The Complexation Between Cu^{2+} and the Salicylate Ion

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The complexation of Cu^{2+} with the hydrogen salicylate ion, HL^-, has been studied by potentiometric measurements with glass and copper amalgam electrodes in 0.25 M $NaNO_3$. The complexes found were CuL, CuL_2 and CuHL. Stability constants are reported.

The predominant salicylate species over most of the accessible pH interval in aqueous solution is the hydrogen salicylate ion, HL^-. This ion is often referred to as the salicylate ion, but in order to avoid confusion this name will be used here only for the fully deprotonated ion, L^{2-}. The hydrogen salicylate ion can be envisaged to behave as a monodentate or a bidentate ligand according to the reaction schemes:

$$Cu^{2+} + n\,HL^- = Cu(HL)_n^{(n-2)-} \quad ; k_n \qquad (I)$$

$$Cu^{2+} + n\,HL^- = CuL_n^{(n-1)-} + nH^+; k_n^*. \qquad (II)$$

The first scheme involves complexation by the carboxylate group only and the corresponding complexes will be referred to here as carboxylate complexes. In the second scheme, chelation by the carboxylate and phenolate groups takes place. The chelates will be referred to here as salicylate complexes.

We have recently studied the complexation in the system Cu^{2+}-3,3′-azobis-(6-hydroxybenzoic acid). The disodium salt of this acid is the active component in a newly introduced drug, Dipentum®, for the treatment of ulcerative colitis. Owing to experimental difficulties, it became necessary in the interpretation of the data to estimate the relative importance of the two above-mentioned complexation schemes on the basis of a simpler system. The Cu^{2+}-salicylate system was then a reasonable choice.

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The $Cu^{2+}-H_2L$ system has been studied frequently. The formation of CuL and CuL_2 is well established. The published values of the formation constants refer to the reaction scheme:

$$Cu^{2+} + n\,L^2 = CuL_n^{(n-1)-} \quad ; \beta_n \qquad (III)$$

We shall prefer here to use scheme II, since the first protonation constant for the salicylate ion need not then be incorporated in the calculations. Its large value ($\log K_1^H > 13$) makes an accurate determination somewhat difficult.

The formation of carboxylate complexes has been reported by Brun and Schrøder[1] on the basis of potentiometric measurements with glass and copper ion selective electrodes. The values of the constants obtained from the glass electrode data only and those obtained from calculations in which the data from both electrodes were combined differed considerably. The authors preferred the results from the glass electrode measurements, and k_1 is reported as 87 M^{-1}. A 'bis' complex was also found with a stepwise formation constant equal to 494 M^{-1}. The second constant is appreciably larger than the first, which is an unusual result. The validity of the values of the formation constants may therefore be questioned.

From polarographic measurements at pH 4.2, Habashy[2] found evidence for the formation of four consecutive carboxylate complexes. The value of the first stability constant was 44 M^{-1}. However, from the reported value of $\log k_1^* = -2.52$ we find that under the conditions

used for the determination of k_1, the concentrations of CuL and CuHL are about equal. Therefore, the value of k_1 is probably overestimated since no correction was made for the presence of CuL.

The results of extensive measurements[3-5] with the glass electrode could be explained by the formation of CuL and CuL_2. No evidence was found for the formation of carboxylate complexes. Although glass electrode measurements are not well suited for the detection of the carboxylate species, these results indicate that the value of k_1 would be smaller than those quoted above.

We have therefore reinvestigated the copper (II)-salicylic acid system. The first dissociation constant for salicylic acid and the formation of the salicylate complexes have been studied by glass electrode measurements, and the carboxylate complexes by measurements with glass and copper amalgam electrodes.

Experimental

All reagents were of analytical grade and solutions were prepared with distilled water purified in a Milli-Q® filtration system. The ionic strength of start solutions and titrants was adjusted to 0.25 M with $NaNO_3$. The stock solutions of $Cu(NO_3)_2$ and HNO_3 were standardized against standard EDTA and TRIS, respectively. Solutions of NaOH and $NaHCO_3$ were standardized against standard HNO_3.

An Ingold glass electrode and a Metrohm Ag/AgCl double junction reference electrode were used. The salt bridge was filled with 3 M NaCl to reduce liquid junction potentials. The copper amalgam electrode was prepared and used as previously described.[6] Calibration of the electrodes was carried out in dilute, i.e. about 2 mM, standard solutions of H^+ and Cu^{2+}.

The titrations were carried out in a Metrohm titration vessel at 25±0.05 °C in an atmosphere of argon passed through wash bottles containing acid, base and ionic medium, respectively. In the amalgam measurements, the gas was also passed through a column of activated copper to remove traces of oxygen. The measurements were performed using an automatic titrator under computer control and the emf was registered to ±0.01 mV.

Titration procedures. Three sets of titrations were performed: set A for the determination of the first acidity constant of salicylic acid, set B for the determination of the stability constants of the salicylate complexes, and set C for the determination of the stability constants of the carboxylate complexes.

Set A. Start solutions of hydrogen salicylate, 5 or 10 mM, were titrated with HNO_3. The total salicylate concentration was kept constant in each experiment.

Set B. The total concentrations in the start solutions were ($[Cu]_t$/mM, $[L]_t$/mM): (2,10); (2,20); (5,20). The composition of the salicylate buffer was chosen to yield ph 3 (p$h = -\log[H^+]$) in these solutions. Titrations were performed with HCO_3^- or OH^- and they were ended by the formation of a precipitate at about ph 7. No attempt was made to keep the total concentrations constant during the experiments. To reach $\bar{n} > 1$, the titrations must be carried out with strong base. In regions of ph overlap, experiments with OH^- and HCO_3^- as titrants gave identical results.

Set C. Start solutions containing 10 mM salicylic acid and $[Cu]_t = 1$ or 2 mM were prepared in the titration vessel by adding the appropriate amounts of the reagents from the carefully deaerated stock solutions to the solution used for the standardization of the electrodes. The start solution was titrated with a 0.140 M hydrogen salicylate solution. The final total salicylate concentration was about 0.03 M. The total copper ion concentration was kept constant only in the titrations with $[Cu]_t = 1$ mM.

Equilibrium models and calculations

The following notations will be used; $[Cu]_t = B$, $[L]_t = L$, $[H]_t = H$, $[Cu^{2+}] = b$, $[HL^-] = l$, and $[H^+] = h$. The species considered are presented in the expressions for the total concentrations. These expressions are:

$$B = b + [CuL] + [CuL_2] + [CuHL] \quad (1)$$

$$L = l + [H_2L] + [CuL] + 2[CuL_2] + [CuHL] \quad (2)$$

$$H = h + [H_2L] - [CuL] - 2[CuL_2]. \quad (3)$$

The equilibrium constants for the copper complexes are defined by reaction schemes (I) and (II). The second protonation constants for the salicylate ion will be denoted by K_2^H and is defined by

$$K_2^H = \frac{[H_2L]}{hl} . \quad (4)$$

With no Cu^{2+} present in the titration, the expression for K_2^H is found to be

$$K_2^H = \frac{H-h}{h(L-H+h)} \quad (5)$$

from eqns. (2)–(4).

The subsequent treatment of the data shows that the complexes CuL and CuL_2 predominate, whereas CuHL is a minor species. Good estimates of the values of the stability constants of CuL and CuL_2 can therefore be found from the usual formation curve by neglecting the species CuHL. The ligand number, $\bar{n}$, is then

$$\bar{n} = \frac{[CuL] + 2[CuL_2]}{B} = \frac{k_1^* x + 2k_2^* x^2}{1 + k_1^* x + k_2^* x^2} \quad (6)$$

where $x = lh^{-1} \cdot \bar{n}$ was calculated from

$$\bar{n} = \frac{h-H}{B} + \frac{K_2^H h(L+H-h)}{B(1+2K_2^H h)} \quad (7)$$

and x from

$$x = \frac{L+H-h}{h(1+2K_2^H h)} . \quad (8)$$

These relationships are obtained by combining eqns. (2)–(4) and (6). The values of the equilibrium constants were determined by fitting eqn. (6) to the experimental data $(\bar{n},x)$ by use of the Simplex method.[7] The error square sum $U = \Sigma (\bar{n}_{exp} - \bar{n}_{calc})^2$ was minimized.

Calculations with the constants so obtained showed, however, that even if k_1 is as small as 5 to 10 M^{-1}, i.e. considerably smaller than the values previously reported, the described procedure yields values of k_1^* that are too low by a few per cent. Hence, a more elaborate calculation procedure was devised which allowed the inclusion of the species CuHL in the treatment of the glass electrode data. We chose a procedure where a theoretical value of $H(=H_{calc})$ was calculated for each experimental point from the known values of B, L and h and the set of equilibrium constants at the current vertex of the Simplex. Combining the expressions for the stability constants with eqns. (1), (2) and (4) gives the expression

$$L = l(1+K_2^H h) + B \frac{k_1 l + k_1^* l h^{-1} + 2k_2^* l^2 h^{-2}}{1 + k_1 l + k_1^* l h^{-1} + k_2^* l^2 h^{-2}} . \quad (9)$$

If the term $k_2^* l^2 h^{-2}$ in the denominator is replaced by $l_0 k_2^* l h^{-2}$, where l_0 is an estimate of l, eqn. (9) can be solved for l. The value of l thus obtained can be used as a new l_0 and the procedure is repeated until a constant value of l is obtained. b can then be calculated from eqn. (1), rewritten as:

$$b = \frac{B}{1 + k_1 l + k_1^* l h^{-1} + k_1^* l^2 h^{-2}} . \quad (10)$$

Then, finally, H_{calc} is found from eqn. (3). The values of the equilibrium constants were determined by Simplex optimization of the error-square sum $U = \Sigma (H_{exp} - H_{calc})^2$.

The measurements with the copper amalgam electrode were designed primarily for the determination of k_1, and were carried out in concentration intervals where only CuHL and CuL need to be considered. Eqn. (1) can then be written

$$\frac{B-b}{bl} = y = k_1 + k_1^* h^{-1} . \quad (11)$$

With b and h known from the emf measurements, the concentration of hydrogen salicylate is calculated from

$$l = \frac{b-B+L}{1+K_2^H h} \quad (12)$$

The formation constant for CuHL is found from a plot of y vs. h^{-1}.

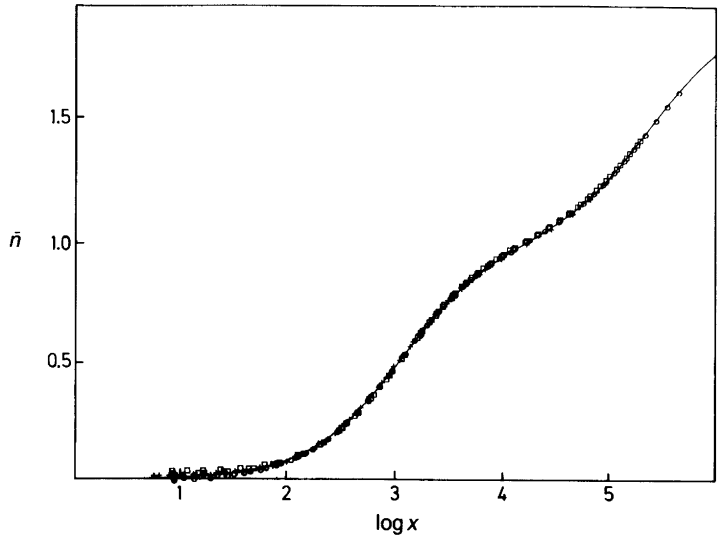

Fig. 1. Formation curve for the salicylate complexes (*B*/mM,*L*/mM): + (2,10), ○ (2,20) and □ (5.20).

Results and discussion

The value of K_2^H found from 5 titrations was 574±3 M^{-1}, or log K_2^H = 2.759±0.002. The reported uncertainty is the standard deviation. No previous value of K_2^H determined in 0.25 M ionic medium is available, but two recent determinations of log K_2^H in 0.1 M ionic medium both give a value of 2.83.[4,5]

Table 1. Determination of k_1^* and k_2^* for restricted ranges in x. All titrations in set B were included in the calculations.

Range	log k_1^*	log k_2^*	$s(\bar{n}_{calc}-\bar{n}_{exp})$
$x > 10$	−3.04	−8.44	0.007
$x > 100$	−3.04	−8.44	0.006
$x > 1000$	−3.03	−8.43	0.005

Table 2. Determination of k_1^* and k_2^* when the species CuHL is included in the calculations. All data from set B were used (218 data points).

k_1/M^{-1}	log k_1^*	log k_2^*	$s(H_{calc}-H_{exp})/10^{-5}$ M
0[a]	−3.03	−8.43	2.9
4.25	−3.01	−8.41	2.1
8[a]	−2.99	−8.39	2.6
12[a]	−2.97	−8.37	3.8

[a]The value of k_1 was kept constant in the optimization.

Fig. 1 shows the formation curve calculated from the data obtained in set B and eqns. (7)–(8). The ligand number is a function of x only and does not depend on total metal ion and ligand concentrations. Since x is proportional to the free salicylate concentration, it can be concluded that $\bar{n}$ is a function of this concentration only. The predominant species must then be the salicylate complexes CuL and CuL_2, in agreement with previous investigations.[3-5] In order to test this hypothesis further, the calculation of the equilibrium constants was carried out for restricted intervals in x (Table 1). The results of these calculations substantiate the predominance of complexes of the salicylate type and yield the following values of the formation constants: log $k_1^* = -3.04$ and log $k_2^* = -8.44$.

Calculations were also made in which the presence of CuHL was allowed for. The parameters k_1, k_1^* and k_2^* of eqns. (9) and (10) were fitted to experimental data h, B, L and H as described earlier. The best fit [i.e. a minimum for $\Sigma(H_{calc}-H_{exp})^2$] was found for the following values of the formation constants: $k_1 = 4.25$ M^{-1}, log $k_1^* = -3.01$ and log $k_2^* = -8.41$. Although the value of k_1 obtained from these data is quite

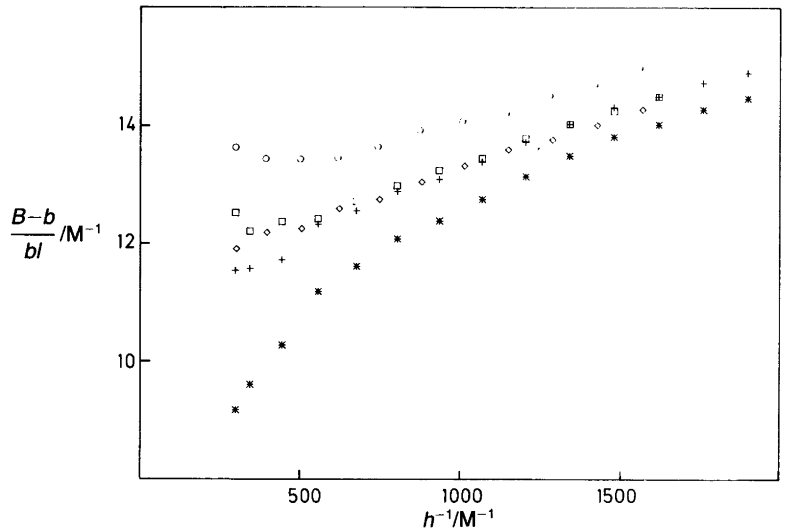

Fig. 2. Plot of y vs. h^{-1} used in the determination of k_1 (Titration number, B/mM); ○ (1,2), □ (2,2), ◇ (3,1), + (4,1). *(Points from titration 4 calculated with a value of $E^{\circ}_{Cu(Hg)}$ 0.1 mV lower than that obtained in the calibration).

uncertain, at least it can be stated with some certainty that it is small. As regards the salicylate complexes, our results are in accord with the extensive measurements made by Cassasas and Tauler[5] in 0.1 and 1 M KNO_3, and suggest that the value of β_2 reported by Lajunen *et al.*[4] is too large (see Table 2 for a more extensive summary of the results).

In order to confirm the low value of k_1, experiments using a Cu^{2+}-selective electrode were carried out. Calculations indicated that a favourable quotient between the concentrations of the car-

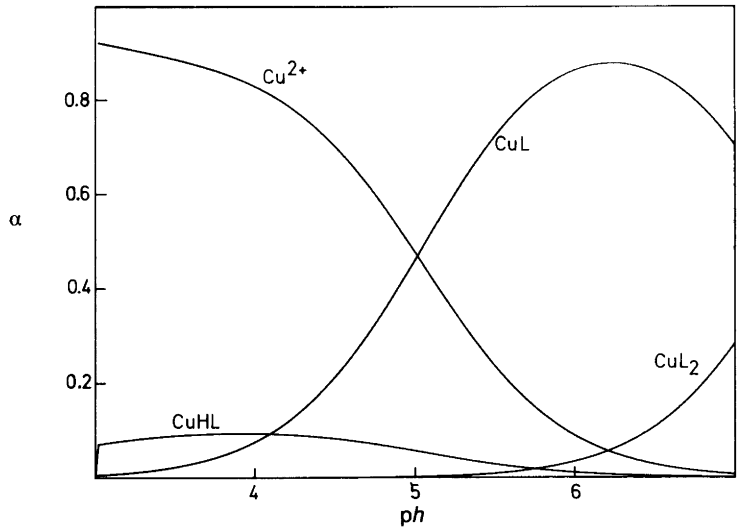

Fig. 3. The distribution of Cu^{2+} at trace concentration as a function of ph at $L = 10$ mM.

boxylate and salicylate complexes existed around p*h* 3. The measurements were therefore carried out in salicylic acid–hydrogen salicylate buffers around this p*h* value, and the total salicylate concentration reached 0.030 M at most.

A plot of the data according to eqn. (11) is shown in Fig. 2. A straight line drawn through the majority of the points extrapolates to $k_1 = 11.5\ M^{-1}$. This estimate of k_1 is quite uncertain due to the sensitivity of y to errors in the emf measurements, as demonstrated in Fig. 2. Furthermore, it is possible that this value is somewhat too high, because of the simple model used for the correction for the liquid junction potential. Only the influence of changes in $[H^+]$ was corrected for. We used the expression $E_j = j \cdot [H^+]$, where j was determined separately to be 10 mV M^{-1}. We also estimated E_j using the Henderson equation[8] and corrected the measured potentials accordingly. We found that the value of k_1 then decreased to 8 M^{-1}. The slope of the line, although somewhat too large, is consistent with the value of k_1^* found from the measurements with the glass electrode. The hydrogen salicylate complex would then be weaker than the corresponding benzoate complex.[9] This might be due to the engagement of the carboxylate group in internal hydrogen bonding.

Considering the results found from the different types of measurements, we find it likely that k_1 lies in the range 5 to 10 M^{-1} and propose the following values of the equilibrium constants for the salicylate complexes: $\log k_2^* = -3.00 \pm 0.02$ and $\log k_2^* = -8.40 \pm 0.02$, where the estimate of the uncertainty is based on the range given for k_1.

The distribution of Cu^{2+} at trace concentration as a function of p*h* at $L = 0.01$ M is shown in Fig. 3.

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