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# Synthesis, IR characterization and antioxidant capacity of Cu(II) complexes with amino acids and melatonin

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**Abstract:** In this paper, the reactions of anhydrous copper(II) chloride in methanolic solution with alanine, glycine, histidine, L-tryptophan, and melatonin were investigated and the resulting products were characterized by FTIR spectroscopy. Based on FTIR characterization, it was shown that these reaction conditions result in the formation of Cu(II) complexes with glycine and alanine, which are more complex structures than bis(glycinato) - and bis(alaninato) copper(II) complexes. Analysis of the FTIR spectrum of the histidine complex shows the participation of several groups in coordination at the Cu(II) center. The complex prepared with melatonin shows unusual changes in the spectral region of the amidic nitrogen bonds. The latter observation is very significant for very few known metal complexes of melatonin, while the synthesis of most of them is an experimentally demanding process with simultaneous control of several parameters. The antioxidant capacity of the synthesized complexes was examined, with the CEAC range from 121.6 to 734.4 μM. The lowest values of antioxidant capacity were recorded for the copper complex with tryptophan, while the highest values were recorded for the copper complex with alanine. A high antioxidant capacity of the copper complex with melatonin (673.8 μM) was also observed.

## INTRODUCTION

Due to the fact that copper is a biogenic element that performs most of its biological functions within coordination compounds with biomolecules in which, as donors of heteroatoms in the coordination sphere of the metal center, amino acids and their prosthetic groups often occur, there is a need to evaluate coordination behavior $Cu^{+}/Cu^{2+}$ according to individual, proteinogenic amino acids. Many reports were devoted to understanding the coordination characteristics of such complexes (Colaneri *et al*, 2009) especially copper(II) complexes with amino acids. Copper is an essential trace element used by both eukaryotic and prokaryotic cells in anabolic and catabolic processes with fine control of the same, given the fact that an excess of this element is associated with toxic effects. Roughly speaking, the essence of copper activity in biochemical processes is reflected in its redox behavior, especially because it can easily donate electrons to oxygen. This fact makes a certain element a potential generator of free radicals, which requires the establishment of a number of control mechanisms by the cell in order to use its reactivity to its advantage, while suppressing potential harmful effects. Therefore, the human body has established a number of biochemical processes that maintain copper homeostasis, along with homeostasis of iron, normal tissue proliferation and oxidative metabolism (Vest *et al*., 2012). Its sudden availability in the biosphere and biologically acceptable redox potential have made

copper an essential component of oxidative metabolism (Scheiber, Dringen & Mercer, 2013). Rigorous control of copper metabolism takes place in order to prevent undesirable, copper-mediated redox processes that would ultimately create reactive oxygen species given the ease of Cu (I) / (II) conversion. Since metabolic processes involving copper have many unresolved metabolites and metabolic pathways (as well as their control), it was useful to study the coordination behavior of this biometal towards selected biomolecules under controlled conditions by the preparation and characterization of appropriate complexes. The most simple biomolecules normally present in the cell cytoplasm, i.e. the environment where copper is metabolized, are amino acids, which made them a logical starting point for studying the behavior and coordination preferences of copper in biological systems. Given the structure of proteins as important building blocks and functional components of living cells, it is certain that the potential binding of copperin one of its two oxidative states will depend on all levels of protein structure with which it interacts and on physicochemical characteristics of the cellular environment. in which the interactions take place and the product is created (Dos Santos Carvalho & Fernandes, 2019). Copper(II) complexes with amino acids have long been known, and represent a special area of interest in the coordination chemistry of this element precisely because they serve as models for the study of copper metalloproteins. In this context, the behavior of Cu(II) in aquatic systems towards histidine is particularly interesting. It has been observed that most copper binding domains of proteins are rich in this amino acid, which is consistent with the coordination preferences of copper in the +2 oxidation side towards N donor ligands. The copper(II) complex with the simplest amino acid, glycine, was prepared in 1841. by Boussingault (Delf, *et al*). It was later shown that this type of complex does not belong to conventional copper complexes precisely because of the properties of the given ligands, i.e. amino acids. Since amino acids have a larger number of potential donor atoms, the structure of the final complex certainly depends on the reaction conditions, i.e. the nature of the solvent, temperature, pH and counterion, as is the case in a living cell. Oxidative stress occurs due to an imbalance between oxidants and antioxidants in biological systems, and is caused by excessive formation of reactive oxygen species or improper functioning of the antioxidant system (Chiurchiu *et al*., 2016). Reactive oxygen species (ROS), although possessing physiological functions, have been implicated in the pathogenesis of a number of diseases including cardiovascular and neurogenerative diseases, muscular dysfunction, and cancer (Zuo *et al*., 2015; He and Zuo, 2015). In addition to the many physiological effects of melatonin, melatonin has been shown to have strong anti-oxidant properties, due to the fact that it reacts with free radicals giving other metabolites that also have a neutralizing effect on free radicals. In this way, the product of one reaction, becomes a reactant of the other in both cases consuming free radicals. Melatonin, as well as its reaction products with hydroxyl radicals, are not extremely effective in neutralizing hydroperoxyl radicals, but still suppress lipid peroxidation in vivo, most likely by eliminating the initial hydroxyl radicals (Galano *et al.*, 2014). In the last two decades, complexes of platinum, ruthenium, copper, cobalt and other metals have been used to modify and / or detect Aβ aggregation. The results of these studies suggest that metal complexes have promising potential in the treatment and diagnosis of Alzheimer's disease (Liu and Wang, 2018). Copper plays a significant role in the pathology of many neurodegenerative diseases, from Wilson and Menkes disease, through amyotrophic lateral sclerosis and Alzheimer's disease, to prion-associated diseases (Waggoner *et al,* 1999*)*. Most of these diseases, directly or indirectly, lead to changes in copper metabolism. Changes in copper metabolism can lead to its accumulation in certain regions of the body or change its bioavailability in the cellular environment. Both are associated with increased oxidative stress and the formation of ROS, of course, due to the well-known redox behavior of copper, which the body significantly utilizes under homeostatic conditions (Waggoner *et al*., 1999). Given the nature of melatonin as a scavenger of destructive radicals and the consequent formation of metabolites of good chelating power for Cu (Galano *et al*., 2014) through the *scavenger cascade* of melatonin, it was interesting to examine the effect of melatonin as a potential inhibitor of Cu-protein complex species formation. Research conducted to determine the role of melatonin as a Cu(II) chelator in preventing its degrading effect on DNA (Wang *et al.*, 2019) has concluded that the copper-detoxifying and antioxidant abilities of melatonin are not based solely on scavenger abilities against hydroxyl radicals which occur in Cu(II)/Cu(I) mediated reactions, but strongly suggest the role of melatonin or its metabolites (formed by the scavenger cascade) as chelators. The final evidence lacking for unequivocal confirmation of these assumptions is the synthesis, isolation, and structural characterization of such complex types of melatonin, its metabolites, and copper.

## EXPERIMENTAL

### *Materials and methods*

All chemicals used were commercially available with analytical grade of purity and used without further purification. Infrared spectra were recorded as KBr pellets on a Perkin Elmer spectrum BX FTIR System in

region 4000 – 400 $cm^{-1}$, resolution 2$cm^{-1}$, 8 scenes. The antioxidant activity was determined using the e-BioQuChem (e-BCQ) lab device, following the manufacturer's instruction manual. The results are expressed in μC or in the charge of the electrons released by the antioxidant to neutralize free radicals. This device makes it possible to distinguish fast-acting antioxidants such as ascorbic acid and coenzyme Q10 from co-producing antioxidants such as polyphenols, astaxanthin or α-lipoic acid. Fast-acting antioxidants are the first to be oxidized and are considered to be more potent antioxidants than general antioxidants even though they are present in lower concentrations. Total antioxidant capacity (QT) is obtained as the sum of the antioxidant capacity of the fast-acting (Q1) and co-producing antioxidants (Q2). The results of antioxidant capacity were also expressed in ascorbic acid equivalents (CEAC), for which it was necessary to construct a calibration curve. For this purpose, a dilution series of a solution of ascorbic acid standard in 0.1 M PBS buffer (pH = 7) was prepared in the concentration range 0 - 1000 μM.

***Synthesis of complexes***

All complexes were synthesized by heating the reaction mixture to 65ºC on a magnetic stirrer, under reflux for 5 to 9 hours. Immediately before the syntheses, anhydrous copper(II) chloride ($CuCl_2$) was prepared by drying copper(II) chloride dihydrate ($CuCl_2 \times 2H_2O$) at 120ºC for 2 hours. This drying gave anhydrous $CuCl_2$, which was observed by changing the color from blue, copper(II) chloride dihydrate to brown colored, anhydrous copper(II) chloride. For the synthesis of each complex, solutions of copper(II) chloride in methanol were prepared by dissolving 268.9 mg (0.002 mol) of anhydrous $CuCl_2$ in 40 mL of methanol preheated to 50ºC.

***Synthesis of Cu(II) complex with alanine***

In 40 mL of methanol previously heated to 50ºC, 356.36 mg (0.004 mol) of alanine were dissolved and a previously prepared solution of copper(II) chloride was added to the solution. After mixing, the solution was stirred a magnetic stirrer at 65ºC under reflux for about 5 hours. Immediately after mixing the solution, the reaction mixture showed light green color. After three hours of heating, the color of the mixture turned dark green and did not change until the end of the synthesis. After cooling, the reaction mixture was filtered and the crystals of the complex were washed with water and ether. Finally, the complex was recrystallized from dimethylsufoxide/water and dried in a vacuum desiccator.

***Synthesis of Cu(II) complex with glycine***

The amount of 303.30 mg (0.004 mol) of glycine was dissolved in 40 mL of methanol preheated to 50ºC, and the previously prepared copper(II) chloride solution was added to the solution. The reaction mixture was heated with a magnetic stirrer at 65ºC under reflux for about 5 hours. Immediately after mixing the solution, the reaction mixture had a light blue color which eventually turned a slightly darker shade of blue. The mixture was cooled and left at room temperature for 24 hours. The blue crystals of the resulting complex were then filtered and washed with water and ether, recrystallized from dimethylsufoxide/water and dried in a vacuum desiccator.

***Synthesis of Cu(II) complex with histidine***

To 620.62 mg (0.004 mol) of histidine was added 40 mL of methanol preheated to 50ºC. To the resulting solution was then added a previously prepared solution of copper(II) chloride. During the reaction, the color of the reaction mixture changed from light green-blue at the beginning to dark purple-blue at the end of the synthesis. After cooling and filtering the mixture, the crystals of the complex were washed with water and ether, recrystallized from dimethylsulfoxide/water and dried in a vacuum desiccator.

***Synthesis of Cu(II) complex with L-tryptophan***

For synthesis, 816.92 mg (0.004 mol) of L-tryptophan were weighed and dissolved in 50 mL of methanol heated to about 50ºC. $CuCl_2$ solution was added dropwise to the resulting solution with continuous stirring. The mixture was heated at 65ºC on a magnetic stirrer under reflux for 5 hours. After the end of the synthesis, the copper(II) complex with L-tryptophan was deposited in the form of a powdery substance of dark brown-blue color. The reaction mixture was filtered and the complex washed with hot water to eliminate chlorides, recrystallized from dimethylsulfoxide/water and dried on filter paper in a vacuum desiccator.

***Synthesis of Cu(II) complex with melatonin***

For the synthesis, 929.11 mg (0.004 mol) of melatonin was dissolved in 40 mL of methanol heated to 50°C. A previously prepared solution of copper(II) chloride was added to the resulting solution. Immediately after mixing, the reaction mixture turned greenish brown. The mixture was heated to 65°C while stirring with a magnetic stirrer under reflux for 9 hours. During the synthesis, the color of the mixture changed, to eventually become dark brown, which did not change until the end of the synthesis. After cooling and filtering the mixture, the crystals of the complex were washed with water and petroleum ether, recrystallized from dimethylsufoxide/water and dried in a vacuum desiccator.

## RESULTS AND DISCUSSION

All complexes were synthesized by the reaction of methanolic solutions of $CuCl_2$ and the corresponding amino acids (alanine, glycine, histidine and tryptophan), and melatonin, at 65°C under reflux for 5 to 9 hours.

***FTIR spectra of amino acids and melatonin***

The FTIR spectra of all amino acids show vibrations typical of the carboxyl group, whose displacements in different amino acids are attributed to its protonated or deprotonated form. The asymmetric stretching of the carboxyl group in the given amino acids occurs at about 1600 $cm^{-1}$ and is extremely important for determining the performance and type of coordination in Cu-complexes. The area above 3000 $cm^{-1}$ is not of special importance for free amino acids, but it becomes more important for their Cu-complexes. Vibrations in the amino acid and melatonin spectra in the range of 2000 to 2800 $cm^{-1}$ are not of particular importance in determining subsequent coordination at the metal center. Extremely significant vibrations in the spectra of amino acids, but also the metal complexes is that attributed to the amino group in either protonated or deprotonated form. These bands are found in alanine at about 1590, 1520 and 1230 $cm^{-1}$. Indispensable are the vibrations of the hydrocarbon skeleton that occur at about 1000 $cm^{-1}$ depending on the type of amino acid, as well as those attributed to the aromatic fragment of the molecule in the case of histidine, tryptophan and melatonin. Vibrations of C-H bonds for the aliphatic part of the molecule occur below 3000 to 2900 $cm^{-1}$, while for the aromatic part of the molecule they occur above 3000 $cm^{-1}$ to 3100 $cm^{-1}$ and are clearly visible in the spectra of histidine, tryptophane and melatonin. The expected deviations in spectral characteristics in relation to amino acids show melatonin as a typical amine where this functionality is shown at about 3280 $cm^{-1}$ and at 1490 $cm^{-1}$, while the indole functionality is found at 3305 $cm^{-1}$ and 1270 $cm^{-1}$, respectively. Other bands in the ligand spectra have a more specific character.

***FTIR spectra of Cu(II) complexes***

Copper spectra with amino acids and melatonin show typical low-band bands attributed to metal-ligand vibrations and are of great importance for determining the coordination type and potential geometry of the complex. As copper(II) chloride was used as the starting substance, the retention of chloride in the coordination sphere in the final complex is not excluded. The previously mentioned typical vibrations of amino acids and melatonin, which now play the role of ligands, show typical shifts that indicate a model of coordination at the Cu(II) center. A typical phenomenon after coordination is the abolition of individual bands or the abolition of degenerate vibrational modes. A typical, spectrally noticeable change shown by a coordinated carboxyl group is the appearance of a band corresponding to the C=O bond as well as a band corresponding to the C-O bond, which indicates the abolition of resonance in the uncoordinated carboxyl group, i.e. its participation in coordination to the metal center. An additional change in relation to the spectra of free ligands is often the deprotonation of the amino group due to its coordination, which is observed by the abolition of bands typical of the - $NH_3$ group and the appearance of bands typical of the - $NH_2$ group. Skeletal vibrations do not suffer significant displacements or their bands are canceled if a certain vibration mode becomes impossible after coordination with the metal center, which is also important data. Other bands in the spectra of the complex have a more specific character and are described in detail for each individual complex.

***FTIR characterization of Cu - alanine complex***

It is known that the reaction of copper(II) acetate, as a salt of a weak organic acid, with alanine in adequate solvents and with good pH control creates bis(alaninato) copper(II) complex which occurs in two geometric isomers, ie *trans*-bis alaninate) copper(II) monohydrate and *cis*-bis(alaninato) copper(II) monohydrate. The difference between these two isomers can be easily determined by IR spectroscopy, with vibrations in the spectral range of 750 to 200 $cm^{-1}$ bei considered relevant. The *trans* isomer generally shows fewer bands in said region as well as *trans*-bis(glycinato) copper(II). In essence, metal-ligand vibrations may be sufficient to perform this distinction (Herlinger, Wenhold, & Long, 1970) where vas (Cu-N) vibration occurs as a weak band at 484 $cm^{-1}$ in the case of the trans isomer, while the cis isomer shows vas (Cu-N) at 483 $cm^{-1}$ and *v*s (Cu-N) at 411 $cm^{-1}$. In the case of the prepared Cu complex with alanine *v* (Cu-N) vibration is observed at 472 $cm^{-1}$, which is not correlated with typical bis(alaninato) copper(II) complexes. A wide band in the spectrum of the complex at about 3429 $cm^{-1}$ as well as an intense band at 1637 $cm^{-1}$ are used to detect crystal bound water, the former being attributed to vibrations of O-H bond stretching water molecules and the latter to their symmetric deformation (Nakamoto, 2009). Bands in the range 3297 - 3140 $cm^{-1}$ were attributed to the (N-H) vibrations of the coordinated amino group. These bands are more visible in the complex in relation to the vibrations of the same bond of the protonated amino group in the ligand. The deformation vibration of this group is in the vicinity of the band for C=O bonding and deformation of water molecules, and has a peak at 1598 $cm^{-1}$ (Han, 2010). Vibration of the protonated amino group, i.e. $v_r$ ($NH_3^+$), is not present in the spectrum of the complex, and has been replaced by "*rocking*" and "*wagging*" vibrations of the coordinated amino group at 1150 $cm^{-1}$ and 1022 $cm^{-1}$ (Nakamoto, 2009) the intense band at 666 $cm^{-1}$ also attributes the "*rocking*" vibration

to this group. The band at 1578 $cm^{-1}$ corresponds to the vibration of the *v*(C=O) coordinated carboxyl group, while the *v*(C-O) vibration occurs at 1396 $cm^{-1}$. Resonance of the carboxyl group is reflected in the alanine spectrum by the $v_{as}$ ($COO^-$) vibration at 1624 $cm^{-1}$. This band is not present in the spectrum of the complex, which confirms coordination through the carboxyl group. The bands corresponding to the in-pane or "*out-of-plane*" vibrations of the carboxyl group at 850 $cm^{-1}$ and 650 $cm^{-1}$, as well as the deformation at 772 $cm^{-1}$ disappear in the spectrum of the complex and are replaced by "*rocking*" or wagging by vibrations of a coordinated carboxyl group at 530 $cm^{-1}$ and 624 $cm^{-1}$ as much less intense bands (Herlinger, Wenhold and Long, 1970). Bands whose positions and intensities have little or no change in the spectrum of alanine and the respective complex originate mostly from C-H vibrations and deformations of alkyl groups. Namely, the bands at 2927 $cm^{-1}$ and 2856 $cm^{-1}$ in the spectrum of the complex were attributed to the (C-H) vibrations of the methyl and (CH) groups (Garcia *et al.*, 2008). The band at 1113 $cm^{-1}$ attributed to $v_{as}$ (C-C) $^+$ ρ ($NH_3$ $^+$), which is in a complex of lower intensity and occurs 1116 $cm^{-1}$, reflects a higher proportion of C-C vibration. Bands of symmetrical and asymmetric deformation of the methyl group in the prepared complex 1366 cm-1 and 1460 cm-1 occur, almost unchanged, relative to the ligand. Bands corresponding to free vibrations of the C-C-N skeleton do not appear in the spectrum of the complex, which is a consequence of coordination through N atoms (Nakamoto, 2009).

**Table 1:** Characteristic vibrations of Cu(II) alanine complex

| Characteristic vibrations of Cu-glycine | Wave number of vibration, ν ($cm^{-1}$) |
|---|---|
| $\nu(O–H)H_2O$ | 3464 b |
| $\delta_s(H_2O)$ | 1640 s |
| $\nu(N–H)NH_2$ | 3356 – 3250 m, b |
| $\nu(C–H)$ | 2984 – 2924 w – m |
| $\delta(NH_2)$ | 1602 s |
| $\nu(C=O)$ | 1578 s |
| $\delta_s(NH_3^+)$ | – |
| $\delta_s(CH_2)$ | 1444 s |
| $\nu(C-O)$ | 1408 s |
| $\rho_w(CH_2)$ | 1338 m |
| $\nu_r(NH_3^+)$ | – |
| $\rho_r(NH_2)$ | 1101 m-s |
| $\rho_w(NH_2)$ | 1060 m |
| $\nu_{as}(C–C–N)$ | – |
| $\rho_r(CH_2)$ | 916 w |
| $\nu_s(C–C–N)$ | – |
| $\rho_w(COO^-)$ | – |
| $\delta(C=O)$ | 742 w |
| $\pi(C=O)$ | 608 m |
| $\nu(Cu–N)$ | 486 m |

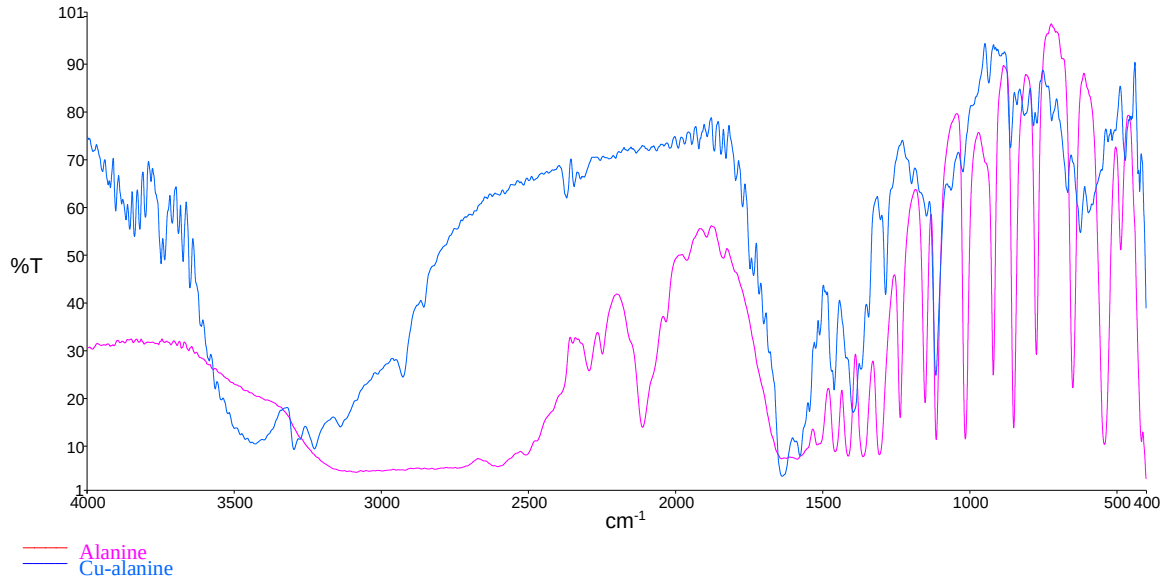


**Figure 1**: Comparative FT-IR spectra of alanine and Cu- alanine complex

***FTIR characterization of Cu - glycine complex***

It is known that the reaction of copper(II) acetate, as a salt of a weak organic acid, with glycine in adequate solvents and with good pH control creates bis (glycinato) copper(II) complex which occurs in two geometric isomers, ie trans-bis glycinato) copper(II) dihydrate and cis-bis (glycinato) copper(II) monohydrate. IR spectroscopy can easily determine the true difference between these two isomers, with vibrations in the spectral range of 750 to 200 $cm^{-1}$ being considered relevant. Having greater symmetry, the trans isomer generally shows fewer bands in said region. In essence, metal-ligand vibrations may be sufficient to perform this distinction (Herlinger, Wenhold and Long, 1970) where *v*(Cu-N) vibration occurs as a weak band at 477 $cm^{-1}$ in the case of the trans isomer, while the cis isomer shows vas (Cu-N) at 471 $cm^{-1}$ and vs (Cu-N) at 454 $cm^{-1}$. In the case of the prepared Cu complex with glycine *v*(Cu-N) vibration is observed at 486 $cm^{-1}$, which is not correlated with typical bis (glycinato) copper(II) complexes. A wide band in the spectrum of the complex at about 3464 $cm^{-1}$ with an intense band at 1640 $cm^{-1}$ is used to prove crystal bound water where the former is attributed to vibrations of stretching O-H bonds of water molecules and the latter to their symmetric deformation (Nakamoto, 2009) . The bands at 3169 $cm^{-1}$ in the glycine spectrum attributed to the (N-H) protonated amino group were replaced by bands in the range of 3356 - 3250 $cm^{-1}$, which are attributed to the (N-H) vibrations of the coordinated amino group. These vibrations for *trans*-bis (glycinato) copper(II) dihydrate occur in the range of 3320 - 3260 $cm^{-1}$, which does not correlate with the bands of the synthesized Cu-glycine complex, which is therefore more complex than simple bis (glycinato) copper (II) complex. The band at 1578 $cm^{-1}$ corresponds to the *v*(C = O) coordinated carboxyl group, while the *v*(C - O) vibration occurs at 1408 $cm^{-1}$, which confirms the coordination of the carboxyl group, as well as the resonance that occurs in the glycine spectrum by vibration at 1612 $cm^{-1}$ which is not present in the spectrum of the complex. The bands corresponding to the "rocking" or "wagging" vibrations of the carboxyl group at 508 $cm^{-1}$ and 698 $cm^{-1}$, as well as the deformation at 610 $cm^{-1}$, disappear in the spectrum of the complex and are replaced by much less intense vibration bands of the coordinated carboxyl group, at 742 $cm^{-1}$ and 608 $cm^{-1}$ (Inomata *et al*., 1988). Bands whose positions and intensities have little or no change in the spectrum of glycine and its complex originate mostly from C - H vibrations and deformations of the $CH_2$ group.

Namely, bands in the range of 3000 to 2900 $cm^{-1}$ appear in both the ligand and the complex, and are attributed to *v*(C-H) vibrations. There is a band "wagging" vibrations of the $CH_2$ group at about 1337 $cm^{-1}$ practically unchanged position in both substances, but much lower intensity in the complex. This change in intensity can be related to electronic changes due to coordination on the charged metal center. The same can be concluded for the "wagging" vibration of the $CH_2$ group, which was shifted from 910 $cm^{-1}$ in the ligand to 916 $cm^{-1}$ in the complex, and significantly reduced in intensity. It is clear that coordination limits the ease of development of certain types of vibrations (especially deformation vibrations and torsional vibrations), which is combined with electrostatic interactions in the crystal lattice of a complex joint and may justify small changes in band positions reflecting vibrations. such as the $CH_2$ group of glycine (Nakamoto, 2009).

**Table 2**. Characteristic vibrations of Cu(II)-glycine complex

| **Characteristic vibrations of Cu-alanine** | **Wave number of vibration, *v* ($cm^{-1}$)** |
|---|---|
| $v(O–H)H_2O$ | *3429 b* |
| $\delta_s(H_2O)$ | *1637 s* |
| $v(N–H)NH_2$ | *3297 – 3140 m, b* |
| $v(C–H)$ | *2927, 2856 w – m* |
| $\delta(NH_2)$ | *1598 m* |
| $v(C=O)$ | *1578 s* |
| $\delta_{as}(CH_3)$ | *1460 s* |
| $\delta_s(NH_3^+)$ | – |
| $\delta_s(CH_3)$ | *1366 s* |
| $v(C–O)$ | *1396 s* |
| $v_{as}(C–C)$ | *1116 m* |
| $v_r(NH_3^+)$ | – |
| $\rho_r(NH_2)$ | *1150 w* |
| $\rho_w(NH_2)$ | *1022 w* |
| $\delta(COO^-)$ | *784, 722 w* |
| $\rho_r(NH_2)$ | *666 m* |
| $\rho_w(COO^-)$ | *624 m* |
| $\rho_r(COO^-)$ | *530 w* |
| $v(Cu – N)$ | *472 m* |

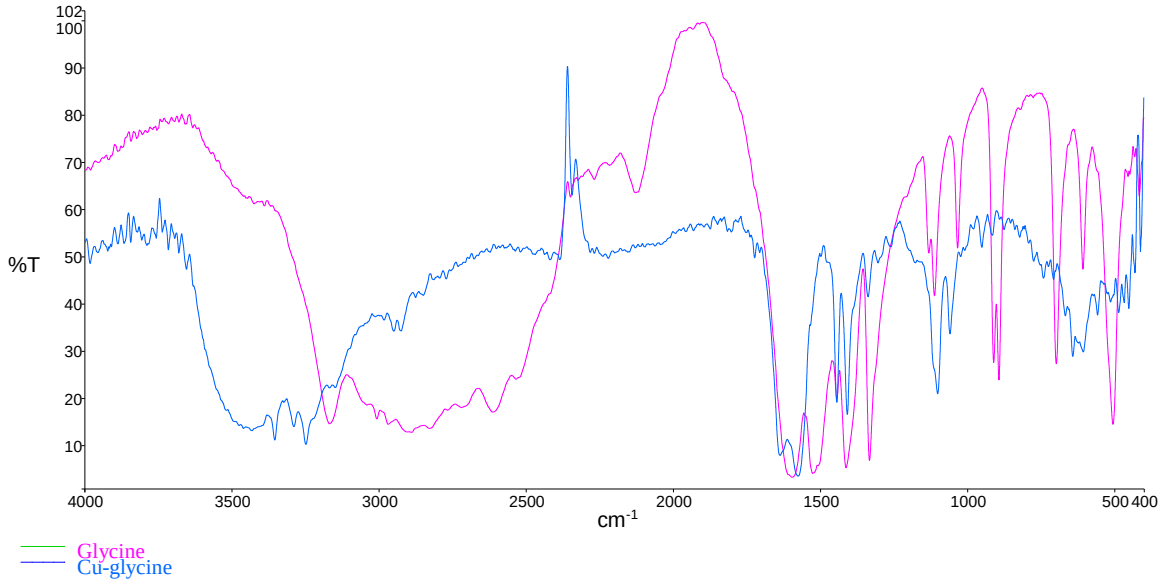


**Figure 2**: Comparative FT-IR spectra of glycine and Cu- glycine complex

**FTIR characterization of Cu - histidine complex**

In terms of coordination chemistry, histidine has been described as a rather complex ligand. Due to the large number of adequately positioned donor atoms, histidine as a ligand can build various complicated complexes with metals that prefer N donor ligands, such as Cu(II). Kruck and Sarkar (1973) described at least six different coordination forms in the Cu(II) histidine system where histidine always occurs as an O, N donor. The N donor atom may come from the amino group of the aliphatic chain or the N atom of the imidazole ring carrying a free electron pair. In the spectrum of the complex at 418 $cm^{-1}$, the band attributed by Drodżewski and Kordon (2000) to *ν*(Cu-N) occurs when the N atom originates from the amino ($NH_2$) group and the assumption was confirmed by isotopic derivatization. This, however, does not exclude the occurrence of histidine as a Nimidazole donor, but only confirms that histidine also acts as an N ($NH_2$) donor in the prepared complex. Coordination to the Cu(II) center via the amino group is supported by changes in other bands, fully or partially attributed to the vibrations of this group in free histidine. Namely, the band attributed to the "scissoring" vibration of the amino group at about 1632 $cm^{-1}$ was moved to 1625 $cm^{-1}$, while the band attributed to *ρw*($NH_2$) at 925 $cm^{-1}$ in the spectrum of the complex disappears. The amino group vibration "rocking" band combined with other histidine vibrations is present at 827 $cm^{-1}$, but expanded and drastically less intense, which also suggests coordination across the amino group (Nakamoto, 2009). The intense band attributed to the combined deformation of the N-H and C-H bonds of the imidazole fragment of the molecule in the histidine spectrum disappears in the spectrum of the complex, which may indicate the participation of the imidazole fragment in coordination with the Cu(II) center. More definite evidence would be found in Cu-Nimidaz. which occurs at about 280 $cm^{-1}$ (Drożdżewski and Kordon, 2000) which is beyond the scope of the performed recordings. The band carrying the highest proportion of carboxyl group vibrations, with a smaller proportion of other histidine vibration modes, was shifted from 1796 $cm^{-1}$ from the ligand spectrum to 1740 $cm^{-1}$ in the complex spectrum (Kruck and Sarkar, 1973), the most significant indicator of histidine coordination over carboxyl groups (Dunbar *et al*., 2018). It should be noted that the Cu(II) complex that two histidine molecules can have multiple forms, one of which contains Cu(II) in the tetragonal distortion of O, N, N donor histidine molecules. The intense band at 625 $cm^{-1}$ attributed to the out-of-plane bending of the N-H bond of the imidazole ring (combined with other vibrations) occurs virtually unchanged in the spectra of both ligands and complexes, which is expected given that this bond remains preserved in complex. Significant is the behavior of the band at 1453 $cm^{-1}$, which is partly attributed to the deformation of the $CH_2$ group, and in the complex occurs at approximately 1400 $cm^{-1}$. This decline is atypical for the group not directly involved in coordination, however the band of this vibration strongly depends on the spatial arrangement of parts of the histidine molecule, so it occurs in different conformations ranging from 1477 to 1424 $cm^{-1}$ (Kumar *et al*., 2010). This band shift in the spectrum of the complex relative to the ligand can be interpreted as

additional evidence of histidine coordination at the Cu(II) center, given that the coordination process almost always causes changes in the conformation of more complex ligands (Nakamoto, 2009). the position of the "*scissoring*" band of the vibration of the $CH_2$ group of histidine.

**Table 3**. Characteristic vibrations of Cu- histidine complex

| Characteristic vibrations of Cu-histidine | Wave number of vibration, ν ($cm^{-1}$) |
|---|---|
| $\nu(C=O) + \delta(O–H) + \delta(C–H)$ | 1740 m |
| $\delta_s(NH_2)$ | 1625 s |
| $\delta_s(CH_2)$ | 1398 s |
| $\delta(C–H) + \delta(N–H)$ | - |
| $\nu(C–NH_2) + \delta(C–H)$ | 1084 m |
| $\rho_w(NH_2)$ | - |
| $\rho_r(NH_2)$ | 827 m, b |
| $\gamma(N_{imidaz.}–H)$ | 625 s |
| $\nu(Cu – N)$ | 418 s |

***FTIR characterization of Cu - tryptophan complex***

The spectrum of the prepared complex shows significant differences in the bands attributed to vibrations in which nitrogen atoms participate, which leads to the first conclusion about its coordination engagement in the complex. The vibration-corresponding bands ($NH_3^+$) of the group completely disappear in the spectrum of the complex and are replaced by vibrations characteristic of the $NH_2$ group. Thus, wild very intense bands appear at 3338 $cm^{-1}$ and 3254 $cm^{-1}$, which correspond to asymmetric and symmetric stretching of the amino group, while at 1627 $cm^{-1}$ there is an intense band of strain deformation in the mentioned group. Vibrations involving the indole nitrogen atom have no significant change in position or intensity. In the vibrations of the nitrogen atom that is directly related to the aliphatic carbon atom, a small shift towards higher wave numbers was observed. Vibration at 3420 $cm^{-1}$ indicates that the nitrogen atom in the indole ring is not deprotonated, and therefore probably not coordinated (Wagner & Baran, 2004). Equally significant changes are observed in the vibration bands of the carboxyl group where symmetrical and asymmetric stretching is not present in the molecule of the complex, thus pointing to the violation of the symmetry of the group and the abolition of resonance between bonds to a single C-O bond and a double C=O bond. Proof of this is the very intense band at 1562 $cm^{-1}$ corresponding to the carbonyl bond from the carboxyl group while at 1382 $cm^{-1}$ the rest of the group occurs in the form of C-O vibration. The intense deformation vibration of this group was shifted toward lower wave numbers at 740 $cm^{-1}$ (Wagner & Baran, 2004). Vibrations corresponding to the hydrocarbon skeleton do not change significantly in position or are eliminated due to differences in the symmetry of the coordinated and free molecules of tryptophan. Metal ligand vibrations are the most convenient form of confirmation of coordination both in terms of the nature and identity of coordinated atoms. Thus, in the spectrum of the complex, typical stretching vibrations of the Cu-N bond occur, which copper forms with the deprotonated amino group of tryptophan, at 475 $cm^{-1}$ as a medium intensity band. Vibrations of Cu-O usually fall below 400 $cm^{-1}$ (about 350 - 310 $cm^{-1}$) so that they are not visible in the given spectrum, but their existence is indicated by changes in the carboxyl group in terms of resonance cancellation due to binding of one oxygen atom from the given group to the Cu center and the accompanying formation of the C=O bond (Nakamoto, 2009; Wagner & Baran, 2004).

**Table 4:** Characteristic vibrations of Cu- tryptophan complex

| Characteristic vibrations of Cu- tryptophan | Wave number of vibration, ν ($cm^{-1}$) |
|---|---|
| $\nu(N–H)_{indole}$ | 3420 vs |
| $\nu_{as}(NH_2)$ | 3338 vs |
| $\nu_s(NH_2)$ | 3254 vs |
| $\nu(NH_3^+) + \nu(C–H)$ | – |
| $\nu(C–H)$ | 2895 w |
| $\delta_{as}(NH_3^+)$ | – |
| $\delta(NH_2)$ | 1627 vs |
| $\nu_{as}(COO^-)$ | – |
| $\nu(C=O)$ | 1562 vs |
| $\delta_s(NH_3^+)$ | – |
| $\delta(CH_2)$ | 1458 s |
| $\nu_s(COO^-)$ | – |
| $\nu(C–O)$ | 1382 m |
| $\tau(CH_2)$ | 1228 m |
| $\nu(C–N)_{aliph.}$ | 1100 m |
| $\delta(COO^-)$ | 740 s |
| $\nu(Cu–N)$ | 475 m |

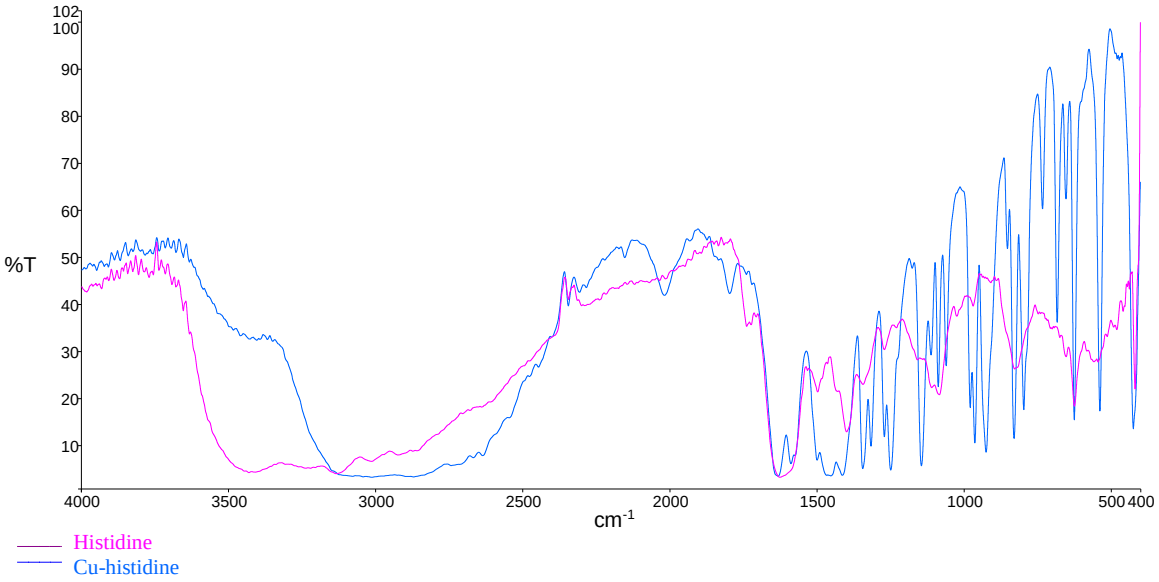


**Figure 3**: Comparative FT-IR spectra of histidine and Cu- histidine complex

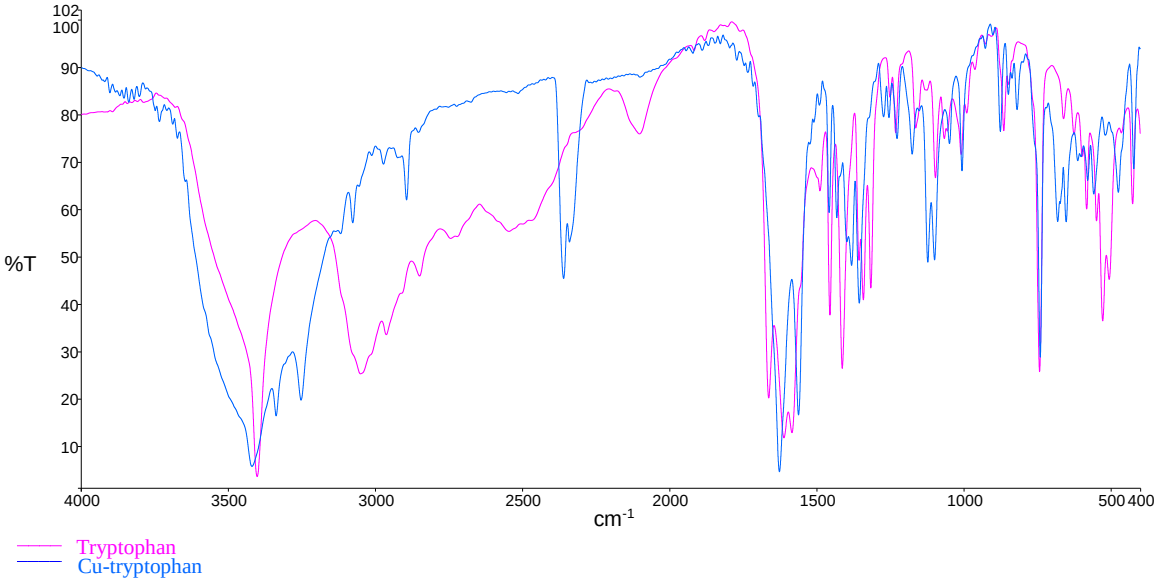


**Figure 4**: Comparative FT IR spectra of of tryptophan and Cu- tryptophan complex

***FTIR characterization of Cu-melatonin complex***

The spectrum of the Cu-melatonin complex shows a band at 3308 $cm^{-1}$ which corresponds to the vibration of the N-H bond of the indole. The appearance of this band, with small changes in symmetric and asymmetric stretching of the C - N bond within the indole ring, leads to the conclusion that this group is intact in the final complex and rejects the possibility of melatonin coordination at the Cu(II) center via N indole atoms (Shimazaki *et al*., 2009). The band carrying the largest share of C=O vibration of the amide group occurs 1632 $cm^{-1}$, is lower in intensity than in the melatonin spectrum, but certainly means that the oxygen atom does not participate in the coordination sphere of the Cu(II) center. This is supported by the sensitivity of this vibration to coordination via the amide oxygen atom, where a shift to higher wave numbers of up to 20 $cm^{-1}$ is expected (Ashok, *et al*., 2006). In contrast to the aforementioned groups, significant changes occur in bands involving vibrations of the amide N atom in the spectra of the melatonin and Cu-melatonin complexes. To evaluate coordination across an amide N atom, $\nu_{as}$ (C-N) amide. + δ (C-N-H) amide, is the most significant band corresponding to the vibration of the amide group and occurs in the spectrum of melatonin at 1490 $cm^{-1}$.

This band is lost in the spectrum of the complex from this spectral region. The band at 954 $cm^{-1}$ in the melatonin spectrum, corresponding to the , *ν*(C-N) amide vibration also disappears in the spectrum of the complex. Vibration γ(N - H) amide + τ(HCCO) amide, which carries a higher proportion of torsional vibrations, changes position and intensity in the spectrum of the complex. These observations suggest the possibility of coordination of melatonin at the Cu(II) center via the N atom of the amide group, which is a common tendency of amide ligands (Marti *et al*., 2012) in the context of Cu(II) coordination chemistry. In the spectrum of the complex, the I-band appears at 480 $cm^{-1}$, which is the area of the IR spectrum where the stretching of the Cu-N bond is expected (Nakamoto, 2009). An extremely interesting phenomenon is the band at 1714 $cm^{-1}$ which is not a common vibrational region of the carbonyl group attached to the N atom as is the case in amides. Ji et al. (2020) provided an interesting overview of the theoretically predicted spectra for simple amide (*N*-methylacetamide) for each individual resonant form. A resonant form that represents said molecule as acetimic acid (where the H atom of the amide group is attached to oxygen while carbon and oxygen form an imine bond (C=N)) shows a stretching vibration of the C=N bond at about 1700 $cm^{-1}$. Coordination at the metal center significantly affects the balance of individual resonant forms, in the direction that favors better coordination with the metal center through the heteroatom that participates in the resonance (Nakamoto, 2009). It can be assumed that the Cu(II) center can coordinate to the N atom of the amide part of the melatonin molecule to induce the formation of (C=N) bonds by stabilizing such a resonant form, which would be manifested by a band at 1714 $cm^{-1}$. Many other experimental data are needed to finally confirm this assumption. Bands of groups that do not participate in coordination occur virtually unchanged in the spectrum of the complex relative to the spectrum of the ligand. Asymmetric and symmetric stretching of the C–H group of the aliphatic part of the molecule occurs in the complex at 2926 $cm^{-1}$ and 2866 $cm^{-1}$, while the "rocking" vibration band of the mentioned bond is also practically unchanged in the complex at 1045 $cm^{-1}$. The band at 1555 $cm^{-1}$ corresponding to the asymmetric stretching of the C=C bond of the indole ring at 2C - 3C is of lower intensity but of the same position, at 1556 $cm^{-1}$ in the spectrum of the complex (Singh *et al*.,2014).

**Table 5:** Characteristic vibrations of Cu - melatonin

| **Characteristic vibrations of Cu-melatonin complex** | **Wave number of vibration, ν ($cm^{-1}$)** |
|---|---|
| $\nu(N–H)_{indole}$ | 3308 s |
| $\nu(N–H)_{amide}$ | - |
| $\nu_{as}(C–H)_{aliph.}$ | 2926 m |
| $\nu_{s}(C–H)_{aliph.}$ | 2866 m |
| $\nu(C=O) + \delta(C–N–H)_{amide}$ | 1632 s |
| $\nu_{as}(C=C)_{2\text{-}3C\text{-}indole}$ | 1556 m |
| $\nu_{as}(C–N)_{amide} + \delta(C–N–H)_{amide}$ | - |
| $\nu_{s}(C–N)_{indole}$ | 1264 w |
| $\nu_{as}(C–N)_{indole}$ | 1206 s |
| $\nu(C–O)_{methoxy}$ | 1174 m |
| $\rho_{r}(C–H)_{aliph.}$ | 1045 ms |
| $\nu(C–N)_{amide}$ | - |
| $\gamma(C–H)_{indole} + \tau(HCCC)_{2\text{-}3C\text{-}indole}$ | 803 m |
| $\tau(HCCO)_{amide}$ | 604 m |
| $\gamma(N–H)_{amide} + \tau(HCCO)_{amide}$ | 538 w |
| $\nu(Cu–N)$ | 480 w |

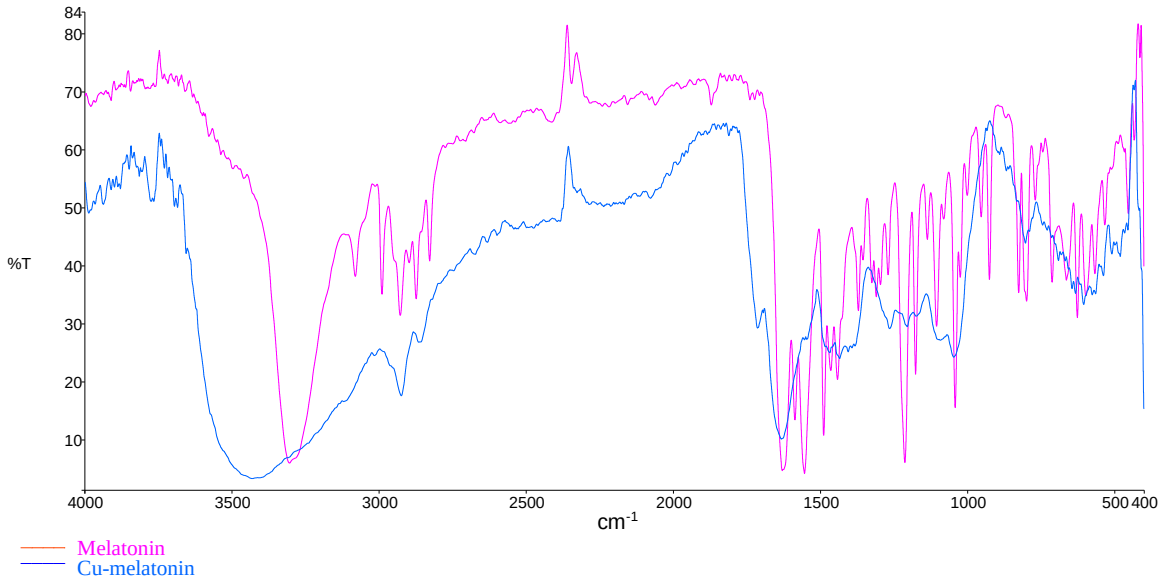


**Figure 5:** Comparative FT IR spectra of melatonin and Cu- melatonin complex

***Determination of antioxidant capacity***

By examining the antioxidant capacity of the synthesized copper complexes, CEAC values in the range of 121.6 - 734.4 μM were obtained. The lowest values of antioxidant capacity were recorded in the copper complex with tryptophan, while the highest values were recorded in the copper complex with alanine. A high antioxidant capacity of the copper complex with melatonin (673.8 μM) was also observed. Melatonin is known to be a good scavenger of hydroxyl radicals, superoxide anion radicals and nitric oxide and is one of the most effective lipophilic antioxidants (Simunkova *et al*., 2019).

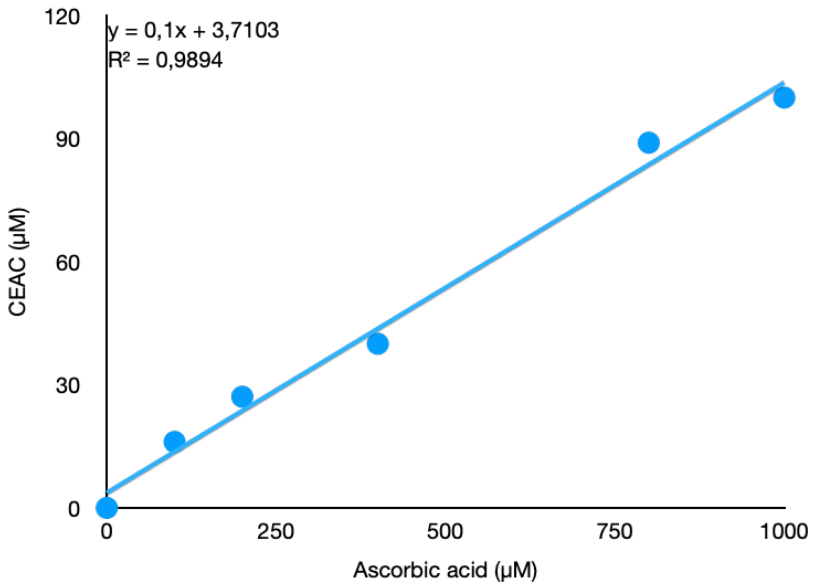


**Figure 6**: Calibration curve with standard ascorbic acid solution

Ascorbic acid is the strongest natural antioxidant and is commonly used in determining antioxidant capacity. To present the results as ascorbic acid equivalents (CEAC), a calibration curve was constructed as shown in Figure 6. The values of Q1 and Q2, as well as QT of the analyzed complexes are shown in Table 6.

**Table 6:** Antioxidant capacity of synthesized complexes expressed in µC

| Complex | Q1 (µC) | Q2 (µC) | QT (µC) |
|---|---|---|---|
| **Cu-Gly** | 3.6 | 20.1 | 23.7 |
| **Cu-Ala** | 24.3 | 50.2 | 74.5 |
| **Cu-His** | 3.9 | 47.2 | 51.1 |
| **Cu-Mel** | 36.2 | 32.6 | 68.8 |
| **Cu-Trp** | 3.9 | 13 | 16.9 |

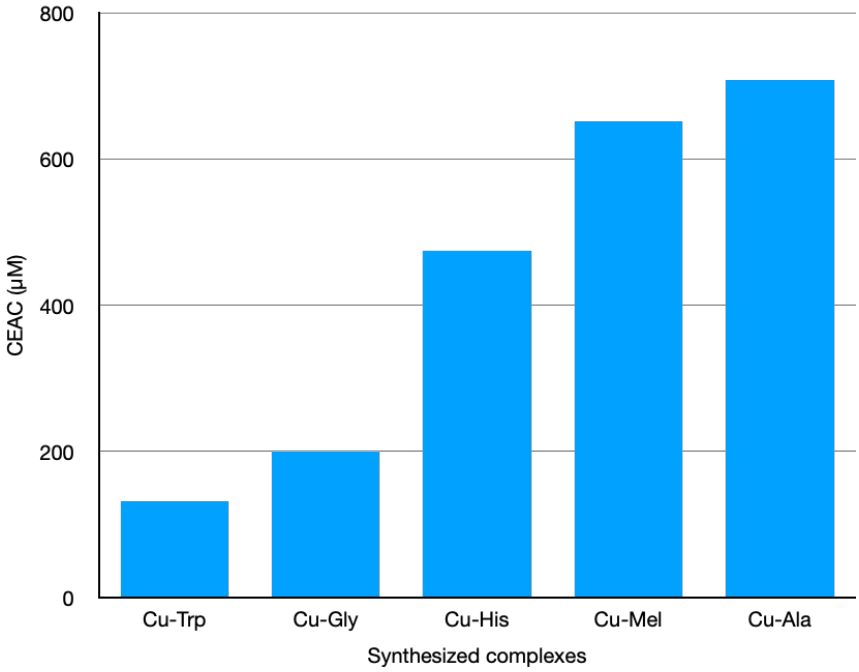


**Figure 7:** Total antioxidant capacity (CEAC) of synthesized complexes

## CONCLUSION

Five complex compounds of copper(II) were prepared following an identical procedure. Four amino acids (glycine, alanine, tryptophan and histidine) and melatonin as a bioactive tryptophan derivative were used as ligands. It was found that this preparative approach in the case of alanine and glycine does not result in the isolation of well-known cis / trans-bis (glycinato) copper(II) or cis / trans-bis (alaninato) copper(II) complexes implying the importance of starting copper(II) salt as well as pH control of the solution, given that said complexes are obtained using copper(II) acetate in approximately neutral aqueous solutions. FTIR characterization of the isolated complexes with glycine and alanine showed deviations from the IR spectral characteristics of the isomeric amino acid carboxylates of copper(II), especially in the region from 800 to 400 cm-1 where isomer-specific vibrations are common. Analysis of the FTIR spectra of prepared complexes of these amino acids provides data on the coordination of both oxygen atoms from the carboxyl group and nitrogen atoms from the amino group of the same, but does not dispute the participation of chlorides and water molecules in the coordination sphere of Cu(II). The histidine complex also shows the participation of oxygen and nitrogen atoms from the aliphatic part of this amino acid, but based on changes in skeletal ring vibrations, potential coordination of nitrogen atoms from the imidazole residue of this amino acid is assumed, which could be concluded based on Cu(II) center coordination preference. In the case of the melatonin complexes, the FTIR spectrum disputes coordination via oxygen atoms either from the amide group of the aliphatic moiety or from the methoxyl substituent on the indole ring, the potential deprotonation of the indole ring and coordination via the nitrogen atom from the same is also challenged. In contrast, the FTIR spectrum of the

complex clearly indicates the coordination of nitrogen atoms from the amide group as well as the potential stabilization of one of the resonant forms of this group based on theoretical considerations. It is important to note that the assumed structures contain coordinated chlorides based on theoretical knowledge and practical data on the behavior of such systems, and that the final judgment on their coordination participation is made by considering the spectral range from 400 to 200 cm-1 not examined in this work. Finally, it can be said that this simple preparative approach results in complex compounds of amino acids and their selected derivatives with copper(II) chloride that are different from the literature described, relatively simple complexes and that additional characterization is needed to establish the final structure of the complex and possible conclusions about mechanistic processes that are ongoing in the given reaction system. The obtained results of the antioxidant capacity of the complexes indicate a possible good antioxidant effect of the copper complex with melatonin and alanine, which indicates the need of further research in terms of the use of other methods to determine antioxidant capacity (Romero-Canelon and Sadler, 2013; Van Rijt and Sadler, 2009; Leung et al., 2015).

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## Summary/Sažetak

Ispitana je reakcija bezvodnog bakar(II) hlorida u metanolnom rastvoru sa alaninom, glicinom, histidinom, triptofanom kao i reakcija s melatoninom. Produkti reakcija ispitani su FTIR spektroskopijom kako bi se izvršila distinkcija produkata reakcije u odnosu na, u literaturi, prethodno opisane komplekse istih aminokiselina sa Cu(II) kao što su *cis*- i *trans*-bis(glicinato)bakar(II). Od velikog interesa bila je reakcija $CuCl_2$ s melatoninom u ovim uvjetima. FTIR karakterizacija sintetiziranih kompleksa pokazala je da ovi reakcioni uslovi rezultiraju nastankom kompleksa Cu(II) s glicinom i s alaninom koji su složenije građe od bis(glicinato)- i bis(alaninato)bakar(II) kompleksa. Kompleks priređen s melatoninom pokazuje interesantne trake u spektralnom području za koje je odgovoran atom azota iz amido grupe melatonina. Posljednje opažanje je vrlo značajno jer je poznat vrlo mali broj metalnih kompleksa melatonina koji su dobro okarakterizirani, dok je sinteza većine njih eksperimentalno zahtjevan proces uz simultanu kontrolu više faktora. Ispitivanjem antioksidativnog kapaciteta sintetiziranih kompleksa bakra dobijene su vrijednosti CEAC u rasponu od 121.6 - 734.4 µM. Najniže vrijednosti antioksidativog kapaciteta su zabilježene kod kompleksa bakra sa triptofanom, dok su najviše vrijednosti zabilježene kod kompleksa bakra sa alaninom. Uočen je i visok antioksidativni kapacitet kompleksa bakra sa melatoninom (673.8 µM).