Attachment 3b

Aleksandra Drzewiecka-Antonik

Self Report

Structure of metal complexes with bioactive organic ligands

Institute of Physics Polish Academy of Sciences

Warsaw, 2023

Table of Contents

1. Personal Data

Name and surname

Aleksandra Drzewiecka-Antonik (maiden name: Drzewiecka)

Education and degrees

2011 Doctoral degree in chemistry (with honors)

Maria Curie-Skłodowska University, Faculty of Chemistry, Department of Crystallography

Thesis title: *Structure of potential O-donor ligands and their organic complexes with metal ions*

Supervisor: prof. Anna E. Kozioł

2006 Master of Science in Chemistry

Maria Curie-Skłodowska University, Faculty of Chemistry, Department of Theoretical Chemistry

Master's thesis title: *Distribution of the potential energy of a molecule into contributions from local vibrations*

Supervisors – prof. Krzysztof Woliński and dr hab. Piotr Borowski, prof. UMCS

2004 Bachelor degree

Maria Curie-Skłodowska University, Faculty of Chemistry, Department of Theoretical Chemistry

Title of the diploma thesis: *Analysis of stretching vibrations of the carbonyl group of selected organic compounds*

Supervisor: prof. Krzysztof Woliński and dr hab. Piotr Borowski, prof. UMCS

Information of employment

2011−present assistant professor, Laboratory of X-ray and Electron Microscopy Research, Institute of Physics Polish Academy of Sciences, Warsaw

2010−2011 specialist, Centre for Functional Nanomaterials, Maria Curie-Skłodowska University in Lublin

2006−2010 PhD student at the Department of Crystallography, Maria Curie-Skłodowska University in Lublin

2008 technician, University of Jaén, Spain

Additional data

ResearcherID	B-9378-2013
ORCID	0000-0003-3396-8571
Number of publications indexed in Web of Science	37
Number of all citations (excluding self-citations)*	339 (255)
Hirsch index*	10

* data according to the Web of Science portal, as of September 26, 2023

2. Description of scientific achievements

Scientific achievement resulting from Art. 219 sec. 1 point 2 of the Act of July 20, 2018, Law on Higher Education and Science (Journal of Laws of 2021, item 478, as amended) submitted for the habilitation procedure is a series of 9 publications with a common title:

Structure of metal complexes with bioactive organic ligands.

Series of publications forming the achievement (in the order of appearance):

H1. **A. Drzewiecka-Antonik**, A. E. Koziol, P. Rejmak, K. Lawniczak-Jablonska, L. Nittler, T. Lis, *Novel Ba(II) and Pb(II) coordination polymers based on citric acid: Synthesis, crystal structure and DFT studies,* Polyhedron 132 (2017) 1.

IF = 2.6, citations 9, corresponding author

H2. **A. Drzewiecka-Antonik**, W. Ferenc, P. Rejmak, A. Wolska, M. T. Klepka, B. Cristóvão, B. Mirosław, J. Sarzyński, D. Osypiuk, *Coordination environment of new Co(II), Ni(II) and Cu(II) complexes with 4-bromophenoxyacetic acid: Structural, spectroscopic and theoretical studies,* Polyhedron 133 (2017) 54.

IF = 2.6, citations = 7, corresponding author

H3. **A. Drzewiecka-Antonik**, W. Ferenc, A. Wolska, M. T. Klepka, B. Cristóvão, J. Sarzyński, P. Rejmak, D. Osypiuk, *The Co(II), Ni(II) and Cu(II) complexes with herbicide 2,4-dichlorophenoxyacetic acid – Synthesis and structural studies,* Chem. Phys. Lett. 667 (2017) 192.

IF = 2.8, citations = 19, corresponding author

H4. **A. Drzewiecka-Antonik**, P. Rejmak, M. T. Klepka, A. Wolska, P. Pietrzyk, K. Stępień, G. Sanna, M. Struga, *Synthesis, structural studies and biological activity of novel Cu(II) complexes with thiourea derivatives of 4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione*, J. Inorg. Biochem. 176 (2017) 8.

IF = 3.9, citations = 17, corresponding author

H5. **A. Drzewiecka-Antonik**, W. Ferenc, A. Wolska, M. T. Klepka, C. A. Barboza, B. Cristóvão, D. Osypiuk, J. Sarzyński, B. Tarasiuk, E. Grosicka-Maciag, D. Kurpios-Piec, M. Struga, *Structural characterization and cytotoxic evaluation of Cu(II), Co(II) and Ni(II) complexes with herbicide 4-chloro-2-methylphenoxyacetic acid*, Polyhedron 165 (2019) 86.

IF = 2.6, citations = 4, corresponding author

H6. **A. Drzewiecka-Antonik**, P. Rejmak, M. Klepka, A. Wolska, A. Chrzanowska, M. Struga, *Structure and anticancer activity of Cu(II) complexes with (bromophenyl)thiourea moiety attached to the polycyclic imide*, J. Inorg. Biochem. 212 (2020) 111234.

IF = 3.9, citations = 9, corresponding author

H7. A. Chrzanowska, **A. Drzewiecka-Antonik**, K. Dobrzyńska, J. Stefańska, P. Pietrzyk, M. Struga, A. Bielenica, *The Cytotoxic Effect of Copper (II) Complexes with Halogenated 1,3-Disubstituted Arylthioureas on Cancer and Bacterial Cells*, Int. J. Mol. Sci. 22 (2021) 11415.

IF = 5.6, citations = 8

H8. **A. Drzewiecka-Antonik**, W. Ferenc, B. Mirosław, D. Osypiuk, J. Sarzyński, *Structure, thermal stability and magnetic behavior of Mn(II) complexes with phenoxyacetic acid herbicides*, Polyhedron 207 (2021) 115370.

IF = 2.6, citations = 3, corresponding author

H9. **A. Drzewiecka-Antonik**, M. Struga, A. Głogowska, E. Augustynowicz-Kopec, K. Dobrzyńska, A. Chrzanowska, A. Wolska, P. Rejmak, M.T. Klepka, M. Wrzosek, A. Bielenica, *Synthesis, Structural Characterization and Biological Activity Evaluation of Novel Cu(II) Complexes with 3-(trifluoromethyl)phenylthiourea Derivatives*, Int. J. Mol. Sci. 23 (2022) 15694.

IF = 5.6, corresponding author

The total impact factor (IF) of the journals in which the works included in the habilitation cycle were published (calculated in accordance with the scores for 2022) is **32.2**.

I have included the original versions of the articles in the Attachment 5. I have included the description of my own contribution and the co-authors' statements regarding their contribution to the preparation of the publication in the Attachment 6.

2.1. Introduction and scientific purpose

The aim of my research was to determine the molecular structures of metal complexes with organic ligands of great biological importance, regardless of structural order of the obtained samples. The samples were both in the form of single crystals and powders. I used X-ray diffraction and X-ray absorption methods to characterize complexes. In the case of X-ray absorption spectroscopy, I combined it with other techniques, such as infrared and ultraviolet-visible spectroscopies. Additionally, I designed and synthesized new coordination compounds. In the case of complexes with potential biological activity, I coordinated multidirectional biological investigation and correlated biological properties with the determined structure of new compounds. The structure-activity relationships that I described allow to modify the potency of the complex by changing its structure and indicate the direction in which to search for potential medicinal substances.

The standard method for determining the molecular structure of metal-organic ligand complex is the X-ray crystal structure analysis. It can be used for complexes obtained in the form of crystals of proper quality and dimensions. This technique allows, in addition to determining the structure, to study intra- and inter-molecular interactions. It is advantageous to obtain new compounds in a crystalline form, suitable for studies using X-ray diffraction. One of the ways of obtaining high-quality crystals as a direct product of the complexation reaction is the gel method. I used this method to obtain Pb(II) and Ba(II) complexes with citric acid [H1]. X-ray crystal structure analysis allowed me to determine the molecular structure of new compounds as well as to describe the interactions that stabilize the crystal structure of novel citrates [H1].

The paper on citrates, H1, was published in 2017 together with three other articles describing transition metal complexes, H2-H4. In articles H2 and H3, the complexes with phenoxyacetic acids are presented. The compounds were obtained in the form of microcrystalline powders. As a result of the recrystallization process from organic solvents, I obtained crystals suitable for X-ray crystallography. The research showed the formation of new compounds containing the solvent molecules. Since it was not possible to obtain complexes in the single crystal form as the direct product of the complexation reaction, the standard diffraction method in coordination chemistry could not be used to identify the structure of the studied phenoxyacetates. I also could not use this technique in the case of the second series of compounds - Cu(II) complexes with thiourea derivatives [H4], for which I did not obtain single crystals, even as a result of recrystallization processes.

In order to describe the molecular structure of the complexes obtained in the form of powders, I used a number of research methods. I determined the stoichiometry of the compounds based on the results of (*i*) elemental analysis, (*ii*) X-Ray Fluorescence analysis, XRF, and (*iii*) thermal analysis. I found out about the oxidation state of the metal and the geometry of the complex using (*iv*) UltraViolet-Visible (UV-Vis) spectroscopy, (*v*) magnetic susceptibility measurements and (*vi*) Electron Paramagnetic Resonance (EPR) spectroscopy. Due to the application of (*vii*) Attenuated Total Reflectance – InfraRed (ATR-IR) spectroscopy, I identified deprotonated atoms and atoms coordinating to metal cations. I obtained precise information about the coordination sphere of metals in complexes using (*viii*) X-ray absorption

spectroscopy (XAS). I used both EXAFS (Extended X-ray Absorption Fine Structure) method and XANES (X-ray Absorption Near Edge Structure) technique. EXAFS analysis provided information about the number and type of atoms around the absorbing metal ion, as well as the distances between the absorbing atom and the atoms surrounding it. Additionally, the analysis of XANES spectra allowed to determine the degree of oxidation of metal cations and the spatial distribution of ligands around the metal ion. Based on the obtained data, I determined the molecular structures of complexes, which were refined using computational methods based on Density Functional Theory (DFT).

For the above methods to be applied, a sample does not have to be a single crystal, which increases the diversity of the physical form of the samples, as well as the methods of synthesis of coordination compounds. Including spectroscopic methods to determine the molecular structure of metal complexes with organic ligands, since 2017 I have focused on two series of compounds, Cu(II), Co(II), Ni(II) and Mn(II) complexes with phenoxyacetate herbicides [H2, H3, H5, H8] and Cu(II) complexes with thiourea derivatives [H4, H6, H7, H9].

My first studies on phenoxyacetates included complexes of Cu(II), Co(II) and Ni(II) with 4-bromophenoxyacetic [H2] and 2,4-dichlophenoxyacetic [H3] acids. 2,4-Dichlophenoxy-acetic acid is one of the oldest and most widely used herbicides. My research has shown that there are differences between the molecular structure of complex determined using synchrotron X-ray absorption spectroscopy and the results of diffraction studies for single crystals obtained from recrystallization of the complexes. This is due to the fact that the molecules of the solvent used for crystallization process modify the coordination sphere of the studied complex and often become incorporated into the structure of the dissolved compound. These incompatibilities initiated further studies on this series of compounds, to which I included another popular and widely used herbicide: 2-methyl-4-chlorophenoxacetic acid [H5] and an element commonly found in nature - manganese [H8]. Bearing in mind that the metal-organic ligand complex often has a different biological potential than the initial organic compound (ligand), I conducted biological activity tests. These studies included the determination of the cytotoxic activity of phenoxyacetate complexes, which were not tested unlike the initial herbicides. I have shown that the structure of the ligand molecule, the type of metal cation or coordination modes of the ligand have no influence on the cytotoxic activity of the complex.

In parallel, I conducted research on Cu(II) complexes with 1,3-disubstituted thiourea derivatives. I developed the conditions of synthesis of these compounds, presented in 2017 in article H4, which I used to obtain complexes with following thiourea derivatives: (*i*) tricyclic imides [H4, H6], (*ii*) with the 4-chloro-3-nitrophenyl substituent [H7] and (*iii*) 3-trifluoro-methylphenyl ring [H9]. The analysis of EXAFS, XANES, ATR-IR, UV-Vis, EPR spectra and DFT calculations allowed me to determine the molecular structure of the studied complexes (as in the case of complexes with phenoxyacetic acids). By using the of UV-Vis spectroscopy, I demonstrated the diverse geometry of the coordination sphere of these compounds, both in the solid and liquid states. Additionally, I determined the influence of copper ions on the change in the biological potential of the starting thiourea ligands. By coordinating multidirectional study of the biological activity of the Cu(II) complexes, I showed the diversity of their

biological properties obtained by changing the structure of their molecules. Additionally, I determined the mechanism of action of the most active compounds.

The research I presented is interdisciplinary in nature, including chemistry and pharmacology, but its main core is based on the use of various physical methods to determine the structure of coordination compounds. My scientific achievement, which makes a significant contribution to the knowledge about citrates, phenoxyacetates and thiourea-based chelates, is the determination of the molecular structure of metal complexes with organic ligands, regardless of the degree of structural order of the studied compounds, due to the application of X-ray diffraction and X-ray absorption methods in combination with other research technique. The presented scientific achievement includes a series of 9 articles [H1-H9] published in 2017-2022.

2.2. The detailed description

Gel method and structure of Pb(II) and Ba(II) complexes with citric acid − X-ray crystal structure analysis, ATR-IR and XPS spectroscopies [H1]

Citric acid, abbreviated H_3cit, belongs to the group of hydroxy acids and contains one hydroxyl group (−OH) and three carboxyl groups (−COOH) in its molecule. It occurs naturally in citrus fruits and its ionized form is an intermediate product in the Krebs cycle (also called the citric acid cycle) which is the final stage of aerobic metabolism.[1] It is also widely used in industry and households, as an antioxidant, flavouring or chelating agent.[1] Citric acid and its anions are flexible multidentate *O*-donor organic ligands. These ligands are widely studied due to their biological importance and ability to create a variety of coordination polymers. The Cambridge Structural Database (CSD) contains over 500 structures of metal complexes with citric acid.[2] Despite such a huge amount of citrates, in 2017 I synthesized two new complexes with Ba(II) and Pb(II) cations [H1]. I used the gel method and carried out a number of tests that allowed me to select the optimal synthesis conditions. The parameters that determine the desired course of the complexation reaction are temperature and pH. The synthesis presented in article H1 was based on preparation a gel by mixing aqueous solutions of sodium metasilicate and citric acid. Such gel was an ideal environment for the diffusion of metal salt particles introduced in the form of aqueous solutions onto its surface. Using this method, I carried out the reaction between barium(II)/lead(II) nitrates(V) and citric acid (Fig. 1). I obtained crystals that I initially examined using X-ray photoelectron spectroscopy (XPS). Based on the analysis of the survey spectrum, I determined the stoichiometry of the obtained complexes and excluded the presence of sodium or silicon atoms that could be incorporated into the structure of the complexes during the crystallization process. The interpretation of the high-resolution XPS spectra (the O 1s line) measured for the starting ligand and its complexes, indicated significant deprotonation of citric acid, also visible in the comparative analysis of ATR-IR spectra of the tested compounds [H1].

[1] R. Reena et al., *Insight into citric acid: a versatile organic acid*, Fuel 327 (2022) 125181; https://doi.org/10.1016/j.fuel.2022.125181
[2] C.R. Groom et al., *The Cambridge Structural Database*, Acta Cryst. B72 (2016) 171; https://doi.org/10.1107/S2052520616003954

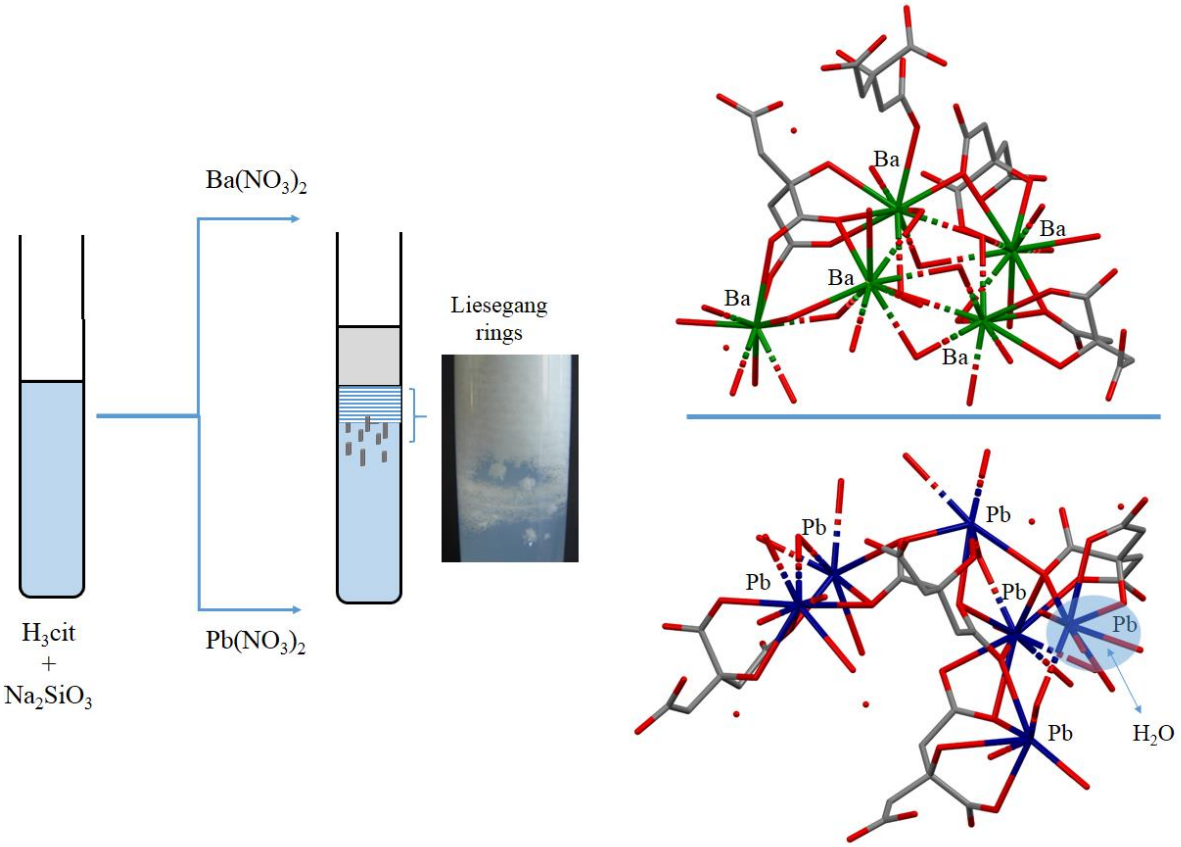

Fig. 1. A synthetic route of Ba(II) and Pb(II) citrates with the molecular structure of the obtained complexes. In the case of Pb(II) citrate, one of the cations is interchange with a water molecule.

Then, I performed X-ray crystal structure analysis for the obtained complexes. The analysis showed the formation of hydrates with the formulas $\{[5Ba^{2+}(cit^{3-})_2(Hcit^{2-})_2 \cdot 6H_2O] \cdot 2H_2O\}_n$ and $\{[5{,}5Pb^{2+}(cit^{3-})_3(Hcit^{2-}) \cdot 5H_2O] \cdot 4{,}5H_2O\}_n$. The structure of the complexes is shown in Figure 1. Both compounds crystallize in the triclinic space group Pī and show a three-dimensional structure with two types of citric acid anions (two and three deprotonated). The asymmetric part of the unit cell of both complexes contain 5 or 6 metal cations. The distances between the metal cation and oxygen atoms in the first coordination sphere range from 2.673(5) to 3.121(4) Å for Ba(II) complex, and the distances of Pb–O are in the range 2.453(9)−2.927(9) Å. The coordination number of Ba(II) varies from 9 to 11, and in the case of Pb(II) from 6 to 9. High coordination numbers cause that one of the citrate anions is linked with thirteen lead cations or fourteen barium cations, respectively. This high denticity of ligands as well as strong O−H…O interactions lead to the formation of stable three-dimensional structures (Fig. 2). A significant difference in the structure of both polymers is related to the different arrangement of oxygen atoms around the cations. Pb(II) cations, in contrast to Ba(II), show a clear anisotropy in the distribution of neighbouring O atoms. Such anisotropic coordination geometry is common among Pb(II) complexes with *O*-donor ligands and is associated with the presence of a stereochemically active pair of electrons located on the Pb(II) cation, which was confirmed by DFT calculations [H1].

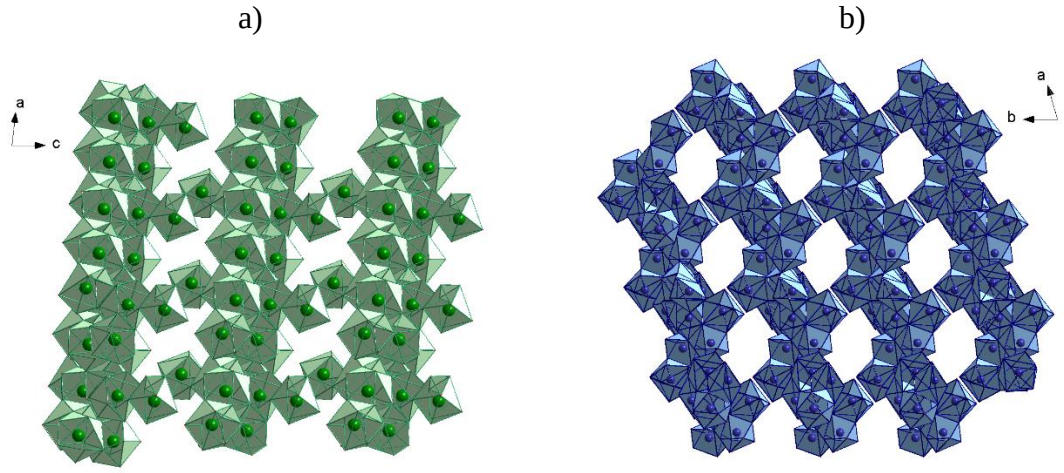

Fig. 2. Three-dimensional network of coordination spheres of Ba(II) (left) and Pb(II) (right) cations in citrate crystals.

Structural changes in Cu(II), Co(II) and Ni(II) complexes with phenoxyacetic acid derivatives − X-ray diffraction and absorption methods, ATR-IR and UV-Vis spectroscopies, magnetic studies, DFT calculations [H2, H3, H5]

Another group of bioactive organic ligands that became the object of my research were chlorophenoxyacetic herbicides. These compounds have been available on the market since the 1940s and are currently among the group of pesticides widely used around the world. These types of compounds are synthetic auxins used to combat broadleaf weeds.[3] The most common herbicides from this group are 2,4-dichlorophenoxyacetic acid and 4-chloro-2-methylphenoxyacetic acid, abbreviated as 2,4-D and MCPA, respectively. Both compounds are only slightly toxic, and reported cases of poisoning resulted from accidental ingestion of these herbicides.[4] It has also been observed that if used incorrectly they can irritate the eyes, mucous membranes and skin. The scope of application of both herbicides is similar and they can be used to protect cereals, sports fields and golf courses. MCPA was discovered in England, making it more popular in Europe, while the herbicide 2,4-D was first synthesized in the United States and is widely used in the US and Canada.

Chlorophenoxyacetic herbicides are introduced into the environment in various forms - as free acids, alkali salts, amine salts or esters. All these forms dissociate in water, forming acid anions and remain in the soil for about a month. Soil microorganisms are primarily responsible for their disappearance. However, before they are degraded by microorganisms, they can react with elements present in the soil or plant tissues. In 2017, the uptake and transfer of metal ions such as Cu(II), Co(II) and Ni(II) by phenoxyacetate herbicides such as 2,4-D and MCPA was documented.[5] Therefore, it has become important to study the structure and biological properties of such connections.

[3] R. Krieger, Hayes' Handbook of Pesticide Toxicology (Third Edition), 2010.
[4] M.E. Peterson, P.A. Talcot, Small Animal Toxicology, 2013.
[5] E. Skiba et al., *Influence of 2,4-D and MCPA herbicides on uptake and translocation of heavy metals in wheat (Triticum aestivum L.)*,Environ. Pollut. 220 (2017) 882; https://doi.org/10.1016/j.envpol.2016.10.072

In the case of Cu(II), Co(II) and Ni(II) connections with the MCPA herbicide, X-ray crystal structure analysis was performed only for mixed Cu(II) and Ni(II) complexes that contain an additional *N*-donor ligand, as phenanthroline or pyridine derivatives.[2] More structural data can be found in the crystallographic database for Cu(II), Co(II) and Ni(II) complexes with the 2,4-D herbicide. Apart from the dominant mixed complexes with an additional *N*-donor ligand, simple connections of metal cations only with phenoxyacetate anions can be found. The copper complex exists both as a monomeric and dimeric compound, and the cobalt complex has a monomer and polymer structure. This structural diversity is caused by the use of different reagents during the synthesis, mainly the solvent. Additionally, the structure of the complex molecule can be modified during the recrystallization process, what I noticed during my previous research on my doctoral dissertation. Furthermore, the solvent used to crystallize the complex often is included into the coordination sphere of the metal cation.

I decided to check whether the complex molecules resulting from the complexation reaction of phenoxyacetic acids would have the same structure as the structure of the compound determined by diffraction on single crystals obtained as a result of the recrystallization process. For this purpose, I tested the complexes of Cu(II), Co(II) and Ni(II) with 4-bromophenoxyacetic acid [H2]. Based on the results of elemental and thermal analyses and measurements using X-ray fluorescence, I determined the stoichiometry of the compounds. In all the cases, the complex molecules contain one metal cation, two anions of 4-bromophenoxyacetic acid and four (complexes of cobalt and nickel) or two (complex with copper) water molecules. The presence of water was confirmed by analysing ATR-IR spectra. Additionally, I observed deprotonation of the –COOH group and I excluded coordination through the O_{ether} and Br atoms (Fig. 3a). The analysis of UV-Vis spectra (Fig. 3b) and magnetic measurements allowed me to conclude that (*i*) the metal ion in the complexes is in the +2 oxidation state, (*ii*) the Co(II) and Ni(II) complexes have octahedral geometry, (*iii*) the geometry of the Cu(II) complex has low symmetry and (*iv*) the tested compounds are mononuclear complexes. Based on experimental data, I proposed structural models of the complexes, which were optimized using density functional theory calculations. In parallel, I conducted experiments at the XAFS station at the Elletra synchrotron in Trieste. The calculated structural models were used as starting models for the EXAFS analysis, which gave information about the number and type of atoms surrounding the metal cation, and the distances between the metal ion and the coordinating atoms. Based on this data, I determined the molecular structure of the studied complexes [H2].

In the case of the Co(II) and Ni(II) complexes, I identified two monodentate carboxylate groups and four water molecules in an octahedral arrangement around the metal cation, while the Cu(II) complex has three O atoms from two carboxylate groups (one monodentate and one bidentate) and two water molecules, in the first coordination sphere (Fig. 4, powders). In parallel, I analysed data obtained from X-ray diffraction on a single crystal of the Cu(II) complex obtained

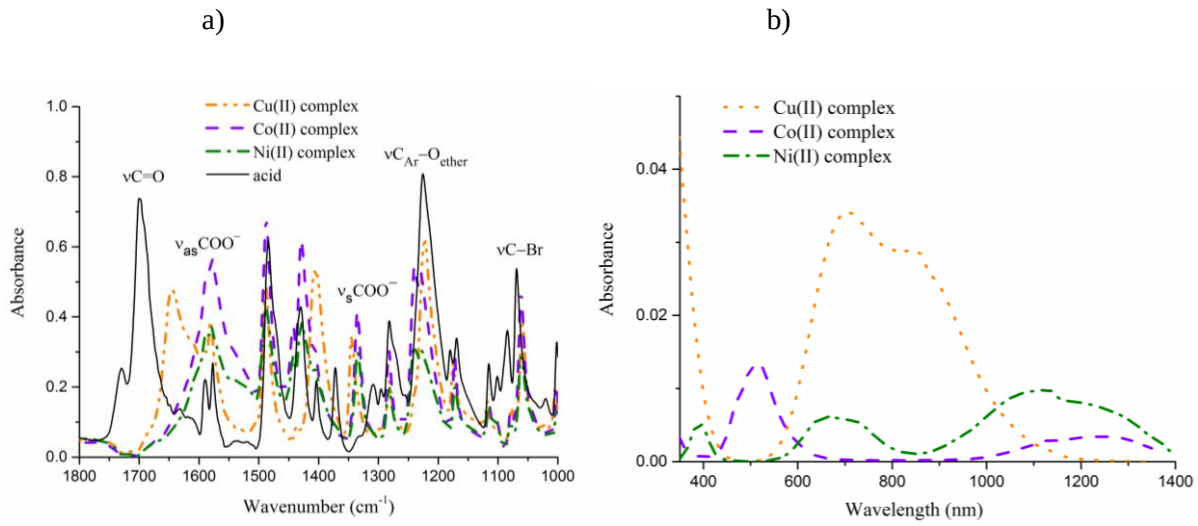

Fig. 3. (a) ATR-IR spectra of 4-bromophenoxyacetic acid and its complexes (b) UV-Vis spectra of complexes.

by recrystallization from *N*,*N*-dimethylformamide (DMF). The analysis showed the formation of a dinuclear complex in which Cu(II) cations are connected by bridging carboxylate groups (Fig. 4, crystals). A tetragonal pyramid is formed around both cations, the top of which is made up of the O atom of the solvent molecule, while the base is made up of four O atoms of four anions of 4-bromophenoxyacetic acid. To sum up, the complex with copper, being the product of the complexation reaction, is mononuclear, and as a result of the recrystallization process it becomes dinuclear, and additionally contains solvent molecules in its structure.

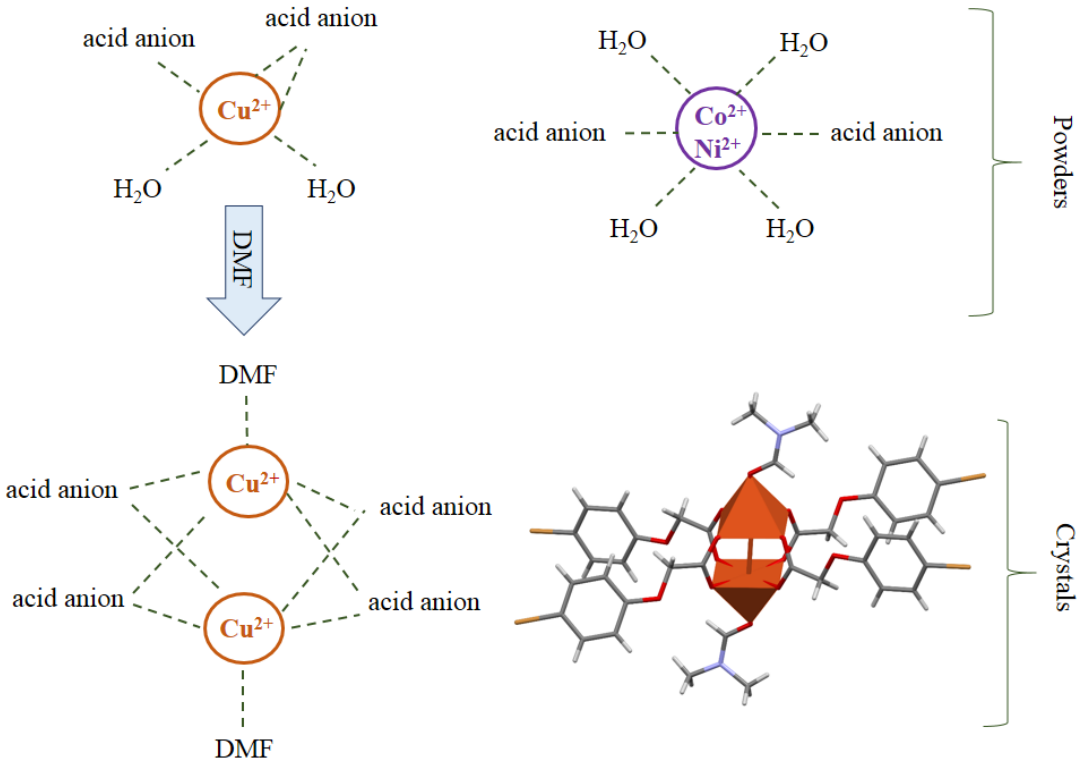

Fig. 4. Scheme: the determined molecular structures of Cu(II), Co(II) and Ni(II) complexes with 4-bromophenoxyacetic acid for powdered samples (top, powders) and the molecular structure of the Cu(II) complex obtained from X-ray crystal structure analysis after recrystallization from dimethylformamide, DMF (bottom, crystals).

Due to the described structural changes occurring for a representative 4-bromophenoxyacetate complex with Cu(II), I decided to perform structural characterization of Cu(II), Co(II) and Ni(II) complexes with two popular herbicides, 2,4-D and MCPA. I presented this research in two subsequent articles H3 and H5. The studied compounds were obtained in the form of microcrystalline powders. In order to describe the molecular structure of these compounds, which were an unmodified product of the complexation reaction, I correlated the results obtained from laboratory techniques as well as synchrotron methods. XAFS measurements were carried out at the Swedish synchrotron MAX-lab (complexes with 2,4-D), and at the Italian Elettra synchrotron (complexes with MCPA).

The structural characterization indicated the formation of complexes in which there are two acid anions per one metal cation. Five complexes are hydrates: $Co(2,4\text{-}D)_2 \cdot 6H_2O$, $[Co(MCPA)_2(H_2O)_4] \cdot H_2O$; $Ni(2,4\text{-}D)_2 \cdot 4H_2O$; $[Ni(MCPA)_2(H_2O)_4] \cdot H_2O$; $Cu(2,4\text{-}D)_2 \cdot 4H_2O$, and one complex is an anhydrous polymer: $[Cu(MCPA)_2]_n$. By comparative analysis of ATR-IR spectra of herbicides and their metal complexes [H3, H5], I demonstrated the deprotonation of the carboxyl group of the phenoxyacetic herbicides. Additionally, I found that the positions and shapes of the bands corresponding to the asymmetric vibrations of the carboxylate group in the spectra of complexes with Cu(II) are different than in the spectra of Co(II) or Ni(II) hydrates. This indicated a different geometry of copper complexes from cobalt and nickel coordination compounds. Moreover, I showed that both the O_{ether} atom and the Cl atom do not enter the coordination sphere of the central ion. Through the analysis of UV-Vis spectra and qualitative XANES analysis, I found that all metal cations in the considered complexes are in the +2 oxidation state [H3, H5]. Additionally, the detailed analysis of electronic transitions in the molecules of the complexes, correlated with magnetic studies, allowed me to draw the following conclusion: Co(II) and Ni(II) connection with both herbicides are high-spin octahedral complexes, while Cu(II) complexes with 2,4-D and MCPA adopt a deformed flat square geometry [H3, H5].

Based on experimental data, I proposed structural models of the complexes, which were initially optimized using DFT methods and verified by EXAFS analysis. Best-fit models were used to generate a theoretical XANES spectrum. The last stage was the comparison of the calculated spectrum with the experimental XANES spectrum for the final verification of the proposed model. In this way, I determined the structure of the molecules of the studied complexes. In the case of metal complexes with 2,4-D herbicide and cobalt and nickel connection with MCPA herbicide, two carboxylate groups (COO^-) coordinate in a monodentate way. The coordination sphere is completed by water molecules: 4 for the Ni(II) and Co(II) complexes and 2 for the copper complex with 2,4-D acid (Fig. 5, powders). For the anhydrous polymer $[Cu(MCPA)_2]_n$, the coordination sphere is formed by 4 O atoms of 4 bridging carboxylate groups (Fig. 5, powders). The spatial arrangement of the ligands forces an octahedral geometry around Co(II) and Ni(II) cations, and deformed flat square geometry is observed for Cu(II) complexes.

The molecular structure determined for the complexes in powder form was then compared with the geometry of two representative compounds, Ni(II) complexes with 2,4-D herbicide and Cu(II) with MCPA acid, determined using X-ray diffraction methods. The crystals suitable for

X-ray crystallography were obtained by recrystallization from *N*,*N*-dimethylformamide, DMF. The asymmetric units of both complexes contains one metal cation, two deprotonated acid molecules and solvent molecule used in the recrystallization process. A tetragonal pyramid is formed around both Ni(II) and Cu(II) cations. Its top is filled with the O atom of the solvent molecule, and the base is built by four O atoms of the four anions of the appropriate herbicides. The anions coordinate through the carboxylate group, which bridges two adjacent coordination polyhedra, resulting in the formation of dinuclear complexes (Fig. 5, crystals). The Ni/Cu−O distances range from 1.95 to 2.12 Å. The oxygen atoms of the solvent molecules are located furthest from the metal canter. The intermetallic distances of Cu−Cu and Ni−Ni are 2.65 Å. These values are typical for similar dinuclear complexes. The weak C−H…O and C−H…Cl intermolecular interactions are responsible for the formation of a three-dimensional structure of both complexes.

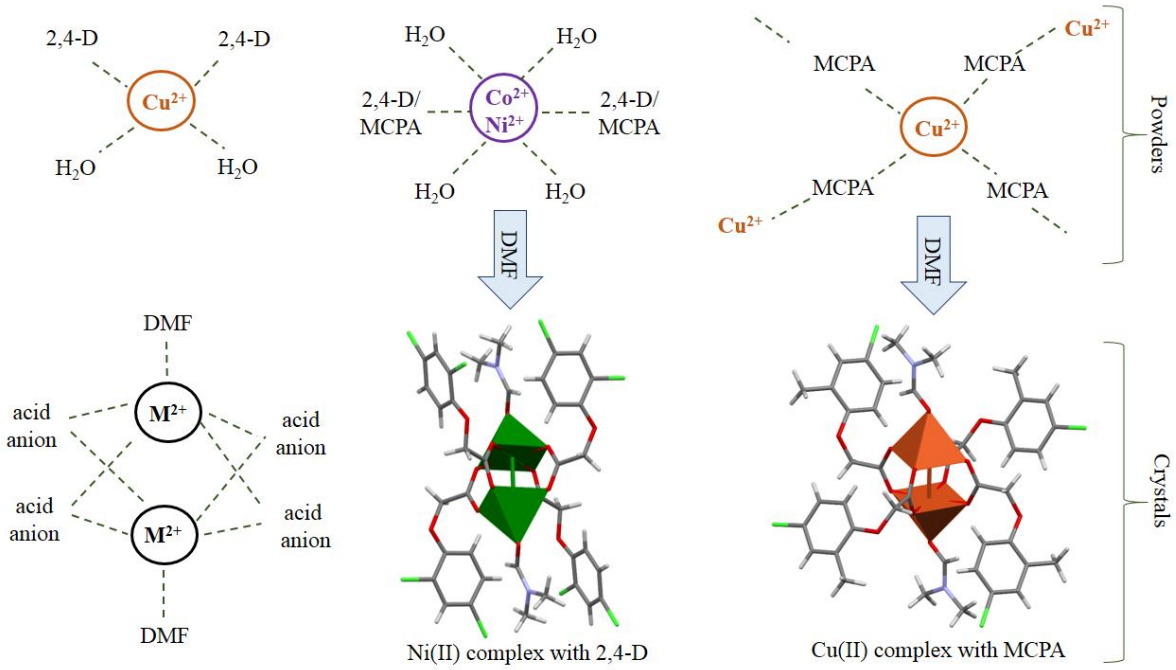

Fig. 5. Diagram presenting the molecular structures of Cu(II), Co(II) and Ni(II) complexes with the herbicides, 2,4-D and MCPA, determined for powdered samples (top, Powders) and the molecular structures of representative complexes, after recrystallization from dimethylformamide, DMF, determined by X-ray diffraction method (bottom, Crystals).

To sum up, I showed, on the example of a representative monomeric complex of Ni(II) with the 2,4-D herbicide, that the recrystallization leads to the formation of a dimeric structure containing the solvent molecules used for recrystallization process. Additionally, the geometry around the metal cation changes from octahedral to tetragonal pyramidal. In the case of the square polymeric complex $[Cu(MCPA)_2]_n$, the recrystallization process resulted in the formation of a dimer with an analogous structure as in the case of the dimeric Ni(II) complex. Due to these studies, I confirmed that the recrystallization process modifies the coordination sphere of the complex and in order to correctly determine the structure of the studied compound, a number of research methods based on elemental and thermal analysis, magnetic studies as well as ATR-IR and UV-Vis spectroscopies should be used. More detailed information provide

X-ray absorption spectroscopy (EXAFS, XANES) correlated with DFT calculations. Using all these methods allowed me to determine the molecular structure of compounds being in the form of microcrystalline powders.

In parallel with the structural studies, biological activity tests of Cu(II), Co(II) and Ni(II) complexes with herbicides (2,4-D and MCPA) were carried out at the Medical University of Warsaw [H5]. Both the initial herbicides and their metal complexes showed low cytotoxic potential towards Chinese hamster lung fibroblasts (V79) and human immortalized keratinocyte cells (HaCaT). The inhibitory concentration at which cell survival is inhibited by 50%, IC_{50}, ranged from 65 to >200 μM. These values indicate the lack of cytotoxicity towards the tested cells of living organisms. By correlating the results of the structural analysis with the activity of the complexes, it can be concluded that the structure of the phenoxyacetate ligand, the type of metal cation or the coordination polyhedron do not influence the cytotoxic effect of the complexes.

Structural characterization of Mn(II) complexes with phenoxyacetic acids − X-ray diffraction, ATR-IR spectroscopy, magnetic studies [H8]

Since the divalent manganese present in soil and plant tissues can interact with anions of phenoxyacetic acids such as MCPA or 2,4-D, forming stable connections[5], I decided to expand my research on this element. Thus, manganese complexes with 4-bromophenoxyacetic acid, MCPA and 2,4-D were included in the studies. The coordination compounds were obtained analogously to Cu(II), Co(II) and Ni(II) phenoxyacetates. The final product of the complexation reaction was in the form of a microcrystalline powder. The fluorescence X-ray analysis as well as elemental and thermal analyses allowed me to conclude that there are two acid anions per one metal cation. Moreover, all analysed compounds were hydrates. By analysing the infrared spectra, I showed (*i*) deprotonation of acids (Fig. 6a), (*ii*) similar binding of phenoxyacetate anions with the metal cation within the studied group of complexes (Fig. 6b), (*iii*) similar binding of ligands to the Mn(II) cation as for Co(II) and Ni(II) cations in the previously presented analogous octahedral complexes [H2, H3, H5], and I excluded (*iv*) coordination of the ligand through the O_{ether} atom and the halogen atom. The measured values of the magnetic susceptibility of the complexes confirmed that the studied compounds have octahedral geometry [H8]. The coordination polyhedron around Mn(II) cations is built by oxygen atoms of the carboxylate group and water molecules.

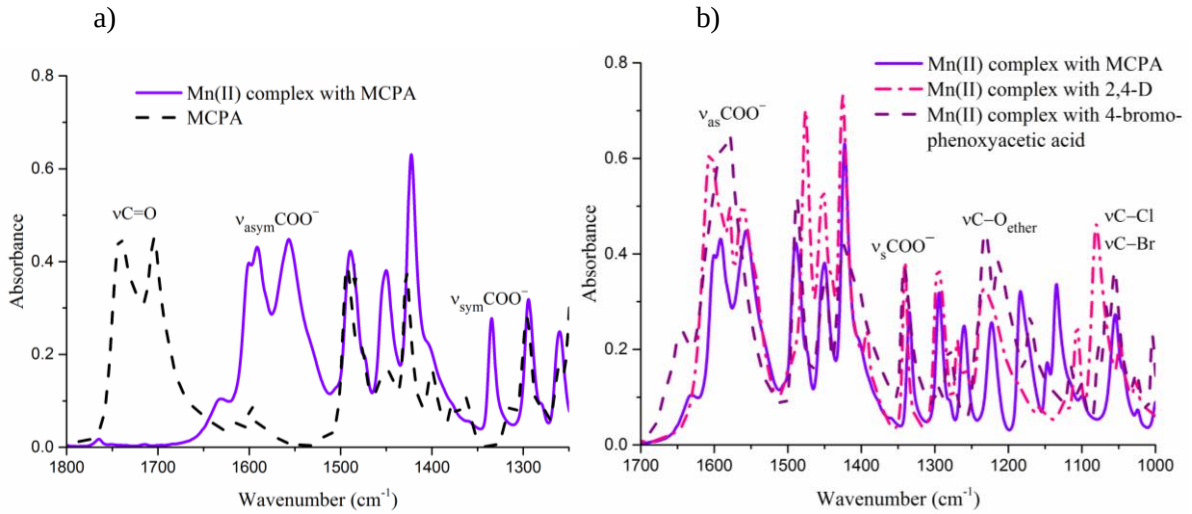

Fig. 6. ATR-IR spectra of (a) the MCPA herbicide and its complex with Mn(II) in the range of 1800–1200 cm^{-1} and (b) the Mn(II) complexes in the range of 1700–1000 cm^{-1}.

During the studies I proved that coordination sphere can be rearranged. The Mn(II) complex with 4-bromophenoxyacetic acid, characterized by the weakest binding of water molecules, dissolved in *N*,*N*-dimethylformamide (DMF), detached water molecules and attached DMF ones. X-ray crystal structure analysis showed that the asymmetric unit of the new compound consists of one metal cation, one DMF molecule and two deprotonated acid anions. This fragment, multiplied by three-fold inversion axis, creates a cyclic closed hexameric unit presented in Figure 7a. In this unit, the Mn…Mn distances are 3.677(6) Å, and the Mn–O distances range from 2.141(2) to 2.223(2) Å. In the crystal lattice, the sixnuclear coordination units were arranged in columns along the crystallographic *c* axis (Fig. 7b).
Due to the hydrophobic outer layer of the complex, only weak intermolecular interactions C−H…O, C−H…Br and Br…Br occur between the molecules. The resulting complex is unique because it contains Mn only in the +2 oxidation state. Analogous multi-ring manganese carboxylate clusters contain manganese cations in two oxidation states simultaneously: +2 and +3.[6]

Additionally, Mn(II) complexes with 4-bromophenoxyacetic acids, MCPA and 2,4-D were tested at the Medical University of Warsaw for cytotoxic activity. The studies were performed on Chinese hamster lung fibroblasts (V79) and human immortalized keratinocyte cells (HaCaT). The results showed no cytotoxicity towards the tested cells of living organisms.

[6] M. Darii et al., *Incorporation of Hexanuclear Mn(II, III) Carboxylate Clusters with a Mn6O2 Core in Polymeric Structures*, Crystals 8 (2018) 100; https://doi.org/10.3390/cryst8020100

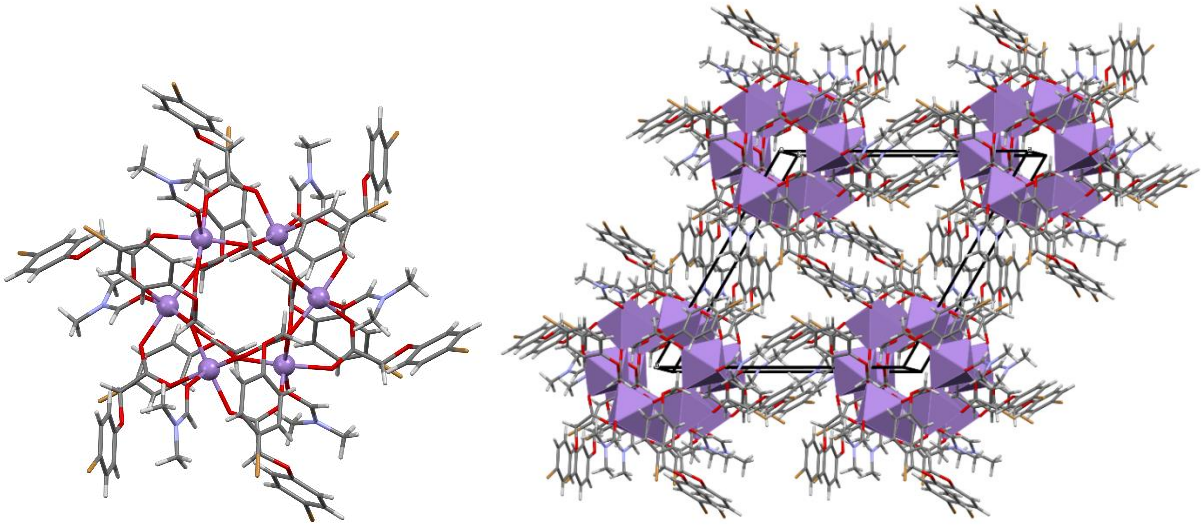

Fig. 7. Mn(II) complex with 4-bromophenoxyacetic acid: a) molecular structure, (b) crystal packing.

Synthesis, structural characterization of Cu(II) complexes with thiourea derivatives − ATR-IR, UV-Vis, EPR, EXAFS, XANES spectroscopies and DFT calculations [H4, H6, H7, H9]

In parallel to studies on citrates and phenoxyacetates, I have been dealing with the synthesis and structural analysis of Cu(II) complexes with thiourea derivatives. Thiourea derivatives, containing the N−C(=S)−N moiety, exhibit a wide spectrum of biological activity, including antibacterial[7], antiviral [8] and anticancer properties [9], and the thiourea system is found in several currently used drugs.[10] Moreover, these compounds can act as organic ligands because they are able of coordinating to metal ions. Their molecules contain sulfur and nitrogen atoms, which can bind to the metal in various ways. So far, complexes with thiosemicarbazones containing the C=N−N−C(=S)−N fragment have been widely studied. These derivatives form stable bonds with metal ions and can easily penetrate cell membranes. Their complexes with copper have antimicrobial, antimalarial and anticancer properties.[11] They are also structurally diverse - their

[7] S. Y. Abbas et al., *Thiourea derivatives incorporating a hippuric acid moiety: Synthesis and evaluation of antibacterial and antifungal activities*, Eur. J. Med. Chem. 64 (2013) 111, https://doi.org/10.1016/j.ejmech.2013.04.002

[8] I. Kucukguzel et al., *Synthesis of some novel thiourea derivatives obtained from 5-[(4-aminophenoxy)methyl]-4-alkyl/ aryl-2,4-dihydro-3H-1,2,4-triazole-3-thiones and evaluation as antiviral/anti-HIV and anti-tuberculosis agents*, Eur. J. Med. Chem. 43 (2008) 381, https://doi.org/10.1016/j.ejmech.2007.04.010

[9] Zhong-Hua Li et al., *Design, synthesis and preliminary biological evaluation of new [1,2,3]triazolo[4,5-d]pyrimidine/thiourea hybrids as antiproliferative agents*, Eur. J. Med. Chem. 139 (2017) 741, https://doi.org/10.1016/j.ejmech.2017.08.042

[10] R. Ronchetti et al., *Recent advances in urea- and thiourea-containing compounds:Focus on innovative approaches in medicinal chemistry and organic synthesis*, RSC Med. Chem. 12 (2021**)** 1046; https://doi.org/10.1039/D1MD00058F

[11] C. Duncan and A.R. White, *Copper complexes as therapeutic agents*, Metallomics 4 (2012) 127; https://doi.org/10.1039/c2mt00174h

complexes with Cu may have a flat square, tetrahedral or octahedral geometry. [12].Despite this fact, only few bioactive copper complexes with thiourea derivatives have been obtained. When I started working at the IP PAS, the only information available was related to a series of Cu(II) complexes based on cinnamoyl thiourea having antibacterial activity[13] or disubstituted cyclic thiourea derivatives complexed with Cu, Ag, Au, having cytotoxic activity towards cancer cells[14]. The authors of the latter work suggested that complexes being a new class of inorganic drugs can be searched for by differentiating thiourea-based ligands and coordinating them to metals with the d^{10} configuration. Bearing this suggestion in mind as well as seeing the growing threat of lifestyle diseases, I decided to design and synthesize copper complexes based on thiourea derivatives in order to obtain new, cheap, non-toxic compounds with antibacterial and anticancer properties.

In 2017, I published the newly design synthesis of copper(II) complexes with thiourea derivatives (Fig. 8, article H4). To carry out the synthesis I used 1,3-disubstituted thiourea derivatives containing various halogenophenyl fragments. The differentiating substituents in the thiourea system as well as the introducing various halogen atoms gave me the opportunity to evaluate the impact of a heterocyclic substituent on the biological activity of a given complex, as well as to obtain coordination compounds with different biological properties. By carrying out the synthesis, shown in Figure 8, I obtained 25 new complexes. These compounds were characterized in four articles that are part of my scientific achievement: H4, H6, H7, H9. Among the obtained complexes, three series can be distinguished, differing in substitutions at the thiourea moiety, namely (*i*) complexes with a cyclic imide and a bromophenyl substituent [H4, H6], (*ii*) complexes with a 4-chloro-3-nitrophenyl ring [H7] and (*iii*) derivatives of 3-(trifluoromethyl)phenylthiourea [H9].

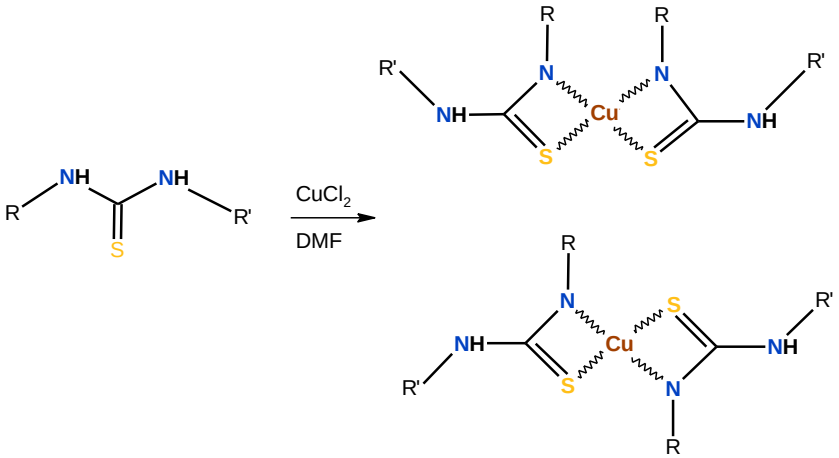

Fig. 8. Synthesis of Cu(II) complexes with thiourea derivatives, where R and R' represent ring substituents.

[12] T.S. Lobana et al., *Bonding and structure trends of thiosemicarbazone derivatives of metals—an overview*, Coord. Chem. Rev. 253 (2009) 977; https://doi.org/10.1016/j.ccr.2008.07.004
[13].M.M. Shoukry et al., *Metal Chelates of Cinnamoylthioureas*, Synth. React. Inorg. Met. Org. Chem. 19 (1989) 749; https://doi.org/10.1080/00945718908048109
[14] K. Yan et al., *Gold(I) complex of N,N'-disubstituted cyclic thiourea with in vitro and in vivo anticancer properties—potent tight-binding inhibition of thioredoxin reductase*, Chem Commun. 46 (2010) 7691; https://doi.org/10.1039/C0CC01058H

The compounds were in the form of powder. I could not obtain a single crystal for diffraction studies despite attempts at crystallization from various solvents. Therefore, I used a number of experimental techniques to describe the molecular structure of synthesized compounds (analogously to structural studies of phenoxyacetic acid derivatives). I applied elemental analysis, ATR-IR, UV-Vis, EPR and XAFS spectroscopies. XAFS measurements were performed at the Elettra synchrotron in Italy.

Based on the results of elemental analysis and interpretation of ATR-IR spectra of synthesized complexes, I found that there are two thiourea anions per one metal cation, and the obtained compounds are mostly hydrates. The analysis of EPR, UV-Vis spectra [H4, H6, H7, H9] and qualitative XANES analysis (Fig. 9) confirmed that the obtained complexes contain Cu in the +2 oxidation state.

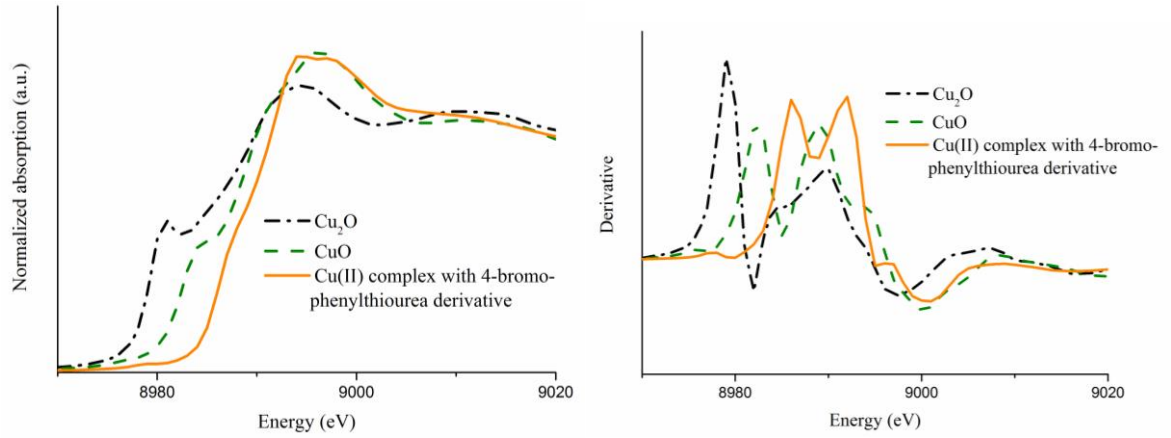

Fig. 9. XANES spectra for two reference oxides and a representative Cu(II) complex with a 4-bromophenylthiourea derivative [H4].

Infrared spectroscopy studies allowed me to identify the atoms coordinating to the metal cation. The complexes presented in articles: H4, H6, H7 contain thiourea derivatives that are potential *N*,*S*,*O*-donor ligands, and the compounds presented in article H9 can act only as *N*,*S*-donor ligands. Halogen atoms, present in the structure of molecules in each of the presented series, may also interact with the metal ion. By analysing the presence, shape and position of the bands corresponding to the vibrational vibrations of the groups present in the molecules of the initial ligands and their complexes (Fig. 10), I indicated that the sulfur and nitrogen atoms of the thiourea moiety coordinate to the metal cation. Moreover, I excluded the presence of oxygen and halogen atoms in the first coordination sphere of Cu(II).

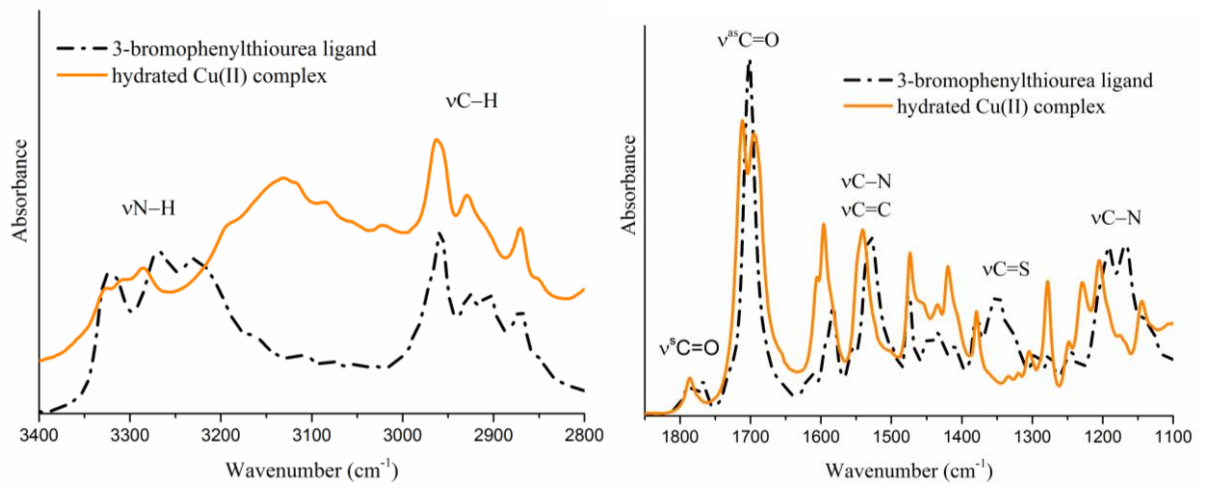

Fig. 10. Assignment of bands in ATR-IR spectra in the ranges (a) 3400–2800 cm^{-1} and (b) 1850–1100 cm^{-1} for a representative complex and the starting ligand with a cyclic imide ring saturated with methyl substituents [H6].

The analysis of the EXAFS spectra indicated that two S and two N atoms coordinate to the metal ion. The nitrogen atom is at a distance of about 2 Å from Cu(II), and the Cu−S bond lengths are in the range of 2.2−2.3 Å. An additional peak could be observed in the EXAFS spectra of selected compounds within individual series of complexes, suggesting the presence of another copper cation slightly below 3 Å (Fig. 11). The EXAFS analysis confirmed the presence of Cu…Cu interactions for these complexes, and also showed the presence of additional C, N or S atoms in the coordination sphere of the analysed cation.

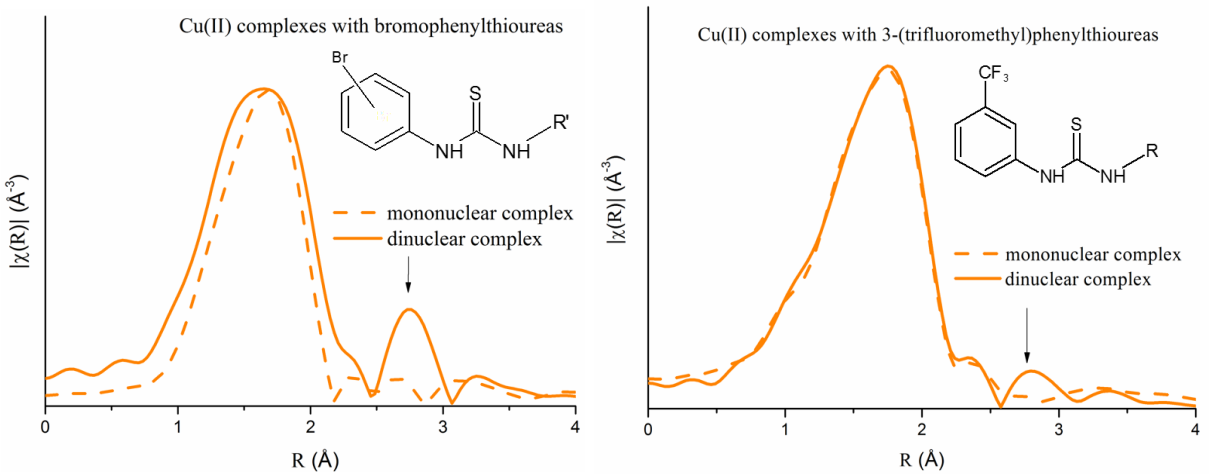

Fig. 11. Experimental functions of the radial distribution of atoms around the Cu(II) cation for two representative complexes with a) bromophenylthiourea derivatives [H4] and b) 3-(trifluoromethyl)-phenylthiourea derivatives [H9].

Based on the conclusions from the experimental data, I proposed structural models of the studied complexes: mononuclear and dinuclear ones, which were optimized using DFT computational methods and verified by reanalysis of EXAFS. The determined molecular

structure of the obtained coordination compounds is presented in the synthesis diagram (Fig.8). As can be seen more detailed in Figure 12, regardless of the symmetry of the compound, the complex molecule consists of two ligand molecules chelating to one copper(II) cation. Chelation occurs via the thiocarbonyl S atom and the deprotonated N atom of the thiourea system. This bidentate coordination causes the Cu(II) ion becomes a part of two four-membered Cu-S-C-N rings.

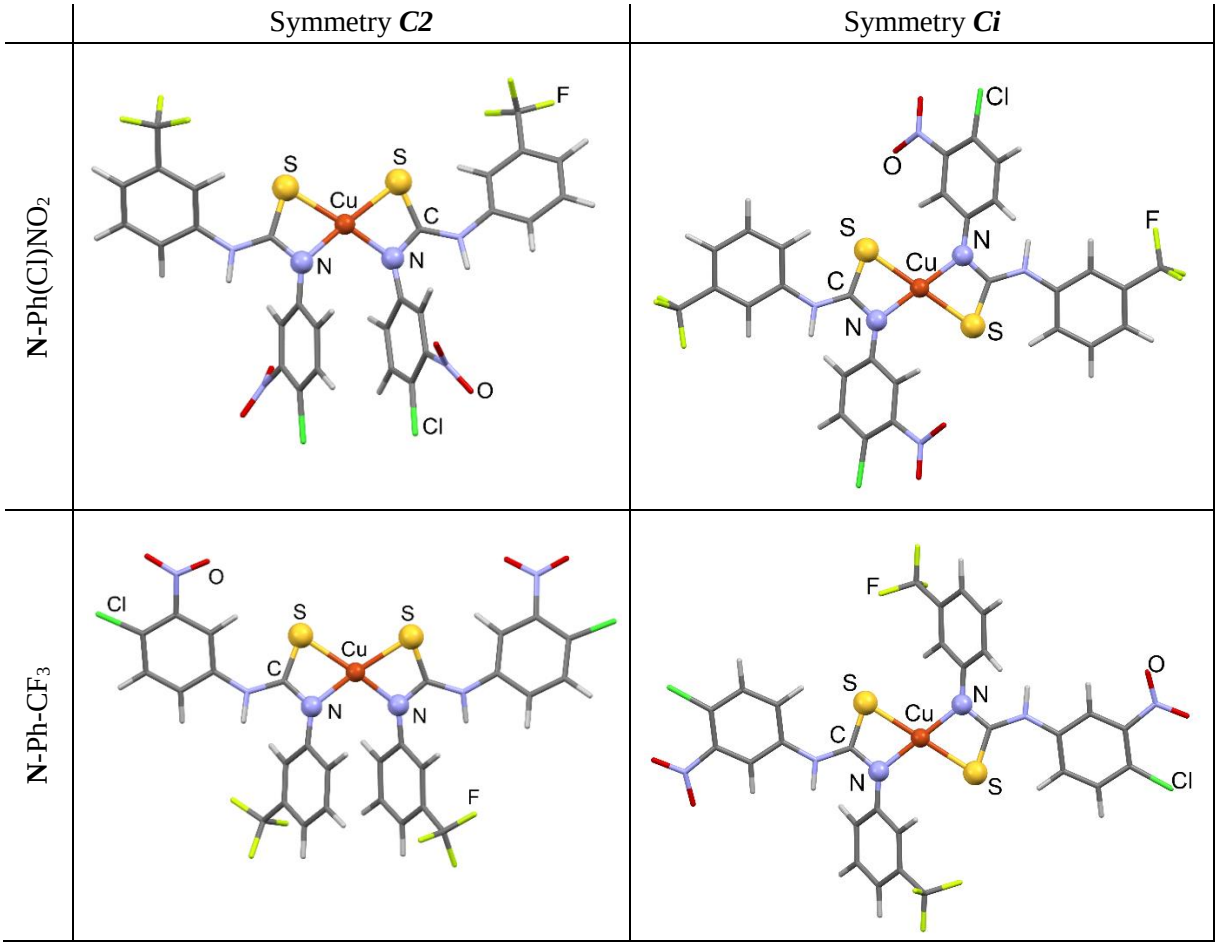

Fig. 12. Molecular structures determined for a representative monomeric complex of Cu(II) with the 3-(trifluoromethyl)phenylthiourea derivative [H9] with the CuN_2S_2 coordination sphere present in the structure of all anayled complexes. For the presented series, the most energetically stable structure turned out to be the compound with *C2* symmetry, where the nitrogen atom attached to the 3-(trifluoromethyl)phenyl substituent does not deprotonate and does not interact with the Cu(II) cation.

These types of rings are rarely found in copper complexes. First, D.P. Singh [15] in 2014, presented the crystal structure of the complex with the Cu(II) cation, which is part of a four-membered ring, chelated by thiourea ligands in a *trans* manner. Most recently, in 2022, another

[15] D.P. Singh et al., *Solvent induced geometry transformation of trigonal planar Cu(I) complexes of N-((2/4-methyoxy carbonyl) phenyl)-N'-(ethoxy/methoxy carbonyl) thiocarbamides to square-planar Cu(II) complexes: Synthesis, spectral, single crystal, DFT and in vitro cytotoxic study*. Inorganica Chim. Acta. 423 (2014) 386; https://doi.org/10.1016/j.ica.2014.08.031

paper was published[16] presenting two polymorphic forms of the complex, where molecules of the deprotonated arenosulfonylthiourea derivative chelate Cu(II) to form four-membered rings and with the centre of symmetry on the copper cation. The complexes I synthesised, depending on the type of substituents on the thiourea system, have *C2* or *Ci* symmetry. *C2* symmetry forces the *cis* orientation of organic ligands around the metal cation, while in a molecule with the centre of symmetry on the Cu(II), the *trans* position of the same ligands is observed (Fig. 12). In Figure 12 the molecular structures considered for one of the series of complexes are presented. I considered not only different symmetry of the molecule but also I defined the nitrogen atom of the thiourea system that was deprotonated and coordinated to the metal central ion. The presented molecules, in some of the studied complexes, formed sandwich dimers [H4, H6, H9]. Analogously to mononuclear complexes, different symmetry of the molecule was considered. Moreover, the nitrogen atom of the thiourea moiety, which deprotonated and coordinated to Cu(II) was identified. The characterization of sandwich dimers is presented in the published articles and in Figure 13.

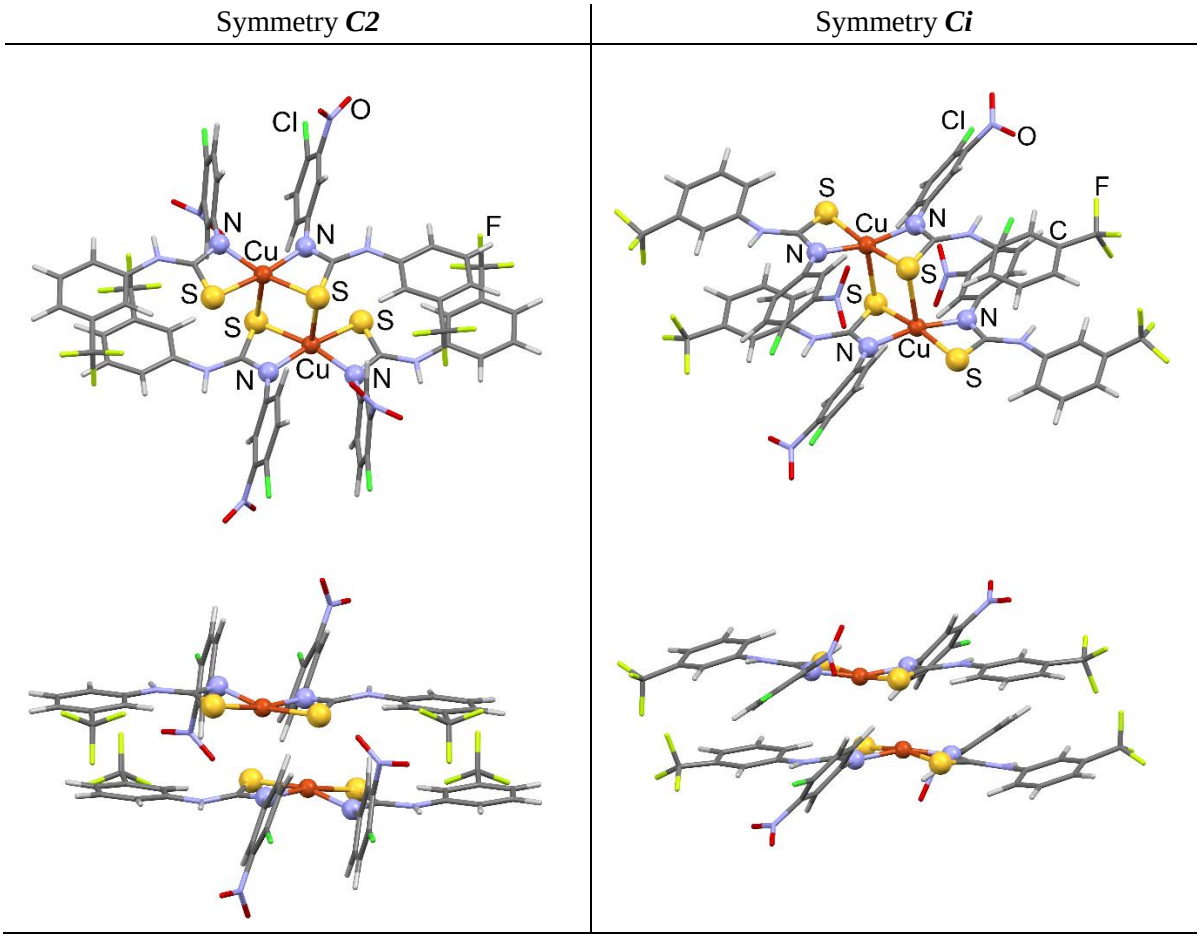

Fig. 13. The molecular structures determined for the dimeric complex of Cu(II) with the 3-(trifluoromethyl)phenylthiourea derivative with the *C2* and *Ci* symmetry of the monomer. A dimer composed of two monomers with *C2* symmetry turned out to be the most energetically stable [H9].

[16] B. B. Beele et al., *S,O or S,N Coordination? Unraveling the Coordination Modes of Arenesulfonylthiourea Ligands*. Cryst. Growth Des. 22 (2022) 3442; https://doi.org/10.1021/acs.cgd.2c00231

Structural changes occurring in the coordination sphere of Cu(II) complexes with thiourea derivatives − studied using UV-Vis spectroscopy [H6, H7, H9]

In the presented studies I used UV-Vis spectroscopy to determine the degree of oxidation of the metal cation in bioactive coordination compounds, as well as to determine the geometry of the synthesized complexes. I investigated compounds in the form of powder, which were a direct product of the complexation reaction, purified with distilled water to remove the excess of one of the reaction substrates. The spectra were recorded using the Diffuse Reflectance Spectroscopy (DRS) method using an integrating sphere. In the electronic spectra of the initial ligands and their complexes I observed very intense bands in the region of 230−300 nm resulting from the π→π* and n→π* transitions in the organic part of the compound [H6, H7, H9]. Additionally, for the complexes, unlike the initial thiourea derivatives, I identified bands corresponding to Ligand-to-Metal Charge Transfer (LMCT) in the range of 370−600 nm. These bands have high intensity in the intra-ligand transition range (covering it partially) and are characterized by slightly lower intensity in the visible region of the spectrum. I attributed the LMCT excitation to the S→Cu(II) transition, which is consistent with the results presented for analogous Cu(II) complexes, with thiosemicarbazone derivatives.[17,18] In the further part of the spectrum of the studied complexes with thiourea derivatives, outside the visible range, d-d bands are visible (range from 700 to 1200/1400 nm). These bands are characterized by varying intensity within the analysed group of coordination compounds. The complex of Cu(II) with a thiourea derivative, presented in the article by Singh et al.[15], showed low intensity of d-d bands, and its molecule had a flat square geometry with two ligands coordinating bidentate through the S atom and the N atom in the *trans* configuration. Therefore, I attempted to explain the variable intensity of the d-d bands observed in the spectra of the synthesised complexes. For this purpose, calculations were performed using the time-dependent density functional theory, TDDFT (Time-Dependent Density-Functional Theory) with the CAM-B3LYP functional for two energetically stable complexes that are geometric isomers. The molecules of both complexes contained one metal cation and two ligand molecules, and differ in symmetry. The centrosymmetric molecule contained ligands chelating to the metal cation in the trans orientation (*Ci* symmetry), and the molecule with *C2* symmetry had atoms arranged around the metal central ion in the *cis* configuration, as shown in Figure 8 and 12. Calculations showed that the optimized non-centrosymmetric complex with the *cis*-N_2S_2 system adopts a pseudo-tetrahedral geometry around the metal cation, while the centrosymmetric complex (with the *trans*-N_2S_2 system) exhibits the geometry of a distorted flat square. Additionally, the calculated vertical energies and intensities of electronic transitions showed that for the *cis* isomer the spectra are more extended towards long wavelengths [H6]. These studies allowed me to conclude that the obtained complexes have diverse geometries, from flat square to tetrahedral, which change with the increase in the intensity of the d-d bands observed in the electronic spectrum. I have presented these changes schematically in Figure 14, which shows spectra for

[17] R.P. John et al., *Spectral studies and structure of a 2-hydroxyacetophenone 3-hexamethyleneiminyl thiosemicarbazonate(−2) copper(II) complex containing 1,10-phenanthroline*, Spectrochim. Acta 59 A (2003) 13491358; https://doi.org/10.1016/S1386-1425(02)00332-3

[18] A. Sreekanth and M.R. Prathapachandra Kurup, *Structural and spectral studies on four coordinate copper(II) complexes of 2-benzoylpyridine N(4), N(4)-(butane-1,4-diyl) thiosemicarbazone*, Polyhedron 22 (2003) 3321; https://doi.org/10.1016/j.poly.2003.07.011

three complexes with different imide substituents. The size of this substituent affects the intermolecular interactions and, consequently, the geometry of the compound. The complexes presented in publication H4 had a flat square geometry, while compounds with a tetrahedral structure dominated among the chelates presented in article H6.

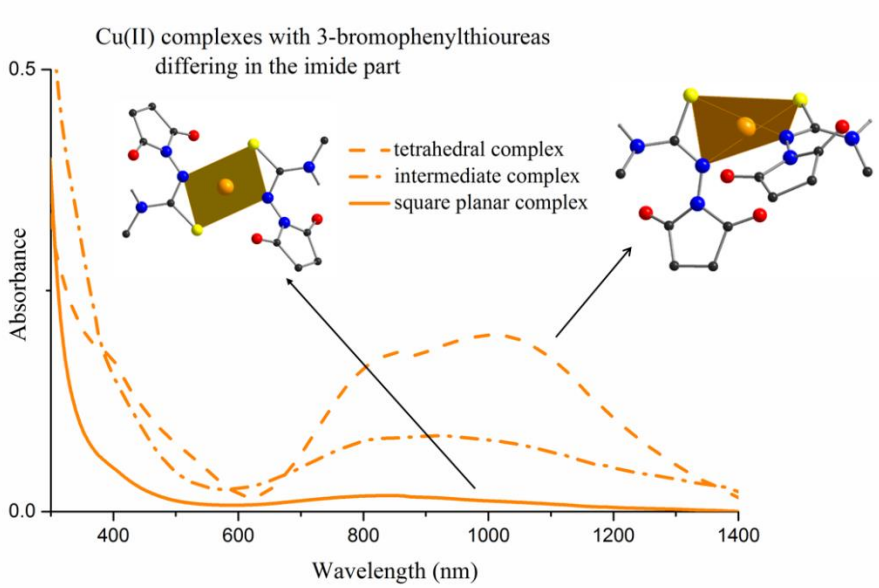

Fig. 14. The influence of the molecular geometry on the intensity of the d-d bands in the UV-Vis spectra of Cu(II) complexes with a 3-bromophenylthiourea derivative differing in the imide substituent.

The described studies were carried out for purified complexes obtained in powder form. However, the biological activity tests are carried out for solutions obtained by dissolving the compound in a solvent, which is most often dimethyl sulfoxide (DMSO), repeatedly diluted with distilled water. I decided to check how the complexes behave after dissolving in DMSO and diluting with water. I prepared solutions analogous to those used by biologists [H6]. While structural differentiation was observed for samples in the solid state, after dissolution in DMSO, all tested compounds adopted centrosymmetric coordination which was pointed by the low intensity of the d-d bands in their electronic spectra. The addition of distilled water forced further structural changes and a transition to tetrahedral coordination was observed in the case of all analysed complexes.

Influence of changing the substituents in the molecules of Cu(II) complexes with 1,3-disubstituted thiourea derivatives on their biological properties [H4, H6, H7, H9]

The aim of my research was to find relationship between structural data and the biological properties of the complexes and to determine the mechanism of action of selected chelates. Therefore, in parallel with the structural studies of the presented compounds, studies of the biological activity of the complexes were carried out, which included determining their:

- antimicrobial activity against standard strains of gram-positive bacteria: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis*, *Bacillus cereus*, *Enterococcus hirae*, *Enterococcus faecalis*, *Micrococcus luteus*, gram-negative bacilli: *Escherichia coli* and *Pseudomonas aeruginosa*, and strains of fungi: *Candida albicans* and *Candida parapsilosis*;

- activities against Methicyllin-Resistant *Staphylococcus Epidermidis* (MRSE) and Methicyllin-Resistant *Staphylococcus Aureus* (MRSA) performed on fourteen isolates of *Staphylococcus aureus* and sixteen clinical strains of *Staphylococcus epidermidis* isolated from patients of clinical hospitals at the Medical University of Warsaw;

- anti-tuberculosis activity against the standard $H_{37}Rv$ strain and two "wild" strains isolated from patients suffering from tuberculosis: the Spec. 210 strain, resistant to isoniazid, p-aminosalicylic acid, ethambutol and rifampicin, and the Spec. 192 strain, completely sensitive to the tuberculostatics used;

- cytotoxic activity against human cancer cell lines: SW480 (primary colon cancer), SW620 (metastatic colon cancer) and PC3 (metastatic prostate cancer), as well as against normal human keratinocytes (HaCaT);

- activity against Human Immunodeficiency Virus type-1 (HIV-1).

This research was conducted in collaboration with Professor Giuseppina Sanna from the Faculty of Life and Environmental Sciences, Section of Microbiology and Virology, University of Cagliari in Monserrato, Italy (antiviral activity), Professor Marta Struga from the Department of Biochemistry of the Medical University of Warsaw (antimicrobial and anticancer activity) and with Professor Ewa Augustynowicz-Kopeć from the Institute of Tuberculosis and Lung Diseases in Warsaw (anti-tuberculosis activity).

The complexes differ on substituents on the N atoms of the thiourea moiety. The change of the substituent did not affect the coordination mode of the thiourea ligands, but significantly modified the biological properties of the synthesized compounds. In the studies describing complexes with bromophenylthiourea derivatives presented in 2017 [H4], I showed that the position of the Br atom in the phenyl ring affects the antimicrobial activity of the entire complex. The dinuclear Cu(II) complex with a 4-bromophenyl substituent (Fig. 15a) showed significant inhibition against standard strains of *S. aureus* and *S. epidermidis*. The range of minimum inhibitory concentrations was 2–4 μg/ml. Additionally, this compound effectively inhibited the formation of biofilm of the methicillin-resistant *S. epidermidis* strain at the highest tested concentrations (64 and 120 μg/mL; inhibition of biofilm formation was above 80%). Such a significant antibacterial profile was not observed for Cu(II) complexes with a 2- or 3-bromophenyl substituent. Moreover, the initial ligands and copper salts were antibacterial inactive, which allowed me to conclude that the complexation of thiourea derivatives with copper significantly modifies their antibacterial profile. Additionally, the complexes were tested for their cytotoxic activity against MT4 cells and for their activity against human

immunodeficiency virus type 1, using efavirenz as the reference drug. The complexes turned out to be non-cytotoxic towards MT-4 cells and none of the complexes showed anti-HIV-1 activity. Taking into account the results of these studies, I decided to stop further testing of these compounds for antiviral activity and focus on examining their antibacterial profile.

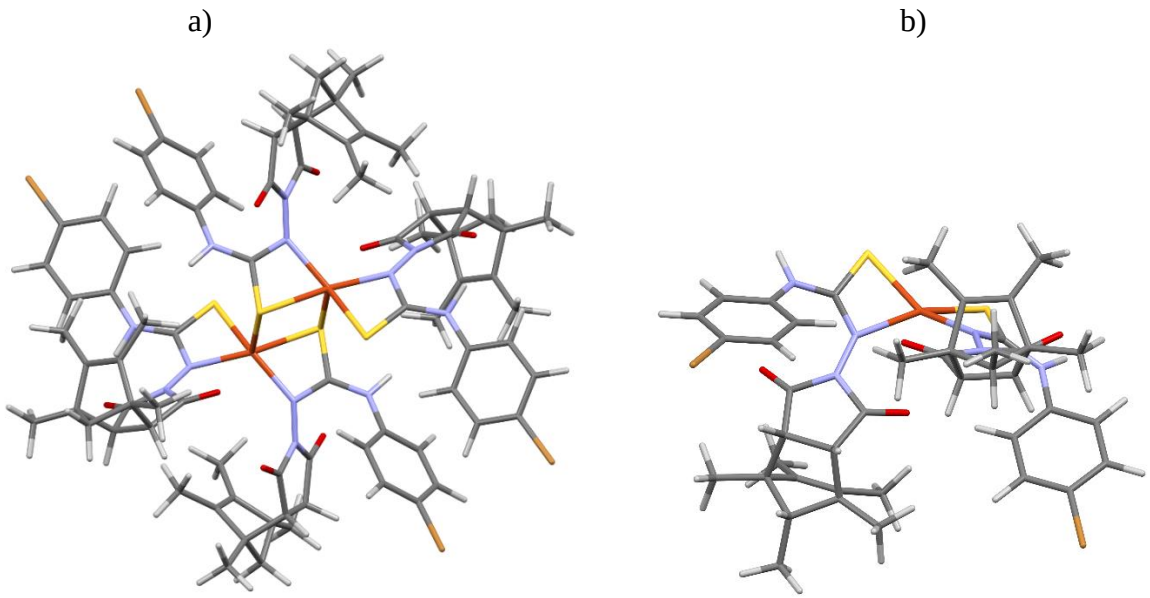

Fig. 15. Structure of bioactive Cu(II) complexes with a 4-bromophenyl substituent differing in the imide fragment a) dimer presented in article H4 and b) monomer [H6].

I obtained another series of copper(II) complexes with bromophenylthiourea derivatives, differing from the previous one by a tricyclic imide at the N atom of the thiourea system [H6]. The obtained compounds were tested for their activity against standard bacterial strains. Despite the structural diversity of the synthesized complexes and the previously presented positive results for the complex with a 4-bromophenyl substituent [H4], all compounds turned out to be inactive already in the initial screening test using the disk-diffusion method. Considering the significant anticancer activity of metal complexes with thiosemicarbazone derivatives, I tested the obtained compounds for their cytotoxic effects on human colon and lung cancer cell lines. These compounds showed a promising anticancer profile towards the SW480 and PC3 cancer cell lines. The most active Cu(II) complexes were mononuclear compounds, namely 4- and 3-bromophenyl derivatives containing five methyl substituents on the cyclic imide (Fig. 15b). The half maximal inhibitory concentration (IC_{50}) was in the range of 4–19 μM [H6].
Both compounds were noncytotoxic to normal HaCaT cells ($IC_{50} \geq 84$ μM), thus being more selective than doxorubicin or cisplatin used in the tests as reference drugs. For these two chelates, further experiments were performed, including the study of apoptosis and the study of the effect of the complexes on the release and level of Interleukin-6 (IL-6). It turned out that the tested compounds not only reduce the growth rate of cancer cells, but also reduce their viability. Both complexes induced late apoptosis primarily in SW480 cells, but also in PC3 cells. The probable mechanism of action of the complexes is correlated with the decreasing release of IL-6 in cancer cell lines.

The high antibacterial and anticancer potential identified for the thiourea coordination compounds prompted me to obtain another series of Cu(II) complexes, this time with a 4-chloro-3-nitrophenyl substituent [H7]. The research procedure included determining the cytotoxic activity against three lines of human cancer cells (SW480, SW620, PC3), human normal keratinocytes (HaCaT) and determining the antibacterial profile of the synthesized complexes. Unlike the starting ligands, complexation with copper ions revealed a cytotoxic profile of the synthesized compounds towards cancer cells and, in lesser extent, towards bacterial strains. The tested coordination compounds did not show cytotoxic effects on normal cells (HaCaT). Moreover, they have been shown to be non-genotoxic. Different positions and numbers of halogen substituents on the phenyl ring allowed to examine the influence of the structure of the synthesized complexes on their bioactivity. The most active Cu(II) complexes with halogenphenylthiourea derivatives (substituent: 2-bromophenyl, 4-bromophenyl, 2-fluorophenyl, 4-iodophenyl) showed a stronger anticancer potential against metastatic prostate cancer cells compared to colon cancer cell lines. They were also more effective than derivatives with following substituents: 3-chloro-4-fluorophenyl, 3,4-dichlorophenyl or 4-chloro-3-nitrophenyl. The research procedure also included a lactate dehydrogenase (LDH) test, an apoptosis test, and an examination of the effect of the complexes on the release and level of IL-6. The Cu(II) complex with 4-iodophenylthiourea derivative achieved the highest percentage of LDH release from PC3 and SW480 cells. The tested complexes, especially those with 4-bromo- and 4-iodo-phenylthiourea derivatives, induced early apoptosis in the above-mentioned pathological cells. Additionally, all coordination compounds reduced the secretion of IL-6 by cancer cell lines. Their interleukin-inhibiting properties in selected cells were as strong as those observed for doxorubicin. Moreover, the studies showed a general tendency of the tested compounds to disrupt the antioxidant and detoxification systems in cancer cells. This is a preliminary signal that this may be one of the mechanisms of cytotoxicity. This weakening effect of the complexes on the antioxidant defence of cancer cells may support the action of other pro-oxidant factors, including drug resistance, as well as support radiotherapy treatment.

The high biological potential of studied complexes prompted me to synthesize the next series of Cu(II) complexes, this time with 3-trifluorophenylthiourea derivatives [H9]. The obtained complexes exerted weak to moderate anticancer activity (towards SW480, SW620 and PC3) while being non-toxic towards normal HaCaT cells. However, subsequent studies revealed a significant antibacterial profile of one of the complexes in the presented series. The experiments showed higher activity against staphylococcal isolates of the complex with the halogenophenyl moiety than with the alkylphenyl part. In particular, the Cu(II) complex with a chloronitrophenyl substituent, exhibiting a dimeric structure (Fig. 13), showed very high potency against 19 tested strains of methicillin-resistant staphylococci. The minimum inhibitory concentration (MIC) was 2 μg/mL, which was the basis for further studies providing information on the mechanism of action of the tested compound. The results showed that the Cu(II) complex with a chloronitrophenyl substituent is an effective inhibitor of both DNA gyrase and topoisomerase IV isolated from *S. aureus*. Additionally, all synthesized complexes were tested *in vitro* for their antituberculosis activity. I observed a similar relationship between their activity and the effect of the substituent on the thiourea moiety as in the case of examining their antistaphylococcal profile. Cu(II) complexes with alkylphenylthiourea derivatives showed

poor activity against *Mycobacterium tuberculosis* strains, in contrast to much better activity of halogenophenyl derivatives. Additionally, Cu(II) complexes with a halogenophenyl substituent strongly inhibited the growth of mycobacteria isolated from tuberculosis patients, even four times more strongly than the reference isoniazid. At the same time, all complexes did not show genotoxic effects.

The studies of biological activity of new complexes showed their different biological profiles, depending on the geometry and chemical nature of the substituents connected with the thiourea system. The presented relationships between the structure and biological activity of the complexes point toward the further direction of research in the search for structures that can be used in pharmacology.

2.3. Summary

My scientific achievement is the molecular structure determination of compounds of great practical importance, i.e. metal complexes with bioactive organic ligands such as citric acid [H1], phenoxyacetic acid derivatives [H2, H3, H5, H8] and thiourea-based chelates [H4, H6, H7, H9], regardless of the degree of structural order of the studied sample. Due to the use of X-ray crystal structure analysis and X-ray absorption spectroscopy (EXAFS and XANES), as well as ATR-IR and UV-Vis spectroscopies correlated with DFT calculations, I obtained results that constitute a significant contribution to the knowledge about the presented coordination compounds.
Moreover, I refined optimal conditions for gel synthesis to obtain single crystals for diffraction studies as well as I designed and carried out complexation reactions of thiourea derivatives. By modifying the structure of the complexes and coordinating studies of their biological activity, I was looking for compounds that could be used in pharmacology. A valuable result is the determination of the relationship between the structure and biological activity of new complexes. The presented scientific achievement includes a series of 9 articles [H1-H9] published in 2017-2022. My most important results, which make a significant contribution to the knowledge of citrates, phenoxyacetates and thiourea-based chelates, can be summarized in the following points:

- I determined the structure of new Ba(II) and Pb(II) coordination polymers with citric acid [H1]. I obtained the complexes in the form of high-quality crystals using the gel method. Based on diffraction measurements on single crystals, I showed different geometries around each metal cation (*i*) symmetrical for Ba(II) ions and (*ii*) anisotropic for Pb(II) cations. I revealed that the anisotropic geometry is caused by the non-bonding electron pair in the valence orbitals of Pb(II), which stereochemically affects the structure of the complex.
- Based on spectroscopic methods, I determined the molecular structure of Co(II), Ni(II) and Cu(II) complexes with three phenoxyacetic acids [H2, H3, H5], two of which are commercially used herbicides (MCPA; 2,4-D). I found 3 different types of coordination

spheres for mononuclear complexes (*i*) octahedral for Co(II) and Ni(II), (*ii*) tetragonal pyramid or (*iii*) flat square for Cu(II) complexes. As a result of recrystallization from the *N*,*N*-dimethylformamide solution, new complexes were formed: (*i*) dinuclear for Cu(II), Co(II), Ni(II) [H2, H3, H5] and (*ii*) sixnuclear for Mn(II) [H8], which structure I determined using diffraction methods.

- I showed that the structure of the ligand, the type of metal cation as well as metal-ligand binding do not affect the cytotoxic activity of the tested metal complexes with phenoxyacetate herbicides [H5, H8]. Both the parent herbicides and their complexes have low cytotoxic potential against human immortalized keratinocyte cells.
- Using spectroscopic methods, I determined the molecular structure of Cu(II) complexes with 1,3-disubstituted thiourea derivatives, which I synthesized using the direct method [H4, H6, H7, H9]. The Cu(II) cation is chelated by two molecules of thiourea ligands. I demonstrated the formation of an unusual four-membered Cu−S−C−N ring. I identified the nitrogen atom of the thiourea moiety that undergoes deprotonation and coordinates to Cu(II). Additionally, I found that some complexes have dimeric sandwich-type structures.
- I demonstrated different geometries of Cu(II) complexes with thiourea derivatives [H6]. A pseudotetrahedral structure is observed for non-centrosymmetric chelates with a *cis* arrangement of atoms around the Cu(II) cation. The flat square geometry is characteristic for centrosymmetric compounds with the *trans*-N_2S_2 system. I described the structural changes of complexes during the preparation of samples for biological activity tests.
- I determined the effect of the molecular structure of thiourea ligands on the biological activity of their complexes with Cu(II) [H4, H6, H7, H9]. I found that the complexation of Cu(II) with thiourea derivative revealed a cytotoxic profile of the synthesized compounds towards the tested cancer cells and selected bacterial strains, not observed in the case of the initial ligands. I selected complexes which bioactivity can compete with standard drugs and determined mechanism of their action.

3. Presentation of significant scientific activity realized in more than one scientific institution

Maria Curie-Skłodowska University in Lublin, Department of Theoretical Chemistry

As part of my bachelor's thesis, I performed DFT calculations of equilibrium geometries and harmonic vibration frequencies for a series of carbonyl compounds. I focused mainly on the analysis of the frequency of stretching vibrations of the C=O group and noticed different contributions of local vibrations to a given normal vibration for the analysed molecules. I could assess these shares qualitatively when visualizing them using a graphic program. Quantitatively, this can be done by determining PED (Potential Energy Distribution) coefficients. Together with my supervisor, Professor Piotr Borowski, we considered important to develop an algorithm for determining PED coefficients and its implementation into the commercial Parallel Quantum Solutions (PQS) program package, which was carried out as part of my master's thesis. PED coefficients were also used in the new method of scaling harmonic vibration frequencies - Effective Scaling Frequency Factor method (ESFF) proposed by Piotr Borowski. My scientific collaboration with Professor Borowski was continued in the following years and resulted in two publications that appeared in 2008 and 2010, respectively in Chemical Physics Letters and Vibrational Spectroscopy [P25,P26 - list of publications point 5.1]. As part of the collaboration, I determined coefficients for scaling harmonic vibration frequencies to the commonly used Scaled Quantum Mechanical Force Field method (SQMFF) and the newly proposed ESFF method.

Maria Curie-Skłodowska University in Lublin, Department of Crystallography

I conducted research on my doctoral dissertation at the Department of Crystallography under the supervision of Professor Anna Kozioł. The object of my studies were derivatives of benzofuran and coumarin, synthesized similarity to substances occurring naturally in nature and having medicinal properties. I obtained single crystals of those compounds and performed X-ray crystal structure analysis. Additionally, I characterized the compounds using IR spectroscopy and DFT calculations [P18, P20, P21]. Then, during my stay at the University of Jaén (Spain), I used benzofuran and coumarin derivatives as organic ligands to obtain complexes with selected metal ions. In the case of the complexes for which I obtained single crystals, I applied X-ray crystallography. To get more information about the synthesized complexes, during the annual Crystallographic Conversatorium in Wrocław, I established collaboration with Professor Krystyna Ławniczak-Jabłońska from the IP PAS. Professor K. Ławniczak-Jabłońska introduced me to X-ray absorption spectroscopy. Then, together with Professor Marcin Klepka and Dr. hab. Anna Wolska, we carried out XAFS measurements at the synchrotron in Hamburg. I performed XANES and EXAFS analyses, and the obtained results allowed me to describe all series of studied complexes [P16, P17, P19].

University of Wrocław, Department of Crystallography

In November 2006, I completed a research internship at the Department of Crystallography of the University of Wrocław at Professor Tadeusz Lis's group. During my stay, I became familiar with the operation of the KUMA KM4 diffractometer with a CCD camera and with X-ray

diffraction data analysis. In the following years, I continued collaboration with Professor T. Lis, which resulted in 7 publications [H1, P17-P20, P23, P27].

University of Jaén, Spain

In 2007-2008, I was conducting research on my doctoral dissertation in two research groups at the University of Jaén, Spain. In Professor Sonia B. Jimenez-Pulido's team, I synthesized metal complexes with the coumarin and benzofuran derivatives using direct and electrochemical methods. Then, at the analytical laboratory of the University of Jaén, I carried out elemental and thermal analysis of the synthesised compounds, as well as performed measurements and analysed data using IR and Raman spectroscopies. The presented research was described in three articles P16, P17 and P19. In Professor Manuel Fernandez-Gomez's group, I performed calculations using density functional theory, including conformational and vibrational analysis of the initial organic ligands, which resulted in 3 publications [P18, P20, P21].

Centre for Functional Nanomaterials of UMCS in Lublin

After completing my doctoral studies, at the turn of 2010 and 2011, I worked at the Centre for Functional Nanomaterials of UMCS, in a team led by Dr. Ewaryst Mendyk. During my half-year of employment, I performed research using an FTIR spectrometer coupled with an FT Raman spectrometer module and an FTIR microscope. The result of my collaboration with Dr. E. Mendyk and Dr. A. Pachuta-Stec from the Medical University of Lublin is publication P23, in which the synthesis and structural characterization of twelve 1,2,4-triazole derivatives is presented.

Ruhr University, Bochum, Germany

In 2011, I completed a month-long training in HREELS measurement and data analysis in the group of Dr. Yuemin Wang at the Ruhr University in Bochum. Additionally, during the internship, Dr. Heshmat Noei introduced me to the study of the phenomenon of gas adsorption on oxide surfaces using UHV-FTIR spectroscopy.

Institute of Physics Polish Academy of Sciences, Warsaw

In 2011, I was employed at the IP PAS as an assistant professor. My scientific activity focused on the study of metal complexes. During the first years, I tested various metal cations and organic ligands in order to obtain a bioactive complex. Finally, I focused on copper complexes due to their high biological potential. In the following years, I obtained and structurally characterized Cu(II) complexes with 1,2-disubstituted thiourea derivatives.

At the same time, I started collaboration with Professor Wiesława Ferenc from Maria Curie-Skłodowska University in studying the magnetic properties of phenoxyacetate complexes with metal ions. I noticed that similar coordination compounds are formed in nature and have not been complementarily described. I decided to fill these gaps and conduct a broader characterization of transition metal complexes with the popular phenoxyacetate herbicides.

To describe the complexes, I conducted research using ATR-IR and UV-Vis spectrometers available in the IP PAS laboratory, I analysed diffraction data and carried out measurements at the XAFS stations in the MAX-lab synchrotron in Lund and Elettra synchrotron in Trieste. The obtained results allowed me to determine the molecular structure of the studied complexes.

I correlated the observed structural changes in the complexes with the results of biological activity tests. This research resulted in many publications, eight of which I included in the series describing scientific achievements [H2-H9].

Jagiellonian University, Cracow

In 2012, I included EPR spectroscopy in my research. Initially, I conducted experiments with Professor Hanka Przybylińska from the IP PAS [P19], and then I established long-term cooperation with Professor Piotr Pietrzyk from the Jagiellonian University, who has an EPR instrument adapted to study both powdered samples and solutions. Collaboration with Professor Pietrzyk resulted in three publications [H4, H7, P4] and is still being continued (article in preparation).

University of Cagliari in Monserrato, Italy

Since 2013 I have been cooperating with Professor Giuseppina Sanna from the Faculty of Life and Environmental Sciences, Section of Microbiology and Virology, University of Cagliari in Monserrato. As part of the collaboration, the cytotoxic activity and antiviral activity studies were carried out for organic compounds [P13, P15] and metal complexes [H4].

Warsaw Medical University

For many years, I have been working with Professor Marta Struga's group from the Medical University of Warsaw. Biological research, including antimicrobial and anticancer activity, was presented in 18 articles from my scientific achievements.

Institute of Tuberculosis and Lung Diseases, Warsaw

I established collaboration with the Institute of Tuberculosis and Lung Diseases in Warsaw. In the team of Professor Ewa Augustynowicz-Kopec, tests of anti-tuberculosis activity are carried out. The standard bacterial strains as well as strains isolated from patients suffering from tuberculosis - disease that is still quite common - are studies. The collaboration resulted in two articles: P13 and H9.

Elettra Synchrotron, Trieste, Italy

During my stay at the Elletra synchrotron, I established cooperation with Dr. Guliana Aquilanti, which focused on the characterization of complexes dissolved in organic solvents. Due to a special device for testing solutions using the XAFS method, we conducted a series of experiments, the results of which are described in article P8.

National Synchrotron Radiation Centre SOLARIS, Cracow

In 2022, I was invited by SOLARIS for test measurements of the XAFS experimental line, which was being opened. Together with my colleagues form IP PAS, we conducted a series of experiments for platinum complexes and plant samples, the results of which will be presented in upcoming articles.

Warsaw University of Technology

Since 2021, I have been taking measurements and analysing data obtained using XPS spectroscopy. The result of collaboration with Dr. Eng. Paulina Trzaskowska from the Warsaw University of Technology, CEZAMAT, is a this year publication in Applied Surface Science [P1] presenting research conducted to increase the biocompatibility of implants. I also collaborates with Eng. Grzegorz Matyszczak from the Warsaw University of Technology. I study SnS nanoparticles and dyes using photoelectron spectroscopy (article in review).

Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw

In collaboration with Professor Anna Sirko from the Institute of Biochemistry and Biophysics PAS, I am examining plant fragments (roots and leaves) of unmodified and genetically modified *Arabidopsis thaliana* - a model plant in genetics. I carried out research using photoelectron spectroscopy as well as X-ray absorption spectroscopy.

Maria Curie-Skłodowska University in Lublin, Department of General Chemistry, Coordination Chemistry and Crystallography

In 2022, I started collaboration with Dr. Justyna Sienkiewicz-Gromiuk. As part of this cooperation, I carry out structural analysis of cocrystals, focusing on supramolecular synthons in molecular adducts. This cooperation has already resulted in the first article [P2] and is continued.

4. Presentation of didactic, organizational and science popularization activities

4.1. Didactic activity

01.2019 Conducting workshops for talented high school students *Synthesis of bioactive metal complexes and their characterization using IR spectroscopy*, IP PAS

07.2016 Supervisor during summer student internships at the IP PAS, *XPS, UV-Vis and FTIR spectra of 4-bromophenoxyacetic acid and its complex with nickel*

08/09.2015 Supervisor during summer student internships at the IP PAS, *Characterization of bioactive organic and metal-organic materials using spectroscopic techniques and molecular modelling*

2006-2010 Academic teacher - conducting seminars on Spectroscopic Methods (IR, NMR, MS) and Organic Crystal Chemistry for UMCS students, supervision of master's students (excluding the period of stay at the University of Jaén)

4.2. Organizational activities

Member of the Scientific Council of the IP PAS for the **2023-2026** term, member of the Education Committee of the Scientific Council

Organization of workshops: *Workshop on Molecular Simulation and Drug Design*, **08-11/09/2015**, IP PAS, as part of the EAgLE project (European Action towards Leading Centre for Innovative Materials) FP7-REGPOT-2012-2013-1

Member of the organizing committee of the workshop: *New challenges and solutions for XAS data analysis part II - FEFF and IFEFFIT for XANES and EXAFS analysis* **14-17/04/2015**, IP PAS, as part of the EAgLE project

Member of the organizing committee of the workshop: *New challenges and solutions for XAS data analysis part I - mXAN code for XANES analysis*; **8-11/04/2014**, IP PAS, as part of the EAgLE project

4.3. Popularization activities

Since 2015, I have been a member of the Polish Synchrotron Radiation Society and I undertake activities aimed at popularizing research using synchrotron radiation, especially among scientists dealing with coordination chemistry.

I wrote two popularizing articles: *Synchrotron radiation - its properties, production and application in science* and *X-ray absorption spectroscopy* published in Neutrino and Foton respectively - magazines published by the Institute of Physics of the Jagiellonian University (**2016**) and one article *Exploring the properties of matter on the atomic scale using the absorption of synchrotron radiation* for LAB (Laboratoria Aparatura Badania), **2012**.

At the invitation of prof. Zbigniew Hubicki, I took part in symposia "Science and industry - spectroscopic methods, new challenges and opportunities", where during the lectures I described application of synchrotron spectroscopic methods. The result of my presentations are two articles: *Studies on the complexation reactions of biologically active organic ligands using laboratory and synchrotron spectroscopic methods*, Science and industry, ISBN 978-83-227-9219-3, p.307-318, UMCS, Lublin **2019** and *X-ray absorption as a tool for exploring the world on an atomic scale*, Science and industry, ISBN 978-83-7784-086-3, p.536-545, UMCS, Lublin **2012**.

5. Other scientific achievements

5.1. List of publications, not included in the discussed scientific achievement

P1 P. Trzaskowska, E. Rybak, K. Jabłońska-Ławniczak, **A. Drzewiecka-Antonik**, A. Wolska, J. Krzemiński, B. Butruk-Raszeja, T. Ciach, *The potential of electropolymerized crosslinked PEGDMA coating on steel for further functionalization: Surface parameters and HMEC-1 cells attachment correlations*, Appl. Surf. Sci. 635 (2023) 157761.

IF=6.7

P2 J. Sienkiewicz-Gromiuk, **A. Drzewiecka-Antonik**, *The First Noncovalent-Bonded Supramolecular Frameworks of (Benzylthio)Acetic Acid with Proline Compounds, Isonicotinamide and Tryptamine*, Molecules 27 (2022) 8203.

IF=4.6

P3 M.T. Klepka, D. Kalinowska, C.A. Barboza, **A. Drzewiecka-Antonik**, K. Ostrowska, A. Wolska, *Structural investigation of Cu(II) complexes with dibromo 7 – hydroxyl-coumarin derivatives using methodology based on XAS*, Radiat. Phys. Chem. 175 (2020) 108047.

IF=2.9

P4 A. Bielenica, **A. Drzewiecka-Antonik**, P. Rejmak, J. Stefanska, M. Kolinski, S. Kmiecik, B. Lesyng, M. Wlodarczyk, P. Pietrzyk, M. Struga, *Synthesis, structural and antimicrobial studies of type II topoisomerase-targeted copper(II) complexes of 1,3-disubstituted thiourea ligands*, J. Inorg. Biochem. 182 (2018) 61.

IF=3.9

P5 M. T. Klepka, **A. Drzewiecka-Antonik**, A. Wolska, P. Rejmak, M. Struga, *Structural studies of Cu(II) complexes with coumarin acid derivatives obtained using direct and electrochemical synthesis*, Chem. Phys. Lett. 691 (2018) 190.

IF=2.8

P6 K. Ostrowska, D. Maciejewska, **A. Drzewiecka-Antonik**, M.T. Klepka, A. Wolska, L. Dobrzycki, A. Sztokfisz, A. Czajkowska, I. Mlynarczuk-Bialy, *Synthesis, spectroscopic characterization, X-ray study and in vitro cytotoxicity of 5-hydroxycoumarin derivatives and their copper complexes*, J. Mol. Struct. 1145 (2017) 292.

IF=3.8

P7 D. Kalinowska, M.T. Klepka, A. Wolska, **A. Drzewiecka-Antonik,** K. Ostrowska, M. Struga, *Structural study of Cu(II) complexes with benzo[b]furancarboxylic acids*, Nucl. Instr. Meth. Phys. Res. B 411 (2017) 116.

IF=1.2

P8 M. T. Klepka, A. Wolska, **A. Drzewiecka-Antonik**, P. Rejmak, K. Hatada, G. Aquilanti, *XAFS study of bioactive Cu(II) complexes of 7-hydroxycoumarin derivatives in organic solvents*, Chem. Phys. Lett. 673 (2017) 113.

IF=2.8

P9 M. Białkowska, W. Chaładaj, I. Deperasińska, **A. Drzewiecka-Antonik**, A. E. Koziol, A. Makarewicz, B. Kozankiewicz, *Single molecules of terrylene in di-substituted naphthalenes crystallizing in the herringbone pattern*, RSC Adv. **7** (2017) 2780.

IF=3.9

P10 M. T. Klepka, **A. Drzewiecka-Antonik**, A. Wolska, P. Rejmak, K. Ostrowska, E. Hejchman, H. Kruszewska, A. Czajkowska, I. Młynarczuk-Biały i W. Ferenc, *Synthesis, structural studies and biological activity of new Cu(II) complexes with acetyl derivatives of 7-hydroxy-4-methylcoumarin*, J. Inorg. Biochem. 145 (2015) 94.

IF=3.9

P11 A. Wolska, M.T. Klepka, W. Ferenc, **A. Drzewiecka-Antonik**, *XAFS studies of Cu(II) and Co(II) complexes with derivatives of cinnamic acid*, X-Ray Spectrometry 44 (2015) 323.

IF=1.2

P12 W. Ferenc, P. Sadowski, B. Tarasiuk, B. Cristovao, **A. Drzewiecka-Antonik**, D. Osypiuk, J. Sarzynski, *Complexes of selected transition metal ions with 4-oxo-4-{[3-(trifluoromethyl)-phenyl]-amino}but-2-enoic acid: Synthesis, structure and magnetic properties*, J. Mol. Struct. 1092 (2015) 202.

IF=3.8

P13 J. Stefanska, G. Nowicka, M. Struga, D. Szulczyk, A.E. Koziol, E. Augustynowicz-Kopec, A. Napiorkowska, A. Bielenica, W. Filipowski, A. Filipowska, **A. Drzewiecka**, G. Giliberti, S. Madeddu, S. Boi, P. La Colla, G. Sanna, *Antimicrobial and Anti-biofilm Activity of Thiourea Derivatives Incorporating a 2-Aminothiazole Scaffold*, Chem. Pharm. Bull. 63 (2015) 225.

IF=1.7

P14 M. Puszynska-Tuszkanow, Z. Staszak, T. Misiaszek, M.T. Klepka, A. Wolska, **A. Drzewiecka-Antonik**, H. Faltynowicz, M. Cieslak-Golonka, *Metallophilic interactions in polynuclear Ag(I) complex with 1-methylhydantoin studied by X-ray absorption, electronic and vibrational spectroscopies*, Chem. Phys. Lett. 597 (2014) 94.

IF=2.8

P15 **A. Drzewiecka**, A.E. Koziol, P. Borowski, G. Sanna, G. Giliberti, P.L. Colla, T. Zawadowski, M. Struga, *Structural and antivirial studies of dipetalactone and its methyl derivative*, J. Mol. Struct. 1054 (2013) 150.

IF=3.8

P16 **A. Drzewiecka**, A.E. Koziol, M.T. Klepka, A. Wolska, S. B. Jimenez-Pulido, M. Struga, *Electrochemical synthesis and structural studies of zinc(II) complexes with derivatives of benzo[b]furancarboxylic acids*, Chem. Phys. Lett. 575 (2013) 40.

IF=2.8

P17 **A. Drzewiecka**, A.E. Koziol, M.T. Klepka, A. Wolska, S.B. Jimenez-Pulido, T. Lis, K. Ostrowska, M. Struga, *Two coordination modes around the Cu(II) cations in complexes with benzo[b]furancarboxylic acids*, Chem. Phys. Lett. 559 (2013) 41.

IF=2.8

P18 **A. Drzewiecka**, A.E. Koziol, M. Struga, T. Pena Ruiz, M. Fernandez Gomez, T. Lis, *Structural characterization of derivatives of 4-methylcoumarin – Theoretical and experimental studies*, J. Mol. Struct. 1043 (2013) 109.

IF=3.8

P19 **A. Drzewiecka**, A.E. Koziol, M.T. Klepka, A. Wolska, H. Przybylinska, S.B. Jimenez-Pulido, K. Ostrowska, M. Struga, J. Kossakowski, T. Lis, *Synthesis and structural studies of novel Cu(II) complexes with hydroxy derivatives of benzo[b]furan and coumarin*, Polyhedron 43 (2012) 71.

IF=2.6

P20 **A. Drzewiecka**, A.E. Koziol, T. Pena Ruiz, M. Fernandez Gomez, M. Struga, J. Kossakowski, K. Ostrowska, T. Lis, *Derivatives of benzo[b]furan. Part II. Structural studies of derivatives of 2- and 3-benzo[b]furancarboxylic acids*, Struct. Chem. 23 (2012) 1617.

IF=1.7

P21 T. Pena Ruiz, **A. Drzewiecka**, A.E. Koziol, M. Fernandez Gomez, K. Ostrowska, M. Struga, J. Kossakowski, *Derivatives of benzo[b]furan. Part I. Conformational studies of khellinone and visnaginone*, Struct. Chem. 23 (2012) 1573.

IF=1.7

P22 M.T. Klepka, **A. Drzewiecka**, A. Wolska, W. Ferenc, *XAS studies on Cu(II) complexes with derivatives of phenoxyacetic and benzoic acids*, Chem. Phys. Lett. 553 (2012) 59.

IF=2.8

P23 E. Mendyk, **A. Drzewiecka**, A. Pachuta-Stec, T. Lis, A.E. Koziol, *Self-assembly of amides of endo-3-(3-methylthio-1H-1,2,4-triazol-5-yl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid directed by N-amide substituents*, Struct. Chem. 22 (2011) 211.

IF=1.7

P24 M. Struga, B. Miroslaw, M. Pakosinska-Parys, **A. Drzewiecka**, P. Borowski, J. Kossakowski, A.E. Koziol, *Synthesis, characterization and supramolecular synthons in crystals of new derivatives of 10-oxa-4-azatricyclo[5.2.1.0-2,6]dec-8-ene-3,5-dione*, J. Mol. Struct. 965 (2010) 23.

IF=3.8

P25 P. Borowski, **A. Drzewiecka**, M. Fernández-Gómez, M.P. Fernández-Liencres , T. Peña Ruiz, *A new, reduced sets of scaling factors for both SQM and newly proposed ESFF methods have been developed*, Vib. Spect. 52 (2010) 16.

IF=2.5

P26 P. Borowski, **A. Drzewiecka**, M. Fernández-Gómez, M.P. Fernández-Liencres, T. Peña Ruiz, *An effective scaling frequency factor method for harmonic vibrational frequencies: The factors' transferability problem*, Chem. Phys. Lett. 465 (2008) 290.

IF=2.8

P27 **A. Drzewiecka**, A.E. Koziol, M. Lowczak, T. Lis, *Poly[tetraaquadi-μ_6-citrato-tetracopper(II)]: a redetermination*, Acta Cryst. E63 (2007) m2339.

IF=0.9

P28 **A. Drzewiecka**, K. Stepniak, A. Barcicka, A.E. Koziol, *Poly[[pentaaquasulfato-μ_4-(R,R)-tartrato-dicadmium(II)] trihydrate]*, Acta Cryst. C63 (2007) m346.

IF=0.8

Impact factor (IF) of journals, calculated in accordance with the scores for 2022

5.2. Reviews of scientific articles

- Dalton Transaction 2020
- Journal of Nanomaterials 2020
- Journal of Inorganic Biochemistry 2023−2018
- New Journal of Chemistry 2021, 2020, 2017
- Journal of Molecular Structure 2022, 2020, 2017, 2014
- Molecules 2017
- Acta Crystallographica C 2022
- International Journal of Organic Chemistry 2017
- Acta Physica Polonica A 2019
- Current HIV Research 2016

5.3. Seminars and lectures

Determination of the structure of molecules of bioactive metal complexes using synchrotron radiation absorption - **invited lecture**, 64th Scientific Meeting of PTChem, Lublin, **11-16.09.2022**

Synthesis and structural characterization of bioactive Cu(II) complexes with thiourea derivatives - lecture as part of the IP PAS reporting session for 2020, **18.02.2021**

Research on complexation reactions of biologically active organic ligands using laboratory and synchrotron spectroscopic methods, **invited lecture**, Science and industry - spectroscopic methods, new challenges and opportunities, Lublin, **25-27.06.2019**

Structural studies of metal-organic ligand complexes using X-ray absorption spectroscopy – **invited lecture**, 11th Polish Meeting of Synchrotron Radiation Users (KSUPS) Chorzów, Poland, **15-20.06.2015**

Basics of Infrared Spectroscopy and CSD database overview, X-ray Seminar IP PAS - **2.06.2015**

Absorption of X-ray radiation as a tool for exploring the world on an atomic scale, **invited lecture**, Science and industry - spectroscopic methods in practice, UMCS, Lublin, **12-14.06.2012**

Structure of potential O-donor ligands and their organic complexes with metal ions - speech by the authors of distinguished doctoral theses, Faculty of Chemistry, Maria Curie-Skłodowska University, Lublin, **6-7.02.2012**

5.4 Oral communication at conferences

Synthesis, structural characterization and biological activity evaluation of novel Cu(II) complexes with 3-(trifluoromethyl)phenylthiourea derivatives The 15th International School and Symposium on Synchrotron Radiation in Natural Science, Cracow, **22-25/08/2022**

Synthesis, structure and biological properties of copper(II) complexes with thiourea derivatives 62. PTCHEM Scientific Meeting, Warsaw, **September 2-6.09.2019**

Structure of new copper(II) and zinc(II) complexes with benzofuran derivatives - studies using X-ray absorption and diffraction, 9th National Symposium of Synchrotron Radiation Users, Warsaw, **September 26-27.09.2011**

In addition, I personally presented over 10 posters at domestic and foreign conferences.

5.5. Awards

Award for a highly cited article in 2019 - *Antimicrobial and Anti-biofilm Activity of Thiourea Derivatives Incorporating a 2-Aminothiazole Scaffold*, Chem. Pharm. Bull. 63 (2015) 225 - awarded by the Editorial Committee of Academic Journals, the Pharmaceutical Society of Japan, February **2020**

Award of the Rector of the Medical University of Warsaw for scientific achievements published in J. Inorg. Biochem. 8 (176) 2017 (article H4), Warsaw **2018**

5.6. Grants

Manager of two tasks under the EAgLE project (received in the FP7-REGPOT 2012-2013-1 competition), **2013-2016**, under two task packages (employing specialists and organizing workshops)

Manager and contractor of research projects carried out on synchrotron radiation sources. The research carried out at MAX-Lab in Lund and at the Elettra synchrotron in Trieste were presented in works H2-H6, H9. This research was partially funded by the EAgLE project from the Twinning work package. A detailed description of projects implemented at synchrotron sources is presented in Attachment 4.

Contractor under the P402/S project (SONATA4 grant received in the NCN competition), **2013-2017** - synthesis of copper and silver complexes, measurements and analysis of IR spectra, testing of purchased equipment (IR spectrometer, ball mill)

5.7. Construction of an experimental station for the synthesis and characterization of metal-organic ligand complexes

Since my employment at the IP PAS, I have been trying to create a research bench for synthesis and characterization of bioactive complexes. This was a new topic in the SL1.2 team where I worked. The first step was to purchase a multi-position mixer with a heating plate, laboratory glassware and basic reagents. This kit enabled me to obtain complexes by direct synthesis. I achieved more specialized conditions for obtaining metal-organic ligand complexes by building a set for electrochemical syntheses. By using an electrochemical method, I obtained transition metals complexes with ligands containing substituents that were difficult to deprotonate, such as a hydroxyl group. In the following years, as part of the SONATA grant, in which I was the main contractor, autoclaves and a ball mill were purchased. These devices enabled me to synthesize complexes using hydrothermal and mechanical methods.

Due to equipment shortages, structural characterization of the products of complexation reaction remained a problem. In the first years of my work at the IP PAS, I measured FTIR spectra in Dr. Jacek Szczepkowski's lab from the Laser Spectroscopy Group of the IP PAS and at the Faculty of Chemistry of UMCS in the laboratory of Professor Anna Kozioł, during multi-day delegations. In 2014, on my initiative, an FTIR spectrometer equipped with an ATR attachment with a diamond crystal was purchased as part of the SONATA grant. Due to the ATR attachment, sample preparation time was shortened. Previously, I performed transmission measurements, which required preparing samples in the form of pellets consisting of a mixture of the tested compound and potassium bromide. In order to obtain a spectrum using the ATR method, a small amount of substance is required and it does not undergo any processing. This is of great importance in the characterization of biological samples, which may change their structure or even disintegrate when grinded or subjected to high pressure.

Using infrared spectroscopy, I was able to control the complexation reaction, determine the purity of the obtained compounds and perform characterization of the complexes. Despite this, I also had been making the attempts to buy a UV-Vis spectrometer. In 2016, I coordinated the purchase of the SHIMADZU UV-2600Plus spectrometer (bought with statutory funds). The purchased equipment enabled me to study solutions of complexes in the transmission mode. The additional purchase of an integrating sphere allowed me to use the Diffuse Reflectance Spectroscopy (DRS) method to examine complexes both in the form of solutions and in the form of powders in a wide spectral range, from 220 to 1400 nm. Analysis of the position of the bands and their intensities in the electronic spectra provided me the information about the symmetry of the complex.

I used both spectrometers to carry out the research presented in articles H1-H9. It is worth mentioning that both devices were placed in the chemical laboratory created - as part of the EAgLE project - for the XPS spectrometer. In article H1, I showed the use of X-ray photoelectron spectroscopy to study complexes (survey spectra - determining the stoichiometry of complexes, high-resolution spectra - structural changes in the ligand-complex system). Both the ATR-FTIR spectrometer and the UV-Vis spectrometer are used to study coordination compounds as well as other samples obtained and characterized by research groups within the IP PAS.

During my research after obtaining my doctoral degree, I gained experience in managing a multidisciplinary project, built a station for the synthesis and characterization of metal-organic-ligand complexes, established collaboration with synchrotron centres and, using several research methods, determined the molecular structures of complexes for samples in the form of single crystals, powders and solutions. The gained experience opens new research paths for me. Currently, I am interested in applying complexes to the surface of implants. Coated implants will be studied for their biological activity, such as inhibition of bacterial biofilms formation or biocompatibility with bone cells. These types of samples can be structurally characterized using ATR-IR, UV-Vis, XPS spectroscopies at the IP PAS and at the Solaris synchrotron in Cracow.

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(the applicant's signature)