UNIVERSITY OF BUCHAREST
FACULTY OF CHEMISTRY
DOCTORAL SCHOOL IN CHEMISTRY

Ph.D. THESIS SUMMARY

COPPER (II) COMPLEXES WITH AZOMETHINE LIGANDS DERIVED FROM PYRIDOXAL AND FROM 4-AMINOANTIPYRINE

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TABLE OF CONTENTS[1]

PART I

CURRENT STATUS OF THE THESIS THEME

[1] *Numbering of figures, tables and bibliographic references is the one from the Ph.D thesis*

PART II

ORIGINAL CONTRIBUTIONS

The Ph.D thesis „*Copper (II) complexes with azomethine ligands derived from pyridoxal and from 4-aminoantipyrine*" describes aspects from the coordinative chemistry of the Cu(II) complexes with condensation compounds of pyridoxal, respectively 4-aminoantipyrine as ligands. The selecion of these compounds as key elements of the research strategy is due to the structural characteristics and specific biological properties.

The purpose of the thesis is the synthesis and characterization of complexes with azomethine ligands derived from vitamin B_6 (pyridoxal), respectively 4-aminoantipyrine.

The objectives are:

(i) synthesis and structural characterization of the ligands derived from the two biological-active compounds;

(ii) synthesis of complexes derived from these ligands;

(iii) structural and thermal characterization of complexes.

The Ph.D thesis targets three categories of compounds: Cu(II) complexes with pyridoxal-hydrazones, Cu(II) complexes with pyridoxal-thiosemicarbazones and Cu(II) complexes with Schiff bases derived from pyridoxal.

The thesis is structured in two parts. Chapter I and II belong to the firt part and present a wide image of the current status of the thesis theme. The second part, Chapters III, IV, V and VI, bring original, valuable contributions in the thesis field. The thesis ends with General conclusions and Annexes.

Chapter I „*Complexes with various azomethine ligands derived from vitamin B_6*„ describes aspects related to the chemistry of interconvertible forms of vitamin B_6, specifically to the form pyridoxal. The main research directions in the field of chemistry and biochemistry of the pyridoxal refer to its involvement in the metabolism of the aminoacids [12, 14-17], the role of co-enzyme [22] and the antioxidant capacity [28, 29]. Many of the biological transformations which involves pyridoxal are possible due to its interaction with molecules with amine function, resulting the azomethine compounds. The compounds resulting from the interaction of azomethine compunds with metal ions are the first structural models of complexes with azomethine ligands derived from pyridoxal [37-39].

Complexes with some metal ions with hydrazones and thiosemicarbazones derived from pyridoxal are discussed. The main discussed aspects are the coordination mode, the tautomerism before and after coordination, the geometry and the biological properties of the complexes.

Pyridoxal-hydrazones coordinate in a bi-, tri- or polydentate manner. Hidrazones derived from hydrazines coordinate via at least two donor atoms: the azomethine nitrogen and

the hydroxyphenol oxygen of the pyridine ring in the pyridoxal moiety. In case of the pyridoxal-hidrazones derived from hydrazides the coordination sphere is supplemented with an oxygen atom. Pyridoxal-N-acyl-hydrazones participate to the *keto-enol* tautomer equilibrium, being able to coordinate to the metal ions in neutral, mononegative or dinegative form [47, 50-56].

In the majority of the cases the pyridoxal-thiosemicarbazones coordinate in a similar way, the only difference is that the hydrazonic oxygen is replaced by the sulfur atom and the tautomer equilibrium is a *thiol-thione* one [69-71].

The geometry of the complexes is influenced by both properties of the metallic ion and the ligand's structure due to the number and type of donor atoms. We can observe a significant versatility among the complexes with pyridoxal-hydrazones and pyrioxal-thiosemicarbazones; square-planar, tetrahedral, octahedral or square-pyramidal complexes have been reported.

The ligands derived from pyridoxal and their complexes have antioxidant [85], antibacterial [102], antitumoral [78] effects and have an important role in the treatment of diabet complications [95].

The second chapter „*Complexes with azomethine ligands derived from 4-aminoantipyrine*„ describes aspects related to the chemistry of Schiff bases derived from 4-aminoantipyrine and their complexes. 4-aminoantipyrine is specific among the pyrazolones because the pyrazolonic fragment is completely substituted which imprint specific electronic and structural properties with an impact on the coordination manner.

Due to the amino group at the atom C4 4-aminoantipyrine has a remarcable potential of derivatization by condensation with carbonyl compounds. Mono Schiff bases derived from 4-aminoantipyrine [8, 13] as well as bis Schiff bases derived from 4-aminoantipyrine [16-18] were synthesized. Those ligands were further used for the synthesis of the complexes. The common coordination manner is ON [12, 20] in which case the ligand coordinates via the azomethine nitrogen and the exocyclic oxygen. Depending on the molecular structure of the carbonyl compound the coordination sphere can be extended resulting the tridentate ONO complexes [7]. In case of complexes with bis Schiff bases derived from 4-aminoantipyrine the specific coodination mode is OONN [16, 17]. Despite rarely reported, have been described also compounds with a special coordination mode, for exemple the metal ion does not interact with the exocyclic oxygen [8] or with the imine nitrogen [24, 2] or when the metal ion is pentacoordinated NNOOS [18].

Among the applications of Schiff bases derived from 4-aminoantipyrine and their complexes we can mention the antimicrobial [11], antifungal [16], antioxidant [8] properties, as well as their role in understanding the interaction mechanisms with the DNA [8, 11, 12].

The second part of the thesis is dedicated to the original contributions. The research strategy is focused on the rational development of a serie of ligands with varied structural properties. The gradual modification of some structural parameters (like the volume of the reagents, the steric positioning of some molecular fragments, the number and type of coordination sites) has a direct impact on the geometry of the complexes. By using different copper(II) salts the influence of the anion of the metal salt on the geometry of the complexes was evaluated.

Chapter III „*Cu(II) complexes with hydrazones derived from pyridoxal*„ describes four classes of complexes prepared by using the ligands L^1-L^4 (fig. III.1).

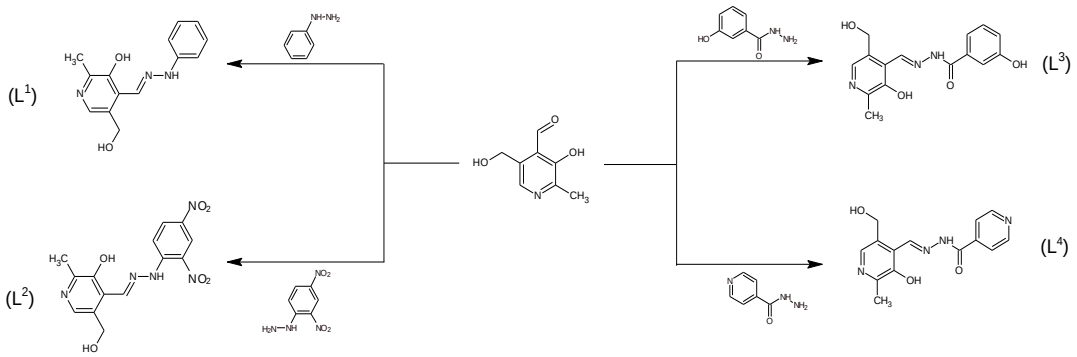


Figure III.1. Development scheme of the hydrazones derived from pyridoxal

The ligands pyridoxal-phenylhydrazone (L^1) and pyridoxal-2,4-dinitro-phenylhydrazone (L^2) are similar, consequently we can observe some similarities also among the structures of their complexes. The azomethine compounds were characterized by spectral analyses, like IR, ^{1}H-RMN, ^{13}C-RMN spectroscopy and electrospray ionization-mass spectrometry (ESI-MS). The structure of the ligand was solved by single crystal X-ray diffraction. The crystalline molecular structure (fig. III.4) consists of a protonated ligand L^1 and a perchlorate anion. The perchlorate anion generates additional interactions in the crystal (fig. III.5). Each perchlorate ion interacts with 3 ligand molecules via hydrogen bonds $N_{piridina}$-H···O, $N_{hidrazinic}$-H···O, O2-H···O.

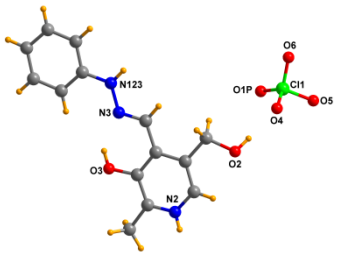


Figure III.4. Molecular structure of $[HL^1](ClO_4)$

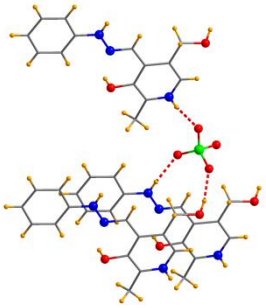


Figure III.5. Interactions between the ligand and perchlorate in the crystal $[HL^1](ClO_4)$

A bidimensional structure is formed due to the perchlorate ion and its interactions with the ligand L^1 (fig. III.6).

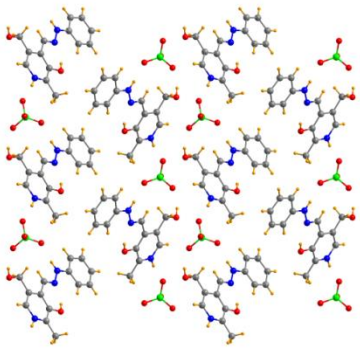


Figure III.6a Extended structure in the crystal $[HL^1](ClO_4)$ – view along *a* axis

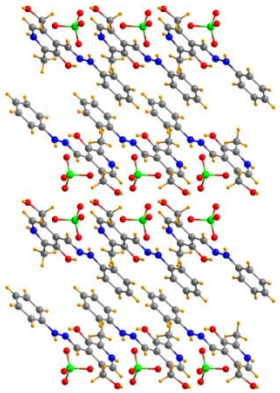


Figure III.6b. Extended structure in the crystal $[HL^1](ClO_4)$ – view along *b* axis

Using the ligands L^1 and L^2 I prepared 8 Cu(II) complexes. The synthesis was repeated and different metal salts were used: $CuCl_2 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, $Cu(NO_3)_2 \cdot 3H_2O$ și $CuSO_4 \cdot 5H_2O$.

The bidentate coordination mode of both ligands was confirmed by comparing the IR spectra of complexes and ligands. The ligands coordinate similarily via the azomethine nitrogen and the deprotonated hydroxyphenol group.

Because of the different metal salts used for the synthesis we can observe different geometries of the complexes C^1-C^4 (fig. III.15). The complex C^1 has a distorted octahedral geometry [46]. Besides the two donor atoms of the ligand the coordination sphere is supplemented by a chloride ion and three water molecules. The complexes C^2 and C^3 are similar in regards to the coordination number and the tetrahedral geometry. Complex C4 is tetrahedral as well. Still, it is different than the previous ones as it is dinuclear, the sulphate ion coordinating bidentate.

Among the complexes C^5-C^8 derived from ligand L^2 we can not observe a significant influence of the contra-anion of the metal salt on the geometry of the complexes. All the four complexes are mononuclear and the coordination number is 4. In regards to the coordination sphere the tetracoordination of the complexes C^5 și C^8 is ensured by two molecules of ligand per each Cu^{2+}, in a square-planar surrounding. In case of complex C^7 the coordination sphere is supplemented by the two oxygen atoms of the nitrate ion coordinated bidentate [34]. For complex C^6 the unidentate coordination mode of the acetate ion is emphasized by the specific bands in the IR spectra [34] while in the forth position a water molecule is present.

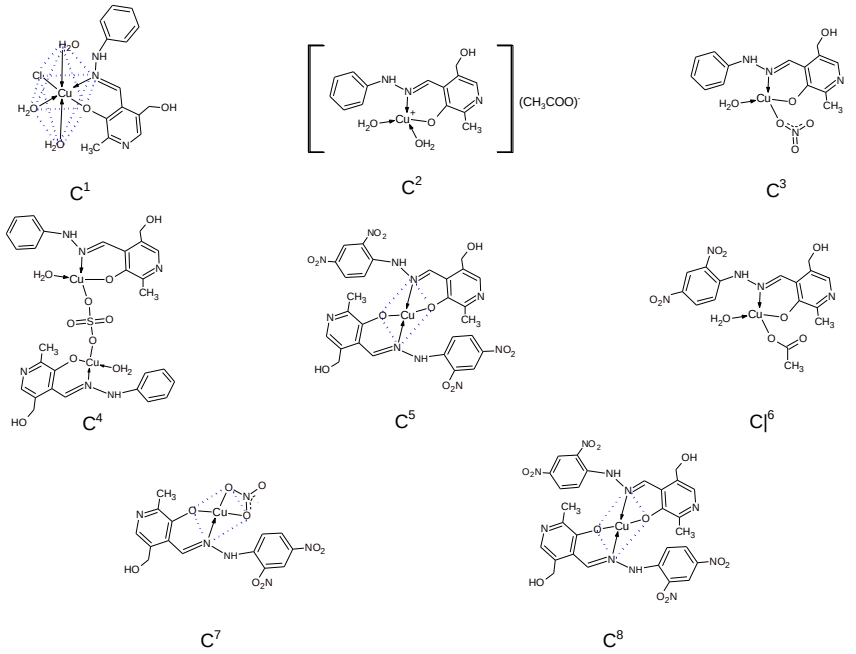


Figure III.15. Structures of the Cu(II) complexes with ligands L^1 și L^2

The ligands pyridoxal-3-hydroxy-benzohydrazone (L^3) and pyridoxal-isonicotinoyl hidrazone (L^4) are different as an additional donor atom is introduced: then oxygen atom of the hydrazonic fragment. These ligands derive from the condensation of pyridoxal with hydrazides and they possess three coordination sites: the azomethine nitrogen, the oxygen atom of the hydroxyphenol group and the hydrazonic oxygen. Consequently, there are formed two chelate rings of five, respectively six atoms which imprint stability to the complex molecule. The hydrazonic fragment can participate to the *keto-enol* tautomer equilibrium described in figures III.28 (L^3) and III.40 (L^4) [19b]. The IR, ^{1}H-RMN și ^{13}C-RMN spectra emphasize the *keto* form in both solid state and in solution.

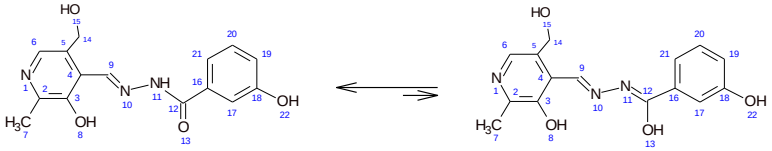


Figure III.28. Tautomer equilibrium for ligand L^3

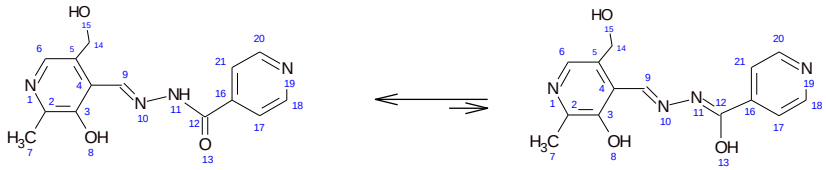


Figure III.40. Tautomer equilibrium for ligand L^4

The crystalline structure of the ligand pyridoxal-isonicotinoyl hidrazone consists of hydrochloride units H_4L^4Cl and DMSO molecules, ratio 1:2 (fig. III.37). For each H_4L^4Cl unit there are two additional DMSO molecules used as crystallization solvent. Multiple hydrogen bonds are formed: O-H···Cl, O-H···N, N-H···Cl, N-H···O și C-H···O.

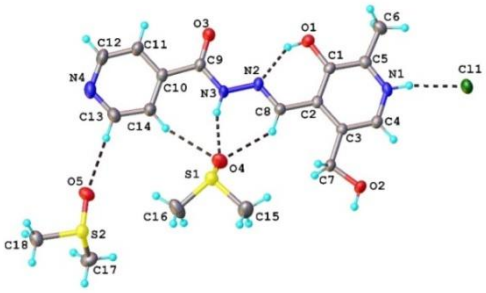


Figure III.37. The asymmetric unit H_4L^4Cl in the crystal of pyridoxal-isonicotinoyl hidrazone

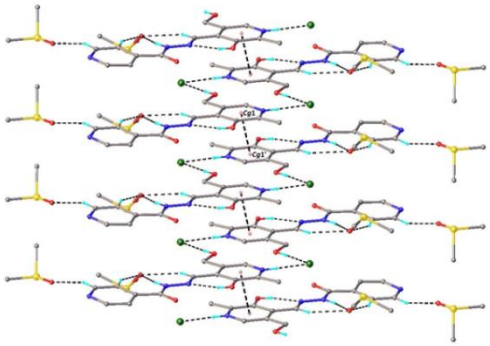


Figure III.38. The „column-type" architecture of H_4L^4Cl

The presence and the influence of the hydrochloride and DMSO molecules is very important in regards to the stabilized supramolecular structure in the crystal. The packing of the molecules describes a parallel distribution of the H_4L^4Cl units generating layers interconnected via the hydrogen bonds. The crystal cohesion is supported by the π-π stacking interactions as well. The distance between the centroids Cg1 și Cg1` of the centro-symmetric units formed by the aromatic rings C1/C2/C3/C4/N1/C5 of two parallel ligand molecules is 4.039 Å. The supramolecular motif in the H_4L^4Cl crystal is supported by the parallel packing of the „column-type" architectures (fig. III.38) [67].

Using the ligand L^3 the complexes C^9-C^{12} (fig. III.32) were prepared and characterized by IR, UV-Viz and EPR spectroscopy. The electronic spectra as well as the EPR spectra recorded on polycrystalline powder at room temperature for complexes C^9 and C^{10} indicates an octahedral geometry [46]. The hexacoordination is ensured by the ligands's donor atoms ONO, two water molecules and a chloride, respectively acetate anion. The complexes C^{11} și C^{12} are square-planar with the forth coordinative position occupied by monodentate nitrate ion, respectively a water molecule. The lack of the signal at half field (aproximative 1600 G) confirms that the complexes are mononuclear.

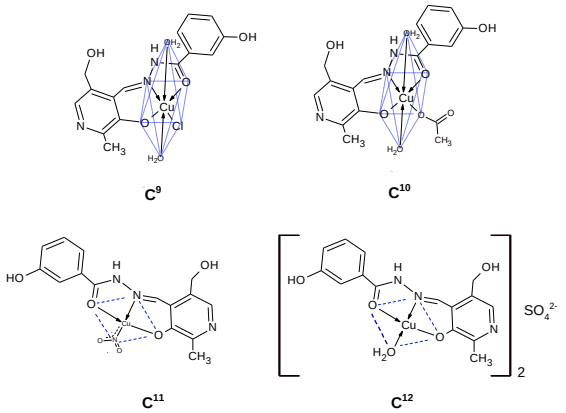


Figure III.32. Structures of Cu(II) complexes with ligand L^3

The complexes C^{13}-C^{17} were prepared by coordination of the ligand L^4 to the Cu^{2+} ion originating from various metal salts. The structures described in figure III.42 were proposed based on the holistic interpretation of the results provided by several techniques.

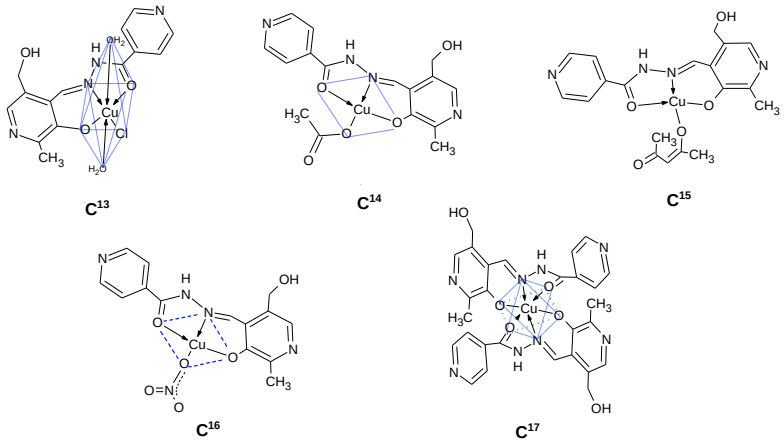


Figure III.42. Structures of Cu(II) complexes with ligand L^4

These complexes emphasize the influence of the anion from the metal salt on the geometry of the complexes. In order to be able to propose the geometry of the complexes we recorded the electronic and X-band EPR spectra (fig. III.47, III.48). The bands recorded in the electronic spectra, as well as the values of the parameter *g*, indicate the octahedral geometry of the complexes C^{13} și C^{17} [46, 76, 77, 83]. Moreover, the effective magnetic moments (μ_{eff} = 1.7 MB for C^{13} and μ_{eff} = 1.8 MB for C^{17}) are similar to 1.73 MB which is specific to an unpaired spin in an octahedral surrounding [78]. Still, we can observe differences in regards to the coordination sphere. While for complex C^{13} the coordination number six is ensured by the three ligand's donor atoms, a chloride anion and two water molecules, in case of complex C^{17} the metal ion is surrounded by two ligands. The complexes C^{14} and C^{16} are square-planar [58], the tetracoordination being ensured by the acetate and nitrate ions coordinated in a

monodentate manner. The UV-Viz and EPR spectral data indicates for complex C^{15} a tetrahedral geometry, characterized by a lower simetry [46].

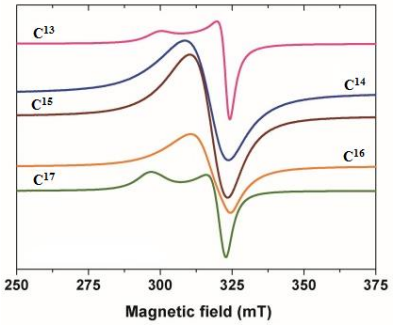


Figure III.47. EPR spectra recorded on microcrystalline powder for complexes C^{13}-C^{17}

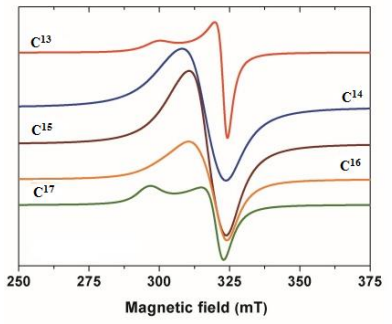


Figure III.48. Simulated EPR spectra for complexes C^{13}-C^{17}

The space group and crystal system, as well as the crystallographic parameters for complexes C^{13}-C^{17}, were identified by microcrystalline powder X-ray diffraction. Both complexes C^{13} and C^{17} share the triclinic system, space group *P 1*. The crystal system for complexes C^{14} and C^{16} is monoclinic. This time the compounds have different space groups: *I 1 c 1* for C^{14} and *P 1 21 1* for C^{16}. The crystallographic parameters for complex C^{15} are different compared with the previous ones; the crystal system is hexagonal and the space group is *P 65*.

The thermal behavior of the complexes with pyridoxal-hydrazones L^1-L^4 was evaluated as well. By heating the samples within a large temperature range (30-900 °C) we obtained a wide picture of the decomposition pattern and the eliminated fragments. At lower temperatures the thermogravimetric curves emphasize the elimination of the fragments outside the coordination sphere, afterwards the small, coordinated fragments are eliminated; at higher temperatures we can observe an advanced thermal degradation of the complex molecule.

The class of complexes derived from L^4 was selected for the purpose of the antimicrobial studies. In order to obtain the antimicrobial spectrum the qualitative and quantitative action of each compound on four pathogenic strains was conducted: *Escherichia coli W3110, Pseudomonas aeruginosa ATCC 9027, Staphilococcus aureus var. Oxford ATCC 6538* și *Bacillus cereus ATCC 14579*. The values of the minimum inhibitory concentration (MIC) emphasize the enhanced antimicrobial activity of the complexes compared to the ligand; namely 8 to 16 time higher (table III.17). In this way it is emphasized the importance of the coordination and the influence of the metal ion for the enhancement of the biologic effect. The antimicrobial effect follows the descending order: $C^{13} = C^{14} = C^{16}$ (MIC=64 μg/mL

against *S. aureus*, *B. cereus*, *P. aeruginosa* and MIC=128 μg/mL against *E. coli*) > C^{15} (MIC=64 μg/mL against *S. aureus*, *B. cereus* and MIC=128 μg/mL against *E. coli*, *P. aeruginosa*) > C^{17} (MIC=128 μg/mL against *S. aureus*, *B. cereus*, *E. coli*, *P. aeruginosa*). Comparing to the antibiotics used as standards an important effect is reported in case of C^{13}, C^{14} and C^{16}; these register a MIC value of 64 μg/mL against *P. aeruginosa* and *B. cereus*, 8 times lower than for ampicillin [67].

Tabel III.17. MIC (μg/mL) for L^4, C^{13}-C^{17}, antibiotics used as standards and solvents

Compus	***B. cereus* ATCC 14579**	***S. aureus* var. Oxford ATCC 6538**	***P. aeruginosa* ATCC 9027**	***E. coli* W3110**
L^4	1024	1024	1024	1024
C^{13}	64	64	64	128
C^{14}	64	64	64	128
C^{15}	64	64	128	128
C^{16}	64	64	64	128
C^{17}	128	128	128	128
Ampicillin	resistant	0.5	resistant	2
Kanamycin	8	4	256	1
Streptomycin	64	32	256	1
Pyridine	1024	1024	1024	1024
DMSO	1024	1024	1024	1024

Chapter IV „*Cu(II) complexes with thiosemicarbazones derived from pyridoxal*„ describes the compounds pyridoxal-4-phenyl-3-thiosemicarbazone (L^5) and pyridoxal-4-benzyl-3-thiosemicarbazone (L^6) and their nine complexes. The formation of the two thiosemicarbazones is confirmed by means of IR, ^{1}H-RMN, ^{13}C-RMN spectroscopy and ESI-MS. Both L^5 and L^6 stabilize the *thione* tautomer [10].

By using the ligands L^5 and L^6 we prepared two classes of Cu(II) complexes: $[CuL^5Cl]$ (C^{18}), $[CuL^5(OAc)(H_2O)]$ (C^{19}), $[CuL^5(ONO_2)]$ (C^{20}), $[CuL^5(H_2O)_2]_2(SO_4)$ (C^{21}), $[CuL^5(OAcac)]$ (C^{22}), $[Cu_2(HL^6)_2Cl_2]Cl_2$ (C^{23}), $[CuL^6(OAc)]$ (C^{24}), $[CuL^6(ONO_2)]$ (C^{25}), $[Cu(L^6)_2]$ (C^{26}). In regards to the coordinating fragment there is no difference between the two compounds. The difference is related to the increase of the thiosemicarbazide's volume because of the methylene fragment -$C^{17}H_2$-. Although this is not probable to generate variations in regards to the coordination number and geometry of the complexes it is probable to induce steric hindrances. Moreover, this saturated, hydrophobic fragment can influence the physical properties of the complexes, their thermal behavior or their applications.

The structures of the complexes derived from ligands L^5 and L^6 as depicted in figure IV.15 were proposed based on the results provided by several analytical techniques (ESI-MS, IR, UV-Viz spectrometry and single crystal X-ray diffraction – for complexes C^{18} and C^{23}).

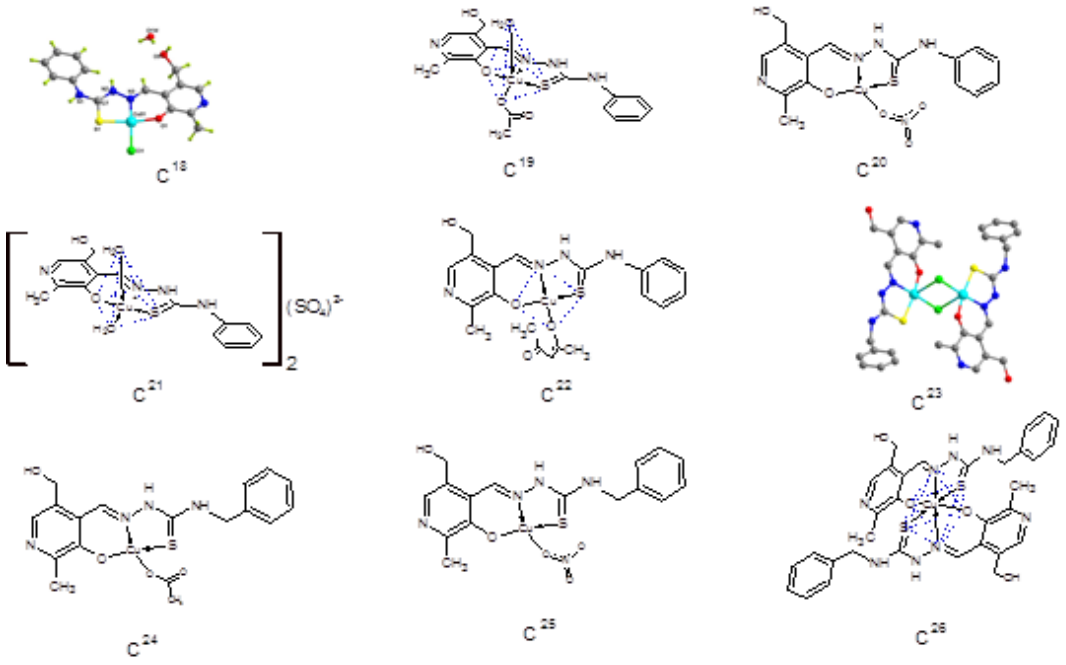


Figure IV.15. Proposed structures for complexes C^{18}-C^{26}

A modern method applied for the characterization of coordinative compounds which was used in case of complexes C^{19}-C^{22} and C^{24}-C^{26} is the mass spectrometry. It was useful to emphasize the formation of the chelates. The ESI-MS spectra for complexes C^{19} (fig. IV.16), C^{20}, C^{21} depict a signal corresponding to the molecular ion $[CuL^5]^+$, while the mass spectra for compounds C^{24} (fig. IV.19), C^{25}, C^{26} depict a signal at *m/z* 392.3 which corresponds to the molecular ion $[CuL^6\text{-}H]^+$.

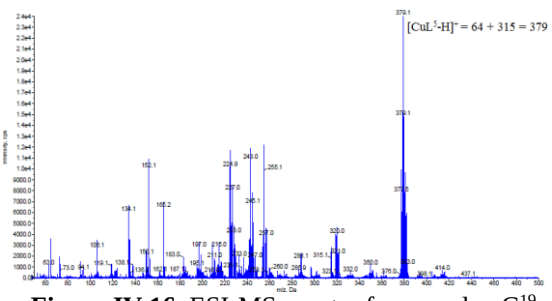


Figure IV.16. ESI-MS spectra for complex C^{19}

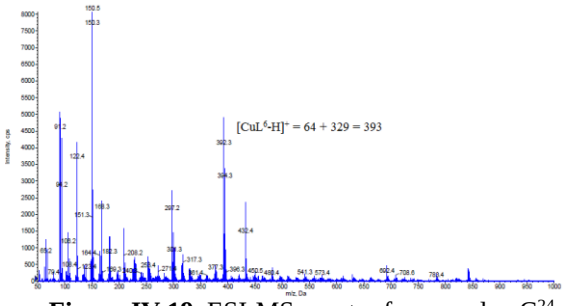


Figure IV.19. ESI-MS spectra for complex C^{24}

Despite the two ligands are structurally similar we can remark a high diversity among the complexes geometries. The complexes derived from ligand L^5 has square-pyramidal (C^{19}, C^{21}), square-planar (C^{18}, C^{22}) and tetrahedral (C^{20}) geometries [40, 41]. As the coordination mode is identical (ONS) the differences among the geometries are driven by the participation in the coordination sphere of the donor atoms of the anions from the metal salts and/or the water molecules. Thus, we can emphasize the influence of the metal salt on the geometry of the complexes.

The stereochimic variety is visible also among the complexes derived from thiosemicarbazone L^6. They stabilize square-pyramidal (C^{23}), tetrahedral (C^{24}, C^{25}) and octahedral (C^{26}) geometries. As a particularity, in case of C^{26} the hexacoordination of the Cu(II) is ensured by two ligand molecules per metal ion.

A very interesting aspect is the crystallographic analysis of complexes C^{18} și C^{23}, obtained by coordination of L^5, respectively L^6 to the Cu^{2+} ion originating from the copper(II) chloride. The ligand coordination is similar via the same set of donor atoms (S1N3O1 – C^{18}, S1N2O2 - C^{23}); still, the coordination manner is different.

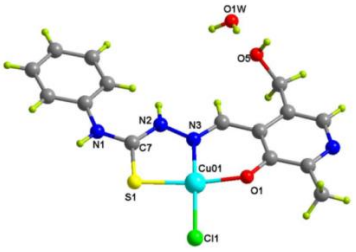
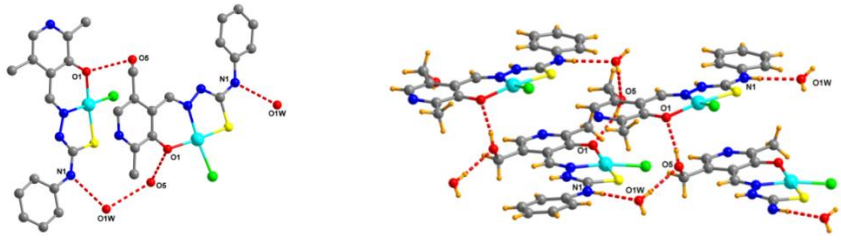


Figure IV.22. Molecular structure of complex C^{18}

The Cu^{2+} ion in complex C^{18} has the coordination number 4 and is square-planar. The structure, as depicted in figure IV.22, consists of one molecule of ligand pyridoxal-4-phenyl-3-thiosemicarbazone and a chloride anion coordinated to the Cu^{2+} ion and a water molecule.

The ligand L^5 coordinates in a mononegative form resulted after the deprotonation of hydroxy group; the monopositive charge of the complex is compensated by a coordinated chloride (Cl1). The crystallographic data confirms the *thione* form of the thiosemicarbazone L^5 post coordination. The bond C7=S1 is 1.735 Å. The interaction between the neighboring molecules of C^{18} is complex. Each molecule interacts with the neghboring one via three hydrogen bonds: O5-H···O1, N1-H···O1w, O1w-H···O5 (fig. IV.23). The packing in the crystal generates a „chain-type" structure (fig. IV.24).



(a) (b)

Figure IV.23. Interactions between the complex molecules in the crystal of C^{18}

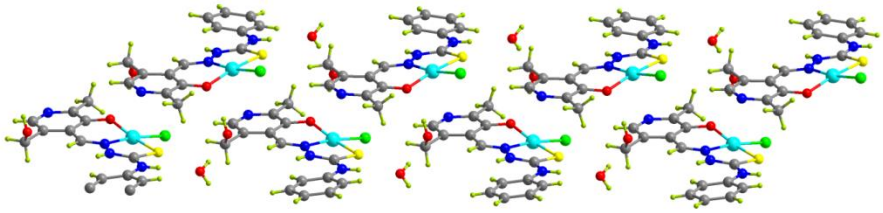
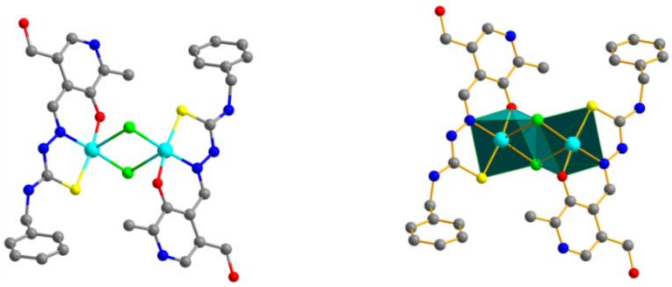


Figure IV.24. „Chain-type" structure in the crystal C^{18}

Complex C^{23} is dinuclear and has a square-pyramidal geometry as described in figure IV.25. The crystal system is monoclinic and the space group is $P2_1/c$.



(a) (b)

Figure IV.25. Molecular structure of dinuclear $[Cu_2(HL^6)_2Cl_2]^{2+}$ (the chloride ions outside the coordination sphere are not depicted)

The dinuclear structure of C^{23} is supported by the presence of coordinated chloride anions which act as „bridge" between the metal centers. Each chloride anion coordinates to a second Cu^{2+} ion. The coordination number of Cu^{2+} is five and its geometry is square-pyramidal. The ligand L^6 keeps its *thione* form after coordination. The asymmetric unit depicted in figure IV.26 describes a ligand molecule and a chloride anion, both coordinated, as well as a second chloride anion outside of the coordination sphere.

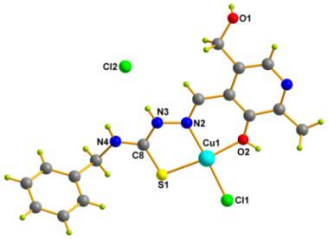


Figure IV.26. Asymmetric unit in complex C^{23}

Complex C^{23} is very interesting in regards to the coordination mode of the ligand to the Cu^{2+} ion. The ligands keeps the neutral form because the hydroxyphenyl group of the pyridine ring is not deprotonated, but participates to the coordination via a O2 → Cu bond. Other two coordination sites are occupied by the imine nitrogen N2 and the sulfur atom S1 which interacts with the metal center via the coordinative bonds N2 → Cu and S1→ Cu. The forth coordination position is occupied by a chloride anion. The monopositive charge is compensated by the chloride anion outside the coordination sphere. The packing of the complex molecules generates a 2D structure (fig. IV.27).

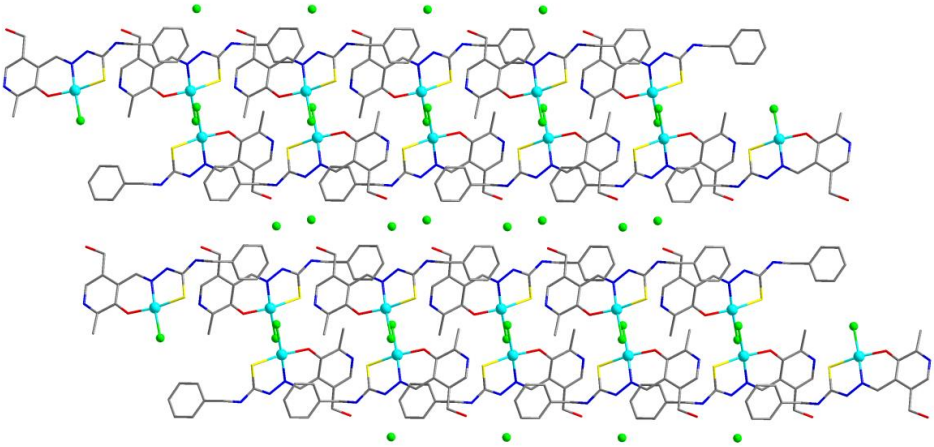


Figure IV.27. Molecular packing for complex C^{23}

Chapter V, named „*Cu(II) complexes with Schiff bases derived from 4-aminoantipyrine*" describes three azomethine ligands sinthesized by condensation of 4-aminoantipyrine with the aldehydes 4-(dimethylamino)benzaldehyde (L^7), 3-benzyloxy-4-methoxybenzaldehyde (L^8) și 4-acetoxy-3-methoxybenzaldehyde (L^9). All the three imines were characterized by means of ESI-MS, IR spectroscopy, ^{1}H-RMN, ^{13}C-RMN, UV-Viz spectrometry and single crystal X-ray diffraction. The crystallographic analysis emphasize the formation of the new azomethine bond and the spatial arrangement of the main fragments of the molecule (fig. V.5, V.7, V.8). We observe the pyrazolonic ring and the benzaldimine fragments are almost coplanar. On the other hand, the phenyl of the 4-aminoantipyrine moiety and the benzyloxy fragment are deviated outside the plan described by the pyrazolone ring and benzaldimine fragment. Also, in case of L^9 the acetate fragment is almost perpendicular to the aromatic ring from the aldehyde moiety.

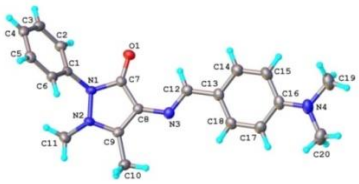


Figure V.5. Molecular structure of ligand L^7

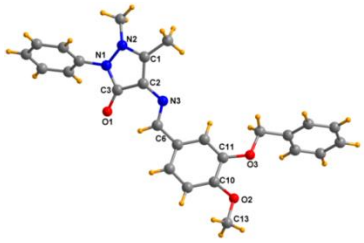


Figure V.7. Molecular structure of ligand L^8

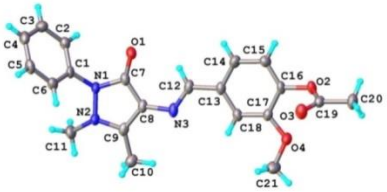


Figura V.8. Molecular structure of ligand L^9

The molecular packing in case of L^7 and L^9 is made via multiple hydrogen bonds and π-π stacking interactions (fig. V.6, V.9).

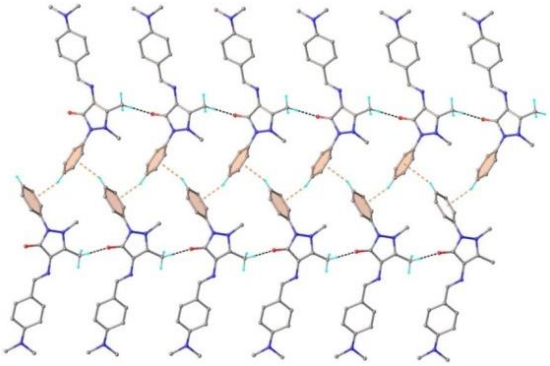


Figure V.6. Interactions in the crystal L^7

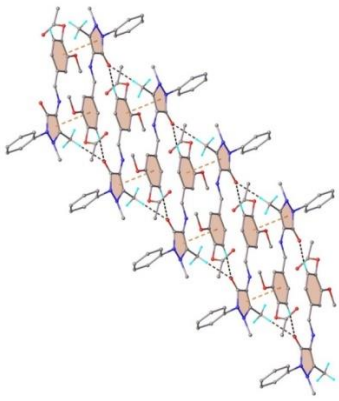


Figura V.9. Interactions in the crystal L^9

Nine complexes were prepared using the ligands L^7 and L^8 and various copper(II) salts: $CuCl_2 \cdot 2H_2O$, $CuBr_2$, $Cu(OAcac)_2$, $CuSO_4 \cdot 5H_2O$ și $Cu(ClO_4)_2 \cdot 6H_2O$. We obtain the complexes C^{27}-C^{31} with ligand L^7 and complexes C^{32}-C^{35} with ligand L^8 (fig. V.23). As a common characteristic all the complexes have been formed by coordination of two ligand molecules per each Cu^{2+} ion. The coordination mode, identified based on IR spectral data, is neutral bidentate via the imine nitrogen and oxygen atom of the pyrazolone moiety. We obtained the square-planar complexes C^{29}, C^{30} și C^{34}. The positive charge of the complexes is compensated by the acetylacetonate (C^{29}, C^{34}) and sulphate (C^{30}) ions. In case of the other complexes the coordination sphere is supplemented, generating complexes with different geometries. The complexes C^{27}, C^{28}, C^{31} and C^{32} are square-pyramidal due to the coordination of a water molecule in the axial position while the anions chloride, bromide and perchlorate are outside the coordination sphere. Complexes C^{33} and C^{35} are hexacoordinated in an octahedral geometry; the bromide anions (C^{33}), respectively the water molecules (C^{35}) are located in the axial positions. The presence of small fragments located inside or outside the coordination sphere is emphasized by means of thermogravimetric analysis.

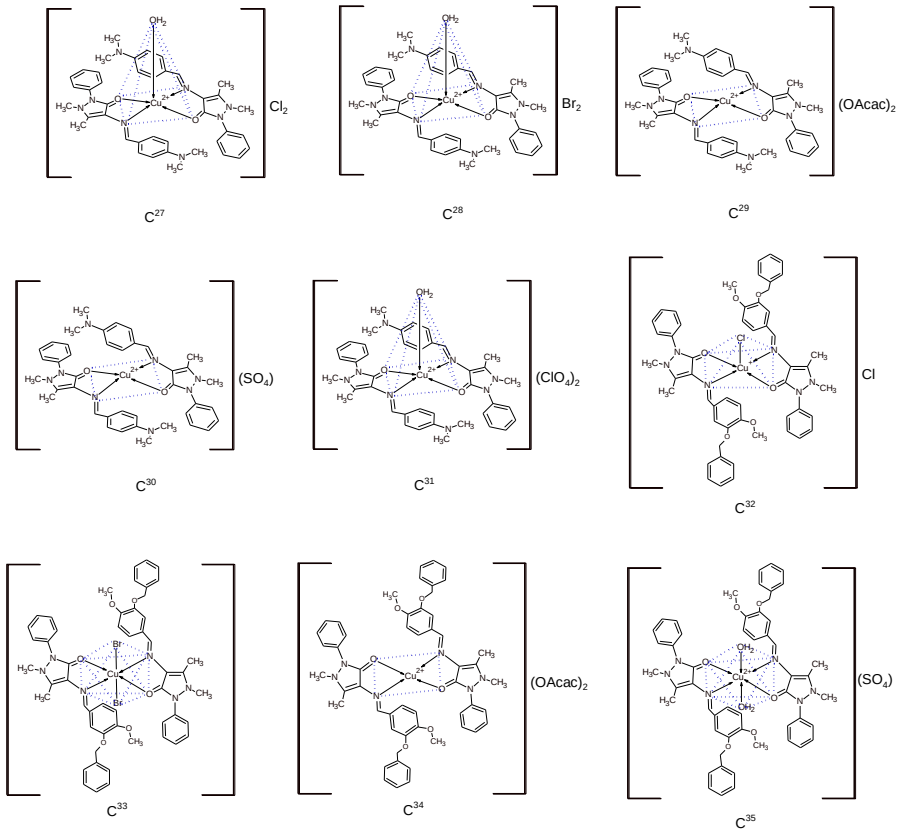


Figure V.23. Proposed structures for complexes C^{27}-C^{35}

As part of the class of complexes with Schiff bases derived from 4-aminoantipyrine it was prepared a complex in which structure the Cu^{2+} ion originates from an organic salt: copper(II) salicylate. The complex C^{36} obtained by coordination of the known ligand ASAAP [28] to the Cu^{2+} ion originating from the copper(II) salicylate has a distorted octahedral geometry. The single crystal X-ray diffraction emphasizes a „chain-type" structure where the asymmetric units are connected via the salicylate fragment (fig. V.34). The hexacoordination is supported by the three ligand's donor atoms ONO, two oxygen atoms of the carboxyl group in the organic salt and the oxygen atom of the hydroxy group belonging to the salicylate fragment of a neghboring molecule (fig. V.35).

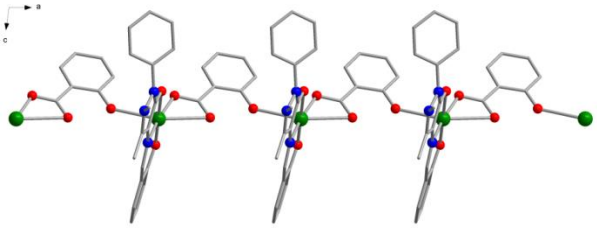


Figure V.34. The „chain-type" structure generated by interactions O5'-Cu1 in complex C^{36}

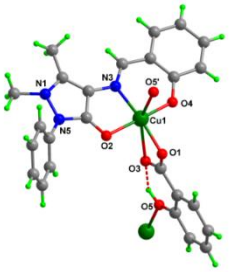


Figura V.35. Asymmetric unit in complex C^{36}

The polinuclear chains are connected via π-π stacking interactions between the pyrazolonic and phenyl fragments in the 4-aminoantipyrine moiety (fig. V.36) resulting a „stair-like" packing (fig. V.37). The „stair-like" units are assembled further via π-π interactions between the phenyl rings in the 4-aminoantipyrine moiety (fig. V.38).

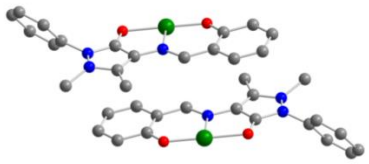


Figure V.36. π-π interactions in crystal C^{36}

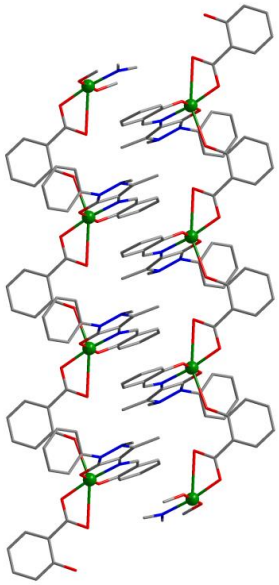


Figure V.37. „Stair-like" packing in complex C^{36}

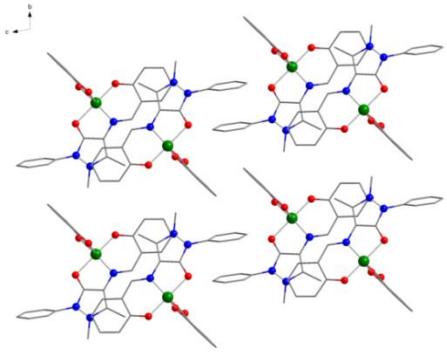


Figure V.38. Packing of the „stair-like" units in crystal C^{36}

The last chapther „*Comparative evaluation of the ligands stability and antioxidant effect of some complexes*" is related to the properties and applications of the synthesized compounds. The ligands L^1-L^3 and L^5-L^9 were characterized in detail in regards to their thermal stability based on chemiluminescence studies, differential scanning calorimetry and thermogravimetry. The results show that the pyridoxal-hydrazone are less stable to high temperature, the pyridoxal-thiosemicarbazones have an intermediate stability while the Schiff bases derived from 4-aminoantipyrine are the most thermally stable. The thermal stability follows the decreasing order: $L^8 > L^7 > L^9 > L^2 > L^1 > L^5 > L^3 > L^6$. The crystallinity degree for ligands L^7-L^9 was evaluated based on the melting enthalpy. The decreasing order of the crystallinity is: L^9 (ΔH_m = 307 J/g) > L^7 (ΔH_m = 92 J/g) > L^8 (ΔH_m = 68 J/g).

The antioxidant effect of the complexes C^2, C^6, C^{10} and C^{19} was determined by comparative evaluation of the stability of ethylen-propylen-terpolimer (EPDM) in the presence and absence of the complexes as protecting agents. The antioxidant effect was quantified with the help of the isotherm chemiluminescence (180 °C) and non-isotherm chemiluminescence studies at 3.7 °C/min, 5.0 °C/min, 10.0 °C/min, respectively 15.0 °C/min. The isotherm studies emphasize significant differences in regards to the antioxidant effect of

the four complexes; it decrease as follows: $C^6 > C^2 > C^{19} > C^{10}$. This is influenced by the ligand and by the electronic particularities of the compounds. The non-isotherm studies emphasize the influence of the heating rate over the evolution of the oxo-degradative process. We can remark that an increase of the heating rate results in a delay of the oxidation process with aproximative 25 °C.

Selective bibliography

Chapter I

[12] D.E. Metzler, M. Ikawa, E.E. Snell, *J Am Chem Soc* 76 **(1954)** 648.

[14] Y.H. Lim, T. Yoshimura, Y. Kurokawa, N. Esaki, K. Soda, *J Biol Chem* 273 **(1998)** 4001.

[15] S. Sharif, D. Schagen, M.D. Toney, H.H. Limbach, *J Am Chem Soc* 129 **(2007)** 4440.

[16] H. Kumagai, H. Yamada, H. Matsui, H. Ohkishi, K. Ogata, *J Biol Chem* 245 **(1970)** 594.

[17] M. Adrover, B. Vilanova, F. Munoz, J. Donoso, *Bioorg Chem* 37 **(2009)** 26.

[22] a) R. Percudani, A. Peracchi, *EMBO Rep* 4 **(2003)** 850; b) Enzyme Commission: http://www.chem.qmul.ac.uk/iubmb/enzyme/

[28] R. Bilski, M.Y. Li, M. Ehrenshaft, M.E. Daub, C.F. Chignell, *Photochem Photobiol* 71 **(2000)** 129.

[29] R. Chumnantana, N. Yokochi, T. Yagi, *Biochim Biophys Acta* 1722 **(2005)** 84.

[37] H.N. Christensen, S. Collins, *J Biol Chem* 220 **(1956)** 279.

[38] H.N. Christensen, *J Am Chem Soc* 79 **(1957**) 4073.

[39] R.H. Holm, in: G.L. Eichhorn (ed.), *Inorganic Biochemistry*, Elsevier, Amsterdam, **1975,** 1165.

[47] N. Galic, I. Brodanac, D. Kontrec, S. Miljanic, *Spectrochim Acta A* 107 **(2013)** 263.

[50] N. Galic, M. Rubcic, K. Magdic, M. Cindric, V. Tomisic, *Inorg Chim Acta* 366 **(2011)** 98.

[51] V.I. Minkin, A.V. Tsukanov, A.D. Dubonosov, V.A. Bren, *J Mol Struct* 998 **(2011)** 179.

[52] a. S. Sharif, D.R. Powell, D. Schagen, T. Steiner, M.D. Toney, E. Fogle, H.H. Limbach, *Acta Cryst* B62 **(2006)** 480; b. S. Sharif, D. Schagen, M.D. Toney, H.H. Limbach, *J Am Chem Soc* 129 **(2007)** 4440; c. S. Sharif, G.S. Denisov, M.D. Toney, H.H. Limbach, *J Am Chem Soc* 129 **(2007)** 6313.

[53] E.W. Ainscough, A.M. Brodie, A. Dobbs, J.D. Ranford, J.M. Waters, *Inorg Chim Acta* 267 **(1998)** 27.

[54] H. Hosseini-Monfared, Z. Kalantari, M.A. Kamyabi, C. Janiak, Z. Anorg, *Allg Chem* 633 **(2007)** 1945.

[55] C. Hao, R. Wang, M. Zhang, H. Yangb, M. Ge, J. Chen, J. Qiu, *J Photochem Photobiol* A217 **(2011)** 219.

[56] H. Hosseini-Monfared, H. Falakian, R. Bikas, P. Mayer, *Inorg Chim Acta* 394 **(2013)** 526.

[57] N. Galic, A. Dijanosic, D. Kontrec, S. Miljanic, *Spectrochim Acta A* 95 **(2012)** 347.

[61] D.F. Back, M.A. Ballin, G. Manzoni de Oliveira, *J Mol Struct* 935 **(2009)** 151.

[69] J.S. Casas, M.S. Garcia-Tasende, J. Sordo, *Coord Chem Rev* 209 **(2000)** 197.
[70] V.M. Leovac, V.S. Jevtovic, L.S. Jovanovic, G.A. Bogdanovic, *J Serb Chem Soc* 70 **(2005)** 393.
[71] T.S. Lobana, R. Sharma, G. Bawa, S. Khanna, *Coord Chem Rev* 253 **(2009)** 977.
[78] M. Belicchi Ferrari, F. Bisceglie, G. Pelosi, P. Tarasconi, R. Albertini, P.P. Dall Aglio, S. Pinelli, A. Bergamo, G. Sava, *J Inorg Biochem* 98 **(2004)** 301.
[85] R. Manikandan, P. Vijayan, P. Anitha, G. Prakash, P. Viswanathamurthi, R.J. Butcher, K. Velmurugan, R. Nandhakumar, *Inorg Chim Acta* 421 **(2014)** 80.
[95] a) T. Taguchi, M. Sugiura, Y. Hamada, I. Miwa, *Eur J Pharmacol* 378 **(1999)** 283; b) H. Miyoshi, T. Taguchi, M. Sugiura, M. Takeuchi, K. Yanagisawa, Y. Watanabe, I. Miwa, Z. Makita, T. Koike, *Horm Metab Res* 34 **(2002)** 371.
[102] a) M.S. Iqbal, I.H. Bukhari, M. Arif, *Appl Organometal Chem* 19 **(2005)** 864; b) M.S. Iqbal, A. H. Khan, B.S. Loothar, I.H. Bukhari, *Med Chem Res* 18 **(2009)** 31.

Chapter II

[2] J.S. Casas, M.S. Garcia-Tasende, A. Sanchez, J. Sordo, A. Touceda, *Coord Chem Rev* 251 **(2007)** 1561.
[7] T. Rosu, E. Pahontu, C. Maxim, R. Georgescu, N. Stanica, G.L. Almajan, A. Gulea, *Polyhedron* 29 **(2010)** 757.
[8] S. Sathiyaraj, K. Sampath, R.J. Butcher, R. Pallepogu, C. Jayabalakrishnan, *Eur J Med Chem* 64 **(2013)** 81.
[11] J. Joseph, K. Nagashri, G. Boomadevi Janaki, *Eur J Med Chem* 49 **(2012)** 151.
[12] M. Selvaganapathy, N. Pravin, K. Pothiraj, N. Raman, *J Photochem Photobiol B* 138 **(2014)** 256.
[13] P. Mosae Selvakumar, E. Suresh, P.S. Subramanian, *Polyhedron* 26 **(2007)** 749.
[16] A.K. Sharma, S. Chandra, *Spectrochim Acta A* 81 **(2011)** 424.
[17] T. Rosu, M. Negoiu, S. Pasculescu, E. Pahontu, D. Poirier, A. Gulea, *Eur J Med Chem* 45 **(2010)** 774.
[18] M. Tyagi, S. Chandra, P. Tyagi, J. Akhtar, A. Kandan, A. Singh, *J Taibah Univ Sci* **(2016).**
[20] A.R. Ibrahim, *Int J Adv Res* 3 **(2015)** 315.
[24] H. Liang, X.W. Wang, Z.F. Chen, L. Huang, H.L. Zou, J. Zhou, K.B. Yu, *Acta Crystallogr* E60 **(2004)** m294.

Chapter III

[19] b. R.S. Mezey, T. Zaharescu, M.E. Lungulescu, V. Marinescu, S. Shova, T. Rosu, *J Therm Anal Calorim* 126 **(2016)** 1763.

[34] K. Nakamoto, *Infrared and Raman spectra of inorganic and coordination compounds*, 5th ed. Wiley-Interscience, New York **(1997)**.

[46] A.B.P. Lever, *Inorganic Electronic Spectroscopy*, 2nd ed., Elsevier Science, New York, **1984**.

[58] R.S. Joseyphus, M.S. Nair, *Arabian J Chem* 3 **(2010)** 195. / D. Banerjea, Coordination Chemistry, Tata McGrwo-Hill Publisher, 1993.

[67] R.S. Mezey, I. Mathe, S. Shova, M.N. Grecu, T. Rosu, *Polyhedron* 102 **(2015)** 684.

[76] R.B. Sumathi, M.B. Halli, *Bioinorg Chem Appl* 2014 **(2014)**

[77] a. S.M. Saadeh, *Arabian J Chem* 6 **(2013)** 191; b. Z. Hong-Yun, C. Dong-Li, C. Pei-Kun, C. De-Ji, C. Guang-Xia, *Polyhedron* 11 **(1992)** 2313.

[78] D.W. Smith, *Inorg Chem* 5 **(1966)** 2236.

[83] B.N. Misra, R. Kripal, *Revue Phys Appl* 16 **(1981)** 411.

Chapter IV

[10] R.S. Mezey, T. Zaharescu, M.E. Lungulescu, V. Marinescu, S. Shova, T. Rosu, *J Therm Anal Calorim* 126 **(2016)** 1763.

[40] A.B.P. Lever, *Inorganic Electronic Spectroscopy*, 2nd ed., Elsevier Science, New York, **1984**.

[41] a. V.M. Leovac, M.D. Joksovic, V. Dicjakovic, L.S. Jovanovic, Z. Saranovic, A. Pevec, *J Inor Biochem* 101 **(2007)** 1094; b. C. Karunakaran, K.R.J. Thomas, A. Shunmugasundaram, R. Murugesan, *J Chem Crystallogr* 29 **(1999)** 413.

Chapter V

[28] T. Rosu, S. Pasculescu, V. Lazar, C. Chifiriuc, R. Cernat, *Molecules* 11 **(2006)** 904.

List of published and presented scientific papers

List of articles in the Ph.D thesis field

1.*Structural characterization and thermal behaviour of some azomethine compounds derived from pyridoxal and 4-aminoantipyrine*. **Réka-Ștefana Mezey**, Traian Zaharescu, Marius Eduard Lungulescu, Virgil Marinescu, Sergiu Shova, Tudor Roșu, *J Therm Anal Calorim* 126 **(2016)** 1763.

2.*Synthesis, characterization and antimicrobial activity of copper(II) complexes with hydrazone derived from 3-hydroxy-5-(hydroxymethyl)-2-methylpyridine-4-carbaldehyde*. **Réka-Ștefana Mezey**, István Máthé, Sergiu Shova, Maria-Nicoleta Grecu, Tudor Roșu, *Polyhedron* 102 **(2015)** 684.

Synthesis, structural and spectral studies of Cu(II) and V(IV) complexes of a novel Schiff base derived from pyridoxal. Antimicrobial activity. Tudor Roșu, Elena Pahonțu, **Réka-Ștefana Mezey**, Diana-Carolina Ilieș, Rodica Georgescu, Sergiu Shova, Aurelian Gulea, *Polyhedron* 31 **(2012)** 352.

List of papers presented at conferences

Synthesis, spectral characterization and structure of some novel copper(II) complexes with thiosemicarbazones derived from pyridoxal. **Réka-Ștefana Mezey**, Modrea Valentina Mihaela, Aurelian Gulea, Tudor Roșu. *International Conference „Physical Methods in Coordination and Supramolecular Chemistry"* XVIIIth ed., 8-9 octombrie 2015, Chișinău, Moldova – poster.

Synthesis, characterization and antimicrobial activity of the ligand pyridoxal isonicotinoyl hydrazone and corresponding copper(II) complexes as potential antibacterial agents. **Réka-Ștefana Mezey**, István Máthé, Tudor Roșu. *Congresul Universității de Medicină și Farmacie Carol Davila București,* ed. III, 28-30 mai 2015, București – poster.

Novel copper(II) complexes derived from azomethine type ligands containing a pyridoxal moiety: Synthesis, structure and spectral characterization. **Réka-Ștefana Mezey**, Cătălin Maxim, Tudor Roșu. *Sesiunea de Comunicări Științifice Studențești* ed. XI. Premiul II. 22 mai 2015, București – oral presentation.

Metal complexes of novel azomethine compounds derived from antipyrine and pyridoxal – synthesis, structural characterization and biological activity. **Réka-Ștefana Mezey**, Tudor Roșu, Elena Pahonțu, Diana-Carolina Ilieș, Sergiu Shova, Rodica Georgescu. *Simpozionul Aniversar „Facultatea de Chimie – 150 de ani de tradiție", Sesiunea Festivă a Școlii Doctorale în Chimie,* 14 iunie 2014, București – oral presentation.