



**TRANSITION METAL COMPLEXES
OF PEPTIDE DERIVATIVES CONTAINING
CHELATING SIDE CHAINS**

PhD Thesis Abstract

Katalin Ósz

Supervisor: *Prof. Imre Sóvágó*

University of Debrecen
Faculty of Science
Department of Inorganic and Analytical Chemistry
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1. Introduction and research objectives

Metal ions play important roles in the synthesis and transport of organic molecules in living organisms, and in catalyzing acid-base and redox processes in biological systems. Proteins are important binding sites for metal ions. Metalloenzymes usually contain metal ions bound to a specific amino acid residue of the polypeptide backbone, e.g. the imidazolyl group of a histidine. Metals in proteins sometimes only stabilize the ternary structures of metalloenzymes but more often have vital roles in the catalytic process. Metals may be important to bind the substrate, stabilize the intermediates of the reaction or may take part in the catalyzed reaction.

Histidine residues have two different roles in metalloenzymes: it can coordinate the metal ion through its imidazole nitrogen or, alternatively, upon deprotonation of the pyrrole nitrogen, it may act as a bridging ligand between two metal centres.

Copper is ubiquitous in plants and animals, and its redox chemistry is involved in a variety of biological oxidation processes. Copper usually binds to proteins (copper proteins) in living organisms. Biologically active copper centres can be divided into three main types:

- *Type 1*: "blue" monomeric copper with very distorted coordination of [2·N(imidazole), S(thiol), S(thioether)] donor atoms. These metalloenzymes mainly catalyze different redox reactions (e.g. laccase and ascorbic oxidase in plants and ceruloplasmin in mammals).
- *Type 2*: "normal" monomeric Cu^{II} is an essentially square planar (equatorial) environment with additional, very weak, tetragonal (axial) interactions (e.g. superoxide dismutases).
- *Type 3*: a pair of copper(I) ions attached to the protein through histidine residues. These enzymes take part in the transport and activation processes of O_2 molecules (e.g. haemocyanin in molluscs).

A further class, *Type 4*, has been proposed recently, which is characterized by a unit containing three $\text{Cu}(\text{II})$ ions. The important enzyme Cytochrome c oxidase cannot be classed in these types, either. It contains significantly different copper ions referred to as Cu_A and Cu_B . The former is situated outside the mitochondrial membrane, whereas the latter, coupled to an iron ion, is inside the membrane.

Until the discovery of **nickel** in *jack bean urease* in 1975 (which was the first enzyme to be isolated in crystalline form 50 years before) no biological role for nickel was known. *Ureases* catalyze the hydrolysis of urea.

Three other nickel containing enzymes found in bacteria. *[NiFe]-* and *[NiFeSe]-hydrogenases* catalyze the reaction $2\text{H}_2 + \text{O}_2 \rightarrow 2\text{H}_2\text{O}$. *CO Dehydrogenase*, also incorporating Fe, catalyzes the oxidation of CO to CO₂. *Methyl-coenzyme M reductase* contains low-spin distorted octahedral nickel(II) and participates conversion of CO₂ to CH₄.

Nickel- and copper(II) ions are also present in the “*ATCUN motif*” (Amino Terminal Cu(II)-, Ni(II)-binding) models, which are the simplest models for serum albumins and have a free terminal amino group and a histidine in the third position. The most important role of albumin is to transport various small molecules and ions, including metal ions in living organisms. In addition, these peptides may be able to cleave the DNA chain at specific sites, i.e. act as artificial restriction endonucleases.

Zinc is one of the most important metal ions in biology, and is more often found in metalloenzymes than copper(II) and nickel(II). The enzymes which catalyze the hydrolysis of carbonic acid esters, amines, peptides or phosphates almost always contain Zn(II) in their active centers. Among the Zn enzymes which have received most attention are *carbonic anhydrase*, *carboxypeptidase*, *termolysine*, *alcohol dehydrogenase*, *superoxide dismutase* and *elastase*. A more recently confirmed function of zinc in proteins is to recognize base-sequences in DNA and regulate the transfer of genetic information during the replication of DNA. These so-called “zinc finger” proteins contain 9–10 zinc(II) ions, each of which is coordinated to 4 amino acids in a tetrahedral environment.

As previously shown, imidazole nitrogen donor atoms are among the most common metal binding sites in metalloenzymes. Polyimidazole ligands are frequently used to mimic the structure and catalytic activity of the active sites of metalloproteins. Our research objective was to study the coordination chemistry of a series of amino acid and peptide derivatives containing the chelating bis(imidazol-2-yl)methyl group with copper(II), nickel(II) and zinc(II). Our goal was to characterize the solution equilibria of these systems and determine the structures of the complexes formed.

The systems containing bis(imidazol-2-yl)methyl derivatives as ligands are rather complicated because of the presence of 2–2 nitrogen donor atoms in all imidazole rings. To make the systems simpler, we also measured the coordination properties of amino acid derivatives containing bis(pyridin-2-yl)methyl group.

Oligopeptide derivatives are very useful ligands for gaining insight into the nature of interactions between metal ions and peptides. These small molecules serve as models of the active centres in metalloproteins, and – using the specific, very strong binding ability of these molecules to metal ions – inhibit the enzymes selectively.

2. Experimental methods

pH-potentiometric measurements were used to determine the protonation constants of the ligands and the stability constants of the copper(II), nickel(II) and zinc(II) complexes in aqueous solution. Metal ion to ligand ratios were ranging between 1:3 and 2:1. Potentiometric titrations were processed using general computational programs. Protonation constants of the ligands and total concentrations of the components were calculated using *SUPERQUAD*, and overall stability constants of the complexes were calculated with *PSEQUAD*. Species distribution curves of the complexes were calculated by *SED* and *CED*, using the calculated stability constant values (β_{pqr}).

UV-Visible spectroscopic measurements were carried out with copper(II) and nickel(II) complexes. To make exact calculations, we measured the spectra of the ligands, too because these ligands have absorption maxima in the near UV range. Processing of the measured spectra was carried out using the software provided by the manufacturer (Hewlett Packard, HP 8453) and the computational program *PSEQUAD*. The latter method made it possible to calculate the spectra belonging to one denominated complex.

Circular dichroism (CD) spectroscopy has been widely used for structural characterisation of optically active, dissymmetric complexes (mainly copper(II) and nickel(II) peptide complexes). We did CD measurements with copper complexes. Measured spectra were processed using the software provided by the manufacturer (JASCO-810) and the *PSEQUAD* program, similarly to the UV-Vis measurements.

¹H-NMR spectroscopic measurements were used to determine the structures of the ligands, to check their purity and to identify the protonation steps and determine the protonation microconstants. We also used this method to characterize the structures of zinc(II) complexes. The measured spectra were processed by the built-in software of the Bruker AM360 instrument and *1D-WinNMR*.

Magnetic moment measurements were carried out using the Evans NMR method in the systems containing copper(II) ion. Copper(I) and ferromagnetically coupled copper(II) complexes are diamagnetic, while copper(II) complexes are paramagnetic so these measurements provided information about the ferromagnetic (spin-spin) interactions in the complexes studied.

Electronspin / electron paramagnetic resonance (EPR) spectroscopy is an important experimental method to study paramagnetic molecules and ions, e.g. copper(II) complexes. The hyperfine structure of EPR spectra ($A_{||}$ and $g_{||}$) is sensitive to even small structural changes in the complexes. Moreover, the broadening of the signals on the parallel region of anisotropic "X-band" EPR spectra and the appearance of a seven-line

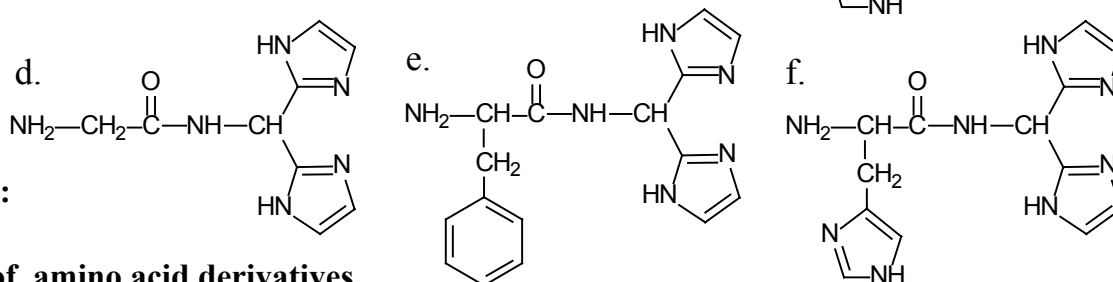
group on the low-field side indicates the existence of dimeric or polymeric structures. In the case of dimers, the perpendicular signals (g_{\perp} és $D[\text{cm}^{-1}]$) make it possible to calculate the approximate copper–copper distance using the *Stevens equation*.

MALDI-TOF-MS (Matrix Assisted Laser Desorption/ Ionisation, Time of Flight, Mass Spectroscopy) is suitable for studying polynuclear copper complexes which contain metal ions in different coordination environments and are otherwise difficult to characterize with other spectroscopic methods. MALDI-TOF-MS measurements give information about the molecular mass of the metal complexes. In addition, fragmentation patterns provide more structural information.

3. Ligands

The amino acid and peptide derivatives was prepared in the *Research Group of Peptide Chemistry of the Hungarian Academy of Sciences and Organic Chemistry Department of Eötvös University* by *Helga Süli-Vargha, Zsuzsanna Likó and Lidia Lennert*. The purity of the ligands was checked by HPLC, NMR, melting-point, TLC and pH-potentiometric measurements and the structures were proved by $^1\text{H-NMR}$.

Scheme 1:



Structures of amino acid derivatives containing bis(imidazol-2-yl)methyl- and bis(pyridin-2-yl)methyl chelating donor groups:

- a.: *N*-Glycylbis(pyridin-2-yl)methylamine (Gly-BPMA)
 b.: *N*-Prolylbis(pyridin-2-yl)methylamine (Pro-BPMA)
 c.: *N*-Histidylbis(pyridin-2-yl)methylamine (His-BPMA)
 d.: *N*-Glycylbis(imidazol-2-yl)methylamine (Gly-BIMA)
 e.: *N*-Penylalanyl-bis(imidazol-2-yl)methylamine (Phe-BIMA)
 f.: *N*-Histidyl-bis(imidazol-2-yl)methylamine (His-BIMA)

Scheme 2:

Dipeptide derivatives containing bis(imidazol-2-yl)methyl chelating donor groups:

- a.: Glycyl-leucylbis(imidazol-2-yl)methylamine (Gly-Leu-BIMA)
- b.: Leucyl-glycylbis(imidazol-2-yl)methylamine (Leu-Gly-BIMA)
- c.: Phenylalanyl-glycylbis(imidazol-2-yl)methylamine (Phe-Gly-BIMA)
- d.: Alanyl-prolylbis(imidazol-2-yl)methylamine (Ala-Pro-BIMA)
- e.: Phenylalanyl-histidylbis(imidazol-2-yl)methylamine (Phe-His-BIMA)
- f.: Histidyl-phenylalanylbis(imidazol-2-yl)methylamine (His-Phe-BIMA)

4. Results

4.1. We characterized the acid-base properties of twelve new bis(imidazol-2-yl)methyl and bis(pyridin-2-yl)methyl amino acid and peptide derivatives (Scheme 1 and 2) using pH-potentiometric and NMR method.

pH-potentiometric measurements were used to determine the protonation constants of the ligands while, $^1\text{H-NMR}$ spectroscopic measurements and literature data of similar ligands were used to identify the protonation/deprotonation steps. Our fully protonated ligands can be deprotonated at their pyridine, imidazole, and amino groups in the measureable pH region. The highest pK values ($7.2 \leq pK(\text{amino}) \leq 8.6$) belong to the amino group in all systems. pK values of histidyl imidazoles are smaller ($5.4 \leq pK(\text{histidyl}) \leq 6.3$), and the smallest values belong to the bis(imidazol-2-yl) and bis(pyridin-2-yl) groups ($2.6 \leq pK_1(\text{imidazole}) \leq 3.2$; $4.5 \leq pK_2(\text{imidazole}) \leq 5.6$; $pK_1(\text{pyridine}) \leq 1.5$; $2.9 \leq pK_2(\text{pyridine}) \leq 3.3$). In the latter cases, the presence of two protonated aromatic nitrogens is sterically and electrostatically unfavourable, which causes the low pK_1 values. Moreover, the pK values

can be increased or decreased by electron donating (aliphatic) or electron withdrawing (amino-, amide-, aromatic, proline-) groups, respectively.

In the case of histidyl derivatives the protonation equilibria significantly overlap, and this fact made it necessary to do NMR measurement to follow the deprotonation/protonation processes of the different groups separately.

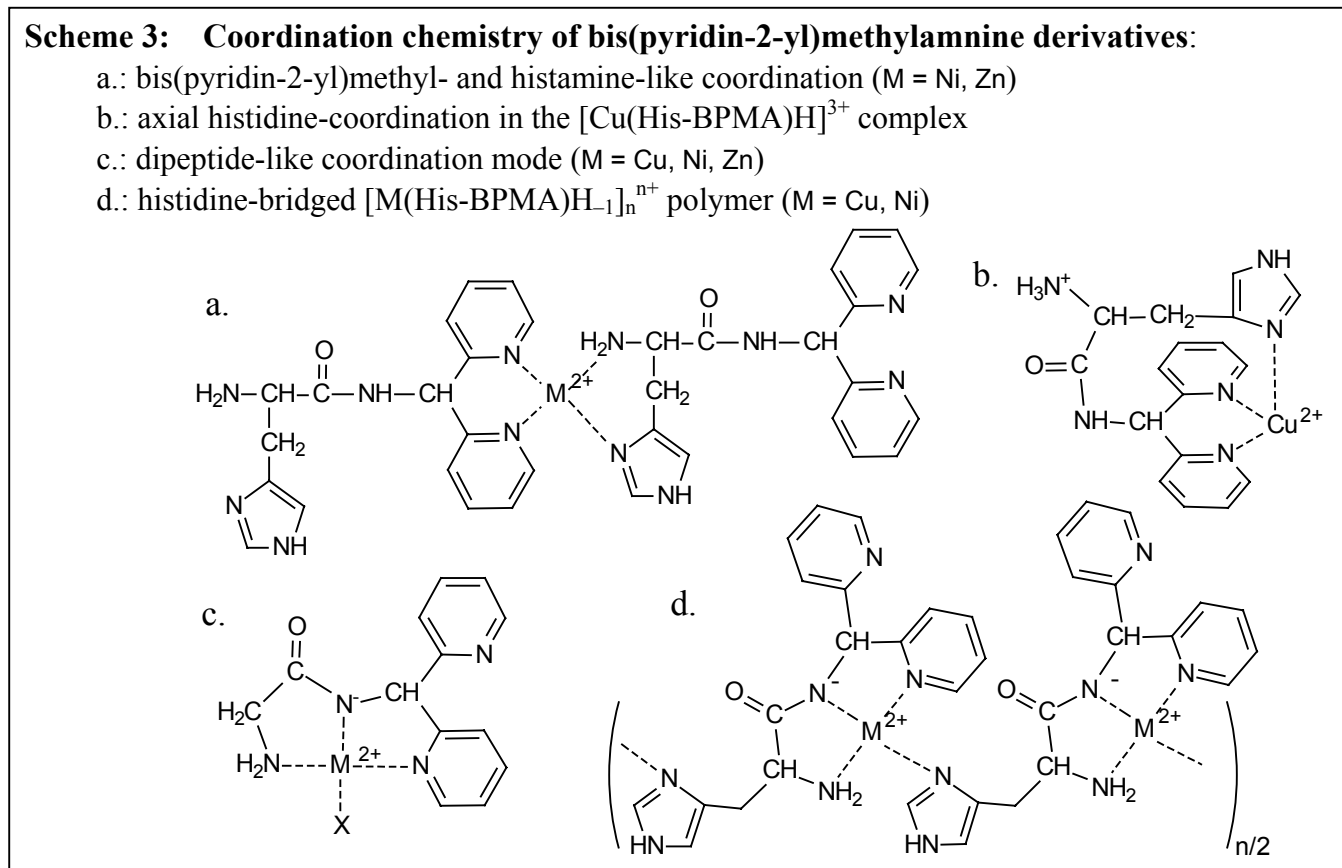
4.2. We used a new calculation method to give the protonation microconstants by NMR measurements, in the case of small molecules, where all deprotonation steps have some effect on all NMR signals. In the case of these small molecules, the individual parts of the ligands are not independent of each other, in contrast with the earlier literature data for larger ligands.

To calculate protonation/deprotonation microconstants, we defined factors characterizing the effect of each microscopic deprotonation step on the chemical shift of each NMR active nucleus. The actual chemical shift of an NMR active nucleus can thus be calculated from factors and the degree of protonation. After measuring the chemical shifts experimentally the factors and the site distribution of protons for a given degree of protonation can be determined with fitting procedures, and the isomerization and protonation microconstants can be calculated.

4.3. We characterized the coordination chemistry of two bis(pyridin-2-yl)methyl amino acid derivatives (Gly-BPMA and His-BPMA) with copper(II), nickel(II) and zinc(II) ion. The results are in good agreement with the earlier literature data obtained with the ligand Pro-BPMA. To interpret the data, we also studied several ternary systems (M(II)–bis(pyridin-2-yl)methane–histamine).

The bis(pyridin-2-yl)methyl groups of Gly-BPMA and His-BPMA are the main metal binding sites for all three metal ions in acidic pH. The binding ability of the six-membered chelate complexes decreases in the order $\text{Cu(II)} > \text{Ni(II)} > \text{Zn(II)}$ in agreement with the Irving-Williams series. With copper(II) ion, only 1:1 complexes are formed because of the distorted octahedral geometry of the copper(II) ion. On the other hand, the octahedral geometry of nickel(II) and zinc(II) complexes results in the formation of bis(ligand) complexes in the excess of ligand.

With the ligand His-BPMA, we can also see the "histamine-like" coordination mode with nickel(II) and zinc(II) ion (**Scheme 3a**) in the case of ligand excess. With copper(II) ion, the stable axial coordination of histidine side chain in acidic pH region is able to prevent the ligand from forming "histamine-like" coordination (**Scheme 3b**).



At higher pH all three metal ions can induce the deprotonation of the amide nitrogens forming a "dipeptide-like" [N(amino), N(amide), N(pyridine)] coordination around the metal center (**Scheme 3c**). The coordination of two ligands to nickel(II) and zinc(II) can saturate the coordination sphere of these metal ions. The non-coordinating pyridine ring of Gly-BPMA and His-BPMA cannot act as a monodentate bridging ligand to form a dimeric structure. However, the non-coordinated histidine imidazole nitrogen acts as a bridging residue giving rise to dimeric or polymeric copper(II) and nickel(II) complexes at 1:1 metal to ligand ratio (**Scheme 3d**).

At basic pH, the formation of mixed-ligand hydroxo complexes can be monitored (**Scheme 3c**, $\text{X} = \text{OH}^-$), which break the dimeric or polymeric structures. All of these structures are well-known in general transition metal ion – peptide systems.

4.4. We complemented earlier literature data about Gly-BIMA by studying the nickel(II)–Gly-BIMA system, as well as the copper(II), nickel(II) and zinc(II) complexes of Phe-BIMA és His-BIMA. To interpret the data, we took into account the results with

bis(pyridin-2-yl) derivatives. We also also studied several ternary systems (M(II)–bis(imidazol-2-yl)methane–histamine).

The measurements showed that the presence of a bulky phenylalanyl side chain has no considerable effect on the coordination modes. On the other hand, an imidazolyl chain significantly influences the complex formation process.

In acidic solutions, the main metal binding sites of Gly-BIMA, Phe-BIMA and His-BIMA ligands are the aromatic rings, similarly to the bis(pyridin-2-yl)methyl derivatives. This coordination mode is also able to form a six-membered chelate structure. The stability of the complexes follows the Irving-Williams series. The imidazole nitrogens has a higher basicity and metal binding ability with respect to the pyridine nitrogens, so in this systems we can monitor the bis(ligand) complex formation, even with copper(II). The coordination of more than two ligands, however, cannot be proved even in these systems.

In addition, with His-BIMA the formation of "histamine-like" coordination can be seen at acidic pH. The simultaneous presence of these two coordination modes makes possible the formation of binuclear complexes at metal ion excess, and the formation of symmetric and asymmetric ligand-bridged dimeric complexes at 1:1 metal ion to ligand ratio (**Scheme 4a–b**).

The presence of the stable bis(ligand) complexes makes the formation of dipeptide-like [N(amino), N(amide), N(imidazole)] coordination more difficult at higher pH – especially at ligand excess.

We can see the formation of dimeric structures with both Gly-BIMA and His-BIMA at neutral pH. The bridging groups are the non-coordinating imidazole groups of the bis(imidazol-2-yl)methyl residues (**Scheme 4c**), and not the histidine imidazole.

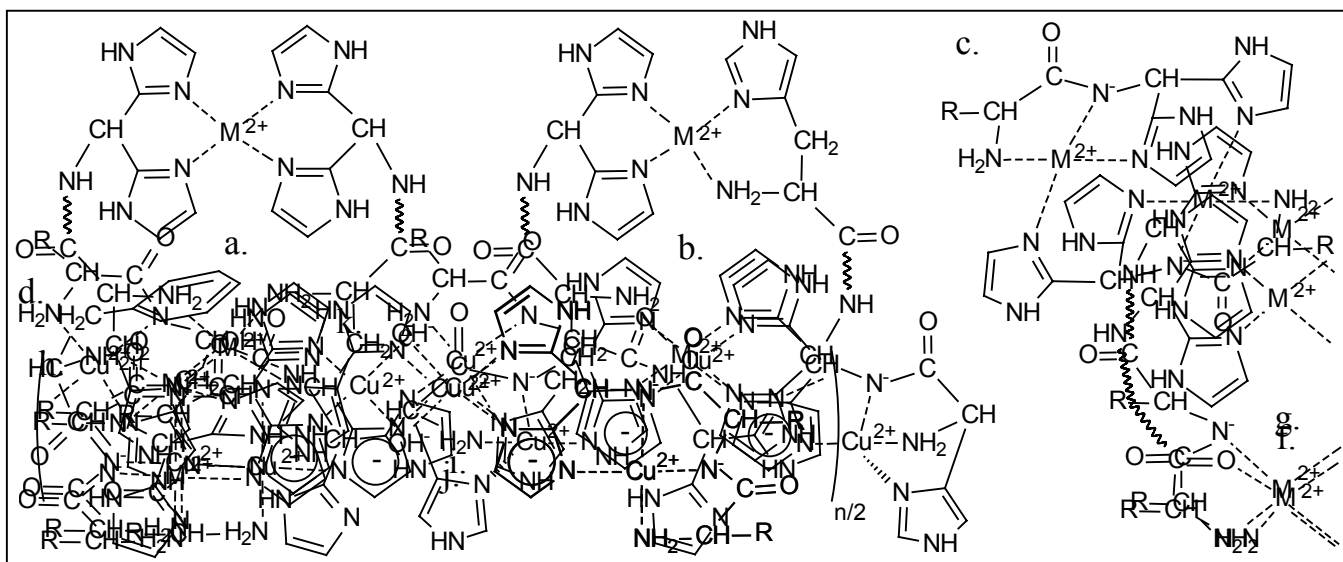
Under mildly alkaline conditions mixed-ligand hydroxo complexes are formed with Gly-BIMA and Phe-BIMA. In the case of Gly-BIMA polynuclear complexes are formed with five-coordinated distorted copper(II). With Phe-BIMA, the stacking interaction of the aromatic rings prevents polymerization (**Scheme 4d**). In contrast with these structures, the dimeric complex of copper(II)–His-BIMA system formed at neutral pH (**Scheme 4c**) contains axially coordinated histidines (–R), which are able to prevent the hydrolysis even at basic pH and makes the deprotonation of pyrrolic type N(1)H-groups possible. This process was characterized with pK 8.5.

Another important consequence of the deprotonation of N(1)H-groups is that they can be considered as additional metal binding sites in the presence of excess metal ions. A trinuclear complex is formed in the system, in which two copper(II) ions are coordinated by dipeptide-like coordination with additional axial histidine interaction, and the third copper(II) acts as bridging metal ion between the two ligands (**Scheme 4e**). The formation of this structure is characteristic at physiological pH 5.5.

4.5. We characterized the coordination chemistry of four bis(imidazol-2-yl)methyl dipeptide derivatives containing non-coordinating side chains (Gly-Leu-BIMA, Leu-Gly-BIMA, Phe-Gly-BIMA and Ala-Pro-BIMA) with copper(II), nickel(II) and zinc(II) ion.

•□ The measurements showed that the presence of a non-coordinating aromatic (phenylalanyl) or aliphatic (leucyl, alanyl) side chain has absolutely no effect on the structure of the complexes formed: it only influences the stability constants somewhat.

At acidic pH the coordination mode is the same bis(imidazol-2-yl)methyl coordination as in the case of amino acid derivatives. The amino end of the molecule is, however, sufficiently far from the bis(imidazol-2-yl)methyl part to be coordinated at the same time in an "amino acid-like" [N(amino), O(carbonyl)] coordination mode. These two coordination modes can form symmetric and asymmetric dimeric structures (**Scheme 4f**). At higher pH and 1:1 metal to ligand ratio we can see the formation of additional dimeric complexes with bis(imidazol-2-yl)methyl and [N(amino), N(amide)] coordination (**Scheme 4g**). The deprotonation of the amide nitrogens start in this complexes, and continues in the formation of a monomeric, "tripeptide-like" [N(amino), N(amide), N(amide), N(imidazole)]-coordinated complex at pH 8-10. This structure is the predominant complex both 1:1 ratio and ligand excess (**Scheme 4h**). These very stable 4N fused chelate rings cannot be broken up even by the hydrolysis, which facilitates the deprotonation of pyrrolic type N(1)H-groups of the coordinated imidazole rings at pH 11. Moreover, the pyrrole deprotonation – similarly to the copper(II)–His-BIMA system – makes the coordination of more than one metal ion per ligand possible. The measurements proved the existence of complexes with 3:2 and 4:2 metal to ligand ratios. In the 3:2 complex two of the copper(II) ions are coordinated in a 4N "tripeptide-like" coordination. The third copper(II) coordinated by four imidazole groups acts as a bridge between the two ligands (**Scheme 4i**). This complex – similarly to the 3:2 complex of the copper–His-BIMA system (**Scheme 4e**) – predominates at physiological pH. At 2:1 metal to ligand ratio, the deprotonation and coordination of the pyrrolic type N(1)H-groups occurs at even lower pH (pH 6) and a tetranuclear mixed dihydroxo complex is formed at pH 8 (**Scheme 4j**).



•□ Compared to the dipeptide-BIMA derivatives containing non-coordinating amino acid units, proline in the peptide chain has larger effect on the coordination chemistry of the ligand. In contrast with the former systems, with the proline derivative we could not show the deprotonation and coordination of the amide nitrogens. At acidic pH bis(imidazol-2-yl)methyl-, at neutral pH "amino acid-like" [N(amino), O(carbonyl)] coordination does exist. Because the amide deprotonation could only be started from the bis(imidazol-2-yl)methyl part of this ligand (Ala-Pro-BIMA does not contain an amide-NH group in chelating position with the amino group) and cannot be seen this deprotonation, this is a further verification that in the former systems the amide deprotonation starts from the amino part of the ligands. Since the absence of the two amide-NH groups prevents the formation of stable 4N "tripeptide-like" coordination, we can see precipitation caused by mixed hydroxo complex formation at higher pH.

4.6. We studied the effect of sidechain histidines in the complex formation of dipeptide-BIMA derivatives (His-Phe-BIMA and Phe-His-BIMA).

Histidine in the peptide sequence is an additional strong donor group for metal ions. We found that the structures of the complexes formed significantly depend on the position of histidine in the peptide chain.

•□ Donor groups of the amino terminal histidine derivative His-Phe-BIMA are similar to those of His-BIMA, so the structures of the complexes formed with these ligands are somewhat similar. At acidic pH bis(imidazol-2-yl)methyl- and "histamine-like" coordination can be detected. The collective presence of these two coordination modes makes the formation of symmetric and asymmetric ligand-bridged dimers possible at 1:1 metal ion to ligand ratio (**Scheme 4a–b**). Dimeric structures with bis(imidazol-2-yl)methyl and "amino acid-like" ([N(amino), O(karbonil)]-) or [N(amino), N(amid)] coordination can also be detected (**Scheme 4f–g**).

At basic pH, the N-terminal histidine side chain cannot stop the stepwise deprotonation and coordination of the amide nitrogens to copper(II). The structure of the complexes formed is the same as that with ligands containing non-coordinating side chain (**Scheme 4h**), but in these systems these complexes can be formed only at higher pH because of the existence of stable histamin-coordinated complexes. This formation pH for "tripeptide-coordinated" complexes is so high that – mainly with ligand excess – amide deprotonation and hydrolysis are overlapping, which prevents the formation of tri- and tetranuclear complexes with pyrrolic type coordination.

•□ The ligand Phe-His-BIMA contains a "Gly-His (or Phe-His)-like" donor function, which is – as the earlier literature data in peptide coordination chemistry shows – even stronger coordinating group than the histamine group. The literature data also show that "Gly-His-like" coordination is only effective at slight alkaline pH. For this reason, we can

see the formation of bis(imidazol-2-yl)methyl coordinated and ligand-bridged complexes (**Scheme 4f–g**) at acidic and neutral pH, respectively. At higher pH, a polymeric species with "Gly-His-like" coordination is precipitated (**Scheme 4k**). However, if we use a water/acetone mixture as solvent (in which OH⁻ concentration is lower hydrolysis is less pronounced), we can monitor the 4N "tripeptide-like" coordination (**Scheme 4h**).

In the case of metal ion excess, 2:1 and 3:2 complexes can be formed with bis(imidazol-2-yl)methyl and "Gly-His-like" coordination. The latter one – similarly to other trinuclear complexes mentioned earlier – one of the copper(II) ions is a bridging ion, coordinated by four imidazole nitrogens. This structure is less stable than the one with other dipeptide-BIMA derivatives and His-BIMA because of the unsaturated 3N coordination of the other two copper(II) ions and it hydrolyses at alkaline pH.

5. Potential use of the results

The study of different oligopeptide derivatives helps understand the interactions between metal ions and proteins. The most important coordinating groups of oligopeptides are imidazole N(1) and N(3) nitrogens. Also the two imidazole nitrogens have essential roles in the forming of ligand-bridged structures in the enzymes superoxide dismutases.

The results obtained for the copper(II) complexes of amino acids and peptides reveal that bis(imidazol-2-yl) analogues of these biomolecules are very effective ligands for metal binding. The nitrogen donor atoms of the chelating bis(imidazolyl) residues are the major metal binding sites under acidic conditions and they remain the exclusive metal binding sites if the terminal amino group or an effective side chain donor function are not present in the molecules. The high thermodynamic stability of the metal complexes of the bis(imidazol-2-yl)methyl ligands suggests that they could potentially be enzyme inhibitors. Moreover, specific enzyme inhibitors may be obtained by attaching the bis(imidazol-2-yl)methyl ligands to the preferred peptide sequence for the enzyme cleavage.

The terminal amino group can be considered as another anchor for metal binding with these ligands. The multidentate character of these ligands results in the formation of various polynuclear complexes including the ligand bridged dimeric species and the imidazole bridged dimeric species. These complexes can be considered as interesting structural models of the various dinuclear species of transition elements.

Finally, the most intriguing feature of the coordination chemistry of these ligands that the deprotonation of the coordinated imidazole-N(1)H groups results in the appearance of a new chelating site in the molecules. It leads to the formation of stable trinuclear complexes *via* negatively charged imidazolato bridges and these species can be considered as promising structural and/or functional models of various metalloenzymes.

6. Scientific publications of the author

6.1. Publications connected to the thesis

Articles:

5. Imre Sóvágó, Katalin Ósz, Katalin Várnagy
Copper(II) complexes of amino acids and peptides containing chelating bis(2-imidazolyl) residues
Bioinorganic Chemistry and Applications, (in press).
4. Katalin Ósz, Katalin Várnagy, Helga Süli-Vargha, Daniele Sanna, Giovanni Micera, Imre Sóvágó
Transition metal complexes of bis(imidazol-2-yl) derivatives of dipeptides
J. Chem. Soc., Dalton Trans., 2003, 2009-2016.
3. Katalin Ósz, Katalin Várnagy, Helga Süli-Vargha, Daniele Sanna, Giovanni Micera, Imre Sóvágó
Copper(II), nickel(II) and zinc(II) complexes of amino acids containing bis(imidazol-2-yl)methyl residues
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Metal complexes of peptides containing monodentate or chelating imidazole nitrogen donors: Factors influencing the coordination of amide groups and imidazole side chains
Comments on Inorg. Chem., 2002, **23 (2)**, 149-178.
1. Katalin Ósz, Katalin Várnagy, Imre Sóvágó, Lídia Lennert, Helga Süli-Vargha, Daniele Sanna, Giovanni Micera
Equilibrium and structural studies on transition metal complexes of amino acid derivatives containing bis(pyridin-2-yl)methyl residue
New J. Chem., 2001, **25 (5)**, 700-706.

Conferences:

15. Imre Sóvágó, Katalin Ösz, Katalin Várnagy, Helga Süli-Vargha, Daniele Sanna, Giovanni Micera
Copper(II) complexes of amino acids and dipeptides containing chelating bis(imidazol-2-yl) side chains (poster)
6th European Conference on Bioinorganic Chemistry (EUROBIC-6), July 29-August 3, 2002, Lund/Copenhagen, Sweden/Denmark.
14. Katalin Várnagy, Katalin Ösz, Csilla Kállay, Imre Sóvágó, Helga Süli-Vargha, Daniele Sanna, Giovanni Micera
The effect of coordinating donor group on the complexation of bis(imidazolyl) derivatives (poster)
XXXVth International Conference on Coordination Chemistry, ICC35, July 21-26, 2002, Heidelberg, Germany.
13. Katalin Ösz, Katalin Várnagy, Imre Sóvágó, Helga Süli-Vargha, Giovanni Micera, Daniele Sanna
Copper(II) complexes of dipeptides containing chelating imidazole-N donors (poster)
XXXVth International Conference on Coordination Chemistry, ICC35, July 21-26, 2002, Heidelberg, Germany.
12. Katalin Várnagy, Katalin Ösz, Csilla Kállay, Imre Sóvágó, Helga Süli-Vargha
Oldalláncbeli donorcsoportok hatása a bis(imidazolil) származékok komplexképző sajátosságaira (lecture in Hungarian: **The effect of side chain donor groups on the complexation of bis(imidazolyl) derivatives**)
XXXVII. Komplexkémiái Kollokvium (XXXVIIth Colloquium on Coordination Chemistry), May 29-31, 2002, Mátraháza, Hungary.
11. Katalin Ösz, Katalin Várnagy, Imre Sóvágó, Helga Süli-Vargha, Giovanni Micera, Daniele Sanna
Transition metal complexes of peptides containing chelating imidazole-N donors
J. Inorg. Biochem., 2001, **86**, 367 (conference abstract).
10. Katalin Ösz, Katalin Várnagy, Imre Sóvágó, Helga Süli-Vargha, Giovanni Micera, Daniele Sanna
Transition metal complexes of peptides containing imidazole-N donors (poster)
10th International Conference on Bioinorganic Chemistry, August 26-31, 2001, Florence, Italy.

9. Katalin Ósz, Katalin Várnagy, Imre Sóvágó, Helga Süli-Vargha
Oldalláncban kelátképző donorcsoportot tartalmazó aminosav- és peptidszármazékok átmenetifém komplexei (lecture in Hungarian: **Transition metal complexes of amino acids and peptides containing chelating side chains**)
XXXVI. Komplexkémiái Kollokvium (XXXVIth Colloquium on Coordination Chemistry), May 23-25, 2001, Pécs, Hungary.
8. Katalin Várnagy, Katalin Ósz, Imre Sóvágó, Helga Süli-Vargha
The effect of C-terminal bidentate group on the complexation of oligopeptides (lecture)
The international conference: Metals in Enviromental Medicine, October 19-21, 2000, Wrocław, Poland.
7. Katalin Várnagy, Julianna Szabó, Katalin Ósz, Imre Sóvágó, Helga Süli-Vargha, Giovanni Micera, Daniele Sanna
The effect of C-terminal imidazole ring on the complexation of oligopeptides containing histidyl or bis(imidazolyl) groups (poster)
5th European Biological Inorganic Chemistry Conference, July 17-20, 2000, Toulouse, France.
6. Lídia Lennert, Katalin Ósz, Katalin Várnagy, Helga Süli-Vargha
Kelátképző ligandumot tartalmazó aminosavszármazékok előállítására és átmenetifém-komplexeik vizsgálata (lecture in Hungarian: **Synthesis of amino acid derivatives with chelating side chains and study of their complexation properties with transition metal ions**)
Peptidkémiái Munkabizottsági Ülés (Meeting of the Peptide Chemistry Working Group of the Hungarian Academy of Sciences), December, 1999, Balatonszemes, Hungary.
5. Katalin Ósz, Katalin Várnagy
Oldalláncban kelátképző donorcsoportot tartalmazó aminosavszármazékok átmenetifém-komplexeinek egyensúlyi vizsgálata (lecture in Hungarian: **Equilibrium study on the complexation properties amino acid derivatives with chelating side chains of with transition metal ions**)
XXII. Kémiai Előadói Napok, Szerves, Gyógyszer és Biokémiai Szimpózium (Young Chemists' Conference, Organic, Pharmaceutical and Biochemistry), November 1-3, 1999, Szeged, Hungary.

4. Katalin Ósz, Katalin Várnagy, Lídia Lennert, Imre Sóvágó, Helga Süli-Vargha, Daniele Sanna, Giovanni Micera
Zinc(II) and copper(II) complexes of amino acid derivatives containing bidentate donor group in the side chain (poster)
V. Symposium on Inorganic Biochemistry towards Molecular Mechanisms of Metal Toxicity, September 23-27, 1999, Wrocław, Poland.
3. Katalin Ósz, Katalin Várnagy, Helga Süli-Vargha, Lídia Lennert
Kelátképző ligandumot tartalmazó aminosavszármazékok előállítása és átmenetifém-komplexeinek oldategyensúlyi vizsgálata (lecture in Hungarian: **Synthesis of amino acid derivatives with chelating side chains and study of their complexation properties with transition metal ions**)
XXXIV. Komplexkémiái Kollokvium (XXXIVth Colloquium on Coordination Chemistry), May 19-21, 1999, Tata, Hungary.
2. Lídia Lennert, Katalin Ósz
Bisz(2-piridil) csoportot tartalmazó aminosavszármazékok előállítása és átmenetifém-komplexeinek egyensúlyi vizsgálata (lecture in Hungarian: **Synthesis of bis(pyridyl)-containing amino acid derivatives and study of their complexation properties with transition metal ions**)
XXIV. OTDK, Kémiai és Vegyipari Szekció, Koordinációs Kémia Alszekció (Conference for Undergraduate Researchers, Chemistry and Chemical Engineering Section, Coordination Chemistry Group), April 7-9, 1999, Veszprém, Hungary.
1. Katalin Várnagy, Imre Sóvágó, Helga Süli-Vargha, Katalin Ósz, Lídia Lennert
The effect of bis(imidazol-2-yl) and bis(pyridin-2-yl) groups on complex formation process of amino acids and peptides (poster)
XXXIII. International Conference on Coordination Chemistry, August 30 - September 4, 1998, Florence, Italy.

6.2. Publications not connected to the thesis

Article:

1. Katalin Ósz, Beáta Bóka, Katalin Várnagy, Imre Sóvágó, Tibor Kurtán, Sándor Antus
The application of circular dichroism spectroscopy for the determination of metal ion speciation and coordination modes of peptide complexes
Polyhedron **2002**, **21** (21), 2149-2159.

Conferences and lectures:

2. Katalin Ósz, Beáta Bóka, Katalin Várnagy, Imre Sóvágó, Tibor Kurtán, Sándor Antus
Cirkuláris Dikroizmus (CD) spektroszkópia és alkalmazása komplex vegyületek vizsgálatában (lecture in Hungarian: **The application of circular dichroism spectroscopy for the investigation of coordination compounds**)
XXXVII. Komplexkémiái Kollokvium (XXXVIIth Colloquium on Coordination Chemistry),
May 29-31, 2002, Mátraháza, Hungary.
1. Katalin Ósz, Imre Sóvágó
Cirkuláris Dikroizmus (CD) spektroszkópia és alkalmazása komplex vegyületek vizsgálatában (lecture in Hungarian based on literature data introducing CD spectroscopy: **The application of circular dichroism spectroscopy for the investigation of coordination compounds**)
University of Debrecen, Seminar of the Inorganic and Analytical Chemistry Department, November 22, 2001, Debrecen, Hungary.