

THESIS OF DOCTORAL (PH.D.) DISSERTATION

**Copper(II) and (η^5 -Cp*)rhodium(III) complexes of some
imidazole and pyridine containing ligands**

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1. Introduction and objectives

The overall goal of my PhD thesis was to characterize (partly design and synthesize) some amide-containing ligands and to study their metal complexes in order to answer some practical problems. The thesis covers three, at first glance, different topics (see below), which are, however, interconnected by (i) the amide-group, which is a common structural element of the studied ligands, (ii) the similar coordination chemical properties of imidazole and pyridine rings, and (iii) the studied metal ions (Cu(II) and $(\eta^5\text{-Cp}^*)\text{Rh(III)}$).

- (i) Alzheimer's disease (AD) is the most common type of dementia, its main hallmarks include cognitive decline, memory loss, and behavioral problems. Alzheimer's disease (AD) affects nearly 50 millions of people worldwide, therefore there is an urgent need for an effective treatment. Amyloid- β ($\text{A}\beta$) peptides are well-known for their potential pathogenic role in the onset of Alzheimer's disease (AD), which is largely associated by the aggregation of these peptides to form oligomers, fibrils, and plaques. The deposition of aggregated amyloid- β ($\text{A}\beta$) peptides results in accumulation of Cu in senile plaques, however the tissues surrounding these senile plaques and *e.g.* in the frontal cortex have significantly lower levels of Cu as compared to the normal age-matched control patients. Consequently, copper accumulation in plaques results in high levels of oxidative stress and abnormal metal homeostasis. To date there is no effective cure for Alzheimer's disease, the only available treatments just alleviating the initial pathological symptoms. One potential cure for Alzheimer's disease is to target copper(II) ions to inhibit both aggregation and oxidative stress. However, a general chelation therapy which may aid in the elimination of Cu ion would be ineffective here, clearly a metallochaperon-like function, binding and redistribution is required. Therefore, the goal of this sub-project was to design artificial metallophores for Alzheimer's disease (AD) therapy, which are specific for Cu(II) even in the presence of excess Zn(II), their copper(II) complexes do not produce ROS, are able to remove Cu(II) ion from its $\text{A}\beta$ peptide complexes and would be able to hand over copper(II) to the membrane transporter CTR1. To this end, we synthesized and studied the ligands (pyridin-2-ylmethyl)picolinamide (PMPA, L^1) and N-(pyridin-2-ylmethyl)-2-((pyridin-2-ylmethyl)amino)acetamide (PDMGA, L^2) (**Figure 1**).

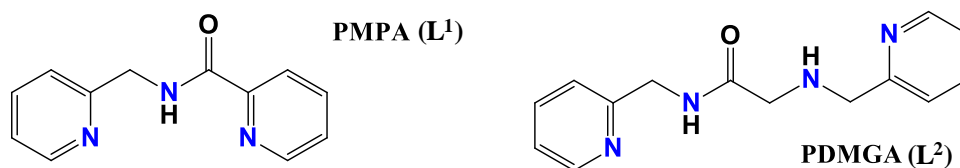


Figure 1. Structure of the ligands studied as artificial metallophores

(ii) Lignocellulose is the most abundant biopolymer on the earth, but also highly recalcitrant due to its insoluble crystalline composite structure and the complex network of lignin, which hinders the ability of carbohydrate acting enzymes to hydrolyse it. Therefore, the conversion of lignocellulose into fuels and other useful chemicals is one of today's major biotechnological challenges. The discovery of copper containing lytic polysaccharide mono-oxygenases (LPMOs) provides a promising opportunity in biomass conversion, since these enzymes cleave the glycosidic bonds via the oxidation of the C1- or C4 atom making the substrate tractable to hydrolases. The catalytic copper in the active centres of LPMOs is surrounded by a surprisingly simple coordination environment, the so-called 'His-brace' motif (Figure 2), which is believed to play an important role in the efficiency of LPMOs. Despite the very extensive studies on the native enzymes, there are several hypotheses in the literature about the exact enzymatic mechanism, the catalytically active form of the copper center, as well as about the role of the active center environment, *e.g.* the function of tyrosine subunit close to the active site. Beside the biochemical investigations, small molecular models may also provide valuable information on the functioning of metalloenzymes. Nevertheless, only a few papers report studies on functional models of LPMOs. Although, some of the studied ligands contain imidazole ring(s), none of them are peptide derivatives. Therefore, the aim of this sub-project was to design appropriate His-peptides that can closely mimic the LPMO active centres, in order to uncover some valuable information on the roles of His-brace structural motif, and the axial Tyr residue, unexplored to date by model compounds. To this end, I synthesized and studied the thermodynamic stability, structure and reactivity of Cu(II) complexes of two histidine containing peptides (**Figure 2**), namely HPH-NH₂ (L³) and HPHPY-NH₂ (L⁴) by means of pH potentiometry, cyclic voltammetry, UV-Vis, CD, EPR spectroscopy and kinetic investigations. Proline

subunits are used to separate the coordination sites, in order to prevent the copper(II) promoted amide deprotonation and to provide relatively rigid structure for the ligands.

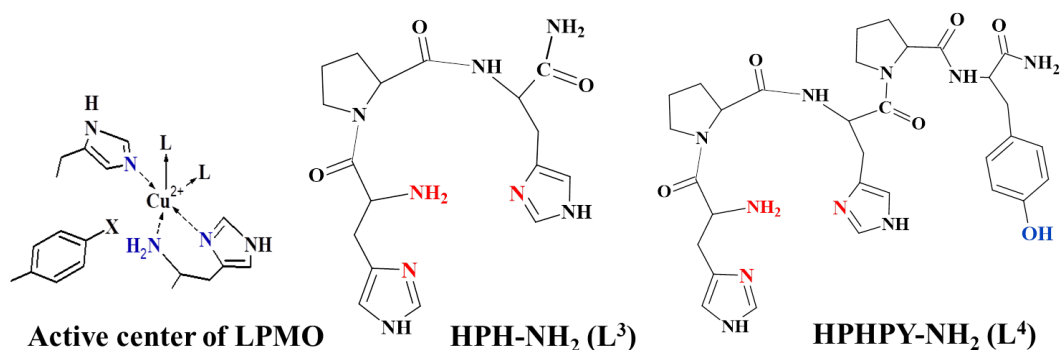


Figure 2. Schematic structure of the LPMO's active centre (X = H or OH, L = H₂O or OH⁻) and the studied model peptides.

- (I) Recently, half-sandwich Rh(III) complexes have emerged as intriguing potential anticancer, antimicrobial and antivirucidal agents. These compounds can act using both DNA or enzymes as target, but their molecular mechanisms of action have not yet been fully elucidated. On the other hand, even DNA targeting compounds may interact with peptides/proteins during drug-transport, e.g. may undergo ligand substitution reactions in biological fluids before reaching their site of action, which may have fundamental effects on their biodistribution, biotransformation and pharmacokinetic properties. Consequently, the interaction of these complexes with endogenous peptides/proteins is of considerable interest not only because of the exploration of feasible modes of action, but explanation of side effects and pharmacokinetic behaviour may become possible as well. However, to our knowledge, no complete solution thermodynamic study on the interaction of (η^5 -Cp*)Rh(III) cation or its potential medicinal complexes with amino acids or peptides are available in the literature. Therefore, in order to understand the thermodynamic factors governing the binding of half-sandwich Rh(III) cation and its complexes to histidine-containing peptides and proteins, I planned to study the interaction of (η^5 -Cp*)Rh(III) cation with imidazole derivatives, synthetic peptides containing histidine in different positions in the sequence (Figure 3), as well as with biogenic His-peptides (Figure 4). In addition, we also studied some (η^5 -Cp*)Rh(III)-A-B ternary systems (where A = 2,2'-bipyridyl (bpy) or ethylenediamine (en); B = the studied peptides), in order to mimic the interaction of the (η^5 -

Cp*)Rh(III)-based potentially anticancer or drug delivery agents with biogenic peptides and proteins.

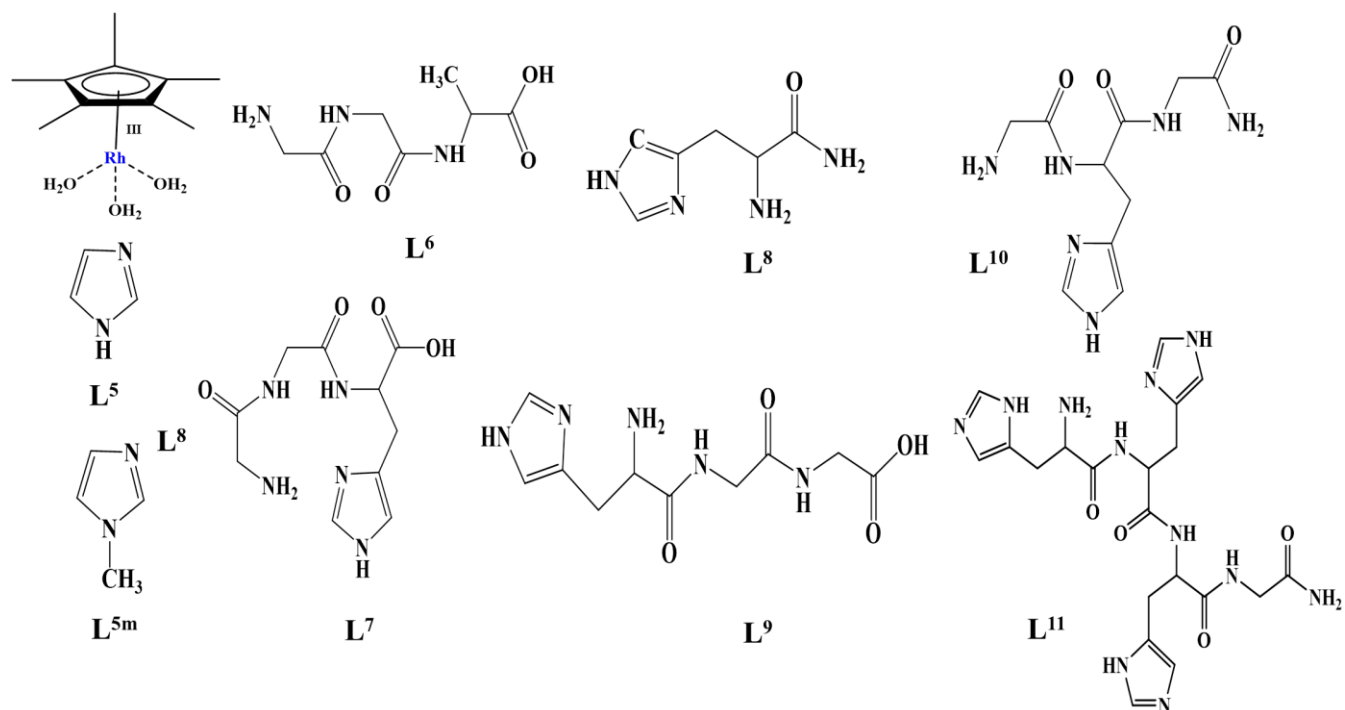


Figure 3. Schematic structures of $(\eta^5\text{-Cp}^*)\text{Rh(III)}$ cation and the studied synthetic peptides

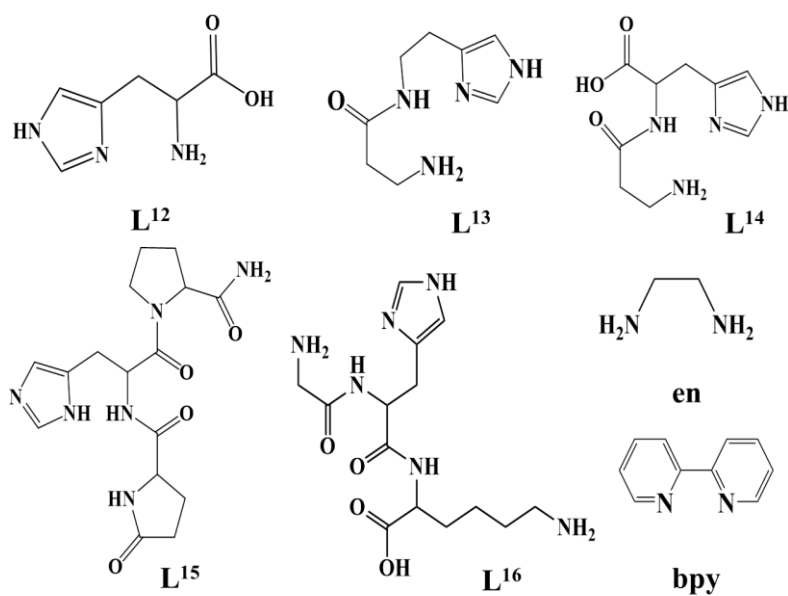


Figure 4. Schematic structures of the studied biogenic peptides, as well as en and bpy.

2. Experimental techniques and methods

The histidine peptides GHG-NH₂, HHHG-NH₂, HPH-NH₂ and HPHPY-NH₂ were prepared in under the guidance of Dr. Lívía Fülöp (University of Szeged, Faculty of Medicine, Institute of Medical Chemistry) using solid phase peptide synthesis (SPPS). While, PMPA and PDMGA were prepared and purified in the preparative laboratories of the Department of Inorganic and Analytical Chemistry, University of Szeged.

Solution equilibrium study

In order to investigate the (de)protonation processes of the ligands and to determine the formation constants of the complexes formed, pH potentiometric titrations were carried out. The measurements were performed in aqueous media, at 0.2 M KCl ionic strength and 25 °C, at different metal-to-ligand ratios. pH values were measured with a combined glass electrode, and a computer-controlled Metrohm 665 Dosimat automatic burette was used for KOH solution dosage after reaching chemical equilibrium in each points. Calculations were performed with HYPERQUAD and PSEQUAD software.

Spectroscopic methods

Several different spectroscopic techniques (UV-Vis, CD, EPR, NMR, MS) were used to confirm and to collect additional information on the speciation obtained by pH-potentiometry, and to obtain structural information (coordinating group, coordination geometry, solution structure) on studied complexes.

Besides, the pH-dependent ***UV-visible (UV-Vis)*** and ***circular dichroism (CD)*** spectra were processed together with potentiometric data in order to obtain individual molar UV-Vis and CD spectra of the main complexes.

The pH-dependent ***Electron paramagnetic resonance (EPR)*** spectra, beside the estimation of geometry and number of N-donor groups in copper(II) complexes; were also used to obtain independent data set of the complex formation constants.

NMR spectroscopy is especially useful to study diamagnetic compounds, such as the (η^5 -Cp*)Rh(III) complexes, with low spin d⁶ electronic configuration. Beside the pH-dependent ¹H NMR spectra, we also recorded two-dimensional NMR spectra (¹H-¹H TOCSY - total correlation spectroscopy, ¹H-¹H NOESY (Nuclear Overhauser Effect Spectroscopy) and EXSY (EXchange Spectroscopy)) in order to confirm the assignment of NMR signals, to gain some information on the 3D structure and on the identity of isomers formed in the solution.

Mass spectrometric measurements (ESI-MS) were performed to confirm the identity of the synthesized ligands and the presence of different metal complexes in solution at various pH and metal-to-ligand ratios.

Fluorescence spectroscopy was used to study the interaction of amyloid β 1-16 peptide with copper(II) cation. In this case, the fluorescence spectra of the tyrosine residue present in amyloid β 1-16 was studied, since the copper(II)-peptide interaction strongly affects the intensity of its emission spectrum.

Kinetic measurements

The LPMO-like activity of copper(II)-HPH-NH₂ and -HPPHY-NH₂ complexes was studied by spectrophotometry using *p*-nitrophenyl- β -D-glucopyranoside (PNPG) as substrate in presence or absence of H₂O₂, by monitoring the formation of *p*-nitrophenolate anion (ϵ (400 nm) = 18900 M⁻¹cm⁻¹, pK = 6.98(2)) during the oxidation process. Enzyme-kinetic parameters (k_{cat} and K_M), used for characterization of LPMO like activity, were calculated based on the Michaelis-Menten equation, using non-linear regression of the data.

Electrochemical studies

Cyclic voltammetry was used to study the redox properties of copper(II)-HPH-NH₂ and -HPPHY-NH₂ complexes in the absence and presence of H₂O₂ both pH 7.4 and 10.5.

3. New scientific results

1. **We demonstrated, that both L^1 and L^2 (Fig. 1) specifically bind copper(II), even in presence of large Zinc(II) excess, are able to remove copper(II) from its $A\beta_{1-16}$ complex, their copper(II) complexes are not redox active, but only the tridentate L^1 has lower conditional binding constant than the copper transporter human CTR1. Consequently, only L^1 may behave as a potential artificial metallophore [2]**
 - 1.1. The comparative evaluation of pH-potentiometric, UV-Vis and EPR spectroscopic data indicated that in mM concentration range, *mono*- and *bis*-complexes are formed in both systems. In excess of the tridentate L^1 , both metal ions form 6N coordinated bis-complexes, with $\{2N_{pyr}, 2N^-\}$ coordination in the equatorial plane. This is somewhat surprising, since the amide deprotonation in zinc complexes is a rare phenomenon, while in case of copper(II) the Jahn-Teller distortion generally prevents the 6N coordination. In case of the tetradentate ligand 6N coordination occurs only for zinc in its *bis*-complexes which is the main species at ligand excess and at neutral pH. In case of copper mostly *mono*-complexes are formed, of which the $\{N_{pyr}, N^-, NH, N_{pyr}\}$ coordinated $[CuLH_1]^+$ complex predominates in a wide pH range.
 - 1.2. In μM concentration range, the formation of bis-complexes is completely diminished for both ligands, even at ligand excess. The pM ($= -\log([M^{2+}]_{free})$) values calculated at pH 7.4 indicate that the metal binding ability of the tetradentate L^2 is three orders of magnitude higher than that of the tridentate L^1 . Furthermore, both ligands bind copper seven orders of magnitude stronger than zinc, consequently these ligands are specific for copper(II) even in presence of excess zinc.
 - 1.3. Both ligands are able to remove copper(II) from its $A\beta_{1-16}$ peptide complex (although L^2 is somewhat more efficient), and are able to efficiently inhibit the ROS production generated by copper(II)- $A\beta_{1-16}$ and - $A\beta_{1-40}$ complexes in presence of ascorbic acid.
 - 1.4. Only the conditional stability constant of the copper(II)- L^1 complexes falls between the corresponding values of $A\beta$ and hCTR1 (the corresponding conditional stability constants are as follows: $\log K'_{CuA\beta} \sim 10.2 < \log K'_{CuL^1} = 11.5 < \log K'_{CuhCTR1} = 13.1 < \log K'_{CuL^1} = 14.0$). Consequently, only the tridentate PMPA has the properties that are essential to behave as a potential artificial metallophore, *i.e.* able to remove Cu(II) from the redox active Cu(II)-

A β species, its Cu(II) complex is redox inactive, and has lower Cu(II) binding affinity as the membrane transporter hCTR1.

2. We proved, that the proline units within the sequences of HPH-NH₂ (L³) and HPHPY-NH₂ (L⁴) peptides (Fig. 2) efficiently prevent the copper(II) promoted amide deprotonation, and consequently above pH 5, the complex formation processes in the Cu(II)-L³ and -L⁴ equimolar systems are fundamentally different from all known Cu(II)-HXH(YZ) (X \neq P) peptide systems [3].

2.1. The comparative evaluation of pH-potentiometric, UV-Vis, CD and EPR spectroscopic data indicated the formation of *mono*- and *bis*-complexes up to pH 5, which are typical for copper(II) complexes of peptides with non-protected N-terminal HXH- sequences. Among them only the CuL³ and CuHL⁴ complexes deserve special mention, since they have similar {NH₂, 2 \times N_{im}} coordination mode to the His-brace motif in LPMOs' active centres. However, in equimolar solutions and above pH 5 the proline residues prevent the formation of ATCUN-like {NH₂, 2N⁻, N_{im}} coordinated fused chelates.

2.2. Instead, in our systems imidazolato-bridged Cu₂H₋₁(L³)₂ and Cu₂H(L⁴)₂ dimer complexes are dominant between pH 6-8, which show antiferromagnetic interactions between the copper(II) centres located 5-7 Å apart from each other. At higher pH two further deprotonations were observed in both equimolar systems. The spectroscopic data indicate, that during the process Cu₂HL⁴₂ = Cu₂L⁴₂ + H⁺ a phenolate coordination takes place, while the other deprotonations are related to the formation of a metal-bound hydroxide ion. The rather positive formal redox potentials of these complexes show stabilized Cu(I) oxidation state compared to other peptide complexes, and are close to the range generally observed for LPMO enzymes.

3. We proved, that the dimer complexes formed in the Cu(II)-L³ and -L⁴ systems are relevant functional models of LPMOs, and their action was proven truly catalytic even at neutral pH. The oxidation proceeds via mononuclear copper(II)-(hydro)peroxo complex, which is reduced at high H₂O₂ excess, allowing the formation of the catalytically active Cu(II)-oxyl species [3].

3.1. The initial rates of PNPG oxidation show saturation kinetics with increasing concentrations of both PNPG and H₂O₂, indicating fast pre-equilibrium between the complex and substrate, as well as co-substrate before the rate determining redox process. The Michaelis-Menten

constants obtained at pH 7.4 are the first values reported in the literature. At pH 10.5 the k_{cat} values determined by us are similar to literature data, but the Michaelis constants (K_M) indicate stronger interaction with the substrate, and especially with the co-substrate H_2O_2 . More interestingly, our complexes present at pH 7.4 bind the substrate PNPG 10-20-fold more strongly than those at higher pH.

3.2. The detailed UV-Vis and EPR study on the interaction of dimer complexes with H_2O_2 , in the absence of PNPG, indicated the formation of mononuclear end-on Cu(II)-OOH and partly 1,2-peroxodicopper(II) complexes in cases of both ligands. The cyclic voltammograms of these peroxo species indicated that copper remains in its +2 oxidation state. The mononuclear Cu-OOH species are surprisingly stable (for 1-2 hours) at low, but decomposes rapidly at high H_2O_2 excess, resulting the formation of Cu(I) species and high amount of O_2 , *i.e.* catalytic disproportionation of H_2O_2 by the Cu(II)/Cu(I) couple takes place.

3.3. In simultaneous presence of PNPG and H_2O_2 no dioxygen bubbles could be visually observed even at 200-fold excess of H_2O_2 and after longer reaction time. Although, after 1-2 turnover the initial Cu(II) completely reduced to Cu(I) , the catalytic cycle continues to proceed. Based on these (and some additional) observations, we were the first in the literature able to propose a complete catalytic mechanism for model complexes mimicking LPMO (Fig. 5): the Cu(I) species produced at high excess of H_2O_2 , in presence of the substrate PNPG, enters into the catalytic cycle for PNPG oxidation by forming the catalytically active Cu(II)-oxyl species, which performs the H-atom abstraction from the substrate.

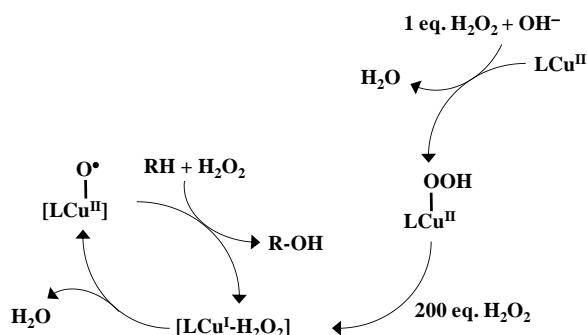


Figure 5 Supposed reaction pathway of PNPG (simplified as RH) oxidation by the Cu(II) -peptide complexes.

4. **We proved, that the (η^5 -Cp*)Rh(III) cation is able to induce the deprotonation of amide nitrogen well below pH 7, the presence histidine units in the peptides results in 2-6 orders of magnitudes stability increase, the stability of (η^5 -Cp*)Rh(III) complexes of histidine containing peptides strongly depends on the position of His unit(s) within the peptide sequence, but this dependency is different from that has already been identified for copper(II) complexes [1].**
- 4.1. Our detailed pH-potentiometric, NMR and ESI-MS study on the (η^5 -Cp*)Rh(III) complexes of ligands **L⁵-L¹⁶** (Figs. 3 and 4) indicated that the pKs of Rh(III) induced amide deprotonation are between 3.2-7.0, depending on the additional donor groups present in the peptides.
- 4.2. The observed order (η^5 -Cp*)Rh(III) sequestering ability of monohistidine peptides is as follows: XYH < HXY < XHY. Although, the ATCUN-like GGH is a very strong Cu(II) binder, it forms the least stable (η^5 -Cp*)Rh(III) complexes among the His-peptides, because its tetradentate in-plane coordination mode does not fit to the three available facial binding sites of Rh(III). HGG (**L⁹**), similarly to histidine-amide (**L⁸**), provide tridentate facial {NH₂,N_{im},N⁻} coordination, therefore these ligands have considerably higher (η^5 -Cp*)Rh(III) binding affinity. However, GHG-NH₂ (**L¹⁰**) and GHK (**L¹⁶**) are even stronger (η^5 -Cp*)Rh(III) binder. This is somewhat surprising considering that these ligands offer a meridional {NH₂,N⁻,N³_{im}} binding mode, while (η^5 -Cp*)Rh(III) prefers a facial one.
- 4.3. Although, carinine (**L¹³**) and carnosine (**L¹⁴**) provide similar {NH₂,N⁻,N³_{im}} binding mode as GHG-NH₂ (**L¹⁰**) and GHK (**L¹⁶**), the higher the size of their fused chelate rings results in a considerably smaller (η^5 -Cp*)Rh(III) binding ability. TRH (**L¹⁵**) also contains histidine in the second position, like GHG (**L¹⁰**) and GHK (**L¹⁶**), however no terminal amino group is present in this molecule. The ({N³_{im},N⁻,N⁻} coordination observed at neutral pH requires the simultaneous deprotonation of two amide nitrogens, which results in a low binding ability. On the other hand, this example proves that interchain histidine is a suitable anchoring group for amide deprotonation promoted by the (η^5 -Cp*)Rh(III) cation. Interestingly, amide coordination was not observed for the multihistidine peptide HHHG.NH₂ (**L¹¹**). Instead, a highly stable {NH₂,N_{im},N_{im}} coordinated species is dominant in the neutral pH. At pH 7.4, the (η^5 -Cp*)Rh(III) binding ability of histidine (**L¹²**, {NH₂,N_{im},COO⁻} coordination), histidine-amide (**L⁸**) and HGG (**L⁹**) ({NH₂,N_{im},N⁻} coordination) and HHHG-NH₂ (**L¹¹**) are

close to each other, thus the histamine-like $\{\text{NH}_2, \text{N}_{\text{im}}\}$ binding mode complemented by either carboxylate, amide or imidazole results in roughly similar thermodynamic stability.

5. We demonstrated, that histidine containing biogenic peptides or proteins with accessible His units may significantly influence the biospeciation of potentially therapeutic half-sandwich rhodium complexes: (i) the $(\eta^5\text{-Cp}^*)\text{Rh(III)}$ cation is able to replace Cu(II) from its complexes formed with endogenous ligands, (ii) His-peptides can efficiently compete with the bidentate ligands present in $(\eta^5\text{-Cp}^*)\text{Rh(III)}$ -based potentially therapeutic complexes [1].

- 5.1. Among the studied peptides $\text{L}^6\text{-L}^{16}$ (Figs. 3 and 4) there are several exceptionally strong copper(II) binder (*e.g.* L^7 , L^{10} , L^{11} , L^{16}), and the physiological effect some of the studied biogenic molecules is strongly related to their copper(II) binding properties (L^{12} , L^{13} , L^{14} , L^{16}). Nevertheless, our simulations for the different $(\eta^5\text{-Cp}^*)\text{Rh(III)}$ -Cu(II)-peptide 1/1/1 ternary systems clearly show that $(\eta^5\text{-Cp}^*)\text{Rh(III)}$ cation has very high affinity towards these peptides, in most cases it is greater than that of the well-known peptide-binder copper(II). The only exceptions are the peptides containing the ATCUN motif (XYH), namely GGH-NH₂ (L^7) and HHHG-NH₂ (L^{11}). But even in these cases, $(\eta^5\text{-Cp}^*)\text{Rh(III)}$ -peptide complexes dominate in the solutions up to pH 6, and only above this pH becomes the formation of copper(II) complexes more favoured.
- 5.2. In order to to mimic the interaction of the $(\eta^5\text{-Cp}^*)\text{Rh(III)}$ -based potentially anticancer agents with peptides and proteins present in biological fluids, we also studied the $(\eta^5\text{-Cp}^*)\text{Rh(III)}$ -A-B ternary systems (where A = 2,2'-bipyridyl (bpy) or ethylene-diamine (en); B = $\text{L}^6\text{-L}^{16}$). The $(\eta^5\text{-Cp}^*)\text{-bpy}$ and -en complexes were used as two simple representatives of Rh-based potentially anticancer agents. Our ¹H-NMR data indicated that the weakest binder GGA (L^6) does not interact, but all histidine derivatives form ternary species with the $(\eta^5\text{-Cp}^*)\text{Rh(III)}$ -en/bpy complexes. Moreover, in the cases of ligands L^8 , L^9 , L^{10} , L^{11} , L^{12} , L^{15} and L^{16} even the signals of binary peptide complexes appeared on the NMR spectra, indicating that these peptides are able to displace ethylene-diamine or bipyridyl from the coordination sphere of $(\eta^5\text{-Cp}^*)\text{Rh(III)}$. These behaviours may have important implication on the biospeciation/biotransformation of $(\eta^5\text{-Cp}^*)\text{Rh(III)}$ -based potential metallodrugs in human bodies.

4. Potential applications

The aims of my PhD thesis were to explore the solution thermodynamic properties of some systems with potential medicinal interest, and to develop new peptide-based chemical models for lytic polysaccharide monooxygenases. Our original results are expected to attract attention mainly in the field of basic research. Nevertheless, we believe that our findings will assist in the future design of (i) new artificial copper-chaperons with potential applications in AD therapy, (ii) new molecular catalysts as robust alternatives of LPMOs for practical purposes, as well as (iii) may help to understand the biodistribution, biotransformation and pharmacokinetic properties of (η^5 -Cp*)Rh(III)-based potential metallodrugs.

5. Scientific publications

Identification number in the Hungarian Collection of Scientific Publications (MTMT):
10078296

Publications related to the dissertation:

1. **Azza A. Hassoon**, Attila Szorcsik, Ferenc Bogár, Ibolya Z. Papp, Livia Fülöp, Zoltán Kele, Tamás Gajda, The interaction of half-sandwich (η^5 -Cp*)Rh(III) cation with histidine containing peptides and their ternary species with (N,N) bidentate ligands, J. Inorg. Biochem., 216 (2021) 111330.
IF= 4.336
2. Tamás Jakusch, **Azza A. Hassoon**, Tamás Kiss, Characterization of copper(II) specific pyridine containing ligands: Potential metallophores for Alzheimer's disease therapy, J. Inorg. Biochem., 228 (2021) 111692
IF = 4.336
3. **Azza A. Hassoon**, Attila Szorcsik, Livia Fülöp, Ibolya Zita Papp, Nóra May, Tamás Gajda, Peptide-based chemical models for lytic polysaccharide monooxygenases, Dalton Trans., 51 (2022) 17241-17254.
IF = 4.569

$$\Sigma IF = 13.241$$

Oral presentations and posters related to the dissertation:

1. **Azza A. Hassoon**, Attila Szorcsik, Ibolya Zita Papp, Livia Fülöp, Zoltán Kele and Tamás Gajda: Interaction of half-Sandwich (Cp*)Rh(III) cation with Histidine-containing peptides and their ternary species with (N,N) bidentate ligands, 54th Colloquium on Complex Chemistry and Meeting of the Coordination Chemistry Working Group of the Hungarian Academy of Sciences, 26-27 May 2021. online, Hungary. (Oral lecture)
2. **Hassoon Azza**, Szorcsik Attila, Bogár Ferenc, Zita Papp Ibolya, Fülöp Livia, Kele Zoltán, Gajda Tamás: Interaction of Half-Sandwich (Cp*)Rh(III) Cation with Histidine-Containing Peptides and Their Ternary Species with (N,N) Bidentate

Ligands, Spring Wind Conference, 28-30 May 2021. online, University of Miskolc, Hungary. **(Oral lecture)**

3. **Azza A. HASSOON**, Abdelrahman AHMED, Péter BORSOS, Attila SZORCSIK, Lívía FÜLÖP, Nóra MAY, Tamás GAJDA : Copper(II) complexes of HPH-NH and HPHPY-NH as structural and functional models of lytic polysaccharide monooxygenases, International Symposium Thermodynamics of Metal Complexes, ISMEC, 16-18 June 2021, online, Białystok, Poland. **(Oral lecture)**
4. **Azza A. HASSOON**, Attila SZORCSIK, Lívía FÜLÖP, Nóra MAY, Tamás GAJDA, International Conference on Metal-Binding Peptides: Methodologies and Applications MBP, Copper complexes as bioinspired models for lytic polysaccharide monooxygenases (LPMO), 5-8 July 2022, Nancy, France. **(Oral lecture)**
5. **Azza Hassoon** and Tamás Gajda, RSC Inorganic Reaction Mechanisms Discussion Group Conference (RSC_IRMG), Pharmacokinetics of the interaction of half-sandwich (Cp*)Rh(III) cation with methionine-containing peptides and their ternary species with (N,N) bidentate ligands, 13-14 Sep 2022, online, London, UK. **(Oral lecture)**
6. **Azza A. HASSOON**, Attila SZORCSIK, Lívía FÜLÖP, Nóra MAY, Tamás GAJDA, Anglo German Inorganic Chemistry conference (AGICHEM), 9-10 September 2021, online, London, UK. **(poster)**
7. **Azza A. HASSOON**, Attila SZORCSIK, Lívía FÜLÖP, Nóra MAY, Tamás GAJDA: Symposium of the Spanish Royal Society of Chemistry (RSEQ), Copper(II) complexes of HPH-NH and HPHPY-NH as structural and functional models of lytic polysaccharide monooxygenases, International Symposium Thermodynamics of Metal Complexes, 9-10 September 2021, online, Spain. **(poster)**
8. **Azza A. HASSOON**, Nóra MAY, Tamás GAJDA, 2022 #RSCPoster Twitter Conference, Copper complexes as bioinspired models for lytic polysaccharide monooxygenases (LPMO), 1-2 March 2022, online, London, UK **(poster)**
9. **Azza A. HASSOON**, Attila SZORCSIK, Tamás GAJDA, Chemical biology symposium 2022, CRITICAL FACTORS AFFECTING THE INTERACTION OF HALF-SANDWICH (Cp*)Rh(III) CATION WITH HISTIDINE AND METHIONINE PEPTIDES, 9 May 2022, online, London, UK. **(poster)**