

Metal ion interactions with penicillins : Part VI—Equilibrium study on the mixed-ligand complex formation of cobalt(II), nickel(II), copper(II) and zinc(II) with 6-aminopenicillanic acid as the primary ligand and bipyridine, glycinate and imidazole as secondary ligands

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Equilibrium study on the complex formation of M^{2+} ions (where $M = Co, Ni, Cu$ and Zn) with 6-aminopenicillanic acid ($apaH^{\pm}$) in the presence of typical ligands, viz., bipyridine, glycinate and imidazole (B) in aqueous solution at $37^{\circ}C$ and ionic strength $I = 0.1 M NaNO_3$ has indicated the formation of mixed-ligand complexes of the types $M(apa)(B)$, $M(apa)(B)(OH)$ and $M(apa)(B)(OH)_2$ in addition to the binary $M(B)$ and $M(apa)$ complexes. The orders of stability constants, viz. $Cu^{2+} > Ni^{2+} > Co^{2+} > Zn^{2+}$ with regard to the metal ions and bipyridine $>$ glycinate $>$ imidazole with regard to secondary ligands have been correlated with the electronic structures of M^{2+} ions, modes of bonding of the ligands and the nature of the metal-ligand bonds.

The active involvement of metal ions in multimetal-multiligand equilibria in biological systems is well known^{1,2}. Therefore, we thought it worthwhile to study the interaction of metal ions, viz. Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} with 6-aminopenicillanic acid ($apaH^{\pm}$, 1) in the presence of typical ligands like bipyridine, glycinate and imidazole, which may be useful in elucidating the molecular mechanism of actions of this class of drugs. The present note describes the results of pH-metric and spectrophotometric study on these systems in aqueous solution at $37 \pm 0.1^{\circ}C$ keeping the ionic strength $I = 0.1 M NaNO_3$.

Experimental

The ligand, $apaH^{\pm}$ (Sigma, USA) was used as obtained. All the other reagents were of AR grade and their solutions were prepared in fresh, doubly distilled CO_2 -free water. The metal ion solutions were standardised by ion-exchange separation

combined with acid-base and complexometric titrations⁴. A carbonate-free NaOH solution⁵ was used as the titrant. the pH measurements were made with a Systronics 335 pH-meter (accuracy $\pm 0.01 pH$) employing a special glass electrode (pH 1-14) in conjunction with a saturated calomel electrode. The pK_w of water at the experimental temperature was obtained from literature^{6,7}. The procedure for the pH-metric titrations were the same as described earlier^{8,9}. Only $M^{2+} : apaH^{\pm} : BH$ ratio of 1:1:1 was used for studying the mixed ligand complexation equilibria to minimise the formation of ternary complexes other than $M(apa)(B)$.

The proton-ligand and metal-ligand constants were calculated by SCOGS programme¹⁰⁻¹² run on a PC-XT computer system. The constants were refined over several cycles of operation and the values corresponding to the minimum standard deviation in the titre ($\pm 0.01-0.04 m/l$) were accepted (Table 1). The complexation equilibria were elucidated from concentration distribution curves (Fig. 1) obtained as computer outputs. The proton-ligand and M^{2+} -ligand binary stability constants^{8,13-16} supplied to the computer as input data, were also redetermined under identical experimental conditions.

Results and discussion

The ligand $apaH^{\pm}$, in the monoprotonated form, $apaH_2^+$, titrates as a biprotic acid and acts as a (N,O) or (N,S) bidentate ligand towards M^{2+} ions depending upon the pH values. It forms only 1:1 binary complexes using the amino nitrogen atom and

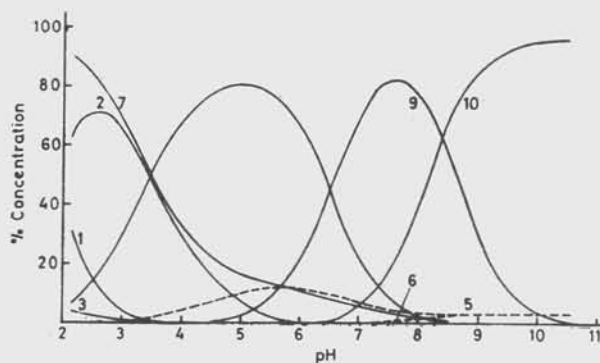


Fig. 1—Species distribution curves of $Cu^{2+}/apaH^{\pm}/bipyridine$ system at $37 \pm 0.1^{\circ}C$: (1) $apaH^{\pm}$; (2) $apaH^+$; (3) $bipyH^+$; (4) Cu^{2+} ; (5) apa^- ; (6) $bipy$; (7) $Cu(bipy)_2^{2+}$; (8) $Cu(bipy)(apa)^+$; (9) $Cu(bipy)(apa)(OH)$; (10) $Cu(bipy)(apa)(OH)_2^-$

Table 1—Stability constants^a of binary, ternary and quaternary hydroxo complexes formed in the M/apaH/B systems with M = Co²⁺, Ni²⁺, Cu²⁺ and Zn²⁺; B = gly⁻, bipy and im in aqueous solution
[Temp. = 37 ± 0.1°C; I = 0.1 M NaNO₃]

Constant	M	H ₂ O	apa ⁻	B		
				gly ⁻	bipy	im
pK_2^H	...	...	1.82	2.14	1.32	
pK_1^H	...	...	4.84	9.42	4.23	7.06
pK_w	...	13.62				
$pK_{(M+H_2O)}^H$	Co ²⁺	8.21				
	Ni ²⁺	8.05				
	Cu ²⁺	6.29				
	Zn ²⁺	7.84				
$pK_{(M+2H_2O)}^{2H}$	Co ²⁺	17.29				
	Ni ²⁺	16.83				
	Cu ²⁺	13.05				
	Zn ²⁺	14.97				
$\log K_{M(apa)}^M$	Co ²⁺		3.13			
	Ni ²⁺		3.30			
	Cu ²⁺		4.10			
	Zn ²⁺		1.90			
$\log K_{M(B)}^M$	Co ²⁺			4.94	5.92	2.29
	Ni ²⁺			5.94	6.97	2.99
	Cu ²⁺			8.12	7.82	4.21
	Zn ²⁺			5.02	5.15	2.54
$\log \beta_{M(apa)(B)}^M$	Co ²⁺			8.57	9.45	5.94
	Ni ²⁺			9.77	10.79	6.85
	Cu ²⁺			12.86	12.54	9.08
	Zn ²⁺			7.06	7.41	4.76
$\Delta \log K_M$	Co ²⁺			0.50	0.40	0.52
	Ni ²⁺			0.53	0.52	0.56
	Cu ²⁺			0.64	0.62	0.77
	Zn ²⁺			0.14	0.36	0.32
$pK_{M(apa)(B)(H_2O)_2}^H$	Co ²⁺			7.62	7.40	7.83
	Ni ²⁺			7.42	7.05	7.65
	Cu ²⁺			6.65	6.50	6.65
	Zn ²⁺			7.84	7.95	—
$pK_{M(apa)(B)(OH)(H_2O)}^H$	Co ²⁺			10.52	10.10	8.55
	Ni ²⁺			9.95	9.60	8.32
	Cu ²⁺			9.05	8.65	7.84
	Zn ²⁺			—	—	—

^a Limits of error : ± 0.04 in log units

carbonyl oxygen atom or the thiazolidine sulphur atom⁸.

The ternary M²⁺/apaH[±]/bipy systems (Fig.1) are dominated by the binary M(bipy)²⁺ complexes (> 90%) at the early stages of reaction (pH < 4). The ternary M(apa)(bipy) complexes are formed in the region 4 < pH < 8 according to Eq.(1),



The charges have been dropped from the equilibrium for simplicity.

In contrast, the ternary M(apa)(B) complexes with B = gly⁻ and imidazole (im) are formed according to

the equilibria (Eq.2),



almost in the same pH region 4 < pH < 8. The Zn(apa)(B) complexes, however, are formed in negligibly small amounts in all the three ternary systems with B = bipy, gly⁻ and im.

With the rise of pH (> 5.5), the ternary M(apa)(B) complexes consume two moles of base, possibly due to stepwise deprotonation of two coordinated water molecules. The pK^H values corresponding to these deprotonation equilibria are significantly lower than the pK_w of water at the experimental temperature by

3-6 log units (Table 1). The polarity of the O-H bonds of coordinated water molecules increases¹⁷ due to the structural change (Equilibria 3) within the coordination complex, in which the (N,O) bonded apa^- ligand species changes to one (N,S) bonded ligand species. The coordinated sulphur atom increases the polarity of the O-H bond through $\text{M}(\text{filled } d\pi) \rightarrow \text{S}(\text{vacant } d\pi)$ back bonding.

The concentration maxima ($\approx 80\%$ formation) of $\text{Cu}(\text{apa})(\text{B})$ and $\text{Cu}(\text{apa})(\text{B})(\text{OH})$ complexes are observed at pH values ~ 5 and 7.5 respectively (Fig. 1). Therefore, the absorption maxima of 1:1:1 $\text{Cu}^{2+} : \text{apaH}^+ : \text{B}$ mixtures at pH $5 \sim 760 \text{ nm}$ and at pH $7.5 \sim 670 \text{ nm}$ corresponds mostly to the complexes $\text{Cu}(\text{apa})(\text{B})$ and $\text{Cu}(\text{apa})(\text{B})(\text{OH})$ respectively. Such a large blue shift in the absorption maxima in going from $80\% \text{ Cu}(\text{apa})(\text{B})$ to $80\% \text{ Cu}(\text{apa})(\text{B})(\text{OH})$ provides an indirect evidence to the existence of the structural equilibria (3). The absorption maxima of these mixtures remain practically unchanged at 670 nm on further rise of pH above 7.5 upto the maximum formation ($\sim 95\%$) of $\text{Cu}(\text{apa})(\text{bipy})(\text{OH})_2$. This is because the ligand field strength around Cu^{2+} remains practically unchanged in going from monohydroxo complex, $\text{Cu}(\text{apa})(\text{bipy})(\text{OH})(\text{H}_2\text{O})$ to the dihydroxo complex, $\text{Cu}(\text{apa})(\text{bipy})(\text{OH})_2$. Similar deprotonation equilibria are also indicated with Co^{2+} and Ni^{2+} systems. In all the $\text{Zn}^{2+}/\text{apaH}^+/\text{B}$ systems, however, the hydroxo species, $\text{Zn}(\text{OH})^+$, $\text{Zn}(\text{OH})_2$ and small amounts of $\text{Zn}(\text{B})(\text{OH})$ complexes are formed in increasing amounts.

The stability of the ternary $\text{M}(\text{apa})(\text{B})$ complexes are found to be in the order, $\text{Co}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+} > \text{Zn}^{2+}$ which is based on the electronic configuration of the metal ions¹⁸. With regard to the B ligands, the stability order is found to be $\text{bipy} > \text{gly}^- > \text{im}$. The ligand bipy due to its σ -basicity and π -acidity forms more stable complexes than gly^- which is σ -basic only. In spite of σ -basic and π -acidic nature of im, ternary $\text{M}(\text{apa})(\text{im})$ complexes have lower stability due to monodentate coordination by im.

The positive values of $\Delta \log K_M$ for all the four metal ions indicate favoured formation of ternary $\text{M}(\text{apa})(\text{B})$ complexes¹⁹ over the corresponding

binary complexes, $\text{M}(\text{apa})_2$ and $\text{M}(\text{B})_2$. The relatively lower $\log K_{Zn}$ values possibly arise due to the preference of Zn^{2+} for tetrahedral geometry as against the octahedral or distorted octahedral structures of the complexes of Co^{2+} , Ni^{2+} and Cu^{2+} .

The higher acidity of coordinated water molecules in $\text{M}(\text{bipy})(\text{apa})(\text{H}_2\text{O})_2$ complexes over the corresponding complexes derived with $\text{B} = \text{im}$ is due to stronger π -acidity of bipy than that of im, as there is a greater scope for π -electron delocalization onto bipy than im. The quaternary hydroxo complexes of these types are not formed with Zn^{2+} , as metal $(d\pi) \rightarrow$ ligand $(d\pi)$ back bonding is unlikely to occur in tetrahedral Zn^{2+} complexes.

References

- 1 Florey K, *Antibiotics (Oxford)*, 2 (1949) 839.
- 2 Eichhorn G L (Ed), *Inorganic biochemistry*, Vols 1,2 (Elsevier, Amsterdam), 1973.
- 3 Perrin D D & Agarwal R P, *Metal ions in biological systems*, Vol 2 edited by H Sigel (Marcell Dekker, New York, Inc USA), 1973, 167-206.
- 4 Kolthoff I M, Sandell E B, Meehan E J & Bruckenstein A, *Quantitative chemical analysis* (Macmillan, London), 1967, Ch 41.
- 5 Schwarzenbach G & Biedermann W, *Helv chim Acta*, 31 (1948) 331.
- 6 Lurie J, *Hand book of analytical chemistry* (MIR Publishers, Moscow), 1978, p 198.
- 7 Woolley E M, Hurkot D G & Hepler L G, *J phys Chem*, 74 (1970) 3908.
- 8 Mukherjee G N & Ghosh T K, *J Indian chem Soc*, 68 (1991) 194.
- 9 Mukherjee G N & Ghosh T K, *Indian J Chem*, 30A (1991) 1033.
- 10 Sayce I G, *Talanta*, 15 (1968) 1397.
- 11 Sayce I G, *Talanta*, 18 (1970) 653.
- 12 Sayce I G & Sharma V S, *Talanta*, 19 (1972) 831.
- 13 Israeli J & Saulnier H, *Inorg chim Acta*, 2 (1968) 482.
- 14 Condi G F & Martell A E, *J inorg nucl Chem*, 31 (1969) 2455.
- 15 Israeli J & Volpe R, *Inorg chim Acta*, 6 (1972) 5.
- 16 Reinert H & Weiss R, *Hoppe Seyler's z physiol Chem*, 350 (1969) 1310.
- 17 McGlynn S P, Azumi T & Kumar D, *Chem rev*, 81 (1981) 475.
- 18 Irving H & Williams R J P, *Nature*, 162 (1948) 746; *J chem Soc*, (1953) 3192.
- 19 Sigel H, *Angew chem Int Edn*, 14 (1975) 394.