

Article

Ternary Copper Complex of L-Glutamine and Phenanthroline as Counterions of Cyclo-Tetravanadate Anion: Experimental–Theoretical Characterization and Potential Antineoplastic Activity

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Abstract: Over the last decade, therapeutic metallodrugs have become substantially effective in the treatment of cancer. Thus, developing new effective anticancer drugs is a significant research area against the continuing increase in cancers worldwide. In the search for heterobimetallic prodrugs containing V/Cu, a new cyclo-tetravanadate was synthesized and characterized by UV-visible and FTIR spectroscopies and single-crystal X-ray diffraction. L-Glutamine and 1,10-phenanthroline allow the crystallization of $[Cu(L-Gln)(phen)(H_2O)]_4[V_4O_{12}] \cdot 8(H_2O)$ (1), in which the cyclo-tetravanadate acts as a free anion. Density functional theory (DFT) calculations were carried out to characterize the frontier molecular orbitals and molecular electrostatic potential. Global reactivity indexes were calculated and analyzed to give insight into the cyclo-tetravanadate anion and complex counterions interactions. Also, using Bader's theory of atoms in molecules (AIM), non-covalent interactions were analyzed. Docking analysis with the Casiopeina-like complex resulting from the hydrolysis of compound 1 provided insights into these complex potential anticancer activities by interacting with DNA/tRNA via H-bonds and hydrophobic interactions. The release of both components could act together or separately, acting as prodrugs with potential dual antineoplastic activities.

Keywords: mixed copper complexes; Cyclo-tetravanadates; L-Glutamine; Phenanthroline DFT calculations; molecular docking; antineoplastic activity

1. Introduction

The synthesis of metallodrugs for cancer treatment has been rising due to its substantial success in the last decade [1,2]. Cancer is a multi-factorial, multibillion-dollar public health epidemic around the world. Considering that in 2020 there were approximately 18.1 million new cases and 9.6 million deaths worldwide, it is important to find safe and low-cost ways to fight it [3]. In the Region of the Americas, it is the second leading cause of death. If no steps are taken to prevent and control cancer, the number of persons diagnosed with cancer will rise by 55 percent by 2040, totaling roughly 6.23 million people. [4]. About 195,499 new cases and 90,222 deaths were estimated in Mexico in 2020, with a higher prevalence of breast cancer, followed by prostate cancer with 15.3% and 13.7%, respectively [3]. While several drugs containing metals based on gold, ruthenium, gallium,



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Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). titanium, iron, and copper are in preclinical and clinical phase I and II trials [5,6], the most effective antitumor agents used in clinical practice remain cis-platinum and also second- and third-generation platinum coordination compounds (carboplatin, oxaliplatin, and picoplatin). Nevertheless, platinum-based products' clinic use carries significant side effects, including nephrotoxicity, neurotoxicity, ototoxicity, hepatotoxicity, and myelosup-pression [7,8]. Endogenous metal-based antitumor drugs (Co, Cu, Zn, and Fe) are less toxic than platinum analogs and display promising pharmacological properties [9,10].

In the specific case of copper, it provides an ideal geometry to interact with DNA molecules, making them a viable alternative to platinum-based anticancer drugs, with the advantage that copper is better tolerated and can be more easily managed in vivo than other transition metals [11,12]. Complexes containing symmetric aromatic binders, such as 1,10-phenanthroline and 2,2'-bipyridine, and how they interact with DNA have received much attention [13–16]. In 1979, Sigman et al. discovered the first metallonuclease by demonstrating that [Cu(phen)₂]²⁺ complex inhibits DNA and RNA polymerase activity and can induce DNA strand scission [17]. Numerous studies since then have demonstrated that the geometry of the metal center, combined with planar bidentate ligands, contains an optimal structure for interacting with a wide variety of biological molecules and possesses antitumoral and antiviral properties [18-22]. The synthesis, design, and development of complexes as anticancer agents have been presented in several reviews over the last decade, indicating an exponential increase in the field [23–35]. Ng et al. (2014) showed that copper(II) complexes containing 1,10-phenanthroline and amino acids were significantly more antiproliferative and induced more apoptotic cell death in the cisplatin-resistant MDA-MB-231 cells than in the non-cancerous MCF10A cells, and only induced cell cycle arrest in cancer cells. Additionally, these compounds were found to be effective against cervical (HeLa), ovarian (SKOV3), lung (A549, PC9), non-small cell lung (NPC) (Hone1, HK1, C666-1), breast (MCF7, T47D), lymphoma and leukemia (Nalmawa, HL60), and colorectal (SW480, SW48, HCT118) cancer cell lines with IC50 values (24 h) ranging from 1.7 to 19.0 μ M. Importantly, these compounds were even more effective than cisplatin in some cases [36]. A series of ternary copper(II)-L-dipeptide-neocuproine complexes demonstrated cytotoxicity against cancer cells, including the triple-negative breast cancer cell line MDA-MB-231 [37]. The complex bis[(2-chloro)chloro(1,10-phenanthroline)copper(II)] exhibited a high degree of reactivity. Anticancer activity was observed against the B16, MDA-MB-32, A549, HT-29, and SF cell lines, with an average of IC50 of 0.726 g/mL $(1.15 \,\mu\text{M})$, compared to cisplatin's 4.88 g/mL (16.3 $\mu\text{M})$. Furthermore, it demonstrated a higher selectivity for cancer cells than human bone marrow stem cells, and in rats, it is less toxic than cisplatin [38]. Copper-based metallodrugs loaded in nanoparticles have also shown promising results. The survival rate of a murine B16 melanoma model, when given chitosan nanoparticles loaded with Cassiopeina, was higher than those that received the drug as such. This was achieved due to a longer residence time at the site of action because the release of the substance from the nanoparticles was achieved at the acidic pH of the tumor [39]. Reina et al. have synthesized second-generation Casiopeina⁽¹⁾ [40] by substituting acetylacetonate for 2-aminomethyl benzimidazole (2AMB) as a bidentate chelate ligand. The change increases hydrophilicity and antiproliferative activity, resulting in two active complexes against the human tumoral cell lines, HeLa and MCF-7. A small group of copper complex exerts an effective inhibitory action on topoisomerases, which participate in the regulation of DNA topology. Copper complexes of topoisomerase inhibitors work via different molecular mechanisms that affect the cell cycle checkpoints and death effectors. Expanding this family of highly active anticancer drugs and their use with other emerging cancer therapies opens new avenues for treating cancers [28]. Complexes of Cu(II)-phenanthroline with L-asparagine and L-methionine were highly toxic to the prostate cancer cell lines (DU-145 and PC3), breast cancer cell lines (MDA-MB-231 and MCF7), and MV3 (melanoma) [41]. The mechanism is a redox reaction of Cu (II)/Cu (I) that catalyzes the formation of reactive oxygen species (ROS). The structure of this type of complex consists of a copper(II) core with a distorted square pyramidal geometry, which, in the presence of ascorbate, exhibits effective DNA cleavage activity at micromolar concentrations, producing hydroxyl radicals as the active species [42]. Recently, it has been demonstrated that sulfonamide copper(II) complexes with 1,10-phenanthroline and 2,2'-bipyridine possess potent nuclease activities with antiproliferative and anti-M. tuberculosis actions [43]. Casiopeinas[®] have gained an important place in the efforts to generate antineoplastic drugs with copper, as expressed in the recent invention of a safe parental solution with Cassiopeia III-ia [44]. In the review of copper coordination compounds as biologically active agents," it is stated that the redox activity of copper ions, as well as the stability of copper coordination compounds in the bloodstream, and the extremely encouraging therapeutic outcomes both in vitro and in vivo, show the potential of copper coordination compounds, which is expected to gain widespread clinical use" [45].

Vanadium, on the other hand, has therapeutic properties that are well known. Its pharmacological properties could be used to treat diabetes, however, concern about toxicity is still an issue [46,47]. However, some studies have also shown that vanadium could be used to treat cancer since it causes cell apoptosis, displaying cytotoxic and antiproliferative effects [48]. In fact, several of the metabolic pathways are used by both diabetes mellitus and cancer [49–52]. Recent studies of pancreatic cancer, malignant melanoma, glioma multiforme, and an aggressive brain cancer have shown that vanadates and oligovanadates function as anticancer drugs [53-55]. Also, in cytotoxicity experiments with human osteosarcoma (MG-63) and human colorectal adenocarcinoma (HT-29) cell lines, the compound bis (4,7-dimethyl-1,10-phenanthroline) sulfatooxidovanadium (IV), known as Metvan, showed altered cell viability of both cancer cell lines in the low concentration range $(0.25-5.0 \ \mu\text{M})$ [56]. Another recent study showed the importance of the interaction of polyoxovanadates with the plasma membrane to subsequently hydrolyze and internalize the compound, thus allowing partial participation in the generation of ROS and electron transfer processes [57,58]. In addition, vanadium-based nanomaterials have been found to be helpful for theranostic applications. Vanadium nitride nanosheets are readily convertible into biocompatible materials that display near-infrared (NIR) absorption, producing ROS and effectively killing cancerous tissue [59]; vanadium oxide has an activity similar to peroxide, which would be helpful in tumor-specific chemodynamic therapy [60]. In addition, it is well known that oxidovanadium complexes with organic ligands have cytotoxic or differentiating properties against various cancer cell types [61–66]. However, their limited use in clinical trials stems primarily from concerns about the long-term toxicity of such complexes due to a lack of data. However, recent administration of [VO(HSHED)dtb] complex in mice did not show any signs of toxicity up to a dose of 300 mg/kg. The complex was less toxic than orthovanadate salt, consistent with the compound being partially intact during the administration [67]. The low toxicity is attributed to the redox properties obtained when combining the redox-active ligand 3,5-di(tert-butyl)catechol with the hydrolytic stability of the [VO(HSHED)dtb], which prevent the formation of the vanadate and catechol ligand. These results point out that the protection of even anionic vanadium species may help increase activity and reduce toxicity. Although anionic compounds of vanadium can survive the transit in the bloodstream and enter the cell by several mechanisms, it is possible to suggest that they generate mainly V1, V2, and V4 vanadates through speciation [63,64]. Thus, it is crucial to investigate the cyclo-tetravanadate anion since it will be the primary species at physiological pH [68]. Anionic compounds of vanadium(V) have shown interesting anticancer properties [69,70]. Recently, the compounds $(NH_4)_4 Li_2 V_{10} O_{28} \cdot 10 H_2 O$ and $Mg(H_2O)_6(C_4N_2H_7)_4V_{10}O_{28}\cdot 4H_2O$ demonstrated dose-dependent antiproliferative activity on human cancer cells U87, IGR39, and MDA-MB-231 [71,72]. Again, nanotechnology provides new possibilities. Cationic liposomes have been used to encapsulate a hydrophobic oxidovanadium complex that has shown cytotoxic properties against neuroblastoma cell lines while also improving bioavailability [73]. V(IV)-curcumin-bipyridine (VCur) was encapsulated in vitro using magnetic cationic liposomes, which gives the compound excellent stability and solubility in physiological media [74]. Biocompatible vanadium nitride nanosheets have shown relevant near-infrared (NIR) absorption that can be used

for imaging and produce reactive oxygen species upon NIR excitation, effectively killing cancer tissue. Recent studies of eleven vanadium species, compounds, and materials, in several human melanoma cells lines, have shown interesting antitumor capabilities to a variety of effects, including: (1) cell viability, (2) cell morphology changes and apoptosis, (3) cell-cycle arrest, (4) ROS production, (5) mitochondrial dysfunction, (6) protein expression, and (7) in vivo tumor regression and survival rates. Therefore, it was concluded that essential questions would be answered this decade to push forward the practice of metals compounds—particularly vanadium—to treat cancer [75].

As for copper, the new results and new strategies for delivery point to significant advances in this decade. It is essential to consider that compounds of vanadium and copper will act as prodrugs since they will undergo interactions with proteins such as human serum albumin and transferrin, and these will release their ligands, or in some robust cases, transport of the intact prodrug in the bloodstream could take place [76–81]. Speciation outside or inside the cells is most probable, but regardless of this, important anticancer actions are provided by polyoxidovanadates (POVs) and Casiopeinas®, so we expect dual anticancer activities of the compounds reported here. It is now clear that both metals will provide new metallodrugs to help in the global problem of cancer treatment in the near future. Also, POVs have a diverse spectrum of structural, biological, and pharmacological properties that are intriguing and potentially useful. Recent research has indicated that these compounds may effectively treat solid tumors, DNA and RNA viruses, and drugresistant bacteria. Changes in cell structure, interference with the ion transport system, inhibition of mRNA synthesis, and disruption of metabolic pathways and communication mechanisms are all known antibacterial modes of action for various POVs. Additionally, POVs have been found to reduce mitochondrial respiration in vitro. However, in the future, researchers need to explore vanadium-containing POV-based nanohybrids rather than pure POVs to reduce toxicity and boost efficacy [82].

As the first collection of V/Cu heterobimetallic compounds with the potential to be used as metallodrugs in cancer treatment, our group has identified several cyclo-tetravanadates [83–85]. We recently reported the synthesis and theoretical–experimental characterization of two compounds resulting from our quest to complete the family of copper cyclo-tetravanadate complexes. Interestingly, the compounds obtained were different, although the same synthetic technique was used; however, it is possible to consider them Casiopeina[®] analogs [86]. Here, a new cyclo-tetravanadate is presented. This compound was characterized by visible and IR spectroscopies as well as single-crystal X-ray diffraction. In addition, the compound was studied using DFT computational methods. The frontier molecular orbitals and global reactivity indexes were analyzed to show interesting characteristics about the donor–acceptor interactions. These insights about the compound's reactivity were corroborated by analyzing the non-covalent interactions using the AIM approach. The Casiopeina-like complex in docking studies shows the potential to interact with DNA/RNA, thus providing a new compound with potential dual anticancer activity in various cell lines.

2. Results

Compound 1 crystallizes in the triclinic space group P1, with only one asymmetric unit filling the unit cell. Figure 1 shows a representation of the molecule and Table 1 presents the corresponding crystal data. The compound contains four $[Cu(L-Gln)(phen)(H_2O)]^+$ cations displaying a squared-pyramidal geometry ($\tau_5 = 0.017$), of which the two N donors of phenanthroline and the amino and carboxyl groups of glutamine are coordinated in basal positions. As shown in Figure 1, four water molecules occupy the apical positions of all the square pyramids. In this case, the glutamine ligands are L isomers. However, two hydrogen atoms in the alpha carbon point in the opposite direction of the coordinated water, so they are considered anti-conformers; the other two pointing in the same direction are considered *syn*-conformers, as seen in Figures 2 and 3. It can be observed that all copper coordination compounds interact non-covalently with the cyclo-tetravanadate structure

through different hydrogen bonds. Figure 2 shows the hydrogen bonds surrounding the cyclo-tetravanadate anion. Eight H₂O molecules stabilize the structure, five of them (O33 to O37) in a chain array connecting one complex molecule with the $[V_4O_{12}]^{4-}$ anion. Tables S1–S5, Supplementary Materials contain more details of structural data.



Figure 1. Representation of Compound 1, where $[Cu(L-Gln)(phen)(H_2O)]^+$ neutralize (V_4O_{12}) anion. L-glutamine is present as two syn and two anti-conformers, data from [87].

Table 1. Crystal data and structure refinement for Compound 1.

Chemical formula	$(C_{17}H_{19}CuN_4O_4)_4V_4O_{12}\cdot 8(H_2O)$		
	2167.49		
Crystal system, space group	Triclinic, P1		
Temperature (K)	293.15		
<i>a, b, c</i> (Å)	12.3849 (3), 14.1023 (3), 14.1516 (3)		
α,β,γ (°)	68.967 (2), 71.327 (2), 77.252 (2)		
 V (Å ³)	2169.86 (9)		
Z	1		
Radiation type	Μο Κα		
μ (mm ⁻¹)	1.47		
Crystal size (mm)	0.35 imes 0.17 imes 0.10		
Absorption correction	Gaussian		
No. of measured, independent and observed $[I > 2\sigma(I)]$ reflections	59,756; 21,452; 17,760		
R _{int}	0.058		
$(\sin \theta / \lambda)_{max} (Å^{-1})$	0.667		
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.045, 0.111, 1.02		
No. of reflections	21,452		
No. of parameters	1171		
H-atom treatment	H-atom parameters constrained research papers		
$\Delta_{\max} \Delta_{\min} (e \text{ Å}^{-3})$	1.03, -0.29		



Figure 2. Representation of Compound **1**, where anti-conformers are on the right and syn-conformers are on the left. Blue lines indicate hydrogen bonds.



Figure 3. (A) anti-conformer and (B) syn-conformer of [Cu(L-Gln)(phen)(H₂O]⁺.

2.1. Infrared Spectroscopy

Due to the relatively rigid structure of the polyoxovanadate ions, the IR spectra of the individual types of polyoxovanadates have characteristic bands in the region of asymmetric and symmetric VO stretching vibrations. As a result, IR spectroscopy can be used to characterize such compounds [88–90]. The spectrum of Compound 1 in the region 1000–500 cm⁻¹ is presented in Figure 4. The complete spectrum is presented in Figure S1 in the Supplementary Materials. Bands resulting from the symmetric and asymmetric vibrations of terminal V(O_t)₂ commonly occur between 910–1000 cm⁻¹ for ν_{as} and 860–900 cm⁻¹ for ν_{s} . On the other hand, bands below 850 cm⁻¹ could be assigned to the asymmetric vibrations of the bridging V–O_b–V groups, and the small band at 530 cm⁻¹

could be assigned to v_s V-O_b-V [91–97]. The positions of absorption bands in the region of VO bond stretching vibrations (500–1000 cm^{-1}) will make it possible to determine whether a compound's structure is made up of cyclic $[V_4O_{12}]^{4-}$ as a free anion or is involved in several hydrogen bond interactions, as shown in Figure 4. Compound 1 shows that cyclo-tetravanadate ions are involved in different hydrogen bond interactions, causing the splitting of the typical bands. Several shoulders appear in the main bands, indicating different $V(O_t)_2$ and $V-O_b-V$ vibration strengths. These are seen in the inset, where the second derivative spectrum is depicted. The presence of several shoulders can be evidenced by second derivative spectroscopy [98–100]. The shoulders are now presented as peaks and show how different environments are experienced by each VO bond, consistent with the hydrogen bond interactions presented in the solid-state structures. As for the bands of phenanthroline, the only bands seen in this region are located at 727 cm^{-1} and 736 cm^{-1} , respectively, and are assigned according to Schilt and Taylor [101] and Baskaran et al. [102], who observed two strong bands at 850 cm^{-1} and 725 cm^{-1} in the free ligand. The band at 850 $\rm cm^{-1}$ was assigned to the out-of-plane motion of the carbocyclic ring's hydrogen atoms and the 725 cm^{-1} to those of the two heterocyclic rings' hydrogen atoms. The band at 850 cm⁻¹ is overlapped with the V-O_b-V antisymmetric bands. As for the amino acid moiety, the strong bands of the amino and carboxylic groups are outside this region [103].



Figure 4. FTIR spectrum of Compound 1 in the 500–1000 cm⁻¹ region. The inset shows the second derivative spectrum in the region 800–1000 cm⁻¹.

2.2. Visible Spectroscopy

Figure S2 shows the visible spectrum of Compound 1 after it had been dissolved in phosphate-buffered saline (PBS) solution at pH 7.4. Compound 1 showed an asymmetric absorption band at λ_{max} value 627 nm, and a molar extinction coefficient $\varepsilon = 45 \text{ L mol}^{-1} \text{ cm}^{-1}$. Valora et al., has shown that several ternary complexes containing 1,10-phenanthroline and amioacidates have d-d bands with λ_{max} value at 618 ± 6 nm and ε of 57 ± 5 due to the promotion of low energy d electrons to the dx²-y² hole, which is the value expected for a CuN₃O in-plane chromophore [104,105]. Thus, although in the solid-state, the geometry of the compound was a square pyramid, it is likely that in aqueous solution, the compound exhibits a unique molecular geometry, which is a tetragonally elongated octahedron.

2.3. Computational Calculations

The molecular structure, molecular electrostatic potential (MEP) map, and isosurfaces of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are shown in Figure 5.



Figure 5. (a) Molecular structure, (b) molecular electrostatic potential (MEP), (c) HOMO isosurface, and (d) LUMO isosurface of Compound 1 at the B3LYP/Def2SVP-LANL2DZ level of theory using the ECP=LANL2DZ for V and Cu atoms in the PCM model.

The MEP distribution of Compound 1 shows the total electronic density mapped with the electrostatic potential using an isovalue of 0.004 a.u., in a range of -0.25 to 0.25 e a.u.⁻³. The red region indicates the negative charge density on cyclo-tetravanadate anion (nucleophilic zone), while the positive charge is mainly located on glutamine and phenanthroline molecules (electrophilic zones). The non-covalent H-bonds between cyclo-tetravanadate and organic counterions and water molecules are located in intermediate regions of electron density (yellow–green regions) (see Figure 5b). Compound 1 shows the isosurfaces of the frontier molecular orbitals (FMO) using an isovalue of 0.03 a.u.

(Figure 5c,d), showing significant contributions of phenanthroline and glutamine ligands for HOMO (-4.87 eV) and LUMO (-2.64 eV).

Global reactivity descriptors, such as chemical potential (μ), electronegativity (χ), hardness (η), softness (s), and electrophilicity index (ω), were evaluated based on a conceptual DFT approach using the following equations: $\mu = (E_{HOMO}+E_{LUMO}) / 2$; $\chi = -(E_{HOMO}+E_{LUMO})/2$; $\eta = E_{LUMO}-E_{HOMO}$; $s = 1/\eta$, $\omega = \mu^2/2\eta$, where E_{HOMO} and E_{LUMO} are the frontier molecular orbitals energies. Table 2 shows the results.

Table 2. Global reactivity descriptors (in eV) of Compound **1** at the B3LYP/Def2SVP-LANL2DZ level of theory using the ECP = LANL2DZ for V and Cu atoms in the PCM model.

	E _{HOMO}	E _{LUMO}	μ	x	η	S	ω
Compound 1	-4.8697	-2.6351	-3.7524	3.7524	2.2346	0.4475	3.1506

The electron charge transfer process can be analyzed in terms of chemical potential (μ) (or electronegativity ($\chi = -\mu$)), hardness (η) (or softness (s = η^{-1})), and electrophilicity (ω). The results show that the chemical potential value, μ , of Compound 1, indicates the capacity for exchanging electrons. The chemical hardness value, η , indicates the resistance for changing its electron distribution. On the other hand, the behavior of the electrophile or nucleophile can be related to a higher or lower ω index. In conjunction with the MEP analysis, global reactivity indexes give insights regarding the electrophilic or nucleophilic power of the compounds' sites, which is important for analyzing the interaction. Topological parameters were used to characterize intramolecular interactions, such as electron density $\rho(r)$, Laplacian $\nabla^2 \rho(r)$, Lagrangian kinetic energy *G*, potential energy density V, Hamiltonian kinetic energy H, interaction energy $E_{H \dots Y}$, and interatomic distance D_{inter} . Results are shown in Table S6. The positive values of $\nabla^2 \rho(r)$ confirm the hydrogen bond behavior of the interactions, and the positive values of H(r) indicate hydrogen bonds of a purely electrostatic nature. The value of equation H(r) = G(r) - G(r)V(r) determines the molecular interaction regions, and interaction energy is calculated from equation $E_{H\dots Y} = \frac{1}{2} |V(r)|$. The molecular graph for Compound 1 is shown in Figure 6. Cyan dots represent the bond critical points (BCPs), yellow dots represent the ring critical points (RCPs), and orange dots represent the cage critical points (CCPs). In Figure 6, the main H-bond interactions between O atoms of the cyclo-tetravanadate anion with water molecules and H-atoms of glutamine are shown. Table S6 presents the $\rho(r)$ values for H-bonds larger than 0.0100 a.u. The maxima $\rho(r)$ were found for the intermolecular O12···H20D, O17···H15A, O7···H5A, and O2···H10A, corresponding to the interactions between one of the H-atoms of the water in the apical position of Cu with the O atom of the $-COO^-$ moiety of glutamine, see Figure 6. Their $E_{H \dots Y}$ values between 5.40-6.93 kcal mol⁻¹ indicate the most stabilized interactions. In addition, the interactions O36···H35A, O35···H34B, and O40···H38C between water molecules have high values of $\rho(r)$ with $E_{H,...,Y}$ values between 5.71–6.59 kcal mol⁻¹. It can be seen that a lot of RCPs are present, indicating the formation of rings and CCPs forming cage structures between glutamine and phenanthroline molecules, providing structural stability to the molecular structure of Compound 1. Regarding interactions O–Cu, four equivalent interactions between Cu and O atoms of water in apical position can be observed. These interactions (O5-Cu1, O10-Cu2, O15-Cu3 and O20-Cu4) have interaction energy values between 13.02-16.44 kcal mol⁻¹. Similar behavior in the non-covalent interactions between Cu with amino acid was observed for the cyclo-tetravanadate complex [Cu(Lys)(phen)]₂[V₄O₁₂] containing lysine and phenanthroline, specifically the Cu-N and Cu-O interactions [83].



Figure 6. Molecular graph of the Compound 1 showing the main H-bonds between ions.

2.4. Molecular Docking

It was hypothesized that in an aqueous solution, because of reduction, re-oxidation, and hydrolysis, the vanadium and copper compounds would be released and act separately; thus, the copper Casiopeina like complex was studied as the corresponding aquo complex. In Table 3, the docked binding energies of the interaction with DNA/RNA test molecules, corresponding to the top molecular pose (lowest energy) for complex ions already reported, are presented for comparison.

Table 3. Molecular docking results, including the binding energies for the best molecular poses of doxorubicin and reported complexes with DNA and tRNA.

Compounds for Comparison	Interaction Energy (kcal/mol) ADN 1BNA	Interaction Energy (kcal/mol) ADN 151D	Interaction Energy (kcal/mol) tRNA 6TNA	Interaction Type
* Doxorubicin	-11.09	-11.54	-9.82	H-bond, π-interaction, van der Waals
* [Cu(acac)(dmbipy)] ¹⁺ CAS III ia	-7.47	-8.76	-6.16	H-bond, π-interaction, van der Waals
* [Cu(phen)(Gly)(H ₂ O)] ⁺ CAS II-Gly	-10.57	-8.86	-9.47	H-bond,π-interaction, van der Waals

Compounds for Comparison	Interaction Energy (kcal/mol) ADN 1BNA	Interaction Energy (kcal/mol) ADN 151D	Interaction Energy (kcal/mol) tRNA 6TNA	Interaction Type
* [Cu(hydroxynaphthaldehyde)(H ₂ O)]	-11.56	-9.12	-7.98	H-bond, π-interaction, van der Waals
* [Cu(Metf)(bipy)(H ₂ O)] ²⁺	-9.69	-7.05	-12.76	H-bond, salt bridges, van der Waals
* [Cu(Gly)(Impy)(H ₂ O)] ⁺	-8.82	-6.73	-8.83	H-bond, π -interaction, van der Waals
[Cu(Lys)(phen)(H ₂ O)] ²⁺	-11.03	-9.98	-8.86	H-bond, salt bridge, π-interaction, van der Waals
[Cu(Orn)(bipy)(H ₂ O)] ²⁺	-11.12	-9.68	-13.15	H-bond, salt bridge, π-interaction, van der Waals, Attractive charges
[Cu(Gly)(phen)(H ₂ O)] ⁺	-9.5	-8.52	-9.12	H-bond, π-interaction, van der Waals
[Cu(Orn)(phen)(H ₂ O)] ²⁺	-11.05	-9.43	-13.05	H-bond, salt bridge, π-Interaction, van der Waals, Attractive charges
[Cu(Lys)(bipy)(H ₂ O)] ²⁺	-11.04	-8.72	-12.23	H-bond, salt bridge, π-Interaction, van der Waals Attractive charges

Table 3. Cont.

* data from [83,86,106–108].

In Table 4, the docked binding energies and the interaction with DNA/RNA corresponding to the top molecular pose (lowest energy) for complex ions $[Cu(L-Gln)(phen)(H_2O)]^+$ are shown. As was expected from previous studies, all docked structures occupy similar positions in the minor groove of the 1BNA/DNA and intercalate in the 151D/DNA fragment structures (Figures 7 and 8). The compounds interact well with the DNA test molecules, yet considering the binding energies among these complexes, the best affinity energy is found in the complex ion anti- $[Cu(L-Gln)(phen)(H_2O)]^+$. Also, it can be implied that ligand phenanthroline has an essential role in the interaction; this result agrees with our previous results [83,84,86]. Regarding the interaction with an RNA test molecule (Figure 9), the hydrogen bonds between L-syn and tRNA involve C24, C40, and PSU39 (pseudouridine). Salt bridge interactions involve A38 and G26 and the van der Waals interactions include A29, G42, and U41. On the other hand, L-anti interactions consist of hydrogen bonds with C27 and G26 and van der Waals interactions with C25, C28, A29, U41, G30, PSU39, A38, and 5MC40 (5-methyl-cytosine).

However, the combination of interactions in this study favors the syn-complex. The interactions involve several H-bonds, hydrophobic interactions, salt bridges, attractive charges, and π -anions, as shown in Figure 10.

Compound	Binding Energies (kcal/mol)	Interactions	
	1BNA		
anti-[Cu(L-Gln)(phen)(H ₂ O]	-9.39	H-bond (3), van der Waals	
syn-[Cu(L-Gln)(phen)(H ₂ O]	-9.37	H-bond (3), van der Waals, Salt bridge, attractive charge	
	151D		
anti-[Cu(L-Gln)(phen)(H ₂ O]	-8.79	H-bond (3), van der Waals, π - π	
syn-[Cu(L-Gln)(phen)(H ₂ O]	-8.35	H-bond (3) van der Waals, π - π	
	6TNA		
anti-[Cu(L-Gln)(phen)(H ₂ O]	-9.64	H-bond (6), van der Waals	
syn-[Cu(L-Gln)(phen)(H ₂ O]	-10.26	H-bond (6), salt bridge, attractive charge, π -anion	

Table 4. Docking results, including the binding energies for the complexes' best molecular poses between DNA and tRNA with the two copper complexes with glutamine.



Figure 7. Docked structures of top molecular pose for: (A) anti- $[Cu(L-Gln)(phen)(H_2O]$ -1BNA and (B) syn- $[Cu(L-Gln)(phen)(H_2O]$ -1BNA.



Figure 8. Docked structures of top molecular pose for: (A) anti- $[Cu(L-Gln)(phen)(H_2O]-151D$ and (B) syn- $[Cu(L-Gln)(phen)(H_2O]-151D$.



Figure 9. Docked structures of top molecular pose for: (**A**) anti-[Cu(L-Gln)(phen)(H₂O]-6TNA and (**B**) syn-[Cu(L-Gln)(phen)(H₂O]-6TNA.



Figure 10. Interactions of Compound **1** and tRNA (6TNA). (**A**): L-syn and (**B**): L-anti. The orange dashes represent the attractive charge and the salt bridge interactions. The conventional hydrogen bonds are represented by green dashes, while light green spheres show the van der Waals interactions.

3. Discussion

In our search to provide vanadium complexes that mimic the interactions of decavanadates and cyclo-tetravanadates with side-chain groups of proteins with positive or hydrogen-bond donor amino acids, the series of amino acids studied has been expanded to L-glutamine. A new heterobimetallic cyclo-tetravanadate was synthesized and characterized. L-glutamine and phenanthroline mixed copper complex was used to provide potential hydrogen bonds to anchor the complexes of planar di-imines, which are well known to interact with DNA and RNA test molecules [109–111]. Compound 1 crystallizes in the non-centrosymmetric space group P1. Interestingly L-glutamine is present in two conformations, where two of the copper complexes show a syn-conformation, while the other two show an anti-conformation.

The existence of $[V_4O_{12}]^{4-}$ was confirmed by FTIR spectroscopy analysis, where the characteristics bands are located between 910–1000 cm⁻¹ for asymmetric and symmetric vibrations of terminal V(O_t)₂. The asymmetric vibrations of the bridge V–O_b–V groups could be allocated to bands below 850 cm⁻¹. It is feasible to establish that cyclo-tetravanadate ions are involved in several hydrogen-bond interactions, causing the usual bands to divide; as a result, there are numerous shoulders, each indicating different V (O_t)₂ and V-O_b-V vibration strengths. Although second derivative spectra are rare, these are very informative since shoulders end up becoming peaks. On the other hand, the visible spectrum shows an asymmetric absorption band at λ_{max} value 627 nm because there is the promotion of d-d electrons from (d_{xz}, d_{yz}), d_{xy}, and d_z² to the orbital d_x²-y². Therefore, although in solid-state, the geometry corresponds to a square-based pyramid, it may change in aqueous solution to elongated tetragonal octahedron.

Using DFT calculations, the structure was minimized from the crystallographic data, allowing the frontier molecular orbitals and the map of electrostatic potential to be calculated. Global reactivity descriptors, such as chemical potential (μ), electronegativity (χ), hardness (η), softness (s), and electrophilicity index (ω), were evaluated based on conceptual DFT approach. The presence of hydrogen bonds dominates all the interactions. Thus an AIM study was conducted to characterize the compound.

It is important to mention that there have only been a few reports on cyclo-tetravanadates: two of them were conducted with organic molecules (C6H9N2)4(V4O12)·4H2O and [(CH3)3-CNH₃]₄(V₄O₁₂) [112,113], vanadium [114,115], iron [116], cobalt [117], nickel [118], zinc [119,120], and Zr [121]. In the particular case of copper [96,122,123], four complexes have been reported; in all those cases, copper ions were in a trigonal bipyramidal geometry. There have also been also four cyclo-tetravanadates containing three metals [124]. Our group has contributed with [Cu(Lys)(phen)]-(V₄O₁₂)-[Cu(Lys)(phen)], [Cu(Orn)(bipy)]-(V₄O₁₂)-[Cu(Orn)(bipy)], [Cu(Gly)(phen)(H₂O)]₂ [Cu(Gly)(phen)]–(V₄O₁₂)-[Cu(Gly)(phen)] [Cu(Orn)(phen)]-(V₄O₁₂)-[Cu(Orn)(phen)], and [Cu(Lys)(bipy)]-(V₄O₁₂)-[Cu(Lys)(bipy)], where the cyclo-tetravanadate acts as a bridge and the copper atoms are in a square pyramidal geometry [83–85]. In this paper, we present $[Cu(L-Gln)(phen)(H_2O)]_4(V_4O_{12})$, the first anionic cyclo-tetravanadate of this type in which the anion is not coordinated to the contraionic copper complexes. Concerning the planarity of the cyclo-tetravanadates, there are many possibilities, ranging from completely flat (D4h symmetry) to Cs symmetry; the compound reported here has Cs symmetry. Although other cyclo-tetravanadates, such as $[Fe(bipy)_3]_2[V_4O_{12}]\cdot 10H_2O$, $Zn(2,2'-bipy)_3]_2V_4O_{12}\cdot 8H_2O$, show uncoordinated (V_4O_{12}) anions, we expected a similar structure as our compound with glycinate. However, the introduction of the chiral carbon of the glutamine aminoacidate requires the use of DL-glutamine to surround the cyclo-tetravanadate. Progress has been made in that direction [125]. As pointed out before, the release of the components upon hydrolysis generates active species of vanadium and copper [83–85]. The cationic copper complexes generated have a strikingly similar molecular structure to Casiopeinas[®] (CAS), a class of copper-based drugs developed by Ruiz-Azuara and colleagues [126–128]. CAS is the first family of antineoplastic copper compounds that have reached the clinical phase in the world [129]. The complexes $[Cu(L-Gln)(phen)(H_2O)](OClO_3)$ and $[Cu(L-Gln)(phen)(H_2O)](OClO_3)$ $Gln(bipy)(H_2O)1/2(SO_4)1/2\cdot 2H_2O$ were synthesized by Patra et al. [130] and represent the cationic part of the compound here reported. Both conformers showed efficient groove binding affinity and "chemical nuclease" activity with DNA. Our docking experiments showed that the cations syn and anti- $[Cu(L-Gln)(phen)(H_2O)]^+$ released by the hydrolysis of the cyclo-tetravanadates can interact with both DNA and RNA test molecules through electrostatic, hydrogen bonds, and hydrophobic interactions. The binding energies of the copper complexes are comparable with well-known compounds with antineoplastic activities, and in the case of RNA, as recently presented by Yunsheng Xu (2019), the closely related Casiopeina II-gly acts on lncRNA MALAT1, a non-coding RNA, thus, opening a

new mode of action for all related compounds [131]. Recently a paper by Garribba et al. has shown that Cas II-gly binds to low-molecular-mass bioligands found in blood serum (citric, L-lactic acid, and L-histidine) and cytosol (reduced glutathione (GSH), reduced nicotinamide adenine dinucleotide (NADH), adenosine triphosphate (ATP), and L-ascorbic acid). The bioligands replaced glycinato in mixed-species Cu^{II}–Me₂phen–bL/cL. The creation of these adducts may aid copper transport to the target organs [132].

Our computational analyses show that several compounds have better binding energies with nucleic acid test molecules than those already in phase 1 clinical trials. It can be observed that the ligand phenanthroline has an essential role in these interactions since it is the moiety that intercalates well into the DNA [133]. On the other hand, when the docking study was carried out considering 6TNA, the binding energies obtained were below -9.3 kcal/mol. The combination of interactions in this study favors the syn-complex. The interactions involved several H-bond, hydrophobic interactions, salt bridges, attractive charges, and π -anions. Therefore interactions with tRNA near the anticodon arm are needed to study experimentally in great detail.

4. Materials and Methods

4.1. General Considerations

The synthesis of Compound **1** was conducted using ammonium metavanadate (NH_4VO_3), L-glutamine, and 1,10-phenanthroline hydrochloride (phen) purchased from Merck Mexico. KOH was purchased from Fermont, and CuCl₂·2H₂O was purchased from Química Dinámica S. A. de C. V, Nuevo Leon, Mexico. All manipulations were conducted without specific purification of solvents and reagents. The complexes' electronic spectra were determined by UV-Vis spectroscopy with a xenon lamp Varian Cary 50 spectrophotometer(Varian, Palo Alto, CA, USA) and using a quartz cuvette of 1 cm path length. The infrared spectrum was obtained from 500 to 4000 cm⁻¹ in KBr pellets using an IR Digilab, Mod. Scimitar Spectrophotometer with FTIR (Digilab, Hopkinton, MA, USA).

4.2. Crystallization and Synthesis

Compound **1** was prepared by adding 1.00×10^{-3} mol (0.198 g) of 1,10-phenanthroline hydrochloride to 30 mL distilled water with stirring and moderate heat; once dissolved, 1.00×10^{-3} mol (0.170 g) of CuCl₂·2H₂O was added, and the clear solution was adjusted to pH 9.5 by slow addition of (10 percent) KOH solution. Subsequently, when a clear blue solution was achieved, 2.00×10^{-3} mol of L-glutamine were added while stirring. Then, NH₄VO₃, 1.00×10^{-3} mol (0.116 g) in 15 mL H₂O, was added dropwise to the solution. The final pH at room temperature was 9. The solution was filtered and left at room temperature. Blue prismatic crystals were recovered by filtration after six days.

4.3. Single Crystal X-ray Diffraction

Single crystal of $[Cu(L-Gln)(phen)(H_2O)]_4[V_4O_{12}]\cdot(H_2O)_8$ (Compound 1), suitable for X-ray diffraction, was selected and mounted on an Xcalibur, Atlas, Gemini diffractometer. The crystal was kept at 293.15 K during data collection. Using Olex2 [134], the structure was solved with the SHELXD [135] structure solution program using dual space and refined with the SHELXL [136] refinement package using least squares minimization. Compound 1 crystallizes in the triclinic space group P1, with only one asymmetric unit filling the unit cell. Figure 1 shows the complete molecule crystal data. Selected crystal data and details are shown in Table 1 and Tables S1–S5 for the compound's structure determination. The CCDC number is 2,081,603 (Compound 1). Additional crystallographic data free of charge from http://www.ccdc.cam.ac.uk/conts/re-trieving.html (accessed on 15 May 2021) (or CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Using Mercury CSD (release 4.3.1) [87].

4.4. Computational Methods

Molecular structure, frontier molecular orbitals (FMO), and molecular electrostatic potential (MEP) of Compound 1 was carried out using the hybrid functional B3LYP [137], including the empirical dispersion method of Grimme with Becke-Johnson damping, GD3BJ [138]. The double zeta split-valence Def2SVP basis set [139] for C, H, O, and N atoms and LanL2DZ basis set [140] for Cu and V atoms were used. In addition, LanL2DZ was used as an effective core potential (ECP) for Cu and V atoms [141]. The effect of the implicit solvation was included with the polarizable continuum model (PCM), using the integral equation formalism variant (IEFPCM) with water as the solvent [142]. Calculations were performed with the Gaussian16 and GaussView programs [143,144]. Global reactivity descriptors were calculated from the FMO energies based on the conceptual DFT approach [145]. Atoms in molecules analysis (AIM) using AIMAll software (Version 14.11.23, TK Gristmill Software, Cambridge, MA, USA) was performed for analyzing the non-covalent interactions [146].

4.5. Molecular Docking

Molecular docking analysis was performed with the semi-flexible method. The DNA fragments used were Dickerson-Drew dodecamer (DDD) with the sequence d(CGCGAATTCGCG) (PDB ID: 1BNA [147]) and DNA fragment with the sequence d(CGATCG) (PDB ID:151D [148]. The RNA docking was carried out using the yeast tRNA (PDB: 6TNA) [149] and considered a rigid entity. Complete flexibility was allowed for the coordination compounds [150], and it was performed using the Autodock Tools 1.5.6 software (accessed on 1 September 2021) [151], which includes the addition of polar hydrogens and empirical particles of atomic charges (Gasteiger-Marsili method). A grid box that encloses the entire DNA fragment was used with sizes 70, 70, and 120 Å for the 1BNA DNA fragment and 60, 60, and 76 Å for the 151D DNA fragment. For tRNA, blind docking was carried out using three different boxes that enclosed the entire tRNA with the sizes 96, 80, 108 Å, followed by a re-docking of the compounds in their docked pose with potential and preferred minimized energy using a box centered on the compounds with the sizes 40, 40, and 40 Å. The grid spacing for all the docking calculations was set to the 0.375 A default value, using the Lamarckian genetic algorithm (LGA) searching methods. The parameters for the copper atom were the sum of VDW radii of two similar atoms (3.50 Å), plus the VDW well depth (0.005 kcal/mol), plus the atomic solvation volume (12.0 Å3), plus the atomic solvation parameter (-0.00110). The H-bond radius of the heteroatom in contact with hydrogen (0.0 Å), the well depth of the H-bond (0.0 kcal/mol), and different integers showed the type of H-bonding atom and indexes for the generation of the auto grid map (0, -1, -1, 1), respectively). The corresponding figures were prepared using Biovia Discovery Studio [152].

5. Conclusions

A new V/Cu heterobimetallic compound was synthesized and characterized by visible and FTIR spectroscopies. Compound 1 crystallizes in the triclinic P1 space group with the cyclo-tetravanadate anion acting as a free ion, only bound to the copper moieties through hydrogen bonds and water molecules. The cyclo-tetravanadate anion provides a hydrogenbonded bridge between two conformers syn and two anti of the [Cu(L-Gln)(phen)(H₂O)] cationic complexes. The cyclo-tetravanadate is not coordinated to the copper, and thus, it can be easily separated in an aqueous solution to act independently. The AIM analysis indicated that the hydrogen-bond interactions govern the structural arrangement in the compound. Additionally, the Cu-O interactions (between Cu with O of apical water or with O of cyclo-tetravanadate) have high interaction energy values, indicating that they are responsible for the supramolecular arrangement. Also, the hydrogen bonds surrounding the cyclo-tetravanadate could serve as models for the interaction of side-chain hydrogen bond donors in hydrophilic pockets in proteins. The copper moieties are reminiscent of Casiopeinas IIa y IIIia, which are in phase I clinical trials in Mexico. Docking studies indicated that both compounds can interact with DNA and RNA test molecules, acting as groove binders and intercalating agents. It is important to point out that a combination of electrostatic and hydrophobic interactions, π - π , and hydrogen bonds, are responsible for binding DNA/RNA molecules. The energies of interaction are comparable with other well-known and proven agents with anticancer activities. The binding energies of the RNA interactions are more favorable than other compounds already reported and point to RNA potential metallodrugs, which has become relevant as an easy-to-reach target since other important RNA molecules have been discovered to be involved in specific cancers [153]. The recently explored direct injection into the tumors or the encapsulation in liposomes or nisomes opens an excellent opportunity to improve the potential antitumor activities of the compound here presented. The recent reports in cancer therapy and the new strategies for delivering vanadium and copper point to significant advances in the near future.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/ 10.3390/met11101541/s1. Figure S1: FTIR spectrum of Compound 1 in the 500–3500 cm⁻¹ region. Figure S2: The visible spectrum of Compound 1. Crystallographic data are presented in Tables S1–S5. Topological parameters (a.u.), interaction energies EH . . . Y (kcal mol⁻¹), and interatomic distances Dint (Å) are presented in Table S6. The check CIF of Compound 1 is also included in the Supplementary Materials.

Author Contributions: N.D.C.-M. and B.M.-V. carried out experimental work (synthesis, crystallization, and experimental characterization). F.J.M.-B., M.E.C. and L.N. carried out the theoretical characterization. A.M. carried out the X-ray diffraction determination. E.G.-V., M.E.C. and B.L.S.-G. wrote and revised the manuscript. N.D.C.-M. and E.G.-V. conceived and designed this study. All authors contributed extensively to the work presented in this paper. All authors have read and agreed to the published version of the manuscript.

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