Kinetic and Equilibrium Studies of the Copper(II) Promoted Hydrolysis of Salicyl Phosphate. A Rate Acceleration of 10^8 for the Hydrolysis of a Phosphate Monoester Dianion

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The dissociation constants of salicyl phosphate (H_3L) at 10 °C and $I = 0.1$ mol dm^{-3} have been determined (pK_a values 1.84, 3.57, and 6.18). At a 1 : 1 ligand to metal ratio the interaction of copper(II) with salicyl phosphate can be described by the equilibria given below. The pK_a values

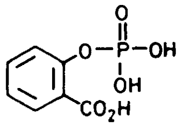
$$Cu^{2+} + H^+ + L^{3-} \rightleftharpoons CuHL \qquad \log \beta_{111} = 8.9 \pm 0.1$$

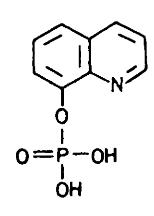
$$Cu^{2+} + L^{3-} \rightleftharpoons [CuL]^- \qquad \log \beta_{110} = 3.8 \pm 0.1$$

$$Cu^{2+} + H_2O + L^{3-} \rightleftharpoons [CuL(OH)]^{2-} + H^+ \qquad \log \beta_{11-1} = -2.1 \pm 0.1$$

for the ionisation processes $CuHL \rightleftharpoons [CuL]^- + H^+$ and $[CuL(OH_2)]^- \rightleftharpoons [CuL(OH)]^{2-} + H^+$ are 5.1 and 5.9 respectively. Kinetic studies establish that in the copper(II) promoted hydrolysis, the complex $[CuL]^-$ is the active species with $k_{CuL^-} = 6 \times 10^{-4}$ s^{-1} at 25 °C and $I = 0.1$ mol dm^{-3}. Copper(II) ions promote the hydrolysis of the dianion of the phosphate monoester by a factor of *ca.* 10^8. Previous work in this area had indicated only a small rate acceleration (*ca.* 10 fold) as comparisons were made between the metal-ion promoted reaction and the intramolecular general acid catalysed hydrolysis of the phosphate monoester dianion.

Copper(II) ions have been observed to catalyse the hydrolysis of a number of phosphate monoesters including salicyl phosphate (**1**),[1,2] 8-quinolyl phosphate (**2**),[3,4] and 2-(4-imidazolyl)phenyl phosphate (**3**).[5]


(**1**)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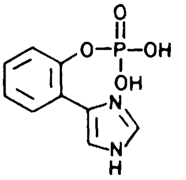

(**3**)

The catalytic effect observed with salicyl phosphate and 8-quinolyl phosphate was *apparently* quite small (*ca.* 10 fold). However, Benkovic and Dunikoski[5] have found that with (**3**) at pH 6 and a copper to substrate ratio of *ca.* 2 the rate enhancement is $> 10^4$ fold. In this case the copper(II) ion promotes the hydrolysis of the normally unreactive phosphate monoester dianion. Bromilow and Kirby[6] have established that the hydrolysis of the phosphate monoester dianion of salicyl phosphate is subject to intramolecular general acid catalysis by the carboxyl group leading to a rate acceleration of some 10^{10} fold when comparisons were made with the hydrolysis of the dianion of phenyl phosphate. The early studies of the copper(II) promoted hydrolysis of salicyl phosphate were carried out prior to the recognition of the significant catalytic effects in the solvolytic reaction. In addition, the nature of the catalytically active copper(II) species in solution was not well defined. For this reason we have reinvestigated the copper(II) promoted hydrolysis of salicyl phosphate and have also carried out a study of the relevant metal–ligand equilibria. The results of this work are reported in the present paper.

Experimental

Salicyl phosphate was prepared by the reaction of salicylic acid with phosphorus pentachloride essentially as previously described:[7] m.p. 161 162 C (lit.,[7] 162.5—163 °C) (Found: C, 38.25; H, 3.10. Calc. for $C_7H_7PO_6$: C, 38.55; H, 3.20%). The ^{31}P n.m.r. spectrum shows a singlet, δ 10.08, for Na_3PO_4 in D_2O solvent.

2,6-Dimethylpyridine-3-sulphonic acid (dmps) was prepared by sulphonation of 2,6-dimethylpyridine essentially as described by McElvain and Goese[8] for the sulphonation of pyridine. The compound was twice recrystallised from hot water after prior treatment with charcoal. The sulphonic acid derivative does not have a sharp melting point, melting in the range 305—310 °C (Found: C, 45.1; H, 4.80; N, 7.50. Calc. for $C_7H_9NO_3S$: C, 44.9; H, 4.85; N, 7.50%). Molecular weight by potentiometric titration, 187 (calc. 187.2). The pK_a of dmps was estimated by potentiometric titration of a 9.79×10^{-3} mol dm^{-3} solution (50 cm^3) with sodium hydroxide (0.2 mol dm^{-3}) at $I = 0.5$ mol dm^{-3} (KNO_3) and 25 °C. The practical pK_a is 4.86 ± 0.01, in good agreement with the value of 4.80 ± 0.05 quoted in the literature.[9]

Kinetics.—The copper(II) promoted hydrolysis of salicyl phosphate was studied using dmps–NaOH buffers. Elias and co-workers[9] have shown that this is an excellent non-co-ordinating buffer which minimises metal–buffer interactions ($K = 1.6$ for $Cu^{2+} + L \rightleftharpoons CuL$). Hydrolysis in the presence of copper(II) was monitored spectrophotometrically using the increase in absorbance at 320 nm due to formation of the copper(II) complex of salicylic acid [copper(II) as reference].

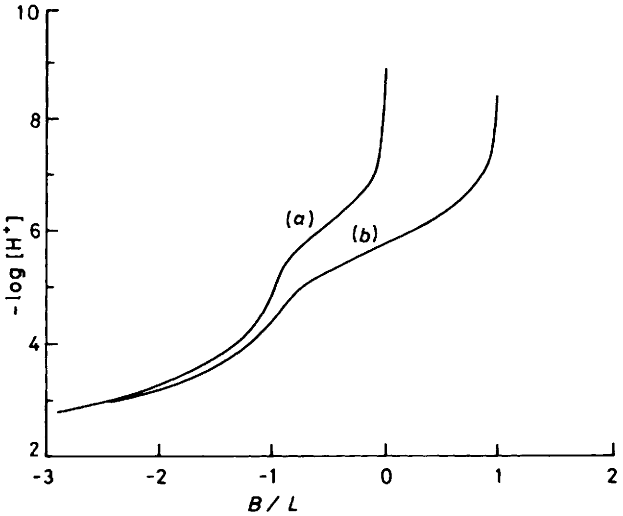


Figure 1. Titration curves for (*a*) salicyl phosphate; (*b*) salicyl phosphate and copper(II) perchlorate (1 : 1)

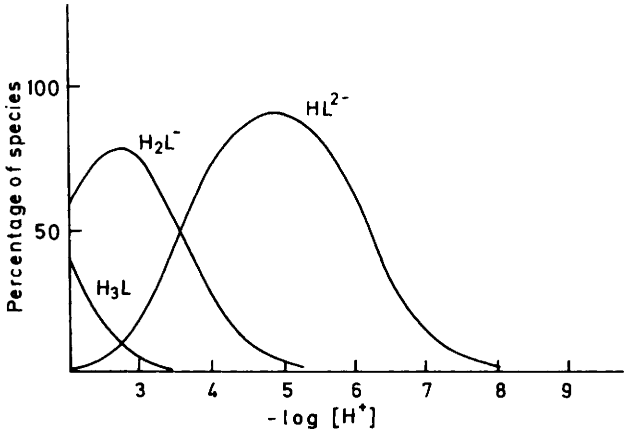


Figure 2. Species distribution curve for salicyl phosphate

Absorbance changes were logged directly by an Apple II computer interfaced with a Gilford 2400S spectrophotometer. Plots of log $(A_\infty - A_t)$ were linear for several half-lives, and values of $k_{obs.}$ were evaluated directly using the computing system. All kinetic runs were carried out at $I = 0.1$ mol dm^{-3}. The concentration of copper(II) perchlorate was varied between 2.5×10^{-4} and 6×10^{-3} mol dm^{-3}. The concentration of stock copper(II) solutions was estimated iodimetrically. The pH of solutions prior to, and on completion of hydrolysis, were checked using a Radiometer PHM-64 Research pH meter. The maximum pH variation was ±0.02 unit.

Potentiometric Measurements.—Potentiometric titrations of salicyl phosphate in the absence and presence of copper(II) (as the perchlorate salt) were carried out in a fully automatic system controlled by an Apple IIe computer. The equipment consisted of (*i*) a Radiometer PHM84 research pH meter equipped with a Beckman Futura glass electrode and an Ingold saturated sodium chloride–calomel reference electrode fitted in an Ingold bridge, (*ii*) a Radiometer ABU80 Autoburette, equipped with a 2.5/0.25 cm^3 B280 burette assembly, (*iii*) a Metrohm thermostatted cell, and (*iv*) a Huber MINISTAT digital thermostat. Typical concentrations used were in the range (0.5—1.0) $\times 10^{-3}$ mol dm^{-3}. The details of the experimental procedure have been published elsewhere.[10] The data were processed on a VAX 11/780 computer using the EXTEQUAD and MINISHORT programs,[11] two modified versions of the MINIQUAD[12] program. In the titration curves $-\log [H^+]$ was plotted *versus* *B*/*L*, the ratio of moles of standard base added (B) per mole of ligand (L). Negative values indicate excess of acid.

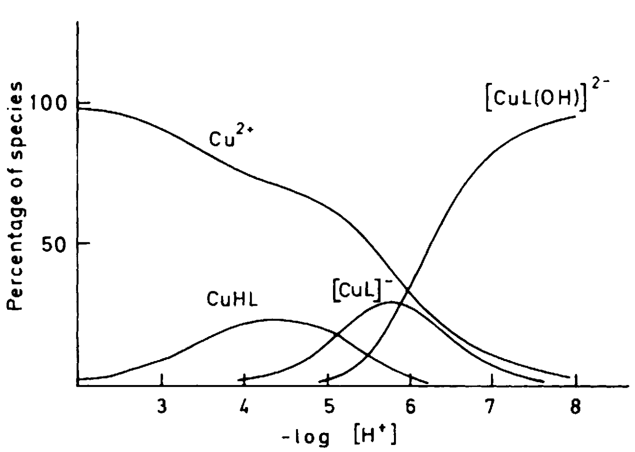


Figure 3. Species distribution curve for copper(II) complexes of salicyl phosphate at a 1:1 ligand to metal ratio, $[Cu^{2+}] = 1 \times 10^{-3}$ mol dm^{-3}

Interval scan spectra were determined using a Perkin-Elmer Lambda 5 instrument using copper(II) as the blank in the metal promoted reactions. ^{31}P N.m.r. studies were made with a Bruker WP80 instrument.

Results and Discussion

The acid–base behaviour of salicyl phosphate (H_3L) in aqueous solution ($I = 0.1$ mol dm^{-3} $NaClO_4$) was investigated by potentiometric titration at 10.0 ± 0.1 °C. In a typical experiment, a solution of H_3L and excess acid ($HClO_4$) was titrated with standard base, Figure 1(*a*). In the $-\log [H^+]$ region investigated (*ca.* 2.0—9.0) three protonation steps (1)—(3) are

$$H^+ + L^{3-} \rightleftharpoons HL^{2-} \qquad \log K_1 = 6.18 \pm 0.01 \qquad (1)$$

$$H^+ + HL^{2-} \rightleftharpoons H_2L^- \qquad \log K_2 = 3.57 \pm 0.02 \qquad (2)$$

$$H^+ + H_2L^- \rightleftharpoons H_3L \qquad \log K_3 = 1.84 \pm 0.04 \qquad (3)$$

observed. These various equilibria are summarised in Scheme 1, and the speciation curve is shown in Figure 2.

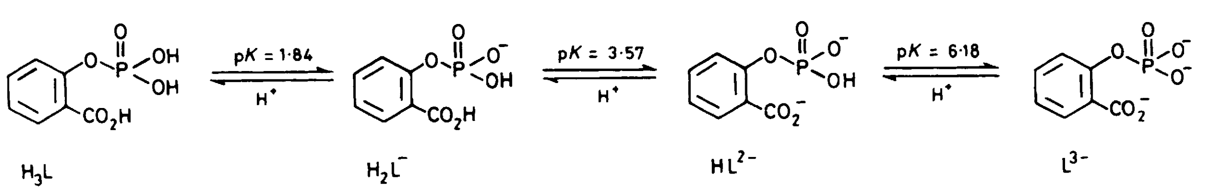
The interaction of copper(II) with salicyl phosphate (molar ratio 1:1) at 10.0 ± 0.1 °C was investigated in the $-\log [H^+]$ range 2.0—8.5. At $-\log [H^+] > 8.5$ some precipitation occurred. The titration curve obtained is shown in Figure 1(*b*). Inflections are observed at $B/L = -1$ and at $B/L = +1$. The titration data can be fitted to the series of three equilibria (4)—(6). The $\beta_{l,m,h}$ values are the corresponding formation

$$Cu^{2+} + H^+ + L^{3-} \rightleftharpoons CuHL \qquad \log \beta_{111} = 8.9 \pm 0.1 \qquad (4)$$

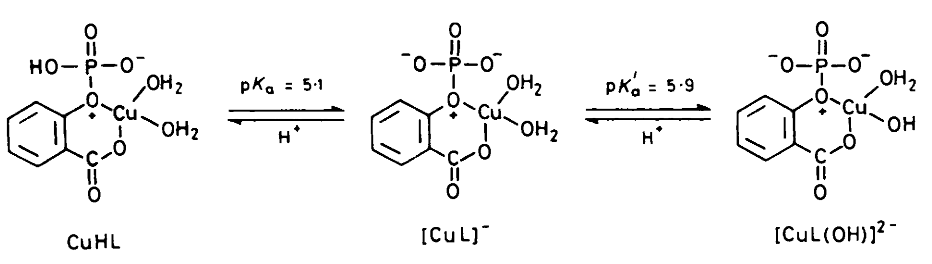
$$Cu^{2+} + L^{3-} \rightleftharpoons [CuL]^- \qquad \log \beta_{110} = 3.8 \pm 0.1 \qquad (5)$$

$$Cu^{2+} + H_2O + L^{3-} \rightleftharpoons [CuL(OH)]^{2-} + H^+ \qquad \log \beta_{11-1} = -2.1 \pm 0.1 \qquad (6)$$

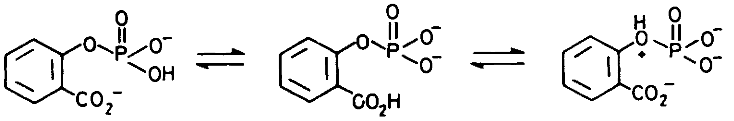
constants (where *l* is the stoicheiometric coefficient of the ligand, *m* that of the metal, and *h* that of the hydrogen ion in the



Scheme 1. Ionisation equilibria of salicyl phosphate



Scheme 2. Ionisation equilibria of the 1 : 1 complexes



Scheme 3. Equilibria involving HL^{2-}

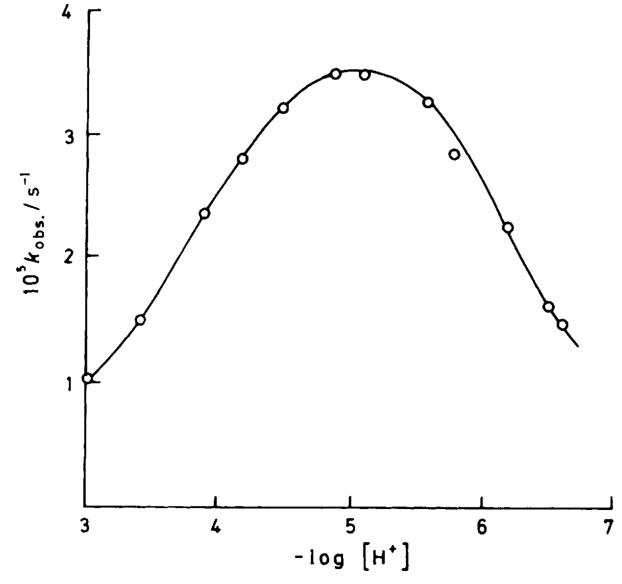
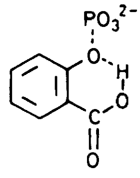


Figure 4. pH–Rate profile for the hydrolysis of salicyl phosphate at 30 °C and $I = 0.1$ mol dm^{-3}; data from ref. 2

complex. The distribution curve obtained is shown in Figure 3, and the various equilibria involved are shown in Scheme 2. It can be readily shown that $pK_a = \log \beta_{111} - \log \beta_{110}$ and $pK_a' = \log \beta_{110} - \log \beta_{11-1}$, giving $pK_a = 5.1$ and $pK_a' = 5.9$. The distribution curve shows that CuHL reaches its maximum concentration (*ca.* 28%) at $-\log [H^+] = 4.3$ and $[CuL]^-$ reaches its maximum (*ca.* 37%) at $-\log [H^+] = 5.65$, where $[CuL(OH)]^{2-}$ is already quite abundant. The complex $[CuL(OH)]^{2-}$ is *ca.* 100% abundant at $-\log [H^+] = 8.5$.

Kinetic Studies.—The hydrolysis of salicyl phosphate as a function of pH at 30 °C and $I = 0.1$ mol dm^{-3} (KNO_3) is illustrated in Figure 4. The reaction exhibits a bell-shaped pH rate profile with a rate maximum around pH 5 indicating that HL^{2-} is the reactive species in the hydrolysis of the phosphate monoester. The reactive species HL^{2-} can be represented by the series of equilibria in Scheme 3. Bromilow and Kirby[6] have shown that the salicyl phosphate dianion HL^{2-} undergoes hydrolysis at 39 °C some 1.57×10^3 times faster than the phenyl hydrogenphosphate monoanion, which lacks the *o*-carboxyl group. They have summarised the evidence for the occurrence of intramolecular general acid catalysis involving a transition state of the type (**4**). Cleavage of the P–O bond, which is well advanced is assisted by general acid catalysis by the neighbouring carboxyl group.



(**4**)

Copper(II) *Catalysis.*—The hydrolysis of salicyl phosphate (1×10^{-3} mol dm^{-3}) in the presence of various concentrations of copper(II) (0.25×10^{-3} to 6×10^{-3} mol dm^{-3}) was studied at 25 °C and three pH values (4.39, 4.72, and 4.96_5) at $I = 0.1$ mol dm^{-3}. Measurements were not possible at higher pH values due to precipitation of copper(II) hydroxide. Solutions were buffered using dmps–NaOH which effectively does not interact with copper(II) ($K_{CuL} = 1.6$).[9] The kinetic data obtained are summarised in Table 1. Values of $k_{obs.}$ (the observed first-order rate constant) as a function of the copper(II) concentration at the three pH values are shown in Figure 5. As the metal ion concentration is increased, the reaction becomes independent of the copper(II) concentration. Promotion by copper(II) is more effective at pH 4.96_5 than at pH 4.39 which would be expected if $[CuL]^-$ were the reactive species, Figure 3.

Within the pH range 4.4—5.0 the main species present are

Table 1. Rate constants for the copper(II) promoted hydrolysis of salicyl phosphate at 25 C and I = 0.1 mol dm ^{3} (KNO_3), total ligand concentration = 1 × 10 ^{3} mol dm^{-3}

pH	$10^3[Cu^{2+}]$/ mol dm^{-3}	$10^5k_{obs.}$/s^{-1}	$10^3[Cu^{2+}]$/ mol dm^{-3}	$10^5k_{obs.}$/s^{-1}
4.96_5	0.00	2.0	2.0	16.2
4.96_5	0.25	6.1	3.0	18.3
4.96_5	0.50	8.8	4.0	18.3
4.96_5	0.75	9.1	5.0	18.9
4.96_5	1.00	10.8	6.0	19.0
4.96_5	1.25	12.9		
4.72	0.00	1.9	2.0	8.9
4.72	0.25	3.4	2.5	9.8
4.72	0.50	4.5	3.0	10.3
4.72	0.75	5.4	4.0	11.6
4.72	1.0	6.6	5.0	12.2
4.72	1.25	7.2	6.0	12.4
4.72	1.50	7.9		
4.39	0.00	1.8	1.50	3.8
4.39	0.25	2.2	2.00	4.3
4.39	0.50	2.6	3.0	5.1
4.39	0.75	3.0	4.0	5.7
4.39	1.00	3.3	5.0	6.1

Table 2. Values of α at various copper(II) concentrations and pH values (L_T = 1 × 10^{-3} mol dm^{-3})

$10^3[Cu^{2+}]$/ mol dm^{-3}	$\alpha_{HL^{2-}}$	α_{H_2L}	α_{CuHL}	α_{CuL}
pH 4.96				
0.50	0.73	0.03	0.11	0.08
1.00	0.59	0.02	0.20	0.14
1.50	0.48	0.02	0.26	0.19
2.00	0.41	0.02	0.31	0.22
3.00	0.30	0.01	0.37	0.26
4.00	0.24	0.01	0.41	0.29
5.00	0.20	0.01	0.44	0.31
6.00	0.17	0.01	0.46	0.32
pH 4.72				
0.50	0.74	0.05	0.13	0.05
1.00	0.62	0.04	0.22	0.09
1.50	0.52	0.04	0.29	0.13
2.00	0.45	0.03	0.35	0.15
3.00	0.34	0.02	0.43	0.18
4.00	0.28	0.02	0.48	0.20
5.00	0.23	0.02	0.52	0.22
6.00	0.20	0.01	0.54	0.23
pH 4.39				
0.50	0.72	0.11	0.13	0.03
1.00	0.62	0.09	0.23	0.05
1.50	0.53	0.08	0.31	0.06
2.00	0.47	0.07	0.38	0.07
3.00	0.37	0.06	0.47	0.09
4.00	0.30	0.05	0.54	0.10
5.00	0.26	0.04	0.58	0.12
6.00	0.22	0.03	0.62	0.12

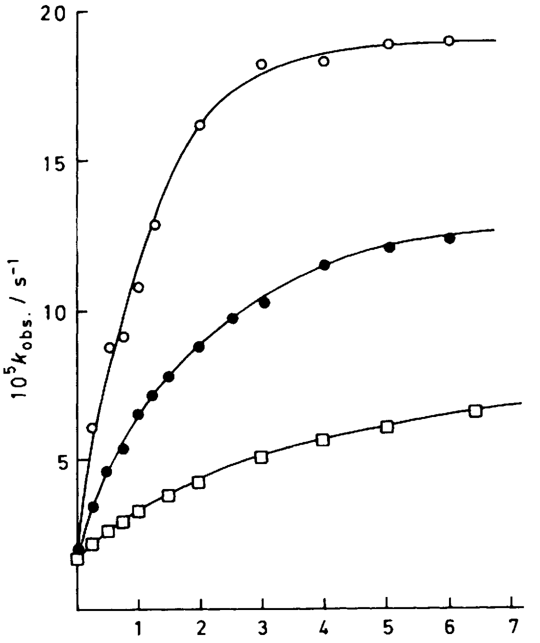


Figure 5. Plots of $k_{obs.}$ *versus* $[Cu^{2+}]$ for the copper(II) promoted hydrolysis of salicyl phosphate at 25 °C and I = 0.1 mol dm^{-3} (KNO_3); pH 4.96_5 (○), 4.72 (●), 4.39 (□)

HL^{2-}, H_2L^-, CuHL, and $[CuL]^-$. The total ligand concentration (L_T) is given by the expression (7). The fractions (α) of

$$L_T = [H_2L^-] + [HL^{2-}] + [L^{3-}] + [CuHL] + [CuL^-] + [CuL(OH)^{2-}] \quad (7)$$

the total ligand present as HL^{2-}, H_2L^-, CuHL, and $[CuL]^-$ can be defined as in equations (8)—(11). If all four species undergo

$$\alpha_{HL^{2-}} = [HL^{2-}]/L_T \quad (8)$$

$$\alpha_{H_2L} = [H_2L^-]/L_T \quad (9)$$

$$\alpha_{CuHL} = [CuHL]/L_T \quad (10)$$

$$\alpha_{CuL} = [CuL^-]/L_T \quad (11)$$

hydrolysis, $k_{obs.}$, the observed first-order rate constant at constant pH, is given by equation (12).

$$k_{obs.} = (k_{HL^{2-}})\alpha_{HL^{2-}} + (k_{H_2L})\alpha_{H_2L} + (k_{CuHL})\alpha_{CuHL} + (k_{CuL})\alpha_{CuL} \quad (12)$$

Values of α for the various species at pH 4.39, 4.72, and 4.96_5 and different $[Cu]/L_T$ ratios were computed from the formation constant data, Table 2. The concentration of H_2L^- is quite small, particularly at pH 4.72 and 4.96. Martell and co-workers[2] have reported a value of $k_{H_2L^-} = 4.5 \times 10^{-6}$ s^{-1} at 30 °C so that the contribution of this species to the overall reaction is very small. The species HL^{2-} is present in quite substantial concentrations and since $k_{HL^{2-}}$ is *ca.* 3.7 × 10^{-5} s^{-1} at 30 °C,[2] this species contributes to the overall reaction. A value of $k_{HL^{2-}}$ at 25 °C was estimated from the data in Table 1 using the expression (13)

$$k_{HL^{2-}} = k_0/\alpha_{HL^{2-}} \quad (13)$$

where k_0 is the value of $k_{obs.}$ in the absence of copper(II). Equation (13) gives $k_{HL^{2-}}$ = 2.6 × 10^{-5} s^{-1} at 25 °C and I = 0.1 mol dm^{-3}.

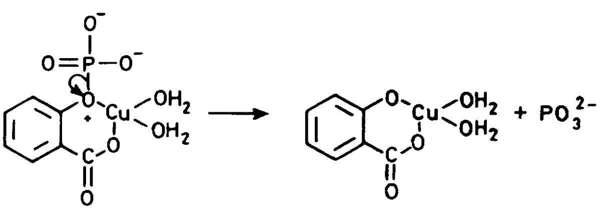
The pH dependence of the copper(II) promoted reaction suggests that $[CuL]^-$ is active but CuHL has negligible activity. As a result, equation (12) can be simplified to equation (14).

$$k_{obs.} = (k_{HL^{2-}})\alpha_{HL^{2-}} + (k_{CuL})\alpha_{CuL} \quad (14)$$

Using equation (14) values of k_{CuL} were calculated at the three

Table 3. Values of k_{CuL^-} at 25 °C and I = 0.1 mol dm^{-3}

$10^3[Cu^{2+}]$/ mol dm^{-3}	α_{CuL^-}	$10^4 k_{CuL^-}$/s^{-1}
pH 4.96		
1.00	0.14	6.6
2.00	0.22	6.8
3.00	0.26	6.7
4.00	0.29	6.1
5.00	0.31	5.9
6.00	0.32	5.8
pH 4.72		
1.00	0.09	5.5
1.50	0.13	5.0
2.00	0.15	5.1
3.00	0.18	5.3
4.00	0.20	5.4
5.00	0.22	5.3
6.00	0.23	5.2
pH 4.39		
3.00	0.09	4.6
4.00	0.10	4.9
5.00	0.12	4.6



(5)

pH values and different copper(II) concentrations, Table 3. The average value over the pH range 4.4—5.0 is $k_{CuL^-} = (6 \pm 1) \times 10^{-4}$ s^{-1} at 25 °C and $I = 0.1$ mol dm^{-3}. Some of the rate constants, particularly at pH 4.39, will be subject to error due to the low values of α_{CuL^-}. The data support the view that, in the pH range 4—5, $[CuL]^-$ is the active species in the copper(II) promoted hydrolysis.

It is likely that $[CuL]^-$ has the structure (**5**) which would provide Lewis acid catalysis by complexation of the leaving group to give the copper(II) complex of salicylic acid and the highly reactive metaphosphate species PO_3^{2-} which is rapidly solvated.[13] The metal ion effectively lowers the pK_a of the leaving group so that facile hydrolysis of the dianion occurs; an effect which is normally only observed with leaving groups of pK_a < 7.[5] The dianion of a phosphate monoester is normally an extremely unreactive species in hydrolysis. For example, the rate constant for the hydrolysis of the phenyl phosphate dianion is *ca.* 4×10^{-12} s^{-1} at 39 °C.[6] It is a reasonable assumption that $k_{L^{3-}}$ for salicyl phosphate will be of a similar order of magnitude (*ca.* 10^{-11}—10^{-12} s^{-1} at 25 °C). As k_{CuL^-} is 6×10^{-4} s^{-1} at 25 °C the rate enhancement for hydrolysis of the L^{3-} species of salicyl phosphate in the complex $[CuL]^-$ is probably $\geqslant 10^8$ fold. The present work highlights the remarkable effectiveness of labile metal ions in promoting the hydrolysis of phosphate monoester dianions when complexation of the leaving group occurs. The present results with salicyl phosphate are in agreement with conclusions of Benkovic and Dunikoski[5] regarding the mechanism of the copper(II) promoted hydrolysis of 2-(4-imidazolyl)phenyl phosphate, (**3**).

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