Uncatalysed and Metal Ion-catalysed Hydrolysis of 8-Quinolyl Sulphate †

By **Robert W. Hay,*** **Charles R. Clark,** and (in part) **John A. G. Edmonds,** Chemistry Department, University of Stirling, Stirling, Scotland

The acid-catalysed hydrolysis of 8-quinolyl sulphate has been studied over the acidity range 1·06—5·29M-HCl at 30 °C. A plot of log k_{obs} against $-H_0$ is linear with a slope of 0·99, and Bunnett–Olsen plots give a value of $\phi = +0{\cdot}04$. The solvent deuterium isotope effect, $k_{D_2O}/k_{H_2O} = 1{\cdot}9$, and the effect of dioxan content on the rate are all consistent with an *A*-1 mechanism for the hydrolysis.

The reaction is subject to pronounced catalysis by copper(II) ions in the pH range 5·4—5·8 at 39·8 °C and *I* = 0·1M. Possible mechanisms for the metal ion catalysis are considered.

RECENTLY there has been considerable interest in the hydrolysis of aryl sulphate esters. Kice and Anderson [1] have shown that the acid-catalysed hydrolysis of aryl sulphates, unlike the hydrolysis of the aryl selenates,[2] probably proceeds by an *A*-1 pathway (Scheme 1). Nucleophilic catalysis by amines has been observed in the hydrolysis of *p*-nitrophenyl sulphate [3] and intramolecular carboxyl group catalysis occurs with salicyl sulphate [4] as with salicyl phosphate.[5,6] The hydrolysis of a number

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† Preliminary communication, R. W. Hay and J. A. G. Edmonds, *Chem. Comm.*, 1967, 969.

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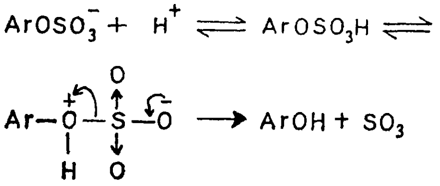
of phosphates and acyl phosphates, *e.g.*, acetyl phosphate,[7,8] salicyl phosphate,[9,10] 3-pyridyl phosphate,[11] and 8-quinolyl phosphate[11,12] is catalysed by metal ions. The present paper discusses a similar metal ion-catalysed hydrolysis of a sulphate ester.



SCHEME 1

EXPERIMENTAL

Potassium 8-quinolyl sulphate, described by Czapek,[13] was prepared by Dodgson and Spencer's method[14] based on the procedure of Burkhardt and Lapworth[15] (Found: C, 41·1; H, 2·3; N, 5·3. Calc. for $C_9H_6KSO_4$: C, 41·2; H, 2·3; N, 5·3%). Analysis by complete acidic hydrolysis and spectrophotometric determination of the liberated 8-hydroxyquinoline established the purity to be 101·0 ± 1·0%. Deuterium chloride (isotopic purity 99%) was obtained from Merck as a 20% solution in deuterium oxide.

Dioxan was refluxed with sodium after preliminary drying (KOH), then distilled from sodium and the fraction of b.p. 100·5—102 °C collected and stored in tightly stoppered amber bottles. Before use it was passed through a column of activated alumina to remove peroxides.[16] AnalaR copper(II) chloride and nitrate, nickel(II) chloride, and zinc(II) sulphate were employed to prepare the metal ion solutions.

Kinetic Measurements.—A Hilger–Watts Uvispek spectrophotometer and a Gilford 2400S spectrophotometer were used for kinetic measurements. Reactions were carried out in stoppered 1 cm silica cells in the thermostatted cell holder of the instrument controlled by a Braun Thermomix II unit to ±0·1 °C.

The concentration of 8-quinolyl sulphate was $1{\cdot}5 \times 10^{-5}$M in all kinetic studies. The acid-catalysed hydrolysis was followed spectrophotometrically by monitoring the release of 8-hydroxyquinoline at 253 nm where the optimum absorbance change occurred. Absorption data for the BH^+ forms (in 0·1M-HCl) are 8-hydroxyquinoline, $\lambda_{max.}$ 251·5 nm (ε 44 000) and 8-quinolyl sulphate, $\lambda_{max.}$ 239·5 nm (ε 39 000). Plots of log $(A_\infty - A_t)$ against time were linear for at least 80% reaction and the pseudo-first-order rate constants, k_{obs}, were obtained from the slope. Infinity readings were taken after at least ten half-lives. Kinetic runs were initiated by adding 5—7 μl of a concentrated aqueous solution of the sulphate ester to the appropriate equilibrated acid medium in the spectrophotometer cell. Reactions in $HClO_4$–dioxan media were initiated immediately after solution preparation to minimise the formation of peroxides; however, no peroxide effect was observed. The copper(II)-catalysed hydrolysis was studied at 39·8 °C by monitoring at 255 nm [$\lambda_{max.}$ for the copper(II) complex of 8-hydroxyquinoline]. Reaction mixtures were maintained at constant ionic strength of 0·10M with potassium chloride (separate experiments established that potassium ions did not catalyse the reaction). Buffers were not employed, the pH being effectively controlled in the range 5·4—5·8 by hydrolysis (1) of the aquo-copper(II) ion. Since the metal ion was always

$$[Cu(H_2O)_6]^{2+} \rightleftharpoons [Cu(H_2O)_5(OH)]^+ + H^+ \qquad (1)$$

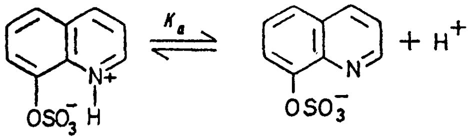
in at least a 100-fold excess over the substrate, pseudo-first-order conditions prevailed.

The pseudo-first-order rate constants at constant metal ion concentration were obtained from the slope of plots of log $(A_\infty - A_t)$ against time.

All pH measurements were carried out with a Radiometer 28 pH meter with G202B glass and K401 calomel electrodes. The electrode system was standardised with 0·05M-potassium hydrogen phthalate.

RESULTS AND DISCUSSION

The ionisation constant K_a of 8-quinolyl sulphate was determined spectrophotometrically at 25 °C as described by Albert and Serjeant[17] by use of the low absorbance acetate buffers (I = 0·01M) described by Perrin.[18] At



(BH+) (B)

239·5 nm the extinction coefficient of the conjugate acid (BH^+) of 8-quinolyl sulphate is *ca.* ten times that of the free base form (B) and this wavelength was employed for the measurements. The mean value of the practical ionisation constant (Table 1) is 4·49 ± 0·03 at I = 0·01M and 25 °C, which may be compared with $pK_a(^+NH)$ =

TABLE 1

The ionisation constant of 8-quinolyl sulphate at 25 °C and I = 0·01M [a]

pH	Absorbance	pK_a ($^+$NH)
4·06	0·565	4·49
4·23	0·508	4·48
4·47	0·426	4·50
4·62	0·359	4·48
4·83	0·288	4·50
5·01	0·224	4·47
5·18	0·185	4·48
<2	0·754 (BH^+)	
<11	0·071 (B)	

[a] Wavelength of measurement 239·5 nm.

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[17] A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases, Methuen, London, 1962.

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5·13 for 8-hydroxyquinoline[19] at 25 °C. The sulphate ester is a somewhat weaker base.

Acid-catalysed Hydrolysis.—In acidic solution, 8-quinolyl sulphate undergoes quite easy hydrolysis. The pseudo-first-order rate constants k_{obs} obtained over a range of hydrochloric acid concentrations (1·06—5·29M) are summarised in Table 2. The reaction is 'well-behaved' in the Hammett–Zucker sense. A plot of log k_{obs} against the Hammett acidity function $-H_0$ is quite linear with a slope of 0·99. Similar observations have been made with *p*-nitrophenyl sulphate and other sulphate esters.[4,20] It has been established[21] that the H_- function obtained for the protonation of $ArSO_3^-$ ions by hydrochloric and perchloric acids parallels H_0 for acid concentrations between 1·5 and 6M, so that a correlation of the Hammett–Zucker type is not unexpected. Bunnett–Olsen plots[22] gave a value for $\phi = +0·04$, a figure close to the zero and negative values indicative of an *A*-1 process and well outside the range of +0·22 to +0·56 considered typical for an *A*-2 hydrolysis.

TABLE 2

The acid-catalysed hydrolysis of 8-quinolyl sulphate

(*a*) Hydrochloric acid solutions at 30·0 °C

HCl/M	10^3k_{obs}/min^{-1}
1·06	1·45
2·11	4·28
3·17	9·90
4·23	24·3
5·29	56·0

(*b*) Solvent deuterium isotope effect at 20·0 °C

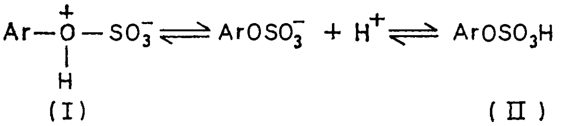
Acid	10^3k_{obs}/min^{-1}	k_{D_2O}/k_{H_2O}
6·54M-DCl	85·4	1·9
6·54M-DCl	46·0	

(*c*) Effect of dioxan content in dioxan–water mixtures at 29·8 °C and [HClO$_4$] = 0·51M

		$k_{obs}/k_{40\%\ dioxan}$	
Solvent	10^3k_{obs}/min^{-1}	8-Quinolyl sulphate hydrolysis	Methyl selenate hydrolysis[a]
40% Dioxan	3·75	(1·0)	(1·0)
60% Dioxan	11·7	3·1	1·6
80% Dioxan	85·0	23·0	6·3

[a] Data are for solutions 0·10M in HClO$_4$ at 25·1 °C from ref. 2.

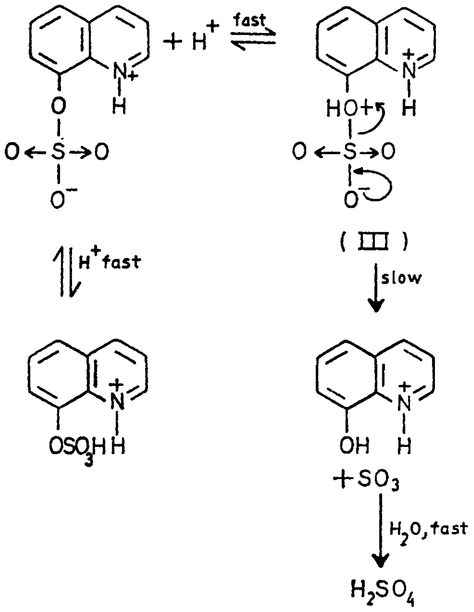
The solvent deuterium isotope effect, $k_{D_2O}/k_{H_2O} = 1·9$ (Table 2) is in the range (1·9—2·6) considered typical[23,24] for *A*-1 hydrolyses and is much larger than the value of concentration the fraction of aryl sulphate ion present at equilibrium as either (I) or (II) should increase significantly with increasing dioxan content.



(I) (II)

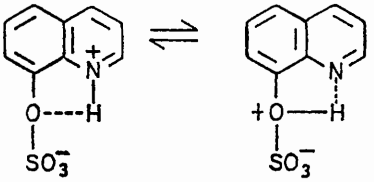
$$\mathrm{Ar{-}\overset{+}{\underset{\displaystyle H}{O}}{-}SO_3^-} \rightleftharpoons \mathrm{ArOSO_3^-} + \mathrm{H^+} \rightleftharpoons \mathrm{ArOSO_3H}$$

In an *A*-1 type hydrolysis, values of k_{obs} should, at a constant hydrogen ion concentration, increase markedly as the dioxan content of the medium is increased.[1] The effect on an *A*-2 hydrolysis should be much less owing to the concomitant decrease in the water concentration. The results (Table 2) are compared with the relevant constants for the *A*-2 hydrolysis of methyl selenate.[2] The results again support the view that the acid-catalysed hydrolysis of 8-quinolyl sulphate proceeds by the *A*-1 pathway previously suggested for the hydrolysis of other aryl sulphate esters (Scheme 2). 8-Quinolyl sulphate and mononitrophenyl sulphates undergo acidic hydrolysis at



SCHEME 2 Acid-catalysed hydrolysis of 8-quinolyl sulphate

to intramolecular general acid catalysis (2). Intramolecular general acid catalysis has been observed in the hydrolysis of 2-pyridylmethyl,[25] 6-methyl-2-pyridylmethyl,[26] 2-pyridylethyl,[26] and 8-quinolyl phosphates.[27] Intramolecular proton transfer from the pyridyl or quinolyl nitrogen to the ester oxygen is facilitated in the pre-equilibrium step by the five- or six-membered chelate ring. It seems likely, therefore, that the hydrolysis of 8-quinolyl sulphate is an example of intramolecular general acid catalysis in sulphate ester hydrolysis, but a detailed mechanistic investigation would be required to confirm this.


(2)

Metal Ion-catalysed Hydrolysis.—The copper(II)-catalysed hydrolysis was studied at 39·8 °C with metal : substrate ratios $\geqslant 130:1$. Under these conditions the reaction was pseudo-first order in the sulphate ester. The kinetic data are in Table 3. A plot of k_{obs} against the copper(II) concentration is linear. The pseudo-first-order rate constant k_{obs} is given by expression (3) where

$$k_{obs} = k_u + k_{cat}[Cu^{II}] \qquad (3)$$

k_u is the rate constant for the uncatalysed reaction in the pH range 5·4—5·8 (which is negligible), and k_{cat} is the catalytic rate constant. At low metal-ion concentrations the value of k_{cat} is 3·5 l mol^{-1} min^{-1} at 39·8 °C and $I = 0{\cdot}1$M. Some runs were also carried out at much higher metal-ion concentrations in the hope that the substrate would be fully complexed (metal : ligand ratios $\geqslant 3{\cdot}3 \times 10^4 : 1$). Even at the highest metal-ion concentrations used the order was still first in metal ion, and it was impossible to obtain the rate constant for hydrolysis of the copper(II) complex. As the copper(II) concentration is increased, the pH falls and competition between the metal ion and the proton becomes important.

TABLE 3

The metal ion-catalysed hydrolysis of 8-quinolyl sulphate at 39·8 °C

(*a*) Low copper(II) concentrations ($I = 0{\cdot}10$M)

$10^3[Cu^{II}]$/M	$10^3 k_{obs}$/min^{-1}
2·01	7·0
3·01	10·8
4·02	14·0
5·02	18·1
6·03	21·3

(*b*) High copper(II) concentrations ($I = 3{\cdot}0$M) [a]

$[Cu^{II}]$/M	pH (40 °C)	$10^2 k_{obs}$/min^{-1}
0·50	2·47	2·90
1·00	2·47	5·85
1·00	2·47	5·76

[a] Reaction monitored at 360 nm, with the metal nitrate as catalyst and KNO_3 as the supporting electrolyte. Rate constants obtained from infinity plots.

(*c*) Nickel(II)-catalysed hydrolysis ($I = 3{\cdot}0$M) [b]

$[Ni^{II}]$/M	pH (40 °C)	$10^3 k_{obs}$/min^{-1}
0·50	5·59	1·51
1·00	5·59	3·17
1·00	4·64	2·91

[b] Reaction monitored at 255 nm, with the metal chloride as the catalyst and KNO_3 as the supporting electrolyte. Rate constants were obtained from computer-extrapolated infinity plots. Substrate concentration $1{\cdot}5 \times 10^{-5}$M in all runs.

It is clear that the catalytic effect of copper(II) on the hydrolysis is very great. Rough estimates suggest that the 1 : 1 copper complex probably hydrolyses some 10^5—10^6 times more rapidly than the free substrate in the pH range 5—6.

It is also interesting to compare proton catalysis with metal-ion catalysis. For the hydrolysis of the ester in 3·17M-HCl at 30 °C, $k_{obs} = 9{\cdot}90 \times 10^{-3}$ min^{-1} while $k_{obs} = 18{\cdot}1 \times 10^{-3}$ min^{-1} at a copper(II) concentration of 5×10^{-3}M and 39·8 °C.

The catalytic effect of zinc(II) and nickel(II) was also briefly investigated. These reactions were considerably slower than the analogous copper-catalysed reactions mainly because of the less favourable formation constants. The data for nickel(II) catalysis at 40 °C are in Table 3. The reaction is independent of pH within the range 4·6—5·6 and k_{cat} is *ca.* 3×10^{-3} l mol^{-1} min^{-1} at $I = 3{\cdot}0$M.

Some reactions were also studied by the sealed-tube technique at 70 °C. In the presence of $2{\cdot}0 \times 10^{-2}$M-nickel(II), the 8-quinolyl sulphate underwent 50% hydrolysis in 4 h at 70 °C. With $2{\cdot}0 \times 10^{-2}$M-zinc(II), no detectable hydrolysis occurred during the same period. Comparative runs with copper(II) gave values of k_{obs} with 5×10^{-5}M- and $1{\cdot}0 \times 10^{-4}$M-copper(II) of $5{\cdot}9 \times 10^{-3}$ and $11{\cdot}3 \times 10^{-3}$ min^{-1} respectively; the half-life of the latter reaction is 61 min and the value of k_{cat} is *ca.* 115 l mol^{-1} min^{-1} at 70 °C. Thorium(IV) has been observed to have a very pronounced catalytic effect on the hydrolysis of 8-quinolyl phosphate and its effect was therefore investigated. Thorium(IV) nitrate ($8{\cdot}9 \times 10^{-3}$M) in 0·100M-HCl (to suppress the formation of hydro-species) did not catalyse the reaction despite spectral evidence for complex formation under these conditions. [In the presence of thorium(IV) the absorption maximum of the BH^+ form of 8-quinolyl sulphate at 239·5 nm moved to 245 nm and the intensity of the absorption band was greatly reduced.]

It seems probable that catalysis by copper(II) is due to the formation of a complex such as (IV) containing a 5-membered chelate ring, polarisation of the oxygen atom by copper(II) assisting the transfer of electrons from the sulphur–oxygen bond undergoing cleavage. The metal ion-catalysed hydrolysis should occur with S–O rather than C–O bond cleavage. Benkovic [4] and Spencer [28] have shown that both S–O (85%) and C–O (15%) cleavage occurs in the spontaneous (*i.e.*, uncatalysed) hydrolysis

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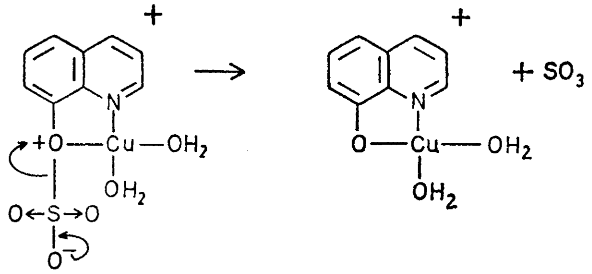
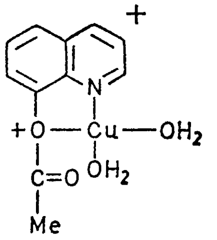
of *p*-nitrophenyl sulphate while the results of Spencer[29] indicate that base hydrolysis occurs with both S–O (33%) and C–O (66%) bond cleavage.

A strong driving force in the metal ion-catalysed reaction is probably the formation of the very thermodynamically stable copper(II) complex of 8-hydroxyquinoline (V), log $K_1 = 14{\cdot}27$ at 25 °C and $I = 0{\cdot}01$M.[30]

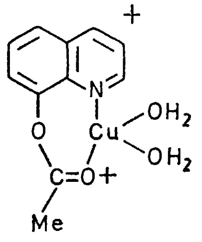


(IV) (V)

A somewhat similar complex (VI) has been considered to account for the copper(II)-catalysed hydrolysis of 8-acetoxyquinoline,[31] although in this case the alternative complex (VII) must also be considered.



(VI)



(VII)

It is noteworthy that most aryl sulphates have pH optima in the acidic range (pH 4—6) and although metal ions do not appear to have been implicated in their action,[32] this point has not been definitely established. The present results indicate that sulphate esters like phosphate esters are susceptible to metal-ion catalysis and such reactions may be important enzymically.

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[3/1066 *Received, 24th May,* 1973]

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