CHAPTER-5

MIXED-LIGAND COMPLEX FORMATION EQUILIBRIA
OF Cu\textsuperscript{II} WITH (a) BIGUANIDE & HISTIDINE AND
(b) GUANYLUREA & HISTIDINE
5.1. Introduction

Metal ions play vital roles in a vast number of widely different processes occurring in the biological systems [1-3]. Copper, the third most abundant transition metal after iron and zinc in the human body, occurs at the active sites of a large number of redox enzymes. In majority of such copper proteins, copper atoms are coordinated by one or more imidazole-N atoms of histidine residues of the protein chains [4, 5]. Histidine, on the other hand, shows ambidentism in its modes of coordination to copper (II) [6-8]. Because of its inherent susceptibility to undergo tetragonal distortion arising from Jahn-Teller effect, CuII (d⁹) prefers to achieve square planar, distorted octahedral or square pyramidal geometry in its complexes. Depending upon the pH and molar proportions of the metal to ligand in the solution, histidine may coordinate CuII ion in three different modes:

(a) as a (N, N) bidentate histamine-like ligand (hism'), using the amino-N and imidazole-N atoms,
(b) as a (N, O') bidentate glycine-like ligand (gly'), using the amino-N and carboxylate-O atoms, and
(c) as a (N, N, O') tridentate histidine-like ligand (his), using the amino-N, imidazole-N and carboxylate-O atoms. Two of these three donor atoms coordinate two equatorial positions on the copper coordination geometry and the third donor atom coordinates from an apical position.

Stepwise stability constants of [Cu(his)₂] complex, earlier revealed the coordination mode (c) for the first his' ligand, with the carboxylate-O atom coordinating from an apical position and coordination mode (b) was indicated for the second his' ligand [6]. Structure involving both the his' ligands coordinating in glycine-like manner (mode-b), does not contribute to the complex formation equilibria. But XRD measurements on the single crystals of the nitrate salt of bis-(l-histamine)CuII dihydrate, isolated at pH~3.7, indicates glycine-like (mode-b) coordination of both the his' ion [9]. However, further studies on the 1:2 CuII:histidine complex at neutral or weakly basic pH reveals histamine-histamine like coordination (mode-a) by both the his' ligands and above pH 8.1, a structure involving mixed glycine-histamine-like (modes-a and b) coordination by the two his' ligands occurs in equilibrium [10-13]. Recent EXAFS study [8] on
1:2 Cu\textsuperscript{II}-histidine complex at pH~7.3 indicates the dominance of a symmetric histamine-
histamine (mode-\textit{a}) of coordination by the two his\textsuperscript{I} ligands forming two coplanar 6-
membered chelate rings. This further confirms the 4-coordinated square planar geometry
for Cu\textsuperscript{II} in this complex, discarding the alternative tetrahedral model. Contribution of the
\textit{mixed histamine-glycine-like} mode is slightly lower, but the glycine-glycine mode makes
no contribution to the equilibria. Thus, although, complex formation of Cu\textsuperscript{II} with
histidine have been extensively studied, there is certainly scope for further investigation.

Due to imidazole-N coordination, histidine, among all the natural amino acids,
shows highest affinity for Cu\textsuperscript{II} (log$\beta_2$=18.3) [6] and histidine bonded Cu\textsuperscript{II} can
discriminate between $\sigma$-basic and $\pi$-acidic ligands in ternary complexes [14]. With a view
to elucidate the modes of coordination of histidine (hisH\textsuperscript{I}) to Cu\textsuperscript{II} in presence of strongly
coordinating [(N, N)] bidentate ligand, biguanide $[\text{H}_2\text{N}C(=\text{2NH})\text{3NH}C(=\text{4NH})\text{5NH}_2,$
Bg] and (O, N) and/or (N, N) bidentate ligand, guany lurea $[\text{H}_2\text{N}C(=\text{O})\text{2NH}C(=\text{3NH})$
$\text{4NH}_2,$ GuH] (Scheme 5.1), mixed-ligand complex formation equilibria of Cu\textsuperscript{II} with
histidine, Bg and GuH have been investigated by combined pH-metric and
spectrophotometric measurements in aqueous solution at 25±1°C at a fixed ionic strength,
I=0.1 mol. dm\textsuperscript{-3} (NaNO\textsubscript{3}).

![Scheme 5.1](image-url)
Formation constants of the most probable complexes formed have been evaluated and the complex formation equilibria have been elucidated by the mathematical modeling of the pH-titration data with the aid of the computer program, SCOGS [15] written in FORTRAN-77 and analysis of the speciation curves.

Biguanide, N-substituted biguanides and their metal derivatives have recently shown antidiabetic, antimalarial properties, effectiveness in reduction of anxiety, pain and memory disorders [16, 17]. Histidine and some of its metal derivatives have been identified as Alzheimer’s Aβ-channel blockers, preventing Aβ-cytotoxicity [18]. Guanylurea and its N, N'-disubstituted derivatives have been extensively used for biological remediation of soils polluted by spilt oil, chemical pollutants etc. [19]. The results of the present equilibrium study may provide useful clues for elucidation molecular mechanism of drug actions of these compounds.

5.2. Experimental

5.2.1. Materials and Methods

All the reagents were of AR grades and their solutions were prepared in double distilled CO2 free water. Procedures for standardization of the reagents, pH metric and spectrophotometric measurements, evaluation of the equilibrium constants using the computer program SCOGS [15] were the same as described in the earlier chapters [Ch-3, 4 and (22a,b,c)]. For the determination of proton-ligand and metal-ligand complex formation constants, a series of solutions, each of initial volume 0.025 dm³, containing known amounts (0.005 mol. dm⁻³) of free HNO₃, known amounts (0.001-0.0002 mol. dm⁻³) of ligands, viz., histidine, biguanide and guanylurea in their protonated forms (H₂hisH)²⁺, (H₂Bg²⁺) and (HG₅H⁺) respectively, in the absence and in the presence of known amounts (0.00021-0.001 mol. dm⁻³) of Cu¹¹ nitrate were pH-metrically titrated with a carbonate free standard 0.1 mol. dm⁻³ NaOH solution, maintaining a fixed ionic strength, 0.1 mol. dm⁻³ (NaNO₃) at 25±1°C (thermostated). Representative pH titration curves are presented in Figs 5.1 and 5.2.
5.2.2. Calculation of Formation Constants

The overall formation constant ($\beta_{pqrs}$) of a homo metallic generalized ternary complex species, $[\text{Cu}_p(\text{his})_q(L)_r(\text{OH})_s]$, (Table 5.1) may be defined according to,

$$p \text{Cu} + q \text{his} + r L + s (\text{OH}) \rightleftharpoons \text{Cu}_p(\text{his})_q(L)_r(\text{OH})_s$$  \hspace{1cm} (5.1)

where, $L = \text{Bg}$ or $\text{Gu}$ as the case may be, the stochiometric members, $p$, $q$ and $r$ may be positive or zero, $s$ is a negative integer for a protonated species such as $H_2\text{his}H^{2+}$, $(H_2\text{his})^+$, $H_2\text{Bg}^{2+}$, $H\text{Bg}^+$, $\text{GuH}_2^+$, $\text{GuH}$ etc., positive integer for a hydroxo or a deprotonated species like $\text{Cu}(\text{OH})^+$, $\text{Cu}(\text{Bg-H})^+$, $\text{Cu}(\text{his-H})$ and zero for a neutral species such as $\text{Cu}(\text{Bg})^{2+}$, $\text{Cu}(\text{Gu})^+$, $\text{Cu}(\text{his})^+$, $\text{Cu}(\text{his})(\text{Bg})^+$ $\text{Cu}(\text{his})(\text{Gu})$ etc. For 1:1 and 1:5 binary $\text{Cu}^{II}$:ligand systems, $p = 1$ and the value of $q$ and $r$ depend upon the molar ratios of metal:ligand in the complexes supposed to be formed in the solution. For 1:1:1 $\text{Cu}^{II}$:his:Bg(or Gu) system, $p = q = r = 1$. Since the pH range of some of the complex formation equilibria were overlapping with the hydrolytic equilibria of $\text{Cu}^{II}$ (aq) ion, formation of binary as well as ternary hydroxo complexes were considered in calculating the stability constants ($\beta_{pqrs}$) of the metal-ligand complexes, however, pH-titration data (Fig. 5.1 and Fig. 5.2) prior to the commencement of any turbidity were subjected to calculation.

Bidentate (N, N) mode of chelation by biguanide is well known [21, 22]. For the histidine ligand ($\text{his}$), bidentate ($\text{NH}_2$, N-imz) i.e., histamine-like (mode-a) and ($\text{NH}_2$, COO$^-$), i.e., glycine-like (mode-b) along with mixed histamine-like glycine-like chelation were considered, but inclusion of complexes with only glycine-like chelation gave larger values of standard deviations. So, such species were excluded from the calculation. Complex formation equilibria were elucidated from analysis of the speciation curves (Figs. 5.3, 5.5 and 5.6) and the modes of coordination of the ligands were established from the shifts of electronic spectral absorption maximum of $\text{Cu}^{II}$ (Fig. 5.4 and 5.7) in binary and ternary systems with change of pH of the solution [20].
Fig. 5.1 Representative pH titration curves of CuII:biguanide:histidine system: ($M = \text{mol. dm}^{-3}$): 1, 0.005 ($M$) HNO$_3$; 2, (1) + 0.001 ($M$) H$_2$Bg$^{2+}$; 3, (1) + 0.001 ($M$) H$_2$hisH$^{2+}$; 4, (2) + 0.001 ($M$) Cu$^{II}$; 5, (3) + 0.001 ($M$) Cu$^{II}$; 6, (5) + 0.001 ($M$) H$_2$Bg$^{2+}$; initial volume = 0.025 dm$^3$, titrant = 0.1 ($M$) NaOH, ionic strength, $I = 0.1$ ($M$) NaNO$_3$. 

Volume of 0.1 (mol. dm$^{-3}$) NaOH
Fig. 5.2 Representative pH titration curves of Cu$^{II}$:guanylurea:histidine system: 
$(M = mol. dm^{-3})$: 1, 0.005 $(M)$ H$\text{NO}_3$; 2, (1) + 0.001 $(M)$ H$_2$Gu$^+$; 3, (1) + 0.001 $(M)$ H$_2$hisH$^{2+}$; 4, (2) + 0.001 $(M)$ Cu$^{II}$; 5, (3) + 0.001 $(M)$ Cu$^{II}$; 6, (5) + 0.001 $(M)$ H$_2$Gu$^+$; initial volume = 0.025 $dm^3$, titrant = 0.1 $(M)$ NaOH, ionic strength, $I = 0.1 (M)$ NaNO$_3$. 

Volume of 0.1 $(mol. dm^3)$ NaOH
5.3. Results and Discussion

5.3.1. Proton-Ligand Equilibria

(i) Protonation-deprotonation equilibria of histidine

In dilute acidic solution (pH<2), histidine (his$^{H^+}$) exists in its diprotonated (H$_2$his$^{H^+}$)$_2^+$ form, in which the added protons remain associated with the imidazole-N$^3$ atom and amino-N atom (Scheme 5.2). The carboxylic acid group remains partly ionized (pK$_{H^3}$$^\sim$1.60). Above pH~3, the zwitterionic (H$_2$his')$^+$ is the dominant species (Fig. 5.3). The imidazolium ($^{3}$NH$^+$) proton is lost above pH 5 (pK$_{H^2}$$^\sim$6.02) and the aminium proton (-NH$_3^+$) is lost above pH 8 (pK$_{H^1}$$^\sim$9.10).

\[
\begin{align*}
\text{(H$_2$his$^{H^+}$)$_2^+$} & \quad \text{pK$_{H^3}$$^\sim$1.60} \\
\text{\textendash} & \text{H$^+$} \\
\text{\Leftrightarrow} & \text{+ H$^+$} \\
\text{\textendash} & \text{H$^+$} \\
\text{\textendash} & \text{H$^+$} \\
\text{(H$_2$his')$^+$} & \quad \text{pK$_{H^2}$$^\sim$6.02} \\
\text{\textendash} & \text{H$^+$} \\
\text{\Leftrightarrow} & \text{+ H$^+$} \\
\text{\textendash} & \text{H$^+$} \\
\text{(his$^-$)} & \quad \text{pK$_{H^1}$$^\sim$9.10} \\
\text{\textendash} & \text{H$^+$} \\
\text{\Leftrightarrow} & \text{+ H$^+$} \\
\text{\textendash} & \text{H$^+$} \\
\text{(HhisH$^+$)} & \\
\end{align*}
\]

Scheme 5.2
Due to tautomerism within the imidazole ring, the $^1$NH hydrogen atom in $^1$his$^+$ and $^1$his$'$ ions may alternate between $^1$N and $^3$N atoms [20].

(ii) Protonation-deprotonation of biguanide

In dilute acidic solution ($pH<2$) biguanide (Bg) exists as its dicationic form ($H_2Bg^{2+}$). The added protons remain bound to the $^1$NH$_2$ and $^5$NH$_2$ groups (Scheme 5.1) [Ch-3, 4 and (21, 22a,c)]. These protonated forms disappear with rise of pH, giving two well separated buffer regions ($2<pH<4$) and ($9.5<pH<11.5$). Due to structural symmetry (Scheme 5.1) of biguanide, it is not possible to specify which group among $^1$NH$_3^+$ and $^5$NH$_3^+$ deprotonates at which buffer region.

(iii) Protonation-deprotonation of guanylurea

In dilute acidic solution ($pH≈2$), guanylurea (GuH) occurs in its monoprotonated ($HGuH^+$) form. With rise of pH, it offer two well separated buffer regions ($pH<4$) and ($7<pH<9$), due to successive deprotonation of either $^1$NH$_3^+$ (or $^4$NH$_3^+$) ($pK_H~2.0$) and $^5$NH ($pK_H~8.20$) moieties to form the mono anion, Gu$^-$. [Ch-3, 4 and (22b)]

5.3.2. Binary Systems

(i) $1:1 Cu^{II}$:histidine equilibria

Stoichiometry of the binary $Cu^{II}$:histidine, $Cu^{II}$:biguanide and ternary $Cu^{II}$:histidine:biguanide complexes are presented in Table 5.1 along with the refined values of their formation constants.

Complex formation of $Cu^{II}$ with histidine in the 1:1 binary system starts at ~ pH 3, where the ligand exists mostly in its [$H_2hisH^+$] form (Scheme 5.2) and the hydroxo species, viz., $Cu(OH)^+$, $Cu(OH)_2$ are totally absent (Fig. 5.3a) The 1:1 $Cu^{II}$:histidine complex (8) (Table 5.1) is the major copper containing species in the pH range 3-8, with a concentration maxima (~80%) at pH ~5-5.5. Two possible modes of bidentate chelation by the his$'$ ligand ion, viz., histamine-like coordination (hism$'$) using the amino-N atom and the imidazole-N atoms (mode-a) and glycine-like coordination (gly$'$) using the amino N-atom and the carboxylate-O atom (mode-b) give two structural possibilities, (8a) and (8b) respectively for the complex (8) (Scheme 5.3).
Table 5.1 Stochiometry of the Cu$^{II}$-histidine-biguanide complexes and refined values of the proton ligand and metal ligand constants.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Complex Species</th>
<th>$p$</th>
<th>$q$</th>
<th>$r$</th>
<th>$s$</th>
<th>$\log K_{pqr}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>[H$_2$hisH]$^{2+}$</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>-3</td>
<td>16.72</td>
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<tr>
<td>2.</td>
<td>[H$_2$his]$^+$</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>-2</td>
<td>15.12</td>
</tr>
<tr>
<td>3.</td>
<td>[His$^+$]</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-1</td>
<td>09.10</td>
</tr>
<tr>
<td>4.</td>
<td>H$_2$Bg$^{2+}$</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-2</td>
<td>14.20</td>
</tr>
<tr>
<td>5.</td>
<td>HBg$^+$</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-1</td>
<td>10.90</td>
</tr>
<tr>
<td>6.</td>
<td>[Cu(OH)$^+$]</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-06.29</td>
</tr>
<tr>
<td>7.</td>
<td>[Cu(OH)$_2$]</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>-13.05</td>
</tr>
<tr>
<td>8.</td>
<td>[Cu(hism)$^+$]</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>10.21</td>
</tr>
<tr>
<td>9.</td>
<td>[Cu(hism-H)]</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>04.18</td>
</tr>
<tr>
<td>10.</td>
<td>[Cu(hism)$_2$]</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>20.28</td>
</tr>
<tr>
<td>11.</td>
<td>[Cu(hism)(gly)]</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>19.80</td>
</tr>
<tr>
<td>12.</td>
<td>[Cu(hism)(hism-H)$'$]</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>13.00</td>
</tr>
<tr>
<td>13.</td>
<td>[Cu(hism-H)$_2$]$^{2+}$</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>04.95</td>
</tr>
<tr>
<td>14.</td>
<td>[Cu(Bg)$^{2+}$]</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>06.74</td>
</tr>
<tr>
<td>15.</td>
<td>[Cu(Bg)(OH)$^+$]</td>
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<td>1</td>
<td>1</td>
<td>01.70</td>
</tr>
<tr>
<td>16.</td>
<td>[Cu(Bg-H)(OH)]</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>-05.18</td>
</tr>
<tr>
<td>17.</td>
<td>[Cu(hism)(Bg)$^+$]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>18.22</td>
</tr>
<tr>
<td></td>
<td>$\triangle \log K_{Cu}$ (17)</td>
<td></td>
<td></td>
<td></td>
<td>(+)</td>
<td>01.27</td>
</tr>
<tr>
<td>18.</td>
<td>[Cu(hism)(Bg)(H)]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>09.95</td>
</tr>
</tbody>
</table>

hism': histamine-like (NH$_2$, N-imz) coordination by histidine
gly': glycine-like (NH$_2$, -COO') coordination by histidine

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Fig. 5.3 Speciation curves of (a) 1:1 and (b) 1:5 Cu\(^{II}\):histidine systems: 1, H\(_2\)hisH\(^2+\); 2, (H\(_2\)his\(^+\)); 3, His\(^+\); 6, Cu(OH\(^+\)); 7, Cu(OH\(_2\)); 8, Cu(hism\(^+\)); 9, Cu(hism-H); 10, Cu(hism\(_2\)); 11, Cu(hism)(gly); 12, Cu(hism)(hism-H); 13, Cu(hism-H\(_2\))\(^2-\); FM = Free Cu\(^{II}\), FB1 = Free his\(^+\).
Cu$^{II}$ in these two isomeric structures (8a and 8b) will take up two molecules of solvent H$_2$O to achieve its preferred 4-coordinated square planar geometry, viz., [Cu(NH$_2$)(N-imz)(H$_2$O)$_2$] (8a) and or [Cu(NH$_2$)(COO')(H$_2$O)$_2$], (8b). Electronic spectral absorption maxima ($\lambda_{\text{max}}$) of Cu$^{II}$ corresponding these two structures may be estimated [20, 22] according to the equation (5.2):

$$\lambda_{\text{max}} (nm) = 10^3 / \left[ 0.294 \ (\text{C}=\text{O}/\text{H}_2\text{O}/\text{OH}/=\text{NH}) + 0.346 \ (\text{COO}') + 0.434 \ (\text{N-imz}) + 0.46 \ (\text{NH}_2) + 0.494 \ (=\text{N}') \right]$$ (5.2)

where, the groups in the parentheses represent the number of such coordinating groups (total not exceeding 4) and the numerical coefficients are their ligand field contributions in $\mu$m$^{-1}$. Estimated $\lambda_{\text{max}}$ values for structure (8a) and (8b) are 675 nm and 733 nm respectively. The experimental $\lambda_{\text{max}}$ value (693 nm) of 1:1 Cu$^{II}$:histidine mixture at pH~5-5.5 (Fig. 5.4a) at which the % of complex (8) passes through a maximum (Fig. 5.4a) is closer to the estimated $\lambda_{\text{max}}$ value corresponding to structure (8a). Slightly higher experimental $\lambda_{\text{max}}$ value (by ~18 nm) suggests apical carboxylate coordination of intermolecular nature. The alternative structure (8b) with glycine-like chelation may be discarded, because of wide difference of the calculated $\lambda_{\text{max}}$ corresponding to this structure from the experimental value.
Fig. 5.4 Electronic spectra of (a) 1:1 Cu$^{II}$:histidine, (b) 1:5 Cu$^{II}$:histidine (c) 1:1:1 Cu$^{II}$:histidine:biguanide system at different pH. Ionic strength, $I = 0.1$ $mol. dm^{-3}$ (NaNO$_3$).
As the speciation curves (Figs. 5.3a) imply, formation of the complex (8) may be described according to the eqn. (5.3):  
\[
\text{Cu}^{2+} + \text{[H}_{2}\text{his}^{(\pm)}\text{]}^+ \rightleftharpoons \text{[Cu(hism)}^{+}\text{]} (8) + 2\text{H}^+ \quad (5.3)
\]
Another buffer region corresponding to the release of one mole of H\(^+\) per mole of Cu\(^{2+}\) is observed between pH 6-8 with a blue shift of the \(\lambda_{\text{max}}\) (~ by \(\geq 20\) nm) to 656 nm around pH 6.5-7 (Fig. 5.4). This buffer region can not be due to deprotonation of a coordinated H\(_2\)O molecule to OH\(^-\) ion within the complex (8, i.e., 8a), since H\(_2\)O and OH\(^-\) are very closely placed in the spectrochemical series. The only possible source of this buffer action is release of the imidazole (\(^1\text{NH} \rightleftharpoons \text{3NH}\)) proton from (8a), producing the complex \([\text{Cu(hism-H)}]\) (9) (Scheme 5.3), according to the eqn. (5.4):  
\[
[\text{Cu(hism)}^{+}] \rightleftharpoons \text{[Cu(hism-H)]} + \text{H}^+ \quad (5.4)
\]
The pK\(^H\) (8) value (~ 6.03) corresponding to the deprotonation (eqn. 5.4):  
\[
pK^H = \log \beta_{1101} - \log \beta_{1100} \quad (5.4a)
\]
reflects the enhancement of acidity of otherwise neutral imidazole -NH of histidine due to coordination of the tertiary N-atom of the imidazole ring to Cu\(^{II}\). Ligand field contribution of deprotonated imidazole moiety of histidine to Cu\(^{II}\) comes around \(-0.48\) \(\mu m\) and \(-0.52\) \(\mu m\) respectively and in the presence and in the absence of apical carboxylate coordination.

(iii) 1:5 Cu\(^{II}\):histidine equilibria

Complex formation in 1:5 Cu\(^{II}\):histidine system commences around pH 2.5 (Fig. 5.3b) with appearance of the 1:1 complex (8) (eqn. 5.2), showing a concentration maximum (~30%) at pH ~3.5-4, where the imidazole deprotonated 1:1 complex (9) does not occur at all. The major Cu\(^{II}\) containing species above pH 4 is the 1:2 Cu\(^{II}\):histidine complex, which may exist in two isomeric structures, viz., \([\text{Cu(hism)}_2]\) (10), involving histamine-histamine-like coordination by the two his' ligands and Cu(hism)(gly) (11) involving mixed-histamine-like (mode-a) and glycine-like (mode-b) coordination by the two his' ligands (Scheme 5.4). The uncoordinated carboxylate-O atoms and imidazole-N atoms in structures (10) and (11), however, can provide apical coordination to Cu\(^{II}\) intermolecularly.
Inclusion of structures involving only glycine-like chelation (mode-6) viz., Cu(gly)$^+$ and Cu(gly)$_2^-$, for the 1:1 and 1:2 Cu$^{II}$:histidine complexes respectively, in the calculation of stability constants, gives higher value of standard deviations, therefore, such species are not considered.

The speciation curves (Fig. 5.3b) of this system shows that almost equal % of free Cu$^{2+}$ ion, the 1:1 complex [Cu(hism)$^+$] (8a) and two forms, viz., [Cu(hism)$_2$] (10) and [Cu(hism)(gly)] (11) of the 1:2 complex remain in equilibrium at pH~3.5-4.

![Scheme 5.4](image)

The estimated average of the $\lambda_{max}$ value (ca. 662 nm) of these species, obtained according to eqn (5.1) is close to the experimental value (654 nm) of 1:5 Cu$^{II}$:histidine mixture at this pH (~4) (Fig. 5.4b). A small blue shift of (~27 nm) to 617 nm, as the pH is raised to ~5, suggests transformation of (11) to (10) in increasing proportions. Since all these three types of complex species, (8a), (10) and (11) occur simultaneously in the complex formation equilibria, the initial stages of complex formation in 1:5 Cu$^{II}$:histidine system may be described according to eqn. (5.5-5.7) as the speciation curves (Fig. 5.3b) imply:
\[ \text{Cu}^{2+} + [\text{H}_2\text{his}^{(\pm)}]^+ \rightleftharpoons [\text{Cu(hism)}] + 2\text{H}^+ \quad (5.5) \]
\[ \text{Cu}^{2+} + [2\text{H}_2\text{his}^{(\pm)}]^+ \rightleftharpoons [\text{Cu(hism)}]_2 + 4\text{H}^+ \quad (5.6) \]
\[ \text{Cu}^{2+} + [2\text{H}_2\text{his}^{(\pm)}]^+ \rightleftharpoons [\text{Cu(hism)}(\text{gly})] + 4\text{H}^+ \quad (5.7) \]

A red shift of the \( \lambda_{\text{max}} \) value to 636-642 nm with rise of pH (above 6) is indicative of apical coordination of CuII by carboxylate-O atom and or uncoordinated imidazole-N atom in the complexes (10) and (11) which pass through their concentration maxima (~55-60 \%) and (40-45 \%) respectively around pH 5.5-6. Above pH 6, both (10) and (11) disappear simultaneously with building up of concentration of the imidazole deprotonated complexes, [Cu(hism)(hism-H)] \(^{-1}\) (12) and [Cu(hism-H)\(^{2-}\)] (13). Finally above pH 8, (12) is transformed to (13) (Scheme 5.5):

\[
\begin{align*}
(11) \quad [\text{Cu(hism)}(\text{gly})] & \rightleftharpoons -2\text{H}^+ +2\text{H}^+ \\
isomerizes \quad & \\
(10) \quad [\text{Cu(hism)}]_2 & \rightleftharpoons -2\text{H}^+ +2\text{H}^+ [\text{Cu(hism-H)}] \quad (13) \\
+\text{H}^+ - \text{H}^+ & \\
+\text{H}^+ & \\
(12) \quad [\text{Cu(hism-H)}(\text{hism})] & \rightleftharpoons +\text{H}^+ \\

\text{Scheme 5.5}
\]

Although small, but a definite final blue shift of the \( \lambda_{\text{max}} \) (~5-6 nm) value is observed above pH 9 (Fig. 5.4b), as increasing proportions of (12) and (13) appear in the solution through deprotonation of coordinated imidazole in (10) and (11) (Scheme 5.5).

(iii) 1:1 Cu\(^{II}\):biguanide equilibria

Complex formation in the 1:1 Cu\(^{II}\):biguanide system starts around pH~5, at which the metal ion exists as Cu\(^{2+}\)(aq), Cu(OH\(^+\))(aq) and Cu(Bg)(OH\(^+\)) and the ligand exists in its monoprotonated (HBg\(^+\)) form. Two moles of H\(^+\) per mole of Cu\(^{2+}\) are released in the pH range 5–6.5, at which the ternary hydroxo complex,
[Cu(Bg)(OH)^+](aq) appears to be the dominant copper containing species. The Bg ligand in this complex provides (N, N) bidentate chelation to Cu^{II} using its (\(\text{^1NH}_2\), \(\text{^-2NH}\)) or (\(\text{^-2NH}, \text{^5NH}_2\)) groups [Ch-3 and (22a)]. Above pH 7, [Cu(Bg)(OH)^+](aq) complex undergoes deprotonation (pK\(\text{H}^+\)=6.88) from its coordinated \(\text{^-2NH}\), (or \(\text{^5NH}\)) group to produce [Cu(Bg-H)(OH)].

(iv) 1:1 Cu^{II}:guanylurea equilibria

Complex formation of Cu^{II} with guanylurea in binary 1:1 metal:ligand system starts around pH>4, at which the metal ion exists as Cu^{2+}(aq), Cu(OH)^+(aq) and the ligand exists as the electroneutral GuH species. [Cu(Gu)^+](aq) and [Cu(Gu)(OH)] complexes appear simultaneously [Ch-3, Fig. 3.7a and (22b)]. Above pH~5.5, the [Cu(Gu)^+](aq) complex is transformed to the ternary hydroxo complex, [Cu(Gu)(OH)], through deprotonation (pK\(\text{H}^+\)=5.85) of a coordinated H\(\text{2O}\) molecule. The latter complex dominates the entire pH range above pH 7. Unlike the analogous 1:1 Cu^{II}:biguanide system [Ch-3, 4 and (22a,c)] in which biguanide \(\text{^-2NH}\), (or \(\text{^4NH}\)) deprotonated [Cu(Bg-H)(OH)] complex dominates above pH 7, no such guanylurea deprotonated complex occurs in the Cu^{II}:guanylurea system.

5.3.3. Ternary Systems

(i) 1:1:1 Cu^{II}:histidine:biguanide equilibria

Complex formation in ternary 1:1:1 Cu^{II}:histidine:biguanide system starts above pH 3 with appearance (eqm. 5.3 and 5.4) of the 1:1 Cu^{II}:histidine complex [Cu(hism)^+], (8a), which passes through its concentration maximum (~70%) around pH 5, at which small amount of free Cu^{II}(aq) ion, the imidazole deprotonated 1:1 Cu^{II}:histidine complex, [Cu(hism-H)], (9), and the 1:1:1 ternary complex, [Cu(hism)(Bg)], (17), (8-10)% each occur (Fig. 5.5). Concentration of (8a) declines above pH 5 with rise in the proportions of the complexes (9) (eqm. 5.4) and of (17) according to the eqm. (5.8):

\[
[Cu(hism)^+] + BgH^+ \rightleftharpoons [Cu(hism)(Bg)^+] + H^+ \quad (5.8)
\]
Fig. 5.5 Speciation curves of 1:1:1 Cu$^{II}$:histidine:biguanide system: 1, $H_2$hisH$^{2+}$; 2, $(H_2$his$^\pm)^+$; 3, Hhis$^\pm$; 4, $H_2$Bg$^{2+}$; 5, HBg$^+$; 6, Cu(OH)$^+$; 7, Cu(OH)$_2$; 8, Cu(hism)$^+$; 9, Cu(hism-H); 14, Cu(Bg)$^{2+}$; 15, Cu(Bg)(OH)$^+$; 16, Cu(Bg-H)(OH); 17, Cu(hism)(Bg)$^+$; 18, Cu(hism)(Bg)(-H); FM = Free Cu$^{II}$, FB1 = Free his$, FB2 = Free Bg$. 

Concentration (%)
Both theses complexes (9) and (17) dominate in the pH range 6-9, i.e, pH of biological relevance and pass through their concentration maxima (~55% and ~40% respectively) around pH 7.5. At still higher pH (7.5-10) the ternary complex (17) disappears with appearance of complex (18) through release of one mole of H⁺ per mole of Cu\(^{II}\), either from the coordinated 2NH (or 4NH) group of the Bg ligand producing (18a) or from the imidazole-NH of coordinated histidine ligand producing (18b) or from both, (Scheme 5.6)

\[
\begin{align*}
\text{(17)} & \quad \text{[Cu(hism)(Bg-H)]} \\
\text{+ H⁺} & \quad \text{[Cu(hism-H)(Bg)]} \quad \text{isomerizes}
\end{align*}
\]

Electronic spectral absorption maximum (λ\(_{\text{max}}\) ~ 660 nm) of 1:1:1 Cu\(^{II}\):histidine:biguanide mixture at pH 4.5-5 (Fig. 5.4c) at which 1:1 Cu\(^{II}\):histidine complex (8a) makes ~ 75% of total Cu\(^{II}\), is close to the estimated λ\(_{\text{max}}\) (~674 nm) corresponding a square planar Cu(NH\(_2\))(N-imz)(H\(_2\)O)\(_2\) geometry of this complex (Scheme 5.3).

With rise of pH, upto 7.5 at which complexes (9) and (17) make ~ 95% of total Cu\(^{II}\), λ\(_{\text{max}}\) value shifts to ~627 nm, which is quite close to the estimated λ\(_{\text{max}}\) (~630 nm), corresponding to square planar structures, [Cu(NH\(_2\))(N-imz)(H\(_2\)O)\(_2\)] (654 nm) and [Cu(NH\(_2\))\(_2\)(N-imz)(NH\(_2\))\(_2\)(NH)] (607 nm) of these complexes (Schemes 5.3 and 5.7). On further rise of pH (pH ~10), at which the deprotonated mixed ligand complex (18) makes ~ 80% of total Cu\(^{II}\), λ\(_{\text{max}}\) value of the 1:1:1 mixture shows another blue shift to 606 nm which is close to the estimated λ\(_{\text{max}}\) value (590 nm) corresponding to structure (18a) than the estimated λ\(_{\text{max}}\) value (541 nm) corresponding to structure (18b) (Scheme 5.7). This suggests deprotonation (Scheme 5.6) of the ternary complex (17) involves release of the proton from the imidazole NH of the (NH\(_3\), N-imz) coordinated histidine ligand, not from the coordinated 2NH (or 4NH) group of the biguanide ligand. Slightly higher value of experimental λ\(_{\text{max}}\) suggests intermolecular apical coordination by carboxylate-O atom and...
or the uncoordinated imidazole-N atom of the histidine ligand. At very high pH (>10), the mixed ligand complex (18, i.e. 18a) disappears with simultaneous building up of concentration of the biguanide deprotonated ternary hydroxo complex, 

\[ \text{[Cu(Bg-H)(OH)(H}_2\text{O)]] (16) \]

suggesting decomposition of (18a), setting free the his' ion, according to,

\[ \text{[Cu(hism-H)(Bg)]} + 2\text{H}_2\text{O} \rightleftharpoons \text{[Cu(Bg-H)(OH)(H}_2\text{O})] + \text{his'} + \text{H}^+ \quad (5.9) \]

This last equilibrium (5.9) shows that biguanide anion, (Bg-H)', shows stronger affinity than even imidazole NH deprotonated bidentate (NH2, N'-imz) dianion, (hism-H)2' in respect of coordination to CuII, a phenomenon of great biological significance, relevant to drug actions of biguanide derivatives and their metal complexes.

\[ \text{[Cu[his-H](Bg)] (18a)} \]

\[ \text{[Cu[his-H](Bg)] (18b)} \]

\[ \text{[Cu(hism-H)(Bg)]} \]

\[ \text{[Cu(hism-H)(Bg)]} \]

\[ \text{his'} \]

\[ \text{[Cu(Bg-H)(OH)] (16)} \]

Scheme 5.7

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Representative pH titration curves and electronic spectral curves of 1:1 and 1:5 Cu\textsuperscript{II}:histidine and 1:1:1 Cu\textsuperscript{II}:histidine:guanylurea mixtures are presented in Fig. 5.2 and Fig. 5.7 respectively. Stochiometry of the most probable binary and ternary complexes along with the refined values of their formation constants are listed in Table 5.2.

Complex formation of equilibria of the binary Cu\textsuperscript{II}:histidine and Cu\textsuperscript{II}:guanylurea systems have been described earlier. In 1:1 Cu\textsuperscript{II}:histidine complex, histidinatet ion (his') coordinate Cu\textsuperscript{II} as a bidentate ligand using the amino-N and the imidazole-N atoms, leaving the carboxylate group uncoordinated, i.e., in histamine-like (hism) manner (mode-a) consequently, the 1:1 Cu\textsuperscript{II}:histidine complex is formulated as [Cu(hism)\textsuperscript+], where, hism\textsuperscript- stands for (NH\textsubscript{2}, N-imz) bidentate his\textsuperscript- ion. The 1:2 Cu\textsuperscript{II}:histidine complex occurs largely as an equilibrium mixture of histamine-histamine like complex, [Cu(hism)\textsubscript{2}] and mixed histamine-like glycine-like complex, [Cu(hism)(gly)], with the latter transforming to the former with rise of pH above 6. At higher pH (>7) these histamine-like complexes undergo deprotonation of their imidazole NH, forming the complexes: [Cu(hism-H)], [Cu(hism-H)(hism)\textsuperscript-] and [Cu(hism-H)\textsubscript{2}\textsuperscript2-].

Guanylurea (Gu') ion may coordinate in three bidentate modes (CO, =N'), (NH\textsubscript{2}, =N'), (=NH, =N') giving three isomeric structures (14a), (14b), and (14c) (Scheme 5.8) for the 1:1 Cu\textsuperscript{II}:Gu complex [Cu(Gu)(H\textsubscript{2}O)\textsubscript{2}\textsuperscript+] (14) [Ch-3, 4 and (22b,c)].

The complex, (14) occurs in the pH range 4-10 and deprotonates to [Cu(Gu)(OH)] \textsuperscript(15) through structure (14c).
Table 5.2 Stochiometry of Cu$^{ll}$-histidine-guanylurea complexes and refined values of the proton ligand and metal ligand constants.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Complex Species</th>
<th>( p )</th>
<th>( q )</th>
<th>( r )</th>
<th>( s )</th>
<th>( \log_{10} \beta_{pqrs} )</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>([\text{H}_2\text{hisH}]^{2+})</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>-3</td>
<td>16.72</td>
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<tr>
<td>2.</td>
<td>([\text{H}_2\text{his}^-]^+)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>-2</td>
<td>15.12</td>
</tr>
<tr>
<td>3.</td>
<td>([\text{Hhis}^+])</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-1</td>
<td>09.10</td>
</tr>
<tr>
<td>4.</td>
<td>([\text{H}_2\text{Gu}^+])</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-2</td>
<td>10.20</td>
</tr>
<tr>
<td>5.</td>
<td>([\text{HG}u])</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-1</td>
<td>08.20</td>
</tr>
<tr>
<td>6.</td>
<td>([\text{Cu(OH)}^+])</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-06.29</td>
</tr>
<tr>
<td>7.</td>
<td>([\text{Cu(OH)}_2])</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>-13.05</td>
</tr>
<tr>
<td>8.</td>
<td>([\text{Cu(hism)}^+])</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>10.21</td>
</tr>
<tr>
<td>9.</td>
<td>([\text{Cu(hism-H)}])</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>04.18</td>
</tr>
<tr>
<td>10.</td>
<td>([\text{Cu(hism)}_2])</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>20.12</td>
</tr>
<tr>
<td>11.</td>
<td>([\text{Cu(hism)(gly)}])</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>19.73</td>
</tr>
<tr>
<td>12.</td>
<td>([\text{Cu(hism)(hism-H)}])</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>13.00</td>
</tr>
<tr>
<td>13.</td>
<td>([\text{Cu(hism-H)}_2^{2-}])</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>07.45</td>
</tr>
<tr>
<td>14.</td>
<td>([\text{Cu(Gu)}^+])</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>05.61</td>
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<tr>
<td>15.</td>
<td>([\text{Cu(Gu)(OH)}])</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>-00.24</td>
</tr>
<tr>
<td>16.</td>
<td>([\text{Cu(hism)(Gu)}])</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>16.38</td>
</tr>
<tr>
<td>Δ(\log K_{\text{Cu}}) (16) &amp; (+) &amp; 0.056</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>([\text{Cu(hism)(Gu)}(-\text{H})^+])</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>07.95</td>
</tr>
<tr>
<td>18.</td>
<td>([\text{Cu(hism)(Gu)}(-2\text{H})^{2-}])</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>-01.74</td>
</tr>
</tbody>
</table>

hism*: histamine-like (NH$_2$, N-imz) coordination by histidine

gly*: glycine-like (NH$_2$, -COO$^-$) coordination by histidine
On the other hand, deprotonation equilibria of the 1:2 Cu$^{II}$:guanylurea complex, [Cu(Gu)$_2$] and mixed ligand, Cu(Gu)(L$'$) complexes, where, L$'$ = glycinate$^-$ and glycylglycinate$^-$ involve release of proton (s) from the coordinated Gu$^-$ ion (Scheme 5.9): [Ch-3, 4]

Electronical spectral $\lambda_{\text{max}}$ of Cu$^{II}$ shows blue shift on deprotonation, due to stronger ligand field provided by deprotonated amide-N atom than the amide carbonyl O-atom [20]. No such blue shift is of course observed for an isolated second step deprotonation, which involves the loss of a proton from an uncoordinated OH group [Ch 3, 4 and (22a,c)].

Complex formation in the 1:1:1 ternary 1 Cu$^{II}$:histidine:guanylurea system starts around pH 3 with appearance of the 1:1 binary Cu$^{II}$:histidine complex, [Cu(hism)$^+$] (8) (Fig. 5.6), according to the equilibrium (5.3) mentioned before:

$$\text{Cu}^{2+}(\text{aq}) + (\text{H}_2\text{his}^\text{H})^+ \rightleftharpoons \text{[Cu(hism)$^+$]} + 2\text{H}^+ \quad (5.3)$$

The complex (8) passes through its concentration maximum (~60%) at pH~ 5, disappears above this pH along with the ligand GuH with concomitant appearance of the ternary complex, [Cu(hism)(Gu)] (16) (eqn. 5.10) and the imidazole NH deprotonated complex, [Cu(hism-H)] (9) (eqn. 5.4):

$$\text{[Cu(hism)$^+$]} + \text{GuH} \rightleftharpoons \text{[Cu(hism)(Gu)]} + \text{H}^+ \quad (5.10)$$

$$\text{[Cu(hism)$^+$]} \rightleftharpoons \text{[Cu(hism-H)]} + \text{H}^+ \quad (5.4)$$

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Fig. 5.7 Speciation curves of (a) 1:1 Cu$^{II}$:guanylurea and (b) 1:1:1 Cu$^{II}$:histidine:guanylurea system: 1, H$_2$hisH$^{2+}$; 2, (H$_2$his$^+$)$^+$; 3, Hhis$^+$; 4, H$_2$Gu$^+$; 5, HGu; 6, Cu(OH)$^+$; 7, Cu(OH)$_2$; 8, Cu(hism)$^+$; 9, Cu(hism-H); 14, Cu(Gu)$^+$; 15, Cu(Gu)(OH); 16, Cu(hism)(Gu); 17, Cu(hism)(Gu)(-H)$^-$; 18, Cu(hism)(Gu)(-2H)$^{2-}$; FM = Free Cu$^{II}$, FB2 = Free Gu.
\[ pK^H(8) = \log \beta_{1100} - \log \beta_{1101} \] (5.4a)

corresponding to the equilibrium (5.4) is a measure of the enhancement of acidity of the imidazole NH of histidine due to coordination of the other N-atom of the imidazole ring to Cu\textsuperscript{II}. Guanylurea anion (Gu\textsuperscript{-}) may coordinate Cu\textsuperscript{II} in binary [Cu(Gu\textsuperscript{+})] complex (14) in three different bidentate modes, using its (O=\textsuperscript{C}), (=N\textsuperscript{-}) and (-NH\textsubscript{2}) groups, giving three possible structures (16a, 16b and 16c) (Scheme 5.10) for the ternary complex (16).

Estimated electronic spectral \(\lambda_{\text{max}}\) values [20] for a square planar geometry of Cu\textsuperscript{II} in the complex (16), represented by the structures (16a), (16b) and (16c) are 595, 595 and 541 nm respectively. Experimental \(\lambda_{\text{max}}\) value (650-652 nm) of 1:1:1 Cu\textsuperscript{II}:histidine:guanylurea mixture, at pH \(\approx 7\) (Fig. 5.7), at which the complex (16) makes \(\approx 70\%\) of total Cu\textsuperscript{II} and passes through its concentration maximum, is closer to the estimated \(\lambda_{\text{max}}\) values for the structures (16a) and (16b). Red shift of \(\approx 55 \text{ nm}\) of the experimental \(\lambda_{\text{max}}\) value may be due to intermolecular apical carboxylate coordination [20]. Thus, the ternary complex (16) is best described by the two isomeric structures, (16a) and (16b). The third structure (16c) may be discarded, as the estimated \(\lambda_{\text{max}}\) value (541 nm) corresponding to this structure is much lower than the experimental value.
Fig. 5.7 Electronic spectra of 1:1:1 Cu$^{II}$:histidine:guanylurea system at different pH. Ionic strength, $I = 0.1 \text{ mol. dm}^{-3}$ (NaNO$_3$). Curve (pH): a (3), b (4.75), c (5), d (6), e (7) f (8), g (9), h (10) and i (11).
The mixed ligand complex (16) passes through its concentration maximum (~70%) at pH ~7, whereas, the imidazole deprotonated 1:1 complex (9) occurs to the extent of 30-35% in a wider pH range (6-10). Above pH 7, the mixed ligand complex disappears with release of two moles of H⁺ per mole of Cu⁺, producing two deprotonated ternary complexes: [Cu(hism)(Gu)(-H)] (17) and [Cu(hism)(Gu)(-2H)] (18) (Scheme 5.11):

However, the above deprotonation equilibria (Scheme 5.11) appear to be of more complex nature. Loss of the first proton may take place either from the imidazole NH moiety of the mixed ligand complex (16), represented by isomeric structures (16a) and (16b), produces the complex, [Cu(hism-H)(Gu')'] (17) which may be described by structures [Cu(hism-H)(CO)(=N')'] (17aj) and [Cu(hism-H)(NHCO)(=N')'] (17a2) respectively (Scheme 5.12). On the other hand, loss of the first proton from the coordinated Gu⁻ ion, produces another isomer of (17), formulated as [Cu(hism)(Gu-H)] and may be described by two isomeric structures [Cu(hism)(O'CNH)(=N')] (17bj) and [Cu(hism)(N'COH)(=N')] (17b2). While the loss of the second proton from (17aj) and (17bj) involves deprotonation of the coordinated guanylurea anion only, producing two isomeric structures [Cu(hism-H)(O'CNH)(=N')] (18a) and [Cu(hism-H)(N'COH)(=N')] (18b) of the complex, [Cu(hism-H)(Gu-H)] (18), loss of the second proton from structure (17b2) may take place in two different ways, viz., loss of one proton from the imidazole NH of coordinated his' ion, to produce (18b) and loss of one proton from the uncoordinated –OH group of (Gu-H)²⁻ ion in this complex to produce [Cu(hism)(Gu-2H)], described by the structure [Cu(hism)(N'CO')(=N')] (18c). Estimated λ_{max} values of square planar Cu⁺ complexes [20] with the structures (9), (16a), (17a1), (17a2), (17b1) and (18a) are 654, 595, 595, 579, 579, 577 and 562 nm and for
Scheme 5.12
those with the structures (17b2), (18b) and (18c) are 531, 531 and 519 nm respectively. Estimated average $\lambda_{\text{max}}$ value (609 nm) (Fig. 5.7) of equal proportions (~30%) of the complexes (9), (16) and (17) described by (17a1), (17a2), occurring around pH~8.5 is quite close to the $\lambda_{\text{max}}$ value (~609-617 nm) of 1:1:1 CuII:histidine:guanylurea mixture adjusted to this pH. This suggests involvement of the structures (16a), (16b), (17a1), (17a2) and (17b1) in the first step deprotonation equilibria of the ternary complex (16) with exclusion of the structure described by (17b2) (Scheme 5.12). Similarly, the concordance of the estimated average $\lambda_{\text{max}}$ value (598 nm) of the complexes (9), (17) and (18, described by 18a) with the experimental $\lambda_{\text{max}}$ value (~598-601 nm) of 1:1:1 CuII:histidine:guanylurea mixture at pH>10, where the complex (18) is the major (~70%) copper containing species, along with the complexes (9) and (17), suggests involvement of the structure (18a) in the second step deprotonation of (16), discarding the structures (18b) and (18c), for which the estimated $\lambda_{\text{max}}$ value (519 nm and 531 nm respectively) are much lower than the experimental value at this pH. Thus, excluding the structures (17b2), (18b) and (18c), the two step deprotonation equilibria of the ternary complex (16) may be described according Scheme 5.13.
Scheme 5.13
Histamine-like bidentate \((\text{NH}_2, \text{N-imz})\) chelation of \(\text{Cu}^{\text{II}}\) prevails in 1:1 \(\text{Cu}^{\text{II}}\):histidine complexes \([\text{Cu(hism)}]^+\) and \([\text{Cu(hism-H)}]\) in the pH range (3-10), with intermolecular apical carboxylate and or uncoordinated N-imz coordination (where, imz = imidazole ring). On the other hand, the 1:2 \(\text{Cu}^{\text{II}}\):histidine complex exists as structural isomers composed of histamine-histamine-like \((\text{NH}_2, \text{N-imz})\) chelated and \([\text{Cu(hism)}]_2\) and mixed histamine-glycine-like \((\text{NH}_2, \text{N-imz})(\text{NH}_2, \text{COO}^-)\) chelated \([\text{Cu(hism)}(\text{gly})]\), with the former slightly dominating (~60%) over the latter(~45%) in the pH range 5-6. With rise of pH, the mixed isomer is transformed to the histamine-histamine-like isomer, which loses its imidazole ring NH proton at still higher pH (≥9). \(\text{Cu}^{\text{II}}\):histidine complexes with structures involving only glycine-like chelation by histidine are totally absent in the equilibrium. Histamine-like chelation also prevails in 1:1:1 \(\text{Cu}^{\text{II}}\):histidine:biguanide ternary complexes. The imidazole deprotonated histamine-like chelated 1:1 complex, \([\text{Cu(hism-H)}]\), (~55 %) and the ternary complex \([\text{Cu(hism)}(\text{Bg})]\) (~40 %) are the dominant copper containing species in the pH range of biological significance. With rise of pH, above 7, both these complexes are transformed to, \([\text{Cu(hism-H)}(\text{Bg})]\), which decomposes to biguanide deprotonated ternary hydroxo complex, \([\text{Cu(Bg-H)}(\text{OH})(\text{H}_2\text{O})]\) above pH 10, setting free the his' ion. This shows stronger affinity (i.e., basicity) of biguanide anion (Bg-H)' over the his' ion in respect of coordination to \(\text{Cu}^{\text{II}}\).

Although guanylurea is structurally similar to biguanide and mixed-ligand \(\text{Cu}^{\text{II}}\):histidine:guanylurea complex, shows structural isomerism like the corresponding \(\text{Cu}^{\text{II}}\):histidine:biguanide complex, even to greater degree of flexibility, but basicity of coordinated guanylurea is not as strong as its biguanide analogue, so as to displace the bound his' ion from the ternary complexes in basic medium.
References


