Propositions of PhD theses

THE METAL ION SELECTIVITY OF THE PEPTIDE FRAGMENTS OF THE PRION PROTEIN

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I. INTRODUCTION AND THE AIM OF THE WORK

Prion diseases, such as Creutzfeldt-Jakob disease, scrapie or bovine spongiform encephalophaty, belong to the neurodegenerative disorders and for its development the conformational changes of the normal form of the protein (PrP^C) to the disease-related scrapie isoform (PrP^{Sc}) are considered to be responsible. The physiological function of PrP^C and the mechanism of the transformation are not well established yet. Recently, however, more and more experimental evidence supports that metal ions, especially copper(II) may take part in the biochemical processes related to the normal function of prion protein and/or its conformational changes. As a consequence, the interaction between copper(II) ion and prion protein and its peptide fragments was widely studied. The high copper(II) binding affinity is due to the imidazole side chains of histidine residues in the sequence, which are primary binding sites for metal ions.

The previous coordination chemistry studies on prion peptide fragments carried out in the *Bioinorganic Research Group* of the *Department of Inorganic and Analytical Chemistry* at the *University of Debrecen* support the high copper(II) binding affinity. Furthermore the studies revealed the order of copper(II) binding affinity of the various histidyl sites: H111 > H96 >> H85 ~ H77. It means the histidine residues outside the octarepeat domain are more efficient in copper(II) binding than histidines inside the octarepeat region.

Former literature data were devoted to the complex formation processes of copper(II) ion. However, from the knowledge concerned about the coordination chemistry of peptides, it was evident that these peptide fragments can interact with other transition metal ions, which explains the necessity of the metal ion selectivity study on prion peptide fragments. They are expected to bind nickel(II) ions significantly and these complexes can be models for understanding the structure of copper(II) complexes.

Since the histidine containing sequences form complexes also with nickel(II) ions, we aimed to investigate the nickel(II) binding affinity of native and mutant prion peptide fragments that contain histidine residues simultaneously from different regions of prion protein, furthermore beside the characterisation of the complex formation process we want to focus on the nickel(II) binding preferences of the histidines.

In biological systems a series of different metal ions can be simultaneously present providing a good reason to investigate the mixed metal systems. Therefore our second aim was to study the complex formation processes in mixed copper(II)/nickel(II) systems of certain prion peptide fragments.

From the obtained results it was clear that the studied prion peptide fragments bind nickel(II) ions, but there is a significant difference in the preferred binding site between copper(II) and nickel(II) ions. So in the second half of our work to find out what causes this difference, we studied one, two and three histidine containing model peptides related to the metal binding site of the prion protein. These measurements help us to decide which factors influence the complex formation in copper(II), nickel(II), zinc(II) and copper(II)/nickel(II) containing systems.

II. EXPERIMENTAL METHODS

Solid phase peptide synthesis was performed in the case of the model peptides related to the metal binding site of prion protein using microwave-assisted Liberty Peptide Synthesizer (CEM, Matthews, NC). Introducing the amino acid derivatives following the TBTU/HOBt/DIEA activation strategy on Rink Amide AM resin we used *N*,*N*-dimethylformamide (DMF) as solvent. The sequences of the synthesised peptides are collected in *Figure 1*.

pH-potentiometric titrations were performed in order to determine the protonation constants of the ligands and the stability constants of the Cu(II), Ni(II) and Zn(II) complexes. All measurements were carried out in aqueous solution (T = 298 K; I = 0.20 mol/dm^3) with different metal ion to ligand ratios. The constants were calculated by means of the general computational programs, PSEQUAD and SUPERQUAD.

UV-visible spectrophotometric measurements were carried out in the case of Cu(II) and Ni(II) containing systems. The UV-vis spectra were recorded from 300 to 800 nm on Perkin Elmer Lambda 25 scanning spectrophotometer in the same concentration range as used for pH-potentiometric measurements.

Circular dichroism (CD) spectroscopy is a widely-used technique for discovering the structure of optically active metal complexes. We used this method for investigating copper(II) and nickel(II) peptide complexes. The CD spectra were recorded on a JASCO J-810 spectropolarimeter using 1 and/or 10 mm cells in the 200-800 nm wavelength range at the same concentration as used for pH-potentiometry.

^{1}H NMR spectroscopic measurements were carried out in the case of certain free ligands and Ni(II) containing systems. ^{1}H NMR spectra were recorded on a BRUKER AM 360 MHz FT-NMR spectrometer. The obtained spectra were analyzed by the software of BRUKER AM360 NMR spectrometer and by 1D WINNMR program. The changes in the chemical shift (compared to the free ligand), the number and the splitting of signs provided information about the coordination modes of the complexes.

III. STUDIED LIGANDS

Two native and two mutant prion peptide fragments studied in our work contain histidine residues both from inside and outside the octarepeat domain of the prion protein which provide us a good chance to compare the binding affinities of the different histidines. These peptides were synthesised at the University of Catania in Italy using solid phase peptide synthesis. The sequences of these peptides are listed below:

HuPrP(84-114)His85Ala: Ac-ProAlaGlyGlyGlyTrpGlyGlnGlyGlyGlyThr**His**SerGlnTrpAsnLys-ProSerLysProLysThrAsnMetLys**His**MetAlaGly-NH_2

HuPrP(84-114)His96Ala: Ac-Pro**His**GlyGlyGlyTrpGlyGlnGlyGlyGlyThrAlaSerGlnTrpAsnLys-ProSerLysProLysThrAsnMetLys**His**MetAlaGly-NH_2

HuPrP(76-114): Ac-Pro**His**GlyGlyGlyTrpGlyGlnPro**His**GlyGlyGlyTrpGlyGlnGlyGlyGlyThr**His**-SerGlnTrpAsnLysProSerLysProLysThrAsnMetLys**His**MetAlaGly-NH_2

HuPrP(60-114): Ac-Pro**His**GlyGlyGlyTrpGlyGlnPro**His**GlyGlyGlyTrpGlyGlnPro**His**GlyGlyGly-TrpGlyGlnPro**His**GlyGlyGly-TrpGlyGlnGlyGlyGlyThr**His**SerGlnTrpAsnLysProSerLysProLysThr-AsnMetLys**His**MetAlaGly-NH_2.

The structures and sequences of the one, two and tree histidine containing synthesised peptides are collected in *Figure 1*.

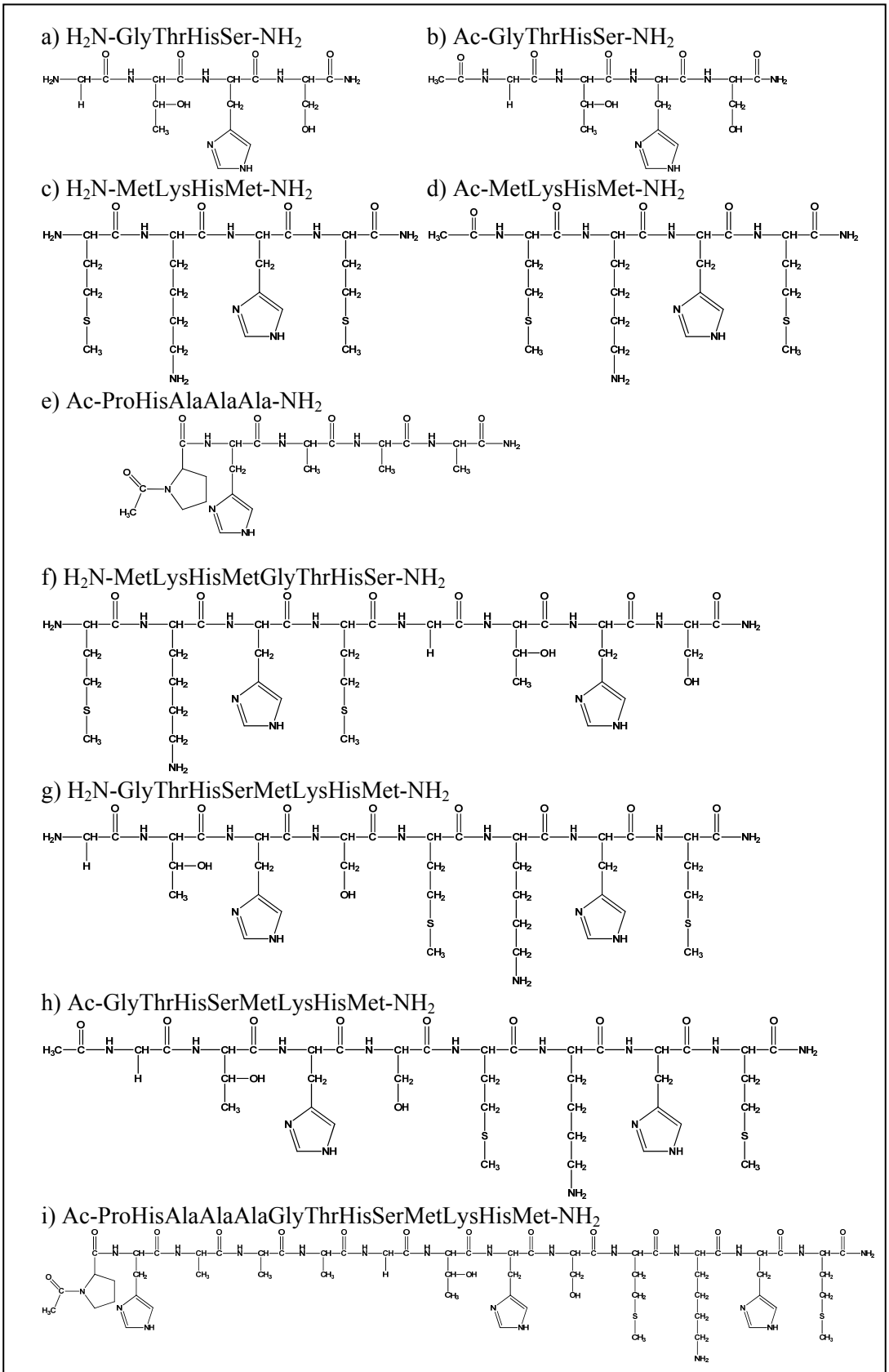

Figure 1: The structures and sequences of the synthesised peptides

IV. NEW SCIENTIFIC ACHIEVEMENTS

Solution equilibrium study on complexes formed between four prion peptide fragments and Ni(II), Ni(II)/Cu(II) or in one case Cu(II) ions has been done in this PhD work. Next we studied the interaction between nine histidine containing model peptides and Cu(II), Ni(II) and Zn(II) ions and in the case of multihistidine peptides the Ni(II)/Cu(II) mixed metal systems. At first the protonation constants of the ligands were determined what was followed by the determination of the stability constants of the complexes by pH-metry in the metal ion containing systems and we plotted concentration distribution curves based on the stability constants. To get information about the structures, bonding modes of the complexes, additional measurements (UV-vis spectrophotometry, CD, NMR and EPR spectroscopy) were performed.

This PhD thesis can be divided into two parts. In the first half in accordance with our aims we investigated Ni(II), mixed metal Ni(II)/Cu(II) and Cu(II) complexes of certain prion peptide fragments.

1. The complex formation processes of prion peptide fragments

1.1. The study of Ni(II) complexes of prion peptide fragments

The two histidine containing HuPrP(84-114)H85A and HuPrP(84-114)H96A, as well the four histidine containing HuPrP(76-114) peptide fragments provide a good chance for comparing the coordination chemistry of histidines from different regions. In the case of Ni(II) systems the following statements can be said:

- These prion peptide fragments bind Ni(II) ions efficiently (*Figure 2*.).
- They are able to bind as many equivalents of Ni(II) ion as the number of histidine residues outside the octarepeat domain in their sequence (the octarepeat domain only in extreme basic solution can bind Ni(II) ions).
- The histidine side chains behave as independent metal binding sites.
- The stability of complexes follows the Irving-Williams order.
- Two major coordination modes can be observed (*Figure 2*):
  - around pH 6 macrochelate structures form with the exclusive involvement of the imidazole nitrogen donor atoms of the histidine side chain (*Figure 2.b*);
  - in 7.5-10 pH range yellow coloured square planar diamagnetic mono- and binuclear complexes were obtained with the cooperative deprotonation of three amide nitrogens towards the N-termini in the (N_{Im},$3N^{-}$) coordination modes (*Figure 2.c*).
- There was no evidence for the formation of hydroxo bridged Ni(II) complexes.

- The ε-amino groups of lysyl residues do not take part in the coordination.
- Based on the comparison of the complex stabilities and the CD spectra of the coordination isomers formed we could state that Ni(II) ions show a significant preference for metal binding at H96 residue (which is completely opposite to those reported for Cu(II) ion).

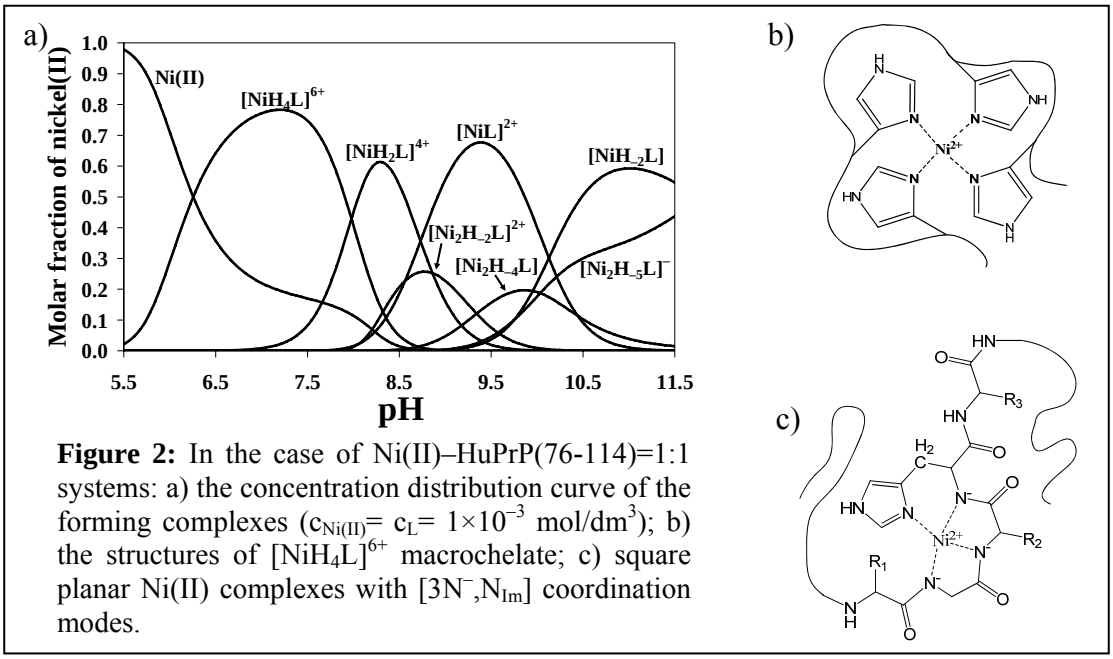

Figure 2: In the case of Ni(II)–HuPrP(76-114)=1:1 systems: a) the concentration distribution curve of the forming complexes ($c_{Ni(II)}$= c_L= 1×10^{-3} mol/dm^3); b) the structures of $[NiH_4L]^{6+}$ macrochelate; c) square planar Ni(II) complexes with [$3N^-$,N_{Im}] coordination modes.

1.2. The study of mixed Ni(II)/Cu(II) metal complexes of prion peptide fragments

Studying the mixed metal Ni(II)/Cu(II) containing systems of the two histidine containing HuPrP(84-114)H85A and HuPrP(84-114)H96A mutant peptide fragments the followings were found:

- In equimolar solution both ligands are able to bind Cu(II) and Ni(II) ions simultaneously.
- With the only involvement of the imidazole nitrogen atoms Cu(II) complexes form in slightly acidic and neutral solution and by increasing the pH the deprotonation and coordination of the amide nitrogen atoms occur resulting in (N_{Im},$2N^-$) and (N_{Im},$3N^-$) coordination modes.
- The interaction with Ni(II) ion starts above pH 8.0 and imidazole and amide nitrogens take part in the coordination.
- In slightly alkaline solution binuclear mixed metal complexes can exist where both metal ions are coordinated by imidazole and amide nitrogen donor atoms.
- The results based on the study of the coordination isomers in the case of HuPrP(84-114)H85A (containing H96 and H111) revealed that the preferred

binding site for Ni(II) ion is H96, while H111 for Cu(II) ion (these are in good agreement with previous findings).

- HuPrP(84-114)H96A binds most of the Ni(II) ions at H111 binding site and Cu(II) ions at H85.
- We can conclude that the Ni(II) ions can not replace the Cu(II) ions, however, they can significantly modify the distribution of Cu(II) among the available metal binding site.

2. Complex formation processes of the model peptides related to the metal binding site of prion protein

In the *second* half of the PhD thesis we modelled the coordination features of prion peptide fragments studying the interaction in Cu(II), Ni(II) and Zn(II) containing systems of histidine containing peptides.

We proved that the amino acid sequence influences greatly the metal ion selectivity and the stability of the complexes follows the Irving-Williams order. Our results strengthen the previous observations that the stability of the metal complexes is:

(1) greatly influenced by the number of imidazole nitrogens (the bigger, the more stable)

(2) increased by the presence of double anchoring agents (NH_2,N_{Im}).

2.1. Metal complexes of one histidine containing model peptides

As the complex formation properties of Ac-GT^{96}HS-NH_2 and Ac-MK^{111}HM-NH_2 have been characterized earlier, we carried out a few additional measurements in order to make comparative analysis. We summarised the results and compared the metal complexes of peptides (GTHS, MKHM, PHAAA) modelling the sequences around the histidines (H111, H96 and $H_{octarepeat}$) from N-terminal domain of prion protein, with the comparison.

- Due to the albumin-like sequence the tetrapeptides with free α-amino group have higher Cu(II) and Ni(II) binding affinity than their N-protected derivatives. It can be explained by the different coordination modes of 4N-complexes:
  - (NH_2,$2N^-$,N_{Im}) in the case of free N-terminus
  - ($3N^-$,N_{Im}) in the case of protected N-terminus
- In the case of Zn(II) ion no amide deprotonation was observed, so reaching its pH range the hydrolysis of the metal ion occurs.

- We obtained the same metal ion selectivity of N-terminally free and protected tetrapeptides like in the case of prion peptide fragments. The Cu(II) ions form more stable complexes with -MKHM- sequences, and Ni(II) ions with -GTHS-.
- According to the DFT calculation we can conclude that Ni(II), forming square planar complexes, is preferentially coordinated to the -GTHS- sequence, while Cu(II), which can form stable penta-coordinated species, has higher affinity for the -MKHM- sequence.
- The pentapeptide models well the complex formation properties of the octarepeat domain. The Cu(II) complexes have lower stability which can easily be explained by the formation of (7,5,5)-membered confused chelate ring system due to the amide deprotonation and coordination toward the C-terminus. The interaction with Ni(II) ions is negligible.

2.2. Metal complexes of two histidine containing model peptides

Joining the two tetrapeptides we wanted to model the two histidines from outside the octarepeat domain (H96 and H111). Therefore the H_2N-MKHMGTHS-NH_2, H_2N-GTHSMKHM-NH_2 and Ac-GTHSMKHM-NH_2 octapeptides were synthesized and studied. All three octapeptides are able to bind two equivalents of Cu(II) or Ni(II) ions, but only in the presence of ligand excess can keep Zn(II) ions in solution.

The octapeptides with free amino terminus: contain two binding sites with two different possible coordination modes; (NH_2,$2N^-$,N_{Im}) close to the N-terminus and ($3N^-$,N_{Im}) at the internal histidine).

- Due to the albumin-like sequence they show enhanced Cu(II) and Ni(II) ion binding affinity.
- In the Cu(II) and Ni(II) systems [$MH_{-1}L$] (=$MH_{-2}LH$) species dominate in wide pH range with (NH_2,$2N^-$,N_{Im}) coordination mode.
- Studies of the coordination isomers show that there is no detectable sequence specifity, the first metal ion (either Cu(II) or Ni(II)) exclusively binds at N-terminus.
- However, according to the comparative analysis of the

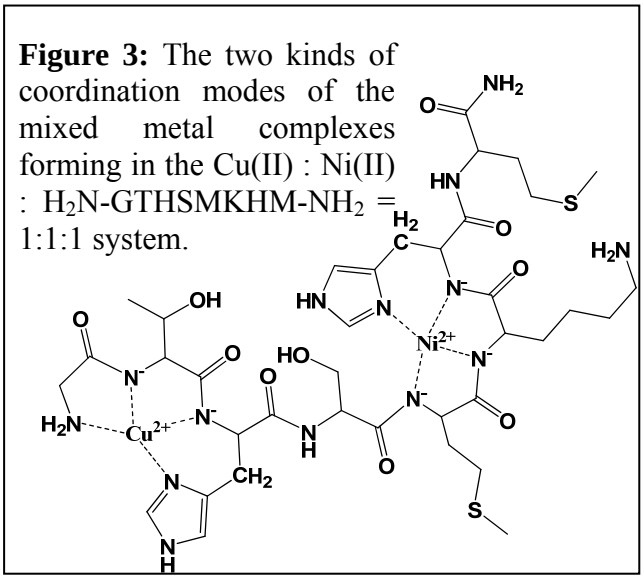

Figure 3: The two kinds of coordination modes of the mixed metal complexes forming in the Cu(II) : Ni(II) : H_2N-GTHSMKHM-NH_2 = 1:1:1 system.

stability the Ni(II) ions form more stable complexes with H_2N-GTHSMKHM-NH_2, while Cu(II) ion with H_2N-MKHMGTHS-NH_2 octapeptide.

- In the mixed Ni(II)/Cu(II) systems as a function of the pH the Cu(II) ions coordinate first occupying the N-terminus, Ni(II) ions go to the remaining place (*Figure 3*).

The octapeptide with protected amino terminus: contains two binding sites with two possible equivalent coordination modes.

- Compared to the free N-terminal derivatives its complex formation processes are slightly shifted to higher pH values.
- The protonated complex [CuHL] predominates between pH 5 and 6 with the involvement of $2N_{Im}$, around pH 7.0 the major species is [$CuH_{-1}L$] as a result of two amide deprotonation and coordination, further deprotonation takes place around pH 8 and [$CuH_{-2}L$] complex forms with ($3N^{-}$,N_{Im}) binding mode. Further proton loss does not effect the coordination sphere. The examination of coordination isomers shows that the Cu(II) ions can be detected at both histidines in the ratio 50:50. Dinuclear complexes are also formed in the presence of excess of Cu(II) ions.
- The octahedral [NiHL] species with $2N_{Im}$ macrochelate structure predominates between pH 6 and 8. Above pH 8 [$NiH_{-2}L$] or [$NiH_{-3}L$] (stoichiometry depending on the protonation stage of lysyl residues) forms with single ($3N^{-}$,N_{Im}) coordination mode and square planar geometry. The study of coordination isomers shows that 90% of Ni(II) ions are bound at -GTHS- sequence. Dinuclear complexes are also formed in the presence of excess of Ni(II) ions.
- The same tendencies were obtained in the Ni(II)/Cu(II) mixed metal system, where the [$NiCuH_{-6}L$] mixed metal complex is almost exclusively formed by pH 11.0 The evaluation of the CD revealed that 90% of Ni(II) ions can be found at -GTHS- and 10% at -MKHM- as well.

2.3. Metal complexes of three histidine containing model peptides

The Ac-PHAAAGTHSMKHM-NH_2 tridecapeptide contains three histidine residues mimicking three metal binding sites from three different regions of the prion protein.

- As it was expected this ligand can bind three equivalents of Cu(II) ions or two Ni(II) ions. All three histidine side chains act as independent metal binding site.
- The first two equivalents of Cu(II) ion coordinate to the sequence modelling histidines from outside octarepeat domain (-GTHS- and -MKHM-) in comparable concentration.
- The first equivalent of Ni(II) ions is bound to the -GTHS- part modelling H96.

- In the Ni(II)/Cu(II) mixed metal system the same tendencies were obtained as previously, most of the Ni(II) ions bound at -GTHS-, while most of the Cu(II) ions coordinate to -MKHM- modelling H111.

3. The study of the Cu(II) complexes of the six histidine containing prion peptide fragment

With the study of the prion peptide fragment containing all the N-terminal binding sites we had the opportunity to investigate the actual binding sites at the same time. Because of the solubility problem we were not able to give the full characterization of its solution equilibrium, but from the spectroscopic studies of the Cu(II) ion containing samples we could concluded the followings.

- The composition of the complexes strongly depends on the pH and the concentration of Cu(II) ion.
- The same coordination preferences exist as found earlier in the case of the prion peptide fragments.
    - At physiological pH the presence of species containing macrochelate is dominant, in the coordination sphere of Cu(II) ion there are only imidazole nitrogens of histidines both from inside and outside of octarepeat
    - Parallel with increasing pH the deprotonation and coordination of amide nitrogens take place.
- The enhanced stability of the macrochelate structure shifts the deprotonation of the amide nitrogens toward higher pH range at low Cu(II) concentration.
- The increase of the Cu(II) concentration of the samples breaks down the macrochelate structure and it facilitates the amide deprotonation in more acidic pH range and it increases the solubility as well.
- Moreover, a binding preference can be observed towards the histidines outside the octarepeat.

V. POSSIBLE APPLICATION OF THE RESULTS

The results obtained in this work are based on basic research study. In the *first* half of the PhD thesis, the stability and the possible structure of the complexes formed in the Ni(II)- and Ni(II)/Cu(II) - prion peptide fragment systems, as well as the order of their Ni(II) binding affinity were determined. In the *second* part of the work, we characterized the complex formation properties of model peptides related to the metal binding site of prion protein in the presence of Cu(II), Ni(II) and Zn(II) ions. In the *third* phase of this study a prion peptide fragments all the N-terminal binding sites we had the opportunity to investigate the actual binding sites at the same time. Our studies took us closer to the better understanding of the differences in metal ion preferences in the case of Cu(II), Ni(II) and Zn(II) ions.

These studies support the high Cu(II) ion affinity of prion peptide fragments and the Ni(II) ion can be effectively applied as a structural model for the comparisons. In the case of Zn(II) ion binding, however, only slight interaction can be detected. This observation strengthens the assumption further, that if the metal ions take part in the biological function of the prion protein, the Cu(II) ion has a primary role in this field.

Our results contribute to the better understanding of the factors influencing the metal ion binding of the proteins related to the neurodegenerative disorders (*e.g*. Alzheimer disease, Parkinson disease, prion disease). These can provide valuable information for biological investigations aimed to determine the cause of neurodegenerative diseases. They may also provide information for planning new and more efficient medicines and therapies for the treatment of patients suffering from neurodegenerative disorders.

VI. PUBLICATIONS

Published articles connected to the thesis

1. Ildikó Turi, Daniele Sanna, Eugenio Garribba, Imre Sóvágó, **Studies on the comparison of the metal ion binding affinities of model peptides related to human prion protein**, *Polyhedron,* 62 (2013) 7-17.
   Impact factor: 1.813 (2012)
2. Viktória Jószai, Ildikó Turi, Csilla Kállay, Giuseppe Pappalardo, Giuseppe Di Natale, Enrico Rizzarelli, Imre Sóvágó: **Mixed Metal Copper(II)-Nickel(II) and Copper(II)-Zinc(II) Complexes of Multihistidine Peptide Fragments of Human Prion Protein,** *Journal of Inorganic Biochemistry*, 112 (2012) 17–24.
   Independent citation: 1
   Impact factor: 3.354 (2012)
3. Ildikó Turi, Csilla Kállay, Dorina Szikszai, Giuseppe Pappalardo, Giuseppe Di Natale, Paolo De Bona, Enrico Rizzarelli, Imre Sóvágó, **Nickel(II) Complexes of the Multihistidine Peptide Fragments of Human Prion Protein,** *Journal of Inorganic Biochemistry,* 104 (2010) 885-891.
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   Impact factor: 3.317 (2010)
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   Independent citation: 3
   Impact factor: 1.356 (2011)

Not published articles connected to the thesis

1. Sarolta Timári, Ildikó Turi, Katain Várnagy, Daniele Sanna, Eugenio Garribba, Imre Sóvágó, **Studies on the formation of coordination isomers in the copper(II) and nickel(II) complexes of peptides containing histidyl residues** (ready for publication)
2. Ildikó Turi, Imre Sóvágó, **Studies on the binding preferences of copper(II) and nickel(II) ions to the histidyl sites of oligopeptides** (ready for publication)

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1. Csilla Kállay, Ildikó Turi, Sarolta Timári, Zoltán Nagy, Daniele Sanna, Giuseppe Pappalardo, Paolo de Bona, Enrico Rizzarelli, Imre Sóvágó, **The Effect of Point Mutations on Copper(II) Complexes With Peptide Fragments Encompassing the 106–114 Region of Human Prion Protein**, in *Metal ions in Neurological Systems*, W. Linert and H. Kozlowski (eds.), © Springer-Verlag Wien 2012, (DOI 10.1007/978-3-7091-1001-0_16) p.189-197.

Proceedings connected to the thesis

1. I. Sóvágó, I. Turi, Á. Grenács: Factors influencing the formation of mixed metal complexes of the peptide fragments of prion protein, *11th European Biological Inorganic Chemistry Conference*, 12-16 September 2012, Granada, Spain, MEDIMOND International Proceedings, p. 31-36.
2. Turi Ildikó, Sóvágó Imre: Multihisztidin peptidek vegyes fémkomplexeinek komplexképződését befolyásoló tényezők vizsgálata, *XXXIII. Kémiai Előadói Napok*, 2010, JATEPress, Szeged (ISBN 978-963-315302037).

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1. I. Turi, I Sóvágó: **Metal Complexes of Model Peptides Related to the Metal Binding Site of Prion Protein**, *12th International Symposium on Biochemistry*, 28 August – 1 September 2013, Wroclaw (Book of Abstract, P-40)
2. S. Timári, I. Turi, K. Várnagy, I. Sóvágó: **Metal binding properties of prion protein mutant peptides**, *12th International Symposium on Biochemistry*, 28 August – 1 September 2013., Wroclaw (Book of Abstract, P-54)
3. I. Turi, I Sóvágó: **Metal Complexes of Model Peptides Related to the Metal Binding Site of Prion Protein**, *16th International Conference on Bioinorganic Chemistry*, 22-26. July 2013., Grenoble
4. I. Turi, I. Sóvágó: **Mixed Transition Metal Complexes of Model Peptides Related to the Metal Binding Site of Prion Protein**, *International Symposium on Metal Complexes*, 18-22. June 2012., Lisszabon (Acta of international Symposia on metal complexes, Vol. 2., ISSN: 2239-2459, 2012, p.163-164)
5. I. Turi, I. Sóvágó: **Copper(II) and Nickel(II) Complexes of Model Peptides Related to the Metal Binding Site of Prion Protein,** *11th International Symposium on Applied Bioinorganic Chemistry*, 2-5. December 2011., Barcelona (Book of Abstract, P-156)
6. V. Jószai, I. Turi, I. Sóvágó, G. Di Natale, G. Pappalardo, E. Rizzarelli: **Mixed Transition Metal Complexes of Histidine Containing Peptide Fragments of Prion Protein and Their Mutants**, *4th European Conference on Chemistry for Life Sciences (4ECCLS)*, August 31- September 3 2011., Budapest (Book of Abstract, p.288)
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