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A Potentiometric Study of the Cu^{2+}–4(5)-Hydroxymethylimidazole System in 0.1 M $NaClO_4$ Medium

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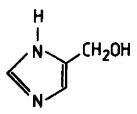
Equilibria between Cu^{2+} and 4(5)-hydroxymethylimidazole ($C_3H_3N_2 \cdot CH_2OH$) were studied at 25 °C by means of potentiometric titrations using a glass electrode in 0.1 M $NaClO_4$ solutions. The total copper, C_M, and the total ligand, C_L, concentrations were varied within the limits $0.001 \leq C_M \leq 0.004$ M and $0.001 \leq C_L \leq 0.020$ M ($0.5 \leq C_L/C_M \leq 15$) with $2.5 \leq -\log[H^+] \leq 8$. At the highest C_L/C_M ratios the experimental data can be explained with the stepwise mononuclear complexes CuL_n^{2+} (L = $C_3H_3N_2 \cdot CH_2OH$) with n=1, 2, 3 and 4. At low C_L/C_M ratios the ternary hydroxocomplexes $Cu(OH)L^+$, $(Cu(OH)L_3^+$ and $Cu(OH)_2L_2$ are formed. The calculations were performed using the least squares computer program LETAGROPVRID.

4(5)-Hydroxymethylimidazole can be used as one of the starting materials in the synthesis of some antihypertensive imidazole derivatives.[1] 4(5)-(2,3-Dimethylbenzyl)imidazole (the generic name detomidine) is a new drug belonging to this class of compounds developed by the Farmos-Group, Ltd. (Domosedan®).[2] The present study is a part of our wider investigations into the chemical characterization of these imidazole derivatives.

In a preceeding paper the protonation of 4(5)-hydroxymethylimidazole (scheme 1) has been studied by ^{13}C NMR spectrometry and potentiometric emf titrations.[3] Both the NMR and potentiometric data clearly showed that only one protonation reaction is taking place in 0.1 M $NaClO_4$ at 25 °C. The title compound can add one proton to the imidazole ring in acidic solutions, but the hydroxyl proton is not dissociated under the experimental conditions used ($2 \leq pH \leq 11$).

In the earlier papers the three-component equilibria in the system copper(II)–imidazole–OH^- have been investigated by means of potentiometric and spectrophotometric methods (3 M (Na)ClO_4 and 3 M (Na)Cl media).[4–6] Besides the copper complexes CuL_n^{2+}, n=1, 2, 3, 4, ternary hydroxy complexes were also formed. Data showed upon the formation of $Cu_2(OH)_2L_2^{2+}$, $Cu_2(OH)_2L_4^{2+}$ and $Cu(OH)L^+$.

The purpose of the present investigation was two-fold: (a) to study the contribution of the hydroxyl group in the imidazole ring on the complexation, and (b) to determine whether hydroxy complexes are formed in the copper(II)–4(5)-hydroxymethylimidazole–OH^-



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system. The results are compared to those obtained earlier for the copper(II)–imidazole–OH^- system.

EXPERIMENTAL

Chemical and analyses. Stock solutions of sodium perchlorate and copper(II) nitrate were prepared and analyzed as described elsewhere.[7] 4(5)-Hydroxymethylimidazole was synthesized and purified as reported earlier.[1,8]

Potentiometric measurements. The emf (E) of a galvanic cell of the following type was measured:

$Hg,Hg_2Cl_2(s)$	0.01 M Cl^- 0.09 M ClO_4^- 0.1 M Na^+	0.1 M $NaClO_4$ C_M $Cu(NO_3)_2$ C_L HL^+, L C_H $HClO_4$	glass electrode (Beckman N 40495)

The system was calibrated before each titration by measuring the emf (E_R) in a solution of known free hydrogen ion concentration, $[H^+]_R$. The unknown hydrogen ion concentration, $[H^+]$, was then calculated from the equation:

$$-2.303\,RT/F \log([H^+]/[H^+]_R)=(E_R-E_j')-(E-E_j'') \quad (1)$$

where R=8.314 J K^{-1} mol^{-1} and F=96 487 C mol^{-1}. E_j' and E_j'' are the liquid junction potentials. The liquid junction potentials depend mainly on the free hydrogen ion concentration in the solutions, and is a linear function of $[H^+]$ ($E_j([H^+])=j\times[H^+]$, where $j=-548$ mV M^{-1}).

The potentiometric measurements were carried out with a Radiometer digital titration system DTS 633 consisting of an autoburette ABU 80, a pH meter PHM 64, and a digital titrator TTT 61, with an equal increment accessory constructed at the Department of Chemistry, University of Oulu.[9]

The stabilities of the copper(II) complexes of 4(5)-hydroxymethylimidazole were determined by measuring the emf values in a galvanic cell of the kind described above. During the titrations the ratio C_L/C_M was kept constant and C_H was varied by adding NaOH. To avoid variations in activity coefficients and E_j, the concentration ranges were restricted as follows: $0.001 \leq C_M \leq 0.004$ M, $0.001 \leq C_L \leq 0.02$ M with $0.5 \leq C_L/C_M \leq 15$ ($2.5 \leq -\log[H^+] \leq 8$).

Data treatment. We will assume the presence of three-component equilibria of the general type (2) together with the two-component equilibria (3) and (4).

$$pH^+ + qCu^{2+} + rHL^+ \Leftrightarrow (H^+)_p(Cu^{2+})q(HL^+)_r;\ \beta_{pqr} \quad (2)$$

$$HL^+ \Leftrightarrow L + H^+;\ k_a \equiv \beta_{-101} \quad (3)$$

$$pH^+ + qCu^{2+} \Leftrightarrow (H^+)_p(Cu^{2+})_q;\ \beta_{pq0} \quad (4)$$

For reaction (3) the value $\log k_a=-6.46$ was used.[3] Within the concentration ranges studied the hydrolytic behaviour of Cu^{2+} is described by the two species $CuOH^+$ and $Cu_2(OH)_2^{2+}$ with $\log \beta_{-110}=-8.0$ and $\log \beta_{-220}=-10.6$ (25 °C, I=0.1).[10]

These results on the two-component equilibria are considered as known and no attempts will be made to adjust their equilibrium constants.

The search for a model (pqr) and corresponding formation constants (β_{pqr}) that give the "best" fit to experimental data was carried out using the least-squares computer program LETAGROPVRID (version ETITR).[11]

The error squares sum $U=\Sigma\{C_H(\text{calc})-C_H(\text{exp})\}^2$ was minimized. The standard deviations $\sigma(C_H)$ and $3\sigma(\log \beta_{pqr})$ were defined according to Sillen.[12]

CALCULATIONS AND RESULTS

The mathematical analysis of experimental data, comprising 8 titrations with 222 experimental points, was started by making $\bar{n}(\log[L])$ and $Z(\log[H^+])$ plots (*cf.* Figs. 1 and 2). Z is here defined as the average number of OH^- reacted per C_L and is given by the relation

$$Z=([H^+]-C_H-k_w[H^+]^{-1})/C_L \quad (5)$$

(In the present study the term $k_w[H^+]^{-1}$ (=$[OH^-]$) can be neglected.) According to Fig. 1 a series of mononuclear species CuL_n^{2+} are formed, as a mononuclear curve can be identified. However, systematic deviations from this curve are also obvious, especially with $C_L/C_M \lesssim 4$ and at the end of the titrations. These effects are due to the formation of additional species. This is clearly demonstrated in Fig. 2, which shows that complexes with $|-p|>r$ (*cf.* (2)) must be formed as Z reaches values >1.

A LETAGROP calculation on a reduced data set (139 points) comprising data belonging to the mononuclear wall clearly showed upon the formation of a series of CuL_n^{2+} complexes with n=1, 2, 3 and 4, giving log β_{-111} =−2.50±0.02, log β_{-212}=−5.66±0.03, log β_{-313}=−9.36±0.06 and log β_{-414}=−13.67±0.09 (C_H)=0.04 mM). As an attempt to determine stability and composition of the ternary complexes, the series $CuL_nH_{-1}^+$, with n=1, 2 and 3, was included in the equilibrium model on the whole data set. In this calculation the complexes $CuLH_{-1}^+$ and $CuL_3H_{-1}^+$ were accepted while $CuL_2H_{-1}^+$ was rejected as $\sigma(\beta_{-321})>\beta_{-321}$.

However, systematic effects still remain at the highest -log[H^+] values studied. Additional complexes with the composition CuL_nH_{-2} and n=1, 2 and 3 were now tested one at a time. The complex CuL_2H_{-2} gave the "best" fit, though CuL_3H_{-2} seemed to fit data almost equally well (*cf.* Table 1 where all calculations are presented). As the existence of binuclear copper(II) complexes frequently are reported (*cf.* the Cu^{2+}–OH^-, and Cu^{2+}–OH^-–imidazole systems) the complexes $Cu_2L_2H_{-2}^{2+}$ and $Cu_2L_4H_{-2}^{2+}$ were tested.

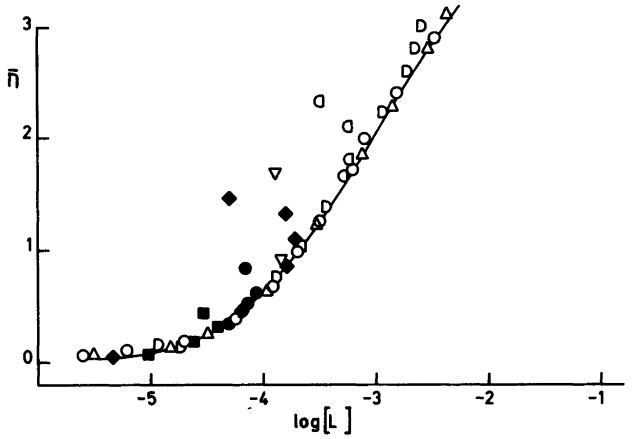

Fig. 1. A part of experimental data plotted as curves $\bar{n}(\log[L])$. The full-drawn curve was calculated using the set of proposed constants for binary Cu^{2+}-L complexes. Different symbols denote the following starting concentration in C_M and C_L (in mM): ○ 1–15, △ 2–15, ▷ 2–12, ▢ 4–4, ▽ 1–2, ◆ 4–6, ● 2–2, ■ 4–2.

Table 1. Results of some final LETAGROP calculations. The errors given correspond to $3\sigma(\log \beta_{pqr})$. If no 3σ is given the corresponding constant was not varied. R denotes a rejected complex.

p q r	$\log \beta_{pqr}$	p q r	$\log \beta_{pqr}$	p q r	$\log \beta_{pqr}$	p q r	$\log \beta_{pqr}$	u	$\sigma(C_H)$/mM	Rem.
−1 1 1	−2.50(2)	−2 1 2	−5.66(3)	−3 1 3	−9.36(6)	−4 1 4	−13.67(9)	0.25	0.04	[a,c]
−2 1 1	−9.04(7)	−3 1 2	R	−4 1 3	−16.29(6)			2.47	0.11	[b]
−2 1 1	−9.03(4)	−4 1 2	−20.68(7)	−4 1 3	−16.46(6)			0.91	0.06	[c]
−2 1 1	−9.18(12)	−4 1 2	−20.68	−4 1 3	−16.46	−4 2 2	−15.80− −15.59	0.81	0.06	
−2 1 1	−9.18	−4 1 2	−20.70(8)	−4 1 3	−16.46	−6 2 4	−23.10− −22.78	0.86	0.06	

[a] A calculation based on data from the "mononuclear curve" (8 titrations, 166 points). In the subsequent calculations given below these constant values were included. [b] Final calculations on the whole data set (8 titrations, 222 points) for some different assumptions concerning ternary complexes formed. [c] Proposed constants.

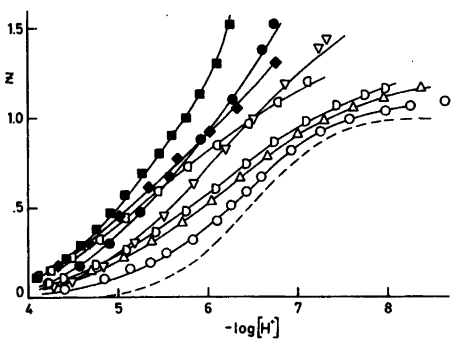

Fig. 2. A part of experimental data plotted as curves $\bar{Z}(\log[H^+])$. The full-drawn curves were calculated using the set of proposed constants given in Table 1. The same symbols as in Fig. 2 were used. Z is defined as the average number of OH^- reacted per HL. The broken curve corresponds to pure ligand (C_M=0).

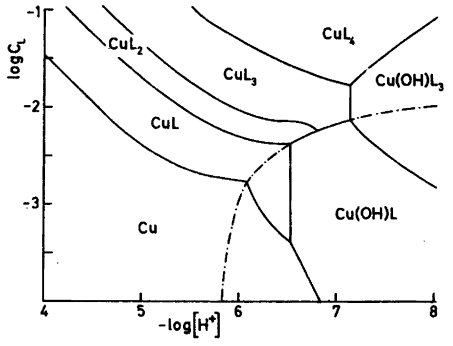

Fig. 3. Predominance area diagram with C_M=0.002 M. The precipitation boundary of $Cu(OH)_2$ is indicated with a broken curve. Areas to the right of this curve show the speciation in the presence of $Cu(OH)_2$(s) (extrapolated ranges). In the calculations log $*K_{so}$=log$[Cu^{2+}][H^+]^{-2}$= 8.68 was used.[14]

However, no significant improvement of the fit to data was obtained (*cf.* Table 1), showing these species to be of minor importance within the concentration ranges studied.

DISCUSSION

The complexation in the present system is characterized by the formation of a series of binary CuL_n^{2+} complexes (n=1, 2, 3 and 4) as well as the mixed complexes $CuL_nH_{-1}^{+}$ (n=1, 3) and CuL_2H_{-2}. All species are formed in significant amounts and do in fact predominate within specified ranges as shown in Figs. 3 and 4.

A comparison between the stepwise constants (log k_n) of Cu^{2+} imidazoles (25 °C, I=0.16; 4.18, 3.48, 2.85, 2.1) and Cu^{2+} 4(5)-hydroxymethylimidazoles (this work; 3.96,

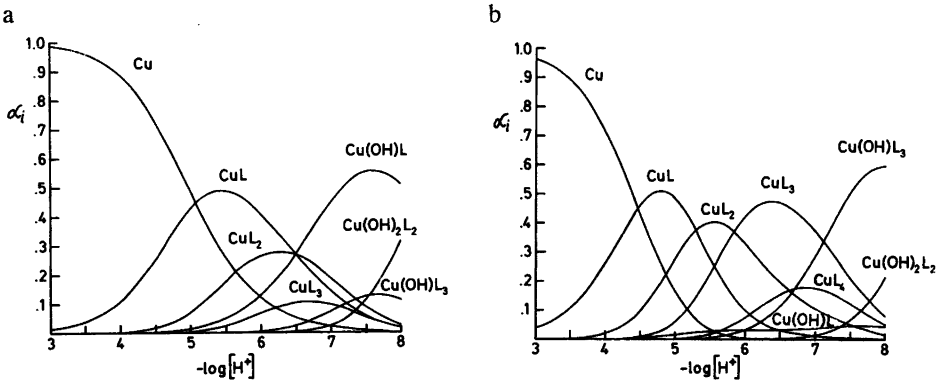

Fig. 4. Distribution diagrams with C_M=0.002 M and C_L=0.004 (a) and 0.012 M (b) resp. The calculations were performed using the computer program SOLGASWATER.[13]

3.30, 2.76, 2.15) shows the latter to be a little less stable. However, the differences might equally well be described by medium effects. Furthermore the ratios of the various stepwise constants ($\log k_{n+1}/k_n$) are practically the same for the imidazole and 4(5)-hydroxymethylimidazole, which indicates the coordination of copper in these two systems to be the same. Due to these findings it might tentatively be assumed that the hydroxy group of the ligand does not coordinate to the Cu^{2+} ion, and has no steric effect on the complex formation.

With this assumption the species $CuL_nH_{-1}^{+}$ (n=1, 3) and CuL_2H_{-2} may tentatively be assigned as mixed hydroxo complexes and should be written as CuL_nOH^{+} and $CuL_2(OH)_2$. This hypothesis is supported by the fact that the species are formed within $-\log[H^+]$ ranges where hydrolysis of the copper(II) ion is extensive (*cf.* Fig. 3). As the alcohol group and the pyrrole nitrogen (NI) exhibit pk_a values $\gtrsim$13, deprotonation of these groups seems less likely within the present $-\log[H^+]$ range.

The acidity constants of CuL^{2+} and CuL_3^{2+} are: $pk_a(CuL^{2+})$=6.53 and $pk_a(CuL_3^{2+})$=7.10. In the imidazole system $pk_a(CuL^{2+})$=7.18 was obtained. Clearly the addition of a CH_2OH group to imidazole reduces the pk_a value not only for the pure ligand but also for the metal complexes.

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