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Research paper

Water Soluble Platinum Complex Featuring a Chelating Bisphosphonate Ligands as Bioactive Compound

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Abstract

A new platinum (II) complex containing ethylenediamine (En) and etidronate (Et) ligands was successfully synthesized and fully characterized. Etidronic acid (HEDP), also known as 1-hydroxyethylidene-1,1-diphosphonic acid, was first prepared and confirmed through a combination of spectroscopic analyses, including ^{31}P NMR, ^{1}H NMR, infrared (IR), and Raman spectroscopy. To enable its coordination to the platinum center, the free acid was neutralized with a stoichiometric amount of sodium hydroxide, yielding its disodium salt form, which exhibits higher solubility and stability in aqueous media. Subsequently, the desired complex [Pt(En)(Et)] was synthesized via a two-step substitution process: first, the chloride ligands in [Pt(En)Cl_2] were replaced by nitrate ions under mild conditions, and then the nitrate groups were displaced by the etidronate ligand to yield the target bisphosphonate complex. The product was isolated as a stable, water-soluble solid, and its composition and coordination environment were confirmed by spectroscopic methods. The combination of both the ethylenediamine chelating agent and the etidronate ligand results in a coordination framework that enhances the chemical stability and water Solubility of the platinum center. These features make the synthesized complex a promising structural prototype for further exploration in medicinal and biomineral chemistry, especially in the development of platinum-based therapeutic and diagnostic agents. The unique combination of stability, solubility, and potential biological activity provides valuable insights into the design of new classes of bioactive platinum (II)-bisphosphonate compounds with improved functional properties.

1. Introduction

Platinum (II) complexes are the focus of extensive research due to their tunable electronic structure and diverse functional domains. Specifically, their photophysical properties enable applications such as organic light-emitting diodes (OLEDs) and chemical sensing, while their interactions with nucleic acids/proteins highlight their significant potential role in chemotherapy [1-4]. In line with this, we previously published a comprehensive review that exclusively focused on group 10 transition metal-cyanide scaffolds, thoroughly examining their properties and applications [5].

Most notably in the biological domain, Cisplatin remains a globally essential and highly effective drug in solid tumor chemotherapy. Its robust efficacy led to its approval in 1978 for the primary

treatment of both testicular and ovarian cancers [6]. However, the widespread clinical utility of Cisplatin is severely limited by its inherently low selectivity toward tumor tissue. This poor targeting profile inevitably results in significant systemic side effects, notably nephrotoxicity and neurotoxicity, and frequently contributes to the development of acquired drug resistance. Consequently, extensive research efforts have been dedicated to the design and synthesis of novel platinum-based complexes aimed at overcoming these therapeutic shortcomings. The primary objective of this contemporary approach is to improve targeted drug distribution and, subsequently, enhance selectivity for malignant cells [7]. Furthermore, Cisplatin is also considered a primary option in the treatment of osteosarcoma, despite its significant side effects. Given these limitations, there is a critical and urgent need for the development of next-generation platinum drugs engineered with the capacity for specific bone tissue targeting. Such a strategic approach is essential to mitigate systemic toxicity and significantly increase antitumoral selectivity against osteosarcoma a cancer recognized as one of the most aggressive and debilitating bone malignancies [8]. This directs our attention toward the use of ligands that inherently target bone tissue.

Bisphosphonates (BPs) are a well-known and long-established group of compounds with broad applications in pharmaceutical sciences. All members of this family share a common structural unit, $C(PO_3H_2)_2$, and the term "bisphosphonates" more precisely refers to the salts and metal complexes derived from BI phosphonic acids (BPAs). A key feature of these compounds is their exceptionally strong affinity for hydroxyapatite (HAP) the main inorganic constituent of bone. This arises from their pronounced ability to chelate calcium ions, allowing bisphosphonates to selectively accumulate at bone surfaces. Because of this unique property, bisphosphonates are widely used as bone-targeting agents in the treatment of several bone-related diseases, such as osteoporosis, multiple myeloma, hypercalcemia, and Paget's disease [9, 10]. In addition to their medical importance, they also serve industrial purposes, notably as scale- and corrosion-inhibiting agents [11, 12]. From a structural perspective, bisphosphonates contain two phosphonate groups linked through a central carbon atom (P-C-P). The remarkable stability of this P-C-P backbone underlies its strong binding to bone minerals. This structural robustness enables them to firmly adhere to the bone matrix and, consequently, to prevent bone resorption and degradation [13]. Crucially, the utility of platinum agents linked to functional phosphonates was demonstrated by Keppler and co-workers in the early 1990s, yielding high activity in transplantable osteosarcoma models (*in vitro* and *in vivo*)[14]. Natile and co-workers developed a series of platinum complexes in which bisphosphonates were used as leaving groups, revealing that these compounds act through a cytotoxic mechanism different from cisplatin [15-17].

The complex $[\{cis\text{-}Pt(NH_3)_2\}_2(ZL)]^+$ has been reported, in which the anticancer drug cisplatin and zoledronic acid a nitrogen-containing bisphosphonate widely used as a standard treatment for osteoporosis are combined into a single molecular structure. Both drugs have previously been approved for clinical use by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). This cisplatin–zoledronic acid complex exhibits lower cytotoxicity than cisplatin but higher than free zoledronic acid, showing the greatest activity against the U937 histiocytic lymphoma cell line [18].

Herein, we report the synthesis and structural characterization of a new Pt (II)-bisphosphonate complex, incorporating the 1,2-ethanediamine co-ligand. The molecular identity and purity of this coordination compound were confirmed by spectroscopic methods, including ^{1}H and ^{31}P NMR, FT-IR, and Raman analysis. Furthermore, this work paves the way for further investigations focusing on the cytotoxic properties of the complex and its mechanism of action against various malignant cell lines, and application in the selective treatment of osteosarcoma.

2. Materials and methods

In this experiment, all reagents, including phosphorus trichloride (PCl_3), acetic acid (CH_3CO_2H), hydrochloric acid (HCl, 37%), nitric acid (HNO_3, 65%), potassium chloride (KCl), sodium hydroxide (NaOH), and ethylenediamine (En), were of analytical grade and purchased from commercial suppliers such as Sigma Aldrich and Merck. The solution NMR spectra in DMSO-d_6 and D_2O were recorded on a Bruker Avance DPX 300 MHz spectrometer at 298 K. The chemical shifts (δ) were referenced to external standards tetramethyl silane (TMS) for ^{1}H and 85% H_3PO_4 for $^{31}P\{^{1}H\}$.

Coupling constant (*J*), constant, and chemical shifts were reported in hertz (Hz) and parts per million (ppm), respectively. Raman spectra were collected using a DL G100 spectrometer, while infrared spectra were recorded on a Thermo Nicolet NEXUS 470 FT IR spectrometer.

The FT-IR measurements were performed in the 400-4000 cm^{-1} region.

Preparation of Etidronic acid ($C_2H_8O_7P_2$, HEDP), (L_1)

In a 1-liter round-bottom flask fitted with a magnetic stirrer, 32 mL of distilled water (1.6 mol) was mixed with 0.9 mol of glacial acetic acid at room temperature. After achieving a uniform solution, phosphorus trichloride (PCl_3, 1.0 mol) was introduced slowly drop by drop over roughly three hours. The mixture, initially clear, turned progressively turbid as the addition proceeded. Once all of the PCl_3 had been added, the temperature was brought up steadily to 104 °C. The reaction was held at this temperature under reflux for two hours, during which the turbulence in the flask subsided and the mixture became more homogeneous. Excess acetic acid was stripped using a rotary evaporator set to 60 °C. The product at this stage was a thick, colorless oily liquid. Left in contact with air for several days, it gradually solidified into transparent crystals, which remained stable under ambient conditions [19]. ^{1}H NMR [DMSO-d_6, δ]: 1.46(t, CH_3), 7.23(s, OH^-).

Preparation of etidronate disodium (HEDP.2Na), (L_2)

A solution of etidronic acid (0.0118 g) in distilled water (4 mL) was prepared, affording a clear medium. The initial pH was measured at approximately 1.8, indicating an acidic environment. For conversion to the disodium salt, two drops of aqueous sodium hydroxide (20 %, NaOH) were added, and the pH shifted to about 3.45. As previously reported, a pH range of 2.0-3.5 provides suitable conditions for disodium etidronate formation [20]**.**

Preparation of [Pt (En)Cl_2] (1)

An aqueous mixture (2 mL) of 1,2-ethanediamine (En) (116.8 µL, 1.75 mmol), sodium chloride (0.205 g, 3.5 mmol), and potassium tetra chloroplatinate (II) (0.7264 g, 1.75 mmol) was stirred overnight at ambient temperature under exclusion of light. The reaction mixture was then cooled to 4 °C. A yellow precipitate formed, which was collected by filtration from the nearly colorless supernatant and washed sequentially with ice-cold 0.1 M hydrochloric acid and ethanol. The solid was air-dried. Recrystallization was carried out by dissolving the crude product in hot (near-boiling) 10^{-3} M hydrochloric acid. Upon cooling, subsequent filtration, and washing under the same conditions as before, afforded yellow needle-shaped crystals (0.34 g, 60 % yield) [21]. ^{1}H NMR [DMSO-d_6, δ]: 2.23(s, CH_2), 5.33(s, NH_2)

Preparation of [Pt(En)$(NO_3)_2$](2)

A suspension of [Pt(En)Cl_2] (1.10 g, 3.373 mmol) in water (200 mL) was treated with $AgNO_3$ (1.146 g, 6.746 mmol) and maintained under continuous stirring overnight at ambient temperature under exclusion of light. The white precipitate formed was separated by filtration, and the filtrate was evaporated to dryness under reduced pressure to give pale yellow solid. (1.20 g, 94 % yield) [22]. ^{1}H NMR [DMSO-d_6, δ]: 2.56(s, CH_2).

Preparation of [Pt(En)(Et)](3)

An aqueous solution of etidronate (1 equiv., pH 3.45) was combined with an equimolar amount of [Pt(En)$(NO_3)_2$] complex. The resulting mixture was stirred at ambient temperature for three days, protected completely from light by aluminum foil. A dark green precipitate formed, which was recovered by filtration, and dried under vacuum. ^{1}H NMR [D_2O, δ]: 1.53(t, CH_3), 2.48(s, CH_2). ^{31}P{^{1}H}NMR[D_2O, δ]: 29.00.

3. Results and Discussion

Synthesis and Characterization

The synthetic procedures adopted for the preparation of platinum (II) complexes [Pt(En)Cl_2](**1**), [Pt(En)$(NO_3)_2$] (**2**), [Pt(En)(Et)] (**3**) together with etidronic acid (**L_1**) and disodium etidronate (**L_2**) , are illustrated in Figure 1. Complex [Pt(En)Cl_2] (**1**) was obtained by the reaction of K_2[$PtCl_4$] with ethylenediamine in in water, giving yellow crystals. Substitution of chloride ligands by nitrate ions proceeded readily when $AgNO_3$ was introduced under light protected conditions, affording [Pt(En)$(NO_3)_2$] (**2**) as a pale-yellow solid in high yield [21, 22]. Etidronic acid (**L_1**, HEDP) was prepared by the controlled reaction of phosphorus trichloride with glacial acetic acid in aqueous medium, followed by heating at 104 °C under reflux. The viscous product gradually solidified upon exposure to air, yielding transparent crystals of pure etidronic acid.

Partial neutralization of L_1 with aqueous NaOH at pH ≈ 3 yielded the disodium salt (**L_2**, HEDP.2Na). Under these mildly basic conditions, the disodium form develops preferentially, providing a water-soluble ligand well adapted for coordination to Pt(II) centers [19, 20]. The final complex, [Pt(En)(Et)] (**3**), was obtained by reacting an aqueous solution of disodium etidronate (**L_2**, pH ≈ 3.4) with an

equimolar amount of [Pt(En)$(NO_3)_2$] (**2**). The mixture was stirred thoroughly at ambient temperature for three days under complete exclusion of light. A dark-green precipitate formed, which was isolated by filtration and dried in vacuo [5]. The reaction demonstrated efficient chelation between the oxygen-rich etidronate and the square-planar Pt (II) center.

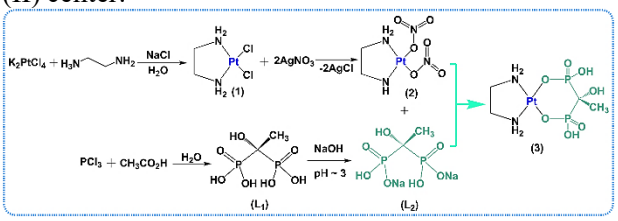

Figure 1. *Synthetic pathway for etidronic acid (L_1), disodium etidronate (L_2), and the Pt(II) complexes [Pt(En)Cl_2] (1), [Pt(En)$(NO_3)_2$] (2), and [Pt(En)(Et)] (3).*

The identity of all compounds was confirmed in solution using ^{1}H NMR spectroscopy. For [Pt (En)Cl_2] recorded in DMSO-d_6, the spectrum exhibits broad resonances corresponding to the coordinated ethylenediamine moiety, with NH_2 protons appearing at δ 5.33 ppm and –CH_2 protons at δ 2.23 ppm. The broadness of the signals reflects weak ^{195}Pt-H coupling and solvent-induced exchange, consistent with the formation of a square-planar Pt (II) complex. When measured in D_2O, the NH_2 signals vanish entirely, owing to the swift exchange between solvent deuterons and the amine hydrogens. Such behavior is typical in protic media, where hydrogen bonding
within polar amine sites facilitates the replacement o f protons by deuterium (Figure 2, S1).
As shown in Figure S2, the ^{1}H NMR spectrum of [Pt (En)$(NO_3)_2$] in D_2O closely resemble that of [Pt (En)Cl_2], reflecting the unchanged chemical surrounding of the ethylenediamine protons.

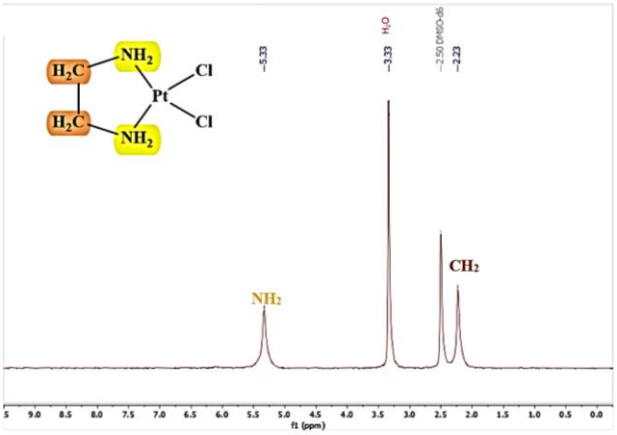

Figure 2. *^{1}H NMR spectrum of [Pt(En)Cl_2] in DMSO-d_6.*

The infrared spectrum of the complex [Pt(En)$(NO_3)_2$] reveals characteristic absorption bands corresponding to the functional groups of both the ethylenediamine ligand and the coordinated nitrate ions bound to the platinum center. A broad band around 3414 cm^{-1} can be seen, which comes from the N-H stretching of the amino groups this broadness points to hydrogen bonding in the solid form of the complex. The peaks near 2925 cm^{-1} belong to the C-H stretches of the –CH_2– groups in ethylenediamine. There's also a clear band at 1639 cm^{-1}, typical for N-H bending, it confirms that the (En) ligand is indeed coordinated to platinum (II). Finally, the two peaks at 1545 cm^{-1} and 1386 cm^{-1} correspond to the asymmetric and symmetric stretching of the NO_2 groups of the coordinated nitrate (see Figure S3).
In the ^{1}H NMR spectrum of HEDP (Figure 3), a clear triplet appears for the methyl (CH_3) group. This splitting is caused by the coupling between phosphorus and hydrogen nuclei ($^3J_{P\text{-}H}$), which produces the characteristic triplet pattern. When the spectrum is recorded in DMSO-d_6 rather than D_2O, an extra signal emerges in the region of 7-8 ppm. This additional peak belongs to the hydroxyl (OH^-) protons. In DMSO-d_6, which is an aprotic solvent, the hydrogen atoms are not exchanged, so the OH^- signal remains visible. In contrast, in D_2O, proton exchange with deuterium occurs, and as a result, the hydroxyl signal disappears (see Figure S4).

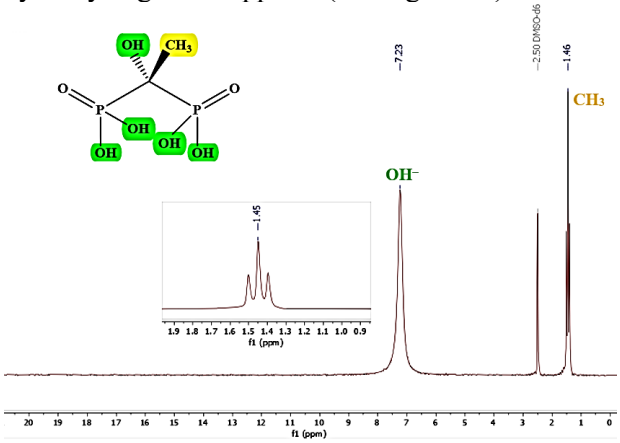

Figure 3. *^{1}H NMR spectrum of the compound HEDP in DMSO-d_6.*

In the ^{31}P NMR spectrum (Figure S5), a clear quartet appears at approximately 19.65 ppm. This splitting arises from the coupling of the phosphorus nucleus with three neighboring methyl protons. The obtained spectrum of this compound shows excellent agreement with previously reported data in the literature [23]. In the Raman spectrum of HEDP, the bands observed at 959 cm^{-1} and 1039 cm^{-1} are assigned to the δ (P-OH) bending vibrations. The

band located at 1100 cm^{-1} corresponds to the ν (P=O) stretching mode. A weak and broad feature appearing in the 2500–3000 cm^{-1} region attributed to the hydroxyl (OH^-) groups (see Figure S6). The IR spectrum of HEDP displays characteristic absorption bands at 3473 cm^{-1} and 3234 cm^{-1}, which are attributed to the O–H stretching vibrations of both phosphonic and hydroxyl groups. A medium band observed at 2854 cm^{-1} corresponds to the C–H stretching mode of the methyl group. A weak absorption near 2200 cm^{-1} can be assigned to combined overtone vibrations of the P=O and P–OH groups. The strong band at 1450 cm^{-1} arises from P–C stretching, confirming the linkage between the phosphorus atom and the central carbon. A distinct absorption at 1100 cm^{-1} is due to the P=O stretching vibration. Finally, the bands appearing at 1012 cm^{-1} and 909 cm^{-1} are characteristic of the P–OH stretching vibrations of the phosphonic acid groups present in HEDP (see Figure S7).

In the ^1H NMR spectrum of the compound, three signals are observed corresponding to the methyl protons of the etidronate ligand and the ethyl protons attached to the amine group (Figure 4). Due to the exchangeable nature of the amine and hydroxyl protons in the D_2O solvent, their signals are not present in the spectrum. Moreover, since the $^{31}P\{^1H\}$ NMR spectrum shown in Figure 5 was recorded under proton-decoupled conditions, and in comparison with similar reported studies, a single resonance is expected around 29 ppm. Therefore, the obtained spectrum is in complete agreement with the expected result [24].

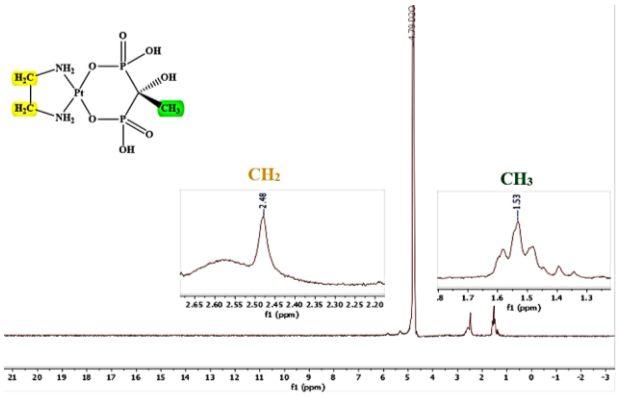

Figure 4. *^1H NMR spectra of the [Pt(En)(Et)] complex in D_2O.*

The IR spectrum of the [Pt(En)(Et)] complex exhibits distinct absorption bands that clearly confirm the coordination of nitrogen atoms from the ethylenediamine ligand and oxygen atoms from the phosphonate groups to the platinum center. The broad band around 3500 cm^{-1} corresponds to the O-H stretching vibration of phosphonate groups, indicating their involvement in hydrogen bonding within the complex structure.

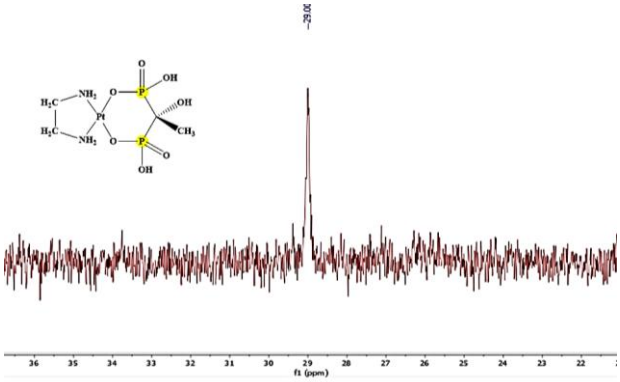

Figure 5. *$^{31}P\{1H\}$ NMR spectra of the [Pt(En)Et] complex in D_2O.*

The absorption observed at 3198 cm^{-1} is assigned to the N–H stretching vibration of the ethylenediamine ligand, while the band at 1641 cm^{-1} relates to NH_2 bending, further supporting the presence of coordinated amine groups in the complex. Furthermore, the bands at 2348 cm^{-1}, 1144 cm^{-1} and 998 cm^{-1} are attributed to P-OH and P=O stretching vibrations, respectively, which provide evidence for the participation of phosphonate oxygen atoms in Pt-O-P bond formation within the complex (see Figure S8).

4. Conclusion

This study reports the synthesis and characterization of a new Pt(II) complex with ethylenediamine (En) and etidronate (Et) ligands. The synthetic route is via HEDP disodium salt and ligand exchange from the $[Pt(En)Cl_2]$ complex to yield an extremely stable and water-soluble platinum-bisphosphonate compound. Spectroscopic confirmation (including ^1H and ^{31}PNMR) confirms the target structural motif. This new coordination compound exhibits a remarkable architectural basis, making it a highly promising candidate for studies on cytotoxic property and more broadly coordination chemistry efforts toward the development of next-generation metallodrugs.

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