

Mixed ligand complex formation of Cu^{2+} ion with 6-aminopenicillanic acid in the presence of bipyridine, glycine and adenine

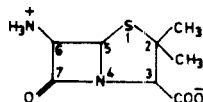
G N Mukherjee* & T K Ghosh

Department of Chemistry, University College of Science,
92 Acharya Prafulla Chandra Road, Calcutta 700 009

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A pH-metric study of the mixed ligand complex formation of Cu^{2+} ion with 6-aminopenicillanic acid (apaH) and bipyridine/glycine/adenine (L) has been carried out at 37°C in aqueous solution ($I = 0.1\text{ M NaNO}_3$). The results show the evidence of formation of ternary complexes of the type $\text{Cu}(\text{apa})(\text{L})$, in addition to the binary complexes $\text{Cu}(\text{apa})$ and $\text{Cu}(\text{L})$. Quaternary hydroxo complexes, $\text{Cu}(\text{apa})(\text{L})(\text{OH})$ and $\text{Cu}(\text{apa})(\text{L})(\text{OH})_2$ have been identified at $\text{pH} > 7$. Complexation equilibria are evaluated with the aid of the computer programme, SCOGS, and correlated with the modes of bonding of the ligand.

Penicillin group of drugs, because of their ability to inhibit protein synthesis in the ribosome, are widely used in medicine as broad spectrum antibiotics¹. A study on the chemical equilibria in the metal-drug-ligand systems may be of importance in exploring the molecular mechanism of action of these drugs. In this note we describe the results of our pH metric study, on the mixed ligand complex formation of Cu^{2+} ion with 6-aminopenicillanic acid, hereafter, apaH (I) in the presence of some typical ligands of biological importance, viz., bipyridine, glycine and adenine in aqueous solution at $37 \pm 0.1^\circ\text{C}$ at a fixed ionic strength ($I = 0.1\text{ M NaNO}_3$).



Experimental

AR quality 6-aminopenicillanic acid, bipyridine, glycine and adenine, obtained from Aldrich Chemical Company, Inc. (USA), were used as such. For the determination of binary Cu^{2+} -ligand stability constants, the Cu^{2+} : ligand ratios in the experimental solutions were kept 1:1, 1:5 and 1:10. For studying the mixed ligand complexation equilibria the Cu^{2+} : apaH:L ratios were 1:1:1 and 1:2:1.

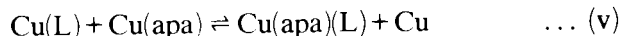
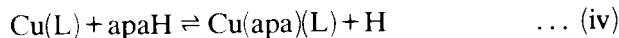
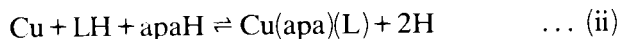
Stability constants, β_{pqrs} , of ternary $[\text{Cu}_p(\text{L})_q(\text{apa})_r(\text{OH})_s]$ complexes as defined below:
 $p\text{Cu} + q\text{L} + r\text{apa} + s\text{OH} \rightleftharpoons \text{Cu}_p\text{L}_q(\text{apa})_r(\text{OH})_s$

$$\beta_{pqrs} = \frac{[\text{Cu}]^p[\text{L}]^q[\text{apa}]^r[\text{OH}]^s}{[\text{Cu}_p\text{L}_q(\text{apa})_r(\text{OH})_s]} \quad \dots (1)$$

were calculated with the aid of SCOGS programme² run on a PC-XT computer system. Proton-ligand and Cu^{2+} -ligand binary stability constants³⁻⁸, supplied to the computer as input data, were also determined under identical conditions.

Results and Discussion

The ligand species apaH₂⁺ titrates as a biprotic acid and acts as a (N,O) and (N,S) bidentate chelating agent towards Cu^{2+} to form only 1:1 binary complexes using the amino nitrogen and carbonyl oxygen or thiazolidine sulphur atoms³. Binary $\text{Cu}(\text{L})$ and $\text{Cu}(\text{apa})$ species are predominant at pH values lower than 5. The region between pH 5 and 8 is dominated by the ternary $\text{Cu}(\text{L})(\text{apa})$ complexes, which are formed according to the following equilibria:



where, L = bipy, gly⁻ and ad⁻. These equilibria are supported by the species distribution curves (Fig. 1). Charges are omitted for clarity. The stability constants of ternary complexes, $\beta_{\text{Cu}(\text{L})(\text{apa})}$, were directly

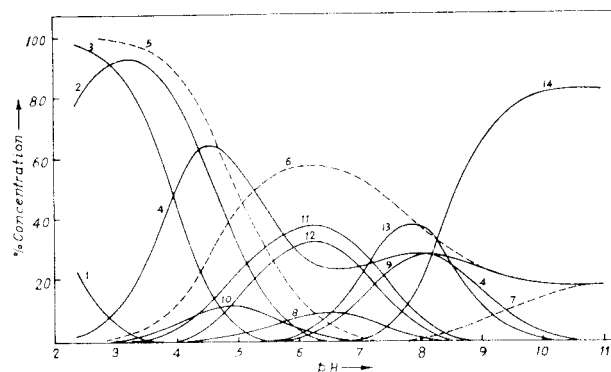


Fig. 1—Species distribution curves of Cu^{2+} -ad-apa system [1. apaH₂⁺; 2. apaH⁺; 3. adH₂⁺; 4. adH; 5. Cu^{2+} ; 6. apa⁻; 7. ad⁻; 8. $\text{Cu}(\text{OH})^+$; 9. $\text{Cu}(\text{OH})_2$; 10. $\text{Cu}(\text{apa})^+$; 11. $\text{Cu}(\text{ad})^+$; 12. $\text{Cu}(\text{apa})(\text{ad})$; 13. $\text{Cu}(\text{apa})(\text{ad})(\text{OH})$; 14. $\text{Cu}(\text{apa})(\text{ad})(\text{OH})_2^+$]

Table 1— $\text{Cu}^{2+}/\text{L}/\text{apa}$ ternary constants, β_{pqrs} with $\text{L} = \text{bipy}$, gly and ad at $37 \pm 0.1^\circ\text{C}$ in aqueous solution ($I = 0.1 \text{ M NaNO}_3$)

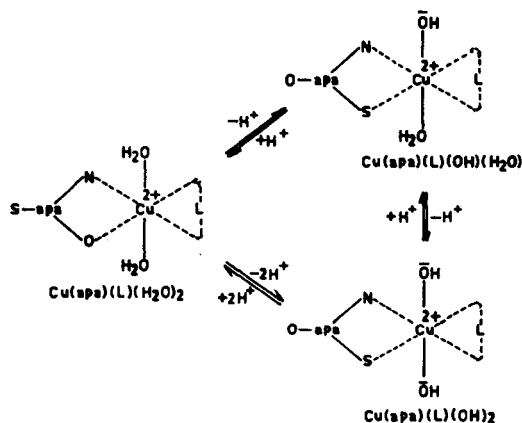
$\log \beta_{pqrs}$	L		
	bipy	gly	ad
$\log \beta_{\text{Cu(L)(apa)}}^{\text{Cu}}$	12.54	12.86	13.17
$\log \beta_{\text{Cu(L)(apa)(OH)}}^{\text{Cu}}$	6.04	6.21	6.12
$\log \beta_{\text{Cu(L)(apa)(OH)}_2}^{\text{Cu}}$	-2.16	-2.84	-2.13
$\log K_{\text{Cu(L)(apa)}}^{\text{Cu}}$	4.72	4.74	4.52
$\log K_{\text{Cu(L)(apa)(L)}}^{\text{Cu(apa)(L)}}$	8.44	8.76	9.07
$pK_{\text{Cu(L)(apa)}}^{\text{H}}$	6.50	6.65	7.05
$pK_{\text{Cu(L)(apa)(OH)}}^{\text{H}}$	8.65	9.05	8.25
$\Delta \log K_{\text{Cu}}$	0.62	0.64	0.42

Ionic product of water pK_w (at 37°C), 13.65; limits of error in the constants ± 0.02 – ± 0.05 log units.

computed from which the other constants, viz., $K_{\text{Cu(apa)(L)}}^{\text{Cu(apa)}}$, $K_{\text{Cu(L)(apa)}}^{\text{Cu(L)}}$ and $\Delta \log K_{\text{Cu}}$ were calculated using standard relations⁹ (Table 1).

$\Delta \log K_{\text{Cu}}$ values are positive suggesting favoured formation of the ternary Cu(L)(apa) complexes.

With rise of $p\text{H}$, all these ternary Cu(L)(apa) complexes disappear and two quaternary hydroxo complexes, $\text{Cu(L)(apa)(H}_2\text{O)(OH)}^-$ and $\text{Cu(L)(apa)(OH)}_2^-$ are formed, obviously due to successive deprotonation of the two coordinated H_2O molecules in these complexes. Intramolecular rearrangement involving the replacement of the carbonyl oxygen atom from the copper coordination sphere by the thiazolidine sulphur atom, according to the following equilibria (Scheme 1), possibly provides the driving force leading to the deprotonation of coordinated H_2O molecules. Such transformation of apa^- from (N, O) bidentate to (N, S) bidentate ligand within the coordination complex increases electronegativity of the Cu^{2+} ion as a consequence of delocalization of metal ion $d\pi$ electrons over to the vacant $d\pi$ orbitals of the sulphur atom, resulting in an increase in acidity of coordinated H_2O molecules. Such π -electron delocalization, however, is not possible when apa^- acts as a bident-



ate (N, O) chelating agent to Cu^{2+} ion, due to the absence of any π -acceptor orbitals on the oxygen atom. Deprotonation constants, $pK_{\text{Cu(L)(apa)}}^{\text{H}}$, $pK_{\text{Cu(L)(apa)(OH)}}^{\text{H}}$ are 5 to 7 log units lower than the pK_w of water. This indicates the extent of π -electron delocalization, $\text{Cu}^{2+}(d\pi) \rightarrow \text{S}(d\pi)$, in these ternary complexes.

Cu(L)(apa)(OH) complexes for $\text{L} = \text{bipy}$ and gly contain about 80% of total copper at $p\text{H}$ 8–9 and Cu(L)(apa)(OH)_2 contribute more than 90% at $p\text{H} \geq 10$, whereas the Cu(ad)(apa)(OH)^- and $\text{Cu(ad)(apa)(OH)}_2^-$ complexes dominated at $p\text{H}$ values greater than 7.

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