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Synthesis and Structures of Nickel(II) Complexes Based on Dianilineglyoxime. Stimulation of the Proteolytic Properties by $[Ni(DAnH)_2]\cdot 0.25H_2O$

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Abstract—Two new bis- and tris(solvatomorphs) $[Ni(DAnH)_2]\cdot 0.25H_2O$ (**I**) and $[Ni(DAnH_2)_3]Cl_2\cdot 6CH_3OH$ (**II**) are synthesized by the reaction of dianilineglyoxime ($DAnH_2$) with nickel(II) chloride under different conditions. The molecular structures of complexes **I** and **II** are determined by X-ray diffraction analysis (CIF files CCDC nos. 1998570 and 1998571, respectively). Complex **I** taken in optimally selected concentrations exerts the stimulation effect on the synthesis of proteases of the biotechnologically significant micromycete strain *Fusarium gibbosum* CNMN FD 12 increasing the activity of acidic proteases by 83.0% and that of neutral proteases by 68.2% compared to the control value. Complex **I** can be considered as a potential biostimulator of enzyme formation for some strains of mycelium fungi.

Keywords: dianilineglyoxime, coordination compounds of nickel(II), IR and NMR spectra, microscopic fungi, proteases

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INTRODUCTION

Dioximes are convenient chelate ligands for the synthesis of stable coordination compounds with a wide range of practical application: in analytical and biological chemistry, medicine, dyeing of cotton fabrics, etc. [1]. In addition to the possibility of cobalt dioximates to serve as models of vitamin B_{12} [2], this class of compounds evokes interest as substances capable of affecting physiological properties of micromycetes, algae, and agricultural plants [3–10]. Clathratochelate tris(dioximines) manifest the properties than can allow them to be involved in research in the field of anticancer therapy, and the self-assembly of clathrochelates and their reactions with nucleic acids can widely be used in immunology and molecular biology [11–13]. The bi- and polynuclear compounds based on dioximes can serve as the start of manufacturing porous and luminescent materials [14–16]. The synthesis of coordination compounds of this class (from mononuclear complexes to coordination polymers) seems interesting [17–24].

The synthesis of *vic*-dioximes provides new possibilities for the enlargement of a variety of complexes with new compositions, structures, and properties that can depend on the nature of "wings" of these chelate ligands in the mono- and polynuclear compounds [25, 26]. Since the Co(III) complexes containing sulfanilamide exhibit the properties of biostimulators of enzyme formation [27], it was of interest to study the attachment of this fragment to the dioxime molecule for the synthesis of new ligands and to elucidate the effect of coordination compounds of transition metals with the new ligands on the biological processes. In addition, more bulky dioximates can provide favorable conditions for the formation of porous materials.

Dianilineglyoxime ($DAnH_2$) was synthesized in steps by three known reactions via glyoxime–dichloroglyoxime–$DAnH_2$, and its reaction with nickel chloride affords new solvatomorphs of the known bis- and tris(ligand) complexes $[Ni(DAnH)_2]$ and $[Ni(DAnH_2)_3]Cl_2$ [28]: $[Ni(DAnH)_2]\cdot 0.25H_2O$ (**I**) and $[Ni(DAnH_2)_3]Cl_2\cdot 6CH_3OH$ (**II**), respectively. The compositions and structures of complexes **I** and **II** were determined by elemental analysis, IR and NMR spectroscopy, and X-ray diffraction analysis (XRD). The stimulation effect on the protease synthesis of the micromycete strain *Fusarium gibbosum* CNMN FD 12 of biotechnological design was studied for compound **I**. We have previously obtained the crystals and determined the structure of $DAnH_2$ in the form of hydrate salts $[DAnH_3](ClO_4)\cdot H_2O$ and $[DAnH_3](ClO_4)\cdot 1.25H_2O$ and three binuclear zinc(II) and manganese(II) compounds with this ligand [29].

EXPERIMENTAL

Commercially available chemicals (including solvents) were used for the syntheses without preliminary purification. The syntheses were carried out according to the known procedures for glyoxime [29], dichloroglyoxime [30], and $DAnH_2$ [31].

Synthesis of complex I. A weighed sample of $DAnH_2$ (0.27 g, 1 mmol) was dissolved in methanol (10 mL), and the solution was heated in a water bath at 50°C for 15 min. Nickel salt $NiCl_2\cdot 6H_2O$ (0.12 g, 0.5 mmol) in methanol (10 mL) was added to the resulting solution. In 5 min, 1–2 droplets of an ammonia solution were added to the solution. The formed brown precipitate was filtered off and washed with cold methanol and ether. The yield was ~56%. The crystals suitable for XRD were obtained by the recrystallization of the complex from methanol. Complex **I** was soluble in DMF and weakly soluble in alcohols and DMSO.

For $C_{28}H_{26.5}N_8O_{4.25}Ni$

Anal. calcd., %	C, 55.88	H, 4.44	N, 18.62	Ni, 9.75
Found, %	C, 55.64	H, 4.36	N, 18.46	Ni, 9.61

Synthesis of complex II. Nickel salt $NiCl_2\cdot 6H_2O$ (0.15 g, 0.5 mmol) in methanol (10 mL) was added to a warm solution containing $DAnH_2$ (0.27 g, 1 mmol) dissolved in methanol (20 mL), and the resulting solution was acidified with 1–2 droplets of HCl (1 : 1) to retain an acidic medium of the solution (pH ~ 2). After 2–3 days, crystals as green prisms were formed in the solution. The yield was ~34%. Complex **II** was soluble in alcohols, DMF, and DMSO.

For $C_{48}H_{66}N_{12}O_{12}Cl_2Ni$

Anal. calcd., %	C, 50.90	H, 5.87	N, 14.84	Ni, 5.18
Found, %	C, 50.77	H, 5.64	N, 14.73	Ni, 5.02

The compositions and structures of compounds **I** and **II** were determined by elemental analysis, IR and UV spectroscopy, and NMR spectroscopy. Their single crystals were studied by XRD. IR spectra were recorded on an FT-IR Perkin-Elmer Spectrum 100 instrument in Nujol in a range of 4000–400 cm^{-1} and in a range of 4000–650 cm^{-1} for the ATR mode. UV spectra were recorded on a Perkin-Elmer Lambda 25 spectrophotometer. ^1H and ^{13}C NMR spectra were detected on a 400 Bruker spectrometer with the working frequency 400.13 MHz for ^1H and 100.61 MHz for ^{13}C in DMSO-d_6 solutions using TMS as the internal standard. The signals were given in ppm.

XRD. The structural data were obtained at room temperature on an Xcalibur E diffractometer in the ω scan mode using MoK_α radiation ($\lambda = 0.71073$ Å) and a graphite monochromator. The unit cell parameters were refined over the whole set of experimental data. The crystal structures were solved by direct methods and refined using full-matrix least squares for F^2_{hkl} in the anisotropic approximation for nonhydrogen atoms (SHELX-97) [32]. The positions of hydrogen atoms were partially calculated geometrically and were partially determined by the Fourier syntheses. All of them were refined isotropically in the rigid body model. The crystallographic data and experimental characteristics for compounds **I** and **II** are presented in Table 1. The interatomic distances and bond angles in the coordination polyhedra are given in Table 2. The geometric parameters of hydrogen bonds are presented in Table 3.

The full structural information for compounds **I** and **II** was deposited with the Cambridge Crystallographic Data Centre (CIF files CCDC nos. 1998570 and 1998571, respectively; http://www.ccdc.cam.ac.uk/data_request/cif).

Biological methods. The biological properties of the synthesized coordination compounds were evaluated by the effect on enzyme formation of the micromycetes *Fusarium gibbosum* CNMN FD 12, which are active producers of proteolytic enzymes [33]. The strains are stored in the National Collection of Nonpathogenic Microorganisms of the Republic of Moldova at the Institute of Microbiology and Biotechnology.

The producers were cultivated by the deep method in 0.5-L conical flasks with a nutrient medium (0.1 L) of the earlier selected optimum composition [34, 35] at 28–30°C with permanent stirring in a rocking device with a rotation rate of 200 rpm. The cultivation time for the strain *Fusarium gibbosum* CNMN FD 12 was 6 days. The complexes in the dissolved form were introduced into a sterile nutrient medium in concentrations of 5, 10, and 15 mg/L simultaneously with the seed material. The medium without coordination compound served as the control. The seed material was an aqueous suspension of spores of the 12–15th-day culture grown on a wort agar slope in an amount of 10% of the inoculated volume with the spore density $1–3 \times 10^6$ per mL.

The activity of the acidic (pH 3.6) and neutral (pH 7.4) proteases was determined by the Wilschtetter method based on the determination of the amount of free carboxyl groups formed by the hydrolysis of a 5% solution of gelatin. The amount of enzyme formed from 1 mg of amine nitrogen within 1 h under standard experimental conditions was accepted to be the proteolytic activity unit [36].

Table 1. Crystallographic data and experimental characteristics for complexes **I** and **II**

Parameters	Value	
	I	**II**
FW	601.78	1132.74
Crystal system	Monoclinic	Trigonal
Space group	$P2_1/c$	$R\bar{3}c$
Unit cell parameters		
a, Å	13.9314(14)	14.5230(5)
b, Å	13.6263(11)	14.5230(5)
c, Å	14.7047(13)	48.521(2)
α, deg	90	90
β, deg	105.468(9)	90
γ, deg	90	120
V, Å^3	2690.3(4)	8862.9(6)
Z	4	6
ρ_{calc}, g/cm^3	1.486	1.273
μ, mm^{-1}	0.774	0.484
F(000)	1250	3576
Crystal sizes, mm	0.18 × 0.12 × 0.04	0.30 × 0.30 × 0.15
Range of θ, deg	2.87–25.50	3.08–25.49
Index ranges	$-16 \le h \le 15$, $-16 \le k \le 8$, $-17 \le l \le 17$	$-16 \le h \le 17$, $-15 \le k \le 13$, $-24 \le l \le 22$
Number of measured/independent reflections (R_{int})	8423/4979 (0.0526)	11279/1848 (0.0302)
Number of reflections with $I > 2\sigma(I)$	1986	1292
Completeness, %	99.3 (θ = 25.50°)	99.8 (θ = 25.49°)
Number of refined parameters	374	147
GOOF	1.006	1.007
R_1, wR_2 ($I > 2\sigma(I)$)	0.0424, 0.0859	0.0290, 0.0722
R factors (for all data)	$R_1 = 0.1339$, $wR_2 = 0.1168$	$R_1 = 0.0468$, $wR_2 = 0.0748$
$\Delta\rho_{max}$, $\Delta\rho_{min}$, e Å^{-3}	0.287, –0.227	0.219, –0.198

RESULTS AND DISCUSSION

The reactions of nickel(II) chloride with dianilineglyoxime afforded nickel(II) bis(dioximate) and nickel(II) tris(dioximine) under different conditions. The formation of tris(dioximine) needs pH ~ 2, while pH ~5–6 is necessary for the formation of bis(dioximate). A lowly acidic or alkaline medium was made by the addition of 1–2 droplets of an ammonia solution, whereas an acidic medium was prepared by the addition of hydrochloric acid.

The crystal structures of the $[Ni(DAnH)_2]\cdot0.25H_2O$ (**I**) and $[Ni(DAnH_2)_3]Cl_2\cdot6CH_3OH$ (**II**) complexes were determined. As a result, it was found (although these coordination compounds are known [28]) that a change in the synthesis conditions afforded new solvatomorphs differed in both the external medium and packing of the components.

The structural studies showed that the compounds with a similar ligand complex as complex **I** and $[Ni(DAnH)_2]\cdot$DMF (**III**) [28] crystallized in the space groups $P2_1/c$ (Table 1) and $P2_1/n$ of the monoclinic crystal system, respectively, but their unit cell parameters turned out to be different (for **III**: $a = 9.2341(4)$, $b = 12.8587(5)$, $c = 15.0715(6)$ Å, $\beta = 102.566(2)$°, $V = 1746.70(12)$ Å^3). Crystalline complex **I** contains residues of water molecules, and complex **III** contains DMF molecules in a ratio of 2 : 1 to the complex. In addition, bis(ligand) complex **III** is centrosymmetric,

Table 2. Interatomic distances (d) and bond angles (ω) in the coordination polyhedra of compounds **I** and **II***

Bond	d, Å	
	I	**II**
Ni(1)–N(1)	1.851(4)	2.075(1)
Ni(1)–N(2)	1.847(4)	
Ni(1)–N(3)	1.863(3)	
Ni(1)–N(4)	1.875(4)	
Angle	**ω, deg**	
N(1)NiN(2)/N(1)$^{\#1}$	82.9(2)	166.32(7)
N(1)NiN(3)/N(1)$^{\#2}$	177.9(2)	76.73(7)
N(1)NiN(4)/N(1)$^{\#3}$	97.4(2)	94.08(5)
N(2)/N(1)NiN(3)/N(1)$^{\#4}$	96.5(2)	96.64(7)
N(2)/N(1)NiN(4)/N(1)$^{\#5}$	175.5(2)	94.08(5)
N(3)NiN(4)	83.1(2)	

* Symmetry transforms: $^{\#1}$ $-x + 4/3, -x + y + 2/3, -z + 1/6$; $^{\#2}$ $y + 1/3, x - 1/3, -z + 1/6$; $^{\#3}$ $-x + y + 1, -x + 1, z$; $^{\#4}$ $x - y + 1/3, -y + 2/3, -z + 1/6$; $^{\#5}$ $-y + 1, x - y, z$ (**II**).

whereas in complex **I** the complexing atom is localized in the common position. However, in both complexes **I** and **III**, the square planar coordination polyhedron of the Ni(1) atom (Fig. 1a) is formed by four nitrogen atoms belonging to two monodeprotonated ligands of dianilineglyoxime. The Ni–N bond lengths lie in a range of 1.847(4)–1.875(4) Å (Table 2) and are comparable with the published values [28]. The *N*,*N*-bidentate coordination of these ligands gave two five-membered metallocycles lying nearly in one plane (±0.020 Å). The shift of the nickel atom from the plane of the N_4 donor atoms does not exceed 0.056 Å. Two intramolecular hydrogen bonds O–H···O with the donor···acceptor distances 2.486(4) and 2.492(4) Å are formed between the dioxime monoanions in the complex. This type of stabilization of two similar ligands with pseudomacrocycle formation was observed in nearly all bis(dioximates) of transition metals found in the Cambridge Structural Database [37].

The crystal of compound **I** contains chains of the complexes linked via the intermolecular hydrogen bonds N–H···O in which the NH are involved as proton donors and the oxygen atoms of the oxime groups additionally stabilized by weak intermolecular hydrogen bonds C–H···O serve as acceptors (Table 3, Fig. 2). However, the Ni(II) complexes are joined both directly via the N–H···O hydrogen bonds and via the molecules of water of crystallization to form hydrogen bonds of the N–H···O(*w*) and O(*w*)–H···O types (Table 3, Fig. 3a). As a result, the complexes in the crystal are joined into a three-dimensional framework. In the crystal of compound **III**, the DMF molecules are also bound to the complexes via the intermolecular hydrogen bonds N–H···O.

Compound **II** crystallizes in the trigonal space group $R\bar{3}c$ (Table 1), unlike the compound with the tris(ligand) complex [Ni(DAnH$_2$)$_3$]Cl$_2$·2C$_2$H$_5$OH (**IV**) [28] containing crystallization molecules of ethanol. Compound **IV** crystallizes in the space group $P2_1/c$ of the monoclinic crystal system (a = 9.2683(2), b = 22.9694(7), c = 24.0707(6) Å, β = 91.484(2)°, V = 5122.6(2) Å^3). Compound **II**, as well as compound **IV**, is ionic and consists of complex cations

Table 3. Geometric parameters of intra- and intermolecular hydrogen bonds in the structures of compounds **I** and **II**

Contact D–H···A	Distance, Å			Angle DHA, deg	Coordinates of atoms A
	D–H	H···A	D···A		
			I		
O(1)–H(1)···O(4)	0.82	1.70	2.492(4)	161	x, y, z
O(3)–H(2)···O(2)	0.82	1.71	2.486(4)	158	x, y, z
N(11)–H(1)···O(3)	0.85	2.37	3.062(5)	139	$x, -y + 1/2, z - 1/2$
N(21)–H(1)···O(1*w*)	0.92	2.20	2.91(1)	133	$-x + 2, -y + 1, -z$
N(31)–H(1)···O(1)	0.88	2.26	3.081(5)	155	$x, -y + 1/2, z + 1/2$
N(41)–H(1)···O(4)	0.87	2.19	2.944(5)	145	$-x + 1, -y, -z$
O(1*w*)–H(1)···O(2)	0.85	2.36	3.21(1)	179	$-x + 2, -y + 1, -z$
O(1*w*)–H(2)···O(2)	0.86	1.95	2.77(1)	158	x, y, z
			II		
O(1)–H(1)···Cl(1)	0.76	2.50	3.223(2)	160	x, y, z
O(2)–H(1)···Cl(1)	0.93	2.33	3.232(2)	164	$-x + 2, -y + 1, -z$
N(2)–H(1)···O(2)	0.79	2.11	2.853(2)	158	x, y, z

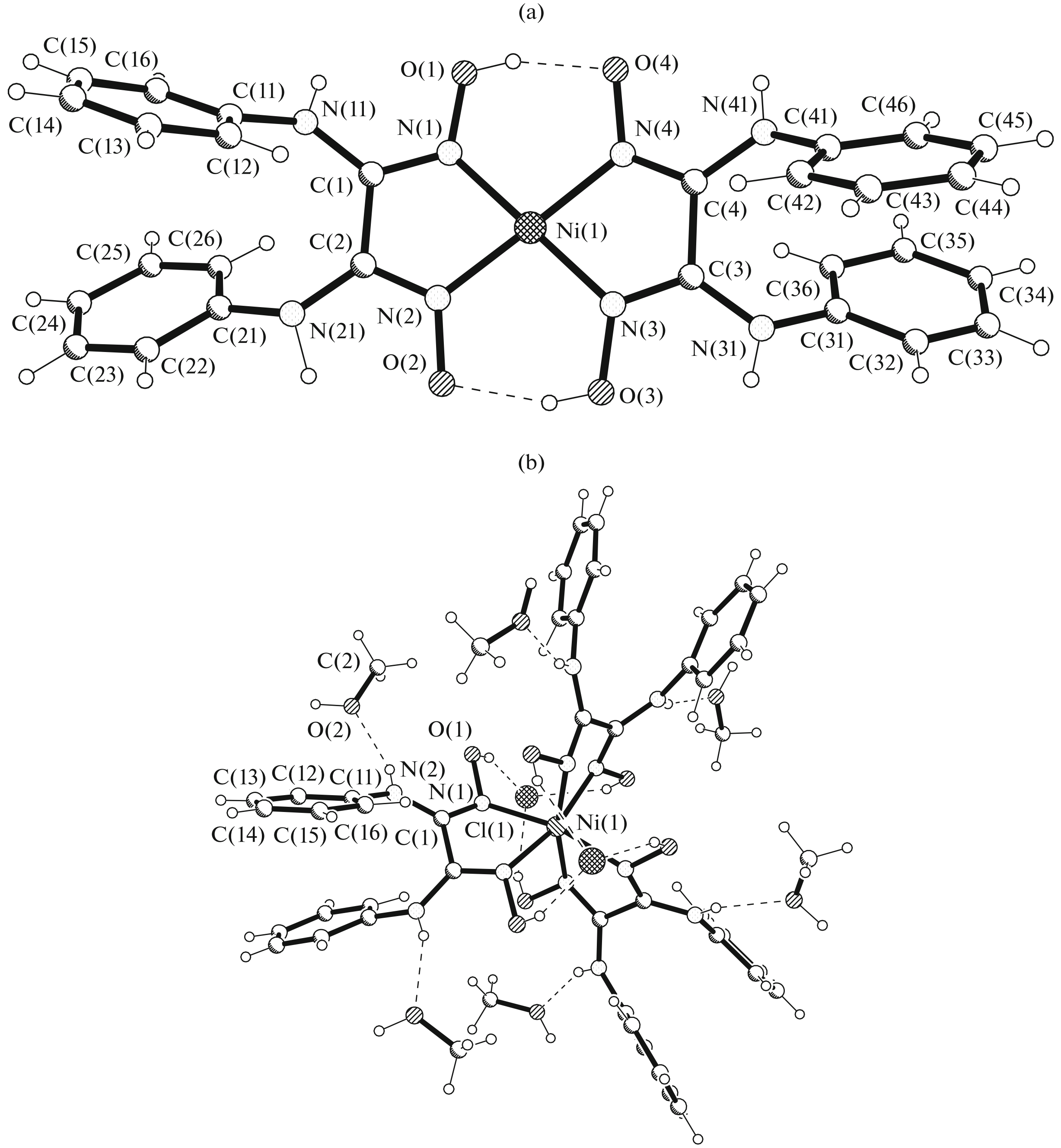

Fig. 1. Structures of (a) complex $[Ni(DAnH)_2]$ in compound **I** and (b) ionic compound $[Ni(DAnH_2)_3]Cl_2·6CH_3OH$ (**II**).

$[Ni(DAnH_2)_3]^{2+}$, Cl^- anions, and crystallization molecules of methanol in a ratio of 1 : 2 : 6 (Fig. 1b), but both these compounds differ in solvate molecules. The symmetries of the $[Ni(DAnH_2)_3]^{2+}$ complex cations in compounds **II** and **IV** are different. The complex cation in compound **II** is characterized by the D_3 symmetry, since the central atom is arranged on the 3-fold inversion axis and the oxime ligand has the C_2 symmetry, and the Cl(1) atom lies on the triple axis. As a result, in the complex cation, three dioxime ligands in the neutral form coordinate to the complexing atom by the nitrogen atoms of the oxime groups via the chelating-bidentate mode to form three five-membered metallocycles. In the octahedral coordination polyhedron of the metal, the interatomic Ni–N distances are 2.075 Å (Table 2) and correspond to similar distances

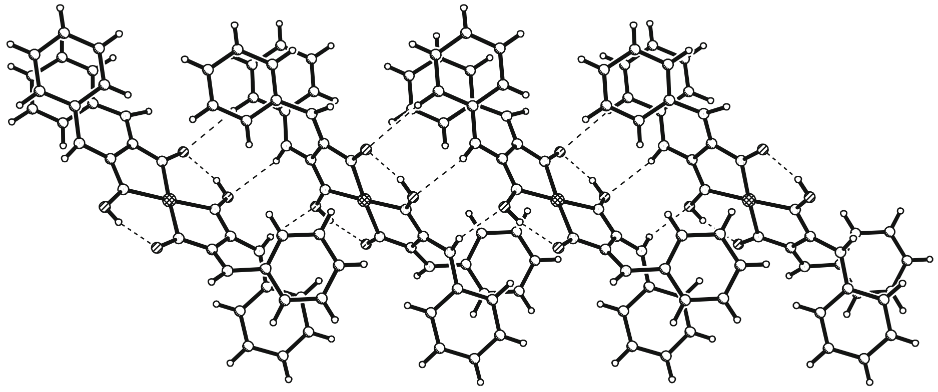

Fig. 2. Binding mode of [Ni(DAnH)$_2$] into a chain in compound **I**.

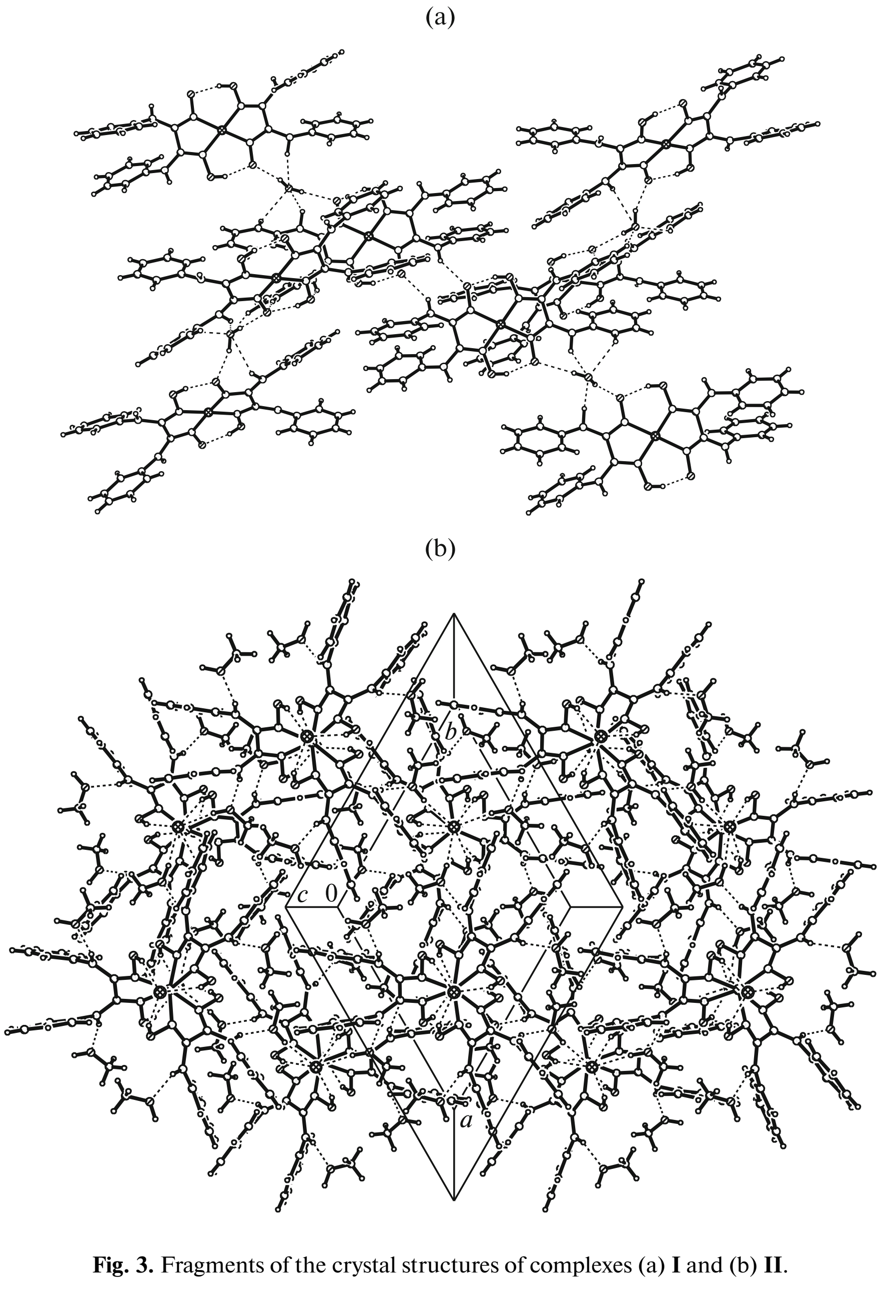

Fig. 3. Fragments of the crystal structures of complexes (a) **I** and (b) **II**.

in compound **IV** [28], where the Ni–N bond length ranges from 2.039(3) to 2.110(3) Å.

In addition to the electrostatic interaction, the complex cations and chloride anions in the crystal of complex **II** are bound by a system of intermolecular hydrogen bonds in which the OH groups of the oxime fragments are involved as proton donors (Table 3, Fig. 3b). The donor···acceptor distances in these hydrogen bonds are 2.223(2) and 2.232(2) Å. The methanol molecules are joined by the hydrogen bonds with both the Cl^- anions (in which they are involved as proton donors) and complex cations already as acceptors in which the NH groups of the $DAnH_2$ ligands act as proton donors. The donor···acceptor distance in N–H···O is 2.853(2) Å.

In the crystal structure of compound **II**, the complex cations are joined only via the hydrogen bonds in which the anions and methanol molecules are involved. Thus, the stability of the crystal lattice of compound **II** depends on the solvent molecules, and the loss of the solvent molecules explains the instability of this compound in air compared to compound **I**. It was found that in compound **I** the loss of the water molecules did not change the crystal structure, because the framework of the crystal structure is formed by the system of intermolecular hydrogen bonds joining the complexes themselves, while the water molecules are only threaded on the lattice formed. It is most likely that other solvent molecules in the crystal structure of compound **II** could affect the whole structure, since the ethanol molecules are involved in Ni(II) tris(dioximine) **IV** as crystallization molecules [28] and form hydrogen bonds with the complex cation only. The role of the NH groups of the dioximine fragment in the formation of the supramolecular structures of the compounds should also be taken into account, since they participate in hydrogen bond formation in the crystals thus favoring their stability.

The recent works indicate the possibility of using the transition metal complexes with various organic ligands as stimulators of the synthesis of secondary metabolites in the microorganisms, including extracellular hydrolytic enzymes [38–40]. In the earlier studies, we revealed the stimulation effect of a series of cobalt dioximates on the biosynthesis of extracellular hydrolases (pectinases, amylases, and lipases). The cobalt(II) complexes with dimethylglyoxime (DH_2), viz., $[Co(DH)_2(Thio)_2]_3F[SiF_6]\cdot1.5H_2O$, $[Co(DH)_2(Thio)_2]_2[SiF_6]\cdot3H_2O$, and $[Co(DH)_2(Thio)_2][BF_4]\cdot3H_2O$, were shown to be efficient stimulators of the pectolytic activity of the strain *Rhizopus arrhizus* FD 03 and increased enzyme biosynthesis by 97.1–115.3% [41], whereas the $[Co(DH)_2(An)_2]_2[TiF_6]\cdot3H_2O$, $[Co(NioxH)_2(Sam)_2]_2[TiF_6]\cdot3H_2O$, and $[Co(NioxH)_2(An)_2]_2[TiF_6]\cdot3H_2O$ complexes provide the shortening of the cultivation cycle of the micromycete *A. niger* 33-19 CNMN FD 02A by 24–48 h with an increase in the amylolytic activity by 23–64% [27].

The influence of compound **I** on protease biosynthesis by the strain of microscopic fungus *Fusarium gibbosum* CNMN FD 12 was studied in dynamics on the 4–6th day of cultivation (the period corresponding to the biosynthesis maximum of the studied enzymes for the clasical cultivation of the producer).

The addition of compound **I** in concentrations of 5 and 10 mg/L to the medium of producer cultivation exerts a pronounced stimulation effect on the biosynthesis of both acidic and neutral proteases. The activity of the enzymes in the experimental variants exceeds the control level within the whole cultivation period. For the concentration 5 mg/L, the stimulation effect is 199.3 (4 days), 183.0 (5 days), and 174.5% (6 days) for the acidic proteases and 188.7 (4 days), 168.2 (5 days), and 150.0% (6 days) for the neutral proteases. For a concentration of 10 mg/L, the stimulation effect is significantly lower: 127.2 (4 days), 148.9 (5 days), and 125.5% (6 days) for the acidic proteases and 136.2 (4 days), 128.9 (5 days), and 133.3% (6 days) for the neutral proteases. The introduction of compound **I** in a higher concentration (15 mg/L) into the cultivation medium exerts an inhibition effect decreasing the activity of the acidic proteases by 78.9 (4 days), 57.4 (5 days), and 71.5% (6 days) and that of the neutral proteases by 27.7 (4 days), 40.2 (5 days), and 48.8% (6 days) compared to the control value (Table 4).

It is seen from the data in Table 4 that the activity maximum of both acidic and neutral proteases in the control variant appears on the 5th day of producer cultivation and is equal to 2.23 and 2.39 units/mL, respectively. A comparison of the obtained results shows that for the use of compound **I** in a concentration of 5 mg/L this maximum is achieved a day (24 h) sooner with exceeding the maximum control (5th day of cultivation) by 31.4% (acidic proteases) and 11.3% (neutral proteases) being 2.93 and 2.66 units/mL, respectively.

On the 5th day of producer cultivation (the day when the maximum appears in the control variant), the activity of the acidic and neutral proteases in the experimental variants is 4.08 and 4.02 units/mL exceeding the control value by 83.0 and 68.2%, respectively (Table 4).

Complex $[Ni(DAnH)_2]\cdot0.25H_2O$ in the optimum selected concentration (5 mg/L) stimulates the biosynthesis of extracellular proteases for the deep cultivation of the micromycete *Fusarium gibbosum* CNMN FD 12 providing the following:

— for the optimum cultivation period of the strain (5 days), an increase in the activity of the acidic proteases by 83.0% and neutral proteases by 68.2% compared to the activity in the control variant;

— shortening (by 24 h) of the cultivation period of the strain (4 days) with a simultaneous increase in the activity by 31.4% (acidic proteases) and by 11.3% (neu-

Table 4. Influence of the $[Ni(DAnH)_2]\cdot 0.25H_2O$ complex on the proteolytic activity of the micromycete *Fusarium gibbosum* CNMN FD 12

Concentration of coordination compound, mg/L	Activity of acidic proteases (pH 3.6)					
	4th day		5th day		6th day	
	units/mL	% of control	units/mL	% of control	units/mL	% of control
5	2.93 ± 0.02	199.3/131.4*	4.08 ± 0.08	183.0	3.49 ± 0.06	174.5
10	1.87 ± 0.04	127.2	3.32 ± 0.05	148.9	2.51 ± 0.01	125.5
15	0.31 ± 0.01	21.1	0.95 ± 0.01	42.6	0.57 ± 0.01	28.5
Control	1.47 ± 0.01	100.0	2.23 ± 0.04	100.0	2.00 ± 0.04	100.0
	Activity of neutral proteases (pH 7.4)					
5	2.66 ± 0.02	188.7/111.3*	4.02 ± 0.07	168.2	1.26 ± 0.01	150.0
10	1.92 ± 0.01	136.2	3.08 ± 0.05	128.9	1.12 ± 0.02	133.3
15	1.02 ± 0.02	72.3	1.43 ± 0.02	59.8	0.43 ± 0.01	51.2
Control	1.41 ± 0.01	100.0	2.39 ± 0.02	100.0	0.84 ± 0.01	100.0

* With respect to the maximum of the control value (5th day of cultivation).

tral proteases) compared to the maximum activity achieved in the control variant 24 h later (5 days).

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