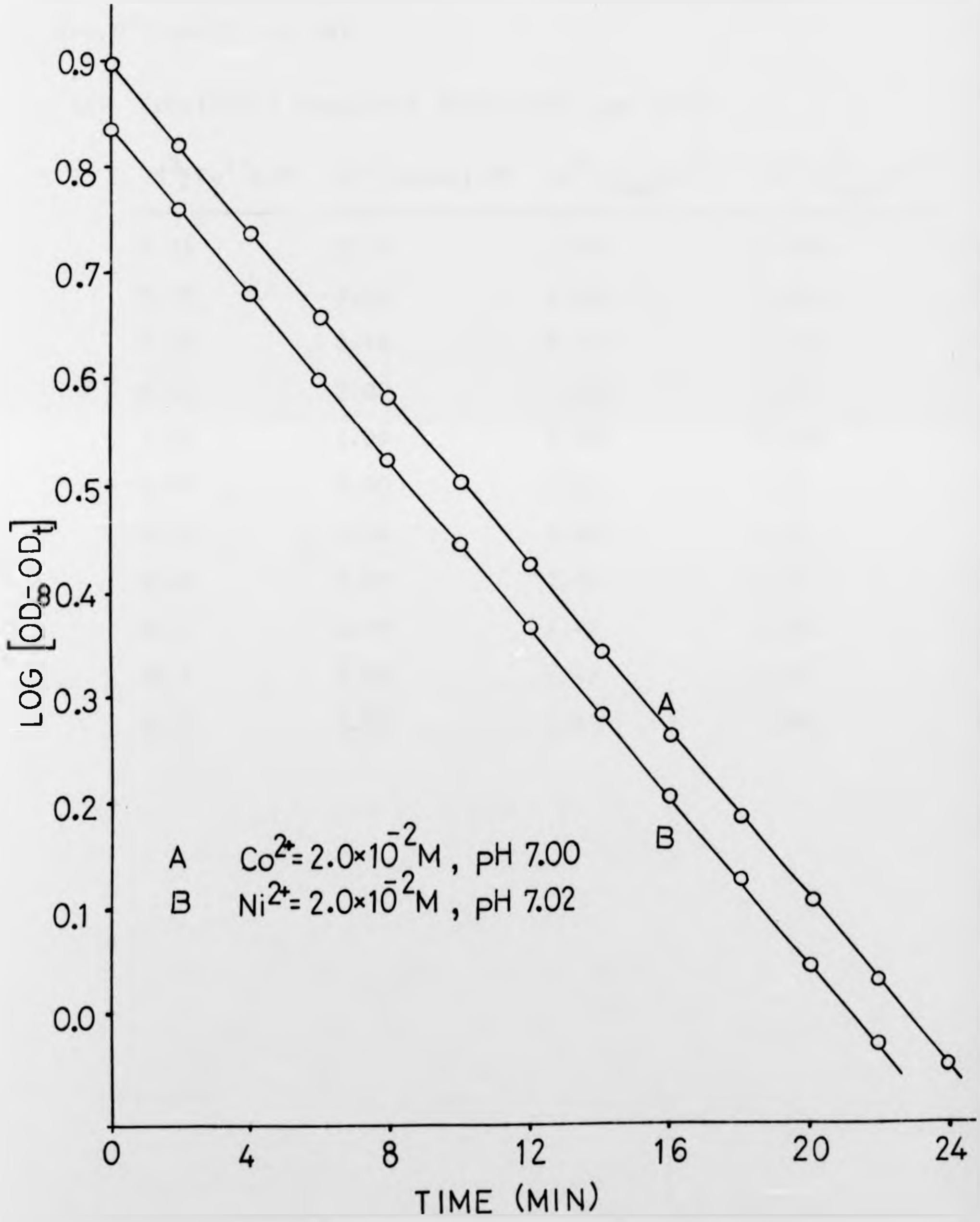


Table 7

The Nickel(II) and Cobalt(II) Perchlorate Catalysed Hydrolyses of 2-Carbomethoxy-8-quinolinol[a]. Metal-ion Dependence (25.0°C and I = 0.1M)

(i) Cobalt(II) Catalysed Hydrolysis, pH 7.005

$10^3[Co^{2+}]/M$	$10^2[Hepes]/M$	$10^3\ k_{obs}/s^{-1}$	$10^3\ k_{calc}$[b]$/s^{-1}$
0.15	0.50	0.381	0.342
0.30	0.50	0.547	0.558
0.60	0.50	0.797	0.817
0.60	1.00	0.815	0.817
1.00	1.00	0.959	0.100
2.00	1.00	1.13	1.21
5.00	1.00	1.34	1.38
10.0	1.00	1.39	1.44
20.0	1.00	1.44	1.48
20.0	2.00	1.48	1.48
30.0	1.00	1.52	1.49

Table 7 (cont.)

(ii) Nickel(II) Catalysed Hydrolysis, pH 7.020

$10^3[Ni^{2+}]$/M	10^2[Hepes]/M	10^3 k_{obs}/s^{-1}	10^3 k^c_{calc}
0.10	0.50	0.365	0.338
0.20	0.50	0.590	0.546
0.20	1.00	0.570	0.546
0.30	1.00	0.633	0.686
0.40	1.00	0.725	0.788
0.50	1.00	0.837	0.862
1.00	1.00	1.08	1.07
2.00	1.00	1.16	1.22
4.00	1.00	1.32	1.31
6.00	1.00	1.36	1.35
10.0	1.00	1.44	1.38
10.0	2.00	1.40	1.38
20.0	1.00	1.44	1.40

[a] Initial concentration of ester lay in the range 1.0-5 x 10^{-5} M. Supporting electrolyte was $NaClO_4$.

[b] Values of k_{calc} obtained assuming k_{lim} = 1.52 x 10^{-3} s^{-1} at pH 7.005 and for K_{CoE^+} = 3.4 x 10^5 $dm^3 mol^{-1}$

[c] Values of k_{calc} obtained assuming k_{lim} = 1.42 x 10^{-3} s^{-1} at pH 7.02 and for K_{NiE^+} = 5.3 x 10^5 $dm^3 mol^{-1}$.

Table 8

The Copper(II) Perchlorate, Manganese(II) Chloride and Zinc(II) Perchlorate Catalysed Hydrolyses of 2-Carbomethoxy-8-quinolinol. Metal-Ion Dependence[a].

(i) Copper(II) Dependence[b], pH 5.616, 25°

$10^4[Cu^{2+}]/M$	$10^3\ k_{obs}/s^{-1}$
4.00	3.30
6.00	3.33
8.00	3.32

(ii) Manganese(II) Dependence[c], pH 7.88, 25°

$10^2[Mn^{2+}]/M$	$10^4\ k_{obs}/s^{-1}$	Fraction MnE^+
0.50	4.63	0.92
1.00	4.74	0.954
1.00	4.81	0.954
1.50	4.83	0.969
2.00	4.90	0.976
3.00	4.81	0.984

(iii) Zinc(II) Dependence[b], pH 6.13, 35°

$10^2[Zn^{2+}]/M$	$10^4\ k_{obs}/s^{-1}$
0.50	1.93
1.00	1.92
1.50	1.95

[a] At I = 0.1M ($NaClO_4$). Initial ester concentration 3.3×10^{-5}M.

[b] Solutions 5×10^{-3}M in Pipes

[c] Solutions 5×10^{-3}M in Hepes

manganese(II) are included in Table 8 and reflect the degree of complexation of the substrate.

The dependence of the reaction rate on the concentration of zinc(II) was studied at 35° rather than at 25° as at the latter temperature the rates of hydrolysis, observed under conditions where precipitation of zinc(II) hydroxide was not a problem, were particularly slow. At pH 6.135 essentially constant values of k_{obs} were obtained when the zinc(II) concentration was increased from 5×10^{-3} to 1.5×10^{-2}M, Table 8.

pH Dependence

The pH dependence of the hydrolysis of the metal ion-ester complexes (M = Cu, Ni, Co and Mn) was studied at 25° and I = 0.1M. Reaction conditions were such that throughout the pH range of the investigations at least 97% complexation of the substrate (calculated from the values of the appropriate formation constants) was realized for the cobalt(II), nickel(II) and manganese(II) promoted reactions. The copper(II) promoted hydrolysis was studied using a metal ion concentration of 4.0×10^{-4}M.

For a given complex the pH range of the investigation extended over ca. 1 pH unit. All hydrolyses exhibited a first order dependence on hydroxide ion concentration as indicated by sensibly constant values of k_{OH} ($= k_{obs}/[OH^-]$).

Provided the concentration of metal ion was sufficiently high to ensure full complexation of the substrate constant values of k_{OH} were also observed in the zinc(II) promoted reaction which was studied over the pH range 6.14 to 7.01 at

35°. Above pH 7.1, however, the rates of reaction were higher than those predicted from the rate data obtained at lower concentrations of hydroxide ion. As precipitated zinc(II) hydroxide was not evident in the kinetic solutions the anomalous reactivity was tentatively ascribed to a reaction involving catalysis by a zinc(II)-hydroxo complex but was not investigated further.

Kinetic data obtained from the pH-dependence studies are displayed in Table 9.

A limited study of the hydrolysis of CuE^+, NiE^+ and CoE^+ in D_2O at 25° and I = 0.1M yielded the following results.

Substrate	$[M^{2+}]/M$	pD	$10^3\ k_{obs}/s^{-1}$	$10^7[OD^-]/M$	$10^4\ k_{OD}/$ $dm^3\ mol^{-1}\ s^{-1}$
CuE^+	4.0×10^{-4}	6.850	11.3 ± 0.03	0.142	79.5 ± 2.5
NiE^+	5.0×10^{-3}	8.085	2.51 ± 0.07	2.41	1.04 ± 0.03
CoE^+	2.0×10^{-2}	8.085	3.67 ± 0.10	2.41	1.52 ± 0.05

pH control in these reactions was effected using the buffer systems employed for the corresponding studies in H_2O. Quoted rate constants are mean values (errors ±3%) derived from duplicate determinations.

Temperature Dependence

The results from the temperature dependence studies of both metal ion promoted and unpromoted hydrolyses (base hydrolysis of E^- only) are given in Table 10. In the case of the former reactions sufficient metal ion was present in the kinetic solutions to ensure that the ester was present exclusively as the 1:1 complex. The reported rate constants

Table 9

The Metal Ion Promoted Hydrolysis of 2-Carbomethoxy-8-quinolinol. pH Dependence[a] (I = 0.1M)

(i) Copper(II) Promoted Hydrolysis[a], 25.0°

pH	$10^3\ k_{obs}/s^{-1}$	$10^9[OH^-]/M$	$10^{-5}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
5.615	3.30	5.34	6.18
5.850	5.98	9.18	6.51
6.120	10.8	17.1	6.32
6.240	14.4	22.5	6.40
6.390	19.8	31.7	6.26
6.48	25.0	39.1	6.40

(ii) Nickel(II) Promoted Hydrolysis[b], 25.0°

pH	$10^3[Ni^{2+}]/M$	$10^3\ k_{obs}/s^{-1}$	$10^7[OH^-]/M$	$10^{-4}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
7.020	10.0	1.42	1.36	1.04
7.460	10.0	4.02	3.74	1.07
7.740	5.0	7.42	7.45	0.96
7.930	3.0	11.1	11.0	1.01
8.070	2.0	15.3	15.3	1.00
8.340	1.0	30.0	28.4	1.06

(iii) Cobalt(II) Promoted Hydrolysis[c], 25.0°

pH	$10^3[Co^{2+}]/M$	$10^3\ k_{obs}/s^{-1}$	$10^7[OH^-]/M$	$10^{-4}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
7.005	30.0	1.52	1.31	1.15
7.310	20.0	3.03	2.64	1.14
7.500	10.0	4.49	4.09	1.10
7.720	5.0	7.35	6.79	1.08
8.035	3.0	15.3	14.0	1.09

Table 9 (cont.)

(iv) Manganese(II) Promoted Hydrolysis[d], 25°

pH	$10^3[Mn^{2+}]$/M	$10^3\ k_{obs}/s^{-1}$	$10^6[OH^-]$/M	$10^{-2}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
7.880	20.0	0.483	0.983	4.91
8.080	15.0	0.716	1.55	4.62
8.265	10.0	1.20	2.38	5.04
8.390	5.0‡	1.56	3.17	4.92
8.565	5.0‡	2.40	4.75	5.05

(v) Zinc(II) Promoted Hydrolysis[e], 35°

pH	$10^3[Zn^{2+}]$/M	$10^4\ k_{obs}/s^{-1}$	$10^8[OH^-]$	$10^{-3}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
6.14	15.0	1.95	3.69	5.29
6.37	6.0	3.18	6.38	4.98
6.52	3.0	4.51	8.93	5.05
6.78	3.0	8.19	16.4	4.99
7.01	2.0	1.42	27.9	5.10

[a] Solutions 4×10^{-4}M in $Cu(ClO_4)$, 10^{-2}M in Pipes. Initial ester conc. 2.1×10^{-5}M, $\lambda = 268$ nm

[b] Solutions 10^{-2}M in Hepes. Initial ester conc. 3.3×10^{-5}M, $\lambda = 270$ nm

[c] Solutions 10^{-2}M in Hepes. Initial ester conc. 4.2×10^{-5}M, $\lambda = 275$ nm

[d] Solutions buffered with 10^{-2}M Hepes except for those designated ‡ where morpholine (5×10^{-3}M) was used to effect pH control. Initial ester conc. 3.3×10^{-5}M, $\lambda = 275$ nm

[e] Solutions 5×10^{-3}M in Pipes. Initial ester conc. 3.3×10^{-5}M, $\lambda = 266$ nm

Table 10

The Metal Ion Promoted and Unpromoted Base Hydrolysis of 2-Carbomethoxy-8-quinolinol. Temperature Dependence (I = 0.1M)[a].

(i) Copper(II) Promoted Hydrolysis[b]

Temp/°C	pH	$10^2\ k_{obs}/s^{-1}$	$10^8[OH^-]/M$	$10^{-5}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
15.0	5.890	0.169	0.452	3.74
25.0	5.820	0.552	0.856	6.44
35.0	5.750	1.51	1.53	9.89

(ii) Nickel(II) Promoted Hydrolysis[c]

Temp/°C	pH	$10^3\ k_{obs}/s^{-1}$	$10^7[OH^-]/M$	$10^{-4}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
15.0	7.100	0.497	0.725	0.684
25.0	6.980	1.31	1.24	1.06
35.0	6.860	3.24	1.97	1.65

(iii) Cobalt(II) Promoted Hydrolysis[d]

Temp/°C	pH	$10^3\ k_{obs}/s^{-1}$	$10^7[OH^-]/M$	$10^{-4}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
15.0	7.490	1.11	1.46	0.587
25.0	7.360	3.22	2.29	1.08
35.0	7.230	8.41	3.55	1.82

(iv) Manganese(II) Promoted Hydrolysis[e]

Temp/°C	pH	$10^4\ k_{obs}/s^{-1}$	$10^6[OH^-]/M$	$10^{-2}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
15.0	8.170	2.19	0.861	2.54
25.0	8.055	7.43	1.48	5.03
35.0	7.930	23.3	2.32	10.0

Table 10 (cont.)

(v) Zinc(II) Promoted Hydrolysis[f]

Temp/°C	pH	$10^4\ k_{obs}/s^{-1}$	$10^7[OH^-]/M$	$10^{-3}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
15.0	6.980	0.614	0.550	1.12
25.0	6.890	2.58	1.005	2.57
35.0	6.810	8.91	1.757	5.07
45.0	6.730	29.6	2.801	10.6

(vi) Unpromoted Hydrolysis in 10^{-2}M NaOH[g]

Temp/°C	$10^3\ k_{obs}/s^{-1}$	$k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
15.0	2.32	0.232
25.0	4.80	0.480
35.0	9.02	0.902

[a] Supporting electrolyte $NaClO_4$ unless otherwise stated. Initial concentrations of ester and monitoring wavelengths were identical with those used in the pH dependence studies.

[b] Solutions 4×10^{-4}M in $Cu(ClO_4)_2$ and 5×10^{-3}M in Pipes.

[c] Solutions 10^{-2}M in $Ni(ClO_4)_2$ and 10^{-2}M in Hepes.

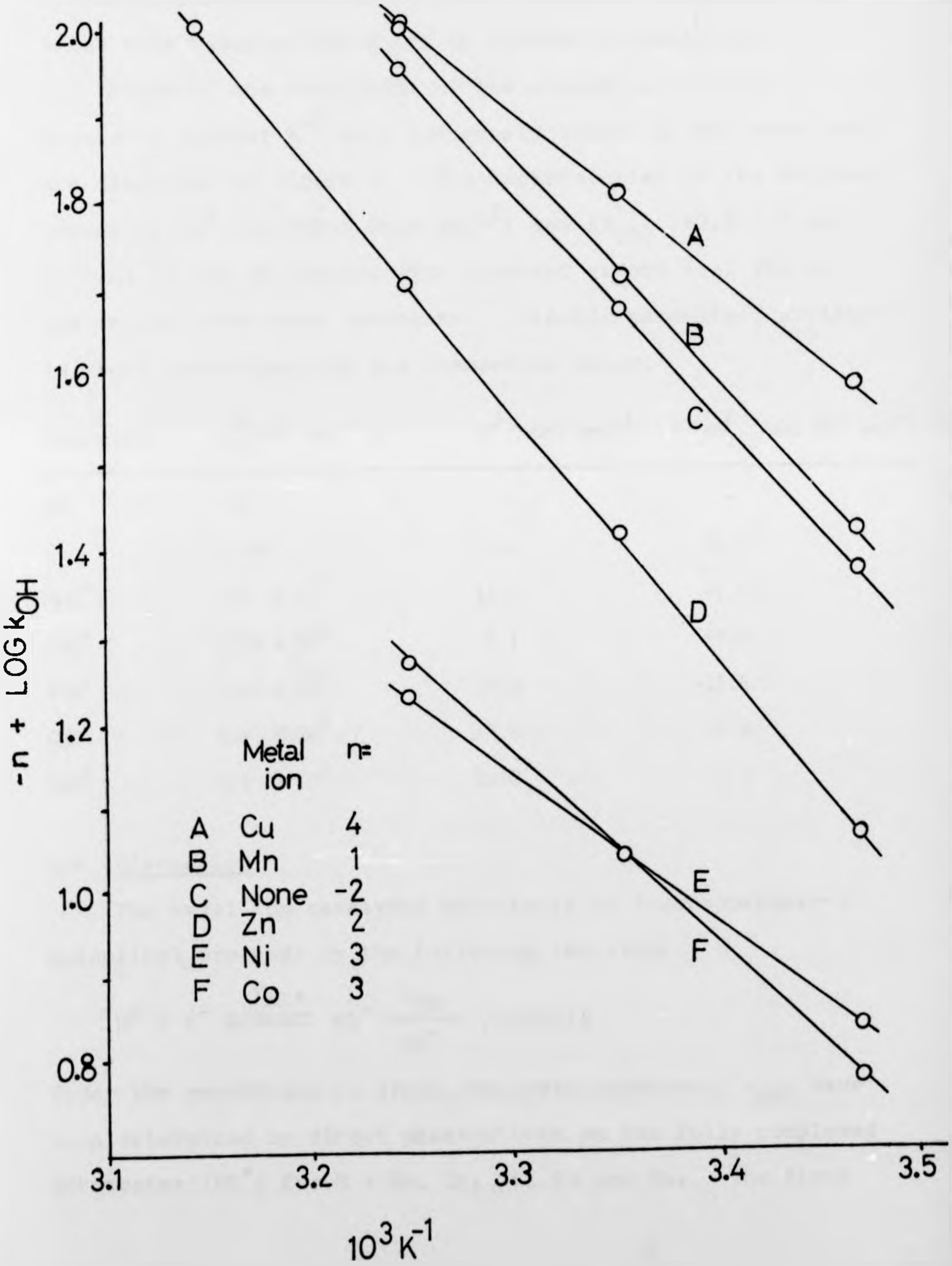
[d] Solutions 2.0×10^{-2}M in $Co(ClO_4)_2$ and 10^{-2}M in Hepes.

[e] Solutions 10^{-2}M in $MnCl_2$ and 5×10^{-3}M in morpholine.

[f] Solutions 3×10^{-3}M in $Zn(ClO_4)_2$ and 5×10^{-3}M in Pipes.

[g] Supporting electrolyte KCl.

Fig 3 ARRHENIUS PLOTS FOR THE BASE CATALYSED HYDROLYSIS OF 2-CARBOMETHOXY-8-QUINOLINATE SPECIES.



are mean values calculated from data obtained from a minimum of 2 kinetic runs. No attempt was made to determine Arrhenius parameters for the base catalysed hydrolysis of EH, since this reaction could not be studied in isolation.

Plots of the logarithms of the second order rate constants against K^{-1} were accurately linear in all cases and are displayed in Figure 3. The uncertainties in the derived values of $\Delta H^{\ddagger}$ ($\pm$0.3-0.4 kcal mol^{-1}) and $\Delta S^{\ddagger}_{298}$ ($\pm$0.8-1.5 cal K^{-1} mol^{-1}) are in keeping with observed errors (ca. 4%) in the second order rate constants. Kinetic parameters obtained in these investigations are summarized below.

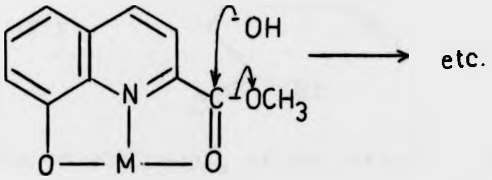
Substrate	k^{25}_{OH}/dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}_{298}$/cal K^{-1} mol^{-1}
EH	4.0	-	-
E^-	0.485	11.4	-21.7
MnE^+	4.9×10^2	11.4	-7.9
CoE^+	1.12×10^4	9.1	-9.5
NiE^+	1.01×10^4	7.3	-15.6
CuE^+	6.3×10^5	7.9	-5.4
ZnE^+	2.6×10^3	13.0	+0.7

4.4 Discussion

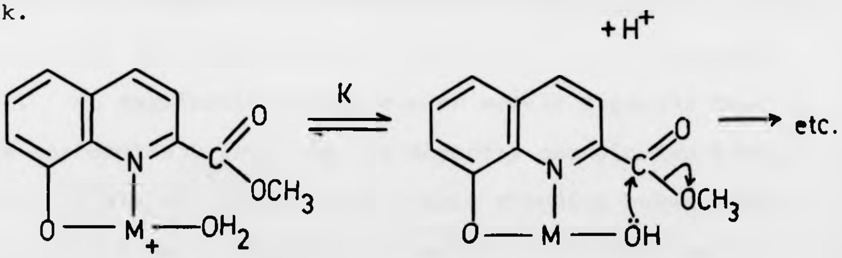
The metal ion catalysed hydrolysis of 2-carbomethoxy-8-quinolinol proceeds by the following two steps.

$$M^2 + E^- \overset{K_{ME^+}}{\rightleftharpoons} ME^+ \xrightarrow[OH^-]{k_{OH}} \text{products}$$

Under the conditions of study, the rate constants, k_{OH}, have been determined by direct observations on the fully complexed substrates (ME^+) for M = Zn, Cu, Ni, Co and Mn. The first order dependence of the hydrolysis rates on the concentration of hydroxide ion may be accounted for by two general mechanisms. The first involves rate determining hydroxide ion attack on the complex where the ester group is coordinated to the metal centre through the carbonyl oxygen.

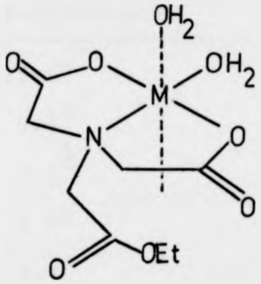


The second mechanism involves the rapid equilibrium formation of a hydroxo complex followed by intramolecular hydroxide ion attack.

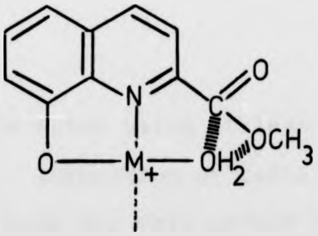


The role for hydroxide ion, whether acting as an intramolecular or intermolecular nucleophile, has not been established in ester hydrolyses catalysed by labile metal ions. Both pathways, however, have been found to be important in the hydrolysis of the complex cis-[Co(en)$_2$BrglyO^{i}Pr].[42] Of particular importance in establishing the route for hydrolysis is to determine whether or not the ester carbonyl group is bonded to the metal ion. N.m.r. and i.r. studies were inconclusive in establishing this point for complexed ethylglycinate-N,N-diacetic acid (XIX)[51]. The carbonyl oxygen of the ester function is not a particularly good donor group; protonation on the weakly basic carbonyl oxygen of uncoordinated esters is

XIX



associated with a pK_a of ca. -6.5[83]. Binding of an ester substrate to an electron withdrawing metal centre would be expected to lower this value somewhat. However, in the 1:1 complexes of 2-carbomethoxy-8-quinolinol the rigidity of the ligand places the ester moiety close to the bound catalytic centre. An examination of molecular models suggests that if the carbomethoxy group is not directly coordinated to the metal ion there would be severe steric crowding between this function and a water molecule normally in the coordination sphere of the metal.



Such a destabilizing effect should be reflected in the stabilities of the 1:1 complexes. The data in Table 11 provide a comparison between the formation constants of the complexes of both ester and parent ligand, 8-quinolinol.

The carbomethoxy group is strongly electron withdrawing and markedly lowers the basicity of the quinolyl nitrogen

Table 11

Metal Ion	Log K_1 8-Quinolinol[a]	log K_1 2-Carbomethoxy-8-quinolinol[b]
Cu^{2+}	12.6[c]	>8.3
Ni^{2+}	9.9[d]	5.7
Co^{2+}	9.1[d]	5.5
Zn^{2+}	8.6[c]	6.6
Mn^{2+}	6.8[d]	4.7
pK_{NH^+}	4.91[e]	<1
pK_{OH}	9.81[e]	9.36

[a] At 20° and $I = 0.01M$ unless otherwise stated

[b] This work, 25° and $I = 0.1M$

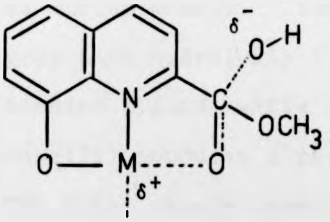
[c] At 20° and $I \rightarrow 0$, ref. 84

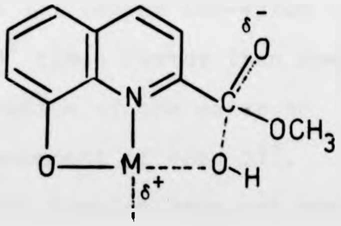
[d] Ref. 85

[e] Ref. 40

atom; the pK_{NH^+} of the ester being at least 4 pK units below that of 8-quinolinol. Inspection of Table 11 shows that when due allowance is made for this effect the formation constants of the metal-ester complexes are not abnormally low. These data suggest, albeit indirectly, that metal-carbonyl bonding may be of importance in the complexes although a detailed i.r. study would be required to confirm this view. It is noted that the thermodynamic stabilities of the zinc(II) and manganese(II) complexes appear least sensitive to the basicity of the nitrogen donor.

It might be hoped that the effect of deuterium oxide on the metal ion catalysed hydrolyses could allow differentiation between the two possible pathways. Unfortunately this is not the case. The kinetic isotope effects are compatible with both mechanisms. The deuterium oxide isotope effect depends on the ground state-transition state free energy differences in H_2O and D_2O. Certainly the ground states for the two mechanisms are identical for one starts with same species. The two transition states are not exactly identical but from the point of view of solvent isotope effects they would appear to give very similar results, for they differ only in the positioning of a single proton.





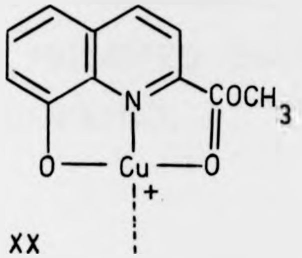
Intuitively, the two pathways should exhibit the same deuterium solvent isotope effect on the grounds that they are identical except that for one a pre-equilibrium step occurs while for the other it does not. The derived values of k_{OH}/k_{OD} for the base catalysed hydrolyses of the copper(II), cobalt(II) and nickel(II) complexes are 0.79, 0.72 and 0.97 respectively. There is some contribution from secondary effects. Not only is hydroxide ion (whether bound or unbound) exchanged for deuteroxide on changing the solvent from H_2O to D_2O, but the hydrogen atoms of water molecules in the coordination spheres of the metal ions are also exchanged for deuterium. A small, but significant, secondary isotope effect has been observed on the dissociation constants of the aquapentaamine cobalt(III) complexes $[Co(NH_3)_5(OD_2)]^{3+}$ and $[Co(ND_3)_5(OD_2)]^{3+}$ which arises from the exchange of the 15 ammine hydrogens[86].

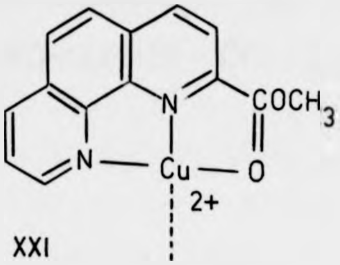
In the present study it appears that secondary effects are also small. For hydroxide ion catalysed hydrolyses of organic substrates the ratio k_{OH}/k_{OD} has been found to vary from 0.71 to 0.83[87].

The order of decreasing reactivity of the various 2-carbomethoxy-8-quinolinate species toward nucleophilic attack by hydroxide ion at 25° is: $CuE^+ > CoE^+ \sim NiE^+ > ZnE^+ > MnE^+ > EH > E^-$. Furthermore, the catalytic effect of the metal centres varies widely. Thus, the 1:1 copper ion-ester complex undergoes base hydrolysis 1.3×10^6 times faster than does the deprotonated ligand, while coordination of the ester to manganese(II) produces a rate enhancement of some 10^3.

The total charge carried by the complex does not appear to be the major factor in determining the hydrolysis rates. At 25° the copper(II)-2-carbomethoxy-8-quinolinate complex (XX), which carries a single positive charge, undergoes base hydrolysis ($k_{OH} = 6.3 \times 10^5$ dm^3 mol^{-1} s^{-1}) faster than the corresponding 2-carbethoxy-1,10-phenanthroline complex (XXI) which carries a dipositive charge ($k_{OH} = 5 \times 10^5$ dm^3 mol^{-1} s^{-1})[79].

If the charge carried by the complex were of primary importance it would be expected that the latter species should hydrolyse much the faster of the two. Further, if the reaction proceeded via the intramolecular pathway the predicted order of

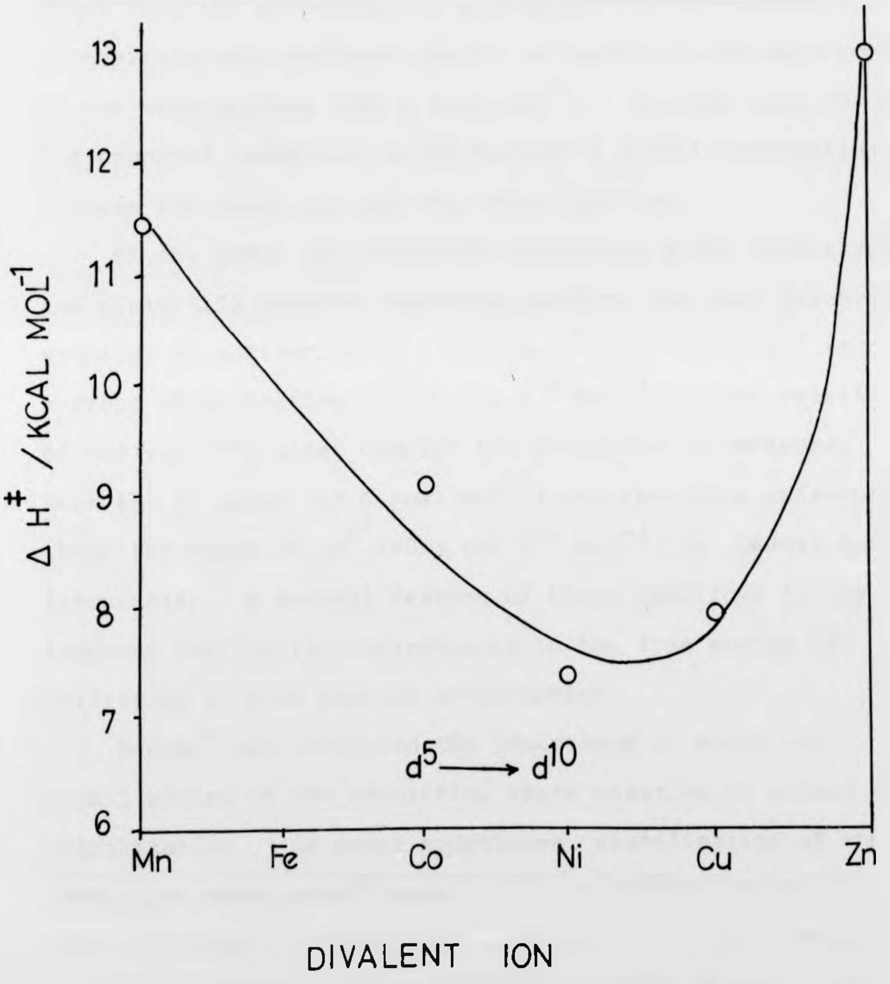

XX


XXI

reactivity of the metal ion-2-carbomethoxy-8-quinolinate complexes (based on the K_a values for the ionization of the aqua-ions[44], $M(H_2O)_n^{2+} \rightleftharpoons M(H_2O)_{n-1}(OH)^+ + H^+$) would be $CuE^+ > ZnE^+ \sim CoE^+ > NiE^+ \sim MnE^+$ which is markedly different from that observed.

Arrhenius parameters for the hydrolysis of the ester species reveal that the rate enhancements in the metal ion promoted reactions arise from more positive values of $\Delta S^{\ddagger}$, and in general, lower enthalpies of activation. Base hydrolysis of the deprotonated ligand, E^-, has $\Delta H^{\ddagger} = 11.4$ kcal mol^{-1} and $\Delta S^{\ddagger} = -21.7$ cal K^{-1} mol^{-1}. Here the large negative entropy of activation is typical of a bimolecular reaction where two anions come together and give rise to a transition state in which more solvent molecules are restricted than in the initial state[88]. In Figure 4 the values of $\Delta H^{\ddagger}$ calculated for the metal ion promoted hydrolyses are plotted out for the various metal centres. When the catalytic centres are small, and when the nuclear charge is not well shielded by the d-orbital electrons (i.e. for $Cu^{2+}(d^9)$, $Ni^{2+}(d^8)$ and $Co^{2+}(d^7)$), the enthalpies of activation are significantly lower than when the catalytic centre is larger, possesses spherical symmetry, and where the nuclear charge is presumably better shielded by the d-electrons[89] (i.e. for $Mn^{2+}(d^5)$ and

Fig 4 ENTHALPIES OF ACTIVATION FOR THE METAL ION PROMOTED BASE HYDROLYSIS OF 2-CARBOMETHOXY-8-QUINOLINOL.



$Zn^{2+}(d^{10})$). These date are consistent with a pathway involving metal-ion carbonyl bonding in the ground state of the reaction, since the former ions should be better able to polarize the carbonyl-oxygen bond and hence lower the energy barrier for nucleophilic attack. Hay and Morris[55] have found that the enthalpies of activation for the hydrolyses of uncomplexed and complexed species of methyl-2,3-diaminopropionate do not vary by more than 1 kcal mol^{-1}. In this case the metal ion promoted reactions do not feature a direct interaction between the metal ion and the ester function.

Of the metal ion catalysed hydrolyses under investigation the nickel(II) promoted reaction exhibits the most favourable enthalpy of activation (7.3 kcal mol^{-1}) but the least favourable entropy of activation (-15.6 cal K^{-1} mol^{-1}). For reaction of the zinc(II)-ester complex the situation is reversed. Here $\Delta H^{\ddagger}$ is large (13.0 kcal mol^{-1}) and therefore unfavourable, while the value of $\Delta S^{\ddagger}$ (+0.7 cal K^{-1} mol^{-1}) is clearly most favourable. A general feature of these reactions is the tendency for the two contributors to the free energy of activation to give partial compensation.

Bender[2] has discussed the importance of metal ion stabilization of the transition state relative to ground state stabilization. In ester hydrolyses, stabilization of the transition state would appear to be of primary importance when the metal ion can interact directly with the developing negative charge on the potential carboxylate group. The metal ion may then be regarded as "solvating" the transition state. The bimolecular reaction of a positively charged 2-carbomethoxy-8-quinolate complex with hydroxide ion should give rise to a charge neutral transition state where less solvent is restricted than in the initial state. In this case a more positive entropy of activation for hydrolysis would be observed than for the unpromoted reaction. This is in agreement with the present results. Furthermore, where a strong interaction occurs between the catalytic centre and the ester function in the ground state of the reaction (as has been postulated for the nickel(II) catalysed hydrolysis) desolvation would be less extensive than for the case where the ester group can gain coordination in the transition state (as may be presumed to occur for the zinc(II) catalysed hydrolysis). The general trends in the entropies of activation for the metal ion promoted hydrolyses may be accounted for by these considerations.

The reactivity of the metal ion-ester complexes toward nucleophilic attack appears to be determined primarily by the factors discussed above. Although other complex and related effects, such as ligand field stabilization of the ground states and transition states, might be expected to be of importance these are not dominant. In this context it may be noteworthy that catalysis in this system is not restricted solely to transition metal ions. In the presence of magnesium(II) 2-carbomethoxy-8-quinolinol is hydrolysed rapidly at pH 7.5.

5. THE HYDROLYSIS OF 8-ACETOXY-2-CARBOXYQUINOLINE

5.1 Experimental

5.1.1 Kinetic Measurements

The hydrolysis of the ester was studied in aqueous media at an ionic strength of 0.1M ($NaClO_4$).

In most cases kinetic measurements were carried out using either a Unicam SP500 spectrophotometer with a Gilford 222 modification or a Gilford 2400S instrument. Reactions too fast to be monitored by conventional spectrophotometric methods were studied using a Canterbury SF3A stopped-flow instrument coupled with a Cossor CDU 110C oscilloscope.

Solutions of the ester (10^{-2}M) were prepared in dry acetonitrile and stored at -10° until required. Runs monitored by conventional spectrophotometry were initiated by the addition of the ester stock solution (10 μl) to the appropriate temperature equilibrated reaction medium (3.0 cm^3) contained in a 1 cm pathlength cell. The cell contents were then mixed and the reaction followed for at least 4 half lives. Conditions were such that pseudo first order kinetics were observed in all cases.

The base catalysed hydrolysis was followed at 268 nm (λ_{max} for the dianion derived from 2-carboxy-8-quinolinol) and the uncatalysed (pH independent) hydrolysis at 254 nm. The copper(II) and nickel(II) catalysed reactions were monitored at 256 and 269 respectively.

For these hydrolyses the pseudo first order rate constants were obtained from conventional infinity plots which were linear to over 90% reaction.

Stopped-flow kinetic measurements of the zinc(II) catalysed hydrolysis were made at 268 nm. The initial concentration of ester was ca. 1.5 x 10^{-5}M but significant hydrolysis of the substrate occurred (via the pH independent pathway) during the equilibration period before the metal ion catalysed reaction was initiated. Under the experimental conditions the optical densities of the solutions at infinite reaction time were below 0.1 (mixing chamber pathlength 0.2 cm) and the observed changes in the intensity of the transmitted light beam could be related directly to changes in the concentration of the absorbing species. As a consequence, pseudo first order rate constants were obtained from plots of log $[V_{\infty} - V_t]$ against time; where V_{∞} represents the voltage recorded on the oscilloscope screen at infinite time and V_t is the voltage recorded at time t.

The reaction media used in the metal ion catalysed hydrolyses were buffered to constant pH with acetate and formate buffers (copper(II) catalysed hydrolysis) and Pipes buffer (nickel(II) and zinc(II) catalysed hydrolyses). No evidence for catalysis by buffer species was observed as reaction rates were unaltered when the total buffer concentration was varied by a factor of two. The u.v. spectra of the reaction solutions recorded after 10 x $t_{\frac{1}{2}}$ were identical with those obtained from buffered solutions of the appropriate metal salt to which the requisite quantity of 2-carboxy-8-quinolinol had been added.

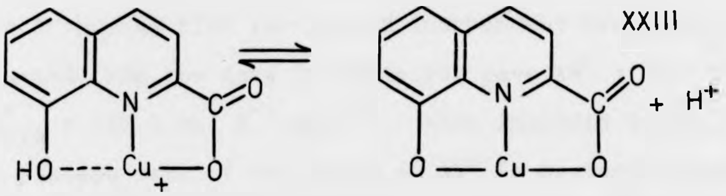
Measurements of pH and pD were carried using a Radiometer 26 pH meter (see Section 2.2). Values of pD were taken as the pH meter readings plus the appropriate correction factor [75].

Pipes and Hepes were B.D.H. biochemical reagents and deuterium oxide (99.8%) was purchased from Stohler Isotope Chemicals. All other reagents were of AnalaR grade.

5.1.2 pK_a Determination

The pK_a for the ionization process:

XXII



XXIII

was determined by spectrophotometric titration of a solution 4×10^{-3}M in copper(II) chloride and 2.8×10^{-5}M in 2-carboxy-8-quinolinol at 25° and I = 0.1M. The neutral copper complex (XXIII) (λ_{max} 268 nm, $\varepsilon = 3.5 \times 10^4$ dm^3 mol^{-1} cm^{-1}) was essentially fully formed at pH 5.7 under these conditions. As the pH of the solution was lowered a single ionization step ($pK_a^M = 3.93 \pm 0.04$) was observed corresponding to addition of the phenolic proton. At pH 2.4 the only complex in solution was (XXII) (λ_{max} 254 nm, $\varepsilon = 4.7 \times 10^4$ dm^3 mol^{-1} cm^{-1}). Dissociation of (XXII) to give the free ligand (λ_{max} 258 nm, $\varepsilon = 4.2 \times 10^4$ dm^3 mol^{-1} cm^{-1}, pH 2.4) was found to be unimportant.

5.2 Results

In the pH range 5.24 to 12, and in the absence of divalent metal ions, the hydrolysis of the 8-acetoxyquinoline-2-carboxylate anion (E^-) follows the rate law

$$\text{rate} = k_o[E^-] + k_{OH}[E^-][OH^-] \qquad .....(23)$$

A justification for the assumption that ester is present entirely in the anionic form in this pH region is given subsequently in this section. The bimolecular term in equation (23) represents the specific base catalysed hydrolysis of the anion and k_o is the rate constant for the uncatalysed reaction. At 25° and I = 0.1M $k_o = 1.67 \times 10^{-4}\ s^{-1}$ and $k_{OH} = 0.84\ dm^3\ mol^{-1}\ s^{-1}$, Table 12.

An Arrhenius plot for the pH independent hydrolysis, constructed from the data in Table 13, gave $\Delta H^{\ddagger} = 13.7$ kcal mol^{-1} and $\Delta S^{\ddagger}_{298} = -37.9$ cal $K^{-1}\ mol^{-1}$. Also included in the table is the plateau rate of the ester at 35° in deuterium oxide. The reaction exhibits a significant solvent deuterium isotope effect, $k^{H_2O}/k^{D_2O} = 2.52$. Rate constants observed for the uncatalysed hydrolysis were unaltered when the reaction media contained a trace (ca. 10^{-5}M) of E.D.T.A.

Trial experiments showed that the ester (initial concentration 3.3×10^{-5}M) was hydrolysed extremely rapidly in the presence of 10^{-3}M copper(II) at pH 5.6 and 25° ($t_{\frac{1}{2}}$ < 10 sec.). However, below pH 4.5 the reaction at 25° was sufficiently slow to be followed by conventional spectrophotometric techniques. At pH 3.40 essentially constant values of k_{obs} were obtained when the copper(II) concentration of the reaction medium was increased from 10^{-3}M to 5×10^{-3}M, Table 14. The observation of a zero order dependence of the reaction rate on the concentration of the metal ion is consistent with a reaction of the fully complexed ligand.

Quinoline-2-carboxylic acid functions as a bidentate ligand the binds copper(II) according to the equilibrium scheme:

Table 12

Rate Constants for the Uncatalysed and Base Catalysed Hydrolysis of 8-Acetoxy-2-carboxyquinoline, 25° and I = 0.1M[a].

Buffer[b]	pH	$10^4\ k_{obs}/s^{-1}$
Acetate	5.24	1.73
Pipes	6.87	1.62
Hepes	7.96	1.60
Hepes	8.45	1.70
Borate	9.12	1.77[c]

$k_o = (1.67 \pm 0.06) \times 10^{-4}\ s^{-1}$

10^2[NaOH]/M	$10^3\ k_{obs}/s^{-1}$	$k_{OH} = (k_{obs}-k_o)[OH^-]/dm^3\ mol^{-1}\ s^{-1}$
1.0	8.48	0.831
2.0	1.69	0.835
3.0	2.54	0.840

$k_{OH} = 0.84 \pm 0.03\ dm^3\ mol^{-1}\ s^{-1}$

[a] Substrate concentration 3.33×10^{-5}M

[b] Buffer concentrations lay in the range 5×10^{-3} to 10^{-2}M

[c] The rate constant contains a small contribution (ca 5%) from the specific base catalysed reaction.

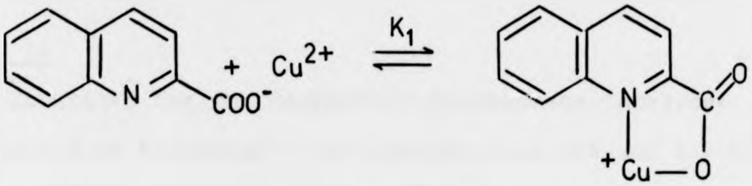
Table 13

Temperature Dependence and the Solvent Deuterium Isotope Effect for the Uncatalysed Hydrolysis of 8-Acetoxy-2-carboxyquinoline[a].

Temp/°C	Solvent	pH or pD	$10^4\ k_o^b/s^{-1}$
25.0	H_2O	6.84	1.63
35.0	"	"	3.41
45.0	"	"	7.45
35.0	D_2O	6.88	1.34
35.0	"	6.29	1.37

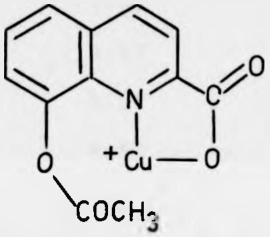
[a] Substrate concentration 3.33×10^{-5}M. Reaction media buffered with 10^{-2}M pipes, I = 0.1M.

[b] Mean values obtained from duplicate estimations.



At 25^{o}, K_1 = 8.1 x 10^{5} dm^{3} mol^{-1} [90]. As 8-acetoxy-2-carboxyquinoline provides an identical binding site the kinetic results obtained at higher copper(II):ester ratios (>33:1) indicate that the reactive species is the 1:1 complex (XXIV).

XXIV



The first order dependence of the hydrolysis on hydroxide ion concentration is clearly demonstrated by the results in the latter part of Table 14. Base hydrolysis of the copper(II)-ester complex (k_{OH} = (1.42 ± 0.06) x 10^{8} dm^{3} mol^{-1} s^{-1}, 25^{o}, I = 0.10M) is faster by a factor of 1.7 x 10^{8} than base hydrolysis of the free ligand under the same conditions (k_{OH} = 0.84 dm^{3} mol^{-1} s^{-1}). Arrhenius parameters for both these reactions were calculated from the results listed in Table 15. A plot of log k_{OH} versus K^{-1} for the copper(II) promoted reaction, Figure 5, gave $\Delta H^{\ddagger}$ = 8.1 ± 0.2 kcal mol^{-1} and $\Delta S^{\ddagger}_{298}$ = +6.0 ± 0.8 cal K^{-1} mol^{-1}. The corresponding parameters for the unpromoted hydrolysis are $\Delta H^{\ddagger}$ = 10.0 ± 0.3 kcal mol^{-1} and $\Delta S^{\ddagger}_{298}$ = -25.0 ± 1.0 cal K^{-1} mol^{-1}.

The results obtained from stopped-flow kinetic measurements of the zinc(II) catalysed hydrolysis are given in Table 16. At pH 6.18 and 25^{o} the observed rate shows a linear increase

Table 14

Rate Constants for the Copper(II) Perchlorate Catalysed Hydrolysis of 8-Acetoxy-2-carboxyquinoline, 25 and I = 0.1M ($NaClO_4$)

(i) Metal Ion Dependence, pH 3.40[a]

$10^3[Cu^{2+}]/M$	$10^3\ k_{obs}/s^{-1}$
0.0	<0.2
1.0	4.61
2.0	4.67
3.0	4.67
5.0	4.67

(ii) pH Dependence[b] at a Copper(II) Concentration of 5 x 10^{-3}M

pH	$10^3\ k_{obs}/s^{-1}$	$10^{11}[OH^-]/M$	$10^{-8}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
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

[a] Reaction media buffered with 5 x 10^{-3}M HCOOH/NaOH

[b] Solutions of pH above 4.195 were buffered with CH_3COOH/NaOH. All other media were buffered with HCOOH/NaOH (conc. 5 x 10^{-3} to 1.5 x 10^{-2}M).

Table 15

Temperature Dependence of the Unpromoted and Copper(II) Promoted Base Hydrolysis of 8-Acetoxy-2-carboxyquinoline[a] at I = 0.1M.

(i) Unpromoted Hydrolysis in 10^{-2}M NaOH

Temp/°C	$10^3\ k_{obs}/s^{-1}$	$k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
15.0	4.60	0.460
25.0	8.66	0.866
35.0	15.4	1.54

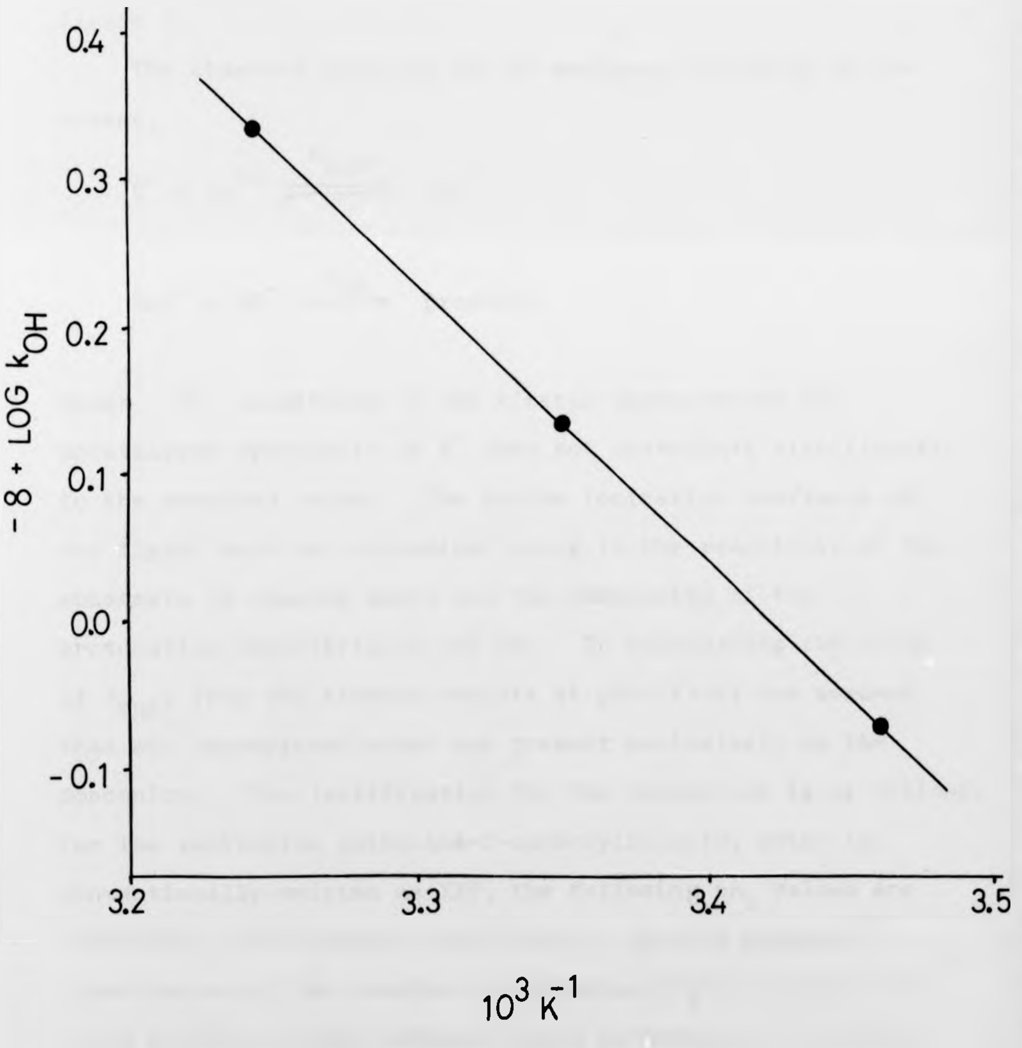
(ii) Copper(II) Promoted Hydrolysis

Temp/°C	pH	$10^3\ k_{obs}/s^{-1}$	$10^{11}[OH^-]/M$	$10^{-8}\ k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
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

[a] Substrate concentration was 3.33×10^{-5}M. Pseudo first order rate constants are mean values calculated from duplicate estimations.

[b] Reaction media 4×10^{-3}M in $Cu(ClO_4)_2$, 8×10^{-3}M in formate buffer.

Fig 5 ARRHENIUS PLOT FOR THE COPPER(II) PROMOTED BASE HYDROLYSIS OF 8-ACETOXY-2-CARBOXYQUINOLINE.



with increasing metal ion concentration of the reaction medium and approaches a limiting value at high concentrations, Figure 6. Full complexation of the substrate could not be achieved in this system as further increases in the metal ion concentration (above 2×10^{-2}M) at this pH resulted in precipitation of zinc(II) hydroxide. A representative kinetic plot of log $[V_\infty - V_t]$ against time is given in Figure 7.

The observed kinetics may be analysed according to the scheme,

$$E^- + Zn^{2+} \overset{K_{ZnE^+}}{\rightleftharpoons} ZnE^+$$

$$ZnE^+ + OH^- \xrightarrow{k_{OH}} \text{products}$$

Under the conditions of the kinetic measurements the uncatalysed hydrolysis of E^- does not contribute significantly to the observed rates. The proton ionization constants of the ligand were not determined owing to the reactivity of the substrate in aqueous media and the complexity of the protonation equilibria at low pH. In calculating the value of K_{ZnE^+} from the kinetic results at pH 6.18 it was assumed that any uncomplexed ester was present exclusively as the monoanion. The justification for the assumption is as follows. For the zwitterion quinoline-2-carboxylic acid, which is conventionally written as XXV, the following pK_a values are available; 4.92 (proton lost) and 1.9 (proton gained)[91]. Substitution of the electron withdrawing CH_3COO- moiety into the 8-position of the molecule would be expected to markedly

Table 16

Rate Constants for the Zinc(II) Sulphate Catalysed Hydrolysis of 8-Acetoxy-2-carboxyquinoline‡ at 25° and I = 0.1M.

(i) Metal Ion Dependence, pH 6.18

$10^3[Zn^{2+}]/M$	$[ZnE^+]/[E^-]$[a]	k_{obs}/s^{-1}	k_{calc}/s^{-1}[b]
0.5	0.065	0.165	0.165
1.0	0.130	0.281	0.310
1.5	0.195	0.386	0.440
2.0	0.260	0.573	0.556
2.5	0.325	0.685	0.662
5.0	0.650	0.983	1.06
7.5	0.975	1.34	1.33.
10.0	1.30	1.63	1.53
15.0	1.95	1.88	1.79
20.0	2.60	2.01	1.95

(ii) pH Dependence at a Zinc(II) Concentration of 2.5×10^{-3}M

pH	k_{obs}/s^{-1}	$10^8[OH^-]/M$	$k_{obs}/[OH^-]/dm^3\ mol^{-1}\ s^{-1}$
6.18	0.685	1.95	3.51
6.42	1.19	3.41	3.49
6.62	1.97	5.40	3.65
6.78	2.77	7.81	3.55
6.87	3.85	9.60	4.01
7.06	5.37	14.9	3.60
7.24	8.01	23.6	3.39

Table 16 (cont.)

[a] Calculated assuming K_{ZnE^+} = 130 dm^3 mol^{-1}

[b] Calculated assuming (a) above and a limiting rate of 2.7 s^{-1} at pH 6.18

‡ Reaction media buffered with 5 x 10^{-3}M Pipes

Fig 6 THE ZINC(II) CATALYSED HYDROLYSIS OF 8-ACETOXY-2-CARBOXYQUINOLINE, 25°, pH 6.18.

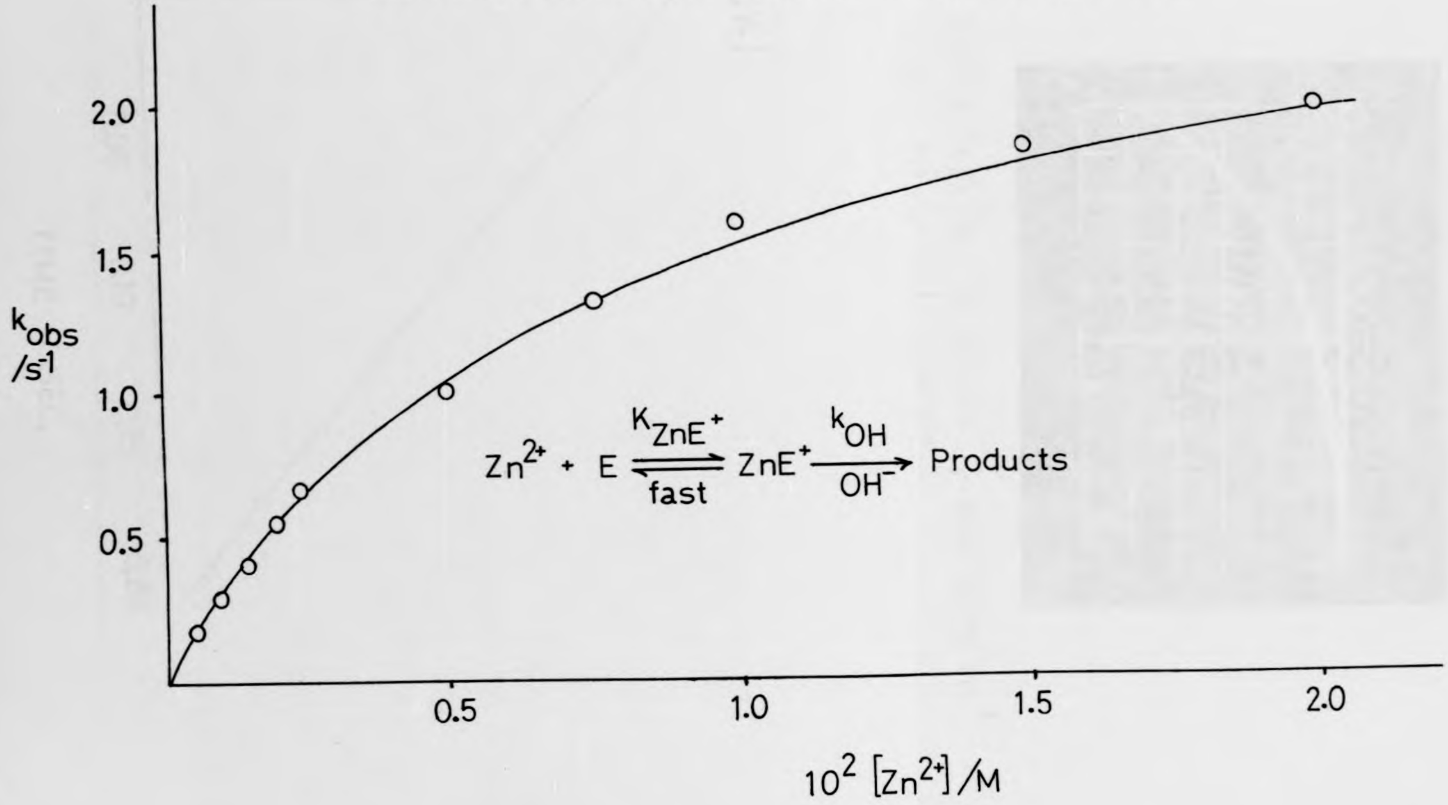
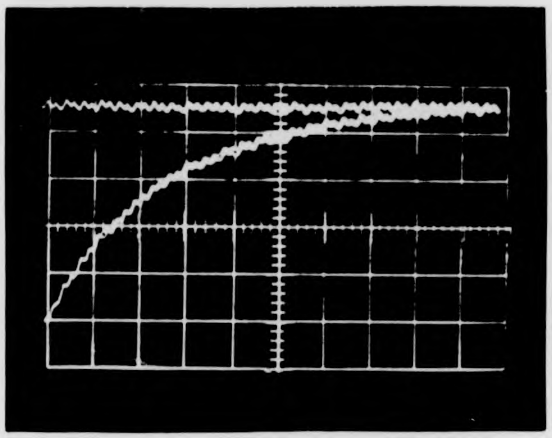
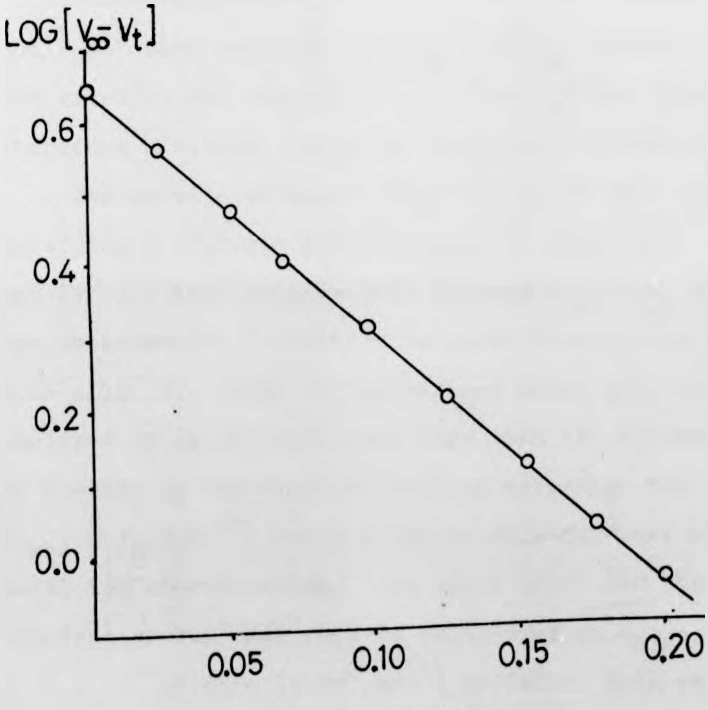
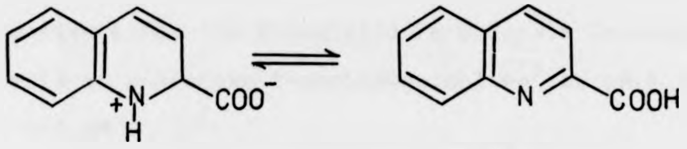


Fig 7 THE ZINC(II) CATALYSED HYDROLYSIS OF 8-ACETOXY-2-CARBOXYQUINOLINE, STOPPED-FLOW KINETICS.



$Zn^{2+} = 2.5 \times 10^{-3}$ M , $\lambda = 268$ nm , y-axis 20 mv cm^{-1}
x-axis 50 ms cm^{-1}, pH 7.2





XXV

decrease the basicity of both the quinolyl nitrogen and the ionized carboxylate group (e.g. 8-acetoxyquinoline has $pK_a = 3.08^{92}$ while quinoline has $pK_a = 4.90^{93}$ at 25°). From these results the pK_a associated with proton loss from 8-acetoxy-2-carboxyquinoline would appear to be ca. 3.2 while the pK_a associated with proton gain should be considerably lower than this value. On this basis the ratio of ester anion:ester zwitterion at pH 6.18 may be estimated as ca. 1000:1.

A good fit between observed and calculated rate data was found when values of 130 $dm^3\ mol^{-1}$ and $(1.38 \pm 0.12) \times 10^8\ dm^3\ mol^{-1}\ s^{-1}$ were assigned to K_{ZnE^+} and k_{OH} respectively. The zinc(II) and copper(II) complexes of the ester are therefore similarly reactive toward base hydrolysis at 25°.

The results obtained from a study of the nickel(II) catalysed hydrolysis are displayed in Table 17. At pH 6.875 and 25° a linear relationship between $k_{obs} - k_o$ and $[Ni^{2+}]$ was observed for nickel(II) concentrations of up to 1.25×10^{-2}M. Even at the highest metal ion concentration employed it is unlikely that more than 15% of the ester could be present as the reactive complex otherwise the values of $(k_{obs} - k_o)/[Ni^{2+}]$ would progressively decrease with increasing metal ion concentration. An upper limit for the formation constant of NiE^+ may then be calculated as $K_{NiE^+} < 0.15/1.25 \times 10^{-2}.0.85 = 14\ dm^3\ mol^{-1}$ at 25°. This result was

Table 17

Rate Constants for the Nickel(II) Perchlorate Catalysed Hydrolysis of 8-Acetoxy-2-carboxyquinoline[a] at pH 6.875, 25^{o}, I = 0.1M

$10^3[Ni^{2+}]/M$	$10^2\ k_{obs}/s^{-1}$	$(k_{obs}-k_o)/[Ni^{2+}]/dm^3mol^{-1}\ s^{-1}$
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] Reaction media buffered with 10^{-2}M Pipes. Substrate concentration 3.33×10^{-5}M

unexpected when reference was made to equilibrium data concerning nickel(II) and quinoline-2-carboxylic acid. Here $K_1 = 8.9 \times 10^4$ dm^3 mol^{-1} at 25°[91], and it has been found that the nickel(II) complex is more stable than the zinc complex ($K_1 = 2.3 \times 10^4$ dm^3 mol^{-1}, 25°)[94]. The kinetic results indicate that 8-acetoxy-2-carboxyquinoline shows some specificity toward the binding of divalent metal ions. Apparently copper(II) and zinc(II) can more readily fulfil the geometric requirements of the ligand binding site than can nickel(II). This phenomenon may be related to the rigid nature of the binding site, where the metal ion is forced to occupy a cavity of clearly defined dimensions (i.e. the 'bite' of the ligand is defined). An additional steric component that might also contribute to selective binding could arise from the interaction of the acetyl moiety of the ligand with a water molecule in the coordination sphere of the metal ion.

In the case of the nickel(II) catalysed reaction the observed rate constants are composite functions of both equilibrium and kinetic constants

$$Ni^{2+} + E^- \overset{K_{NiE^+}}{\rightleftharpoons} NiE^+$$

$$E^- \xrightarrow{k_o} \text{product}$$

$$NiE^+ + OH^- \xrightarrow{k_{OH}} \text{product}$$

$$k_{obs} = k_o + k_{OH} \cdot K_{NiE^+}[Ni^{2+}][OH^-] \qquad \text{.....(24)}$$

At 25° and I = 0.1M the function $k_{OH} \cdot K_{NiE^+}$ takes the value 6.4×10^7 dm^6 mol^{-2} s^{-1}.

Barca and Freiser have investigated the hydrolysis of 8-acetoxyquinoline in the presence of metal ions[92]. The catalytic constants reported for this system similarly reflect both rate and equilibrium data. It was found that catalytic effect of copper(II) was 300 fold greater than zinc(II) and that the order of catalytic ability for divalent metal ions was:

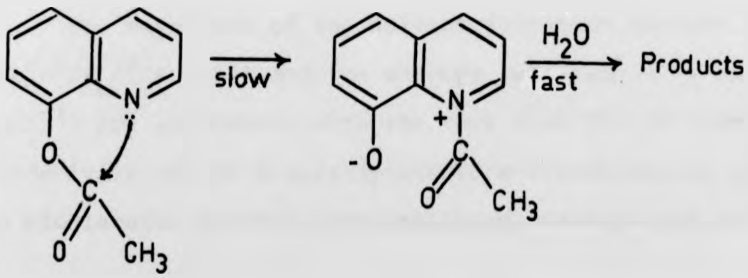
$$Cu^{2+} > Zn^{2+} > Pb^{2+} > Cd^{2+} > Ni^{2+}$$

The results obtained in the present investigation indicate that the very large differences in the catalytic effect of these metal ions may be related more to differences in the stability constants for metal ion-ester complex formation than to any other single factor.

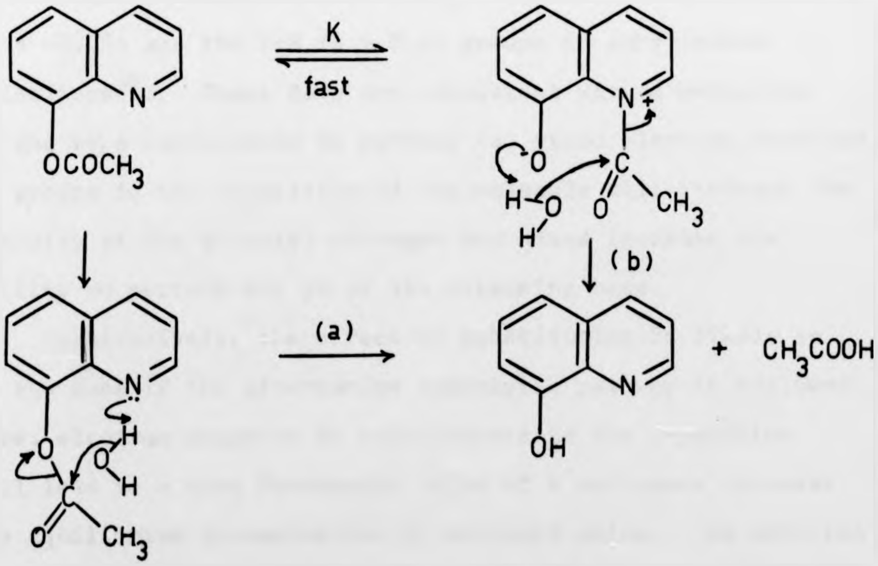
5.3 Discussion

Barca and Freiser[92] have observed that the rate of hydrolysis of 8-acetoxyquinoline (XXVI) is independent of pH in the region 4-8 and is 500 times faster than that of the 7-acetoxy compound at 55°. These workers proposed that the rate enhancement exhibited by the 8-isomer was attributable to intramolecular catalysis by the pyridine nitrogen, involving rate determining formation of the acylated amine.

XXVI



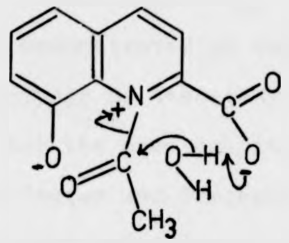
A subsequent detailed investigation of the reaction by Felton and Bruice[95] yielded kinetic parameters, k^{H_2O}/k^{D_2O} = 2.35 and $\Delta S^{\ddagger}$ = -29 cal K^{-1} mol^{-1} that were inconsistent with the simple nucleophilic mechanism. It is now believed that the reaction is due to intramolecular general base catalysis by the quinoline nitrogen[72], a mechanism which is analogous to that now accepted for aspirin hydrolysis[96]. The kinetic parameters, however, do not distinguish between this pathway and one involving rapid formation of the acylated amine, followed by intramolecular general base catalysis of its hydrolysis by phenoxide ion. These hydrolytic pathways are shown below.



The magnitude of the solvent deuterium isotope effect ($k_o^{H_2O}/k_o^{D_2O}$ = 2.52) and the entropy data ($\Delta S^{\ddagger}$ = -37.9 cal K^{-1} mol^{-1}) are consistent with the view that the pH independent hydrolysis of the 8-acetoxyquinoline-2-carboxylate anion is a bimolecular general base catalysed reaction and are inconsistent with a mechanism featuring rate determining intramolecular nucleophilic attack. General base catalysis of ester hydrolysis usually leads to values of k^{H_2O}/k^{D_2O} in the range 2-3[97], although there are some exceptions to this generalization[98].

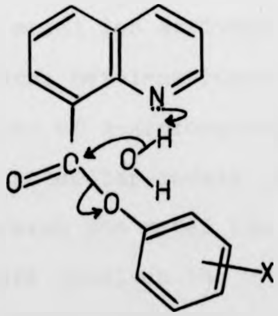
The first order rate constant for the reaction may be compared with the rate constants reported[92] for the uncatalysed hydrolyses of both 2-methyl-8-acetoxyquinoline and 8-acetoxyquinoline. At 25° the relative hydrolysis rates of 2-methyl-8-acetoxyquinoline, the 8-acetoxyquinoline-2-carboxylate anion and 8-acetoxyquinoline may then be calculated as 4:3.5:1; which are correlated reasonably well with the inductive substituent constants of the 2-CH_3 (σ = -0.10), the 2-COO^- (σ = -0.03) and the 2-H (σ = 0.0) groups in substituted quinolines[80]. These data are consistent with a mechanism of the type represented by pathway (a) since electron donation by groups in the 2-position of the molecule will increase the basicity of the quinolyl nitrogen and hence increase its ability to perturb the pK of the attacking base.

Qualitatively, the effect of substitution is likely to be the same if the alternative hydrolytic pathway is followed. Here, electron donation by substituents in the 2-position will lead to a more favourable value of K and hence increase the equilibrium concentration of acylated amine. In addition, the effect would be enhanced by the concomitant increase in the basicity of the phenoxide ion. Although the ionized 2-carboxylate group appears ideally situated to supply anchimeric assistance of the hydrolysis in the same manner as phenoxide ion, viz:



the presence of this group need not lead to a greatly enhanced rate since it is probably insufficiently basic (in comparison with phenoxide ion) to participate effectively.

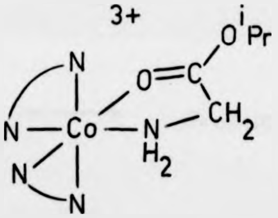
The arguments of Kirby and Fersht[72] support the simple general base catalysis mechanism for the hydrolysis of 8-acetoxyquinoline. The present findings allow no clear distinction between the alternative routes, but it may be noteworthy that the pH independent hydrolysis of substituted phenyl quinoline-8-carboxylates, where a mechanism involving O → N acyl transfer is not feasible, occurs by an intramolecular general base catalysed pathway[99].



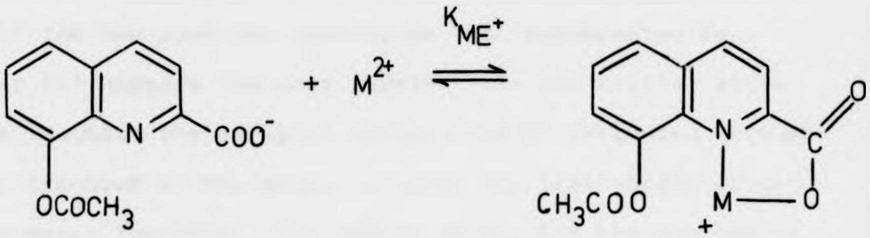
The rate enhancement of 1.7 x 10^8 found for the copper(II) and zinc(II) promoted base hydrolyses of 8-acetoxy-2-carboxyquinoline exceeds by a factor of at least 10^2 the largest rate enhancement previously observed in a metal ion promoted ester hydrolysis[60,100]. That the presence of the 2-COO^- group does not produce an abnormally slow base catalysed hydrolysis of the free ligand (k_{OH} = 0.84 dm^3 mol^{-1} s^{-1}, 25°, I = 0.1M) may be demonstrated by reference to the value of k_{OH} for the hydrolysis of 8-acetoxyquinoline (1.14 dm^3 mol^{-1} s^{-1}) obtained under the same conditions[92].

Buckingham, Foster and Sargeson[60] have found that base hydrolysis of the cobalt(II)-glycinate complex (XXVII) is 10^6 times faster than base hydrolysis of uncoordinated ethylglycinate. The i.r. spectrum of the complex exhibits $\nu_{C=O}$ at 1625 cm^{-1}; a marked reduction in the carbonyl stretch frequency observed for simple aliphatic esters ($\nu_{C=O}$ = 1750 - 1735 cm^{-1}). The rate enhancement has been attributed to this direct metal ion activation of the carbonyl centre. For steric reasons metal-carbonyl bonding cannot occur within the 1:1 complexes of 8-acetoxy-2-carboxyquinoline. An examination of molecular models suggests that the primary interaction between the metal ion and the ester function in the initial state involves the phenoxy oxygen.

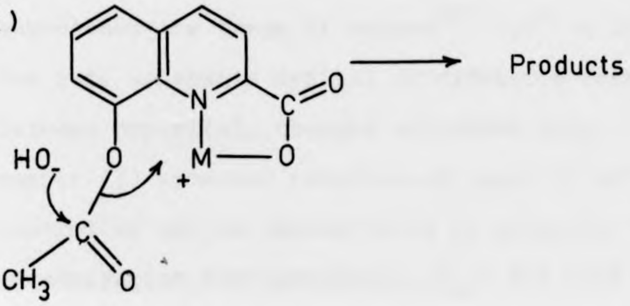
XXVII



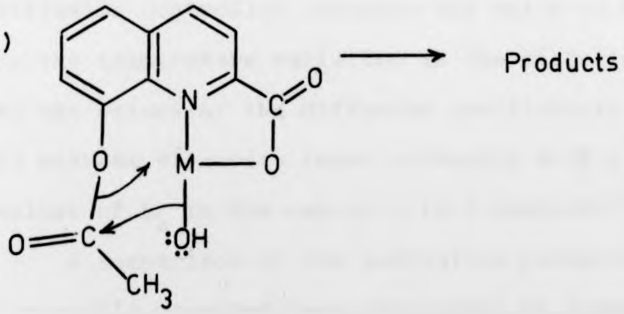
On the basis of the kinetic data the mechanism for the base hydrolysis of the metal ion-ester complexes cannot be assigned unequivocally. The results are consistent with the fast equilibrium formation of the reactive 1:1 complex followed by (i), attack by external hydroxide ion or (ii), attack by coordinated hydroxide ion.



(i)



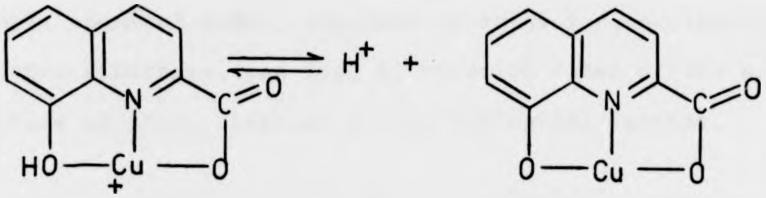
(ii)



Although both mechanisms account for all the kinetic observations pathway (ii) appears least favourable since in the transition state the nucleophile is associated both with the acyl moiety and, via coordination to the metal ion, with the carboxyquinolinate leaving group. This unfavourable geometry may be avoided if the mechanism for reaction involves acyl transfer to the bound hydroxyl group. In the alternative pathway the very fast hydrolysis rates suggest that one problem to be solved is that of supplying a sufficient concentration of nucleophile[101].

Of the two possible mechanisms that represented by pathway (i) appears the most likely. In the initial state of the reaction the carbonyl carbon atom is activated through the interaction of the metal ion with the least basic oxygen of the ester function. The values of k_{OH} for the copper(II) and zinc(II) promoted reactions (ca. $1\text{-}2 \times 10^{8}$ dm^{3} mol^{-1} s^{-1}) approaches the range of values[102] (10^{9} to 10^{11} dm^{3} mol^{-1} s^{-1}) for rate constants typical of diffusion controlled processes between oppositely charged univalent ions. That the copper(II) promoted reaction at least is not encounter controlled may be demonstrated by reference to the energy of activation for hydrolysis, $E_a = 8.7$ kcal mol^{-1}. For a diffusion controlled reaction the value of E_a is determined by the temperature variation in the diffusion coefficients. As the values of the diffusion coefficients are proportional to solvent viscosity (more correctly to $\eta.K^{-1}$) this leads to values of E_a in the region 1 to 3 kcal mol^{-1}.[103]

A comparison of the activation parameters for the copper(II) promoted base hydrolysis of 8-acetoxy-2-carboxyquinoline ($\Delta H^{\ddagger} = 8.1$ kcal mol^{-1}, $\Delta S^{\ddagger} = +6.0$ cal K^{-1} mol^{-1}) with those for the unpromoted base hydrolysis ($\Delta H^{\ddagger} = 10.0$ kcal mol^{-1}, $\Delta S^{\ddagger} = -25.0$ cal K^{-1} mol^{-1}) shows that the rate acceleration of 1.7×10^{8} is due primarily to the difference in the entropies of activation of the two processes. The positive value of $\Delta S^{\ddagger}$ for the metal ion promoted reaction, which appears inconsistent with that expected for a bimolecular process[45], may be rationalized if the transition state for hydrolysis involves bonding of the developing phenoxide ion to the metal centre. In such a structure all internal charges are compensated for since the leaving group separates as the neutral carboxyquinolinate complex. The liberation of solvent molecules on passing from an initial state where both reactants are charged (and are therefore expected to be highly solvated) to a transition state with minimal solvation requirements are considered to account for the observed effects. The pK_a^M for the equilibrium



has been determined as 3.93 ± 0.04 at 25° and I = 0.1M. Thus the leaving group is comparable with the 2,4-dinitrophenolate ion (pK_a 2,4-dinitrophenol = 4.08, 25°[104]). Binding of 2-carboxy-8-quinolinol to copper(II) results in a lowering of the pK_a for the phenolic proton ionization by ca. 6 pK units. The activation of the leaving group by the metal ion, coupled with the effects of desolvation in the transition state, appears to have lead to the very large rate enhancement observed in this system.

The 1:1 complexes of 2-carboxy-8-acetoxyquinoline with zinc(II) and copper(II) are identical in their reactivity toward base hydrolysis. In the zinc metalloenzyme carboxypeptidase A the zinc(II) ion is bound in the active site by three ligands from the protein. In addition to the metal ion, three amino acid residues are believed to be directly involved in the mechanism of peptide hydrolysis. Two of these (Arg 145 and Tyr 248) are implicated in the substrate binding while the carboxylate of a third (Glu 270) assists hydrolysis through a nucleophilic or general base catalysed mechanism[105]. Some evidence has been presented indicating that at least some features of the active centre are common to both peptidase and esterase sites[106].

It is tempting to speculate that a mechanism of the type represented by pathway (i) may be of importance in enzymic reactions. In any case the present results demonstrate that a simple chemical model, composed of metal ion, nucleophile and ester substrate, can lead to reaction rates of the same magnitude as those observed in the biological systems.

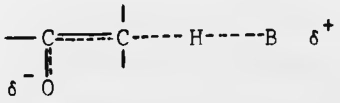
6. THE IODINATION OF 2-ACETYL-8-QUINOLINOL

6.1 Introduction

The halogenation of ketones is catalysed by both acids and bases, and is believed to proceed through the enol or enolate ion. When the rate of these reactions is found to be independent of halogen concentration it is believed that enolization or ionization is the rate determining step[8]. Thus, in general base catalysis the reaction scheme is:

$$SH \underset{k_{-1}[BH^+]}{\overset{k_1[B]}{\rightleftharpoons}} S^- \xrightarrow{k_2[X_2]} SX$$

If $k_2[X_2] >> k_{-1}[BH^+]$ the observed rate constant is $k_1[B]$ and the transition state may be represented as:



Metal ion catalysis of this reaction has been demonstrated in a number of systems. Bonding of the carbonyl oxygen to a suitably placed metal ion has been found to facilitate ionization of the active H atom. Cox[107] has recently shown that complexation of 2-acetylpyridine to zinc(II), nickel(II) or copper(II) leads to large increases in the rates of ionization. The 1:1 complex of copper(II) with 2-acetylpyridine, for example, undergoes acetate catalysed iodination 2 x 10^5 faster than the uncomplexed ligand. Complexes of 2-acetylpyridine have been isolated from alcohol solutions in both ketonic and enolic forms.[108,109]

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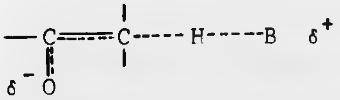

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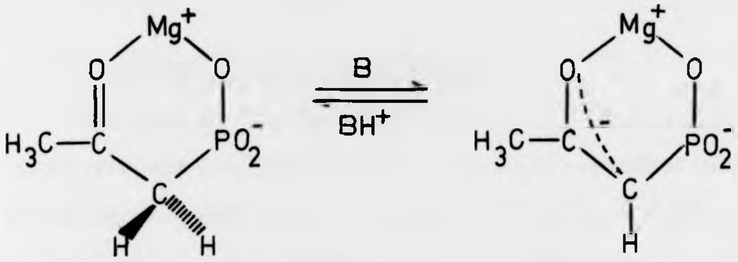
Pedersen[110,111] has demonstrated that the general base catalysed halogenation of both ethyl acetoacetate and ethyl-2-oxocyclopentane carboxylate is accelerated by copper(II). A recent study[112] has shown that complex formation with magnesium(II) enhances the deuteroxide ion catalysed deuteration of acetonyl phosphonate by a factor of 2000. Exchange at the 2-position is proposed to occur via the following pathway.



In the light of the current interest in the enolization of coordinated ketones[113] the iodination of 2-acetyl-8-quinolinol in the presence of divalent transition metal ions has been investigated.

6.2 Experimental

6.2.1 Materials

Pipes and Hepes were B.D.H. biochemical reagents. The latter was purified by recrystallization from ethanol-water (2:1). Hexafluoroacetone sesquihydrate was supplied by Koch-Light and its solutions were standardized by titration with NaOH. The presence of trace quantities of acetone in the fluorinated compound (n.m.r. measurements indicated 0.07%) did not interfere with halogenation experiments. 2-Acetylpyridine (Koch-Light) was redistilled (bp 190-191°). All other materials were of AnalaR grade.

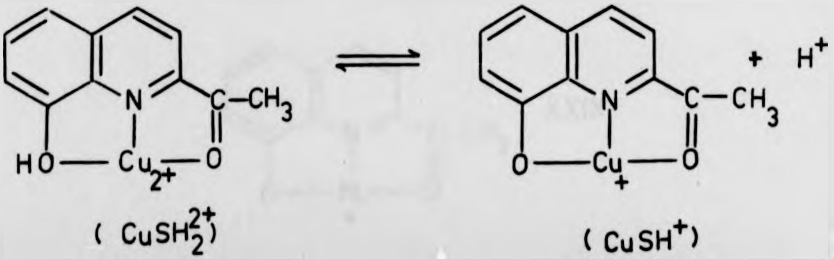
6.2.2 Kinetic Measurements

Reactions were studied in aqueous media maintained at I = 0.1M ($NaClO_4$). Rates of iodine loss were followed spectrophotometrically using a Gilford 222 instrument with the cell compartment held at a temperature of 25 ± 0.2°.

pH measurements on the kinetic solutions were made with a Radiometer 26 pH meter.

6.2.3 Proton Ionization Constants

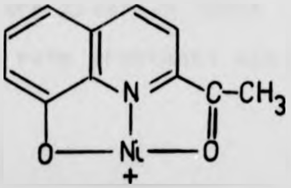
The proton ionization constants of Hepes, Pipes, hexafluoroacetone hydrate[114] (1,1,1,3,3,3-hexafluoro-2,2,-dihydroxypropane) and 2-acetyl-8-quinolinol (phenolic group ionization) were determined by potentiometric acid-base titration at 25.0° and I = 0.1M (KCl). Hepes was found to have $pK_1^M = 7.48 \pm 0.01$ ($pK_1 = 7.59$) and $pK_2^M = 3.02 \pm 0.02$ ($pK_2 = 2.91$). The value for the mixed constant, pK_1^M, is in exact agreement with that calculated from the data of Goode et al.[82]. Pipes has $pK_1^M = 6.73 \pm 0.02$ (previously reported, $pK_1^M = 6.77$[82]); pK_2 is not readily accessible owing to the sparing solubility of the di-zwitterion in aqueous media. The titration curve for hexafluoroacetone hydrate gave $pK_1^M = 6.54 \pm 0.01$ ($pK_1 = 6.65$), corresponding to the ionization process $(CF_3)_2C(OH)_2 \rightleftharpoons (CF_3)_2C(OH)(O^-) + H^+$. 2-Acetyl-8-quinolinol has $pK_1^M = 8.96 \pm 0.03$, Appendix 3.3. Spectrophotometric measurements indicated that protonation of the quinolyl nitrogen is associated with a pK_a of ca. 0.3. The pK_a for the ionization step:



was determined by potentiometric titration of a solution 3.75×10^{-4}M in 2-acetyl-8-quinolinol and 5×10^{-3}M in copper(II) perchlorate at 25° and I = 0.1M. In the pH region 2-3 the u.v. spectra of solutions of copper(II) and the ligand, showed that only $CuSH_2^{2+}$(λ_{max} 264 nm, $\varepsilon = 3.4 \times 10^4$ dm^3 mol^{-1} cm^{-1}) was present under these conditions (the charge neutral form of the ligand has λ_{max} 259.5 nm, $\varepsilon = 4.0 \times 10^4$ dm^3 mol^{-1} cm^{-1}). Titration data were collected over the pH range 3 to 5.4 and were corrected for formation of copper(II)-hydroxo species by carrying out an appropriate "blank" titration. The results indicated that deprotonation of $CuSH_2^{2+}$ is linked with pK_a^M of 5.0 ± 0.1. The deprotonated complex $CuSH^+$ has λ_{max} ~285 nm.

6.3 Results

The effect of nickel(II) on the rate of iodination of 2-acetyl-8-quinolinol (SH_2) was studied in the pH region 6-8. Ketone concentrations were 1.0×10^{-5}M and reactions were carried out in the presence of 0.01M KI. In all cases sufficient nickel(II) perchlorate was present in the kinetic solutions ($0.25 - 2.0 \times 10^{-2}$M, depending on pH) to ensure that the substrate was fully complexed as $NiSH^+$ (XXIX). The free ligand was observed to undergo rapid iodination of the phenyl ring giving 2-acetyl-5,7-diiodo-8-quinolinol in an undesired side reaction (Section 2.1). The 1:1 complex of 2-acetyl-8-quinolinol with nickel(II) has λ_{max} 288.5 nm, $\varepsilon = 2.7 \times 10^4$ dm^3 mol^{-1} cm^{-1}.



XXIX

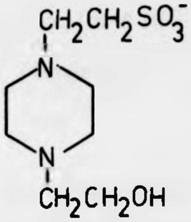
Reaction media were buffered to constant pH with known concentrations of $(CF_3)_2C(OH)_2$ (pH range 6.04 to 6.86) and Hepes (pH range 6.96 to 8.04). Halogenation reactions were carried out using an excess of iodine ($3.6 - 7.2 \times 10^{-5}$M). Plots of absorbance against time were not strictly first order over the whole of their course. They exhibited a first order dependence over ca. the first 5-6 reaction half lives, followed by a linear decrease of absorbance at long reaction times. With the use of the extinction coefficient for I_3^- at 353 nm (2.55×10^4 dm^3 mol^{-1} cm^{-1}) and K (1.40×10^{-3} mol dm^{-3}) for the equilibrium $I_3^- \rightleftharpoons I_2 + I^-$[115] the initial fast reaction was shown to consume 3 mol of iodine per mol of ketone. The reaction rates were independent of the iodine concentration, indicating that ionization of the first C-H bond in the methyl group was rate determining, with two further iodine atoms reacting in rapid subsequent steps. The slope of the linear portion of the kinetic trace increased with increasing tri-iodide concentration suggesting nuclear iodination of the complexed product. Halogenation of the fluorinated alcohol was unimportant, and although Hepes underwent slow iodination this reaction could be excluded by simultaneously monitoring the absorbance of solutions of Hepes and I_3^- in the absence of ketone. The correction was significant only for solutions of pH >7.4.

First order rate constants were evaluated from conventional infinity plots using values of OD_∞ obtained by extrapolation of the linear part of the spectrophotometer traces to zero reaction time. The results are given in Table 18 and plots of the observed first order rate constants against total buffer concentration in the case of catalysis by Hepes are shown in Figure 8. The contribution of catalysis by base species to the observed rate may be written formally as equation (25).

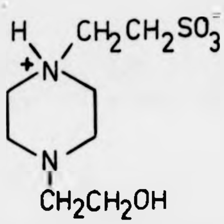
$$\text{rate} = \sum_i k_{B_i}[\text{NiSH}^+][B_i] \qquad .....(25)$$

where $[B_i]$ represents the concentration of any base in solution. In principle, both the monoanion of Hepes (XXX) and the zwitterion (XXXI) are capable of catalysing the reaction. In fact, catalysis by the zwitterion was not observed presumably

XXX



XXXI



as a consequence of the low basicity of the tertiary nitrogen atom (Hepes, pK_2 = 2.91). The non-zero intercepts for plots of k_{obs} against total buffer concentration have been reconciled with catalysis by hydroxide ion, but the relatively low values of the intercepts give an uncertainty of ca. 20% in k_{OH}. Attempts to study to the hydroxide ion catalysed reaction in isolation by pH-stat methods were unsuccessful. The technique required minimum concentrations of complex and I_2 in solution of ca. 10^{-4} to 3×10^{-4}M. Under these conditions nuclear iodination of NiSH^+ was significant.

In solutions of zinc(II) (5×10^{-4}M) the ketone ($0.5 - 2.0 \times 10^{-5}$M) is fully complexed as ZnSH^+ (λ_{max} 284 nm, $\epsilon = 3.5 \times 10^4$ dm^3 mol^{-1} cm^{-1}) in the pH region 6-7. The iodination of the zinc(II) complex was investigated using

Table 18

The Nickel(II) Promoted Iodination of 2-Acetyl-8-quinolinol[*] at 25° and I = 0.1M ($NaClO_4$).

(i) Hepes Buffer

(a) pH 6.96, [B]/[BH^+] = 0.302

10^3 [Hepes]$_T$/M	2.0	4.0	6.0	8.0	10.0
10^3 k_{obs}/s^{-1}	1.38	2.66	3.79	5.11	6.36

(b) pH 7.46, [B]/[BH^+] = 0.955

10^3 [Hepes]$_T$/M	1.0	2.0	3.0	4.0	5.0
10^3 k_{obs}/s^{-1}	1.75	3.10	4.63	5.85	7.53

(c) pH 8.04, [B]/[BH^+] = 3.63

10^3 [Hepes]$_T$/M	1.0	2.0	3.0	4.0
10^3 k_{obs}/s^{-1}	3.66	6.42	8.37	11.1

(ii) $(CF_3)_2C(OH)_2$ Buffer

(a) pH 6.04, [B]/[BH^+] = 0.316

10^3 [$(CF_3)_2C(OH)_2$]$_T$/M	5	10	15	20	25
10^3 k_{obs}/s^{-1}	0.425	0.810	1.27	1.66	2.08

(b) pH 6.27, [B]/[BH^+] = 0.725

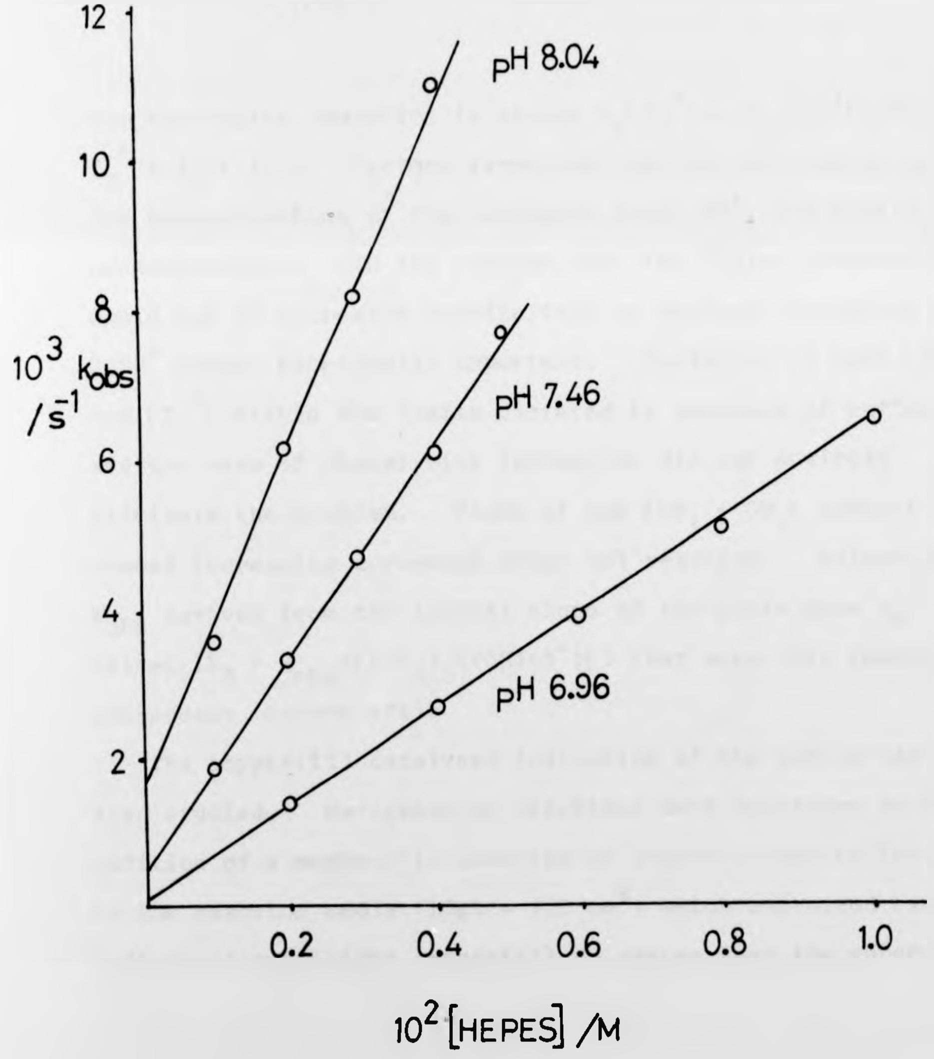
10^3 [$(CF_3)_2C(OH)_2$]$_T$/M	4.46	8.92	13.4	17.8	22.3
10^3 k_{obs}/s^{-1}	0.625	1.22	1.81	2.29	2.87

(c) pH 6.86, [B]/[BH^+] = 2.09

10^3 [$(CF_3)_2C(OH)_2$]/M	1.73	3.46	5.19	6.92	8.65
10^3 k_{obs}/s^{-1}	0.590	0.965	1.37	1.81	2.30

[*] Analytical wavelength 353 nm. Ketone concentration was 10^{-5}M. The concentration of nickel(II) (0.25-2.0 x 10^{-2}M depending on solution pH) was sufficient to fully complex the substrate.

Fig 8 THE NICKEL(II) CATALYSED IODINATION OF 2-ACETYL-8-QUINOLINOL, 25°, I = 0.1 M.



iodine concentrations of 0.6 - 1.2 x 10^{-4}M in media buffered with $(CF_3)_2C(OH)_2$/NaOH. Poor scavenging of the enol or enolate species by iodine prevented a detailed study of the reaction.

$$\mathrm{ZnSH^+} \underset{k_{-1}[\mathrm{BH^+}]}{\overset{k_1[\mathrm{B}]}{\rightleftharpoons}} \mathrm{ZnS} \xrightarrow{k_2[\mathrm{I_2}^*]} \mathrm{ZnSI^+} \longrightarrow \text{etc.}$$

The scavenging condition is simply $k_2[I_2^*] >> k_{-1}[BH^+]$ where $I_2^* = I_2 + I_3^-$. Factors favouring improved scavenging are low concentrations of the conjugate acid, BH^+, and high I_2^* concentrations. In the present case the iodine concentration could not be increased indefinitely as nuclear iodination of $ZnSH^+$ became kinetically important. Variation of both $[BH^+]$ and $[I_2^*]$ within the limits dictated by adequacy of buffering and the rate of phenyl ring iodination did not entirely eliminate the problem. Plots of log $[OD_t - OD_\infty]$ against time showed increasing curvature after 50% reaction. Values of k_{obs} derived from the initial slope of the plots gave k_B values ($k_B = k_{obs}/[(CF_3)_2C(OH)(O^-)]$) that were only reasonably concordant (errors ±8%).

The copper(II) catalysed iodination of the ketone was also studied. Halogenation reactions were initiated by the addition of a methanolic solution of 2-acetyl-8-quinolinol to the reaction media (10µl → 3.0 cm^3) which contained excess iodine and sufficient copper(II) to ensure that the substrate was initially fully bound at $CuSH_2^{2+}$ or $CuSH^{+}$*. Pipes was used as a buffering medium (pH range 5.90 to 6.80) and solutions were 0.01M in KI. Kinetic measurements at 390 nm showed the reaction to be first order with respect to the total ketone concentration and zero order in iodine. The loss of iodine after 10 x $t_{\frac{1}{2}}$ corresponded to 3 mol per mol of ketone (this value was obtained using an effective extinction coefficient of 8.8 x 10^3 dm^3 mol^{-1} cm^{-1} at 390 nm for iodine in the presence of 0.01M I^-). The observed rates of iodination, Table 19, were analysed in terms of the kinetic sequence given in Scheme 3, where the rate limiting steps involve proton abstraction from both $CuSH_2^{2+}$ and $CuSH^{+}$.

$$SH_2 + Cu^{2+} \underset{fast}{\overset{K}{\rightleftharpoons}} CuSH_2^{2+}$$

$$CuSH_2^{2+} \underset{fast}{\overset{pK_a^M=5.0}{\rightleftharpoons}} CuSH^{+} + H^{+}$$

$$CuSH_2^{2+} + B \xrightarrow[slow]{k_B'} \{CuSH^{+}\} + BH^{+}$$

*On mixing copper(II) and 2-acetyl-8-quinolinol solutions of pH 5.6-6.5 a single relaxation is observed in the time scale > 10 sec. at 25°. The process may be readily monitored spectrophotometrically by following the decrease in absorbance at 285 nm or the increase at 260 nm. Measurements at both wavelengths provide identical relaxation times, which are dependent on the initial ketone concentration. Time constants for the process were significantly higher than the half times observed for iodination reactions carried out under similar conditions.

U.v. spectral measurements on the mixtures at equilibrium suggested a complex distribution of copper(II) species; ketonic, enolic and hydroxo complexes may be expected. This, together with the concentration dependence of the process, prevented a detailed kinetic investigation of this system.

Table 19

The Copper(II) Promoted Iodination of 2-Acetyl-8-quinolinol*, Pipes Buffer, 25° and I = 0.1M ($NaClO_4$)

(a) pH 5.90, $[B]/[BH^+]$ = 0.148

10^2 $[Pipes]_T/M$	0.75	1.5	2.25	3.0
10^2 k_{obs}/s^{-1}	0.92	1.77	2.64	3.50

(b) pH 6.35, $[B]/[BH^+]$ = 0.417

10^2 $[Pipes]_T/M$	0.5	1.0	1.5	2.0	2.5	3.0
10^2 k_{obs}/s^{-1}	1.45	2.41	3.47	4.58	5.40	6.37

(c) pH 6.80, $[B]/[BH^+]$ = 1.18

10^2 $[Pipes]_T/M$	0.5	0.75	1.0	1.25	1.5
10^2 k_{obs}/s^{-1}	2.80	3.67	4.48	5.02	5.94

* Solutions 5 x 10^{-5}M in ketone. Analytical wavelength 390 nm. The concentration of copper(II) was 2 x 10^{-3}M at pH 5.90 and 4 x 10^{-4}M at pH 6.80. Rates of iodination were unchanged when the metal ion concentrations of the reaction media were varied by a factor of two.

$$CuSH^+ + B \xrightarrow[\text{slow}]{k''_B} \{CuS\} + BH^+$$

$$\{CuS\} \text{ or } \{CuSH^+\} + I_2 \xrightarrow{\text{fast}} \text{products}$$

Scheme 3

The rate law for the reaction takes the form:

$$-d[I_2^*]/dt = k_{obs}[\text{Total Ketone}] \qquad .....(26)$$

$$= \sum_i k'_{B_i}[CuSH_2^{2+}][B_i] + \sum_i k''_{B_i}[CuSH^+][B_i] \qquad .....(27)$$

when the second order rate constants (k_B) were assigned the values included in Table 20, and when the fractions of substrate present at $CuSH_2^{2+}$ and $CuSH^+$ were calculated from the observed proton ionization constant for $CuSH_2^{2+}$ ($K_a^M = 10^{-5}$ mol dm^{-3}, 25°, I = 0.1M) a good fit between experimental and calculated data

Table 20

Rate Constants[a] (k_B) for the Iodination of 2-Acetyl-8-quinolinol at 25° and I = 0.1M.

	Substrate			
Base (B)	$ZnSH^+$	$NiSH^+$	$CuSH_2^{2+}$	$CuSH^+$
Pipes (dianion)	-	-	35	5.3
$(CF_3)_2C(OH)(O^-)$	0.30[b]	0.33	-	-
Hepes (monoanion)	-	2.90	-	-
OH^-	-	1.2×10^3	-	1.0×10^5

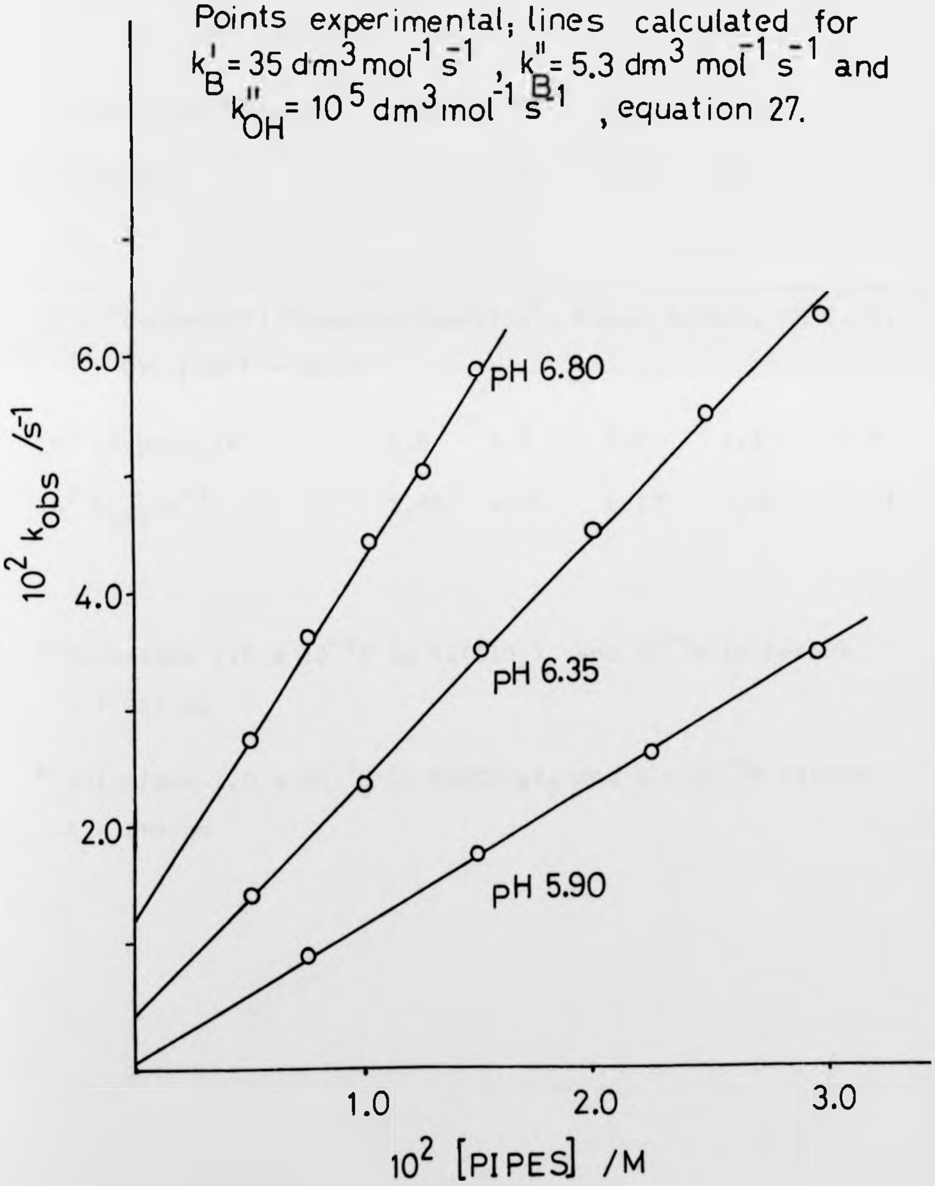
[a] Second order rate constants in units of dm^3 mol^{-1} s^{-1}.

[b] Approximate value.

was achieved, Figure 9. The iodination rates of $CuSH^+$ at pH 6.8 showed a significant contribution from catalysis by hydroxide ion. Probably as a consequence of the experimental conditions this pathway was not disclosed for reaction of $CuSH_2^{2+}$. It should be noted that the reaction of $CuSH_2^{2+}$ with Pipes dianion is kinetically equivalent to the reaction of $CuSH^+$ with Pipes monoanion. The latter species, however, is only weakly basic (Pipes, $pK_2 < 3$[82]). Further, as the related base derived from Hepes is ineffective in catalysing the iodination of $NiSH^+$ the data would appear to be more consistent with the former interpretation.

The metal ion catalysed reactions exhibit large kinetic deuterium isotope effects. Experimental conditions for the iodination of 2-acetyl-d_3-8-quinolinol (Section 2.1) in the presence of copper(II) and nickel(II) were identical with those described for the reactions of the protio substrate. As product iodination occurred at long reaction times first order rate constants (Table 21) were calculated from Guggenheim plots, using data collected over the first four reaction half lives. The observed primary deuterium isotope effects, k_B^H/k_B^D, were 7.8 for the nickel(II) catalysed reaction ($B = (CF_3)_2C(OH)(O^-)$) and 9.0 for the copper(II) catalysed reaction (B = Pipes dianion, pH 6.35).

Rates of iodination of 2-acetylpyridine were measured in $(CF_3)_2C(OH)_2$/NaOH buffers of varying buffer ratios. Concentrations of 2-acetylpyridine were ca. 5×10^{-2}M and the reactions were carried out in the presence of trace amounts of E.D.T.A. (ca. 2×10^{-5}M). Initial iodine concentrations were 10^{-4}M and solutions were 0.01M in KI. Kinetic measurements, Fig 9 THE COPPER(II) PROMOTED IODINATION OF 2-ACETYL-8-QUINOLINOL, 25°, $I = 0.1\,M$.



Points experimental; lines calculated for $k'_B = 35\ dm^3\,mol^{-1}\,s^{-1}$, $k''_B = 5.3\ dm^3\,mol^{-1}\,s^{-1}$ and $k''_{OH} = 10^5\ dm^3\,mol^{-1}\,s^{-1}$, equation 27.

Table 21

The Metal Ion Promoted Iodination of 2-Acetyl-d_3-8-quinolinol at 25^o and I = 0.1M ($NaClO_4$)

(i) Nickel(II) Promoted Reaction[a], $(CF_3)_2C(OH)_2$ Buffer, pH 6.37, $[B]/[BH^+] = 0.725$

$10^3\ [(CF_3)_2C(OH)_2]_T/M$	4.46	8.92	13.4	17.8	22.3
$10^4\ k_{obs}/s^{-1}$	0.975	1.70	2.37	3.17	3.90

(ii) Copper(II) Promoted Reaction[b], Pipes Buffer, pH 6.35, $[B]/[BH^+] = 0.417$

$10^2\ [Pipes]_T/M$	1.0	1.5	2.0	2.5	3.0
$10^3\ k_{obs}/s^{-1}$	3.00	4.03	5.27	6.40	7.32

[a] Solutions $2.0 \times 10^{-2}M$ in $Ni(ClO_4)_2$ and $10^{-5}M$ in ketone, $\lambda = 353$ nm

[b] Solutions $1.0 \times 10^{-3}M$ in $Cu(ClO_4)_2$ and $5 \times 10^{-5}M$ ketone, $\lambda = 390$ nm

made at 400 nm, showed the reactions to be zero order with respect to iodine for at least 85% reaction. Several successive additions of iodine were made to each reaction mixture and the rate of iodination was found to increase by 5-10% after each addition. Under the above conditions, the monoiodo ketone first formed should iodinate at least 100 times more rapidly than the parent compound[116]. This should lead to an acceleration of iodine uptake with increasing concentration of iodinated product. First order rate constants for the reaction of the parent compound (monoiodination only) were calculated by means of equation (28):

$$k_{obs} = \frac{1}{\varepsilon_{eff}[\text{ketone}]} \cdot \frac{dOD}{dt} \qquad .....(28)$$

where ε_{eff} is the effective molar extinction coefficient (5.9×10^3 dm^3 mol^{-1} cm^{-1}) for iodine in the presence of 0.01M I^- at 400 nm, and dOD/dt is the slope of linear plot of optical density against time for the reaction observed after addition of the initial aliquot of iodine. Rate constants for the iodination are given in Table 22, the derived value of k_B ($B = (CF_3)_2C(OH)(O^-)$) is 5×10^{-4} dm^3 mol^{-1} s^{-1}.

Table 22

Rate Constants for the Iodination of 2-Acetylpyridine[a] at 25° and I = 0.1M.

10^2 [BH$^+$] /M	10^2 [B] /M	10^6 k_{obs}/s^{-1}	$10^4 k_B$ (=k_{obs}/[B]) /dm^3 mol^{-1} s^{-1}
4.30	0.40	1.97	4.93
2.80	0.40	2.06	5.15
2.40	0.80	3.80	4.75
1.48	0.40	1.98	4.95
1.08	0.80	4.02	5.02
0.54	0.40	2.03	5.08

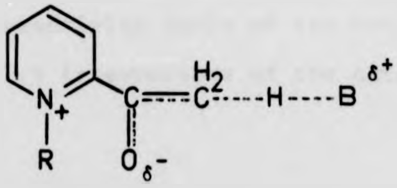
[a] In $(CF_3)_2C(OH)_2$/NaOH buffers.

6.4 Discussion

The results for the iodination of the metal ion complexes of 2-acetyl-8-quinolinol show clearly that the rate determining step in the reactions is ionization of the active H atom in the methyl group. The reactions exhibit the features normally expected for enolizations in all respects. Thus, the iodination rates are independent of iodine concentration, and the reactions are both general base catalysed and show large kinetic deuterium isotope effects.

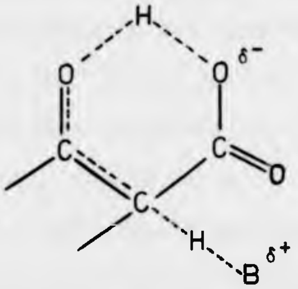
Cox[107] has found that N-methylation or N-protonation considerably enhances the rate of iodination of 2-acetylpyridine. It was suggested that there may be direct electrostatic stabilization of the negative charge forming on the carbonyl oxygen during proton loss (XXXII).

XXXII



Although intramolecular general acid catalysis of enolization has been observed for substrates possessing suitably oriented carboxylic acid groups (XXXIII)[117,118] this pathway does not

XXXIII



contribute significantly to the reaction rates of XXXII with R=H since the N-methyl derivative is similarly reactive.

The metal ion complexes (MSH^+) of 2-acetyl-8-quinolinol are closely related to XXXII, both structurally and in charge type. For the former system the best comparisons of rate data are made between the observed second order rate constants for $NiSH^+$ and $ZnSH^+$ with $(CF_3)_2C(OH)(O^-)$ (0.33 and 0.30 dm^3 mol^{-1} s^{-1} respectively) and the value for 2-acetylpyridine with the same base (5×10^{-4} dm^3 mol^{-1} s^{-1}). These results indicate a rate acceleration of $6 - 7 \times 10^2$ due to catalysis by the metal ions, which is somewhat higher than that expected (ca. 10^2) from electrostatic considerations alone.

The results obtained using Pipes buffers demonstrate significant catalysis of the reaction by copper(II). Reaction of $CuSH^+$ with Pipes dianion proceeds ca. 5 times more slowly than the corresponding reaction of $CuSH_2^{2+}$. This is as it should be since the normal inductive effect of a divalent metal ion will be reduced on binding to a negatively charged donor atom. If the reactivity ratio of the two copper(II) complexes remains at 1:5 irrespective of the catalyst base strength, this would also be consistent with our failure to observe hydroxide ion catalysis of the enolization of $CuSH_2^{2+}$, for which k_{OH} would be predicted as 5×10^5 dm^3 mol^{-1} s^{-1}. In the kinetic experiments the maximum fraction of substrate present as $CuSH_2^{2+}$ was 0.11 at pH 5.90 ($[OH^-] = 10^{-8}M$). Therefore, the maximum contribution from this type of catalysis to the values of k_{obs} would be ca. $5 \times 10^5 \times 0.11 \times 10^{-8} = 5 \times 10^{-4}$ s^{-1} at pH 5.90, which would escape detection.

The metal ion complexes of 2-acetyl-8-quinolinol undergo hydroxide ion catalysed deprotonation at very rapid rates ($k_{OH} = 10^3 - 10^5$ dm^3 mol^{-1} s^{-1}). These are comparable with those recently observed[119] for the reaction of the highly activated substrate 1,1-dinitroethane with OH^- ($k_{OH} = 3.6 \times 10^5$ dm^3 mol^{-1} s^{-1}).

The results of Cox[107] would indicate that the complexes of 2-acetylpyridine, which carry a dipositive charge, are ca. 5 - 20 fold more reactive than the corresponding complexes of 2-acetyl-8-quinolinol which carry a single positive charge. Only semi-quantitative comparisons are valid, for the two studies involved bases differing radically in strength and structure.

In both cases the reactions almost certainly feature a strong ground state interaction between the metal ion centres and the carbonyl oxygen atom. It has been suggested[107] that the rate enhancements observed in the 2-acetylpyridine system can be accounted for in terms of metal ion stabilization of the negative charge forming on the oxygen atom in the transition state for enolization. The present results are explicable in much the same terms, however, this effect may not be dominant when the group undergoing reaction is already strongly bound in the initial state, and there is undoubtedly considerable facilitation of proton loss through electrostatic effects.

APPENDIX 1

TRANSITION METAL COMPLEXES OF 2-CARBETHOXYPYRIDINE

Introduction

The donor properties of the ester group have been the subject of a number of investigations. In particular, there has been considerable interest in the coordination chemistry of bidentate ligands such as the α-amino acid esters where chelation involves both oxygen and nitrogen donor atoms[120-122]. As the introduction of a carbalkoxy group into the 2-position of pyridine provides a bidentate chelating agent closely related to the amino acid esters a general study was made of the coordination chemistry of 2-carbethoxypyridine (epic*). The complexes $[Cu(epic)_2Cl_2]$, $[Cu(epic)_2Br_2]$ and $[Co(epic)_2Cl_2]$ have been previously prepared[123-126], and interactions between the ligand and various divalent metal ions in solution investigated[127,128]. After the completion of the experimental work in this section a paper appeared[129] describing the preparation and characterization of a number of complexes of epic, two of which were prepared during the present study.

Experimental

Physical measurements were made using the instrumentation previously described (Section 2.3). 2-Carbethoxypyridine was purchased from Koch-Light Laboratories. Zinc(II) perchlorate was prepared from the neutralization of basic zinc carbonate by perchloric acid. Other metal salts were of reagent grade.

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*The abbreviation "epic" is derived from the trivial name of the ligand, ethyl-2-picolinate.

Dichlorobis(2-carbethoxypyridine-*N*,*O*) metal(II) and Diaquobis(2-carbethoxypyridine-*N*,*O*) metal(II) perchlorate complexes

To a warm solution of 2-carbethoxypyridine (6.04g, 0.04 mol) in absolute ethanol (10 cm^3) was added a solution of the appropriate hydrated transition metal salt (0.02 mol) in hot ethanol (15 cm^3). The complexes either crystallized on cooling or were readily induced to do so by the addition of diisopropyl ether to the warm solutions. The crystalline products were collected by vacuum filtration, washed with ethanol-ether and dried over silica gel.

Dichloro(2-carbethoxypyridine-*N*,*O*) copper(II)

This was prepared by mixing a hot ethanolic solution of 2-carbethoxypyridine (0.02 mol) with an ethanolic solution of copper(II) dichloride hexahydrate (0.02 mol). Concentrated hydrochloric acid (1 cm^3) was added and the bright green crystals of the complex separated from the cooled solution. The product was washed with ether and dried under vacuum.

Diaquobis(2-carbethoxypyridine-*N*-*O*) zinc (II) chloride perchlorate

A solution of anhydrous zinc chloride (2.72g, 0.02 mol) in ethanol (30 cm^3) was added to a solution of 2-carbethoxypyridine (6.04g, 0.04 mol). Soidum perchlorate monohydrate (2.8g, 0.02 mol) in ethanol was added and the mixture allowed to stand for 1 hour. The precipitated sodium chloride was removed by filtration and the complex recovered on slow evaporation of the filtrate. The highly hygroscopic product was washed thoroughly with ether and dried under vacuum.

Dichlorobis(2-carbomethoxypyridine-N,O) copper(II) and Dichloro(2-carbomethoxypyridine-N,O) copper(II)

Both complexes were readily obtained by refluxing the corresponding 2-carbethoxypyridine complexes (1g) with anhydrous methanol (15 cm^3). The bis-complex crystallized on cooling the solution after ca. 1 hour reflux, $\nu_{C=O}$ = 1705 cm^{-1} yield 70%. In an analogous preparation the mono-complex precipitated from the reaction mixture after 15 min. reflux in 95% yield. A small quantity was recrystallized from acetonitrile to give the analytical sample, $\nu_{C=O}$ = 1660 cm^{-1}.

Results and Discussion

The analytical data obtained for the complexes are listed in Table 23. The perchlorate complexes are stable toward atmospheric oxidation. The complex $[Fe(epic)_2Cl_2]$ is oxidised on prolonged exposure to air and $[Cu(epic)_2Cl_2]$ and $[Ni(epic)_2Cl_2]$ discolour during storage for appreciable periods.

With the exceptions of $[Cu(epic)Cl_2]$ and $[Cu(mepic)Cl_2]$ the chloro complexes are soluble in chloroform and other non polar solvents. All complexes are soluble in ethanol, dimethylformamide, dimethylsulphoxide and nitroethane.

The solution spectra of complexes of the type $[M(epic)_2Cl_2]$ in chloroform reveal a high intensity band ($\varepsilon \sim 10^4$ dm^3 mol^{-1} cm^{-1}) in the ultraviolet region. As the band position (37.6 kK, 1 kK = 1000 cm^{-1}) is constant for the different complexes it is probable that this is due to a $\pi \rightarrow \pi^*$ transition rather than a charge transfer transition. The intensities of the bands attributable to d-d transitions, taken with the band

Table 23

Analytical Data for the Complexes

Complex	Colour	C%		H%		N%	
		Found	Calc.	Found	Calc.	Found	Calc.
$Cu(epic)_2Cl_2$	Bright blue	44.19	43.99	4.19	4.15	6.28	6.41
$Cu(epic)Cl_2$	Green	33.75	33.66	3.05	3.16	4.77	4.90
$Ni(epic)_2Cl_2$	Green	44.63	44.49	4.51	4.20	5.99	6.49
$Co(epic)_2Cl_2$	Mauve	44.53	44.45	4.28	4.17	6.54	6.48
$Fe(epic)_2Cl_2$	Deep red	44.58	44.75	4.40	4.24	6.54	6.53
$Mn(epic)_2Cl_2$	Pale yellow	44.22	44.89	4.50	4.20	6.41	6.54
$Cu(mepic)_2Cl_2$[a]	Bright blue	41.09	41.12	3.41	3.45	6.82	6.85
$Cu(mepic)Cl_2$[a]	Pale green	31.26	30.95	2.88	2.72	5.23	5.16
$Cu(epic)_2(H_2O)_2(ClO_4)_2$	Blue	32.27	32.24	3.87	3.70	5.00	4.71
$Ni(epic)_2(H_2O)_2(ClO_4)_2$	Pale blue	32.34	32.25	3.89	3.72	4.90	4.70
$Co(epic)_2(H_2O)_2(ClO_4)_2$	Straw	32.46	32.24	3.83	3.72	4.74	4.70
$Zn(epic)_2(H_2O)_2(ClO_4)_2$[b]	White	33.32	33.46	3.80	3.51	4.80	4.88
$Zn(epic)_2(H_2O)_2(Cl)(ClO_4)$[c]	White	36.21	35.70	4.43	4.46	5.23	5.20

[a] Mepic = 2-carbomethoxypyridine.

[b] Zinc(II) estimated by E.D.T.A. titration at pH 10, Found: 12.03; Calc: 12.15%

[c] Zinc(II) similarly determined, Found: 11.52; Calc: 11.38%

positions (Table 24), indicates that the complexes are six-coordinate in this solvent[130]. All the chloro complexes are non electrolytes in nitroethane demonstrating that they are predominantly covalent in character. The low solubilities of [$Cu(epic)Cl_2$] and its 2-carbomethoxypyridine analogue in non polar solvents may indicate polymeric structures, involving bridging chlorine atoms, for these complexes.

The i.r. spectra of complexes of the general formula [$M(epic)_2(H_2O)_2$]$(ClO_4)_2$ show a broad absorption band at 3390 ± 10 cm^{-1}, suggesting coordinated water. These compounds are 1:2 electrolytes in nitroethane.

The reflectance spectrum of [$Cu(epic)_2Cl$] reveals two bands at 14.1 and 17.2 kK indicative of a tetragonally distorted structure[131]. The solid state spectrum of [$Cu(epic)Cl_2$] is normal for a copper(II) complex having an octahedral stereochemistry about the metal atom. The magnetic moments of the complexes are 1.81 and 1.85 B.M. respectively at 290°K, which are in the range of values (1.7 - 2.2 B.M.) typical for copper(II) complexes having octahedral or tetragonally distorted structures. No appreciable change in the stereochemistry of [$Cu(epic)_2(H_2O)_2$]$(ClO_4)_2$ occurs on dissolution of the complex in nitromethane. A single band at 14.1 kK is observed in both solution and solid state spectra.

Bands at 9.0 and 14.5 kK in the reflectance spectrum of [$Ni(epic)_2Cl_2$] may be assigned to the transitions $^3A_{2g} \rightarrow {}^3T_{2g}$ (ν_1) and $^3A_{2g} \rightarrow {}^3T_{1g}$ (ν_2) respectively. In the spectrum of [$Ni(epic)_2(H_2O)_2$]$(ClO_4)_2$ the band of lowest frequency occurs at 10.5 kK while the higher frequency band is split into two

Table 24

Magnetic, Conductivity and Electronic Spectral Data for Selected Complexes

Complex	μ_{eff}[a] (B.M.)	Λ[b] (Ω^{-1} mol^{-1} cm^{-1})	Absorption Maxima (kK) $CHCl_3$ Solution[c]	Absorption Maxima (kK) Solid State
$[Cu(epic)_2Cl_2]$	1.81	12.7	12.5 (57)	17.2, 14.1
$[Cu(epic)Cl_2]$	1.85	14.9	insol	13.0
$[Ni(epic)_2Cl_2]$	3.05	2.0	14.2 (17)	14.5, 9.0
$[Co(epic)_2Cl_2]$	4.83	9.6	17.0 (110), 14.8 (4.0)	17.2, 14.3
$[Fe(epic)_2Cl_2]$	5.24	decomp	20.0 (400)	-
$[Mn(epic)_2Cl_2]$	5.85	7.0	-	-
$[Cu(epic)_2(H_2O)_2](ClO_4)_2$	-	148, 178[d], 155[e]	-	14.1
$[Ni(epic)_2(H_2O)_2](ClO_4)_2$	-	154	-	17.2, 15.1, 10.5
$[Co(epic)_2(H_2O)_2](ClO_4)_2$	-	147	-	21.1
$[Zn(epic)_2(H_2O)_2](ClO_4)_2$	-	159	-	-

[a] Mean values (±0.01 B.M.) from measurements at three field strengths, 17.0°.

[b] In nitroethane solution at 25°, complex concentration ca. 1.5×10^{-3}M

[c] Extinction coefficients given parenthetically

[d] In nitromethane

[e] In dimethyl formamide

components (15.1 and 17.2 kK) presumably through spin-orbit coupling. The ratio of ν_2/ν_1 is 1.61 for the chloro complex, which is in the range of values (1.5 - 1.7) considered diagnostic for six-coordinate nickel(II) structures[132].

The measured magnetic moments of the remaining complexes of the type $[M(epic)_2Cl_2]$ all indicate a weak octahedral field about the metal centres[11]. The magnetic moment of the manganese(II) complex at 5.85 B.M. is in good agreement with the value expected (5.92 B.M.) from the "spin only" approximation, $\mu = (n(n + 2))^{\frac{1}{2}}$. The weak ligand field exerted by the chloro and pyridyl groups is insufficient to effect spin pairing in iron(II).

The i.r. spectra of complexes of the type $[M(epic)_2(H_2O)_2](ClO_4)_2$ are essentially identical in the region 1100 - 600 cm^{-1}. The presence of a strong band at 1050 cm^{-1} together with bands at 930 (w) and 620 (s) cm^{-1} is expected for complexes in which perchlorate ion does not function as a ligand. It has been claimed on the strength of i.r. evidence that both perchlorate groups are coordinated in the complex formulated as $[Cu(epic)_2(ClO_4)_2]$[129]. The perchlorate ion has a regular tetrahedral structure (symmetry T_d), and nine vibrational degrees of freedom are distributed among four normal modes of vibration. The band at 1050 cm^{-1} in the spectra of the 2-carbethoxypyridine complexes may be assigned to the assymetric stretch vibration (ν_3) of the perchlorate anion. The non degenerate frequency (ν_1) which is theoretically forbidden in the infrared, occurs as a weak absorbtion at 930 cm^{-1}. The absorption becomes weakly allowed owing to distortion of the ion in the crystal lattice[133].

Table 25

Principle Bands in the I.R. Spectra of the Ligand and Complexes

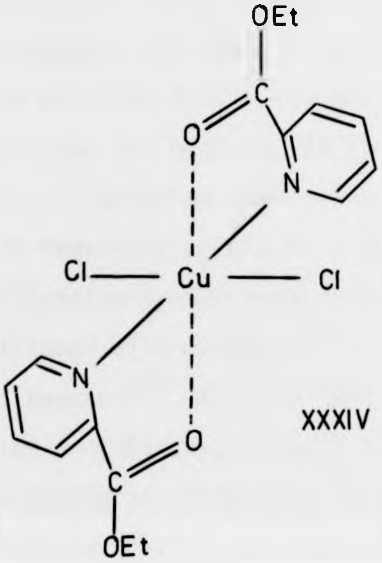
Compound	$\nu_{C=O}$	$\nu_{C=N}$ C=C	ν^{as}_{C-O-C}	Other Bands[a]
epic	1729	1592	1245	
$Cu(epic)_2Cl_2$	1709	1598	1260	
$Cu(epic)Cl_2$	1659	1597	1269	
$Ni(epic)_2Cl_2$	1671	1598	1260	
$Co(epic)_2Cl_2$	1678	1595	1261	
$Fe(epic)_2Cl_2$	1689	1596	1258	
$Mn(epic)_2Cl_2$	1688	1592	1260	
$[Cu(epic)_2(H_2O)_2](ClO_4)_2$	1650	1601	1275	1050, 930, 618
$[Ni(epic)_2(H_2O)_2](ClO_4)_2$	1665	1602	1271	1050, 930, 618
$[Co(epic)_2(H_2O)_2](ClO_4)_2$	1670	1600	1270	1050, 930, 620
$[Zn(epic)_2(H_2O)_2](ClO_4)_2$	1678	1600	1268	1050, 931, 628

[a] Bands due to perchlorate

The assymmetric bending vibration (ν_4) occurs at 620 cm^{-1}. Coordination of perchlorate lowers the symmetry of the ion to C_{3v}. The spectra of complexes containing bound perchlorate exhibit two well resolved bands between 1200 and 1000 cm^{-1} and an equally strong absorption at ca. 920 cm^{-1}. A detailed analysis of the i.r. spectra of compounds containing coordinated perchlorate has been given by Hathaway and Underhill[133].

Coordination of 2-carbethoxypyridine results in a lowering of $\nu_{C=O}$ by up to 79 cm^{-1}. In the free ligand $\nu_{C=O}$ is taken as 1729 cm^{-1}; which is the mean value of the two carbonyl stretch frequencies which occur at 1718 and 1740 cm^{-1}. Coordination also increases ν_{C-O-C} (free ligand value 1245 cm^{-1}) by ca. 15 - 30 cm^{-1}. These results indicate coordination of the ligand through the carbonyl oxygen.

Within a given series of complexes (i.e. $[M(epic)_2Cl_2]$ and $[M(epic)_2(H_2O)_2](ClO_4)_2$) the decrease in $\nu_{C=O}$ on coordination is roughly paralleled by the increase in the Lewis acidity of the central metal ion. Thus, in the latter series the carbonyl stretch frequency is decreased by 79, 64 59 and 51 cm^{-1} for M = Cu, Ni, Co and Zn respectively. The one exception to this generalization is found for $[Cu(epic)_2Cl_2]$ for which the magnitude of $\Delta\nu_{C=O}$(-20 cm^{-1}) would indicate only a weak interaction between the carbonyl oxygens and the metal centre. As a consequence of the Jahn-Teller effect the copper(II) ion in an octahedral environment forms four strong bonds coplanar with the metal ion with two longer bonds completing a distorted octahedron. Accordingly, the complex $[Cu(epic)_2Cl_2]$ has been assigned the structure (XXXIV) where the carbonyl oxygen atoms occupy these apical coordination sites.



XXXIV

Possibly the most interesting aspect of the present study has been the observation that the mono- and bis-ligand complexes of copper(II) with 2-carbethoxypyridine undergo facile transesterification with methanol. A number of complexes of ligands containing carboxylic acid esters have been found to undergo transesterification on refluxing with alcohols[134-136]. Consequently, it was of interest to explore the reaction further. The reaction appears highly sensitive to α-substitution in the alcohol. Thus, after 30 min. reflux in allyl alcohol or n-propanol the complexes [Cu(epic)$_2$Cl$_2$] and [Cu(epic)Cl$_2$] were recovered unchanged when the reaction media were cooled to room temperature. The complex [Zn(epic)$_2$(H$_2$O)$_2$](ClO$_4$)$_2$ reacted in the presence of methanol, but the n.m.r. spectrum (in CD_3SOCD_3) of the products recovered after a 1 hour reflux period suggested that exchange was incomplete. An extended reflux period (24 hours) led to the recovery of a highly hygroscopic solid. Analysis of the n.m.r. spectrum of the product indicated that while exchange was complete methanolysis had also occurred. The peaks in the spectrum were attributable to the presence of water, 2-carbomethoxypyridine and methanol in the structural unit. Attempts to fully characterize the product were prevented owing to its very hygroscopic nature. Methanolysis rather than transesterification occurs when bis(ethylacetoacetato) copper(II) is refluxed with methanol[136].

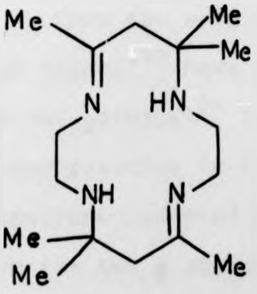
The work of Barnard[137] suggests that 2-carbomethoxypyridine should be obtained from [Cu(mepic)$_2$Cl$_2$] and [Cu(mepic)Cl$_2$] in good yield following sequestration of the metal ion by E.D.T.A. The transesterification reactions may therefore constitute a useful new route to the methyl ester. 2-Carbomethoxypyridine is not readily prepared by standard methods[138,139].

APPENDIX 2

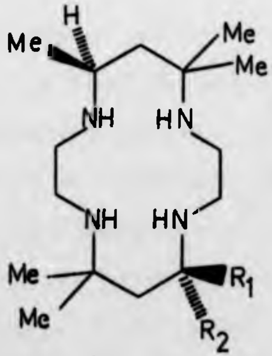
THE REACTION OF COPPER(II) WITH 5,7,7,12,14,14-HEXAMETHYL-1,4,8,11-TETRAAZACYCLOTETRADECANE

Tetraazacyclotetradecanes are 14-membered macrocyclic ligands containing 4 nitrogen donor groups that react with metal ions 10^3-10^4 times more slowly than analogous open chain amines, for which the rate determining step is formation of the first metal-nitrogen bond[140]. A number of explanations have been considered to account for the slower reaction rates of the macrocycles: a) multiple desolvation, such as accompanies the binding of metal ions into the more rigid porphyrin structures[141]; b) a high energy barrier to internal rotation, since some degree of ligand twisting or folding may be necessary to effect complexation[141-143]; c) steric effects due to N-substitution[144].

The macrocycle 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradec-4,11-diene (XXXIV) gives on reduction two diastereoisomeric hexamethyltetraazacyclotetradecanes (XXXV) and (XXXVI): designated tet a (meso) and tet b (racemic) by Curtis[145]*.



XXXIV



XXXV R_1= H , R_2=Me

XXXVI R_1= Me , R_2= H

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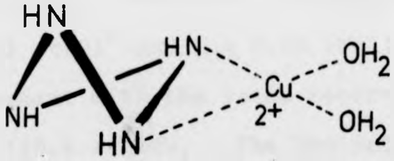
*An abbreviated nomenclature for the macrocycles has been described by Dabrowiak et al[146], according to which XXXIV is given as trans-Me_6[14]dieneN$_4$. It follows that meso- and racemic-Me_6[14]aneN$_4$ refer to tet a and tet b respectively. The saturated parent compound, 1,4,8,11-tetraazacyclotetradecane, is then [14]aneN$_4$.

Cabbiness and Margerum[141,147] have investigated the kinetics of formation of the copper(II) complexes of tet a. In neutral or slightly acidic solution copper(II) reacts with the ligand to give initially a blue complex $(Cu(tet\ a)(blue)^{2+}$ (λ_{max} 620 nm, ε = 193 $dm^3\ mol^{-1}\ cm^{-1}$) which readily converts to a more thermodynamically stable red form $Cu(tet\ a)(red)^{2+}$ (λ_{max} 520 nm, ε = 140 $dm^3\ mol^{-1}\ cm^{-1}$) at higher pH. Similar behaviour is exhibited by tet b.

Curtis[148] has assigned a square planar configuration to $Cu(tet\ a)(red)^{2+}$. The visible spectral data for $Cu(tet\ a)(blue)^{2+}$ would indicate that the copper(II) ion is bound by an N_2O_2 sequence of donor atoms (XXXVII) were it not for the exceptional stability of the complex $(Cu(tet\ a)(blue)^{2+}$, log K = 20, 25°[147]). For example, with copper(II) and ethylenediamine log K_1 = 10.5 at 25°.[149]

XXXVII



From the results of recent structural study[150] Buxtorf and Khaden[143] have inferred that the copper(II) ion in $Cu(tet\ a)(blue)^{2+}$ is penta-coordinate. However, this interpretation is based on an incorrect assumption, since the structure reported was for $[Cu(tet\ b)]_2Cl(ClO_4)_3$, rather than for its tet a analogue as was assumed by these workers. Moreover, an unusual feature in the structure of the dimer is a single chlorine bridge linking the two metal atoms, whereas $Cu(tet\ b)(blue)^{2+}$ is known to be monomeric in aqueous solution[150].

The stereochemistry about the copper(II) ion in Cu(tet a)(blue)$^{2+}$ cannot be definitely assigned from the results presently available.

Khaden[142], and later Lawrance[151], noted that the rate of formation of Cu(tet a)(blue)$^{2+}$ in acetate buffers was dependent on the buffer concentration but did not investigate this aspect of the reaction further. The following is a study of the kinetics of complexation of copper(II) by tet a in both the presence and absence of acetate ion to give Cu(tet a)(blue)$^{2+}$.

Materials and Measurements

Tet a was prepared as the dihydrate by Lawrance[151] from the sodium borohydride reduction of trans-$Me_6[14]dieneN_4$[152]. The compound was accepted as pure, m.p. 146-147° (Lit.,[145] 146-148°). Pipes was purchased from B.D.H. Other chemicals were of AnalaR quality.

Potentiometric titration of a saturated solution of tet a (8.5×10^{-4}M) at 25° and I = 0.1M (KCl) gave $pK_2^M = 10.30 \pm 0.05$ in good agreement with the value reported by Cabbiness and Margerum[147] (10.4 ± 0.1). The low solubility of the ligand prevented the determination of other protonation constants. A solvent extraction procedure has given $pK_1^M = 12.6$, and pK_3^M has been reported as 0.8 at 25° and I = 0.1M[147].

Spectrophotometric kinetic measurements were made with a Gilford 2400S instrument. Cu(tet a)(blue)$^{2+}$ exhibits a strong charge transfer band at 275 nm ($\varepsilon \sim 10^4$ dm^3 mol^{-1} cm^{-1}) and the complexation reaction was followed at this wavelength. A limited number of runs were followed by pH-stat methods using instrumentation previously described (Section 2.4). The copper(II) concentration was at least 20 times that of the ligand so that pseudo first order conditions were fulfilled. Under the conditions of measurements the conversion Cu(tet a)(blue)$^{2+}$ → Cu(tet a)(red)$^{2+}$ was not observed.

Rate constants were obtained from linear plots of $\log[OD_t - OD_\infty]$ against time except for slower reactions ($t_{\frac{1}{2}} > 100$ min.) where Guggenheim's method was applied.

Potentiometric measurements were made with a Radiometer 26 pH meter.

Results and Discussion

Rate constants for the reaction between copper(II) and tet a to give Cu(tet a)(blue)$^{2+}$ at 25° and I = 0.1M are tabulated in Table 26. At a particular hydrogen ion concentration the observed first order rate constant for the reaction is given by the three term equation (29), which is equivalent to (30).

$$k_{obs} = k_1\frac{[Cu^{2+}]}{a_{H^+}} + k_2\frac{[Cu^{2+}][OAc^-]}{a_{H^+}} + k_3\frac{[Cu^{2+}][HOAc]}{a_{H^+}} \qquad .....(29)$$

$$= k_1\frac{[Cu^{2+}]}{a_{H^+}} + k_2\frac{[CuOAc^+]}{K_{CuOAc^+}\cdot a_{H^+}} + k_3\frac{[CuOAc^+]}{K_{CuOAc^+}\cdot K^M_{HoAc}} \qquad .....(30)$$

In evaluating the relative contributions of the three terms to k_{obs} three parameters, k_2, k_3 and K_{CuOAc^+}, have been treated as variables. The value of the constant k_1 was fixed from the kinetic results obtained for reactions carried out in the absence of acetate. The value of K_{CuOAc^+} was set within the limits $60 < K_{CuOAc^+} < 120$ dm^3 mol^{-1}; which is the range of literature values[153] for this constant. The

Table 26

Rate Constants[a] for the Reaction of Copper(II) Chloride with Tet a at 25 and I = 0.1M ($NaClO_4$)

(i) In the Presence of Acetate

pH	$10^5\ a_{H^+}$/M	$10^3[OAc^-]$/M	$10^3[HOAc]$/M	$10^3[CuOAc^+]$/M	$10^3[Cu^{2+}]$/M	$10^4\ k_{obs}/s^{-1}$	$10^4\ k_{calc}{}^{b}/s^{-1}$
4.080	8.32	0.79	2.89	1.32	18.68	0.80	0.75
4.485	3.27	1.37	1.98	1.65	13.35	1.50	1.44
4.600	2.51	3.59	3.97	2.44	7.56	1.74	1.80
4.790	1.62	4.23	3.02	2.75	7.25	2.71	2.78
4.860	1.38	3.34	2.03	4.63	15.37	6.44	5.77
4.970	1.07	2.25	1.06	1.69	8.31	3.29	3.10
5.010	0.977	4.84	2.08	3.08	6.92	4.64	4.56
5.055	0.881	7.83	3.04	4.13	5.87	6.15	6.13
5.440	0.363	6.94	1.11	1.95	3.05	6.75	6.63

Table 26 (cont.)

(ii) In the Absence of Acetate[c]

pH	10^6 a_{H^+}/M	$10^3[Cu^{2+}]$/M	10^4 k_{obs}/s^{-1}	10^7 k_1^d/s^{-1}
5.000[e]	10.0	9.48	1.68	1.77
5.100[e]	7.94	9.48	2.13	1.78
5.200[e]	6.31	9.48	2.91	1.93
5.640	2.29	5.00	3.71	1.70
5.945	1.14	2.50	3.91	1.77
6.200	0.631	1.49	4.43	1.87
6.220	0.602	1.01	3.07	1.83
6.270	0.537	0.503	1.72	1.84

[a] Reactions monitored spectrophotometrically unless otherwise stated. Ligand concentration 2.7-3.3 x 10^{-5}M

[b] Calculated from equation (29) with k_1, k_2 and k_3 taking values of 1.8 x 10^{-7} s^{-1}, 8.3 x 10^{-5} dm^3 mol^{-1} s^{-1} and 3.0 x 10^{-5} dm^3 mol^{-1} s^{-1} respectively.

[c] Reaction media buffered with 5 x 10^{-3}M Pipes for spectrophotometric runs. A two fold variation in the buffer concentration did not appreciably alter the observed rates.

[d] Calculated from the expression $k_1 = k_{obs} \cdot a_{H^+}/[Cu^{2+}]$.

[e] pH-stat runs. Ligand concentration 1.0 x 10^{-4}M.

concentration of the various acetate species were obtained from pH measurements on the kinetic solutions and a knowledge of the total acetate concentration, using $K_{CuOAc} = 90$ dm^3 mol^{-1} and a calculated value for K^M_{HOAc} of 2.27×10^{-5} mol dm^{-3}[154] ($\gamma_1 = 0.772$) at 25° and I = 0.1M. Formation of $Cu(OAc)_2$ was not significant.

The rate law for the reaction may be written as (32)

$$\text{rate} = k_{obs}[\text{Total Tet } \underline{a}] \qquad \text{.....(31)}$$

$$= k_1\frac{[Cu^{2+}][\text{tet } \underline{a}\ H^+]}{K^M_2} + k_2\frac{[CuOAc^+][\text{tet } \underline{a}\ H^+]}{K_{CuOAc^+}\cdot K^M_2}$$

$$+ k_3\frac{[CuOAc^+][\text{tet } \underline{a}\ H_2^{2+}]}{K_{CuOAc^+}\cdot K^M_{HOAc}} \qquad \text{.....(32)}$$

where K^M_2 (5.0×10^{-11} mol dm^{-3}) is the mixed proton ionization constants for: tet $\underline{a}$ $H_2{}^{2+} \rightleftharpoons$ tet $\underline{a}$ $H^+ + H^+$. Substitution of the appropriate values for the equilibrium constants in (32) gives the simplified expression (33),

$$\text{rate} = k_1'[Cu^{2+}][\text{tet } \underline{a}\ H^+] + k_2'[CuOAc^+][\text{tet } \underline{a}\ H^+]$$

$$+ k_3'[CuOAc^+][\text{tet } \underline{a}\ H_2^{2+}] \qquad \text{.....(33)}$$

with k_1', k_2' and k_3' taking values of 3.6×10^3, 1.8×10^4 and 1.5×10^{-2} dm^3 mol^{-1} s^{-1} respectively at 25°.

The third term in equation (33) could arise from a number of pathways: (i) a bimolecular reaction between tet $\underline{a}$ H_2^{2+} and $CuOAc^+$, (ii) HOAc acting a general acid catalyst in the reaction of Cu^{2+} with tet $\underline{a}$ H^+ or (iii) OAc^- acting as a basic catalyst in the reaction between Cu^{2+} and tet a H_2^{2+}.

In the latter event, it would be expected that bases stronger than acetate should also contribute to catalysis, but the reactions carried out in the presence of Pipes (pK_2^M = 6.73, Section 6.2.3) show this is not the case. A pathway involving general acid catalysis also seems unlikely because complex formation between Cu^{2+} and tet a H^+ is not subject to hydrogen ion catalysis. This leaves (i) as the most probable pathway which is consistent with the absence of terms involving Pipes concentration in the rate equation. Under the conditions of the present study binding of copper(II) to Pipes species was negligible.

The term involving k_2' in equation (33) is similarly ambiguous as this can result either from the reaction of $CuOAc^+$ with tet a H^+ or from the kinetically equivalent OAc^- catalysed reaction between Cu^{2+} and tet a H_2^{2+}. Application of the arguments above would indicate that the former interpretation is correct.

Although tet a H_2^{2+} is the predominant form of the ligand in the pH range over which the reaction was studied the major contribution to the observed rate comes from the reaction of tet a H^+. The macrocyclic structure causes the two protons in tet a H_2^{2+} to be nearer one another than would be the case for an open chain polyamine. It has been suggested[141] that the relatively high value of pK_2^M (10.3) indicates strong internal hydrogen bonding within the di-protonated ligand and this may compensate for electrostatic repulsion between the two protons. While the reaction of $CuOAc^+$ with tet a H_2^{2+} has been detected the corresponding reaction of Cu^{2+} has not.

Presumably because of electrostatic repulsion it is kinetically more difficult for Cu^{2+} to react with tet a H_2^{2+}.

The rate constants for the reaction of Cu^{2+} and $CuOAc^+$ with tet a H^+ are 3.6×10^3 and 1.8×10^4 dm^3 mol^{-1} s^{-1} respectively; while for $CuOAc^+$ with tet a H_2^{2+} the value is 1.5×10^{-2} dm^3 mol^{-1} s^{-1}. Electrostatic repulsion of the ions may account for the five-fold difference in the reaction rates of Cu^{2+} and $CuOAc^+$ with the mono-protonated ligand. These relatively slow rates are in marked contrast to those observed for the reaction of Cu^{2+} with non-cyclic polyamines. For example, with 1,4,7,10,13-pentaazatridecane (tetraethylenepentamine = tetren) the various protonated forms tetren H_2^{2+}, tetren H_3^{3+} and tetren H_4^{4+} can all react with Cu^{2+} with resolved rate constants of 4.2×10^7, 1.6×10^5 and 1.4×10^4 dm^3 mol^{-1} s^{-1} respectively. Here also, the inclusion of acetate as a buffer in the reaction mixtures causes an increase in the rates of reaction[140].

In the present case the reaction of copper(II) species with tet a show no evidence for the accumulation of intermediates, and the final product is Cu(tet a)(blue)$^{2+}$. The conversion of the blue isomer to the square planar form, Cu(tet a)(red)$^{2+}$, is believed to proceed through a conjugate base mechanism featuring deprotonation of a secondary nitrogen donor group[142]. At 25° Cu^{2+} reacts with the mono-protonated form of 1,4,8,11-tetraazacyclotetradecane ([14]aneN_4) with a second order rate constant of 2.6×10^5 dm^3 mol^{-1} s^{-1}, which is two orders of magnitude greater than the rate constant for the reaction of Cu^{2+} with tet a H^+, and the product is the square planar red complex[155]. Buxtorf and Khaden have suggested[143] that species analogous to Cu(tet a)(blue)$^{2+}$ are intermediates on the reaction path for the formation of all square planar copper(II)-tetraazacyclotetradecane complexes. If this is the case the decrease in the complexation rates on passing from [14]aneN$_4$ to tet a is most probably a consequence of the steric restraint imposed by the six methyl groups in the latter ligand. Whether the conformation change occurs in a rapid pre-equilibrium step before metal-nitrogen bond formation, or takes place later in the complexation process is difficult to decide at the present time.

APPENDIX 3

PROTON IONIZATION CONSTANTS OF 2-SUBSTITUTED 8-QUINOLINOLS

3.1 Spectrophotometric Determination of the pK_a of 2-Cyano-8-quinolinol (LH) at 25° and I = 0.01M

pH	6.3	8.065	8.290	8.495	8.770	9.040	9.290	12
OD_{414nm}	0.053 (LH)	0.181	0.252	0.343	0.451	0.563	0.625	0.809 (L^-)
pK_1^M	-	8.75	8.73	8.76	8.72	8.72	8.73	-

Mean $pK_1^M = 8.73 \pm 0.03$, $pK_1^T = 8.78$

3.2 Spectrophotometric Determination of the pK_a of 2-Carbomethoxy-8-quinolinol (EH) at 25° and I = 0.1M

pH	7.0	8.510	8.750	8.940	9.130	9.320	9.575	9.770	11.5
OD_{399nm}	0.196 (EH)	0.307	0.358	0.427	0.504	0.583	0.687	0.749	0.909 (E^-)
pK_1^M	-	9.24	9.28	9.26	9.25	9.24	9.23	9.25	-

Mean $pK_1^M = 9.25 \pm 0.03$, $pK_1^T = 9.36$

3.3 Potentiometric Titration of 2-Acetyl-8-quinolinol (HA)

Conditions: 100cm^3 of a solution 3.75 x 10^{-4}M in 2-acetyl-8-quinolinol and 0.1M in NaClO$_4$ titrated under nitrogen with 10^{-3}M KOH at 25°.

pH	Titrant /cm^3	10^4 a_{OH^-} /M	10^4[HA] /M	10^4 a_{A^-} /M	[HA]/a_{A^-}	log Col.6	pK_1^T
5.908	-	-	3.750	-	-	-	-
7.898	0.3	0.008	3.447	0.224	15.4	1.188	9.09
8.180	0.6	0.015	3.143	0.448	7.02	0.846	9.03
8.432	0.9	0.027	2.844	0.668	4.26	0.629	9.06
8.620	1.2	0.042	2.548	0.884	2.88	0.459	9.08
8.770	1.5	0.059	2.254	1.099	2.05	0.312	9.08
8.900	1.8	0.080	1.964	1.310	1.50	0.176	9.08
9.030	2.1	0.107	1.679	1.514	1.11	0.045	9.08
9.146	2.4	0.140	1.402	1.713	0.818	-0.087	9.06
9.259	2.7	0.182	1.133	1.902	0.596	-0.225	9.03
9.439	3.0	0.234	0.875	2.086	0.419	-0.378	9.06

Mean $pK_1^T = 9.06 \pm 0.03$, $pK_1^M = 8.95$

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