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Synthesis, Structure Characterization, and Antimicrobial Activity Of 2-Amino-3-[(2-Amino-2-Carboxyethyl) Disulfanyl] Propanoic Acid Dihydrogen Triiodide Coordination Compound

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Abstract

The aim of this study was the synthesis of iodine coordination compounds for the treatment of nosocomial infections caused by drug-resistant bacteria. A new 2-amino-3-[(2-amino-2-carboxyethyl) disulfanyl] propanoic acid dihydrogen triiodide coordination compound was synthesized in basic and water media with a stoichiometric ratio of 1:2:2 of Cystine:LiI:iodine. The physico-chemical properties of complex 2-amino-3-[(2-amino-2-carboxyethyl) disulfanyl] propanoic acid dihydrogen triiodide were examined. Obtained crystals were studied by single-crystal X-ray diffraction, FTIR spectroscopy, UV-Vis spectrophotometer and Thermogravimetry/Differential Scanning Colorimeter (TG/DSC). The compound crystallizes in the orthorhombic $P2_12_12_1$ with lattice parameters a = 9.5739(19) Å, b = 13.558(3) Å, c = 16.405(3) Å, α = 90, β = 90, γ = 90, V = 2129.4(7) Å^3; Z = 4. The antimicrobial activity of the synthesized compound was investigated. Activity evaluations were done against ATCC bacterial and clinical isolates, including WHO-prioritised drug-resistant strains. In the study, the effectiveness of a new coordination compound of iodine against bacteria with multidrug resistance was shown. This fact, as well as the semi-organic nature of the compound, determine the prospects for its use in medicine as an antimicrobial agent.

Keywords: Cystine; Crystal structure; Iodine; X-ray diffraction analysis; Antimicrobial activity.
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1. Introduction

Despite the increasing number of new antimicrobial drugs emerging on the market, antibiotic resistance has become a global medical and social problem.[1] As such, it is crucial to develop fundamentally new antimicrobial drugs that will be effective against infectious diseases caused by multidrug-resistant organisms.

Antimicrobial resistance in clinically significant microorganisms has become an unresolved problem in global public health. Recently, multidrug-resistant bacterial pathogens have emerged that are not susceptible to the action of the latest generation antibiotics, as well antibiotics of as reserve. This has resulted in a huge burden on the health sectors and increased morbidity and mortality worldwide. The overuse of antibiotics and lack of new discoveries have sparked urgent calls for action. On February 2017, the WHO published the list of global priority pathogens (GPP) – a catalog of 12 species of bacteria grouped under three priority levels according to their antibiotics resistance: critical, high, and medium. This is a list of priority pathogens to guide and promote research and development (R&D) of new antibiotics, as part of WHO's efforts to address growing global resistance to antimicrobial medicines (WHO. Media Centre. News Release. WHO publishes list of bacteria for which new antibiotics are urgently needed. 2017.[2]

Compounds of chlorine, iodine, and other halogens have a strong bactericidal effect on gram-positive and gram-negative bacteria. Besides, they also increase the lipophilicity of drugs, thus facilitating their passage through biomembranes.[3] Developing complexes of coordination compounds (derivatives of carbohydrates and amino acids) with halogens can unfold new types of bioactivities or lead to a noticeable increase in existing ones. Our previous studies, demonstrated how the coordination compound of lithium and iodides with biologically active organic ligands (amino acids and oligosaccharides) could be used to obtain materials with

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different optoelectric and magnetic properties.[4,5] The expanding range of applications and the presence of a unique particular molecular configuration has led to an increased interest in iodine compounds in recent years. Yuldasheva G.A. *et al*[6] in their works found that such compounds, located inside the dextrin helix, contain three active centers: molecular iodine coordinated by the polypeptide and lithium halide, lithium triiodide, and halides. These iodine compounds inhibit the active site of topoisomerase I by affecting amino acid residues of arginine and tyrosine.

Much attention has been paid to coordination compounds as potential antimicrobial agents recently. This is due to the improved activity of drugs administered as complexes.[7–10] Coordination compounds of amino acids, such as histidine,[11] arginine, glutamic acid,[12] and cystine[13,14] have been studied. These coordination compounds were reported to demonstrate antimicrobial properties varying from marginal to significantly good. However, little attention has been given to coordination compounds of cystine as a tridentate ligand. As a result of resistance to the drugs currently in use and the emergence of new diseases, there is a continuous need for the development and identification of new compounds as potential antimicrobial agents.

Of particular importance are iodine-containing drugs, which have a number of advantages. The development of methods for obtaining new types of drugs based on iodine is an important and relevant issue today. Iodine is a unique medicinal substance characterized by high biological activity and versatile action on biological systems. In this regard, iodine is widely used to manufacture various dosage forms.
All microbial pathogens of infections are sensitive to iodine, and the resistance acquired to iodine-containing drugs has never been recorded. Therefore, these drugs occupy a leading position among modern antiseptics. Iodine is known for having a local resorptive effect and its antimicrobial, antiviral, and antimycotic properties. When iodine penetrates the cell, it interacts with the amino groups of proteins, thereby suppressing vital enzyme systems.[15] Thus, to summarize developing new drugs active against infectious agents with multiple drug resistance remains an urgent problem of modern medicine.

Before developing a new coordination compound of iodine, an array of literature sources with drugs of similar chemical nature was analyzed. At the same time, both chemical and biological properties identified during the search for substances were taken into account to form the physicochemical basis of the coordinated compound [Cys(HI_3)$_2$]. The study carried out in silico experiments on the design of the active part of the iodine complex and the calculation of components for the synthesis.[16,17] Quantum chemical calculations and spectroscopic studies carried out in model experiments showed the possibility of the formation of stable complexes. In aqueous solutions during the hydrolysis of polyiodides, molecular iodine interacts with the oxygen atom of the carboxy group of amino acids of peptides and lithium halide; triiodide forms a complex with a protonated amino group and the lithium cation with the carboxy group of any amino acid of the peptide. The amino acid–cation system ensures the complex's stability in the body's protein environment.[18] Therefore, cystine:LiI:iodine was chosen to synthesize the iodine coordination compound under the code [Cys(HI_3)$_2$]. The novelty of this article lies in the study of its physicochemical characteristics and the determination of their antimicrobial properties.

We considered it important to study both the structure of the coordination compound of 2-amino-3-[(2-amino-2-carboxyethyl)disulfanyl] propanoic acid dihydrotriiodide ([Cys(HI_3)$_2$]) and its antimicrobial activity. These data will provide us with information useful for further establishing the relationship between the structure and biological activity of this class of compounds. This paper presents a method for the synthesis of the coordinated compound [Cys(HI_3)$_2$] in an aqueous medium, its structure and antimicrobial activity.

2. Experimental section

2.1 Reagents and materials

The following materials were used in the work: glasses for 50; 100 ml, volumetric flask; for 100 ml, cylinders for 10; 25 ml (Duran, Czech Republic), filter paper “red ribbon, Russia”, Schott filter (Simax, Czech Republic). The reagents used for the present work were of analar grade obtained from commercial sources and used without further purifications. Lithium iodide Sigma-Aldrich (St. Louis, MO, USA, ≥ 99%), iodine Labpharm (JSC "Troitsky iodine plant" Russia, ≥ 98%), L-Cystine, (*R*, *R*)-3,3′-Dithiobis(2-amino propionic acid) from Sigma-Aldrich (St. Louis, MO, USA, ≥ 99%).

2.2 Instrumentation

Nicolet 6700 FTIR spectrophotometer was used to record the infrared spectra in the range 375-7500 cm^{-1} (Thermo scientific, USA). The electronic absorption spectra of the complexes in the range 190–1100 nm were obtained using a LAMBDA-35 UV-Vis spectrophotometer (PerkinElmer, USA). Melting points or decomposition temperatures (m.p./d.t.) were measured using Gallenkamp (variable heater) melting point apparatus. Thermal analysis (TG/DSC) was conducted on a STA 449 F1 Jupiter (NETZSCH, Germany) instrument in flowing N_2 with a heating rate of 10 ^0C min^{-1}. The X-ray diffraction analysis were investigated using an Enraf-Nonius CAD4 autodiffractometer (Netherlands) (graphite monochromator, Mo-Kα radiation, θ/2θ scan, CAD4 software). Elemental analysis of the [Cys(HI_3)$_2$] coordination compound was performed using energy-dispersive spectroscopy (EDS) equipped on SEM instrument (Quanta 3D 200i (FEITM (Netherlands).

2.3 Synthesis of [Cys(HI_3)$_2$] coordination compound

2.39 g (0.01 mol) of cystine and 10 mL of purified water (water purification system UltraClear TWF (SG Wasseraufbereitungund Regenerierstation GmbH, Germany))

were added to a 50 mL beaker. The mixture was heated in a water bath at 40 ℃ and stirred with a glass rod until the amino acid completely dissolved. The molar ratio of cystine:LiI:I_2 was 1:2:2. An excess of lithium iodide and iodine in order for the cystine to react completely. In a flask with a volume of 100 ml, equipped with a stopper, 3.20 g (0.02 mol) of lithium iodide, 5.06 g (0.02 mol) of iodine, ground into a fine powder with an agate pestle and mortar was added, as well as 20 ml of water. The mixture was stirred at room temperature (RT) until complete dissolution. The Lithium triiodide solution was added to the cystine solution. The resulting reaction mixture was capped and stirred at RT for 5 minutes. The resulting product was placed in a dark place at room temperature for 48 hours to establish equilibrium in the system. Then the solution of the complex was heated for 10 min on a water bath (+50 °C) and filtered under vacuum through a Schott filter into a crystallizer. The crystallizer with the complex solution was placed in a dark glass desiccator with a desiccant (anhydrous calcium chloride) at room temperature to evaporate most of the water. The precipitated crystals were separated under vacuum on a Schott filter, washed twice with a small amount of ethanol cooled to 0 °C. The crystals were additionally dried on a black tape ashless filter, weighed and placed in a glass stoppered flask and stored in a refrigerator. Yield is 9.50 g (95%) single crystals. The synthesis of [Cys(HI_3)$_2$] coordination compound is summarized in Fig. 1.

2.4 X-ray diffraction analysis

To carry out the diffraction experiment, a small crystal sample *A* in the form of a plate with a size of 0.15 × 0.18 × 0.21 mm was chosen. All diffraction measurements were carried out using Enraf-Nonius CAD4 auto diffractometer (Netherlands) (graphite monochromator, Mo-Kα radiation, θ/2θ scan, CAD4 software).[19]

Software CAD4 (Michel Fleck, 2008): 222–232) was used with default parameter settings if not indicated otherwise. Different methods determined the coordinates of heavy metal atoms: (i) direct methods; (ii) the Patterson function; (iii) superflip method. The coordinates of the missing atoms of light elements, as well as most of the hydrogen atoms coordinates, were determined from the difference Fourier syntheses. At the final stage, the temperature parameters of non-hydrogen atoms were specified in the anisotropic approximation, whereas the temperature parameters of hydrogen atoms were in the isotropic approximation.[20]

25 diffraction reflections were used to determine the unit cell parameters that determine the monoclinic syngony. The experimental conditions and primary crystallographic data are listed in Table 3. Based on the results of performed calculations, the chemical structure of the compound can be represented as $[C_6H_{14}N_2O_4S_2]^{+2}[I_3^{-1}]_2$. (2-amino-3-[(2-amino-2-carboxyethyl) disulfanyl] propanoic acid dihydrogen triiodide). Interatomic distances and valent angles in the crystal structure are given in Table 4.

2.5 Antimicrobial activity two-fold serial dilution assay

The antimicrobial activity of the [Cys(HI_3)$_2$] was studied using the two-fold serial dilution method in a liquid nutrient medium,[15] Performance Standards for Antimicrobial Susceptibility Testing, 33rd Edition, CLSI, March 3, 2023].

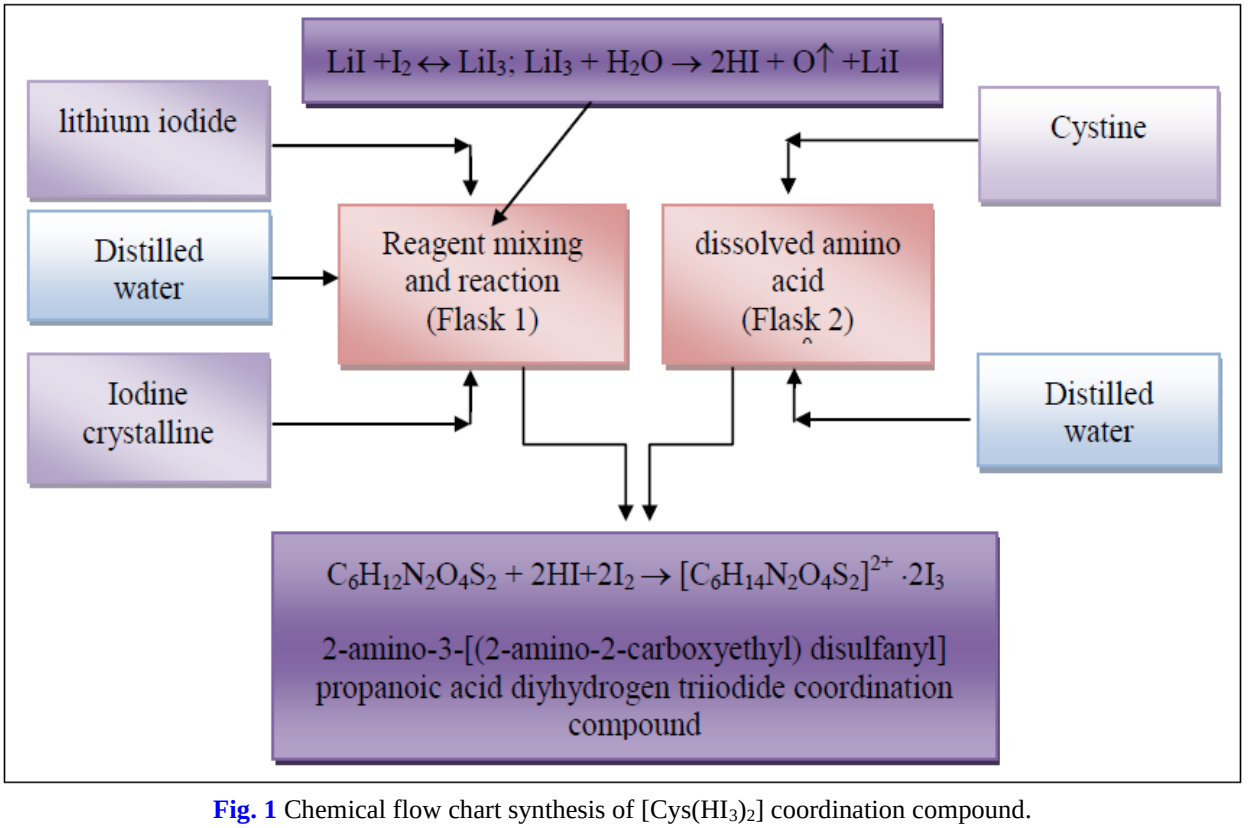

Fig. 1 Chemical flow chart synthesis of [Cys(HI_3)$_2$] coordination compound.

Test strains used in the study were obtained from the American Type Culture Collection (ATCC). The susceptible, resistant, and one clinical test strains were used in the experiment: Staphylococcus aureus ATCC-BAA-39, Escherichia coli ATCC 8739, Escherichia coli ATCC-BAA-196, Escherichia coli ATCC-BAA-2523, Pseudomonas aeruginosa ATCC 9027, Pseudomonas aeruginosa TA2. The selection criteria for strains were based primarily on the medical importance of the microorganism and its belonging to WHO priority strains. Two groups of strains were formed. The first group included 3 strains with multidrug resistance (WHO-prioritized drug-resistant strains). So, the E. coli ATCC BAA-196 is a multidrug-resistant strain, producing TEM-10 extended-spectrum β-lactamase (ESBL). S.aureus ATCC BAA-39 – is an MRSA strain (SCCmec: Type III), also resistant to cefuroxime, erythromycin, clindamycin, gentamycin, oxacillin, tetracycline, tobramycin, cefaclor, and penicillin. A.baumannii ATCC BAA-1790 is resistant to cefazolin, cefepime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, doripenem, imipenem, levofloxacin, meropenem, piperacillin, piperacillin-tazobactam, ticarcillin. The second group included susceptible - E.coli ATCC 8739, P.aeruginosa ATCC 9027 and resistant - E.coli ATCC BAA-196 (WHO-prioritized multidrug-resistant), P.aeruginosa TA2 (WHO-prioritised clinical multidrug resistant) bacteria species to study the difference between MBC value against antibiotic-resistant and susceptible strains.

The *in vitro* antimicrobial properties of the complex were determined according to[15] and with modification.
The bacterial strains grown on nutrient agar at 37±1 °C for 18 h were suspended in a saline solution (0.9 %, w/v) NaCl and adjusted to 0.5 MacFarland standard ($1.5x10^8$ CFU/ml) turbidity. To achieve the final concentration of the inocula ($1,5x10^6$ CFU/ml), these suspensions were diluted 100 times in saline.

The $[Cys(HI_3)_2]$ coordination compound was suspended in distilled water. The concentration of the basic solution was 4000 µg/mL. 0.5 mL of Mueller-Hinton broth was added in the wells of a 48-well plate. 0.5 mL of the $[Cys(HI_3)_2]$ solution was added in the first well of the row, and a 1:1 dilution was obtained. Then, from the first well with the 1:1 dilution, 0.5 mL were stirred and transferred to the second well of the row, diluted two times (1:2 dilution). In the same way, twofold serial dilutions up to 1:8192 (final dose in the range of 0.1-2000 µg/mL) were prepared. Each well was subsequently inoculated with 100 µL of an overnight culture of the corresponding strain. In each row of dilutions, two controls were set: control of the medium sterility and control of test strain growth.

A solvent, distilled water, was used as a negative control. The comparison drug (positive control) was a "Betadine" commercial iodine-containing (povidone-iodine) drug. The samples were incubated in an incubator for 18-24 hours at (37±1) °C. After the incubation, seeding was carried out on Petri dishes to determine living cells. After seeding, the Petri dishes were placed in an incubator for 18-24 hours at (37±1) °C.

The results were considered by the presence of visible growth of microorganisms on the surface of a solid nutrient medium. The minimum bactericidal concentration (MBC) was considered the highest concentration in which there was no growth of microorganisms. All experiments were conducted in three repetitions.

The modification of the method was proposed to identify some limitations when iodine-containing substances were tested on a standard nutrient media containing polypeptides, protein fragments and amino acids (casein hydrolyzate). It is known that iodine forms halogen bonds with amino acids,[21] which may decrease its biological activity. So, the testing of antimicrobial activity in saline was carried out. The exposition time for bacteria with the test compound took 30 minutes, after which they were cultured on Muller-Hinton agar medium and incubated for 18-24 hours at 37±1 °C. The minimum bactericidal concentration (MBC) was considered as described above.

3. Results and discussion

3.1 Physico-chemical analysis $[Cys(HI_3)_2]$ coordination compound

The colors, percentage yields and melting points (M.P) or temperature of decomposition (d) of the coordination compounds are presented in Table 1. The complexes showed dark brown colors. $[Cys(HI_3)_2]$ coordination compound did not dissolve in most of the organic solvents (chloroform, cyclohexane, benzene, o-xylene) but was readily soluble in water. The solubility of $[Cys(HI_3)_2]$ coordination compound in water was determined by the Flask method (to determine values above 0.01 g/L), according to the OECD guideline for the testing of chemicals (Water Solubility). The results are obtained in Table 1.

Table 1. Physico-chemical properties of the synthesized $[Cys(HI_3)_2]$ coordination compound.

No	Name of indicators	Results
1	pH	5.40
2	Solubility in water, g/100 ml	20g (at 25 °C)
3	Melting temperature (°C)	177.0-179.0
4	Colour	Dark brown
5	Empirical formula	$[C_6H_{14}N_2O_4S_2]^{2+}[I_3^{1-}]_2$
6	Iodine content, (%)	43.24
7	Iodide content, (%)	20.50
8	Final mass, g	9.50
9	Yield (%)	95

The stability of the $Cys(HI_3)_2]$ coordination compound largely depends on the chemical composition and storage conditions.[21] Studies of the stability of the $Cys(HI_3)_2]$ coordination compound were carried out on three laboratory series in accordance with the requirements of the regulatory

documents of the European pharmacopoeia and ICH, according to the following quality indicators: description, solubility, melting-decomposition temperature, pH, weight loss on drying, microbiological purity and quantitative determination of iodine and iodide ions. Over the studied storage period (0, 3, 6, 9, 12 months), the $Cys(HI_3)_2]$ coordination compound showed a constant composition and no significant changes in the quality indicators of the coordination compound (Table 2).

3.2 Crystal structure of $[Cys(HI_3)_2]$ coordination compound

The structures of the complexes (Fig. 2) formed in the aqueous solution of the system $[Cys(HI_3)_2]$ are calculated using the DFT / B3PW91.[22] approximations Calculations were made using the program GAUSSIAN09.[23]

The structure of the coordination compound $[Cys(HI_3)_2]$ is shown in Fig. 3. The independent part of the unit cell contains one cystine molecule and two I_3^{-1} polyanions. All nitrogen atoms of cystine molecules are quaternary, and the positive charge on them is compensated by polyanions I_3, which are linked to amino acids via hydrogen atoms in a 3D structure.

Selected bond distances and angles, with their standard deviations, are given in Table 4. The bond length in the iodine molecule (I1-I2, Table 4) is 2.9705 Å, while the bond length of ions I_2^- and I_3^- attached to the molecule is as follows: I2-I3 - 2.8863 Å I4-I5 - 2.8308 Å and I5-I6 - 3.1050 Å. In the polyanion I_3^- a rare case is observed when two iodide anions polarize the electrons of the iodine molecule with the formation of forming a partially positive charge on each atom.

Table 2. Results of studying the stability of $Cys(HI_3)_2]$ coordination compound at a temperature of 25 ± 2 °C and a humidity of 60 ± 5%.

Index quality	Storage interval, months				
	0	3	6	9	12
Description	dark brown	dark brown	dark brown	dark brown	dark brown
Solubility in water, g/100ml	20.0	20.0	20.0	20.0	20.0
Melting point, °C	177.0	176,8	176,5	176,9	177.0
pH	5,40	5,38	5,42	5,38	5,39
Weight loss on drying, %	3,50	3,52	3,55	3,51	3,55
Iodine content, %	43,24	43,25	43,23	43,25	43,24
Iodide content, %	20,50	20,51	20,50	20,53	20,53

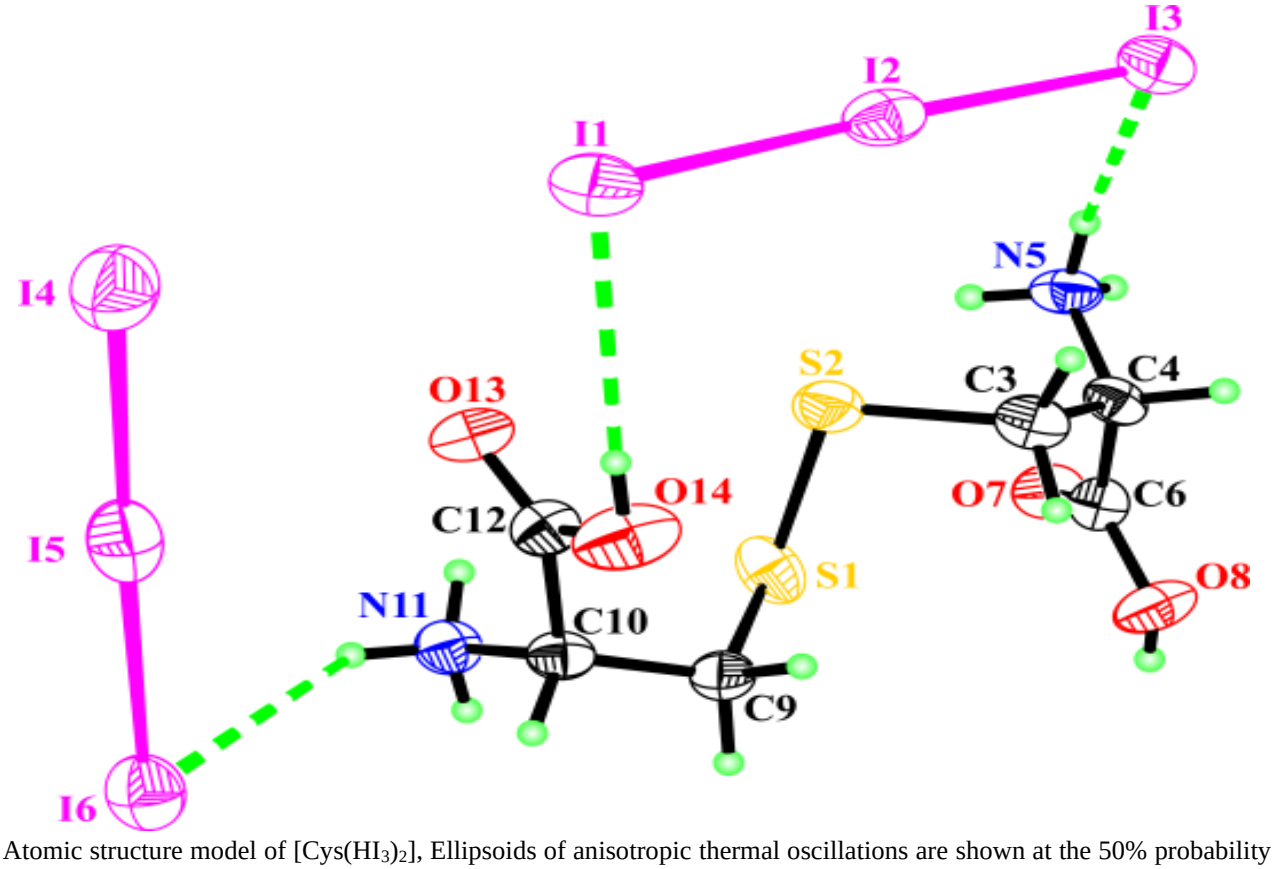

Fig. 2 Atomic structure model of $[Cys(HI_3)_2]$, Ellipsoids of anisotropic thermal oscillations are shown at the 50% probability level. Black ellipsoids represent carbon atoms, blue - nitrogen, red - oxygen, pink – iodine, and yellow – sulfur.

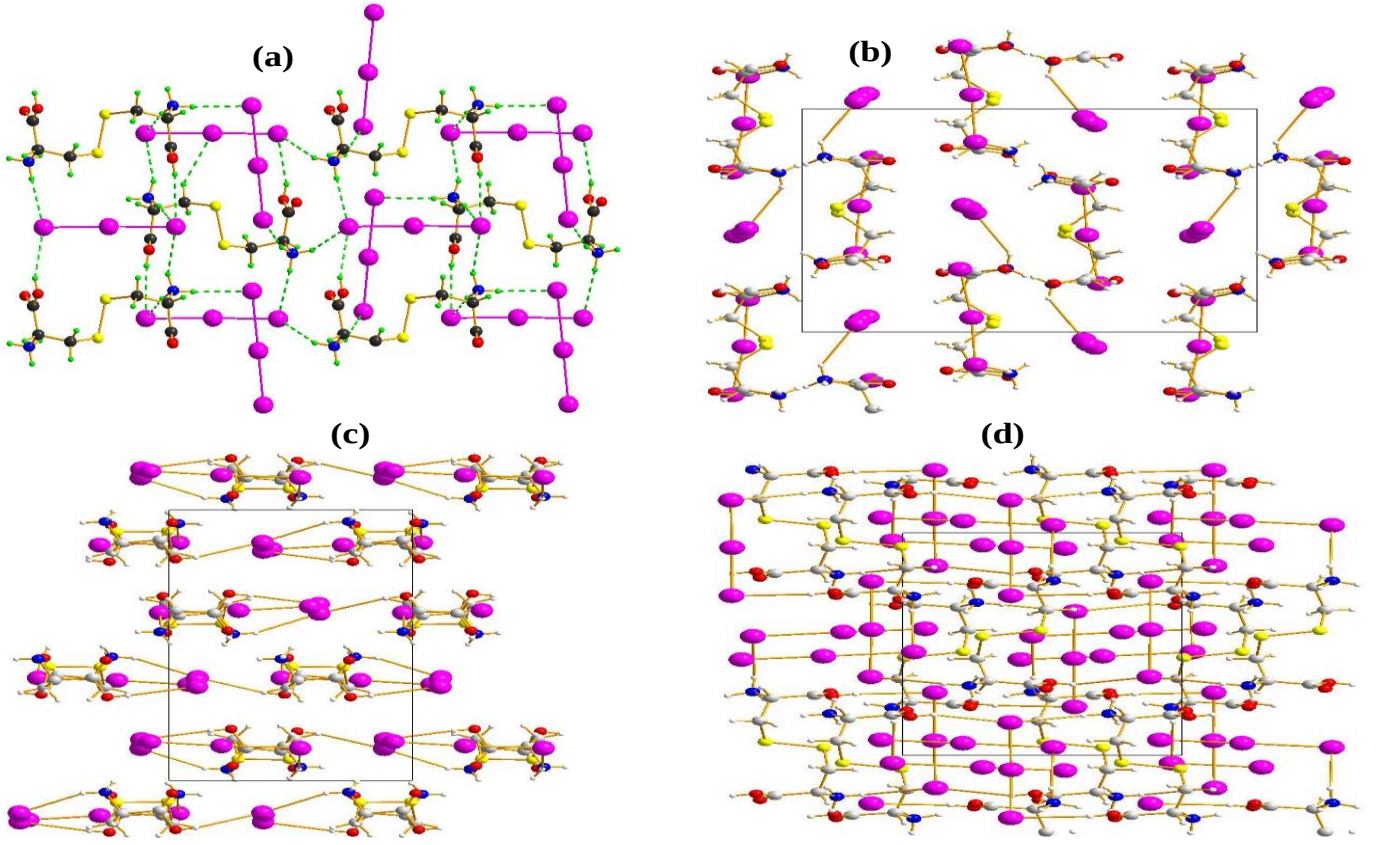

Fig. 3 Perspective view of the crystal structure of $[Cys(HI_3)_2]$ coordination compound. Projection of the structure onto the plane a-100, b-050 c-010, d-001, Black ellipsoids represent carbon atoms, blue - nitrogen, red - oxygen, pink – iodine, and yellow – sulfur.

Table 3. Crystallographic data and structure refinement of $[Cys(HI_3)_2]$.

Crystallographic data for $[Cys(HI_3)_2]$ coordination compound	
Formula	$[C_6H_{14}N_2O_4S_2]^{+2}[I_3^{-1}]_2$
Molecular weight	1003.71
Syngony; Space group	orthorhombic $P2_12_12_1$
Lattice parameters a, b, c [Å]	9.5739(19) 13.558(3) 16.405(3)
alpha, beta, gamma [Å]	90 90 90
V [Å]^3 ; Z	2129.4(7); 4
D(calc)[g/cm^3]; F(000)	3.131; 1784
Mu(MoKα) [mm^{-1}]	8.959
Crystal sizes [mm]	0.15 × 0.18 × 0.21
Temperature (K); Radiation+ [Å]	200; MoKα; λ=0.71073
$\theta_{min};\theta_{max}$ [Deg]	1.9, 30.0
Measuring area	0: 13 ; 0: 19 ; -23: 23
Number of reflexes., независимых, R(int)	6944, 6186, 0.015
Observed data [I > 2.0 sigma(I)]	5708
Number of reflexes, Number of parameters	6186, 186
R, wR^2, S	0.0281, 0.0645, 1.11
Flack x	0.02(2)
w = 1/[\s^2^(Fo^2^)+(0.0374P)^2^+0.2440P], where P=(Fo^2^+2Fc^2^)/3	
Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Å ^{3}]	-0.58, 1.02

Table 4. Selected bond distances and angles in $[Cys(HI_3)_2]$.

Atoms	Distance, Å	Atoms	Angle degree
I1-I2	2.9705(8)	I1-I2-I3	174.41(2)
I2-I3	2.8863(7)	I4-I5-I6	177.43(2)
I4-I5	2.8308(8)	S2-S1-C9	102.25(14)
I5-I6	3.1050(9)	S1-S2-C3	103.35(14)
S1-C9	1.813(5)	S2-C3-C4	114.4(3)
S1-S2	2.0410(17)	N5-C4-C3	112.7(3)
O13-C12	1.196(5)	C3-C4-C6	113.4(3)
O14-C12	1.321(5)	N5-C4-C6	106.8(3)
N5-C4	1.478(5)	O7-C6-O8	125.6(4)
C3-C4	1.517(6)	N11-C10-C9	111.6(3)
C4-C6	1.521(5)	C9-C10-C12	112.6(3)
S2-C3	1.812(5)	N11-C10-C12	107.3(3)
O7-C6	1.198(6)	O7-C6-C4	123.7(4)
O8-C6	1.330(6)	S1-C9-C10	114.9(3)
C9-C10	1.519(6)	O13-C12-O14	126.0(4)
C10-C12	1.515(5)	O14-C12-C10	110.1(3)
O8-H8	0.8200	O13-C12-C10	123.9(3)
N11-C10	1.489(5)	O8-C6-C4	110.6(4)
O14-H14	0.8200		

3.3 Electronic spectra of $[Cys(HI_3)_2]$ coordination compound

Spectral characteristics of the L-cystine ligand and coordination compound are presented in Table 5. The absorption band at 196.38 nm (2.57 A) from Fig. 4

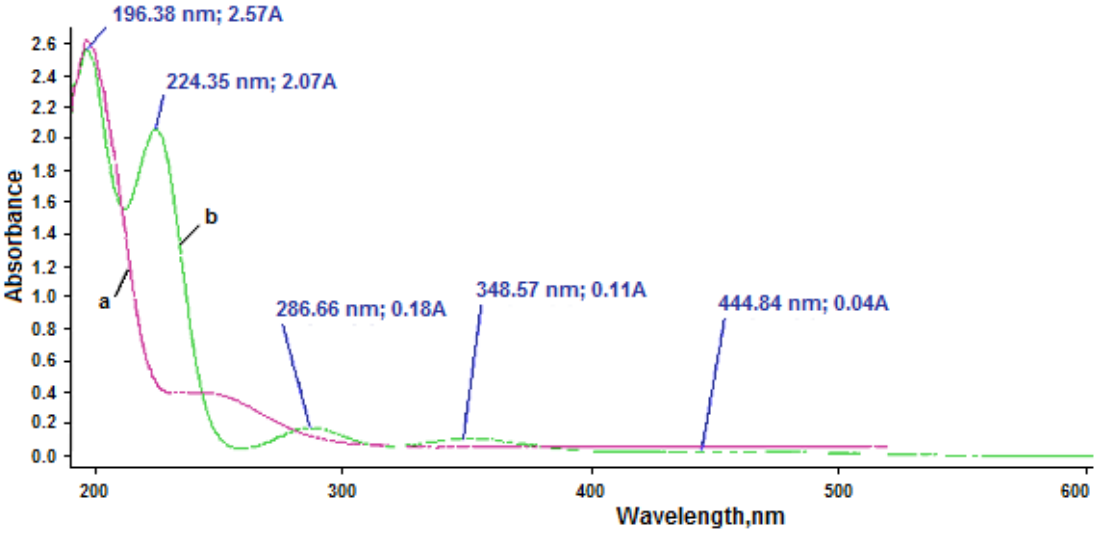

Fig. 4 UV spectrum of (a) cystine and (b) [Cys(HI$_3$)$_2$] coordination compound.

Table 5. Spectral characteristics of the cystine and synthesized [Cys(HI$_3$)$_2$] coordination compound.

Substance (components)	λ_{max}, nm	A_{max}	Attribution
L-Cystine	196.38	2.57	π-π* transition C=O, transitions n-σ* *и* n-π* в NH_2 и NH_2→C=O;
			n-π* transition C=O
	243.25	0.40	
$[C_6H_{14}N_2O_4S_2]^{+2}[I_3^{-1}]_2$.	196,38	2,57	π-π* transition C=O, transitions n-σ* *и* n-π* в NH_2 и NH_2→C=O;
			n-π* transition C=O
	224,35	2,07	charge transfer I^- → σ* H_2O, C-OH
	286,66	0,18	charge transfer n_b-σ* C=O→I^+-I^-
			charge transfer n_b-σ* NH_2→ I^+-I^-
			charge transfer I_n^-→ σ* H_2O, C-OH

corresponds to cystine in water and can be attributed to (π→π*) transition of (C=O) in the biguanide group.[24] On the contrary, [Cys(HI$_3$)$_2$] coordination compound showed three major absorption bands at 196.38 (2.57 A), 224.35 (2.07 A), and 286,66 nm (0.18 A) assigned as the $n \rightarrow \sigma^*$, $n \rightarrow \pi^*$, and $\pi^* \rightarrow \pi^*$ transitions respective of the major chromophores, NH_2 and COO^- (Table 5), present in the ligand molecules. These results confirm that the coordination compound [Cys(HI$_3$)$_2$] consists of an iodine - L-Cysteine complex.

Thus, the results of UV spectrum analysis and their comparison with the literature data allow us to infer the complexity of the interaction mechanism and the nature of bonds in the studied compounds. Overall, we determined that components in substances can form various types of hydrogen bonds, both intra- and intermolecular electronic transitions occur, and new charge-transfer bonds appear, in which molecular iodine, iodide or polyiodide anions take part. Furthermore, the formation of two iodine-containing complexes with charge transfer were formed was established: $NH_2 \rightarrow I^+$ -I^-; C = O → I^+ -I^-.

As a result of analysis by UV-Vis spectrophotometry, the spectral characteristics of the studied solutions of the coordination compound [Cys(HI$_3$)$_2$] in various media were determined (Fig. 6); a neutral aqueous solution has absorption bands with maxima at 196.38 nm (optical density 2.57), 224.35 nm (optical density 2.07), as well as intense bands in the range from 260 - 400 nm. In an acidic solution, absorption bands with maxima at 197.74 nm (optical density 2.64), 224.35 nm (optical density 2.27), and intense bands range from 260 to 400 nm. An alkaline solution does not have absorption bands in the 260–400 nm range, and in the wavelength range from 190 to 260 nm, strong signal

Table 6. Generalized results of determining the UV-Visible spectra of the coordination compound [Cys(HI$_3$)$_2$] in various media.

No	Neutral environment		Acidic environment, 0,1 H HCl		Alkaline environment , 0,1M NaOH	
	λ, nm	A	λ, nm	A	λ, nm	A
1	196.38	2.57	197.74	2.64	-	-
2	224.35	2.07	224.10	2.27	224.13	2.21
3	286,66	0.18	286.76	0.21	-	-

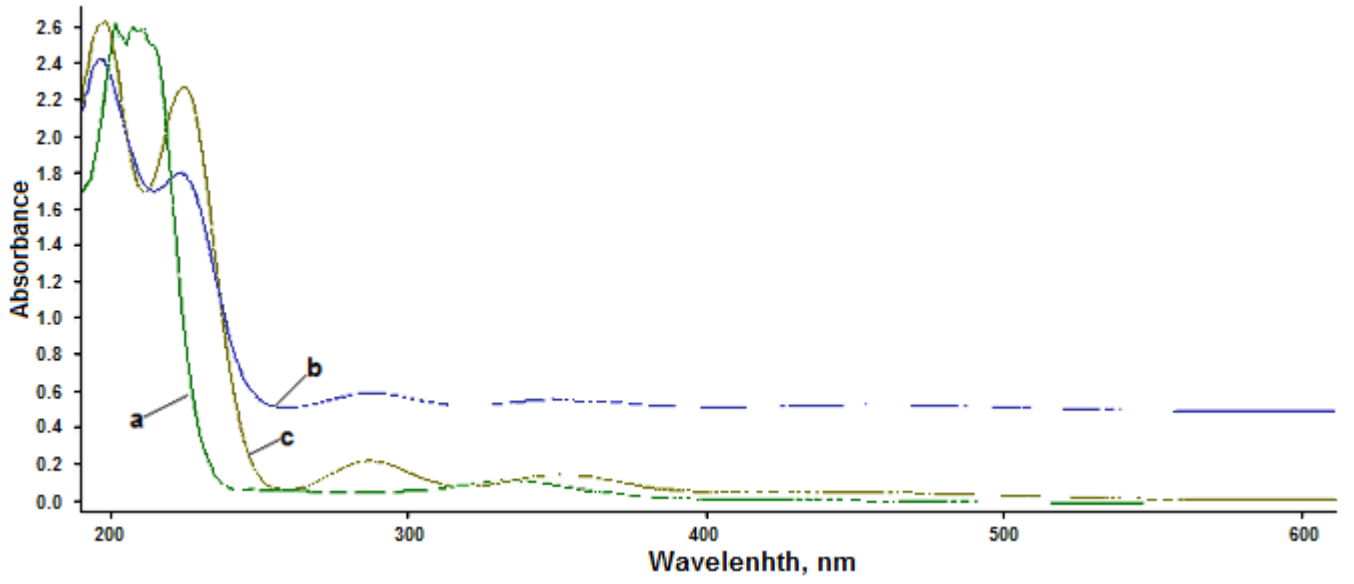

Fig. 5 UV spectrum of the [Cys(HI$_3$)$_2$] coordination compound in various media, (a- alkaline environment, b- acidic, c- neutral).

reabsorption is observed (Table 6). Thus, this study showed that neutral and acidic environments do not affect the coordination compound [Cys(HI$_3$)$_2$], but alkaline environments have a significant effect. It can be concluded that the coordination compound [Cys(HI$_3$)$_2$] is stable in an acidic environment but not stable in an alkaline environment.

3.4 Infrared spectra of [Cys(HI$_3$)$_2$] coordination compound

Vibrational IR spectra of the synthesized compound and cystine are shown in Fig. 6.[25,26] Comparative study of the IR spectrum of the coordination compound [Cys(HI$_3$)$_2$] revealed that the test substance is a polyiodide cystine complex, formed by hydrogen bonds. The 1620.6 band shift by 13 cm^{-1} (a), which is characteristic of the deformation vibrations of quaternary amino groups, possibly suggests that amino acids bind to the iodine anion via hydrogen bonds.

The central ion in the system is represented by a large, negatively charged polyiodide anion. Cystine can be coordinated around polyiodide through the formation of by forming hydrogen bonds with the quaternary hydrogen of the amino group. This assumption is based on the disappearance of band 2096.0 (a), characteristic of the stretching vibrations of the quaternary amino group, and the 1481 band shift by 15 cm^{-1} towards the long-wavelength region of the spectrum in the complex, characteristic of bending vibrations of the quaternary amino group.

The disappearance of bands 1088.8 and 1040, characteristic of stretching vibrations of –CN groups in the complex, also indicates that the amino acids nitrogen atom

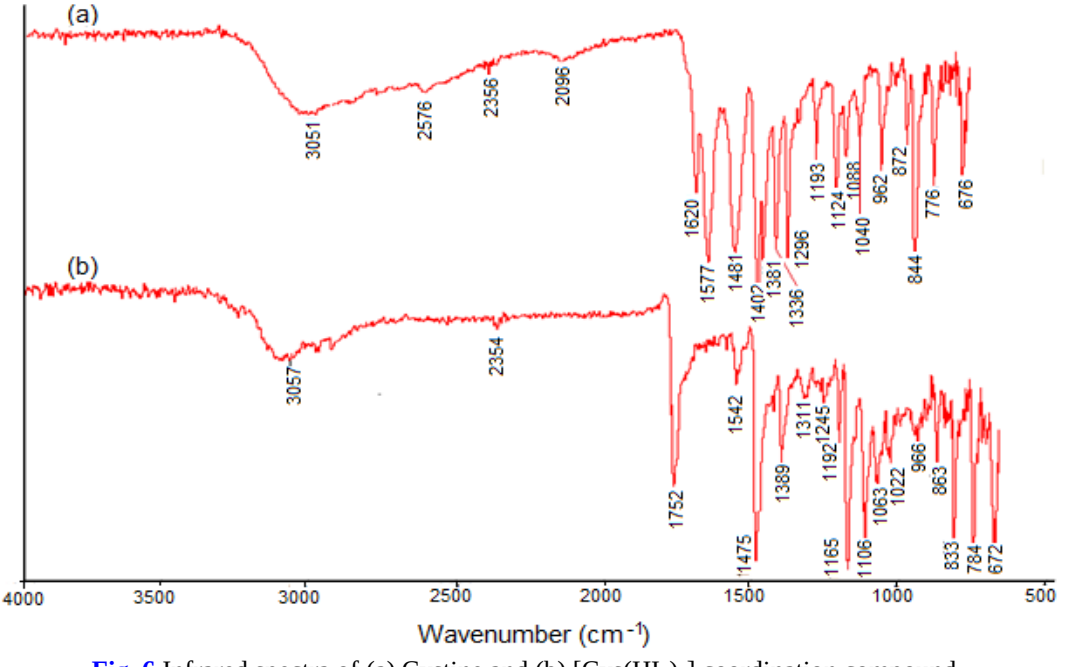

Fig. 6 Infrared spectra of (a) Cystine and (b) [Cys(HI$_3$)$_2$] coordination compound.

interacts with iodine anions via hydrogen bonds.

3.5 EDX spectra of [Cys(HI$_3$)$_2$] coordination compound

EDX can be used to determine which chemical elements present in the sample, and can be used to estimate their relative abundance. The data generated by EDX analysis consist of spectra showing peaks corresponding to the elements making up the true composition of the samples being analyzed. Elemental mapping of a sample and image analysis are also possible as showed in Fig. 7. EDX results of [Cys(HI$_3$)$_2$] coordination compound showed that, the Weight percentage of Carbon, Nitrogen, Oxygen, sulfur and iodine are 7.11, 2.68, 6.27, 6.23 and 74.78 % respectively. (Table 7). The Weight percentage of the component elements were compared in all the point analyzed and the results were found to be in agreement with each other indicating the uniform distribution of the component elements in the sample compound. Furthermore, the results are in conformity with the proposed structure of the complex.

3.6 Thermal analysis by TGA/DSC

Thermal analysis of [Cys(HI$_3$)$_2$] is depicted in Fig. 8. The peak at 179.1 °C represents the melting point of the complex. This value matches the one measured by the Gallenkamp (variable heater) melting point apparatus (Table 1). Fig. 8, as well as Table 8, suggest that the thermal decomposition of the coordination compound takes place in three stages. In the first stage, that which is between 28 and 140 °C, residual water molecules are removed in a single step with a mass loss of 3.71%. In the second stage (140 to 220 °C) corresponds to the vaporization of iodine with a mass loss of 49.68%. The melting point pristine of cystine is known to be 238.7 °C.[27] On that account, the decomposition of cystine probably occurs in the third stage (220 to 260 °C), where DSC curve peaks at 221.5, and 238.7 °C. In the last stage (260 to 340 °C) corresponds to the decomposition of Hydroiodic acid with a mass loss of 23.78 %. Overall, 100 % by mass was lost in TGA/DSC analysis. It can be concluded that synthesized [Cys(HI$_3$)$_2$] is chemical pure and thermostable.

Table 7. Energy Dispersive X-ray (EDX).

Element	Weight % (theory)	Weight % (found)	Line type
C-Ka	7.17	7.11	K Series
O-Ka	6.39	6.27	K Series
N-Ka	2.80	2.68	K Series
S-Ka	6.39	6.23	K Series
I-La	75.86	74.78	L Series
H	1.39	-	-
Totals	100	97.03	

Table 8. Thermal analysis of coordination compound [Cys(HI$_3$)$_2$] by TGA/DSC method.

S/N	Name of the complex	TGA range (°C)	Stage	Mass loss (%)	DSC (°C)	Process	Evolved moiety
1	$[C_6H_{14}N_2O_4S_2]^{+2}[I_3^{-1}]_2$.	28-140	I	3.71	75.1	Endo	Dehydration of H_2O
		140-220	II	49.68	176.5	Endo	Vaporization of iodine molecule
		220-260	III	22.83	238.7	Endo	Removal of Cystine
		260-340	IV	23.78	319.3	Endo	Removal of HI

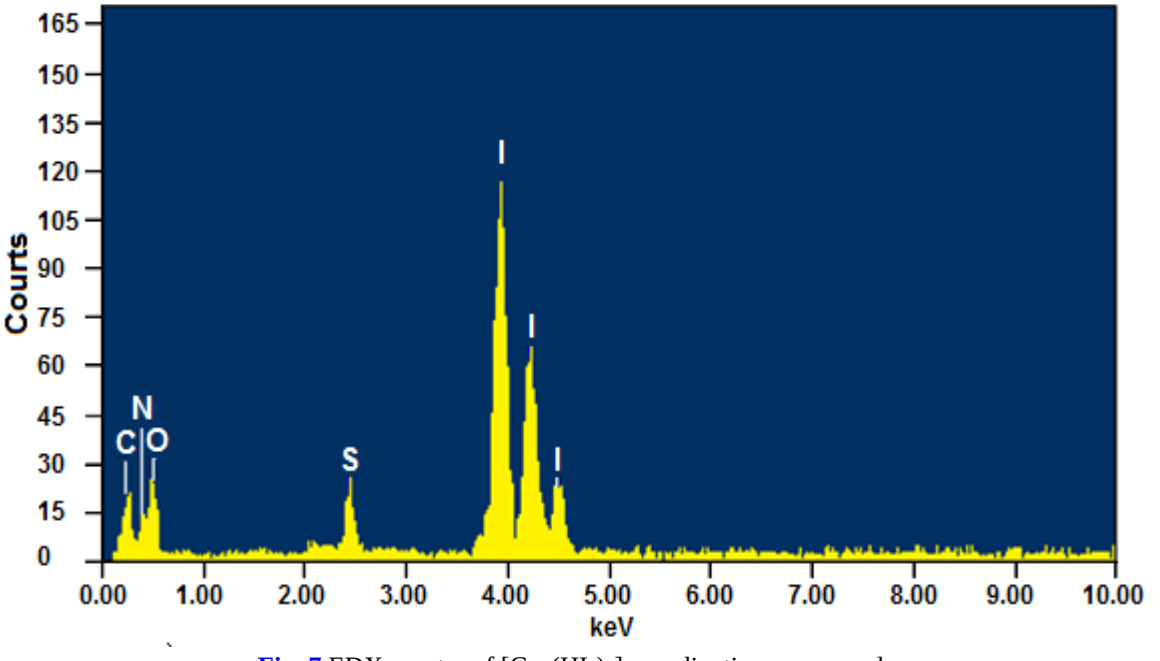

Fig. 7 EDX spectra of [Cys(HI$_3$)$_2$] coordination compound.

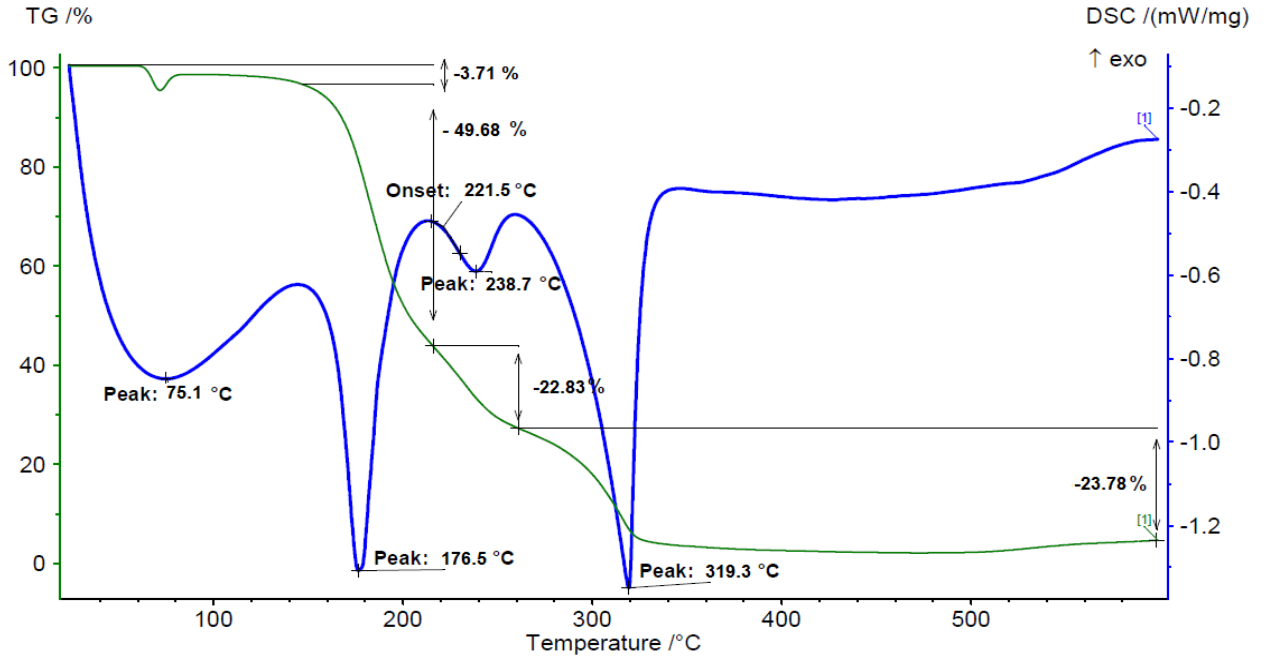

Fig. 8 TGA/DSC analysis curve of coordination compound [Cys(HI$_3$)$_2$].

3.7 Antimicrobial activity of [Cys(HI$_3$)$_2$] coordination compound

The [Cys(HI$_3$)$_2$] coordination compound was tested on 5 WHO priority multidrug-resistant bacterial strains and 2 susceptible strains. The results of the screening study of the antimicrobial activity in saline/MHB of the [Cys(HI$_3$)$_2$] compound in comparison to the drug "Betadine" are shown in Figs. 9 and 10.

As shown in Fig. 9, [Cys(HI$_3$)$_2$] compound displayed higher antibacterial activity than the reference drug. The [Cys(HI$_3$)$_2$] coordination compound had MBC between 0.1 and 0.2 μg/mL, whereas MBC values of Betadine were between 0.29 – 0.6 μg/mL in the modified test, respectively. Concerning the E. coli ATCC BAA-196 resistant strain, MBC values of "Betadine" are 2.9 times higher than the MBC of the claimed complex. For E. coli ATCC 8739 and P. aeruginosa TA2 cultures MBC of "Betadine" were increased by 1.5 times, while for the strain P. aeruginosa 9027 this concentration was 5.7 times higher compared to the MBC of the claimed compound. The lowest MBC value of 0.1 μg/mL was obtained with [Cys(HI$_3$)$_2$] against the strain of sensitive strain P.aeruginosa ATCC 9027 and multidrug-resistant strain E.coli ATCC BAA-196. [Cys(HI$_3$)$_2$] demonstrated equal MBC 0.2 μg/ml for the tested sensitive E.coli ATCC 8739 and multidrug-resistant P.aeruginosa TA2 pathogens. Based on these data, it can be concluded that the [Cys(HI$_3$)$_2$] compound is equally effective against both antibiotic-sensitive and antibiotic-resistant bacteria.

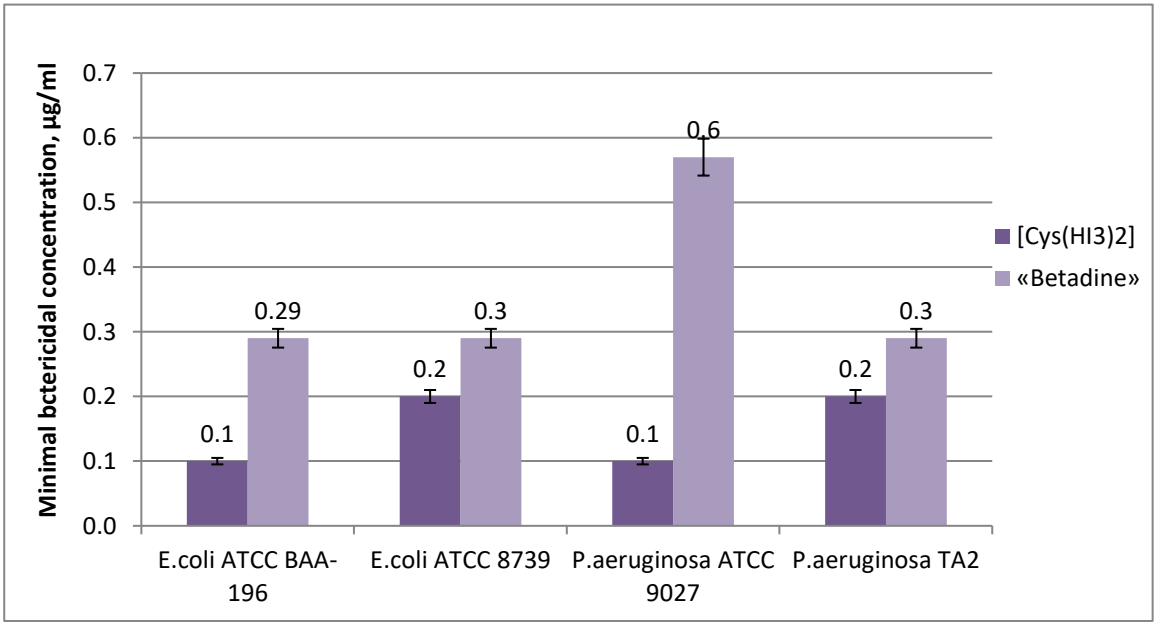

Fig. 9 Antimicrobial activity of [Cys(HI$_3$)$_2$] and the "Betadine" drug (saline, 30´ exposition).

The antibacterial activity of the [Cys(HI$_3$)$_2$] is depicted in Fig. 10. The results indicated that the compound showed antibacterial activities at variable degrees against MDR bacteria, with MBCs values varying from 100 to 250 μg/mL. The [Cys(HI$_3$)$_2$] displayed the highest activity against gram-positive S.aureus ATCC BAA-39 (MRSA) with MBC value of 102.5 μg/mL . Moreover, the [Cys(HI$_3$)$_2$] showed high activity against resistant gram negatives E.coli ATCC BAA-196 and A.baumannii ATCC BAA-1790 with a MIC value of 250 μg/mL. The reference item – Betadine, shows lower antibacterial activity against the bacteria tested, its inhibitory effect being noted against E.coli ATCC BAA-196, A.baumannii ATCC BAA-1790 and S.aureus ATCC BAA-39, known for their multi-resistance to drugs, in concentrations of 328.3 μg/mL and 164.1 μg/mL, respectively.

The present study showed that [Cys(HI$_3$)$_2$] semiorganic iodine-containing compound possesses promising antimicrobial activities.

Iodine was first discovered by Bernard Courtois, and for more than 150 years, its antibacterial properties have been used to treat or prevent infection in wounds. A solution of iodide was first used to cure wounds in 1839.[28] In the 1950s, a water-soluble molecule called polyvinylpyrrolidone-iodine (PVP-I or povidone-iodine complex) was developed by combining molecular iodine and polyvinylpyrrolidone.[29] Povidon is an iodophore with a powerful broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria, including antibiotic-resistant and antiseptic-resistant strains,[30,31] protozoa and fungi. When released from the complex (PVP-I), free iodine (I_2) penetrates the cell wall of microorganisms quickly, and the lethal effects are believed to result from disruption of protein and nucleic acid structure and synthesis. Iodine is expected to block essential bacterial cellular functions and structures and oxidize nucleotides, lipids, or amino acids in bacterial cell membranes, while the exact mechanism of action is still not entirely understood. Additionally, free iodine disrupts the function of the cytosolic enzymes involved in the respiratory chain, causing them to become denatured and deactivated.[32,33]

Our previous studies of the transcriptomics analysis of the effects of iodine containing complexes and drug FS-1 have made a ground for further studies by identifying the biological systems and individual genes affected by the complexes.

The treatment with iodine containing compounds and drug FS-1 of the two model microorganisms Gram-positive S. aureus and Gram-negative E. coli lead to changes in regulation of the bacteria central metabolism such as the glycolytic pathways, TCA, carbohydrate, and amino acid metabolism, aerobic and anaerobic respiration. Also, it caused the osmotic and oxidative stresses in the bacterial cells.

A significant activation of heavy metal efflux pumps, which may imply a degradation of cell wall barriers and an increase in cellular membrane permeability, was a common reaction of both of these model microorganisms to the treatment with compounds.

The genes involved in oxidation-reduction balancing were also strongly affected in both bacteria that suggested oxidative stress. The same results were demonstrated in the previously published studies on the effect of FS-1 on bacterial cells (S. aureus BAA-39 and E. coli BAA-196) during a long-term cultivation with the sublethal concentrations of the drug.

All of these data indicate that the bacterial cell wall was the primary target of the iodine released by the complexes. The bacterial cell wall disintegrated as a result of the iodine's

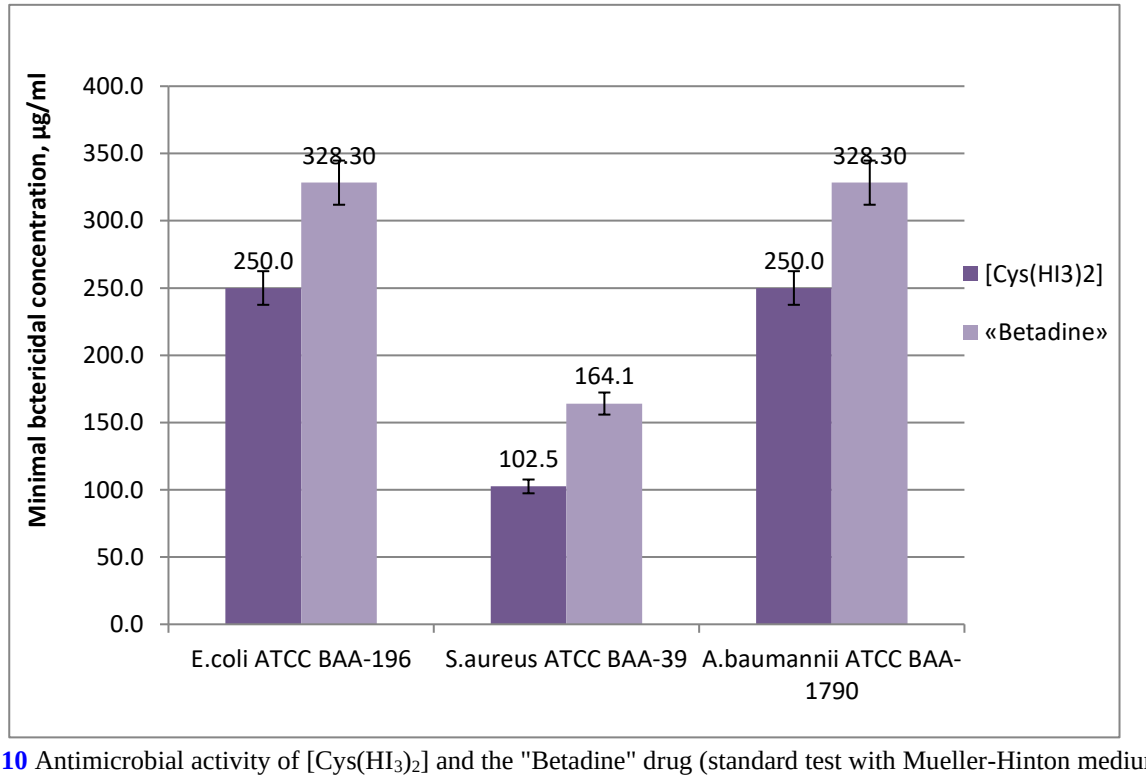

Fig. 10 Antimicrobial activity of [Cys(HI$_3$)$_2$] and the "Betadine" drug (standard test with Mueller-Hinton medium).

oxidative capability, which increased the penetrability of the damaged cells for metal ions and other toxic compounds, such as antibiotics.

Also it was found that the effect of iodine-containing complexes and drug FS-1 on bacterial metabolism varied significantly depending on the moiety of organic molecules of the compounds. It may be explained by a different distribution of iodine in the forms of iodide ion, molecular iodine, and triiodide in these complexes.[34-40]

The synthesized coordination compound [Cys(HI_3)$_2$] is a semi-organic compound containing the amino acid cystine. There are reports that in comparison to solutions of molecular iodine and potassium iodide, complexes of iodine with organic compounds-where iodine or iodide ions are bound by coordination bonds with organic macromolecules - are more stable and less toxic.[34] Recent research has produced encouraging findings about the effectiveness of the iodine-containing compound FS-1 against bacteria that are resistant to antibiotics. It was proposed that the organic component of the complex, specifically the amino acids, may influence the antibacterial action of iodine-containing complexes.[41]

Moreover, there are reports that the amino acid cysteine, a monomer of the cystine dimer, which is part of coordination compounds, also has antimicrobial activity. Recent research[42] shows the enhancing activity of cysteine with some bactericidal antibiotics, where cysteine effectively potentiates multiple bactericidal antibiotics, killing in the fight against various Gram-negative bacterial persisters through stimulating bacterial respiration and triggering the production of ROS, and converting persister cells to metabolically active cells.

The research[43] describes the proposed mechanism of action of various cysteine monomers. Thus, among the four (*Escherichia coli, Salmonella enteritis, Listeria monocytogenes, Staphylococcus aureus*) bacteria, L-Cys exhibited preferred antibacterial activity against *S. aureus*. At the same time D-Cys showed stronger antibacterial activity against other three (*Escherichia coli, Salmonella enteritis, Listeria monocytogenes*) bacteria compared with L-Cys. It was shown by studying the cell structure of *E. coli* that D/L-Cys might compromise the integrity of the cell membrane, leading to the leakage of internal contents and cell death.

Taking into account the structure of the coordination compound and the ability of the organic component to moderate the antimicrobial activity of iodine, the proposed mechanism of action of this compound is the synergistic effect of cystine and iodine, where cysteine separately affects the metabolism and permeability of the bacterial membrane, followed by the action of iodine on the amino acid and protein components of the bacterial cell.

Considering the high antimicrobial activity of the compound, as well as the clinical significance (resistance) of strains against which it is effective, the [Cys(HI_3)$_2$] is promising in the development of drugs based on it and requires additional studies, such as establishing the mechanism of action and antimicrobial activity against more a wide range of bacteria.

4. Conclusion

A new coordination compound was first synthesized from system Cystine:LiI:iodine and structurally characterized as 2-amino-3-[(2-amino-2-carboxyethyl) disulfanyl] propanoic acid dihydrogen triiodide. The molecular structure of the new coordination compound was determined using the X-ray single-crystal technique. The physicochemical properties of the complex were studied. Thermal decomposition behavior of 2-amino-3-[(2-amino-2-carboxyethyl) disulfanyl] propanoic acid dihydrogen triiodide was investigated. The antimicrobial activity of the 2-amino-3-[(2-amino-2-carboxyethyl) disulfanyl] propanoic acid dihydrogen triiodide was also studied. The coordination compound exhibited antimicrobial activity against sensitive and multi-resistant strains of microorganisms. Due to their high antimicrobial efficiency, these complexes can be promising developing in the development of new antibacterial substances against bacteria resistant to antibiotic strains.

Acknowledgments

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Conflict of Interest

There is no conflict of interest.

Supporting Information

Not applicable.

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