MIXED-LIGAND COMPLEXES INVOLVING BIOLOGICALLY IMPORTANT LIGANDS

Summary of the
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SUMMARY

Metal complexes in which two different ligands are bound to the metal ion are termed ternary complexes or mixed - ligand complexes. The ternary complexes in which a metal ion is bound to two biologically significant ligands are being studied exhaustively because they are important as models for metalloenzyme-substrate complexes and as components of multimetal - multiligand species in biochemical systems [1]. Investigations of the stability of the ternary complexes may, therefore, help towards understanding the driving forces which lead to the formation of such complexes in biological systems.

In enzymatic reactions involving ligands with large non-coordinating side groups, there may be non-covalent interaction between them in ternary complexes, causing stabilisation of the metal-apoenzyme-substrate complex, leading to specific and selective nature of the metalloenzyme [2,3]. Copper containing proteins are involved in a variety of biological functions. These functions include electron transport, copper storage, oxygen transport and oxidase activities [4]. Oligopeptides can be used as model compounds for such studies, since they are able to mimic to a great extent the metal binding sites of much more complicated protein molecules. For a less specific and rather general study of metal binding ability of peptides, even studies of dipeptides can provide much information.

The initial complex formation at low pH, between a dipeptide and copper (II) in the binary systems results in a chelate, involving a terminal amino group and oxygen of neighbouring amide group, the

carboxylate group remaining free [2,3,5-13]. At higher pH values the dipeptide undergoes deprotonation of the amide group and it becomes tridentate coordinating through N-amino, N-peptido and O-carboxylate groups [5,9].

It has been observed that the dipeptides retain their coordination properties in ternary complexes also [10-13]. It was also observed that various kinds of intramolecular interligand interactions exist in mixed-ligand complexes involving dipeptides [14,15]. Hence it was thought worthwhile to study mixed-ligand complexes of copper (II) involving dipeptides as one of the ligands.

The first chapter of the thesis presents an introduction to the subject and a survey of literature regarding research in related areas.

The second chapter deals with the study of stability constants of the ternary complexes CuAL where A = dipeptides such as glycyl-glycine (gg), glycyl - L - alanine (ga) and glycyl - L - leucine (gl) and L = α - alanine (ala), phenylalanine (phe), tryptophan (trp), tyrosine (tyr), 3,4 - dihydroxy-phenylalanine (L-dopa) and histidine (hist).

In the third chapter, electrochemical studies of mixed - ligand complexes CuAL, where A = the dipeptide glycylglycine and L = α - alanine and tyrosine have been carried out. Electrochemical studies were also carried out for the mixed amino acid complexes, CuhistL, where L = α - alanine, phenylalanine, tyrosine and trptophan.

The fourth chapter presents an account of the stability of

ternary complexes CuAL where A = the dipeptides glycylglycine, glycyl-L-alanine and glycyl-L-leucine and L = catechol and its derivatives, such as pyrogallol (pyr), tiron and 2,3 - dihydroxynapthalene (nap).

The fifth chapter comprises of the study of ternary complexes CuAL where A = dipeptides mentioned above and L = auxins such as indole acetic acid (IAA), indole propionic acid (IPA) and indole butyric acid (IBA).

In the sixth chapter of the thesis, formation constants of the mixed - ligand complexes CuAL, where L = aromatic tertiary amines such as 5-nitro-1, 10-phenanthroline, 1, 10 - phenanthroline, 2 (2'-pyridyl) benzimidazole and 2 (2'-pyridyl) imidazoline and the primary amine, ethylenediamine have been reported. Electrochemical studies of the binary copper-ethylenediamine complex and the ternary copper-glycylglycine-ethylenediamine complex have also been carried out.

Formation Constants of Mixed-Ligand Complexes :

The formation constants of mixed-ligand complexes were determined by carrying out titrations using the digital pH-meter with an accuracy of ±0.01. The proton-ligand formation constants AH_2, AH, LH_2 and LH and the formation constants of binary complexes CuA, CuA_{-H}, CuL and CuL_2 were first refined using the computer program SCOGS [16]. These values were used as fixed parameters for the refinement of the formation constants of mixed-ligand complexes.

The formation of the ternary complexes was considered to take

place by the simultaneous addition of two ligands with the metal ion

$$Cu + A + L \rightleftharpoons CuAL$$

The species considered to be present in solution are AH_2, AH, LH_2, LH, A, L, Cu, [CuA], $[CuA_{-H}]$, [CuL], $[CuL_2]$, [CuAL] and $[CuA_{-H}L]$.

As already mentioned, in case of the mixed-ligand complexes involving dipeptides, there is possibility of formation of two types of ternary species CuAL and $CuA_{-H}L$. The equilibrium constant for the ternary species CuAL is represented by equations (1) and (2)

$$Cu + A + L \rightleftharpoons CuAL \qquad (1)$$

$$K^{Cu}_{CuAL} = \frac{[CuAL]}{[Cu]\,[A]\,[L]} \qquad (2)$$

The stability of the above ternary complex can be quantified by calculating the value of $\Delta \log K$

$$\Delta \log K = \log K^{CuA}_{CuAL} - \log K^{Cu}_{CuL}$$

$$= \log K^{Cu}_{CuAL} - \log K^{Cu}_{CuA} - \log K^{Cu}_{CuL} \qquad (3)$$

The equilibrium constants for the ternary complex $CuA_{-H}L$ can be represented by equations (4) and (5)

$$CuA_{-H}L + H^{+} \rightleftharpoons CuAL \qquad (4)$$

$$K^{CuA_{-H}L}_{CuAL} = \frac{[CuAL]}{[CuA_{-H}L]\ [H]} \qquad (5)$$

For this ternary complex, only the protonation constant can be determined. Hence, the deprotonation of the dipeptide A in the ternary complex CuAL can be compared with the deprotonation in the binary complex CuA.

In case of the CuAL complexes where A = dipeptides and L = amino acids, Δ log K was found to be less negative or positive for L = tryptophan, tyrosine or L - dopa, as compared to alanine or phenylalanine. The less negative or positive Δ log K values for these complexes is due to hydrogen bonding between the uncoordinated indole, hydroxyphenyl or dihydroxyphenyl group of tryptophan, tyrosine or L - dopa and free COO^{-} group of the peptides.

Histidine is ambidentate in nature. In Cu (II) - dipeptide (A) - histidine (L) mixed ligand system, three ternary species of stoichiometry (CuALH), where histidine has amino acid type of coordination and (CuAL) and ($CuA_{-H}L$) with histamine type of coordination of histidine, are obtained. The species (CuALH) is stable due to electrostatic interaction between free protonated imidazole of histidine and COO^{-} group of dipeptides. For (CuAL) species, Δ logK is negative due to electrostatic repulsion between A^{-} and L^{-} monoanions. There is also no possibility of intramolecular hydrogen bonding.

Electrochemical studies of the mixed-ligand complexes were carried out on a EG & G PARC electrochemistry system which included the 174 A polarographic Analyzer, 175 Universal Programmer, RE 0089 X - Y Recorder and a 303A Electrode system. The three electrode assembly consisted of a hanging mercury drop working electrode (HMDE), a platinum auxiliary electrode and a silver-silver chloride (Ag-AgCl) reference electrode.

At a low pH, a reduction peak corresponding to the reduction of ternary Cu(II)AL species to Cu(I)AL species is observed. At a higher pH, a reduction peak at a comparatively higher negative potential is observed due to the reduction of ternary $Cu(II)A_{-H}L$ species to $Cu(I)A_{-H}L$. The reduction of the ternary $CuA_{-H}L$ species takes place at a more negative potential, because of the coordination of deprotonated peptide N^-, which is a strong σ donor. This increases the electron density around the metal centre and hence reduction of Cu(II) to Cu(I) occurs at a more negative potential. In case of copper-histidine-amino acid (L) complexes, reduction peaks for both CuhistHL species and CuhistL species are observed.

The enhanced stability of the ternary (CuAL) complexes where A = dipeptides and L = catechol and catechol derivatives is attributed to hydrogen bonding between the two ligands through a solvent water molecule.

In all the above mentioned ternary systems, it was found that -NH deprotonation, in the case of ternary CuAL species, is very much

reduced, as compared to binary CuA species. This is attributed to two factors. First, there is a strong repulsion between the dipeptide dianion and L monoanion or dianion. Also there is destabilization of the ternary $CuA_{-H}L$ complex with the tridentate ligand A_{-H}, due to Jahn-Teller effect.

Δlog K was found to be positive for CuAL complexes where, A = dipeptides and L = auxins such as indole acetic acid (IAA), indole propionic acid (IPA) and indole butyric acid (IBA). This is due to hydrogen bond formation between indole - NH and free COO^- group of the dipeptide.

In case of the ternary complexes CuAL where L = aromatic tertiary amines, Δ log K was found to be negative due to statistical reasons. It was also observed that increase in π - acidity of the aromatic amine has marked influence on the deprotonation of the dipeptide in the ternary CuAL complex. The π - acidic ligands favour N - N^- coordination of the dipeptide to N - O coordination in the ternary complex. This is because of the fact that a metal, when bound to a π - acidic ligand, possesses more class A character, due to $d\pi$ - $p\pi$ back bonding, and becomes a hard acid. Hence, during the formation of a ternary complex, it will prefer a ligand which is a hard base i.e. the dipeptide coordinated from N - N^- sites, rather than N - O.

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