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Ternary Complexes of Cimetidine and Phenobarbital with Cu(II) in Methanolic Solution

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The formation constants of the binary complexes $Cu(CM)^{2+}$ and $Cu(CM)_2^{2+}$ as well as those of the ternary complexes $Cu(CM)L^+$ and $Cu(CM)_2L^+$ (CM = Cimetidine = N-Cyano-N′-methyl-N″[(5-methyl-1*H*-imidazol-4-yl)methyltioethyl]-guanidine; HL = Phenobarbital = 5-ethyl-5-phenyl-barbituric acid) have been determined in 0.1 and 1.0 mol dm^{-3} $NaClO_4$ methanol solutions at 25 $\pm$ 0.2 °C. The values of $\log X$, $\log \beta_{stat.}$, and $\Delta \log K$ confirm the stability of the ternary complexes.

[Keywords: Cimetidine; Complex stabilities; Phenobarbital; Copper(II)]

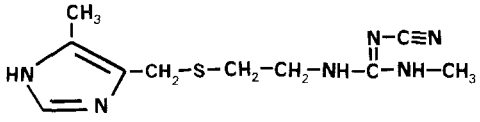
Ternäre Komplexe von Cimetidin und Phenobarbital mit Cu(II) *in methanolischer Lösung*

Die Stabilitätskonstanten der binären Komplexe $Cu(CM)^{2+}$ und $Cu(CM)_2^{2+}$ sowie die der ternären Komplexe $Cu(CM)L^+$ und $Cu(CM)_2L^+$ (CM = Cimetidin = N-Cyan-N′-methyl-N″-[(5-methyl-1*H*-imidazol-4-yl)methylthioethyl]-guanidin; HL = Phenobarbitalum = 5-Ethyl-5-phenyl-barbitursäure) wurden in 0.1 und 1.0 M Lösungen von $NaClO_4$ in Methanol bei 25 $\pm$ 0.2 °C bestimmt. Die Werte von $\log X$, $\log \beta_{stat.}$ und $\Delta \log K$ bestätigen die Stabilität der ternären Komplexe.

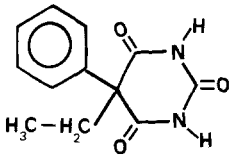
Introduction

Much attention has been paid recently to the study of ternary complexes between essential trace elements and molecules of biological and pharmaceutical interest[1—3]. Furthermore, it has been suggested that the presence of metal ions in biological fluids could have a significant effect on the therapeutic action of drugs[4,5].

The present work studies the formation of ternary complexes of Cu(II) with cimetidine as the primary ligand and phenobarbital as the secondary ligand. Cimetidine is used in the treatment of gastric hyperacidity[6], while phenobarbital has a sedative action[7,8]. Both drugs are often administered simultaneously showing interactions between them[9,10].



Cimetidine



Phenobarbital

Ternary complexes of Cu(II) with *CM* and L^- have not been studied yet, while formation of complexes of Cu(II) with barbituric acids of type $CuL(Base)_2 \times H_2O$ and $CuL_2(Base)_2$, where pyridine, picoline etc. can all act as the base, have been extensively studied[11—13].

Therefore it seems of importance to study the formation of ternary complexes between Cu(II), cimetidine and phenobarbital.

The potentiometric techniques described elsewhere were used in the present work[14—17]. All measurements were carried out at 25 ± 0.2 °C and 0.1 and 1.0 mol dm^{-3} ($NaClO_4$) ionic strengths in methanolic media.

Experimental

All the reagents used were of a. r. grade. Cimetidine, in its basic form, was kindly provided by Antibiotics S. A. Phenobarbital in its protonated form was provided by Q. F. Bayer. All compounds were recrystallized from methanol. $Cu(NO_3)_2 \cdot 3\,H_2O$ Merck was used.

The experimental method employed consists of a set of potentiometric titrations at 25 ± 0.2 °C for 2.10^{-3} mol dm^{-3} Cu(II) concentrations, and 1 : 1 and 1 : 2 $Cu^{2+} : CM$ or 1 : 1 : n and 1 : 2 : n', $Cu^{2+} : CM : L^-$ molar ratios ($n = 3$, 6; $n' = 2$, 3, 6 for $I = 0.1$ mol dm^{-3} and $n = 6$; $n' = 2$, 3 for $I = 1.0$ mol dm^{-3}).

The *pH* measurements in methanolic media were obtained using the *De Ligny*'s technique[18,19]. A *pH*-meter Radiometer model *pH* M 62 digital with an accuracy of $\pm$ 0.01 *pH* units was used. Pure nitrogen gas was bubbled through the solution during the titration with tetrabutyl ammonium hydroxide (Merck).

Calculations

In order to calculate the stability constants of $Cu^{2+}:CM$ binary complexes and $Cu^{2+}:CM:L^-$ ternary complexes the following equations were used:

$$Cu^{2+} + CM \overset{\beta^{Cu^{2+}}_{Cu(CM)^{2+}}}{\rightleftharpoons} Cu(CM)^{2+}$$

$$\beta^{Cu^{2+}}_{Cu(CM)^{2+}} = \frac{[Cu(CM)^{2+}]}{[Cu^{2+}][CM]}$$

$$Cu(CM)^{2+} + CM \overset{\beta^{Cu(CM)^{2+}}_{Cu(CM)^{2+}}}{\rightleftharpoons} Cu(CM)_2^{2+}$$

$$\beta^{Cu(CM)^{2+}}_{Cu(CM)_2^{2+}} = \frac{[Cu(CM)_2^{2+}]}{[Cu(CM)^{2+}][CM]}$$

$$Cu(CM)^{2+} + L^- \overset{\beta^{Cu(CM)^{2+}}_{Cu(CM)L^+}}{\rightleftharpoons} Cu(CM)L^+$$

$$\beta^{Cu(CM)^{2+}}_{Cu(CM)L^+} = \frac{[Cu(CM)L^+]}{[Cu(CM)^{2+}][L^-]}$$

$$Cu(CM)_2^{2+} + L^- \overset{\beta^{Cu(CM)2+}_{Cu(CM)_2L^+}}{\rightleftharpoons} Cu(CM)_2L^+$$

$$\beta^{Cu(CM)_2^{2+}}_{Cu(CM)_2L^+} = \frac{[Cu(CM)_2L^+]}{[Cu(CM)_2^{2+}][L^-]}$$

Dissociation constants of cimetidine and phenobarbital as well as stability constant calculations were performed using the Miniquad program[20].

Results and Discussion

Fig. 1 (5) shows the mixed ligand titration curve for $Cu^{2+} : CM : L^{-}$ in 1 : 1 : 6 molar ratio at $I = 0.1\ mol\ dm^{-3}$. The curve contains an inflection at $m = 1$ (where "m" represent moles of base added per mole of metal ion) indicating formation of the binary complex $Cu(CM)^{2+}$. A second inflection at $m = 2$ indicates that a ternary complex, $Cu(CM)L^{+}$, forms between $m = 1$ and $m = 2$. Stability constants, $\beta^{Cu^{2+}}_{Cu(CM)^{2+}}$ and $\beta^{Cu(CM)^{2+}}_{Cu(CM)L^{+}}$ are given in Tables 1 and 2 respectively.

Fig. 2 (5) shows the potentiometric curve for $Cu^{2+} : CM : L^{-}$ in 1 : 2 : 6 molar ratio at $I = 0.1\ mol\ dm^{-3}$. An inflection corresponding to the formation of $Cu(CM)_2^{2+}$ is observed at $m = 2$. A second inflection at $m = 3$ indicates formation of $Cu(CM)_2L^{+}$. Stability constants, $\beta^{Cu(CM)^{2+}}_{Cu(CM)_2^{2+}}$ and $\beta^{\omega\Psi CM)^{2+}}_{Cu(CM)_2L^{+}}$, are given in Tables 1 and 2 respectively.

The parameters generally used to indicate the stability of ternary complexes with respect to the binary ones are $\log X$, $\log \beta_{stat.}$ and $\Delta \log K$. According to *Sigel*[21] these parameter are used as a measure of stability instead of $\log \beta^{M}_{MAB}$ or $\log K^{MA}_{MAB}$ because they are only indirectly dependent on ligand basicity.

Values of $\log X$ for $Cu(CM)L^{+}$ where calculated from the following equation[1,22]:

$$\log X = 2 \log \beta^{Cu^{2+}}_{Cu(CM)L^{+}} - (\log \beta^{Cu^{2+}}_{Cu(CM)_2^{2+}} + \log \beta^{Cu^{2+}}_{CuL_2})$$

Table 1. *Dissociation constant of methanol, acid dissociation constants of ligands, and 1.0 mol dm^{-3} ($NaClO_4$) and 25 ± 0.2 °C*

Ionic strength mol dm^{-3}	pKs	$pK_{HCM^{+}}$	pK_{HL}	$\log \beta^{Cu^{2+}}_{Cu(CM)^{2+}}$
0.1	15.32 (0.02)	8.26 (0.01)	11.17 (0.02)	5.95 (0.04)
1.0	15.07 (0.03)	8.65 (0.01)	10.62 (0.01)	6.23 (0.03)

Table 2. *Stability constants for the ternary complexes $Cu^{2+} : CM : HL$ in deviations are given*

Ionic strength mol dm^{-3}	$\log \beta^{Cu^{2+}}_{Cu(CM)L^{+}}$	$\log \beta^{Cu^{2+}}_{Cu(CM)_2L^{+}}$	$\log \beta^{Cu(CM)L^{+}}_{Cu(CM)_2L^{+}}$
0.1	11.75 (0.04)	15.99 (0.02)	4.24
1.0	11.06 (0.01)	15.41 (0.02)	4.35

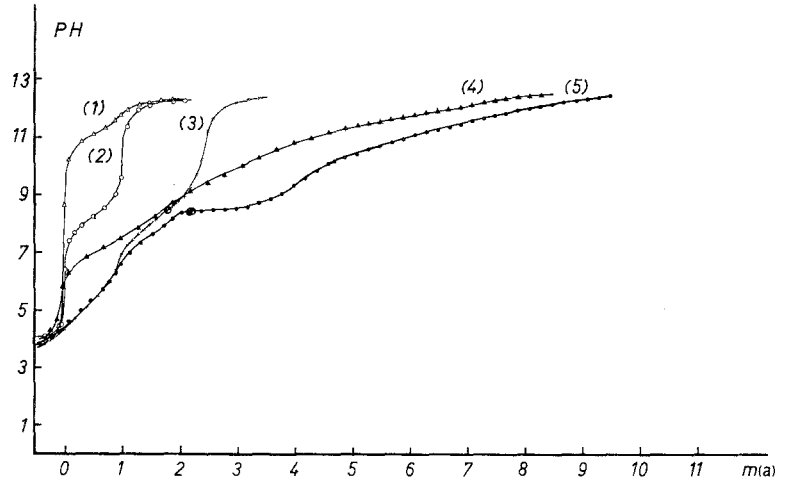


Fig. 1. Potentiometric titration curves for the Cu(II) : cimetidine : phenobarbital system in a 1 : 1 : 6 molar ratio at 25 ± 0.2 °C, $I = 0.1$ mol dm^{-3} ($NaClO_4$). (1) = free protonated cimetidine, HCM^+; (2) = free phenobarbital, HL; (3) = $Cu^{2+}:HCM^+$ 1 : 1; (4) = $Cu^{2+}:HL$ 1 : 6; (5) = $Cu^{2+}:CM:HL$ 1 : 1 : 6. All titrations were obtained with an excess of 10^{-4} mol of HNO_3; "m" = moles of base added per mole of ligand [for curves (1) and (2)]; 0 Point at which precipitation begins

and formations constants of binary complexes in methanol solution at $I = 0.1$ (standard deviations are given in parentheses)

$\log \beta^{Cu^{2+}}_{Cu(CM)_2^{2+}}$	$\log \beta^{Cu(CM)^{2+}}_{Cu(CM)_2^{2+}}$	$\log^a \beta^{Cu^{2+}}_{CuL^+}$	$\log^a \beta^{Cu^{2+}}_{CuL_2}$
10.85 (0.01)	4.90	6.07	10.80
11.31 (0.01)	5.08	5.04	9.45

[a] Ref.[25].

methanol media at $I = 0.1$ and 1.0 mol dm^{-3} ($NaClO_4$) and 25 ± 0.2 °C (standard in parantheses)

$\log \beta^{Cu(CM)^{2+}}_{Cu(CM)L^+}$	$\log \beta^{Cu(CM)_2^{2+}}_{Cu(CM)_2L^+}$	$\log \beta^{CuL^+}_{Cu(CM)L^+}$	$\log \beta^{CuL^+}_{Cu(CM)_2L^+}$
5.80	5.14	5.68	9.92
4.83	4.10	6.02	10.37

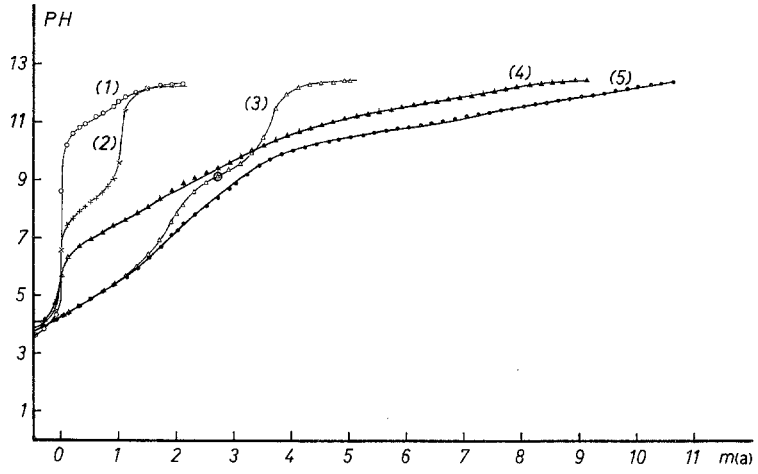


Fig. 2. Potentiometric titration curves for the Cu(II):cimetidine:phenobarbital system in a 1:2:6 molar ratio at 25 ± 0.2 °C, $I = 0.1$ mol dm^{-3} ($NaClO_4$). (1) = free protonated cimetidine, HCM^+, (2) = free phenobarbital, HL; (3) = $Cu^{2+}:HCM^+$ 1:2, (4) = $Cu^{2+}:HL$ 1:6; (5) = $Cu^{2+}:CM:HL$ 1:2:6; all titrations were obtained with an excess of 10^{-4} mol of HNO_3; "m" = moles of base added per mole of metal ion [for curves (3), (4) and (5)]; "a" = moles of base added per mole of ligand [for curves (1) and (2)]; 0 Point at which precipitation begins

The results are reported in Table 3 at 0.1 and 1.0 ionic strengths. These results indicate that $\log X$ has a positive value at both ionic strengths, reflecting that the ternary complex $Cu(CM)L^+$ is more stable than both $Cu(CM)_2^{2+}$ and CuL_2 binary complexes.

The statistical factor may be calculated from the following equation[1,23]:

$$\log \beta_{\text{stat.}} = \log 2 + \tfrac{1}{2} \log \beta^{Cu^{2+}}_{Cu(CM)_2^{2+}} + \tfrac{1}{2} \log \beta^{Cu^{2+}}_{CuL_2}$$

Table 3. *Stability parameters of ternary*

Ionic strength mol dm^{-3}	$\log X_{Cu(CM)L^+}$	$\log \beta_{Cu(CM)L^+_{stat.}}$
0.1	1.85	11.13
1.0	1.36	10.68

Table 3 gives the values of $\log \beta_{\text{stat.}}$ and $\log \beta^{Cu^{2+}}_{Cu(CM)L^+} - \log \beta_{\text{stat.}}$ obtained from the difference between stabilities measured and calculated by statistical methods. This difference is positive at $I = 0.1$ and $I = 1.0\,\text{mol dm}^{-3}$. This stability enhancement has been referred as a "ligand effect"[1] which is related to electrostatic factors originated by charge neutralization since in the formation of $Cu(CM)L^+$ one positive charge of $Cu(CM)^{2+}$ is neutralized. This effect is also related with an increase in σ-covalence which takes place when solvent molecules of $Cu(CM)^{2+}$ are replaced by a ligand such as L^-. Finally, this stability enhancement also reflects an increase in π-participation, since E.P.R. studies have showed that, in fact, heteroatomic N ligands, such as imidazole and bipyridyl, receive π-electron density from Cu(II).

$\Delta \log K$ for $Cu(CM)L^+$ is defined as[1, 22, 23]:

$$\Delta \log K = \log \beta^{Cu^{2+}}_{Cu(CM)L^+} - (\log \beta^{Cu^{2+}}_{Cu(CM)^{2+}} + \log \beta^{Cu^{2+}}_{CuL^+})$$

The values of $\Delta \log K$ at $I = 0.1$ and $1.0\,\text{mol dm}^{-3}$ are listed in Table 3.

The value of $\Delta \log K$ is a measure of the coordination tendency of phenobarbital towards the complex $Cu(CM)^{2+}$ relative to Cu^{2+}_{aq}[21]. In general, it can be stated that the greater $\Delta \log K$, the greater the stability of the ternary complex $Cu(CM)L^+$ with respect to the binary complexes $Cu(CM)^{2+}$ or CuL^+[22]. Negative values for $\Delta \log K$ were expected since usually $K^M_{ML} > K^{ML}_{ML_2}$.

Values of $\Delta \log K$ at both ionic strengths (0.1 and 1.0) are negative—as expected—since $\beta^{Cu^{2+}}_{Cu(CM)^{2+}} > \beta^{Cu(CM)^{2+}}_{Cu(CM)^{2+}_2}$ (see Table 1). However, the negative values for $\Delta \log K$ does not preclude the formation of ternary complexes. The stability of mixed ligand complex formation is also determined by the reproportionate constant from statistical considerations. However, formation of $Cu(CM)L^+$ is not only determined by statistical factors. These is an additional stability originated by a ligand effect (see above).

complexes with respect to the binary ones

$\log \beta^{Cu^{2+}}_{Cu(CM)L^+} - \log \beta_{\text{stat.}}$	$\Delta \log K_{Cu(CM)L^+}$	$\Delta \log K_{Cu(CM)_2L^+}$
0.62	−0.27	−0.93
0.38	−0.21	−0.94

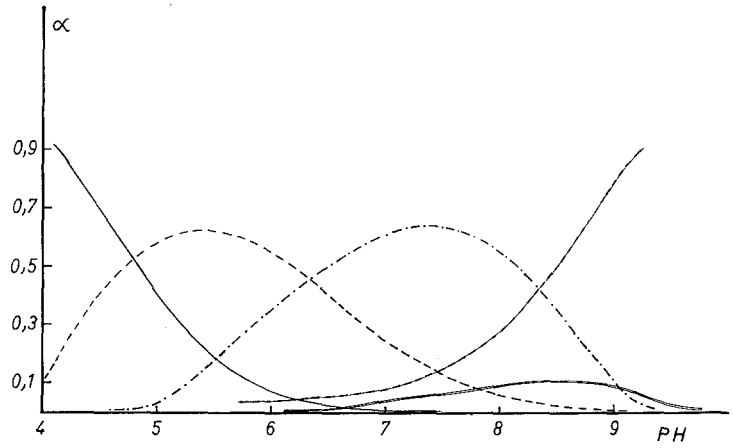


Fig. 3. Cu(II) : cimetidine : phenobarbital system. Distribution of complex species as a function of pH at $I = 0.1$ mol dm^{-3} ($NaClO_4$) and [Cu] $= 2 \cdot 10^{-3}$ mol dm^{-3}: ——— Cu(II); – – – – Cu$(CM)^{2+}$ —·—·—· Cu$(CM)_2^{2+}$; ═══ Cu$(CM)L^+$; ═══ Cu$(CM)_2L^+$

According to *Martin* and *Prados*[24] electrostatic effects contribute differently to the $\Delta \log K$ and $\log X$ formulation depending upon the ligand charge. Thus, in a mixed ligand complex of bipyridyl and negatively charged ligand, the electrostatic contribution (or the ionic strength) to mixed complex stability is absent in $\log K$ but likely to be significant in $\log X$.

From the results on Table 3 it can be concluded that $\Delta \log K$ for Cu$(CM)L^+$ is essentially independent of ionic strength. This is in agreement with the fact that cimetidine has no charge while phenobarbiturate has one negative charge.

For Cu$(CM)_2L^+$ only the calculation of $\Delta \log K$[22] is possible.

$$\Delta \log K = \log \beta^{Cu^{2+}}_{Cu(CM)_2L^+} - (\log \beta^{Cu^{2+}}_{Cu(CM)_2^{2+}} + \log \beta^{Cu^{2+}}_{CuL^+})$$

The results are reported in Table 3 showing that $\Delta \log K$ is independent of ionic strength.

The distribution diagrams of various species as a function of pH has been calculated for the $Cu^{2+} : CM : L^-$ system for $I = 0.1$ and 1.0 mol dm^{-3}. Fig. 3 shows the distribution diagrams corresponding to solution of Cu(II), CM and L^- in molar ratios 1 : 2 : 2 respectively, of $I = 0.1$ mol dm^{-3}. It can be seen in this diagram that the molar fraction of the free metal ion is almost negligible near pH 6, justifying the assumption that hydrolyzed metal complexes are absent in the pH ranges employed in

this investigation. The concentrations of the binary complexes $Cu^{2+}:L^-$ are also negligible. In the 5–6 pH range $Cu(CM)^{2+}$ is the major species, while $Cu(CM)_2^{2+}$ predominates at pH 7–8. Finally, above pH 8.9 $Cu(CM)_2L^+$ is by far the major species, being almost the only one present.

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