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STRUCTURE FEATURES AND PHARMACOLOGICAL PROPERTIES OF GERMANIUM(IV) COMPLEXES WITH 1-HYDROXYETHANE-1,1-DIPHOSPHONIC ACID.

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The review article presents the results of systematic research by the authors of a number of heterometals and mixed-ligand 1-hydroxyethane-1,1-diphosphonatogermanates, their structure, biological and pharmacological properties. It was observed, that hexanuclear cyclic complex anions of the general composition $[Ge_6(\mu\text{-}OH)_{6-n}(\mu\text{-}O)_n(\mu\text{-}hedp)_6]^{(6+n)-}$ were present in the aqueous solutions of investigated compounds. At the same time, the composition and charge of the anion in each compound obtained in the solid state depends on the nature of the cation. They all have a common hexameric structure, with germanium atoms connected in pairs by 1-hydroxyethane-1,1-diphosphonate, hydroxo-, or oxo- and hydroxo-bridges. The coordination polyhedron Ge is a curved octahedron with two six-membered GeO_2P_2C cycles and an eight-membered bimetallic $Ge_2O_4P_2$ closing, and each ligand performs a tetradentate tris(chelate)-μ-bridging function. The ratio of formed oxo- and hydroxo-bridges and, as a result, the charge of the anion varies under the influence of cation parameters and electrostatic interactions. Acute and chronic toxicity studies proved the safety of 1-hydroxyethane-1,1-diphosphonatogermanates. Complexes show a wide spectrum of pharmacological activity: antihypertensive, antiarrhythmic, hepatoprotective, cerebroprotective etc.The pharmacological and biological activities of 1-hydroxyethane-1,1-diphosphonatogermanates(IV) are ensured by the combined action of all biologically active components, which do not compete but show synergistic action. It was concluded that the preparation of new complexes of germanium(IV) with etidronic acid by chemical modification of their composition is a promising area of research in the field of creating coordination compounds with a wide range of pharmacological effects.

Keywords: germanium(IV), 1-hydroxyethane-1,1-diphosphonic (etidronic) acid, nitrogen heterocycles, coordination compounds, biological activity.

INTRODUCTION. As a result of years of systematic research providedat the Odesa I.I. Mechnikov National University, the authors have synthesized a wide range of coordination compounds of germanium(IV) and implemented a new approach to developing biocoordination chemistry of germanium(IV) as an independent scientific field. The complexes demonstrated significant advantages compared to organic compounds of germanium such as low toxicity, solubility in water and environmentally friendly synthetic route.

The authors have synthesized germanium(IV) coordination compounds with O, P, N-containing chelating organic ligands with physiological activity [1, 2]. It was shown that the synergism of germanium and bioligands provides their pharmacological properties.

The uniqueness of germanium as a complexing agent and biogenic element is most clearly demonstrated by the example of 1-hydroxyethane-1,1-diphosphonic (etidronic) acid (H_4hedp), a well-known multifunctional phosphonic complex with various valuable properties used in pharmacy and cosmetology.

Etidronic acid, due to its specific stereochemistry and mutual interaction of phosphonic fragments, is capable of forming both monomeric complexes with s-, p-, d-, and f-element ions and coordination di-, oligo-, and polymers. Compared to other phosphonic complexing agents, a considerable number of coordination compounds of etidronic acid with various metals have been synthesized and structurally characterized using different methods [3–9].

The uniqueness of germanium as a complexing agent and biogenic element is most clearly demonstrated by the example of 1-hydroxyethane-1,1-diphosphonic (etidronic) acid (H_4hedp), a well-known multifunctional phosphonic complex with various valuable properties used in pharmacy and cosmetology. H_4hedp belongs to the class of moderately toxic substances and does not possess sensitizing or cumulative properties, which makes it suitable for use as a pharmaceutical agent [10–14]. The high efficacy of metal coordination compounds with H_4hedp has been demonstrated in applications for pain relief in cases of bone metastases (^{186}Re) and the diagnosis (^{188}Re) of bone cancer [15].

The aim of this work is analysis of the array of experimental data on the structure, biological and pharmacological properties of homo- and heterometallic, mixed-ligand 1-hydroxyethane-1,1-diphosphonatogermanates(IV) and identify promising areas of their application.

Structural insights into 1-hydroxyethane-1,1-diphosphonatogermanates. Previously spectrophotometric measurements have proved that an acidic complex with a molar ratio Ge : ligand = 1:1 exists in solution in the GeO_2 - H_4hedp - H_2O system at pH = 2 [16]. Subsequently, methods were developed for the isolation of germanium(IV) coordination compounds with ethidronic acid. It was shown that the interaction of germanium dioxide and germanium tetrachloride with H_4hedp in water produces the same X-ray amorphous glassy compound. As a result of complexation, hydrolysis of germanium tetrachloride is inhibited. Detailed methods for the synthesis of various types of 1-hydroxyethane-1,1-diphosphonatogermanates(IV) are given in [1, 16–18].

The idea of introducing an outer-sphere (exo-) ligand into the reaction medium, for example, an organic molecule capable of protonation, such as nicotinic acid, nicotinamide, piracetam, etc., was proposed to obtain crystals [1]. Also, alkali and alkaline earth metals were introduced and bimetallic complexes were obtained.

X-ray crystallographic data of complexes with nicotinic acid
$(HNic)_6[Ge_6(\mu\text{-}OH)_6(\mu\text{-}hedp)_6]\cdot 12H_2O$,
magnesium
$[Mg(H_2O)_6]_2H_2[Ge_6(\mu\text{-}OH)_6(\mu\text{-}hedp)_6]\cdot 28H_2O$
and barium
$Ba_3[Ge_6(\mu\text{-}OH)_6(\mu\text{-}hedp)_6]\cdot 25H_2O$
were received.

It was found that the crystals of the compounds were based on identical hexanuclear

cyclic complex anions $[Ge_6(\mu\text{-}OH)_6(\mu\text{-}hedp)_6]^{6-}$ (рис. 1) in which six germanium atoms are interconnected by six bridging ligand molecules (phosphonium groups are completely deprotonated, each of them is connected to different germanium atoms), as well as six bridging hydroxo-groups. The coordination polyhedron is a curved octahedron typical of tetravalent germanium. The cations are cations of $NicH^+$ protonated on the nitrogen atom of the nicotinic acid heterocycle and hexaquacations of s-metals.

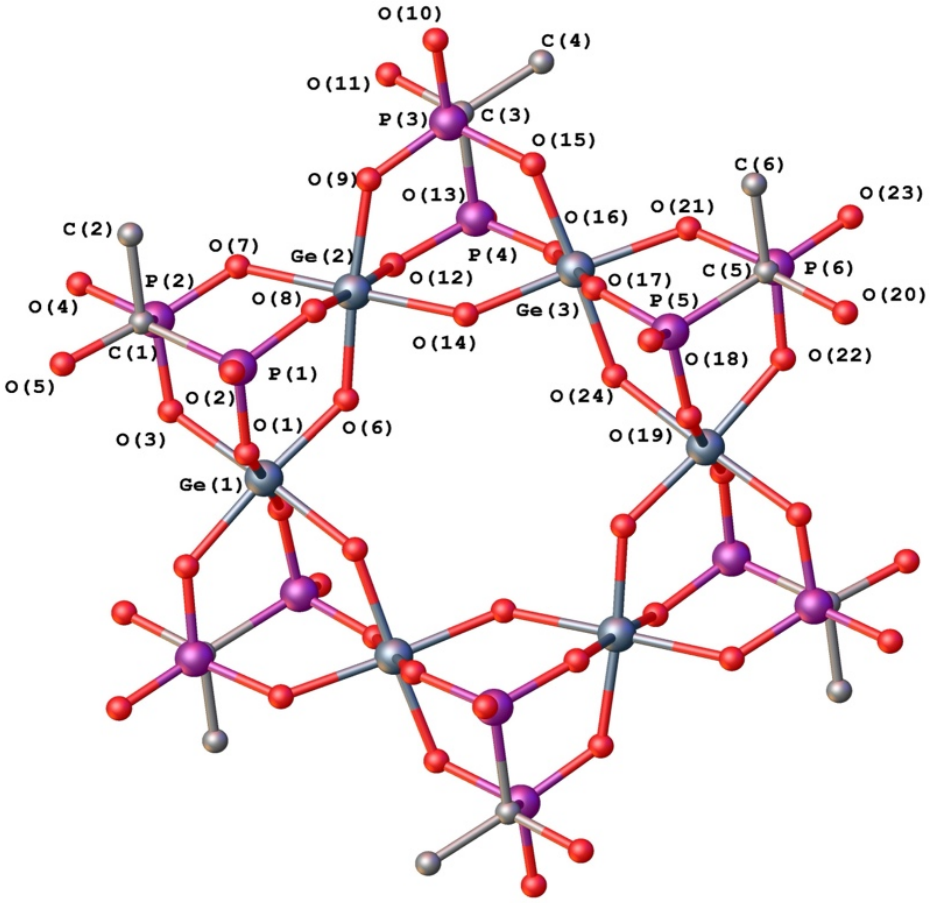


Fig. 1. Crystal structure of the anion $[Ge_6(\mu\text{-}OH)_6(\mu\text{-}hedp)_6]^{6-}$ [1].

In the structure $Ba_3[Ge_6(\mu\text{-}OH)_6(\mu\text{-}hedp)_6]\cdot 25H_2O$ the barium atoms are coordinated exclusively by the oxygen atoms of water molecules. However, the significant disorder of all Ba^{2+} cations and some water molecules prevented the precise determination of the crystal structure, coordination number and coordination polyhedron of barium atoms, and the way the structural units are packed in the crystal.

The structure of 1-hydroxyethane-1,1-diphosphonatogermanates(IV) of metals of other electronic units was investigated. After obtain-

ing the structural data of the bimetallic complex with zinc, $Zn_4[Ge_6(\mu\text{-}OH)_4(\mu\text{-}O)_2(\mu\text{-}hedp)_6]\cdot 38H_2O$, it was found that there is a change in the structure of the hexanuclear anion (2 hydroxo-bridges out of 6 are converted to oxo-bridges). This structure also contains octahedral complex zinc cations with different ligand environments: hexaquacations and cations in which two of the six adjacent (cis) vertices of the zinc octahedron are occupied by the terminal ligand atoms of the two hexanuclear anions, and the remaining four vertices contain oxygen atoms of water molecules (Fig. 2). That is, the molecular formula of these compound can be written as $[Zn_4(H_2O)_{18}][Ge_6(\mu\text{-}OH)_4(\mu\text{-}O)_2(\mu\text{-}Oedph)_6]\cdot 20H_2O$.

The complex cations and hexanuclear anions are connected by an extensive network of hydrogen bonds through coordinated and crystallising water molecules. A single independent hydrogen bond is also implemented, which directly connects each hexanuclear anion with four neighbouring ones, thus forming a polymeric anionic layer.

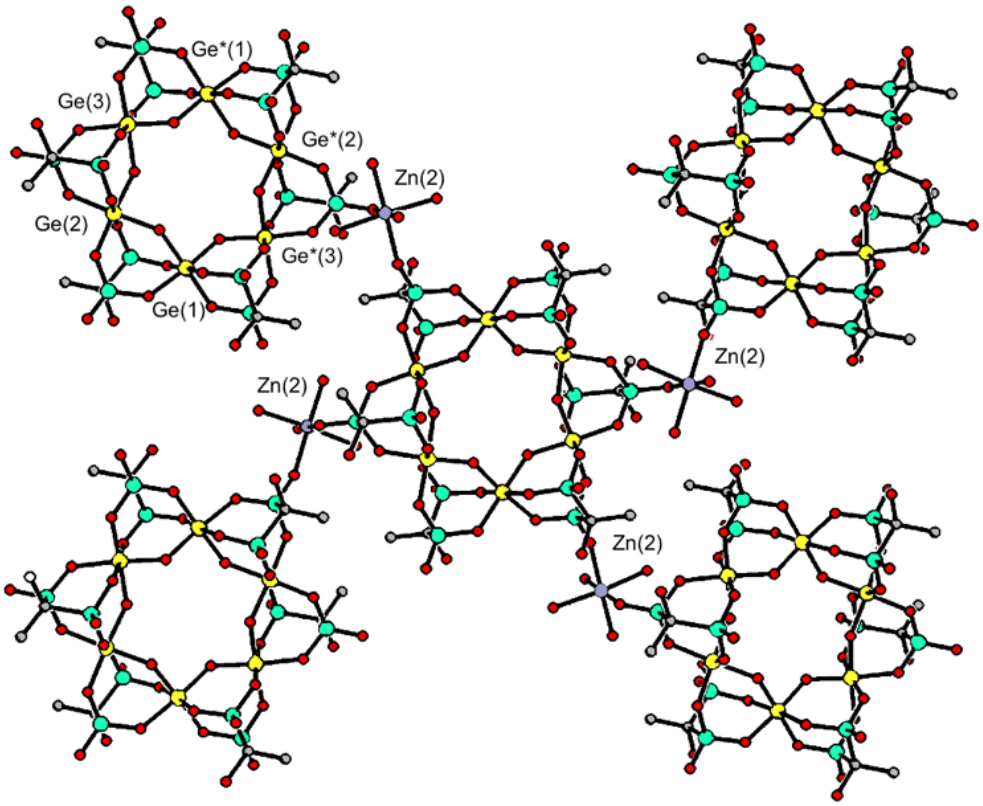


Fig. 2. Fragment of the domain layer $[Zn(2)\{Ge_6(\mu\text{-}OH)_4(\mu\text{-}O)_2(\mu\text{-}hedp)_6\}]_n$ in the crystal structure of $[Zn_4(H_2O)_{18}][Ge_6(\mu\text{-}OH)_4(\mu\text{-}O)_2(\mu\text{-}Oedph)_6]\cdot 20H_2O$.

Coordination compounds with lanthanides are coordination polymers. The X-ray diffraction study of three heterometallic coordination polymers of general formula $\{Ln_2[LnGe_6(\mu\text{-}hedp)_6(\mu\text{-}O)_3(\mu\text{-}OH)_3(H_2O)_4]\cdot xH_2O\}_n$ (Ln = Nd, x ~ 26; Er, x ~ 24; Tm, x ~ 20) is perfor-

med. The basis element of structures is a hexanuclear complex anion $[Ge_6(\mu\text{-hedp})_6(\mu\text{-O})_3(\mu\text{-OH})_3]^{9-}$, in which bridging hydroxo- and oxo-ligands are statistically disordered with equal probability. Hexameric units are connected by $Ln1(H_2O)_4$ fragments into a framework (fig. 3). In structures are channels accommodating disordered lanthanide atoms and water molecules. The complete disordering of lanthanide atoms in the channels and the almost complete disordering of water molecules coordinating them do not allow us to determine the actualhydrate composition of complexes.

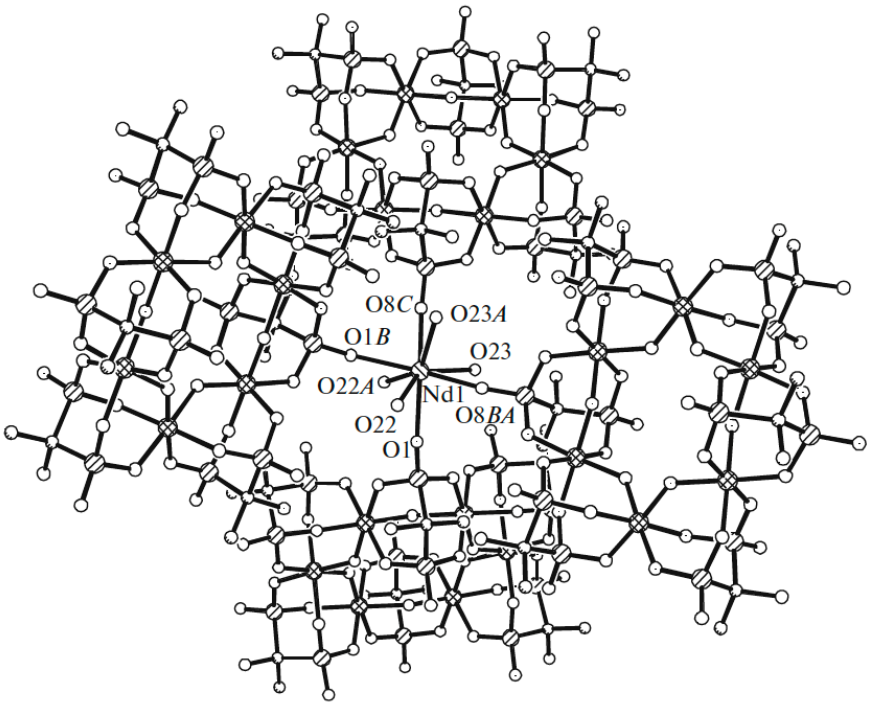
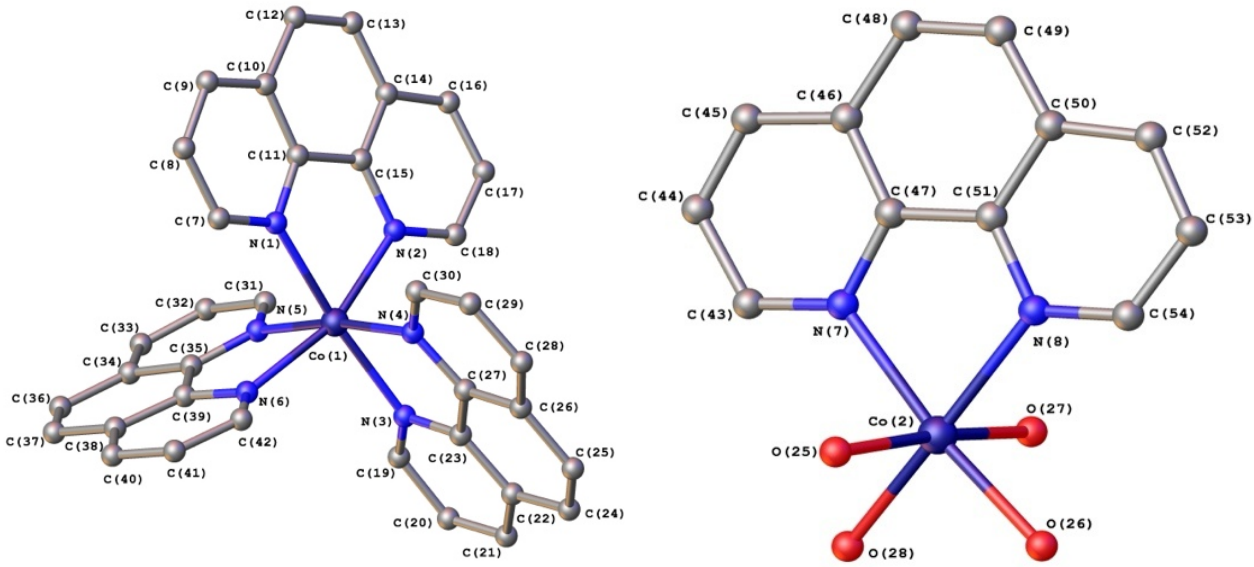


Fig. 3. Fragment of thestructure of $\{Nd_2[NdGe_6(\mu\text{-hedp})_6(\mu\text{-O})_3(\mu\text{-OH})_3(H_2O)_4]\cdot 26H_2O\}_n$

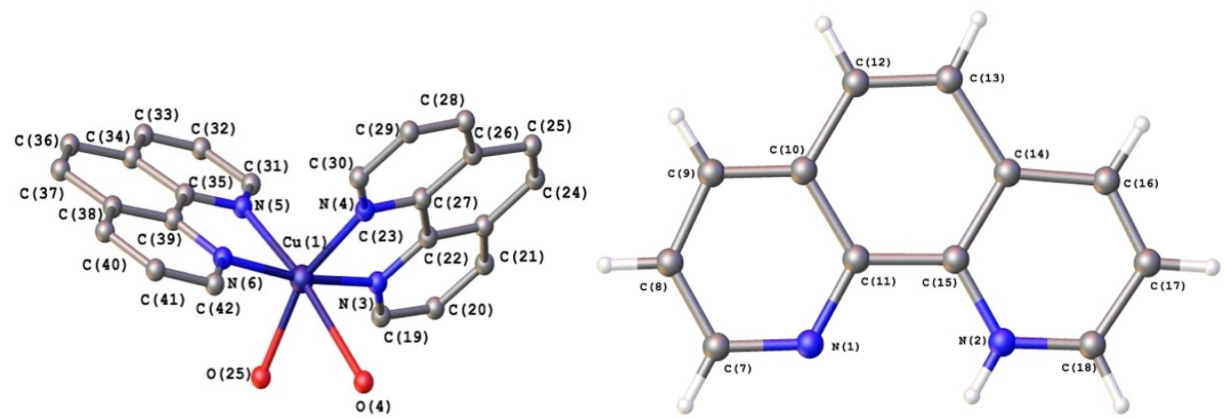
The next step was the introduction of additional ligands (1,10-phenanthroline, phen; 2,2'-bipyridine, bipy) and the preparation of different-ligand and heterometal complexes with 3d metals. The result demonstrated the presence of the hexanuclear anion $[Ge_6(\mu\text{-OH})_6(\mu\text{-hedp})_6]^{6-}$ (fig. 1) in the obtained compounds. However, there is a diversity in the structure of cations depending on the d-metal.

Complexes with structure $[\{Co(phen)_3\}_2\{Co(phen)(H_2O)_4\}_2][\{Ge(\mu\text{-OH})(\mu\text{-hedp})\}_6Cl_2]$, $[\{Cu(phen)_2(H_2O)\}_2(Hphen)_2][Ge(\mu\text{-OH})(\mu\text{-hedp})]_6\cdot 20H_2O$ were synthesized byusing the initial chlorides of 3d metals. According to X-ray diffraction data, these compoundsare cation–anion type complexes in which the anions are represented by $[Ge_6(\mu\text{-OH})_6(\mu\text{-hedp})_6]^{6-}$ (in the case of Co-complex two additional Cl^- ions too), while the cations are $[Co(phen)_3]^{2+}$,$[Co(phen)(H_2O)_4]^{2+}$in Co-complex (fig. 4) and $[Cu(phen)_2(H_2O)]^{2+}$, $Hphen^+$ in Cu-complex (fig. 5).



(a) (b)

Fig. 4. Molecular structure of cations $[Co(phen)_3]^{2+}$ (a) and $[Co(phen)(H_2O)_4]^{2+}$ (b).

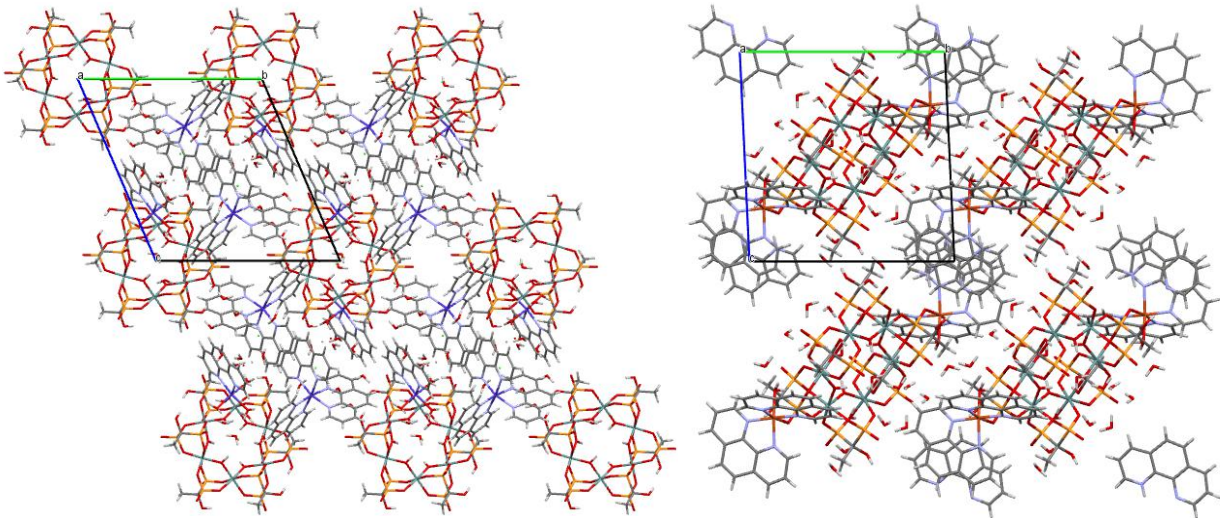


(a) (b)

Fig. 5. Molecular structure of cations $[Cu(phen)_2(H_2O)]^{2+}$ (a) and $Hphen^+$ (b).

In the crystals of compounds the cations, anions, andwater molecules are combined by numerous intermolecular hydrogen bonds, giving rise to a 3D network (fig. 6).

A distinction of these coordination compounds from the previously studied 1-hydroxyethane-1,1-diphosphonatogermanates(IV) [1] is the formation of supramolecular assemblies based on simple and complex cations and anions, which mutually counterbalance their charges. This is caused by both the replacement of Co^{2+} by Cu^{2+} and the incorporation of 1,10-phenanthroline, which can function simultaneously as a bidentate chelating ligand and an outer-sphere cation in the Hp hen$^+$ monoprotonated form.



(a) (b)

Fig. 6. Crystal structure of compounds $[\{Co(phen)_3\}_2\{Co(phen)(H_2O)_4\}_2][\{Ge(\mu\text{-}OH)(\mu\text{-}hedp)\}_6Cl_2]$ (a) and $[\{Cu(phen)_2(H_2O)\}_2(Hphen)_2][Ge(\mu\text{-}OH)(\mu\text{-}hedp)]_6\cdot 20H_2O$ (b).

The developed synthesis methods allowed us to obtain Ge(IV)-3d-metals coordination compounds with 1-hydroxyethane-1,1-diphosphonic acid and 2,2'-bipyridine. Complexes are characterized by the methods of elemental analysis, IR-spectroscopy, thermogravimetric analysis. It was established that the obtained compounds to the cation-anion type. They consist of the hexanuclear cyclic anions $[Ge6(\mu\text{-}OH)_4(\mu\text{-}O)_2(\mu\text{-}hedp)_6]^{8-}$, complex cations $[M(bipy)_3]^{2+}$ (M = Co, Ni), $[Cu(H_2O)(bipy)_2]^{2+}$ (Fig. 7) and crystallization water molecules. In the cation of complexes with Co(II) and Ni(II) the octahedral coordination polyhedron of the 3d-metals formed by the six nitrogen atoms of three 2,2´-bipyridine. The coordination number of Cu atoms is five, and the polyhedron is formed by the four nitrogen atoms of two molecules of 2,2´-bipyridine and the oxygen atom of the water molecule. The synthesized complexes correspond to the formulas $[M(bipy)_3]_4[Ge_6(\mu\text{-}OH)_4(\mu\text{-}O)_2(\mu\text{-}hedp)_6]\cdot nH_2O$ (M = Co, n = 20; Ni, n = 12), $[Cu(H_2O)(bipy)_2]_4[Ge_6(\mu\text{-}OH)_4(\mu\text{-}O)_2(\mu\text{-}hedp)_6]\cdot 14H_2O$ [18].

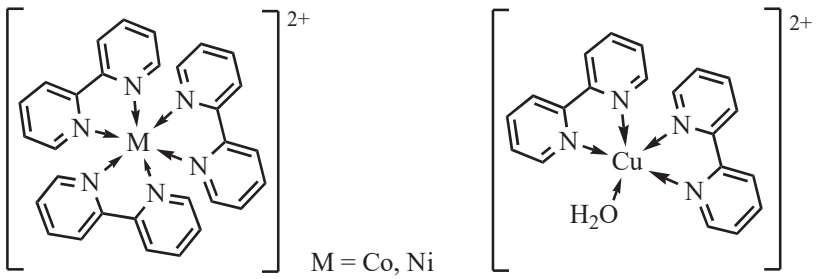


Fig. 7. Scheme of structures of cations $[M(bipy)_3]^{2+}$, $[Cu(H_2O)(bipy)_2]^{2+}$.

Pharmacological and biological activity of 1-hydroxyethane-1,1-diphosphonatogermanates(IV).

The pharmacological activity of a number of 1-hydroxyethane-1,1-diphosphonatogermanates(IV), which according to the results of acute toxicity testing are classified as low-toxic, was investigated [19–22].

The specific effect of complexes with nicotinic acid and magnesium on the cardiovascular system was established on the model of arrhythmia caused by intraperitoneal administration of aconitine alkaloid to rats. The antiarrhythmic effect was found, and it was more pronounced in the complex with magnesium [23–25].

In acute cerebral ischemia caused by carotid artery occlusion, 1-hydroxyethane-1,1-diphosphonatogermanates(IV) with piracetam has a pronounced anti-ischemic effect and is also characterised by high absorption and elimination rate constants in the body [26].

A high hepatoprotective effect of the complex with nicotinic acid was also determined; it prevents changes in total cholesterol, phospholipids and maintains the qualitative and quantitative composition of phospholipid fractions at the level of control values in erythrocyte membranes and in the liver [27].

Studies of the in vitro interferonogenic activity of these compounds on a fibroblast cell culture line showed that the complex with nicotinic acid induces interferon, and at a concentration of 25 to 100 μg/ml leads to a 100% delay in the cytopathic effect of vesicular stomatitis virus in cell culture, which is superior to the comparison drugs.

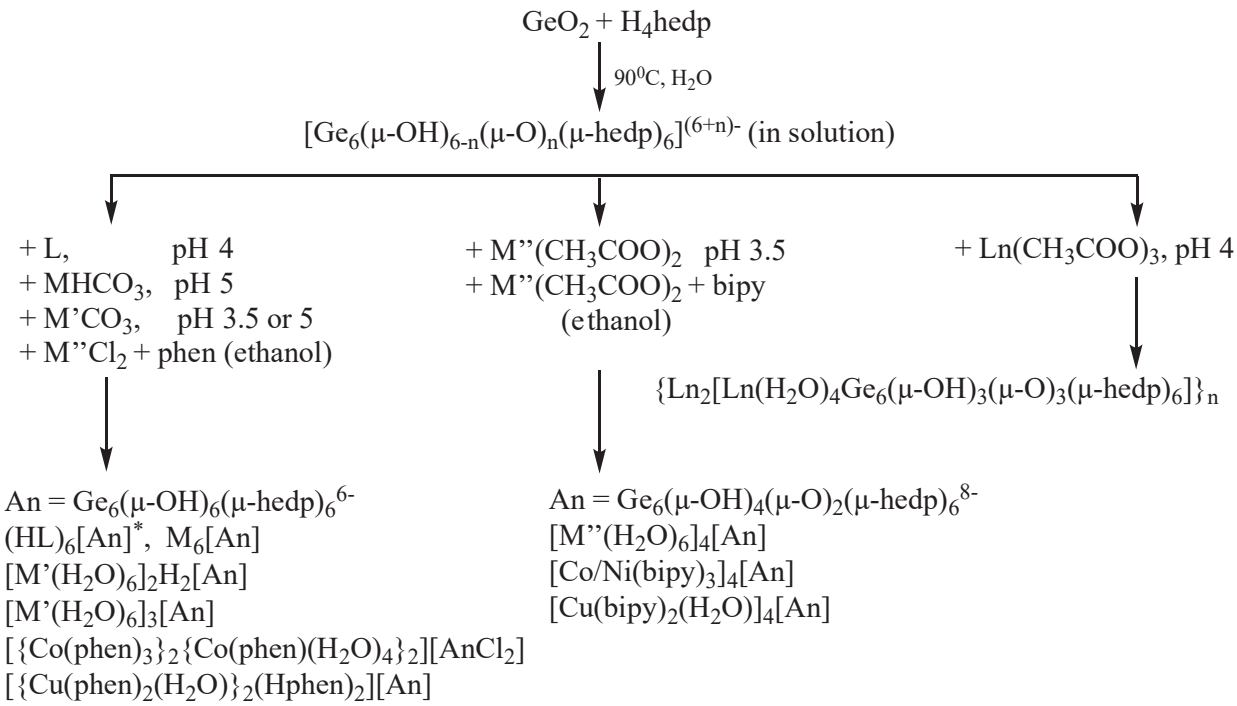
In the model of endotoxemia of post-traumatic genesis (which can occur, for example, in peritonitis), the detoxifying effect of the complex with magnesium was shown, which is expressed in a decrease in the level of medium-weight molecules in the blood serum – a universal marker of endogenous intoxication and lipid peroxidation products in the liver homogenate, i.e. the degree of damage to cellular and subcellular membranes [28].

The screening for hepatoprotective activity among compounds with 3d-metals revealed that the administration of the complex with copper resulted in a significantly lower increase in the activity of cytolysis and cholestasis enzymes than in untreated animals with hepatitis. The compound also reduced bilirubin levels in blood serum and liver tissue. Importantly, it has low toxicity with different types of administration: oral, intraperitoneal and subcutaneous [29–30].

It was studied the effect of mixed-ligand complexes of Ge(IV) – Co(II) (Ni(II), Cu(II)) with 1-hydroxyethane-1,1-diphosphonic acid and 2,2′-bipyridine on the activity of elastase and fibrinogenase isolated from Bacillus sp. IMV B-7883. It has shown that complexes Co(II) and Ni(II) inhibited the activity of elastase by 54 and 71% respectively, while complex Cu(II) enhanced it by 30%. All three complexes have a stimulating effect on fibrinogenase activity in more than 50% [18].

CONCLUSION. As a result of systematic studies of the structure of a number of mixed-ligand 1-hydroxyethane-1,1-diphosphonatogermanates(IV) with different metals, it was observed, that hexanuclear cyclic complex anions of the general composition $[Ge_6(\mu\text{-}OH)_{6-n}(\mu\text{-}O)_n(\mu\text{-}hedp)_6]^{(6+n)-}$ were present in the aqueous solutions of investigated compounds.

At the same time, the composition and charge of the anion in each compound obtained in the solid state depends on the nature of the cation (fig. 8).



L= nicotinic acid, niacinamide, isoniazid, imidazole, piracetam;
M = Na, K; M' = Mg, Ca, Sr, Ba; M'' = Co(II), Ni(II), Cu(II), Zn; Ln = Nd(III), Er(III), Tm(III);
bipy – 2,2'-bipyridine; phen – 1,10-phenanthroline; *all compounds are hydrates

Fig. 8. Synthetic route and structures of different types of 1-hydroxyethane-1,1-diphosphonatogermanates.

They all have a common hexameric structure, with germanium atoms connected in pairs by 1-hydroxyethane-1,1-diphosphonate, hydroxo-, or oxo- and hydroxo-bridges. The coordination polyhedron Ge is a curved octahedron with two six-membered GeO_2P_2C cycles and an eight-membered bimetallic $Ge_2O_4P_2$ closing, and each ligand performs a tetradentate tris(chelate)-μ-bridging function. The ratio of formed oxo- and hydroxo-bridges and, as a result, the charge of the anion varies under the influence of cation parameters and electrostatic interactions. However, the structure of complex anions is quite stable and is not destroyed even by interactions with complex cations.

Most obtained compounds refer to the cation-anion type with various cations (protonated organic molecules, hexaaqua-, bipyridine-, and phenanthroline metal cations). In the structure of lanthanide compounds complex hexanuclear anions $[Ge_6(\mu\text{-}OH)_3(\mu\text{-}O)_3(\mu\text{-}hedp)_6]^{9-}$ and $Ln(H_2O)_4$ fragments are combined into a 3D-framework.

The pharmacological and biological activities of 1-hydroxyethane-1,1-diphosphonatogermanates(IV) are ensured by the combined action of all biologically active components,

which do not compete but show synergistic action.

In view of the above, it can be concluded that the preparation of new complexes of germanium(IV) with etidronicacid by chemical modification of their composition is a promising area of research in the field of creating coordination compounds with a wide range of pharmacological effects.

This work was done according to the theme "Chemical construction of organo-inorganic ensembles of coordinating, supramolecular, polymeric nature for use as new materials and pharmaceuticals", No state registration: 0122U201403, 2022-2026.

ОСОБЛИВОСТІ БУДОВИ ТА ФАРМАКОЛОГІЧНІ ВЛАСТИВОСТІ КОМПЛЕКСІВ ГЕРМАНІЮ(IV) З 1-ГІДРОКСИЕТАН-1,1-ДИФОСФОНОВОЮ КИСЛОТОЮ

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В оглядовій статті представлено результати систематичних досліджень авторів низки гетерометалів і різнолігандних 1-гідроксиетан-1,1-дифосфонатогерманатів, їхньої структури, біологічних і фармакологічних властивостей. Встановлено, що у водних розчинах досліджуваних сполук присутні шестиядерні циклічні комплексні аніони загального складу $[Ge_6(\mu\text{-}OH)_{6-n}(\mu\text{-}O)_n(\mu\text{-}hedp)_6]^{(6+n)-}$. При цьому склад і заряд аніона в кожній сполуці, отриманій в твердому стані, залежить від природи катіона. Усі вони мають спільну гексамерну структуру аніона, в якій атомами германію попарно з'єднані 1-гідроксиетан-1,1-дифосфонатними, гідроксо- або оксо- та гідроксомістками. Координаційний поліедр Ge є викривленим октаедром з двома шестичленними циклами GeO_2P_2C та восьмичленним біметалічним циклом $Ge_2O_4P_2$, кожен ліганд виконує тетрадентатнутрис(хелатну)-μ-місткову функцію. Співвідношення утворених оксо- і гідроксомістків і, як наслідок, заряд аніона змінюється під впливом параметрів катіонів і електростатичних взаємодій. Дослідження гострої та хронічної токсичності довели безпечність 1-гідроксиетан-1,1-дифосфонатогерманатів. Комплекси виявляють широкий спектр фармакологічної дії: антигіпертензивну, антиаритмічну, гепатопротекторну, церебропротекторну та ін. Фармакологічна та біологічна активність 1-гідроксиетан-1,1-дифосфонатогерманатів(IV) забезпечується спільною дією всіх біологічно активних компонентів, які не конкурують, а виявляють синергічний ефект. Зроблено висновок, що отримання нових комплексів германію(IV) з етидроновою кислотою шляхом хімічної модифікації їхнього складу є перспективним напрямком досліджень у галузі створення координаційних сполук із широким спектром фармакологічної дії.

Ключові слова: германій(IV), 1-гідроксиетан-1,1-дифосфонова (етидронова) кислота, нітрогенвмісні гетероцикли, координаційні сполуки, біологічна активність.

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