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SELECTIVITY, SYNTHESIS, CRYSTAL STRUCTURE AND BIOLOGICAL ACTIVITY OF THE ANION-COORDINATION PHENANTHROLINIUM TARTRATOGERMANATE

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Abstract. Novel supramolecular cation-anionic coordination compound $(HPhen)_4[(\mu\text{-}O)\{Ge_2(OH)(\mu\text{-}Tart)_2\}_2]\cdot 9H_2O$ was synthesised and characterised by the X-ray, elemental, IR- and Hirshfeld surface analysis. It was established that original synthesis method and ability of 1,10-phenanthroline to be protonated promotes the formation of $[(\mu\text{-}O)\{Ge_2(OH)(\mu\text{-}Tart)_2\}_2]^{4-}$ anion. In this anion, dimeric fragments are connected by a bridging oxygen atom, and the coordination polyhedra around the germanium atoms adopt a distorted trigonal bipyramidal geometry. The cations $HPhen^+$ serve as effective building blocks, strengthening the overall structure through classical hydrogen bonding and additional π-π stacking interactions. Biological screening of $(HPhen)_4[(\mu\text{-}O)\{Ge_2(OH)(\mu\text{-}Tart)_2\}_2]\cdot 9H_2O$ demonstrated its remarkable enzyme-effector and antimicrobial activity. The compounds' efficacy can be attributed to the synergistic effects of the independent cations and anions, as well as the ability of protonated 1,10-phenanthroline to inhibit metal ions in enzymes and form stacking interactions with specific protein components. These characteristics make such compounds highly effective and promising antibacterial agents that minimize the risk of developing bacterial resistance.

Keywords: supramolecular chemistry, germanium, coordination compound, structure, biological activity.

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Introduction

The intricate task of designing complex metal-chelate anions and their selective receptors involves a complex interplay of factors, including geometric considerations, stability assessments, and the nature of intramolecular interactions. Furthermore, the inherent pH sensitivity commonly observed in complex anions adds a complexity layer, making it challenging to identify and employ suitable cations. The key to selective binding lies in finding the right match between cations and anion-substrates. Study of noncovalent interactions (electrostatic, staking, hydrogen) allows to develop the strategic approach for the controlled synthesis of novel double supramolecular compounds tailored to specific biological and functional properties [1-5].

The advancement of anion coordination chemistry through the incorporation of highly coordinated *p*-elements like Ge(IV) and Sn(IV) broadens the possibilities for solving fundamental and practical challenges related to the selective interactions of various cations and anions. It achieves this by enabling the deliberate creation of supramolecular salts, offering innovative solutions to a wide range of scientific problems [6].

Notably, authors have achieved significant success in creating supramolecular double coordination cation-anionic compounds by utilizing essential tartratogermanates in combination with 1,10-phenanthroline(phen)/ 2,2'-bipyridine(bipy) complexes of 3*d*-metals (Fe, Co, Ni, Cu, Zn) [7-9]. Through systematic research, a substantial amount of experimental data has been gathered, enabling the development of original synthesis methods and the synthesis of over 20 novel supramolecular salts of essential germanium(IV) [7-9]. These compounds have been thoroughly characterized using various analytical methods. It has been proved that positively charged $[M(phen)_3]^{2+}$ and $[M(bipy)_3]^{2+}$

were able to recognize selectively different tartratogermanate anions $[Ge_2(OH)_2(\mu\text{-Tart})_2]^{2-}$, $[Ge_2(OH)(H_2Tart)(\mu\text{-Tart})_2]^{3-}$, $[Ge_2(OH)(HTart)(\mu\text{-Tart})_2]^{4-}$, that exist in the solution. The presence of cations as complementary metallic exoreceptors plays a crucial role in achieving the supramolecular organization of compounds through strong electrostatic interactions among their components. These cations are strategically located according to their nature and octahedral geometry, ensuring the desired arrangement. The synthesized compounds, characterized by their double structure (independent cations and anions), exhibited notable antimicrobial and enzymatic activity. This can be attributed to the synergistic effects of the individual units, the variability of electrostatic interactions, and the combination of different mechanisms of action [10-14]. The nature of the cation not only influenced the selectivity but also played a significant role in determining the level of demonstrated biological activity.

To further expand the research, the compound 1,10-phenanthroline was selected as a cationic component. This molecule, known for its π-donating properties, exhibits exceptional antimicrobial activity against a broad range of pathogens [15-21]. It has demonstrated its efficacy as a bidentate chelating ligand, and has been utilized in the formation of cocrystals [6-9,22]. Additionally, its protonated form has the potential to act as an outer sphere cation.

Therefore, the goal of the present study was to synthesize a supramolecular salt, namely $(HPhen)_4[(\mu\text{-O})\{Ge_2(OH)(\mu\text{-Tart})_2\}_2]\cdot 9H_2O$, which comprises a tartratogermanate anion and the protonated form of 1,10-phenanthroline as the cationic component. Herein, the authors determined the crystalline structure of the compound, investigated the intermolecular interactions using Hirshfeld surface analysis, conducted antimicrobial and enzyme-effector activity screenings, and compared the compound to previously described heterometallic germanium(IV) complexes [23].

Experimental

Materials

The starting reagents for the synthesis - germanium(IV) oxide (GeO_2, 99.99%), tartaric acid (H_4Tart, 99%), 1,10-phenanthroline (phen, 99%) (all were purchased from Sigma Aldrich).

Instruments

Elemental analysis for germanium was performed using inductively coupled plasma atomic emission spectroscopy with an Optima 2000 DV instrument (PerkinElmer). Analysis for C, H and N were performed in Elemental Analyzer CE-440.

The IR spectra in the range of 4000-400 cm^{-1} were recorded as potassium bromide pellets on a Frontier spectrometer (PerkinElmer).

Crystallography data for the compound $(HPhen)_4[(\mu\text{-O})\{Ge_2(OH)(\mu\text{-Tart})_2\}_2]\cdot 9H_2O$ were measured on an "Xcalibur-3" diffractometer (graphite monochromated MoK_α radiation, λ= 0.71073 Å, CCD detector, ω-scanning). Olex2 [24], SHELXT [25] SHELXL [26] programs and were used to solve the structures. In the establishment of *crystalline structure*, the full-matrix least-squares refinement against F^2 in anisotropic approximation was used for the non-hydrogen atoms. Hydrogen atoms were located using electron density difference maps and refined by the "riding" model with $U_{iso}= nU_{eq}$ of the carrier atom (where n= 1.5 for hydroxyl groups and water molecules and n= 1.2 for other hydrogen atoms). The positions of the hydrogen atoms bonded to the nitrogen atoms of the phenantroline molecules were determined experimentally from the electron density difference maps. Final crystallographic data, geometrical parameters and atomic coordinates have been deposited to the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/structures/) and are available on request of CCDC 2201618 number. Selected bond lengths and bond angles are listed in Table S1. The hydrogen bonding interactions are presented in Table S2. The geometry of stacking interactions is listed in Table S3.

The *intermolecular interactions* in the crystal phase were studied using the Hirshfeld surface analysis and 2D fingerprint plots generated by the CrystalExplorer program [27-29].

Methods

Synthesis and composition of the compounds

On the first step of synthesis GeO_2 and tartaric acid (H_4Tart) in the molar ratio 1:1 (0.5 mmol : 0.5 mmol) were dissolved in the 100 mL of hot H_2O and evaporated up to 5 mL. The obtained working solution was cooled to the room temperature and then dry sample of 1,10-phenanthroline (phen) (0.05 mmol) was added to it. Transparent crystals suitable for the X-ray analysis were obtained within 3 days (Scheme 1). Yield: 30%.

Such stepwise synthesis allowed to obtain dimeric tartratogermanate anion, that was proved

to exist in the aqueous solution. The addition of the 1,10-phenanthroline to the reaction medium leads to the condensation reaction and formation of novel tartratogermanate anion $[(\mu\text{-O})\{Ge_2(OH)(\mu\text{-Tart})_2\}_2]^{4-}$.

Elemental analysis calculated for $C_{64}H_{64}Ge_4N_8O_{36}$ (M= 1811.78 g/mol) in %: C, 42.43, H, 3.56, N, 6.18, O, 31.79, Ge, 16.04; found C, 42.8, H, 3.5, N, 6.1, Ge, 16.0.

Crystal data for $(HPhen)_4[(\mu\text{-O})\{Ge_2(OH)(\mu\text{-Tart})_2\}_2]\cdot 9H_2O$: $C_{128}H_{128}Ge_8N_{16}O_{72}$, M= 3623.18 g/mol, triclinic, space group $P1$, a= 14.3948(8) Å, b= 14.4209(8) Å, c= 17.1185(9) Å, α= 89.166(4)°, β= 89.135(4)°, γ= 82.192(4)°, V= 3519.9(3) Å^3, Z= 1, T= 110 K, μ(Mo Kα)= 1.797 mm^{-1}, $Dcalc$= 1.709 g/cm^3, 30717 reflections measured, 21907 unique (R_{int}= 0.0791, R_{sigma}= 0.1398) which were used in all calculations. The final R_1 was 0.0732 ($I > 2\sigma(I)$) and wR_2 was 0.1824 (all data).

IR (ν_{max}, cm^{-1}, spectrometer Frontier PerkinElmer, KBr): 500 ν_{sym}(Ge-O-Ge); 680 ν(Ge-O); 842 δ(Ge-OH); 851 ν_{asym}(Ge-O-Ge); 1339 ν_{arom}(C-N); 1425 ν_{sym}(COO$^-$); 1575 ν_{arom}(C-C); 1665 ν_{asym}(COO$^-$).

Enzyme effector activity evaluation

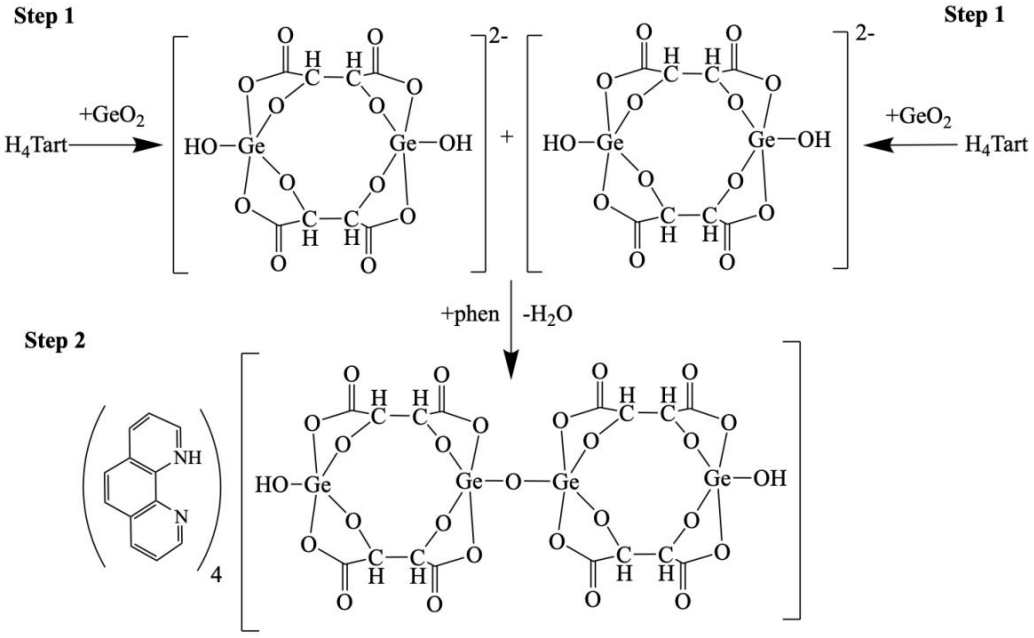
α-L-Rhamnosidases from *Penicillium tardum* IMB F-100074, *Eupenicillium erubescens* 248 and *Cryptococcus albidus* 1001 were used for the screening of compound on the *enzyme effector activity*. They were obtained by the precipitation with ammonium sulfate at concentration 90% in the culture liquid supernatant. Further purification is described in the literature [21]. Davis method was used to measure the activity of studied enzymes [30].

Antimicrobial evaluation

The study was performed on the pathogenic and opportunistic strains of gram-positive *Planococcus citreus* (B-6245) 628, *Micrococcus luteus* (B-6003), *Bacillus cereus* ATCC 10702 (B-6644), *Staphylococcus aureus* ATCC 6538P (FDA 209P), *Streptococcus sp.* (B-3872) H 46A and gram-negative *Escherichia coli* ATCC 25922 (B-6645), *Agrobacterium tumefaciens* (Smith and Townsend 1907) Conn 1942, (American collection of typical cultures and All-Russian collection of industrial microorganisms STATE DIGENETICS). Minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) were determined using the procedure presented in the previous publications [11]. MIC is minimal concentration of compound in that inhibits reproduction of the microorganisms; MBC is concentration that suppresses 99.99% of microbial population.

Results and discussion

The $(HPhen)_4[(\mu\text{-O})\{Ge_2(OH)(\mu\text{-Tart})_2\}_2]\cdot 9H_2O$ compound is a salt of a complex Ge-based anion and a protonated 1,10-phenanthroline cation. Two anions $[(\mu\text{-O})\{Ge_2(OH)(\mu\text{-Tart})_2\}_2]^{4-}$ (molecules A and B) are located in the asymmetric part of the unit cell. The charge of one $[(\mu\text{-O})\{Ge_2(OH)(\mu\text{-Tart})_2\}_2]^{4-}$ anion is compensated by four protonated phenanthroline ($HPhen^+$) cations.



Scheme 1. Stepwise synthesis of $(HPhen)_4[(\mu\text{-O})\{Ge_2(OH)(\mu\text{-Tart})_2\}_2]\cdot 9H_2O$.

In two complex anions (molecules A and B), the Ge1 and Ge2, as well as Ge3 and Ge4 atoms are connected through two bridging ligands of completely deprotonated tartaric acid (Figure 1). The Ge2 and Ge3 atoms are connected through a bridging oxygen atom. Each Ge atom is coordinated by two O atoms of the deprotonated carboxyl groups and two deprotonated hydroxyl groups of the two tartaric ligands, and a hydroxyl anion or bridging oxygen atom. The coordination polyhedron of the Ge atoms is distorted trigonal bipyramid. The oxygen atoms of the deprotonated hydroxyl groups of tartaric acid and the OH^- ligands (Ge1 and Ge4) or bridging oxygen atom (Ge2 and Ge3) are located in the equatorial positions and form the base of the bipyramid. The oxygen atoms of the deprotonated carboxyl groups of tartaric ligand are found in the axial positions. The Ge–O bonds have smaller lengths in the equatorial directions (1.741 (8) ÷ 1.808 (7) Å) then axial directions (1.903 (8) ÷ 1.929 (8) Å) (Table S1). The O–Ge–O valence angles vary in the range 86.4 (3) ÷ 94.0 (3)° and 109.2 (4) ÷ 128.7 (3)° in the equatorial and axial directions of the coordination polyhedron, respectively. The phenanthroline molecules have planar structure.

Cations and anions form columns in the *b* crystallographic axis in the crystal phase (Figure 2). Columns of cations and anions are arranged in a "checkerboard" order. Phenanthroline cations are bound in these columns through stacking interactions (Table S3). The anions are bound by O – H··· O hydrogen bonds (Table S2). The cavities between the columns are filled with hydrate water molecules which form a network of intermolecular hydrogen bonds (Table S2).

Results of the IR-spectroscopy were attributed according to the reference data [31] and our earlier obtained germanium(IV) coordination compounds with hydroxycarboxylic acids [6-9]. They correlate with the X-ray data: absorption bands $\nu_{asym}(COO^-)$, $\nu_{sym}(COO^-)$ and ν(Ge-O) characteristic for the dimeric tartratorgermanate anions are presented in the IR-spectrum of compound. This confirms full deprotonation of carboxylic and hydroxylic groups from bridging tartaric ligands and their coordination to Germanium. The bands δ(Ge-OH) and ν_{asym}(Ge-O-Ge), ν_{sym}(Ge-O-Ge) evidence that central atom additionally binds with terminal hydroxyl ligand or bridging oxygen respectively. Presence of aromatic 1,10-penanthroline in the cation of compound is confirmed by the absorption bands ν_{arom}(C-N) and ν_{arom}(C-C).

Electrostatic interactions in the compound were established using Hirshfeld surface analysis. The short contacts are red-colored circles on the d_{norm} surfaces, while other contacts, that are weaker and longer, are light-colored areas and small spots (Figure 3).

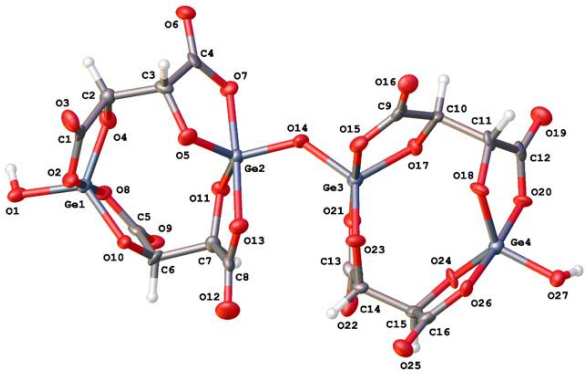


Figure 1. The molecular structure of the $[(\mu\text{-O})\{Ge_2(OH)(\mu\text{-Tart})_2\}_2]^{4-}$ anion (suffixes A and B in the numbers of atoms to molecules A and B, respectively).

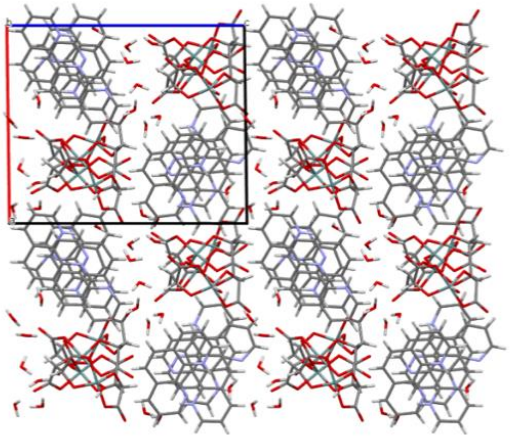


Figure 2. The crystal packing of $(HPhen)_4[(\mu\text{-O})\{Ge_2(OH)(\mu\text{-Tart})_2\}_2]\cdot 9H_2O$ viewed along the *b* axis.

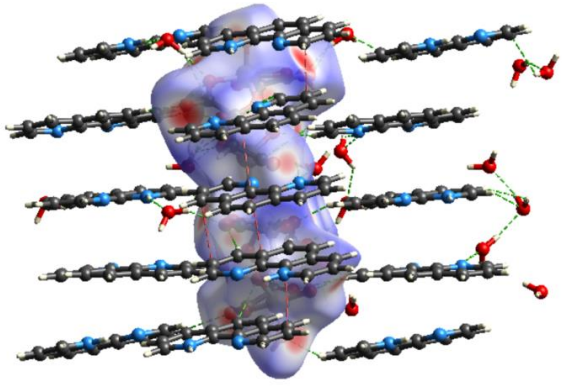
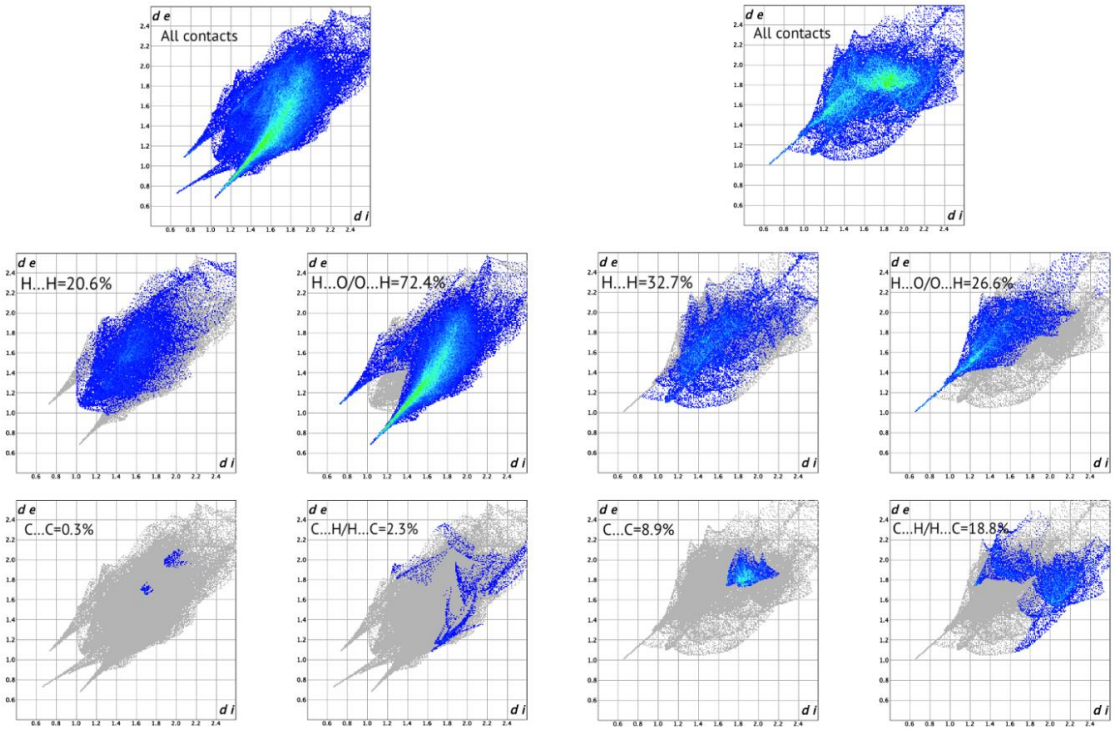


Figure 3. Hirshfeld surfaces (designated in accordance d_{norm}) of anion.

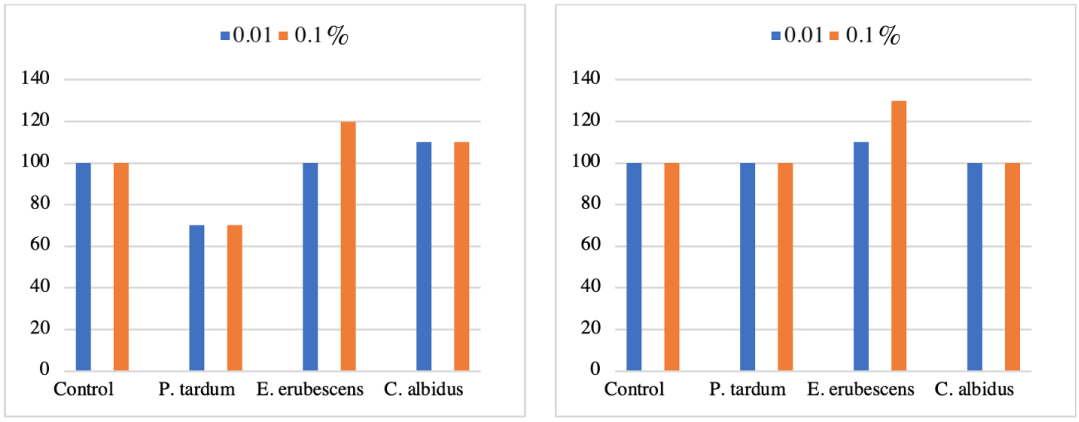
The biggest contribution to the total area of the Hirshfeld surfaces in anions is provided by H···O/O···H – 72.4% and H···H - 20.6% bonds, while in the cations together with H···O/O···H – 26.6%, H···H – 32.7%, also C···C – 8.9% and C···H – 5.9% interactions are presented (Figure 4). It can be concluded that $HPhen^+$ molecules are good building blocks that hold the structure by the branch net of classical hydrogen bonding and additional C···C staking interactions. Molecules of water perform bridging function and connect cations and anions between each other.

It was established that compound $(HPhen)_4[(\mu\text{-}O)\{Ge_2(OH)(\mu\text{-}Tart)_2\}_2]\cdot 9H_2O$ shows both enzyme activating and inhibiting activity against α-L-Rhamnosidases from *Penicillium tardum*, *Eupenicillium erubescens* and *Cryptococcus albidus* (Figure 5). At the exposure time of 30 minutes at the concentrations of 0.01% and 0.1%, the supramolecular salt has inhibited more than 30% of *P. tardum*, but after 24 hours its activity was graded to the initial level. The effect on the *E. erubescens* and *C. albidus* was opposite, namely, at the concentration of 0.1%, the compound activated 30% of enzymes.



(a) ***(b)***

Figure 4. The relative contribution of main interactions types into total Hirshfeld surfaces (in %) shown as fingerprint plots for anion *(a)* and cation *(b)*.



(a) ***(b)***

Figure 5. Enzyme-effector activity of compound on the *P. tardum*, *E. erubescens* and *C. albidus* strains after 30 minutes *(a)* and 24 hours *(b)*.

Table 1

Antimicrobial activity of the studied compound.

Strain of the microorganism	*Concentration, μg/mL*		
	MBC	*MIC*	*MIC of reference*
Planococcus citreus	23.44	23.44	-
Micrococcus luteus	23.44	23.44	750
Bacillus cereus	46.90	46.90	750
Staphylococcus aureus	23.44	23.44	>1000
Streptococcus lactis	23.44	23.44	>1000
Escherichia coli	>500	>500	-
Agrobacterium tumefaciens	>500	>500	-

The given data doesn't differ significantly from the results obtained for heterometallic supramolecular salts described earlier [23], thereby specific cation-anionic structure of effector, presence of tartratogermanates(IV) in its composition and the nature of the studied enzyme play the crucial roles in the catalytic activity.

Compound $(HPhen)_4[(\mu\text{-}O)\{Ge_2(OH)(\mu\text{-}Tart)_2\}_2]\cdot 9H_2O$ turned out to be one of the most effective antimicrobial agents among to the described tartratogermantes because of the presence of protonated molecule of 1,10-phenanthroline as cation in its composition (Table 1) [11]. The complex inhibits the activity of *Planococcus citreus*, *Micrococcus luteus*, *Bacillus cereus*, *Staphylococcus aureus*, *Streptococcus lactis*, *Escherichia coli*, *Agrobacterium tumefaciens* at the minimal inhibitory concentrations (MIC) and minimal bactericidal concentrations (MBC) from 23.44 μg/mL to 46.90 μg/mL. Protonated 1,10-phenanthroline is able to react with metals in biosystems and block them in this way. The complex structure of supramolecular salt allows it to suppress the vital activity of microorganisms using combination of different mechanisms. This advantage excludes possibility of microbial resistance and makes such type of compounds more effective and perspective antibacterial agents then antibiotics [4]. The closest analogue of the presented compound is derivative of amino-free crown ether, in particular, di(perfluoro-n-hexyl)dibenzo-18-crown-6, the structure and activity of which are described in the literature [32]. As shown in the Table 1, the investigated biocomplex is ten times more effective than the reference drug.

Conclusions

Using 1,10-phenanthroline as a cation leaded to the selective recognition of new anion $[(\mu\text{-}O)\{Ge_2(OH)(\mu\text{-}Tart)_2\}_2]^{4-}$, that differs from the ones in the previously described compounds. It is formed by the condensation reaction between two hydroxylic ligands of dimeric $[Ge_2(OH)_2(\mu\text{-}Tart)_2]^{2-}$ connected with the bridging oxygen atom. In the studied compound, 1,10-phenanthroline is present as a cation in the protonated form, and not as a chelating ligand, as it was in the previously described salts. The location in the outer sphere of protonated 1,10-phenanthroline molecules as cations plays a crucial role in the formation of a branched network of hydrogen bonds and π-π stacking interactions between aromatic rings. This unique arrangement enhances the biological activity of the investigated complex. Biological screening of $(HPhen)_4[(\mu\text{-}O)\{Ge_2(OH)(\mu\text{-}Tart)_2\}_2]\cdot 9H_2O$ revealed its potent antimicrobial and enzyme-effector activity. This can be attributed to the combined effects of the independent cations and anions, as well as the presence of $HPhen^+$ which can interact with metal ions in enzymes and various protein components, leading to enhanced activity. Therefore, the utilization of nitrogen-containing organic bases capable of acting as cations represents a promising approach for increasing the biological activity of supramolecular salts.

The identification of regularities among the composition, structure, electrostatic interactions, and properties of the described supramolecular salt provides a crucial foundation for the future development of multifunctional drug substances with predefined properties.

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