Applied Chemical Engineering (2025) Volume 8 Issue 3 ISSN: 2578-2010 (O)
doi: 10.59429/ace.v8i3.5723

REVIEW ARTICLE

Oxaliplatin chemistry: Anticancer platinum-based complex of third-generation oxaliplatin (Eloxatin)

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ABSTRACT

Oxaliplatin (Eloxatin) is a coordination complex featuring a central platinum atom. Its coordination sphere consists of a trans-1,2-diaminocyclohexane ligand and a bidentate oxalate ligand coordinated through its oxygen atoms. Stereochemical studies confirm a square planar geometry around the platinum(II) center, with the trans-1,2-diaminocyclohexane and oxalate ligands arranged within this plane. The complex exhibits dsp^2 hybridization and is diamagnetic. The antineoplastic mechanism of this third-generation platinum-based drug, oxaliplatin (Eloxatin), involves cytotoxicity primarily mediated by interference with cell growth and multiplication. This occurs via a two-stage process: first, the aquation (displacement of the oxalate ligand by water molecules, analogous to chloride displacement in cisplatin); second, the coordination of the activated complex to DNA (primarily), causing DNA adduct formation. This blocks DNA replication and transcription, ultimately triggering programmed cell death (apoptosis).

Keywords: alkylated agents; anticancer platinum-based complexes; oxaliplatin (eloxatin); the complexes stereochemistry; oxaliplatin uses as anticancer; aufbau principle

ARTICLE INFO

Received: 6 August 2025
Accepted: 20 August 2025
Available online: 11 September 2025

1. Introduction

In the mid-1960s, the focusing studies on the medications that represent platinum anti-cancer agents was started , and the beginning of these studies were concentrated on the cisplatin complex[1,2], which later evolved to include other important compounds such as carboplatin and oxaliplatin, which share a central platinum atom that forms the core of their mechanism of action[3,4]. These drugs work mainly by harmonizing to deoxyribonucleic acid (DNA) in the nucleus of the cancer cell, where irreversible damage occurs through the formation of intrastrand and interstrand crosslinks between DNA strands[5]. This crosslinking disrupts transcription and cell division, eventually inducing apoptosis in rapidly dividing cells[6]. These agents are widely used as a cornerstone in the treatment of a variety of solid tumors. This includes testicle, ovarian, lung, bladder, head and neck cancers, where cisplatin which is the key primary options and were regarded as first generation, another new types were become as the second generation such as the carboplatin which also shows great efficacy, especially in the treatment of colorectal cancer, and these drugs are often combined with other therapeutic agents to enhance efficacy[7].

As part of continuous program directed toward the study of important biologically active agents[8-10], it is become of interest to study the first drug in the antineoplastic chemotherapeutic platinum – based complex of the third-generation which is Oxaliplatin (Eloxatin) to treat of colorectal cancer, it is also called Sanofi-Synthelabo as named by Sanofi, the global healthcare and pharmaceutical company[11]. In Japan at beginning of 1976 oxaliplatin was patented and approved for medical use, It is on the WHO's list of essential medicines at 2023[12] Uses[13]:

Oxaliplatin is an alkylated agent used for treatment of the following cancers:

1. Colorectal:

Especially, metastatic colorectal neoplasm, in which the first-generation cisplatin and second-generation carboplatin had been confirmed to be inactive[14].

2. Gastric
3. Pancreatic

Also, it is undertaking clinical trials to treat the following cancers:

1. Ovarian
2. Breast
3. Non–small cell lung Neoplasm[6,13,16,17].

1.1. Chemistry

Oxaliplatin (Eloxatin) is an alkylated complex (coordinating compound) of platin consists of two bidentate ligands, the first is cyclic aliphatic of cyclohexane-1,2-diamine (also called diaminocyclohexane (DACH) with two doner atoms (two nitrogen atoms of the amino groups) the red color, and the second is acyclic aliphatic malonate (the two anionic oxygen atoms of hydroxyl groups) the blue color[18], **Figure 1**.

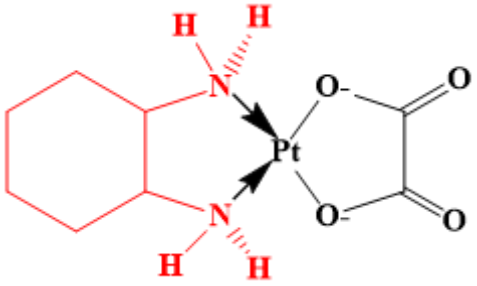

Figure 1. The cyclohexane-1,2-diamine (Ethanedioate-O,O-)platinnum(II) complex.

1.2. Complexation

These two ligands which are the basic (the Lewis definitions of acids and bases) with four lone pairs doner atoms are coordinated with the metal Platine), as shown in Fig (1)**.** According to Werner's theory, Platine is the central metal atom (the acid that accept the lone pairs of electrons to it's unfilled d orbitals)[8].

Thus, the palatine which is the central metal atom and the two ligands of cyclohexane – 1,2- diamine and the ethane dioates oxygen directly bonded to it make up the coordination sphere of the complex.

In this complex, the total charge of this complex compound is neutral, because of two oxygen of (-2 charges are equaled to the bivalent Platine. The number of donor atoms (that supplies the lone pairs of electrons for the metal-ligand bond) is the complex coordination number, which is four[19].

1.3. Stereochemistry

The stereochemical study of this complex (the three-dimensional structure of the molecule) indicated a square planar platinum (II) center of *trans*-1,2-diaminocyclohexane in addition to the bidentate oxalate group[20]. This structure is indicated the presence of pseudosymmetry in the crystal that produced confusion in its interpretation molecule has been elucidated by X-ray crystallography, **Figure 2**[21,22].

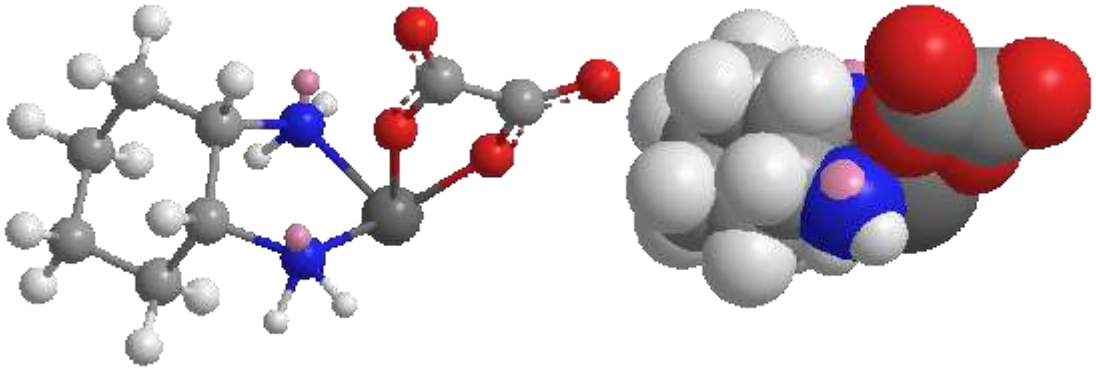

Figure 2. The 3D Structure of cyclohexane-1,2-diamine (Ethanedioato-O,O-)platinum (II) complex: **a.** Display Mode: Cylindrical Bonds, **b.** Display Mode : Space Filling.

The general rules effects of oxaliplatin isomeric conformations stereochemistry on the structure–activity relationships (SAR) were studied by Tyagi and colleagues[23], the first criteria of this rules, the conformation must be *cis*-$PtX_2(N)_2$ for bivalent platinum atom where N: (the nitrogen of the two amine groups doner atoms) of the cyclohexane-1,2-diamine ligand. The second criteria is X: the leaving ligands, usually anions, should consist of groups that have intermediate binding strength to Pt(II)[24]. Examples here of the two anionic dioates oxygen donor atoms) of the ligand acyclic aliphatic malonate. Finally, the third criteria is the amine ligands, either monodentate or bidentate, should have at least one NH group[25], **Figure 3**.

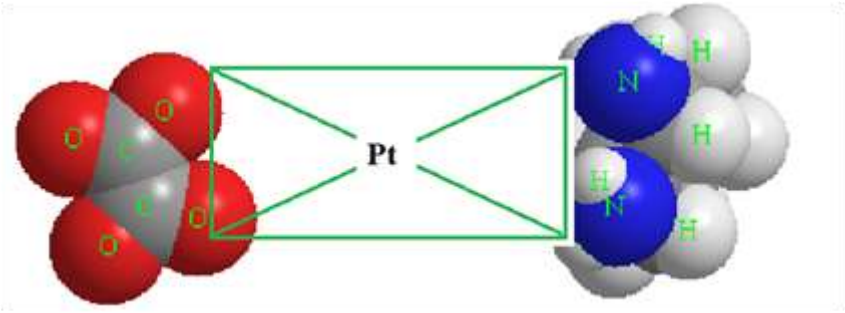

Figure 3. The coordinating complex, drawn by 3D.

Model Display: Space Filling with the four coordinating bonds, the doner atoms, (the two nitrogen atoms, the blue atoms) and (the two oxygen atoms, the red atoms) with the central Platine atom.

1.4. The coordination

The fifth shell of the transition metal element platinum which its atomic number (78) has eighteen electrons of the atomic configuration according to electron configuration through orbit (Bohr principle):

$5s^2 5p^6 5d^{10}$

But the fifth shell of platinum will have seventeen electrons and the remaining one electron will be in the sixth shell, according to Aufbau principle:

$5s^2 5p^6 5d^9\ 6s^1$

This specific rule is due to that the 5d is less energy and more stable according to Aufbau principle which states that in the ground state of an atom or ion, electrons first fill subshells of the lowest available energy, then fill subshells of higher energy[26,27] as show in **Figure 4**:

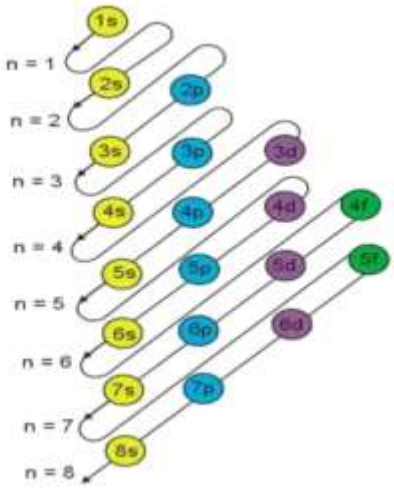

Figure 4. The electrons occupy the shells and subshells of an atom in approximate accordance with the Aufbau principle.

The electronic platinum arrangement according to Aufbau principle because of the presence of 9 electrons in d orbitals gives the atom additional stability due to the proximity of the orbital to the semi-fill $5d^9$, which relatively stable position, and the Azimuthal quantum number of 6S orbital is less than the 5d orbital:

Azimuthal quantum number of 5d orbital = l = (5 + 2) = 7

Azimuthal quantum number of 6S orbital = l = (n + 1) = 6+0 = 6

As seen here the palatine metal ion with d^8 configuration has often 4 coordinates of the common geometry is the square planar complex molecule, a Platine central atom is coordinated by the four doner atoms, which form the angles of a square on the same plane, **Figure 5**[28,29]. Because of no unpaired electron (no single electron), i.e all of the electrons are paired in this Platine coordinating complex, this complex is paramagnetic compound[30,31].

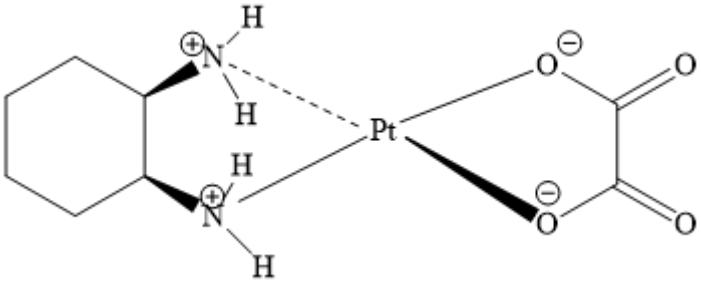

Figure 5. The oxaliplatin square planer complex geometry.

2. The antineoplastic mode of action

The antineoplastic chemotherapeutic platinum -based complex third generation oxaliplatin (eloxatin), is one of cytotoxic medication that is type of alkylated platinum complexes used as chemotherapy drug (CTX) which is **treat neoplasm by** interfering with the growing and multiplying a cell[32,33], through two stages:

2.1. The first stage (the aquation of ethanedioate ligand's two dentate anions via the two-chloride analog)

This drug is firstly exchanges with chloride ions into (cyclohexane-1,2-diamine dichloro) platinum (II) complex, this results from exchanging of ethanedioate ligand with the two chloride ions, (the drug's anionic monodentate ligands), because of the high concentration of these chloride ions in blood (about 105 mM) . The loss of these ligands is blocked by this high concentration according to Le Chatelier's principle, as shown in Figure 6. Then, in the cell the low concentrations of chlorine help in exchanging of the anions with water and undergoes aquation to form [Pt $CH(NH_2)_2(OH_2)_2]^{2+}$, therefore, it becomes more reactive to DNA. This substitution is occurred easily due to square geometry which helps in Cl-Pt bond-breaking and Cl-OH_2 bond making which is a substitution mechanism[34,35], **Figure 6**.

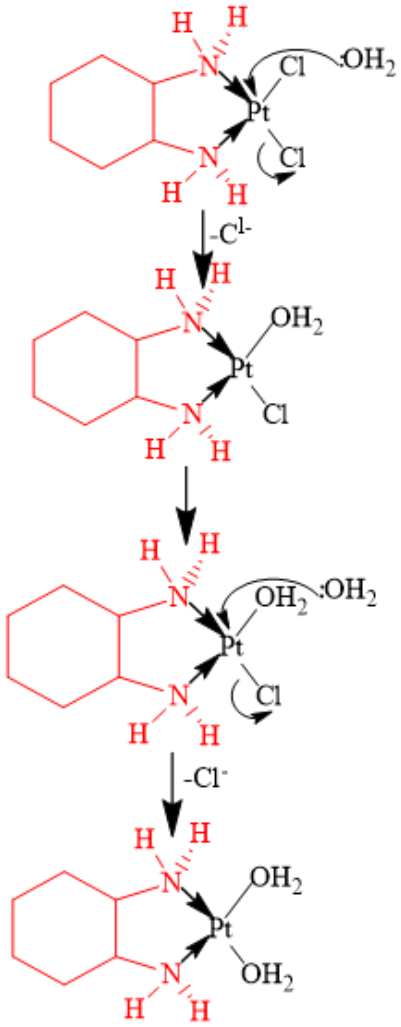

Figure 6. The mechanism of water-chloride ion substitutionNote that water is the entering group can approach from top or botom since saqure planer is easily get into chloride which is a good leaving group.

2.2. The second stage (coordinating with DNA, s amino acids)

Finally, this coordination of two monoaqua species (water) to the Pt^{2+} ion makes the medium very acidic and help the dissociation of this final complex to coordinate in the cytoplasm with DNA's two of glycine molecules inter or intra cross links and/or with glycine and adenine molecules, which denatures the DNA by blocking the duplication of **DNA**, this stop the transcription and causing cell death, Oxaliplatin, encourages programmed cell death or apoptosis[36,37], **Figure 7**.

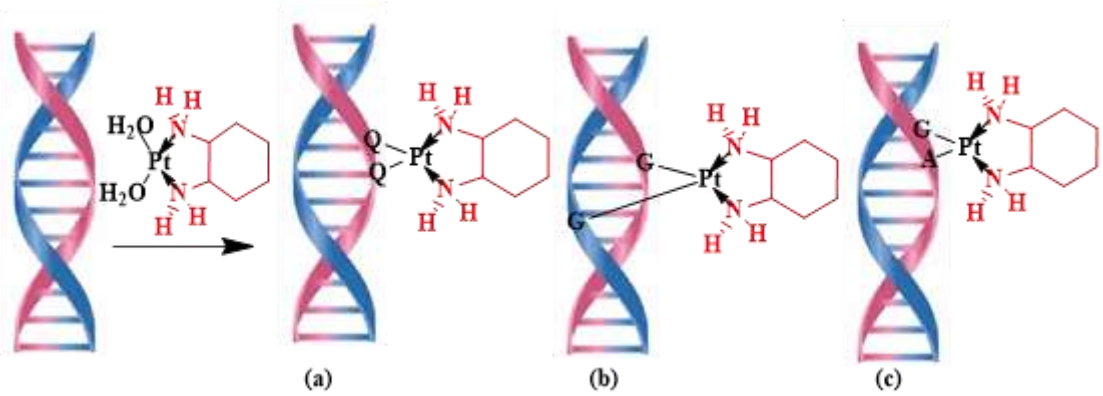

Figure 7. The platine complex coordinate to cytoplasm with DNA:

a) With two Glycine molecules intra.

b) With two Glycine molecules inter.

c) With Glycine and Adinine molecules intra

The importance of above three-dimensional structure descriptions of oxaliplatin is its coordinately arranges both inter- and intra-strand cross links with the DNA electrons donating atoms of amino acids functional groups.

3. Conclusion

The third generation oxaliplatin (eloxatin) is antineoplastic alkylated complex (coordinating compound) of platin central metal atom and the two ligands of cyclohexane – 1,2- diamine and the ethane dioates oxygen directly bonded to it make up the coordination sphere of the complex.

This complex has stereochemical geometry of a square planar (molecule) with paramagnetic charachter. The antineoplastic mode of action of this platinum-based complex, is the cytotoxic effect by its alkylated properties via its _interfering with the growing and multiplying a cell, through the first stage of the aquation of ethanedioate ligand's two dentate anions via the two chloride analog and the second stage by the coordinating with DNS, s amino acids and by blocking the duplication of **DNA**, this stop the transcription and causing cell death (programmed cell death or apoptosis).

Conflict of interest

The authors declare no conflict of interest.

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