J. Chem. Sci., Vol. 118, No. 5, September 2006, pp. 411–418. © Indian Academy of Sciences.

Mixed-ligand complex formation equilibria of Cu^{II} with biguanide in presence of glycine as the auxiliary ligand

TANNISTHA ROY BARMAN and G N MUKHERJEE*
Department of Chemistry, University College of Science, University of Calcutta, 92, Acharya Prafulla Chandra Road, Kolkata 700 009
e-mail: gmchem@rediffmail.com

MS received 26 June 2006; revised 19 July 2006

Abstract. Equilibrium study on the mixed ligand complex formation of Cu^{II} with biguanide(Bg) and glycine (HG), indicated the formation of the complexes: $Cu(Bg)^{2+}$, $Cu(Bg)_2^{2+}$, $Cu(Bg\text{-}H)(Bg)^+$, $Cu(Bg\text{-}H)_2$, $Cu(Bg)(OH)^+$, $Cu(Bg\text{-}H)(OH)$; $Cu(G)^+$, $Cu(G)(OH)$, $Cu(G)_2$; $Cu(G)(Bg)^+$, $Cu(G)(Bg\text{-}H)$; $(G)Cu(Bg)Cu(G)^{2+}$, $(G)Cu(Bg\text{-}H)Cu(G)^+$, and $(G)Cu(Bg\text{-}2H)Cu(G)$. From the deprotonation constants of coordinated biguanide (Bg) in the complexes $Cu(Bg)(OH)^+$, $Cu(Bg\text{-}H)(Bg)^+$ and $Cu(G)(Bg)^+$, the Lewis basicities of the coordinated ligand species $(Bg\text{-}H)^-$, OH^- and glycinate (G^-) were found to be of the order: $(Bg\text{-}H)^- >> OH^- > G^-$. Bridging ($N^1$-$N^4$, N^2-N^5) tetradentate mode of coordination by biguanide species Bg, $(Bg\text{-}H)^-$ and $(Bg\text{-}2H)^{2-}$ was indicated from the occurrence of biguanide-bridged dinuclear mixed ligand complexes $(G)Cu(Bg)Cu(G)^{2+}$, $(G)Cu(Bg\text{-}H)Cu(G)^+$, $(G)Cu(Bg\text{-}2H)Cu(G)$ in the complexation equilibria.

Keywords. $Copper^{II}$-biguanide; glycinate; ternary complex; formation constants.

1. Introduction

Biguanide or guanylguanidine (Bg) is an extensively studied (N,N) donor bidentate ligand. Transition metal complexes of biguanide, and its various N-substituted derivatives and related ligands have been investigated by many workers.[1,2] Most of these studies were aimed at isolation of transition metal complexes with these ligands and their characterization and structure elucidation by various physicochemical techniques. Modes of metal ion coordination by biguanide were extensively investigated by many workers and (N,N) bidentated chelation by the N^2 and N^4 atoms were established to be the most acceptable mode of coordination.[3–7] Protonation–deprotonation equilibria of biguanide and substituted biguanides were also investigated by several workers.[7–11] Stepwise formation and decomposition of Cu^{II} and Ni^{II} binary complexes with biguanide and some substituted biguanides were studied by pH metric, polarographic and spectrophotometric methods[8–14] and the order of relative stabilities of such complexes were established. Stability constant of Ag^{III}-ethylenedibiguanide complex was determined by pH metric and potentiometric methods.[15] Instability constants of Co^{III} and Cr^{III} *tris*(biguanide) and *tris*(phenylbiguanide) complexes were determined by potentiometric investigation on the decomposition of the corresponding complexes with acid.[16–18] Literature survey revealed the absence of any report of a systematic equilibrium study on the mixed ligand complex formation of metal ions with biguanide and related derivatives. In view of the importance of biguanide, substituted biguanides and their metal derivatives as antimalarial and antidiabetic agents,[19,20] as well as antimicrobial, antifungal and ovicidal activities of certain metal biguanide complexes,[21] it was considered worthwhile to study the mixed ligand complex formation equilibria of biological metal ions with biguanide and related ligands in the presence of typical biomolecules, such as, amino acids and small peptides and other biomolecules as auxiliary ligands, to throw some light upon the molecular mechanism of actions of biguanide derivatives as drugs. Results of such investigation would provide useful clues to the design of new bioinorganic drugs with greater selectivity and specificity at the same time lower toxicity.

In this paper we describe the results of a combined pH-metric and spectrophotometric equilibrium study on the mixed ligand complex formation of Cu^{II} with biguanide (Bg) in presence of the simplest amino

---

*For correspondence

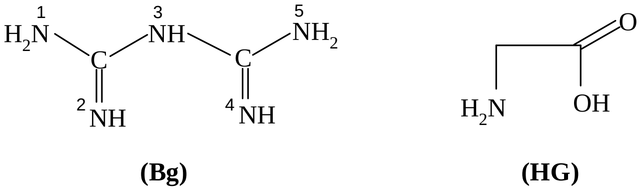
acid, glycine, (HG) as the auxiliary ligand (scheme 1) in aqueous solution at 25 ± 1°C, at a fixed ionic strength, $I = 0{\cdot}1$ mol dm^{-3} ($NaNO_3$).

2. Experimental

2.1 *Materials and methods*

Biguanide sulphate $Bg.H_2SO_4.1{\cdot}5\ H_2O$ was prepared and purified following the literature procedure.[22] Its purity was checked from elemental analysis and by determining its equivalent weight by acid–base titration.[23] All the other reagents were of AR grades and their solutions were prepared in double-distilled CO_2 free water. Cu^{II} nitrate solution was prepared by dissolving freshly precipitated alkali free $Cu(OH)_2$ in AR nitric acid and was standardized by combined ion-exchange separation, acid-base and complexometric EDTA titration methods.[23] Equilibrium study for the determination of proton-ligand and metal-ligand complex formation constants involved pH-metric titrations of series of solutions, each of initial volume 0·025 dm^{-3}, containing known amounts (0·001–0·002 mol dm^{-3}) of the ligands, biguanide and/or glycine in their protonated forms (H_2Bg^{2+} and/or H_2G^+ respectively) in presence of known amounts (0·0002–0·001 mol dm^{-3}) of Cu^{II} nitrate and known amount of free HNO_3 (0·005 mol dm^{-3}) with a carbonate-free standard 0·1 mol dm^{-3} NaOH solution,[24] maintaining a fixed ionic strength, $I = 0{\cdot}1$ mol dm^{-3} ($NaNO_3$) at 25 ± 1°C (thermostated).

pH measurements were carried out with a *Systronics* digital pH meter (type 335) using a special glass electrode (pH 1–14, accuracy ± 0·01 pH) in conjunction with a saturated calomel electrode. Electronic spectral measurements were carried out with a Hitachi UV-3501 spectrophotometer using water as the blank. pH-volume (of standard NaOH) data (figure 1) as the average of three titrations, were accepted for calculating the equilibrium constants using the computer program SCOGS,[25] run on a Pentium-4 computer and the values of the constants (table 1) corresponding to minimum standard deviations were accepted. The complex formation equilibria were elucidated from analysis of the speciation curves (figures 2–4), obtained as computation outputs. Preliminary values of some of the constants supplied to the computer as input data were obtained from literature[26] or calculated according to the method of Irving and Rossotti.[27] Ionic product of water at the experimental temperature and the activity coefficient of hydrogen ion at the experimental ionic strength were obtained from literature.[28,29] Analytical concentrations of hydrogen ion [H$^+$], at different pH meter readings were calculated by following the usual procedure.[30]



(Bg) (HG)

Scheme 1.

2.2 *Calculation of formation constants*

The overall formation constant (b_{pqrs}) of a generalized complex species, $Cu_p(Bg)_q(G)_r(OH)_s$, may be defined according to,

$$p\mathrm{Cu} + q\mathrm{Bg} + r\mathrm{G} + s(\mathrm{OH}) \rightleftharpoons \mathrm{Cu}_p(\mathrm{Bg})_q(\mathrm{G})_r(\mathrm{OH})_s, \quad (1)$$

$$b_{pqrs} = \frac{[\mathrm{Cu}_p(\mathrm{Bg})_q(\mathrm{G})_r(\mathrm{OH})_s]}{[\mathrm{Cu}]^p[\mathrm{Bg}]^q[\mathrm{G}]^r[\mathrm{OH}]^s}, \quad (1a)$$

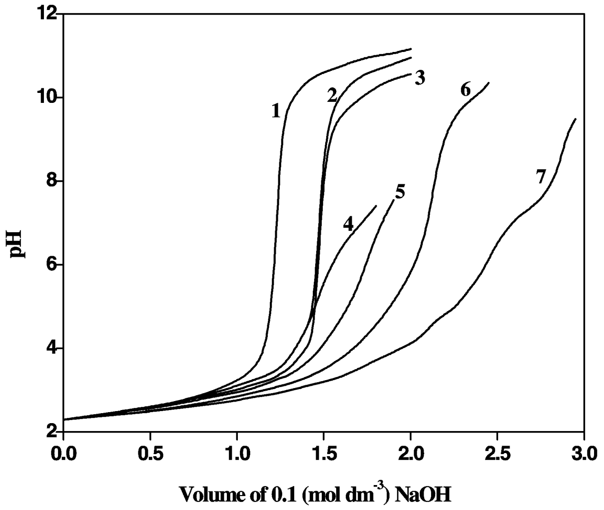


Figure 1. Representative pH titration curves (*M* = mol dm^{-3}): 1, 0·005 (*M*) HNO_3; 2, (1) + 0·001 (*M*) H_2Bg^{2+}; 3, (1) + 0·001 (*M*) H_2G^+; 4, (2) + 0·001 (*M*) Cu^{II}; 5, (3) + 0·001 (*M*) Cu^{II}; 6, (5) + 0·001 (*M*) H_2Bg^{2+}; 7, (2) + 0·002 (*M*) H_2G^+ + 0·002 (*M*) Cu^{II}; initial volume = 0·025 dm^3, titrant = 0·1 (*M*) NaOH, ionic strength 0·1 (*M*) $NaNO_3$.

Table 1. Formation constants (b_{pqrs}) of binary and mixed ligand Cu^{II} complexes with biguanide (Bg) and glycinates (G^-) in aqueous solution, ionic strength, $I = 0{\cdot}1$ mol dm^{-3} ($NaNO_3$) at 25 ± 1°C.

Complex species	p	q	r	s	$\log b_{pqrs}$
H_2Bg^{2+}	0	1	0	–2	14·20
HBg^+	0	1	0	–1	10·90
H_2G^+	0	0	1	–2	11·87
HG	0	0	1	–1	09·61
$Cu(OH)^+$	1	0	0	1	–6·29
$Cu(OH)_2$	1	0	0	2	–13·05
$Cu(G)^+$	1	0	1	0	08·23
Cu(G)(OH)	1	0	1	1	01·11
$Cu(G)_2$	1	0	2	1	15·19
$Cu(Bg)^{2+}$	1	1	0	0	06·74
$Cu(Bg)(OH)^+$	1	1	0	1	01·70
Cu(Bg-H)(OH)	1	1	0	2	–5·18
$Cu(Bg)_2{}^{2+}$	1	2	0	0	12·51
$Cu(Bg)(Bg\text{-}H)^+$	1	2	0	1	05·99
$Cu(Bg\text{-}H)_2$	1	2	0	2	–3·34
$Cu(G)(Bg)^+$	1	1	1	0	16·84
Cu(G)(Bg-H)	1	1	1	1	10·74
$G(Cu)(Bg)Cu(G)^{2+}$	2	1	2	0	31·24
$G(Cu)(Bg\text{-}H)Cu(G)^+$	2	1	2	1	25·36
G(Cu)(Bg-2H)Cu(G)	2	1	2	2	19·48

Deprotonation constants of coordinated biguanide (Bg)

$\log K^H_{Cu(Bg)(Bg\text{-}H)}$	$\log K^H_{Cu(Bg)(OH)}$	$\log K^H_{Cu(G)(Bg)}$
–16·09	–6·88	–6·10

Limits of error: ± 0·02

where, p, q, r and s are stochiometric numbers. p, q and r may be positive integers or zero. s is a negative integer for a protonated species, zero for a neutral species and a positive integer for a deprotonated or a hydroxo species. In dilute solution, for binary 1 : 1, 1 : 5 Cu^{II} : ligand systems, p is 1 and the values of q and r depend upon the molar proportions of the metal : ligand. For 1 : 1 Cu^{II} : ligand systems, q or r does not exceed 1, but for the 1 : 5 Cu^{II} : ligand systems, higher values may be possible. For the ternary 1 : 1 : 1 Cu^{II} : Bg : HG system, $p = q = r = 1$ and for the 2 : 1 : 2 Cu^{II} : Bg : HG system, $p = 2$, $q = 1$, $r = 2$. The stochiometries of the possible complexes occurring in all the binary and ternary systems are presented in the combined table 1, which also includes the computer-refined values of $\log b_{pqrs}$ and some other relevant constants of the binary and mixed ligand complexes. As the pH range of complex formation equilibria are overlapping with the hydrolytic equilibria of the $Cu(aq)^{2+}$ ions, formation of the hydroxo species, $Cu(OH)^+$ and $Cu(OH)_2$ have also been considered in calculating the formation constants. However, all the pH-titration data have been collected at pH values prior to the appearance of any turbidity.

Although (N, O^-) bidentate mode of coordination of glycinate ligand in its metal complexes is well known, models involving methyl amine-like only N-coordinated glycine, acetate-like only O^--coordinated glycinate and bridging (N, O^-) coordinated glycinate containing mixed ligand complex species, viz. $(Bg)Cu(H_2NCH_2COOH)$, $(Bg)Cu(O^-OCCH_2NH_3{}^+)$ and $(Bg)Cu(H_2NCH_2COO^-)Cu(Bg)$ respectively, have been also considered in the calculation in addition to the expected complexes involving (N, O^-) bidentate coordinated glycinate ligand species.[26] However, in all these cases the standard deviations are large and the percentage concentrations of the corresponding complex species are negligibly very small and are not even identifiable on the speciation curves (figures 2–4). Hence, these complexes have been excluded in the final calculation of the formulation constants.

3. Results and discussion

3.1 *Proton-ligand equilibria with biguanide (Bg)*

In weakly acidic solution (pH ~ 2), biguanide (Bg) exists in its dipronated form, H_2Bg^{2+}, and with rise of pH, undergoes successive depronation to form the monoprotonated (HBg^+) and neutral (Bg) species, providing two well-separated buffer regions.[1]

$$2 < pH < 4 \qquad H_2Bg^{2+} \rightleftharpoons HBg^+ + H^+, \qquad (2)$$

$$9{\cdot}5 < pH < 11{\cdot}5 \qquad HBg^+ \rightleftharpoons Bg + H^+. \qquad (3)$$

In the pH range 2–4, glycine (HG) exists in its monoprotonated form (H_2G^+), which with rise of pH also provides two well-separated buffer regions[26] due to successive deprotonation of the –COOH group (equilibrium (4)) and the NH_3^+ group (equilibrium (5)).

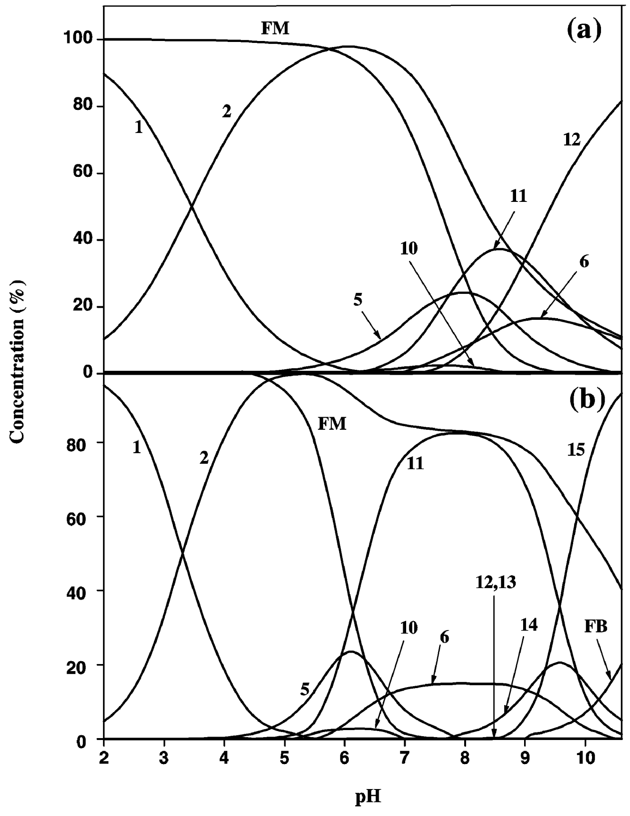


Figure 2. Speciation curves of (**a**) 1 : 1 and (**b**) 1 : 5 Cu^{II} : Bg systems: 1, H_2Bg^{2+}; 2, HBg^+; 5, $Cu(OH)^+$; 6, $Cu(OH)_2$; 10, $Cu(Bg)^{2+}$; 11, $Cu(Bg)(OH)^+$; 12, Cu(Bg-H)(OH); 13, $Cu(Bg)_2^{2+}$; 14, $Cu(Bg\text{-}H)(Bg)^+$; 15, $Cu(Bg\text{-}H)_2$; FM = Free Cu^{II}, FB = Free Bg.

$$2 < pH < 4 \qquad H_2G^+ \rightleftharpoons HG + H^+, \qquad (4)$$

$$8 < pH < 10 \qquad HG \rightleftharpoons G^- + H^+. \qquad (5)$$

3.2 *Binary Cu^{II} : Bg equilibria*

Complex formation equilibria in both (1 : 1) and (1 : 5) Cu^{II} : Bg systems start above pH 5 (figures 2a,b), where, Cu^{II} exists as $Cu(aq)^{2+}$, $Cu(OH)^+$ and $Cu(OH)_2$. The predominant complex species at pH < 6·5 in the 1 : 1 Cu^{II} : Bg system is the ternary hydroxo complex, $Cu(Bg)(OH)^+$, formed out of Cu^{2+}, $Cu(OH)^+$ and HBg^+ according to equilibria (6) and (7) as the speciation curves (figure 2a) imply :

$$pH < 6{\cdot}5 \qquad Cu^{2+} + HBg^+ + H_2O \rightleftharpoons Cu(Bg)(OH)^+ + 2H^+, \qquad (6)$$

$$Cu(OH)^+ + HBg^+ \rightleftharpoons Cu(Bg)(OH)^+ + H^+. \qquad (7)$$

With rise of pH, the 1 : 1 Cu^{II} : Bg system shows another buffer region of one mole of H^+ per mole of

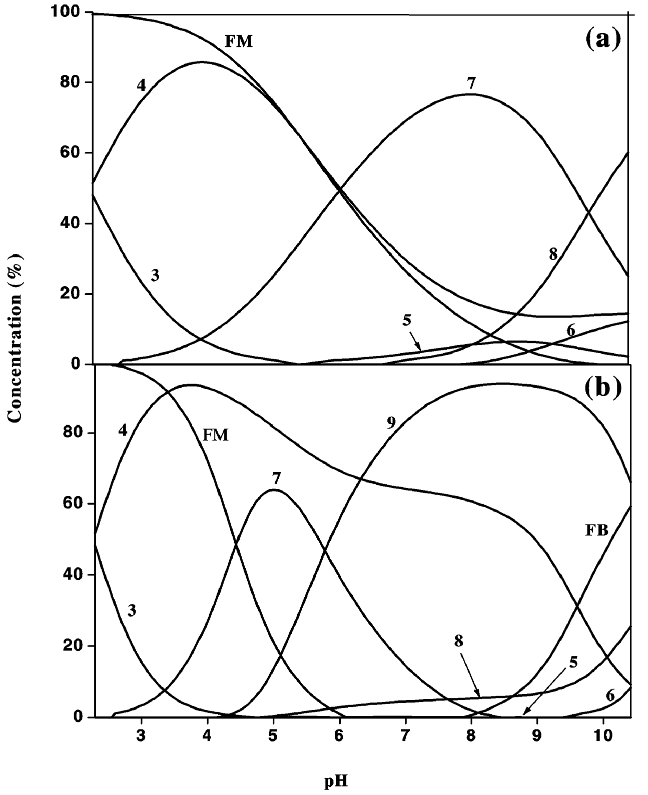


Figure 3. Speciation curves of (**a**) (1 : 1) and (**b**) (1 : 5) Cu^{II} : HG systems: 3, H_2G^+; 4, HG; 5, $Cu(OH)^+$; 6, $Cu(OH)_2$; 7, $Cu(G)^+$; 8, Cu(G)(OH); 9, $Cu(G)_2$; FM = Free Cu^{II}, FB = Free G^-.

Cu^{II}, obviously due to the formation of biguanide (N^2 or N^4) deprotonated ternary hydroxo complex, Cu(Bg-H)(OH), according to equilibria (8) and (9), the latter involves deprotonation of a coordinated biguanide molecule:

$$Cu^{2+} + HBg^{+} + H_2O \rightleftharpoons Cu(Bg\text{-}H)(OH) + 3H^{+}, \quad (8)$$

$$Cu(Bg)(OH)^{+} \rightleftharpoons Cu(Bg\text{-}H)(OH) + H^{+}. \quad (9)$$

Titration cannot be continued beyond pH 8 due to appearance of turbidity, possibly because of precipitation of Cu(Bg-H)(OH) and/or $Cu(OH)_2$. Deprotonation constant of coordinated biguanide ligand in the complex, $Cu(Bg)(OH)^{+}$, defined according to

$$K^{H}_{Cu(Bg)(OH)} = \frac{[Cu(Bg\text{-}H)(OH)][H]}{[Cu(Bg)(OH)]}, \quad (9a)$$

may be calculated using the relation,

$$\log K^{H}_{Cu(Bg)(OH)} = \log b_{1102} - \log b_{1101}, \quad (9b)$$

where b_{1101} and b_{1102} are the formation constants of the complexes, $Cu(Bg)(OH)^{+}$ and Cu(Bg-H)(OH) respectively. Charges are not shown in the mathematical expressions for simplicity.

The ternary hydroxo complex, $Cu(Bg)(OH)^{+}$, is also the predominant Cu^{II} bearing species in the (1 : 5) Cu^{II} : Bg system in the pH range 5·5–7·5. As the speciation curves (figure 2b) imply, it is formed out of $Cu(OH)^{+}$, mainly according to equilibrium (7) in addition to equilibrium (6). Above pH 7·5, this ternary hydroxo complex, $Cu(Bg)(OH)^{+}$, and the dihydroxo species, $Cu(OH)_2$ gradually disappear due to the formation of the (1 : 2) Cu^{II} : Bg complexes, $Cu(Bg\text{-}H)(Bg)^{+}$ and $Cu(Bg\text{-}H)_2$ according to equilibria (10–12) as the speciation curves (figure 2b) imply,

$$Cu(Bg)(OH)^{+} + HBg^{+} \rightleftharpoons Cu(Bg\text{-}H)(Bg)^{+} + H^{+} + H_2O, \quad (10)$$

$$Cu(Bg\text{-}H)(Bg)^{+} \rightleftharpoons Cu(Bg\text{-}H)_2 + H^{+}, \quad (11)$$

$$Cu(OH)_2 + 2HBg^{+} \rightleftharpoons Cu(Bg\text{-}H)_2 + 2H^{+} + 2H_2O. \quad (12)$$

The $Cu(Bg)_2^{2+}$ complex is formed in negligibly such small amounts that it cannot even be identified in the speciation curves. The biguanide deprotonated complex, $Cu(Bg\text{-}H)_2$, is the major Cu^{II} species at pH > 9·5. Titration cannot be continued above pH 10, as the solution becomes turbid, possibly due to precipitation of the $Cu(Bg\text{-}H)_2$ complex. The deprotonation constant, $K^{H}_{Cu(Bg)(Bg\text{-}H)}$, of coordinated biguanide (Bg) in the 1 : 2 complex, $Cu(Bg\text{-}H)(Bg)^{+}$, (equilibrium (11)) may be calculated using the relation,

$$\log K^{H}_{Cu(Bg)(Bg\text{-}H))} = \log b_{1202} - \log b_{1201} + \log b_{1002} + \log b_{1001}, \quad (11a)$$

where, b_{1201} and b_{1202} are the formation constants of the complexes, $Cu(Bg\text{-}H)(Bg)^{+}$ and $Cu(Bg\text{-}H)_2$, and b_{1001} and b_{1002} are the first and second step hydrolysis constants of $Cu(aq)^{2+}$ ion.

3.3 *Binary Cu^{II} : HG equilibria*

Complex formation of Cu^{II} with glycine in the 1 : 1 Cu^{II} : HG system starts at pH < 3·5. The major Cu^{II} species in the pH range (3·5–7) is the 1 : 1 binary complex, $Cu(G)^{+}$, formed according to the equilibria (13) as the speciation curves (figure 3a) imply:

$$Cu^{2+} + HG \rightleftharpoons Cu(G)^{+} + H^{+}. \quad (13)$$

The hydroxo complexes, $Cu(OH)^{+}$ and $Cu(OH)_2$ are practically non existent in this pH range. At pH > 5·5, the solution, containing the $Cu(G)^{+}$ complex, shows another buffer region corresponding to one mole of H^{+} per mole of Cu^{2+}, obviously due to deprotonation of a coordinated water molecule of the $Cu(G)^{+}$ complex to form the ternary hydroxo complex, Cu(G)(OH) according to,

$$Cu(G)^{+} + H_2O \rightleftharpoons Cu(G)(OH) + H^{+}. \quad (14)$$

With increase of pH, the percentage of the dihydroxo species, $Cu(OH)_2$, increases gradually and the solution becomes turbid, possibly due to precipitation of either or both of $Cu(OH)_2$ and Cu(G)(OH). In the 1 : 5 Cu^{II} : HG system, the major Cu^{II} species are $Cu(G)^{+}$ and $Cu(G)_2$. The binary and ternary hydroxo species are practically non existent (figure 3b).

3.4 *1 : 1 : 1 Cu^{II} : Bg : HG ternary equilibria*

Complex formation in the ternary 1 : 1 : 1 Cu^{II} : Bg : HG system (figure 4a) starts around pH ~ 2·5 with the formation of the $Cu(G)^{+}$ complex (equilibrium (13)), which passes through a concentration maximum (~40%) around pH 5. Except traces

(<2%) of $Cu(OH)^+$ and Cu(G)(OH), no other binary or ternary hydroxo species are identifiable in the speciation curves above pH 4·5. The ternary complexes, $Cu(G)(Bg)^+$ and Cu(G)(Bg-H), appear around pH ~ 4 and 4·5 according to equilibria (15) and (16) respectively,

$$Cu(G)^+ + HBg^+ \rightleftharpoons Cu(G)(Bg)^+ + H^+, \tag{15}$$

$$Cu(G)(Bg)^+ \rightleftharpoons Cu(G)(Bg\text{-}H) + H^+. \tag{16}$$

The biguanide deprotonated ternary complex, Cu(G)(Bg-H), appears as the major Cu^{II} containing species at pH > 6·5. Deprotonation constant, $K^H_{Cu(G)(Bg)}$, of coordinated biguanide (Bg) in the mixed ligand complex, $Cu(G)(Bg)^+$, (equilibrium (16)), may be calculated using the relation,

$$\log K^H_{Cu(G)(Bg)} = \log \boldsymbol{b}_{1111} - \log \boldsymbol{b}_{1110}, \tag{16a}$$

where, $\boldsymbol{b}_{1110}$ and $\boldsymbol{b}_{1111}$ are the formation constants of the complexes, $Cu(G)(Bg)^+$ and Cu(G)(Bg-H) respectively. Deprotonation constants of coordinated biguanide (Bg) in these ternary complexes are found to be of the order: $Cu(G)(Bg)^+ > Cu(Bg)(OH)^+ >> Cu(Bg)(Bg\text{-}H)^+$, which indicates the Lewis basicity order of: $(Bg\text{-}H)^- >> OH^- > G^-$, when they are coordinated to Cu^{II}. This may be very useful information in relation to drug actions of biguanide derivatives and their metal complexes.

Electronic spectral l_{max} values of 1 : 1 : 1 Cu^{II} : Bg : HG mixtures show successive blue shifts with rise of pH (figure 5). At pH ~ 5 the major Cu^{II} species is the $Cu(G)^+$ complex (~50%) and Cu^{2+}(aq) ion (~50%). $Cu(G)^+$ complex is likely to take up two molecules of solvent H_2O for completing a square planar geometry around Cu^{II}. The calculated l_{max} value of $[Cu(COO^-, NH_2)(H_2O)_2]$ geometry[31] as in the complex $Cu(G)(H_2O)_2{}^{2+}$ ion, is around 716 nm, which is in close agreement with the experimental value of 723 nm. Concentration of the ternary $Cu(G)(Bg)^+$ complex passes through a maximum around pH ~ 6, where the concentration of $Cu(aq)^{2+}$ is only ~10% and those of $Cu(G)(H_2O)_2{}^+$, $Cu(G)(Bg)^+$ and the biguanide deprotonated Cu(G)(Bg-H) complex are around ~25% each. The estimated l_{max} values of $Cu(aq)^{2+}$, square planar $[Cu(COO^-, NH_2)(H_2O)_2]$ geometry as in $Cu(G)(H_2O)_2{}^+$ $[Cu(COO^-, NH_2)$ $(NH_2, NH)]$ geometry as in $Cu(G)(Bg)^+$ and $[Cu(COO^-,$

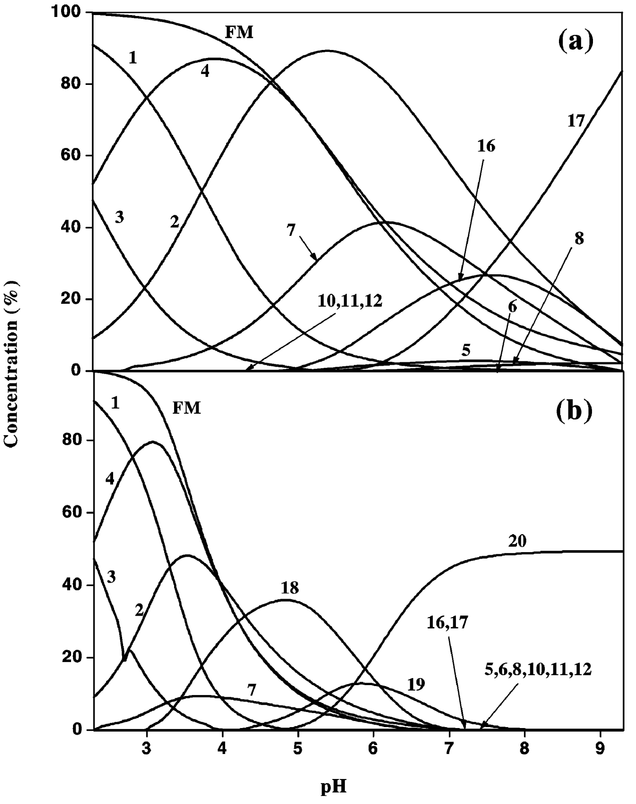


Figure 4. Speciation curves of (**a**) 1 : 1 : 1 and (**b**) 2 : 1 : 2 Cu^{II} : Bg : HG systems: 1, H_2Bg^{2+}; 2, HBg^+; 3, H_2G^+; 4, HG; 5, $Cu(OH)^+$; 6, $Cu(OH)_2$; 7, $Cu(G)^+$; 8, Cu(G)(OH); 10, $Cu(Bg)^{2+}$; 11, $Cu(Bg)(OH)^+$; 12, Cu(Bg-H)(OH); 16, $Cu(G)(Bg)^+$; 17, Cu(G)(Bg-H); 18, $G(Cu)(Bg)Cu(G)^{2+}$; 19, $G(Cu)(Bg\text{-}H)Cu(G)^+$; 20, G(Cu)(Bg-2H)Cu(G); FM = Free Cu^{II}.

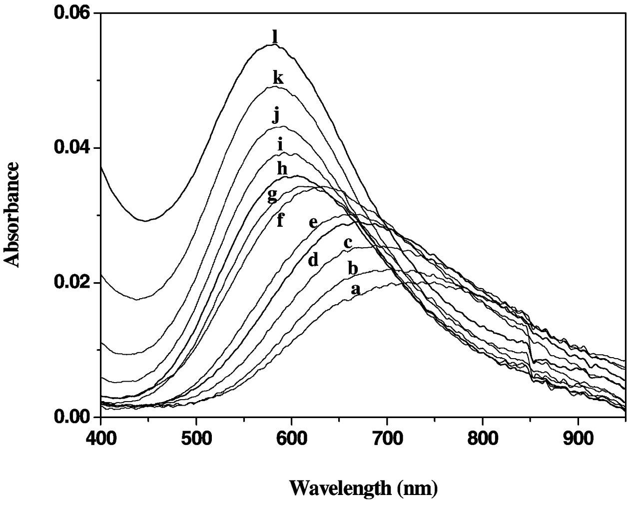


Figure 5. Electronic spectral curves of 1 : 1 : 1 Cu^{II} : Bg : HG mixtures at different (pH): a (4·06), b (4·30), c (4·57), d (5·00), e (5·50), f (6·00), g (6·50), h (7·00), i (7·50), j (8·00), k (8·50), l (9·00). Ionic strength 0·1 mol dm^{-3} ($NaNO_3$).

NH_2)(N^-, NH_2)] geometry as in the Cu(G)(Bg-H), assuming a (>C=NH) moiety as equivalent to a (>C=O) moiety of a neutral peptide (–CONH) bond and (>C=N^-) moiety as equivalent to a (–C(=O)N^-–) moiety of a deprotonated peptide bond, are around 830, 716, 645 and 577 nm respectively. The weighted average of these $l_{\max}$ values at pH ~ 6 comes to ~646 nm. The experimental $l_{\max}$ value of the solution at this pH is 668nm. With rise of pH, the $l_{\max}$ value shows a further blue shift to 583 nm at pH ~ 7, indicating an increase of ligand field strength, as a coordinated neutral biguanide ligand as in the $Cu(G)(Bg)^+$ complex is transformed to its monoanionic $(Bg\text{-}H)^-$ species due to deprotonation at N^2 or N^4 atom, to produce the complex, Cu(G)(Bg-H), according to equilibrium (16).

3.5 *2 : 1 : 2 Cu^{II} : Bg : HG ternary equilibria*

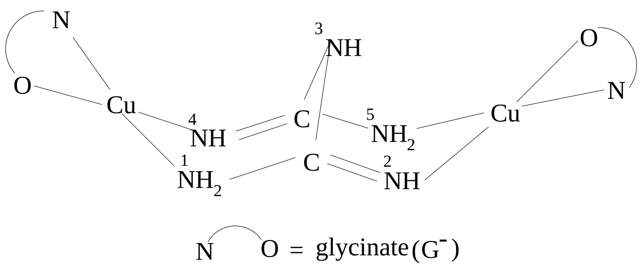
In the 2 : 1 : 2 Cu^{II} : Bg : HG system, an additional 1·5 mole of H^+ per mole of Cu^{II} is released over those in the 1 : 1 : 1 system (figure 1). This indicates the release of at least 2 H^+/Cu^{II} after the formation of the $Cu(G)(Bg)^+$ complex. The only source of such proton release, of course, may be the formation of dinuclear mixed ligand complexes, $(G)Cu(Bg)Cu(G)^{2+}$, (G)Cu(Bg-H)Cu(G), (G)Cu(Bg-2H)Cu(G), according to equilibria (17–19) as the speciation curves (figure 4b) imply:

$$2Cu(G)^+ + HBg^+ \rightleftharpoons (G)Cu(Bg)Cu(G)^{2+} + H^+, \quad (17)$$

$$(G)Cu(Bg)^+ + Cu(G)^+ \rightleftharpoons (G)Cu(Bg\text{-}H)Cu(G)^+ + H^+, \quad (18)$$

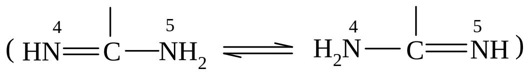
$$(G)Cu(Bg\text{-}H)Cu(G)^+ \rightleftharpoons (G)Cu(Bg\text{-}2H)Cu(G) + H^+. \quad (19)$$

These 2 : 1 : 2 Cu^{II} : Bg : HG dinuclear complexes may be formed if biguanide in its neutral, monoanionic and even in dianionic forms, Bg, $(Bg\text{-}H)^-$ and $(Bg\text{-}2H)^{2-}$ respectively, can act as a bridging ligand, that can exist in a puckered boat like conformation (scheme 2), providing two pairs of chelating (N,N-donor sites, viz., ($N^1$and N^4) and (N^2 and N^5) for bridging two square planar complex $Cu(G)(H_2O)_2^+$ ions, displacing the coordinated H_2O ligands from this complex.

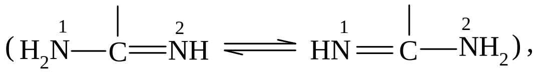


Scheme 2.

Due to the possibility of tautomeric equilibria of the types (20) and (21) below,



$$(\overset{4}{HN}{=}\overset{|}{C}{-}\overset{5}{NH_2} \rightleftharpoons \overset{4}{H_2N}{-}\overset{|}{C}{=}\overset{5}{NH}), \quad (20)$$



$$(\overset{1}{H_2N}{-}\overset{|}{C}{=}\overset{2}{NH} \rightleftharpoons \overset{1}{HN}{=}\overset{|}{C}{-}\overset{2}{NH_2}), \quad (21)$$

within the coordinated biguanide molecule, the N^4-C-N^5 and N^1-C-N^2 sequences may form two separate triangular inclined planes, e.g. N^4-C(-N^3)-N^5 and N^1-C(N^3-)-N^2, meeting at the common point at N^3 (scheme 2). Such a conformation may function as a bridging quadridentate ligand providing two sets of bidentate (N,N) chelating sites to the Cu^{II} atoms of two different $Cu(G)^+$ complexes, as described above, thereby forming the dinuclear complex, $(G)Cu(Bg)Cu(G)^{2+}$. With rise of pH above 4·5 the biguanide deprotonated dinuclear mixed ligand complexes appear in the equilibrium through release of protons from the coordinated =N^2H and =N^4H sites, (18) and (19).

4. Conclusions

Equilibrium study of the complex formation of Cu^{II} with biguanide (Bg) in the absence and in the presence of the simplest amino acid glycine (HG) in different molar proportions of the metal ion and the ligands revealed that biguanide may coordinate Cu^{II} as a neutral (N,N) and anionic (N,N^-) bidentate chelating ligand in mononuclear binary and ternary complexes, using its N^1 and N^4 or N^2 or N^5 atoms. In forming 2 : 1 : 2 Cu^{II} : Bg : HG dinuclear mixed ligand complexes, the biguanide ligand species may exist in a puckered boat-like conformation, serving as neutral, monoanionic and dianionic bridging tetradentate ligand, chelating one Cu^{II} ion with N^1 and N^4 atoms and the other Cu^{II} ion with N^2 and N^5 atoms. Deprotonation constants of $Cu(Bg)(OH)^+$, $Cu(Bg)(G)^+$, $Cu(Bg)(Bg\text{-}H)^+$ complexes indicate the

Lewis basicity order of $(Bg\text{-}H)^{-} >> OH^{-} > G^{-}$ for these coordinated ligand species.

Acknowledgement

The authors thank the University of Calcutta for the award of the Sir Rashbehary Ghose Research Fellowship (2004–2005) to TRB.

References

1. Ray P 1961 *Chem. Rev.* **61** 313, and references therein
2. Ray R K and Kauffman G B 1999 In *Metal and non metal biguanide complexes* (New Delhi: New Age Int.), references therein
3. Swartz W E Jr and Afanzo R A 1974 *J. Electron. Spectrosc. Relat. Phenom.* **4** 351
4. Nandi S N and Banerjee D 1974 *Z. Anorg. Allg. Chem.* **406** 124
5. Syamal A 1987 1988 *Chem. Educ.* **4** 33; **5** 26
6. Creitz T C, Gsell R and Wampler D L 1969 *J. Chem. Soc., Chem. Commun.* 1371
7. Fabbrizzi L, Micheloni M, Paoletti P and Schwarzenbach G 1977 *J. Am. Chem. Soc.* **99** 5574; Fabbrizzi L, Micheloni M and Paoletti P 1978 *Inorg. Chem.* **17** 494
8. Das Sarma B and Ray P 1952 1956 *J. Indian Chem. Soc.* **29** 217; **33** 891
9. Gage J C 1949 *J. Chem. Soc.* 221
10. Ray A K and Das Sarma B 1960 *Z. Anorg. Allgem. Chem.* **305** 207
11. Sengupta N R and Ray P 1960 *J. Indian Chem. Soc.* **37** 303
12. Sieefker J R and Wence R L 1965 *Indiana Acad. Sci.* **75** 104; Banerjea D 1966 *Z. Anorg. Allg. Chem.* **344** 72; Doornbos D A 1968 *Pharm. Weekbl. Ned.* **103** 1213; Poddar S N, Poddar N G and Bhattacharya S M 1975 *Indian J. Chem.* **13** 393
13. Ray M M and Ray P 1959 *Sci. Culture* (*Calcutta*) **25** 38
14. Ray A K 1955 *Naturwissenschaften* **42** 415
15. Sen D, Ghosh N N and Ray P 1950 *J. Indian Chem. Soc.* **27** 619
16. De A K, Ghosh N N and Ray P 1950 *J. Indian Chem. Soc.* **27** 493
17. Lumiere A, Lumiere L and Feerin F 1905 *Bull. Soc. Chem.* **3** 33, 205
18. Bandyopadhyay (Banerjea) D, Ghosh N N and Ray P 1952 *J. Indian Chem. Soc.* **29** 157
19. Curd F H S and Rose F L 1946 *J. Chem. Soc.* **343** 729
20. Rose F L 1946 *Endeavour* **18** 65
21. Dey K, Maiti R K, Bhar J K, Banerjee R D, Sarkar G M, Malakar A, Das S and Banerjee P 1981 *Agents Actions* **11** 762
22. Rackmann V K 1910 *Justus Liebig Ann. Chem.* **376** 163
23. Kolthoft I M, Sandell E B, Meehan E J and Bruckenstein S 1967 In *Quantitative chemical analysis* 4th edn (London: Macmillan) ch. 41
24. Schwarzenbach G and Biederman W 1948 *Helv. Chem. Acta* **31** 331
25. Sayce I G 1968 *Talanta* **15** 1397; Sayce I G 1970 *Talanta* **18** 653; Sayce I G and Sharma V S 1972 *Talanta* **19** 831
26. Perrin D D 1979 In *Stability constants of metal ion complexes*: *Part B, Organic ligands*, IUPAC Chemical Data Series No-22 (Oxford, New York, Toronto, Sydney, Paris, Frankfurt: Pergamon) pp 14, 38, 73
27. Irving H M and Rossotti H S 1954 *J. Chem. Soc.* 2904
28. Harned H S and Owen B B 1958 *The physical chemistry of electrolytic solutions* (New York: Reinhold) pp 66, 662, 713–756
29. Wolleym E M, Hurkot D G and Hepler L G 1970 *J. Phys. Chem.* **74** 3908
30. Irving H M, Mills M G and Petit L D 1967 *Anal. Chim Acta* **38** 475, 163
31. Sigel H and Martin R B 1982 *Chem. Rev.* **82** 385