

SYNTHESIS OF Cu (II), Co (II), Mn (II) COMPLEX COMBINES WITH ASPARAGIN ACID AND DETERMINATION OF THEIR MEDICAL-BIOLOGICAL PROPERTIES

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Abstract. Geometrically isomeric coordination compounds of Cu(II), Co(II), Mn(II) with asparagin acid have been synthesized, competitive coordination of asparagin acid donor atoms to metal ions has been revealed, the conditions for the transformation of some isomers into others have been studied, and medical and biological properties have been studied.

Keywords: complex compound, biometals, ligands, cis-trans isomers, IR absorption spectra, diffuse reflection spectra (DRS), octahedral structure, biological activity.

Relevance. Aspartic acid plays an important role in the human body. It participates in the formation of other amino acids, participates in the construction of protein molecules. Aspartic acid is necessary for the normal functioning of the immune system, the synthesis of DNA and RNA, the apparatus of heredity, cell growth, an indispensable assistant of the nervous system, responsible for the correct transmission of a signal from one neuron to another. It also improves concentration and learning ability. Aspartic acid, as it were, drags potassium and magnesium inside the cell, improves concentration and learning ability. The intake of aspartic acid into the body is necessary for constant fatigue, depression, poor memory, unstable emotional state, low working capacity. Regular intake is necessary for people suffering from diseases of the cardiovascular system, brain, and eyes.

Biogenic trace elements cobalt, copper and manganese are also necessary for the normal functioning of the body. The lack of these elements in the body leads to severe pathologies. Inorganic salts of these trace elements are toxic and cannot be used in medical practice. In this regard, it becomes necessary to synthesize and study coordination compounds of aspartic acid with microelements Co(II), Cu(II) and Mn(II). Currently, the drug Cisplatin, which is a complex compound of platinum [Pt(NH₃)₂Cl₂]. Cisplatin has pronounced cytotoxic, bactericidal and mutagenic properties. The biological properties are based on the ability of the compound to penetrate into the cell nucleus to form a stable complex with DNA, which prevents DNA replication, i.e. DNA synthesis is inhibited and cell division stops. This platinum complex is currently widely used in medicine as an anti-cancer agent.

The drug Kobavit is a complex compound of vitamin U with cobalt Co³⁺. Kobavit has pronounced hepatoprotective, antianemic and anti-ulcer activity. As a hepatoprotector, Kobavit is used in acute, prolonged and chronic forms of hepatitis, cirrhosis of the liver, etc. The use of Kobavit in acute forms of viral hepatitis prevents the development of chronic forms of the disease, and in chronic forms – prevents further progression of the pathological process, including the development of cirrhosis of the liver. Kobavit has a high antianemic effect in the treatment of anemia of various etiologies and varying degrees of severity.

The drug Kupir is a complex compound of pyridoxine with Cu^{2+} copper. Kupir affects the intensity of metabolic processes, has antitoxic properties, increases the production of melanin. It is used in the treatment of vitiligo. The drug Cobalt 30 is a complex compound of methionine with cobalt Co^{3+} . It has the effect of ionizing radiation with accompanying disorders of hematopoiesis (hematopoiesis process) and leukopenia. Under the influence of the drug Cobalt-30, the content of rod-shaped leukocytes increases. Cobalt 30 is easily tolerated by patients and has no side effects. The drug is used in the clinic for the treatment of leukopenia.

The drug Feramide is a complex compound of iron Fe^{2+} with nicotinamide. Feramide restores the lack of iron in the body, stimulates erythropoiesis. Promotes the elimination of laboratory and clinical signs of anemia. Feramide is widely used in the treatment of posthemorrhagic anemia, iron deficiency anemia of various origins.

The drug Coamide is a complex compound of cobalt Co^{2+} with nicotinamide. Coamide is a stimulant of hematopoiesis, promotes the absorption of iron by the body and stimulates its transformation processes (formation of protein complexes, hemoglobin synthesis), normalizes erythropoietic activity and eliminates anemia. It is used in the treatment of hypochromic and hypoplastic anemia (with iron deficiency anemia simultaneously with iron preparations). It can be seen from the above that complex compounds of biometals with biologically active ligands are more active than inorganic salts of biometals.

Materials and methods of the research. This study is devoted to the synthesis and study of geometrically isomeric coordination compounds of Cu(II), Co(II), Mn(II) with aspartic acid, identifying the competitive coordination of donor atoms of aspartic acid to metal ions, expanding the number of cis-trans isomeric compounds, and elucidating the conditions converting some isomers into others, identifying their medical and biological properties, as well as introducing synthesized compounds into healthcare practice as medicines.

Aspartic acid (AspH_2) is a dibasic acid and therefore can form both acidic and moderate salts.

The synthesis of the compound $\text{K}_2[\text{Cu}(\text{Asp} - 2\text{H})] \cdot 4\text{H}_2\text{O}$ was carried out according to the following procedure: 0.1 mol of aspartic acid was dissolved in a solution of 0.2 mol of KOH (1:2) in 5 ml of water, 0.1 mol of $\text{Cu}(\text{CH}_3\text{COO})_2$ was added and stirred on a magnetic stirrer until the latter is completely dissolved. The resulting bright blue solution was repeatedly treated with alcohol until a powder was obtained, washed with ether and dried in air. A purple powder has been isolated, highly soluble in water, insoluble in acetone, alcohol, and ether.

When the resulting compound was dissolved in the smallest amount of water and heated to 90 – 100°C, a blue compound with the composition $\text{K}_2[\text{Cu}(\text{Asp} - 2\text{H})] \cdot 4\text{H}_2\text{O}$ was obtained.

The synthesis of the water-soluble compound $\text{Mn}[\text{Cu}(\text{Asp} - 2\text{H})] \cdot 4\text{H}_2\text{O}$ was carried out according to the following procedure: 0.1 mol of aspartic acid was dissolved in a solution of 0.1 mol KOH (1:2) in 5 ml of water, 0.1 mol Cu was added ($\text{CH}_3\text{COO})_2$ and stirred on a magnetic stirrer until complete dissolution. 0.1 mol $\text{Mn}(\text{CH}_3\text{COO})_2$ was added to the resulting blue solution and stirring was continued on a magnetic stirrer for 1 hour. The product was salted out with ethyl alcohol and treated with alcohol until a powder formed. The powder was separated, washed with alcohol and ether and dried in air. The resulting compound is a light blue powder, soluble in water, insoluble in acetone, alcohol, and ether.

Synthesis of the water-insoluble compound $\text{Mn}[\text{Cu}(\text{Asp} - 2\text{H})_2] \cdot \text{H}_2\text{O}$. The soluble compound $\text{Mn}[\text{Cu}(\text{Asp} - 2\text{H})_2] \cdot 4\text{H}_2\text{O}$, obtained according to the method described above, it was

dissolved in a small amount of water and heated to 90 – 100°C. In this case, a blue compound precipitated, insoluble in water, alcohol, acetone and ether.

Synthesis of the water-soluble compound $\text{Co}[\text{Cu}(\text{Asp}-2\text{H})_2] \cdot 4\text{H}_2\text{O}$. 0.1 mol $\text{Cu}(\text{CH}_3\text{COO})_2$ and then 0.1 mol $\text{Co}(\text{CH}_3\text{COO})_2$ were added to the disubstituted potassium salt of aspartic acid while stirring on a magnetic stirrer. The product was also salted out with alcohol and repeatedly treated with alcohol until a powder formed, since the substance is hygroscopic. The isolated powder is light purple in color, highly soluble in water, insoluble in acetone, alcohol, and ether. The reaction proceeds according to the following scheme:

To synthesize the water-insoluble compound $\text{Co}[\text{Cu}(\text{Asp}-2\text{H})_2] \cdot 3\text{H}_2\text{O}$, a small amount of water was added to the soluble compound $\text{Co}[\text{Cu}(\text{Asp}-2\text{H})_2] \cdot 4\text{H}_2\text{O}$ and heated to 90 – 100°C. A blue precipitate formed, insoluble in water, alcohol, acetone, and ether.

The compound $\text{Mn}[\text{Co}(\text{Asp}-2\text{H})_2] \cdot \text{H}_2\text{O}$, soluble in water, was prepared similarly to the procedure above. With stirring on a magnetic stirrer, 0.1 mol of $\text{Co}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$ and then 0.1 mol of manganese acetate were added to the disubstituted potassium salt of aspartic acid. The product was salted out with alcohol and treated with alcohol until a powder formed. The resulting violet powder is very soluble in water, insoluble in alcohol, acetone, and ether.

The compound $\text{Mn}[\text{Co}(\text{Asp}-2\text{H})_2] \cdot \text{H}_2\text{O}$, which is insoluble in water, was synthesized by dissolving the compound $\text{Mn}[\text{Co}(\text{Asp}-2\text{H})_2] \cdot \text{H}_2\text{O}$ in a small amount of water and heating to 90 – 100°C. A burgundy-colored precipitate formed, insoluble in water. The compound is also insoluble in alcohol, acetone and ether.

Analysis of coordination compounds of aspartic acid composition

$\text{Mn}[\text{Cu}(\text{Asp}-2\text{H})_2] \cdot 4\text{H}_2\text{O}$ and $\text{Co}[\text{Cu}(\text{Asp}-2\text{H})_2] \cdot 4\text{H}_2\text{O}$ were carried out according to the following procedure. A sample of the substance was decomposed by heating under the influence of a mixture of concentrated HNO_3 and H_2SO_4 in a ratio of 5:1 until the H_2SO_4 layer became discolored, diluted with water to 100 ml and neutralized with a NaOH solution. Copper was determined from the solution by iodometry. To do this, add 3 ml of concentrated acetic acid, 3 g of KJ, cover the flask with a watch glass, and leave (to complete the reaction) in the dark for 5 minutes. The mixture was titrated with a solution of $\text{Na}_2\text{S}_2\text{O}_3$ to a light yellow color, then 2–3 ml of starch was added and titrated until the blue color discolored from one drop of $\text{Na}_2\text{S}_2\text{O}_3$ [1].

After quantitative determination of copper, the amount of solution was brought to 200 ml and left for a day. Copper was precipitated from solution in the form of Cu_2I_2 . After complete sedimentation of copper, 100 ml of solution was measured and the quantitative content of Co(II) and Mn(II) was analyzed using the complexometric method.

In the $\text{Mn}[\text{Co}(\text{Asp}-2\text{H})_2] \cdot \text{H}_2\text{O}$ compound, the quantitative content of Mn(II) was determined by the persulfate method [2]. To do this, a sample of the substance of about 0.01 mg was decomposed by heating in the presence of a mixture of concentrated HNO_3 and H_2SO_4 in a ratio of 5:1 until the sulfuric acid layer became discolored, 3 ml of concentrated H_2SO_4 , 10 ml of a 0.8% solution of AgNO_3 , 10 ml of a 25% solution of ammonium persulfate were added and boiled within 1 min. Then a given amount of oxalic acid was added and the excess was titrated with a solution of potassium permanganate to a light yellow color.

To determine the Co(II) content, acetone was added to a sample of about 0.1 mg of this compound after dissolving in 5–10 ml of water in such a way that at the end of titration the acetone content in the liquid was at least 50%; 2–3 g of ammonium thiocyanate was added as indicator and 1 ml of saturated sodium acetate solution. In this case, the liquid acquired a turquoise color due to

the formation of $(\text{NH}_4)_2[\text{Co}(\text{CNS})_4]$. The colored solution was titrated with a solution of complexone III until the turquoise color disappeared and a pink color appeared.

The quantitative nitrogen content in the synthesized complex compounds was determined using the Dumas micromethod [3], and the water content was determined by the gravimetric method.

IR absorption spectra were recorded in the range $400 - 4000 \text{ cm}^{-1}$ on a UR-20 spectrophotometer. In this case, the technique of pressing a sample with KBr or the suspension technique was used. Hydrated compounds were preliminarily dehydrated.

Diffuse reflectance spectra (DRS) were measured on an SF-10 device in the region of 350-700 nm with an interval of 5 nm for polycrystalline samples.

From the literature references it is known that glycine forms isomeric compounds being not only part of kinetically inert complex compounds, but also kinetically labile complexes. Needle and plate modifications of copper glycinate with the composition $\text{Cu}(\text{NH}_2\text{CH}_2\text{COO})_2 \cdot \text{H}_2\text{O}$ were isolated [4].

Subsequently, A.V. Ablov and his co-workers found that in the lamellar form the functional groups of the ligand have a trans arrangement, and in the needle form its amine nitrogen and carboxyl group have a cis arrangement. Using IR spectroscopy, the authors found that in the spectrum of copper glycinate monohydrate in the region of 1390 cm^{-1} there is a band of symmetrical stretching vibrations of the COO group. For the plate modification, i.e. For the cis isomer, the band splits into two components at 1393 and 1402 cm^{-1} .

Similar differences are observed in the IR spectra of the copper and cobalt compounds we synthesized with aspartic acid.

In the IR spectrum of the disubstituted potassium salt of aspartic acid, the νNH_2 bands are located at 3410 and 3270 cm^{-1} . In the IR spectrum of the compounds $\text{K}_2[\text{Cu}(\text{Asp}-2\text{H})_2]$, $\text{Mn}[\text{Cu}(\text{Asp}-2\text{H})_2]$, $\text{Co}[\text{Cu}(\text{Asp}-2\text{H})_2]$ and $\text{Mn}[\text{Co}(\text{Asp}-2\text{H})_2]$ a shift is observed this band to the low frequency region, which indicates the formation of an M-NH₂ bond, where M=Cu, Co. In addition, in the IR spectra of these compounds there are bands at 1625 and 1410 cm^{-1} , characteristic of the carboxylate group, which indicates the replacement of acidic hydrogens with Cu(II), Mn(II), Co(II). To clarify the relative position of the amino and carboxyl groups of two molecules of aspartic acid in the synthesized compounds, a comparison of the absorption bands of the soluble and insoluble forms of these compounds was carried out.

The IR spectra of the soluble and insoluble forms in the dehydrated state are generally similar, but there are also differences. Thus, the insoluble form of the compound $\text{Mn}[\text{Cu}(\text{Asp}-2\text{H})_2]$ in the region of $3200-3400 \text{ cm}^{-1}$ has three absorption bands at 3240 , 3300 and 3340 cm^{-1} , caused by stretching vibrations of the NH₂ group, while the soluble form has good Only two bands are allowed at 3250 and 3310 cm^{-1} . A similar picture is observed for the blue and violet forms of the compound $\text{K}_2[\text{Cu}(\text{Asp}-2\text{H})_2]$, which coincides with the differences in the IR spectrum of the cis- and trans-isomeric compounds of copper glycinate $\text{Cu}(\text{NH}_2\text{CH}_2\text{COO})_2 \cdot \text{H}_2\text{O}$.

In the region of 1410 cm^{-1} there is a band of symmetrical stretching vibrations of the COO group. The soluble form of aspartic acid complex compounds containing two microelements has a single frequency in the region of 1410 cm^{-1} , while the insoluble form splits the band into two components. From the theory of molecular orbitals it is known that in the case of planar square complexes of the $\text{M}(\text{AB})_2$ type, the trans isomer, which has a center of symmetry, vibrations symmetrical with respect to the center of the group should be inactive. In this regard, the cis isomer

should have a greater number of bands in the spectrum than the trans isomer. This requirement was met for platinum bisglycinate [5], as well as for octahedral complexes [6].

The presence of Cu(II) in the inner sphere in the compounds $Mn[Cu(Asp-2H)_2]$ and $Co[Cu(Asp-2H)_2]$ was established by studying the reaction of an aqueous solution of these compounds with lead acetate. In this case, after 24 hours, a blue precipitate containing Cu(II) precipitated.

Thus, the soluble form is a trans isomer, the insoluble form is a cis isomer, and for the compound $K_2[Cu(Asp-2H)_2]$ the blue form is a trans isomer, and the violet form is cis.

Results and discussion. It was revealed that trans-mers exhibit more pronounced biological activity compared to cis-mers of the same composition. Currently, a medical and biological study of the obtained complex compounds is being carried out for introduction into healthcare practice as a medicinal product.

Conclusion. Geometrically isomeric coordination compounds Cu(II), Co(II), Mn(II) with aspartic acid were synthesized, competitive coordination of donor atoms of aspartic acid to metal ions was revealed, and medical and biological properties were studied.

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