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CHELATE FORMS OF BIOMETALLS. THEORETICAL ASPECTS OF OBTAINING AND CHARACTERISTICS.

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Abstract. The problem of microelements bioavailability is highlighted and the correct ways of its solution are substantiated as a result of generalization of theoretical aspects of obtaining of the biometals chelate forms. The characteristics of the main biogenic elements, their physiological significance, electrochemical properties are presented. The main examples of the participation of biometals in various biological processes are given. The properties and the structure peculiarities of biometals coordination complexes are considered in detail. It is shown that in obtaining of biometals chelate forms, there is the mutual selectivity and the affinity of biometals and ligands. The main factors of obtaining a hard metal complex are given. Potential bioligands for obtaining bioavailable forms of microelements are detailed. Among them there are amino acids, peptides, proteins, nucleic acids, carbohydrates. The possible character of complexation depending on the nature of the bioligand is indicated. Practical examples of preparation of biometals mixed ligand complexes are given. The expediency of using metabolic products and processing of lactic acid bacteria as promising components of mixed ligand chelate complexes is substantiated. These substances contain in their composition a mass of potential donor atoms that are capable to form covalent and coordination bonds with biomethalles, and also possess high biological and immunotropic activities. The use of this system in the biocoordination compounds of the "metals of life" can provide a synergistic effect of the components, significantly to expand the range of their physiological activity and to increase the degree of assimilation by the body.

Key words: biometals, bioavailability, chelate complexes, bioligands, lactic acid bacteria, metabolites, immunotropic substances.

ХЕЛАТНІ ФОРМИ БІОМЕТАЛІВ. ТЕОРЕТИЧНІ АСПЕКТИ ОТРИМАННЯ І ХАРАКТЕРИСТИКИ

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Анотація. Висвітлено проблему біодоступності мікроелементів і обґрунтовано коректні шляхи її вирішення в результаті узагальнення теоретичних аспектів отримання хелатних форм біометалів. Надано характеристику основних біогенних елементів, їх фізіологічне значення, електрохімічні властивості. Наведено основні приклади участі біометалів в різних біологічних процесах. Детально розглянуто властивості і особливості будови координаційних комплексів біометалів. Показано, що при одержанні хелатних форм біометалів має місце взаємна вибірковість і спорідненість біометалів і лігандів. Наведено основні чинники отримання стійких металлокомплексів. Детально розглянуто потенційні біоліганди для отримання біодоступних форм мікроелементів: амінокислоти, пептиди, білки, нуклеїнові кислоти, вуглеводи. Вказано можливий характер комплексоутворення в залежності від природи біолігандів. Наведено практичні приклади отримання змішано-лігандних комплексів біометалів. Обґрунтовано доцільність використання продуктів метаболізму і переробки молочнокислих бактерій в якості перспективних компонентів змішано-лігандних хелатних комплексів. Дані субстанції містять в своєму складі масу потенційних донорних атомів, здатних до утворення ковалентних і координаційних зв'язків з біометалами, а також мають високу біологічну і імунотропну активності. Застосування даної системи в складі біокоординаційних сполук «металів життя» може забезпечити синергетичний ефект складових, значно розширити спектр їх фізіологічної активності, підвищити ступінь засвоєння організмом.

Ключові слова: біометали, біодоступність, хелатні комплекси, біоліганди, молочнокислі бактерії, метаболіти, імунотропні речовини.

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Introduction

Among the food factors having special value for maintenance of health, working capacity and active longevity of the person, the major role belongs to biometals. Biometals maintain the balance and the coordination of the main regulatory systems of the organism cages, be-

cause they participate in a difficult biochemical metabolism, enter into a number of enzymes, coenzymes and hormones, etc [1-4]

At the same time, the deficiency of the vital minerals, including biometals, which has been widely spread today, is an extremely serious problem not only for developing countries but also for economically developed

countries. The deficiency of macro- and micronutrients in the human body is the cause of the growth of many diseases: hypertension, anemia, atherosclerosis, diabetes, musculoskeletal system diseases, gastrointestinal and endocrine diseases, metabolic diseases, etc [2].

In the literature two types of micro- and macroelement deficiency are highlighted. The primary deficiency is directly related to poor nutrition (starvation): a long period of unbalanced food intake, various diets, improper culinary processing. It should be noted that the modern geochemical environment, intensive methods of plant management and animal husbandry led to a significant decrease of minerals content in the flour, vegetables, fruits, meat, milk, etc. The insufficient nutrition of many people is aggravated by the fact that they take certain medications that excrete mineral elements from the body, and also they are exposed to high physical and psychological stresses.

The secondary micro- and macroelement insufficiency is formed at the violation of minerals absorption in conditions of diseases of internal organs, endocrinopathies, genetic defects of enzyme systems, violations of minerals transport and their metabolism.

Currently, there are three main approaches [4] to a solution of the deficiency problem of macro- and microelements, and also to the prevention of diseases caused by their deficiency in the diet. The first approach is the additional consumption of foods with a high minerals content. The second approach is the use of medicines and dietary additives to food on the basis of various compounds of macro- and microelements. The third approach is the purposeful enrichment of foodstuffs of mass consumption with deficient bioelements.

Formulation of the problem

The biological efficiency of the biometals use in an organism is determined by the balance level of the diets relatively to nutrients and biologically active substances, by the degree of assimilation and deposition of microelements, their interaction with each other and other nutrients in the process of absorption, transport and excretion; by the state of the regulatory systems, age, sex and the physiological state of the organism. In this regard, it is necessary to use such forms of biomaterials that will be most physiologically adequate to the needs of the human body [5-8].

Biometals in the composition of inorganic compounds at hit in an organism with food have bioavailability level no more than 2 – 20 %, and often at the long-term use they have a negative effect on an organism. In addition, there are significant losses of them in the production process, negative changes in the organoleptic properties of foods, and also the presence of serious side effects.

The increase of microelements bioavailability is one of the topical problems of modern science. At present, there has been a special interest in the prophylaxis and treatment of many hypomicroelementoses with the help of second-generation microelement preparations. It

is biocoordination compounds in which vitall minerals are contained as a complex with bioligands, natural carriers of microelements.

The use of the chelate compounds of biogenic elements with organic ligands (amino acids, peptides, organic acids, nucleic acids, carbohydrates, etc.) Is of particular interest for the microelementoses prevention

Chelates of biometals have a number of valuable properties: they are almost not toxic, in most cases they are highly soluble in water, they are stable in a wide range of pH values, they are not destroyed by microorganisms, at their use the antagonism between microelements is erased, the bioavailability of trace elements and their activity increases.

At the heart of the efficiency and safety of the use of chelate compounds for the prevention of microelementoses lie the natural physiological and biochemical mechanisms for the assimilation of minerals that correspond to the processes of «organic chelation».

Thus, the use of biometals in the chelate bioavailable form for microelementoses elimination at the population is preferable. The creation of dietary additives on the basis of complexes of essential biometals with bioligands for their individual use, and also for enriching deficit food products is especially important according to the main approaches to solving the problem of micro- and macroelements deficiency [9-11].

The aim of the work is the generalization of the theoretical aspects of obtaining and the characteristic of the chelate forms of biometals, the search of the new decisions for creation of the chelate systems, having high bioavailability and an expanded range of physiological effects for use as nutraceuticals and parapharmaceuticals in dietology, and also as nutritive support at complex treatments of microelementoses and other diseases.

Biogenic elements. Value. Electrochemical properties

In the composition of live organisms more than 60 chemical elements have been discovered. Their role in the organism life activity and their content are not the same. Six of them – C, N, H, O, P, S – form the basis of living matter (organogens). Ten more elements are extremely important for maintaining the structure and functional activity of biopolymers. It is so-called «life metals»: Na, K, Ca, Mg, Zn, Fe, Mn, Cu, Co, Mo. From a chemical point of view, they can be classified as follows: intranion elements (Na, K, Mg, Ca, Zn); transition elements (Mn, Fe, Co, Cu, Mo). Table 1 shows the characteristics of biometals [12-17].

Sodium and potassium are most important from the alkali metals. As is known, they do not form stable complexes, but they form associates according to the mechanism of the ion-dipole interaction. Thus, because of the greater surface charge density, the radius of the hydrated sodium ion is higher than the hydrated ion of potassium. Na^+ ion is the main extracellular cation of the body, whereas the K^+ ion is intracellular. Despite the similarity in chemical behavior, these ions demonstrate biological antagonism. These biometals are key elements in

the osmotic pressure maintain, the nerve impulse transfer and muscle contractions regulation.

The ions of alkaline earth biometals of **magnesium and calcium** can to form complex compounds with a coordination number 6. The chemical bonds in many magnesium compounds are covalent. Mg^{2+} ions participate in the formation of the tertiary structure of DNA, transfer of the nerve impulse, activate a number of enzymes (hexokinase and other transferases of phosphates, arginase, ligases in the synthesis of nucleic acids).

Table 1 – Position in the periodic table, biological role and ability to complex formation of metals necessary for the human body [15]

Met al	Position in the periodical system and electronic structure	Biological role	Donor atoms are the preferred coordination centers
Na K	Group I A, s1	The charge transfer, osmotic equilibrium	O
Mg Ca	Group II A, s2	The formation of the bone system, "trigger" reactions	O
Mn Fe Co Cu Mo	First transitional row	Catalysis of redox reactions, the formation of active enzyme centers	O N, O N, O N, S S
Zn	Group II B, d10	Catalysis involving Lewis Acid	N, S

Ca^{2+} ions are necessary for the formation of bone tissue, during lactation, in the implementation of cardiac contractions, and they are factor of the blood coagulation, and activate a number of enzymes.

Despite a variety of possible degrees of oxidation, the manganese in live organisms is presented by Mn (II) and Mn (III) complexes with a coordination number 6. Its increased affinity to carboxyl and phosphate groups, and also some functional interchangeability with a magnesium is noted. Manganese is necessary for work of such enzymes as aminoacyl transferase, carboxylase, metabolon of Krebs cycle.

Iron is the most important biometal. For its bio-coordination compounds are typical two degrees of oxidation – Fe (II) and Fe (III) and coordination number 6. Iron distribution in the human body is as follows: 70% is contained in hemoglobin, 15 % – in oxidoreductase, 15 % – in ferritin and hemosiderini. The main functions of iron biocomplexes (II, III) are the participation in oxygen transport, the work of enzyme systems and the electron transport chains. The degree of iron oxidation in bi-

ocomplexes depends on the its role (+2 in hemoglobin, +3 in oxidases and the variable in cytochromes).

Cobalt in the body is in the form of Co (II) complexes with a coordination number 4 or 6 and Co (III) with a coordination number 6. This biometal is a part of vitamin B₁₂, and its lack leads to the anemia development. The most important function of Co (II) is the activation of enzyme systems, such as aldolase, carbonic anhydrase. The possibility of reversible oxygen transport with the participation of C (II) ions was established, as well as their participation in proteolysis.

Copper in the body is also found in two oxidation degrees – Cu (I) with a coordination number 2 or 4 and Cu (II) with a coordination number 4 or 6. This element is deposited in the liver and is the central part of oxidoreductases (ascorbate oxidase, polyphenol oxidase).

Zinc exists in biosystems only in the form of Zn (II) complexes (tetrahedral with a coordination number 4, or octahedral with a coordination number 6). Zinc participates in the formation of multimers of protein molecules, activates a number of enzymes (carboxypeptidase, DNA polymerase).

Despite the diversity of oxidation degrees of **molybdenum**, the complexes of Mo (VI) dominate in the body. This biometal activates xanthine-oxidase, the most important enzyme in nitrogen metabolism. The role of molybdenum ions in the formation of a bond between the flavin coenzyme and apoenzymes is also noted.

Main examples of the biometals participation in various biological processes:

1. The implementation of start-up and control mechanisms. Na^+ , K^+ , Mg^{2+} and Ca^{2+} ions regulate muscle contraction, release of hormones and mediators.
2. Control of the biopolymers structure and the course of matrix processes. Ions of Mn^{2+} , Mg^{2+} and Ca^{2+} are extremely important for maintaining a definite conformation of nucleic acids. The ions Mg^{2+} and Ca^{2+} participate in the strengthening of numerous lipoprotein membranes. These biometals serve as a matrix for the orientation of functional groups under the enzymatic one.
3. The biometal is Lewis acid. In this case it is necessary to consider the preferable coordination to the particular donor centers and polarization of a ligand as a result of formation of a coordination bond.
4. The catalysis of oxidation-reduction reactions. In this aspect, a group of transition metals, capable to realize several stable degrees of oxidation is isolated. Among them Fe (II, III), Cu (I, II), Co (II, III), Mo (IV, VI).
5. Transport and deposition of metal.

Thus, it is difficult to underestimate a role of biometals in activity of an organism, the long-lived deficiency at least of one of them can provoke development of the cascade of undesirable consequences. For a conscious comprehension of the organization and functioning of biometals in a live organism let us consider the basic principles of the formation of their coordination complexes.

Coordination complexes of biometals. Characteristic. Features of the structure [18-20]

The organism represents a system of multiple complexing agents and ligands, with a certain relationship between them. The components imbalance (metal-ligand homeostasis) leads to the development of pathological conditions. Therefore, the study of the interaction processes «metal-ligand» is the key to finding new bioavailable forms of metals-micronutrients.

Helate is the most energy-efficient form of interaction between a metal and a ligand for an organism. The activity of the element in these complexes often increases in hundreds and thousands times in comparison with the activity of the metal in the ionic state.

Between coordination and complex compounds, in fact, put an equal sign. Coordination compounds contain cationic, anionic or neutral complex, consisting of a central atom (ion) and associated molecules or ions – ligands. The central atom (complexing agent) is usually an acceptor, and the ligands are electron donors, with the formation of a complex between them, there is a pre-nor-acceptor or coordination bond. The complex can be electrically neutral, or non-electrolyte, have a positive (complex cation) or negative charge (complex anion).

Coordination compounds can exist both in the crystalline state and in solution. Ligands are capable to stepwise and reversibly split off from the central atom by the heterolytic type.

In the existing definitions of coordination compounds the existence of electronic transfer from the donor to an acceptor is emphasized. However, there is no real movement of electron density in chemical compounds. Representations of this effect appeared in semi-empirical quantum-chemical methods for calculating the electronic structure. Therefore in formulations of the considered concepts it is more preferable to base on the structure data.

Thus, the complex compound is an individual chemical compound that meets three characteristics:

1. Contains atoms of at least three varieties (except hydrogen)
2. Contains at least one polyatomic structural fragment (ion) in which atoms of not less than two kinds are presented, at least in one structural fragment of the compound (ion), at least one of the atoms is central.
3. A metal atom acts as the central atom.

The method of ligands packing in complexes is characterized by the term «coordination polyhedron». This is a virtual molecular polyhedron, whose vertices are the atoms of ligands, directly connected with the central atom. The virtuality is determined by the presence of a chemical bond between the central atom and the vertices of the polyhedron, but not between the last ones.

The number of vertices is equal to the coordination number of the complexing agent. The edges of coordination polyhedrons are the segments of straight lines that pairwise connecting atoms of its coordination sphere.

Polyhedrons of the highest symmetry are realized if all ligands are identical and close in structure. In most real molecules deviation from regular coordination polyhedrons is observed.

The concept about a coordination number correlates with a concept of a coordination polyhedron. In coordination compound the coordination number (CN) of the central atom is the number of the electron-donating centers of ligands (atoms or π - bonds) directly interacting with the complexing agent. For complex compounds with monodentant ligands, the CN is equal to the number of ligands multiplied by dentant.

The ligand dentant is determined by the number of coordination sites, using which the ligand can join to the central atom in the complex. If two, three, and more ligand atoms are directly connected to the central atom, then such groups are called bi-, three- or polydentant. Neutral molecules (for example, ethylenediamine, propylenediamine), acid residues of polybasic acids, anions of amino acids, dioximes and other groups can appear as polydentant ligands.

Coordination compounds containing polydentant ligands attached to central atoms through several bonds formed by different atoms of a polydentant substituent and forming cycles are called the chelate compounds.

To explain the nature of bonds in complex compounds, their spatial configuration, chromaticity and other properties, three methods are currently used: the valence bond method (VBM); the method of the crystalline field (MCF); method of molecular orbitals (MMO). Let's consider the most available and often treated – VBM.

VBM well explains the spatial structure of complex ions, that is, the location of the ligands relative to the complexing agent and each other, and the valence angles between them. The starting point, which forms the principal basis of VBM, is the donor-acceptor interaction between the complexing agent and ligands, in which the complexing agent serves as an acceptor, and the ligands as donors of electron pairs.

Positively charged metal ions, having free orbitals, capable of accepting, are most often used as the complexing agent. At the same time, in the molecules or ions of the ligands there are always ready-made electron pairs, which can be provided by them in common use with the complexing agent. Thus, it becomes possible to coordinate ligands around the complexing agent due to the donor-acceptor mechanism of bond formation. It is possible to give a number of typical symmetrical hybridizations leading to idealized configurations of the coordination sphere (Table 2).

This method is based on the idea of an electrostatic interaction between ligands and a complexing agent. In this case, ligands are taken as point electric charges, and the complexing agent is a quantum mechanical system located in the center of the crystalline field of the ligands.

The theory of the crystal field considers the influence of ligands on the electron orbitals of the complexing agent. Most successfully it is applied to d-elements (metals of subgroups), in which d-electrons are valence.

Table 2 – Geometrical forms of complexes [15]

CN	Hybridization of the orbitals of the central ion	Geometrical form of complex
2	sp, dp p ² , ds, d ²	Linear Angular
3	sp ² , dp ² , d ² s, d ³ dsp p ³ , d ² p	Correct triangle Incorrect triangle Trigonal pyramid with metal in the top
4	sp ³ , d ³ s dsp ²	Tetrahedron Flat square
5	sp ³ d _z	Trigonal pyramid
6	d ² sp ³	Octahedron

Relative selectivity and affinity of biometals and ligands. There is a huge number of potential complex formers and ligands at an organism. The quantitative quantum chemical description is more precise and universal, however, the complexity of the objects structure and the variety of life activity processes acted as a prerequisite of development of the semiempirical concepts that characterize the relative selectivity and affinity of an ion of metal and a ligand at formation of a coordination bond like M:L at the qualitative level. In this connection, the most important aspects are: the establishment of groups of polyfunctional biomolecules with which the metal ion is coordinated; control of competitive processes involving various bioligands.

One of the most productive approaches in this area is the use of R. Pearson's principle of hard and soft acids and bases (HSAB). According to this principle, the acid-base interactions proceed in such a way that the hard acids are preferentially bound to hard bases, and soft acids – with soft bases.

At assigning compounds to a particular group, their chemical composition, electronic structure and comparative stability of their complexes are considered: A +:B = A:B (where A is Lewis acid, B is Lewis base) (Table 3).

Table 3 – Characteristics of acids and bases according to the principle HSAB [15]

A type	Acids	Bases
Hard	Acceptors; have high positive charges, low polarizability, low energy; difficult to recover	Donors; have a low polarizability, high electronegativity, low energy; difficult to oxidize
Soft	Acceptors; Have lower positive charges, high polarizability, high energy; easily restored	Donors; have high polarizability, low electronegativity, high energy; easily oxidized

The preferred binding of the same name reagents is explained by the fact that the interaction of energy similar orbitals is most effective. In the case of rigid reagents, electrostatic interaction is realized primarily, and for weak ones covalent interaction is realized.

The HSAB principle has proved itself well at the account of the specific interactions, consideration of the

competing processes, at the explanation of the metal ions binding in biological systems. Thus, the increase of the metal oxidation degree increases its rigidity on this classification. It is noted, that various oxidation states are stabilized by the corresponding ligands.

In this regard, it is necessary to point out to such phenomenon as the symbiosis of ligands. It consists in the preferential inclusion of a ligand, close in degree of rigidity or softness, to a ligand already located in the coordination node. Thus, alkaline and alkaline-earth biometals preferably form complexes with water, inorganic anions (CO₃²⁻, PO₄³⁻, SO₄²⁻) and carboxyl- organic substances (lactate, glutamate). The transition metals also have an affinity for nitrogen-containing and sulfur-containing molecules, and the nature of the most efficient donor group depends on the oxidation degree of the complexing agent.

In considering other aspects of the "metal-ligand" interaction, it should be noted that the metal ion can change the selectivity of the organic ligand:

- influencing on the electron distribution in the ligand;
- increasing the active center reactivity of the ligand;
- causing a change in the conformation of the ligand;
- providing the possibility of an electron attaching or detaching;
- increasing the lipophilicity of the ligand and, consequently, its ability to penetrate into the living cell.

Major factors of sustainable metal complexes production. A lot of researches is devoted to the study of the factors determining the mutual affinity of a metal and a ligand in complex formation. The nature of the reagents and the strength of the bond formed can be justified using the HSAB concept. However, it mainly considers the characteristics of atoms that directly form a bond, although spatial factors also play no less importance in complex formation.

The structure of the ligand assumes the presence of suitable donor atoms and their correspondence to the required geometric environment of the metal- ion of the chelating agent. Two aspects can be distinguished here: the initial structural organization of the ligand and the possibility of realization of the molecule required conformations; complementarity, that is, the degree of structural correspondence between the donor and acceptor of the binding sites.

If the size of the spatial ligand zone, where the donor atoms are localized, is too large, then a small amount of coordination bonds is formed. The reverse is also true: metal can't to penetrate into a too small zone. The concept of dimensional correspondence is widely used both for coordination explanation in biosystems and for development of model systems. It is considered that the most durable complexes with a metal form a ligand with a suitable cavity size. A particularly good

agreement is observed for conformationally rigid molecules and complex three-dimensional structures.

However, the optimal distance for reaction centers is an essential but not sufficient condition for the formation of a stable complex. An important factor is the topography of the ion of the complexing metal, that is, the optimal form of the coordination polyhedron. And if for alkaline and alkaline-earth biometals there are no rigid requirements for the polyhedron form, then for the transition metals the direction of the bonds is the determining condition for the complex stability.

The effectiveness of the trace elements assimilation from chelate compounds depends on their stability constants.

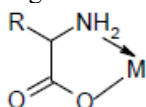
The sufficient assimilation is observed in that case when the stability constant of the chelate is higher than that of the trace element with the components of food or feed, and is lower than that of its compounds in the tissues of the organism. In this case, the chelating agent transports the bound element from the food (feed) through the intestinal wall and gives to the tissues.

Bioligands [7-12]. Mixed ligand complexes [21-25]. By numerous researches it is established that in the all minerals exchange, the various organic compounds participate. Among them are proteins, peptides, amino acids, phospholipids, carbohydrates, carboxylic acids, nucleic acids, nucleotides and other ligands, which through coordination bonds with mineral substances form complexonates. Let's consider the properties of certain bioorganic ligands.

Amino acids. In the composition of any amino acid there are at least two donor centers. They are carboxyl and amino groups. Besides, the side chain may contain carboxyl, hydroxyl, thiol, and amino groups. Such molecules structure makes it possible for the chelation at the interaction with metal ions, and in the case of the side groups participation, the ligand's denticity can exceed 2. In the side chain of natural amino acids, the following donor centers are presented:

- carboxyl group (aspartic and glutamic acid);
- hydroxyl group (serine, threonine, tyrosine);
- sulfur-containing groups (cysteine, cystine, methionine);
- Nitrogen-containing groups (arginine, lysine, histidine).

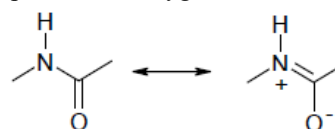
The effectiveness of amino acids coordination strongly depends on the pH of the medium, since protons are able to compete with biometal for the ligand. Therefore, in acidic medium, when most of the above groups are protonated, the complexation proceeds less intensively. In most cases, amino acids form chelate complexes containing the following fragment:



The formation of a chelate complex involves a gain in entropy, so the cases when amino acids act as monodentate ligands are quite rare and are realized only

under special preferences, which can be explained from the position of the HSAB concept. Thus, stable complexes of Ag (I) and Pt (II), where the amino acid is bonded to a metal ion via an amino group, are investigated. On the contrary, only the carboxyl group is involved in a number of complexes of Ca^{2+} and Mg^{2+} . The carboxyl group is also able to participate as a bridge in the composite complexes and as a bidentate ligand, however the formed four-membered cycle is not too stable.

Peptides. The complication of molecules organization at the transition from amino acids to their oligomers (peptides) leaves an imprint on the character of the complexation with their participation. To understand the causes of such changes, one should look at their structural features. The carboxyl group and the amino group in the peptide, which are terminal, are divided by a significant number of atoms, that imposes conformation restrictions and raises a role of side groups at the complexation. It should be noted the emergence of a new donor center. It is a peptide bond. However, due to its flat geometry, transorientation of fragments and delocalization of charge, this group is not very effective as a ligand. As a rule, a nitrogen atom acts as a donor center of the peptide bond, although a number of examples of coordination with participation of an oxygen atom are known:



The role of side chains of amino acids in the complexation increases with the number of peptide bonds on transition to proteins:

- carboxyl group (Asp and Glu) tends to bind to hard acids (Mg^{2+} , Ca^{2+} , Mn^{2+}); the interaction efficiency decreases with decreasing pH.
- hydroxyl group (Ser, Tyr, Thr) capable for the deprotonation only in alkaline medium (for example, a limited number of complexes of Cu^{2+} and Zn^{2+}).
- sulfur-containing groups (Cys, Met); they form strong complexes with soft Lewis acids, in particular Cu (I), Ag (I), Cd (II), Pt (II), especially stable complexes are cysteine ones.

Nitrogen-containing groups (Arg, Lys); they form the coordination links with the largest number of biometals, but more often with Co (II), Ni (II), Cu (II), Zn (II); the medium acidity serves as an obstacle, since protonated amino groups are not ligands.

Peptides form less stable complexes in comparison with the amino acids entering into their composition. Differences in the values of the constants are gradually leveled with increasing number of amino acid residues, and the sharpest difference is observed between the constants corresponding to complexes of biometals with a free amino acid and a dipeptide.

At an increase of the residues number of amino acid in the peptide, the intramolecular interactions play an increasing role. The existing structural organization can favor to complexation, and vacant sites in the coordi-

nation sphere of the metal ion, as a rule, are filled of the water molecules. But the converse is also true: a metal ion can stabilize the structure of a biologically important peptide and to help in the realization of its functions.

Proteins. Features of the structure of protein molecules, providing their functions as bioligands:

- the role of peptide groups and side radicals of amino acid residues increases in comparison with the terminal groups due to the large extent of the polypeptide chain;

- tertiary structure implies the convergence in space of a number of functional groups that are significantly spaced from each other in the chain; as a result, a number of potential donor zones are formed in the macromolecule and the possibility of selecting donor centers is given to the metal ion;

- the combination of amino acid residues of different nature in the protein leads to a change in the charges of functional groups and their donor capacity.

The main competitor of biometals is protons. Since complex formation often occurs in the cavity of the macromolecule, where the conditions are significantly different from the aqueous medium and desolvation is realized, it is problematic to investigate the process on model systems. The process is affected by the ionic strength of the medium and by the presence of extraneous substances that capable to change the tertiary structure of the protein.

According to the literature, proteins complexes with Cu (II) and Zn (II) are most studied. The donor centers in which are the side groups of Cys, His, Arg and Glu.

Nucleic acids. Metal ions are necessary for the normal functioning of nucleic acids and take an active part in their reactions. One of the key is the question of the centers of binding of these molecules with metal ions and their mutual competition. For nitrogenous bases, such are donor nitrogen and oxygen atoms. Nucleosides, in addition, contain hydroxyl groups of carbohydrate, and nucleotides contain another donor group, it is a phosphate group. It should be noted that, for free bases, complex formation actively takes place due to displacement of the mobile proton, and the positions of N-1 pyrimidines and N-9 purines in their derivatives are deprived of this possibility.

Because of the large number of donor centers, the study of complexation in such systems is not an easy task. However it is possible to mark out the following patterns:

- in process of complication of a molecule in the base-nucleoside-nucleotide series, the stability of the complexes is increased (comparison with nucleic acids is not justified here due to their polymeric nature);

- for most metal ions, the strength of the coordination bond weakens in the phosphate > base > carbohydrate series;

- among molecules with different bases, the stability of complexes varies in the guanine > cytosine > adenine > uracil > thymine series;

- DNA complexes are more stable than those of RNA.

Carbohydrates. Complexes of natural carbohydrates with metal ions participate in vital processes and therefore cause increased interest. Potential donor centers in carbohydrate molecules are carbonyl and hydroxyl groups. But since carbohydrates are mainly in a cyclic form, the hydroxyl groups play a decisive role in the coordination interaction. Carbohydrates in a cyclic form are conformationally homogeneous systems. Consequently, at the interaction with a metal-complexing ion, unlike the conformationally labile amino acids, the relative spatial arrangement of hydroxyl groups in the carbohydrate cycle is strictly determined.

Even if the inversion of the cycle is allowed in the system, the position of the hydroxyl groups varies only between the equatorial and axial carbons. In comparison, for example, with side chains of amino acids, hydroxyl groups (except for glycosidic and hydroxyalkyl groups) of sugars are conformationally fixed, that imposes the rigid restrictions on the mutual correspondence of the metal ion and ligand.

Complexes of monosaccharides have been studied both in solution and in the solid phase. It has been established that complexes of composition 1: 1 are most stable. Dentacy of 3 (triaxial and diaxial-equatorial orientation of hydroxyl groups) and 2 (vicinal diols) is preferred at the same time .

In the transition to oligosaccharides, the stability of the complexes, as a rule, decreases. The exception is cyclodextrines: their hydrophobic cavities are able to include existing complexes with the formation of the inclusion compounds.

As for polysaccharides, the metal complexes of their neutral representatives are studied poorly. In this case, the complex formation is considered more correctly as the formation of the «guest-host» structure, that is, the compound of the inclusion. The chemistry of anionic polysaccharides, which are polyelectrolytes, is more diverse.

Mixed ligand complexes. Most of the processes occurring in biological systems involve the interaction of metal ions with several ligands, therefore the particular interest is the preparation and study of the mixed ligand complexes properties of biometals with biologically active ligands [21-29].

The biometal assimilation will occur if it is firmly connected with a chelating agent that is a participant in metabolic processes: amino acids, polybasic acids (citric, gluconic, malic, succinic), vitamins.

The study of mixed ligand complexes of biomaterials has become widely spread, the methods of obtaining and characteristics of some of them have been described in the literature.

In [26], ion complexes of some d-metals (Co²⁺, Cu²⁺, Zn²⁺) were obtained in the form of salts and in so-

lution with ligands containing donor nitrogen and oxygen atoms to which the d-metal cations have an affinity. As an oxygen-containing ligand was used, an oxycarboxylic acid (malic), as a nitrogen-containing ligand – imidazole.

The synthesis methods of a series of metallic (copper-, nickel-, cobalt-, iron-) derivatives of arabinogalactan were developed in [27]. The metal content in these derivatives depend on the reaction conditions and the chemical composition of the initial reagents, can vary from 1 to 5 %. As a result of the research, it was shown, that depend on the metal properties, arabinogalactan is able to act as a ligand or to exhibit the properties of a hydrophobic stabilizer of colloidal systems. So, in the case of the interaction of arabinogalactan with copper ions, the complex formation takes place, in which two vicinal hydroxyls of arabinogalactan take part. In this case, two types of complexes are formed depending on the pH of the medium. They differ in their spectral characteristics. In the case of interaction with iron salts in an alkaline medium, arabinogalactan stabilizes the hydrophobic colloidal system of iron oxides formed, transforming them into a water-soluble state.

In [28] the possibility to prepare soluble iron complexes based on polysaccharides of mushroom (*Agaricus bisporus*) was proved. Their yield and composition depend on the ratio of iron: polysaccharides, pH medium, concentration of reactants. The maximum yields of complexes with high iron content can be obtained at mass ratio of the inorganic and organic components of 1:1.0 at pH=12.0 and 1:2.5 at pH=8.5.

According to IR and UV spectroscopy, the products obtained are complexes of polycyclic ferric hydroxide, linked with polysaccharide molecules by hydrogen bonds. The complex, which includes 47.9 % share of iron, does not contain the nonmetal polysaccharide com-

ponent and has a molecular mass of 100 –120 kDa. The complex belongs to the nanoscale structures.

In [29] the formation of binary and ternary complexes of metal ions such as Cu (II), Co (II), Pb (II), Zn (II) and Cd(II) with biologically important ligand were investigated. Where nucleic acid Adenine (A) used as primary ligand and amino acid Histidine (B) used as secondary ligand. Potentiometric technique was applied for determination of complexation behavior of binary and ternary species in aqueous media at 37±1 °C under ionic strength I = 0.1 M NaNO₃. Stability constant have been determined through the method suggested by Irving & Rossetti and further refined through SCOGS computer program. The mixed ligand ternary complexes were occurring simultaneously in most cases generally at high pH with gradually declination of binary complexes of particular metal complexes. The percentage of ternary species of 56 at 6.4 pH for A-Cu(II)-B, 67.7 at 6.3 pH for A-Co(II)-A, 65.56 at 7.2 pH for A-Pb(II)-B, 48.5 at 7.4 pH for A-Zn(II)-B and 56.5 at 7.3 pH for A-Cd(II)-B. The overall stability constant of mixed ligand Adenine(A)-M(II)-Histidine(B) ternary system are obtained in the following order A-Cu(II)-B > ACo(II)-B > A-Pb(II)-B > A-Zn(II)-B > A-Cd(II)-B.

In paper [30] the preparation and characterization of mixed ligand complexes of Co (II) and Fe (III) ions with maleic acid and heterocyclic amines of general formula [M(ME)L] and K[M(ME)L] (where M = Co(II) (1-4), Fe(III) (5-6); ME = C₄H₂O₄ (1-4), 2C₄H₂O₄ (5-6); L = C₅H₆N₂ (1), C₉H₇N (2-3), C₉H₆NO (4), C₃H₅N*H₂O (5), C₆H₇N (6)) were described. The molecular structures of the complexes have been determined by spectral, magnetic studies and elemental analysis. The structure of Co (II) and Fe (III) complexes are tetrahedral and octahedral respectively (fig. 1)

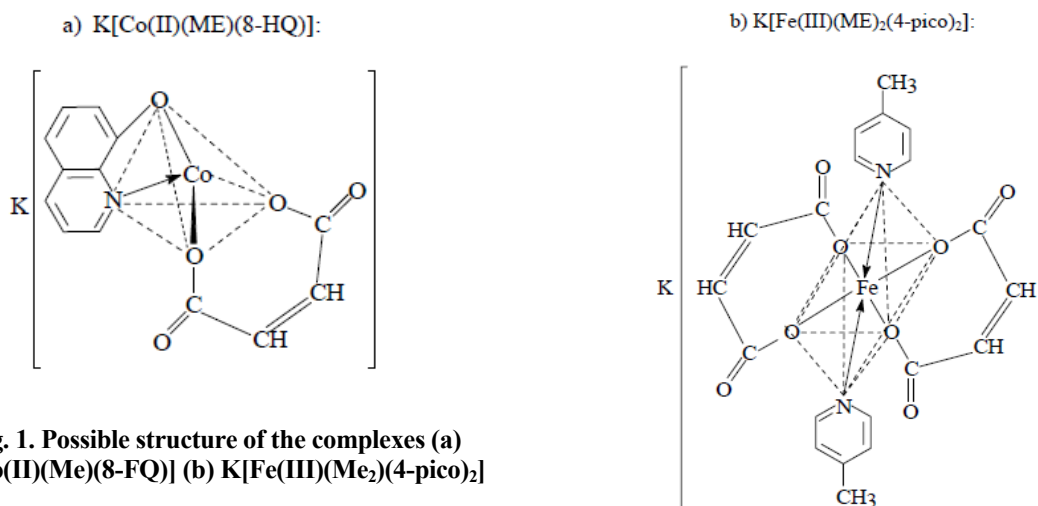


Fig. 1. Possible structure of the complexes (a) $K[Co(II)(Me)(8-FQ)]$ (b) $K[Fe(III)(Me)_2(4-pico)_2]$

In [31] the mixed ligand complexes of Cu (II), Ni (II) and Co (II) with uridine and amino acids, L-alanine, L-phenylalanine and L-tryptophan were synthesized and characterized by elemental analysis, conductivity data, infrared spectra, electronic spectra and magnetic

susceptibility data. In these complexes, the nucleoside (uridine) acts as a monodentate ligand coordinating through O (4) under the conditions of investigation, whereas the amino acids coordinate through the carboxylate oxygen and the amino nitrogen. Distorted octahe-

dral geometry for Cu (II) and octahedral geometries for both Ni (II) and Co (II) are proposed.

In paper [32] the synthesis and characterization of mixed ligand complexes of Co (II) and Ni (II) have been described. Organic dibasic acid, malic acid plays role as primary ligand and Heterocyclic amine bases play role as secondary ligands in the complexes. The prepared complexes of Co (II) and Ni (II) were found to form octahedral structure. Elemental analysis correspond to metal: ligand stoichiometry for Co (II) and Ni (II) complexes are 1:2:2.

Magnetic susceptibility measurement shows that the complexes are paramagnetic. The IR spectral data shows that the ligands coordinate to the metal through O and N atoms. The electronic spectral data are in conformity with the transitions of octahedral complexes. The ¹H-NMR studies of the complex indicates two pyridine and two malic acid molecules coordinate with Co (II) metal ion and represents the complex as $2K^+[Co(II)(MaH)2(Py)2]^{2-}$. Based on the above analysis the structure of complex $2K^+[Co(II)(MaH)2(Py)2]^{2-}$ has been proposed as shown in Fig.2.

In [33] mixed ligand complexes of Co (II), Ni (II) and Cu (II) with L-glutamine and succinic acid was studied in varying amounts (0.0 – 2.5 %, w/v) of sodium dodecyl sulfate (SDS) in aqueous solutions while maintaining an ionic strength of 0.16 mol/L⁻¹ (NaCl) at 303.0 K. Titrations were performed in the presence of different

relative concentrations (M:L:X = 1:2:2, 1:4:2 and 1:2:4) of metal (M) to L-glutamine (L) to succinic acid (X) using sodium hydroxide. The best-fit chemical models were selected based on statistical parameters and residual analysis. The species detected were ML₂X, MLX, MLXH and MLXH₂ for Co (II), Ni (II) and Cu (II). The increased stability of the ternary complexes compared to their binary complexes was believed to be due to electrostatic interactions of the side chains of the ligands, charge neutralization, chelate effect, stacking interactions and hydrogen bonding. The species distribution with pH at different compositions of SDS and plausible equilibria for the formation of the species are also presented (Fig. 3).

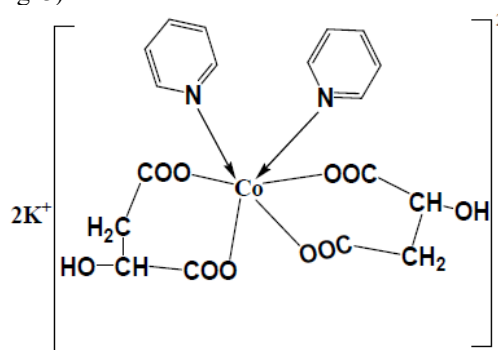


Fig. 2. Structure of the complex $2K^+[Co(II)(MaH)2(Py)2]^{2-}$.

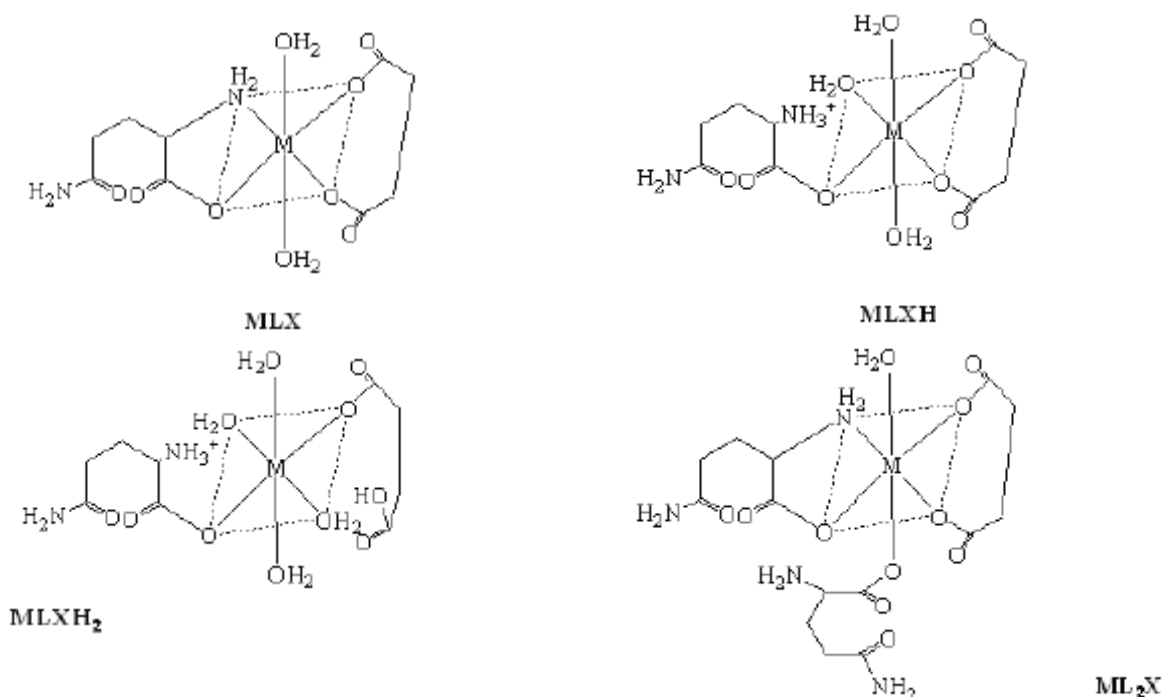


Fig. 3. Structures of the mixed ligand complex

The complexation of Cu²⁺ ions with 1-hydroxyethylidene diphosphonic acid and N-(2-hydroxyethyl) iminodiacetic acid in the presence of two additional low-dentant ligands (2-aminoethanol and ethylenediamine in aqueous solutions) was studied in [37]

by the spectrophotometry and ionometry methods. The formation of mixed ligand complex compounds is shown and their stability constants are calculated. The formation of mixed ligand complexes with 1-hydroxyethylidenediphosphonic and ethylenediamine, as

ligands with different donor centers (O, N), makes it possible maximally effectively to realize in the coordination sphere of the Cu^{2+} ion two ligands of different nature. This fact is well correlated with the principle of formation and stability of multiligand complexes.

In [34], reactions of the formation of homogeneous and mixed ligand complexes of cobalt (III) with ethylenediamine and ethylenediaminetetraacetic acid in aqueous solutions were studied by methods of spectrophotometry and nuclear magnetic relaxation. Optimal conditions for the formation of complex particles in solutions, which ensure the stabilization of the highly oxidized state of cobalt, were established. Stability values of mixed ligand complexes were calculated. In aqueous solutions, the cobalt (III) cations are predominantly coordinated by the anion of the aminocarboxylate reagent with the formation of an extremely thermodynamically stable chelate, due to the formation of five f-membered cycles: one ethylenediamine and four glycinate ones.

In [35] complexes with microelements (Mg, Zn, Mn, Cu and Co) were obtained using enzymatic hydrolysates of milk whey protein concentrates. To increase the content of trace elements in chelates and increase their bioavailability for the production of chelating complexes, a hypoallergenic low-molecular fraction (<10 kD) of whey protein hydrolysates obtained by ultrafiltration was used. The toxicity of chelate compounds of zinc, magnesium, manganese, cobalt, iodine and iron, as well as their mixtures in various doses, has been studied.

Products of metabolism and processing of lactic acid bacteria (LAB) are perspective components of mixed ligand chelate complexes

Are presently known various positive effects of lactic acid probiotic bacteria, confirmed by numerous clinical studies. First of all it should be noted that these bacteria have an important role in maintaining colonization resistance, that is, have pronounced antagonistic ac-

tivity against pathogenic microorganisms. Such effects are due to by the fact that LAB produce the various organic acids, hydrogen peroxide, bacteriocins, short chain fatty acids, diacetyl [36-40]. These substances have got antagonist activity, implicitly affect on the immune system, reducing the antigenic load caused by pathogenic microorganisms.

LAB are also an integral link of the immune system functioning of the macroorganisms. Structural components of the LAB cell walls are peptidoglycans, muramyl dipeptide, teichoic acids [41-43]. They are objects for recognition by the system of innate immunity and signals for start of an adaptive immune response. To obtain such structural components, a number of methods of the direct destruction of the LAB cell walls with the use of physical, chemical, biochemical and combined methods have been developed. Substances containing metabolites and products of destruction of the LAB cell walls have proved themselves as effective immunotropic agents [44-48].

The use of such substances as bioligands to produce mixed-ligand chelate complexes of biometals is very perspective. Metabolites and structural components of the LAB cell walls contain in their composition a mass of potential donor atoms that are capable to form covalent and coordination bonds with biometals. As the donor centers of the considered bioligands there can be carboxylic, hydroxyl also amino groups, peptide bonds, nucleic acids and carbohydrate components.

The products of the metabolism of the LAB and of the their cell walls degradation are a unique system with a high biological and immunotropic activity. The use of this system in the biocoordination compounds of the "metals of life" can provide a synergistic effect of the constituents, significantly expand the range of their physiological activity, assimilation by the body and, consequently, rationalization of their use.

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ХЕЛАТНЫЕ ФОРМЫ БИОМЕТАЛЛОВ. ТЕОРИТИЧЕСКИЕ АСПЕКТЫ ПОЛУЧЕНИЯ И ХАРАКТЕРИСТИКИ

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Аннотация. Освещена проблема биодоступности микроэлементов и обоснованы корректные пути ее решения в результате обобщения теоретических аспектов получения хелатных форм биометаллов. Представлена характеристика основных биогенных элементов, их физиологическое значение, электрохимические свойства. Приведены основные примеры участия биометаллов в различных биологических процессах. Детально рассмотрены свойства и особенности строения координационных комплексов биометаллов. Показано, что при получении хелатных форм биометаллов имеет место взаимная избирательность и сродство биометаллов и лигандов. Приведены основные факторы получения усойчивых металлокомплексов. Детально рассмотрены потенциальные биолиганды для получения биодоступных форм микроэлементов: аминокислоты, пептиды, белки, нуклеиновые кислоты, углеводы. Указан возможный характер комплексообразования в зависимости от природы биолиганда. Приведены практические примеры получения смешаннолигандных комплексов биометаллов.

Обоснована целесообразность использования продуктов метаболизма и переработки молочнокислых бактерий (МКБ) в качестве перспективных компонентов смешаннолигандных хелатных комплексов. Данные субстанции содержат в своем составе массу потенциальных донорных атомов, способных к образованию ковалентных и координационных связей с биометаллами, а также обладают высокой биологической и иммунотропной активностями. Применение данной системы в составе биокоординационных соединений «металлов жизни» может обеспечить синергический эффект составляющих, значительно расширить спектр их физиологической активности, повысить степень усвоения организмом.

Ключевые слова: биометаллы, биодоступность, хелатные комплексы, биолиганды, молочнокислые бактерии, металлиты, иммунотропные вещества.

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