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Review Article

Contribution of Cis and Trans-platinum (II) Complexes in Synthetic Drug and Medicinal Chemistry from the view of Coordination Chemistry

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ABSTRACT

The application of cis and trans-platinium (II) complexes in Medicinal Chemistry to Medicine is rapidly developing field and novel therapeutic and diagnostic for biological life. Cis and trans-platinium (II) complexes are now having an impact on biological antidrug and medical practice. Advances in Bio-coordination Chemistry are crucial for improving the design of compounds to reduce toxic side effect and understand the mechanism of action. Cis-platinum, as one of the leading metal based drugs is widely used in the treatment of cancer. But the application and contribution, significant side effects and drug resistance of trans-platinium (II) limited its clinical application. Biological carriers conjugated to cisplatin, analogs have improved specificity for tumor tissues, thereby reducing sides' effects and drug resistance. Platinum complexes with distinctively different DNA binding modes from that of cis platinum also exhibit promising pharmacological properties. This review focuses on recent advances in development platinum anticancer agents with an emphasis on platinum coordination complexes, shift to the Cis platinium rather than consider trans-platinium as cis-geometry. Therefore present review is exceptionally explaining the application of Trans-platinium (II) consider as Cis-platinium (II) and minimize the knowledge gap between both isomers. This review is also initiating the altitude of researchers toward the trans-geometry of platinium (II) to be concerned as Cis geometry for medicinal application.

Keyword: Platinum (II) complexes; Anticancer; Medicinal chemistry; Trans effect.

1. INTRODUCTION

Medicinal inorganic chemistry is a fairly recent offshoot of bioinorganic chemistry, itself a science still with much to learn. It is at the interface between medicine and Inorganic chemistry, and includes metal-based drugs, metal sequestering or mobilizing agents, metal-containing diagnostic aids, and the medicinal recruitment of endogenous metal ions[1].

Medicinal application of metals can be traced back almost 5000 years[2]. The development of modern Medicinal Inorganic Chemistry, stimulated by the discovery of cisplatin, has been facilitated by the inorganic chemist's extensive knowledge of the coordination and redox properties of metal ions. Metal centers, being positively charged, are favored to bind to negatively charged bio-molecules; the constituents of proteins and nucleic acids offer excellent ligand for binding to metal ions. The pharmaceutical use of metal complexes therefore has excellent potential[3]. A broad array of medicinal applications of metal complexes has been investigated, and several recent reviews summarize advances in these fields[4,5].

The application of Inorganic Chemistry to medicine is a rapidly developing field, and novel therapeutic and diagnostic metal complexes are now having an impact on medical practice. Advances in biocoordination chemistry are crucial for improving the design of compounds to reduce toxic side effects and understand their mechanisms of action[3].

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In spite of an alarming intensity of drug discovery and development in the field of metallopharmaceuticals, the group of platinum (II) complexes still leads in the number of treated patients, as well as in the number of marketed drugs[6]. The success of platinium (II) complexes group began with the discovery of anticancer activity of the *cis*-isomer of Peyrone's salt [diammine-dichloridoplatinum(II)], known as *cisplatin*, by the group of Rosenberg *et al*. [7], while the other, biologically nearly inactive *trans*-isomer (*transplatin*) remained just a scientific oddity for a long time. But the discoveries of trans-isomer was also concerned as cis-isomer before twenty years ago, when some aromatic heterocyclic derivatives trans-platinium (II) showed the behaviour to exhibit some biological activity as cis-isomer and fired up the recent development in the area and proved that *trans*-platinum complexes must be considered as biologically relevant, even if the mechanisms of their action are much more complex than in the case of *cisplatin*[6].

Cisplatin, as one of the leading metal-based drugs, is widely used in the treatment of cancer. Significant side effects and drug resistance, however, have limited its clinical applications. Biological carriers conjugated to cisplatin analogs have improved specificity for tumor tissue, thereby reducing side effects and drug resistance. Platinum complexes with distinctively different DNA binding modes from that of cisplatin also exhibit promising pharmacological properties. This review focuses on recent advances in developing platinum anticancer agents with an emphasis on platinum coordination complexes[3].

For a number of years platinum based chemotherapeutic regimens have been the mainstay for the management of epithelial ovarian cancer, testicular cancers, head and neck and a number of other solid tumor types. Cisplatin and carboplatin are frequently used in combination chemotherapy and their antitumor activity contributed significantly to the improvement in survival rates for patients with ovarian and testicular cancers when they were first introduced into the clinic[8,9].

1.1 Platinum coordination compounds

Structure-activity relationships for a class of platinum coordination compounds confirmed that only those compounds having ***cis*** geometry block cell growth. The most active complex, cisplatin (Dichlorodiammineplatinium (II)), was found to exhibit antitumor activity, whereas its *trans* isomer showed no such activity[3]. Many derivatives of cisplatin also inhibit growth, and these compounds have at least one N-H group, which is responsible for important hydrogen-bond donor properties, either in the approach of the biological target or the final structure. Most of the well-known platinum anticancer complexes have the general formula *cis*-$[PtX_2\ (NHR_2)_2]$**,** in which R = organic fragment and X = leaving group, such as chloride or (chelating *bis*) carboxylate. Many other active Pt (II) compounds are known now, even with *trans*-geometries, and these will be dealt with below[10,11].

The key factor explaining why Pt is most useful clearly relates to ligand-exchange kinetics. An important property of the platinum coordination compounds is the fact that the Pt-ligand bond, which has the thermodynamic strength of a typical coordination bond, is much weaker than (covalent) C-C and C-N or C-O single and double bonds[3]. However, the ligand-exchange behavior of Pt compounds is quite slow, which gives them a high kinetic stability and results in ligand-exchange reactions of minutes to days, rather than microseconds to seconds for many other coordination compounds. Pt (II) has a strong thermodynamic preference for binding to S-donor ligands. For that reason, one would predict that platinum compounds would perhaps never reach DNA, with many cellular platinophiles (S-donor ligands, such as glutathione, methionine) as competing ligands in the cytosol [3].

1.1.1 Cis and trans Platinium(II) complexes

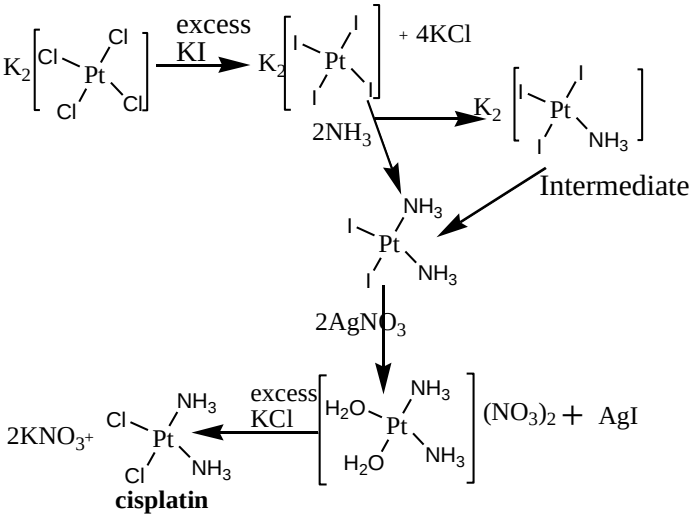
Cis and Trans dichlorodiammineplatinium (II) Complexes

Cis-Diamminedichloroplatinum (II) (cisplatin) is one of the most widely used and effective on ecological agents against cancers of the testicles, ovaries, bladder, head and neck[12]. It is also an important adjunct for cancers of the lung, cervix and breast. It's most spectacular success has been in the treatment of testicular cancer, a form of cancer previously resistant to any therapy, but now considered to be curable in most cases. However, its clinical usefulness has frequently been limited by severe side effects, such as nephrotoxicity, ototoxicity and neurotoxicity, and by the emergence of cancer cells resistant to cisplatin[12-14].

Cis-Diammine (1, 1-cyclobutanedicarboxylato) platinum (II) (carboplatin) is the only clinically successful second-generation platinum complex, being less nephrotoxic and emetogenic than cisplatin[13]. These properties have been attributed to the greater pharmacokinetic stability of its 1, 1-cyclobutanedicarboxylate ligand in solution. Like cisplatin, it only exhibits a relatively narrow spectrum of antitumor activity, and it is not effective in the treatment of cancer cells resistant to cisplatin[14].

Cis-Diaminedichloro-Platinum (II)

Cis-Diamminedichloroplatinum (II) (cisplatin) has been widely used in chemotherapy for almost 30 years. Hence, mechanisms underlying biological effects of this purely inorganic, simple, but outstanding compound have been intensively examined[15]. The successful development of metal-containing anticancer drugs clearly starts with *cis*-$[PtCl_2(NH_3)_2]$, often referred to as cisplatin (**1**). Although the compound was first described in 1845, its anticancer properties were not discovered until 1964. *Cis-Diaminedichloro-platinum* (II) is one of the most potent and effective antitumor agents discovered in the last century serendipitously by Barnett Rosenberg[3,16].



Scheme 1: Synthesis of Cisplatin

Cisplatin is usually administered intravenously rather than orally because of solubility problems. Once in the blood stream, cisplatin diffuses across the cell membranes into the cytoplasm. The intracellular Cl- concentration is less than that beyond the cell walls, so a complex equilibrium process is set up[3]. Cationic platinum complexes, such as $[Pt(NH_3)_2(OH_2)Cl]^+$, are formed when a water molecule attacks the platinum metal centre, thus eliminating a chloride ion which acts as a non-coordinating anion. The cell essentially traps the cisplatin by transforming it into a cationic component of a neutral molecule. After losing two Cl- ions, hydrolyzed cisplatin reacts with DNA, forming coordinative bonds to nitrogen atoms of the nucleobases. The active species in the cell is thus $(NH_3)_2Pt^{2+}$, not cisplatin [3.17].

Trans platinum complexes

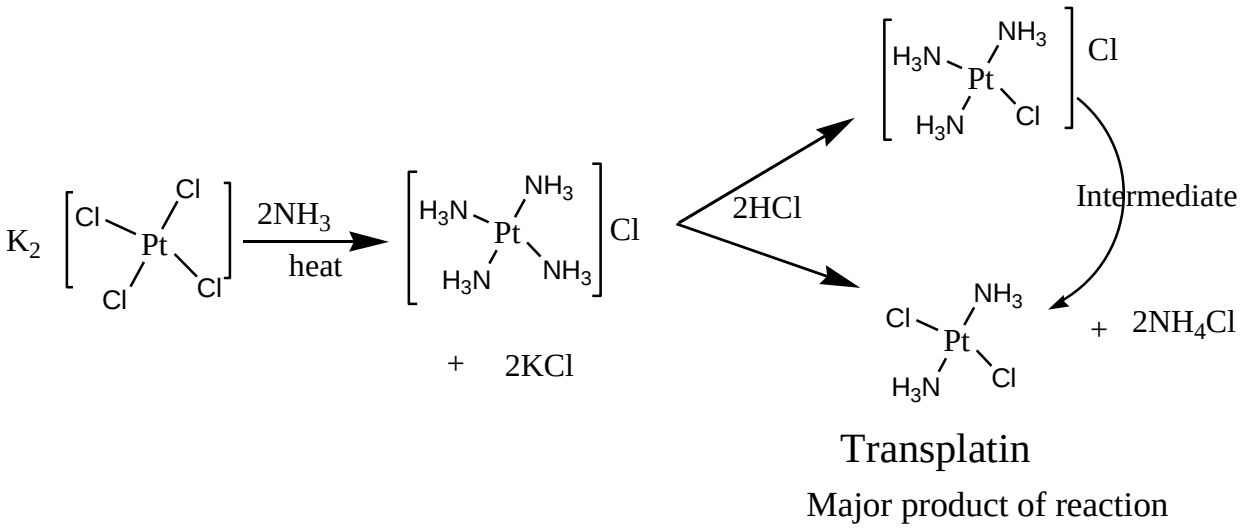
The original empirical Structure activity relationships considered the trans-isomer of antitumor cisplatin (cis-Diamminedichloroplatinum (II) and other transplatin analogues to be inactive. However, a series of bifunctional trans-platinum (II) complexes have been synthesized that show anticancer activity distinct from cisplatin (some times even more efficient than cisplatin itself and its analogs) and bind to DNA in a manner distinctly different from that of cisplatin. Increased steric bulk around the platinum center in these trans-platinum complexes can stabilize them and increase anticancer efficacy [18].

Hitherto, it has been generally accepted as a paradigm of the biochemical pharmacology of platinum antitumor drugs that a *cis*-configuration of the leaving groups is necessary for antitumor activity of platinum compounds. However, it has been recently observed that certain *trans*-platinum complexes have both *in vitro* and *in vivo* antitumor activity[3,19].

Platinum complexes with distinctively different DNA binding modes from that of cisplatin may provide higher antitumor activity against cisplatin-resistant cancer cells[19].

Among such complexes are those with amine ligands having *trans*-stereochemistry. The *trans* analog of cisplatin, *trans*-Diamminedichloroplatinum (II) (*trans*-DDP), is inactive, but its inertness may originate in part from kinetic instability and consequent susceptibility to deactivation. Substitution of one or both ammine ligands in *trans*-DDP with more bulky ligands can retard ligand substitution reactions of the two chloride ions, thereby reducing undesired reactions between platinum and cellular components and facilitating its interaction with DNA. Discovery of these properties has stimulated the development of additional complexes with *trans*- geometry. Several classes of *Trans*-platinum complexes have been characterized, showing

favorable cytotoxicity against cancer cells, especially cisplatin-resistant cells[3,19-21].



Scheme 2: Synthesis of Transplatin

1.2 Transplastin complexes water soluble and anticancer activity

The present review also generally relates to water soluble trans-Pt (II) complexes, their synthesis routes, and their methods of use as anti-cancer agents. The use of cisplatin, cis-$[PtCl_2(NH_3)_2]$, and carboplatin, $[Pt(CBDCA)(NH_3)_2]$ (CBDCA=l,l-cyclobutanedicarboxylate), in the treatment of certain cancers is well-established. Nevertheless, there is a continued interest in the design of structurally novel platinum compounds that show antitumor activity complementary to that of the clinical drugs. The fact that transplatin, trans-$[PtCl_2(NH_3)_2]$, was found to be therapeutically inactive, has been considered a paradigm for the structure-activity relationships (SAR) of platinum (II) antitumor compounds; However, the presence of a planar ligand such as pyridine or quinoline, e.g., in trans-$[PtCl_2 (NH_3)$ (quinoline)], dramatically enhances the in vitro cytotoxicity of the trans-geometry.

One of the intentions of the present review was to provide a trans-Pt compound (containing a planar ligand) with high water solubility and bioavailability[20-21]. In particular, the compounds having the general structural formula: $[PtBX_m (NR^*_3)]$ wherein B represents a planar, heterocyclic ring (such as thiazole, benzothiazole, quinoline, isoquinoline, acridine, imidazole, oxazole or pyrazine) containing: at least one N atom (to coordinate the metal and a pendant chelating group (such as carboxylates [$RCOO^{"}$, where R^{**}=CH_3, C_2H_5, or other lower alkyls] phosphonates, or sulfonates) that is available to chelate the metal center through one of the oxygen atoms of the group; and wherein R*= represents a hydrogen or lower alkyl moiety (e.g., C,.$_{12}$ alkyl) and each of the R* constituents can be the same or different (e.g. NH_3, NH_2R^* or NR^*_2H); and X represents an anionic ligand such as halogens (Cl, Br, or I), alkoxides (e.g. OR where R=CH_3, C_2H_5, or other lower alkyls), sulfhydryls (SR where R=CH_3, C_2H_5, or other lower alkyls), nitrates (NO_3), perchlorates (ClO_4) and carboxylates (RCOO- where R=CH_3, C_2H_5, etc.).; and where m=l or 2, depending on the protonation state of B (when B is protonated, m = 2; when B is deprotonated, m=l). The geometry of the complex is Trans for NH_3 related to the nitrogen atom of B that is covalently bonded to Pt, and the square-planar entity is electroneutral[20].

1.3 The differences between Trans and Cis Platinium (II) in drugs and synthetic medicinal chemistry

In this context, *trans*-configured platinum compounds have found increasing interest, and a number of promising drug candidates could be identified as for example Kelland's Pt(IV) complexes bearing NH_3 and aliphatic amines in *trans* position to each other[22-25]. Farrell introduced mixed ligand $PtCl_2(L_1)(L_2)$ complexes where L_1 and L_2 can be both aromatic nitrogen heterocycles and one of the ligands can be ammine or a sulfoxide. Similarly, Navarro-Ranninger's group successfully developed compounds bearing branched aliphatic amines as ligands, and Natile introduced imino-type ligands, which were synthesised in the coordination sphere of the ligand by addition

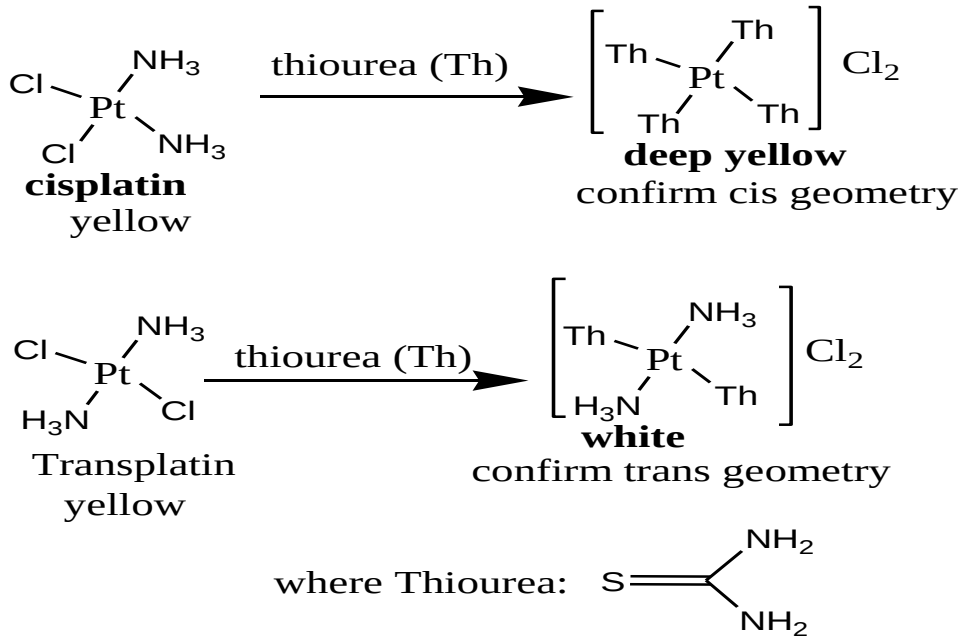
of an alcohol to a coordinated nitrile, others by condensation of acetone with a platinum-ammine precursor[26-27].

In the framework of our review, we inform new class of *trans*-configured platinum (II) compounds whose in vitro properties suggest good potential for the development of new therapeutics that are able to overcome the resistance against conventionally used platinum based antitumor agents.

Table 1: Comparison of Cis and Trans Platinium (II) complexes

Cis Platinium Complexes	Trans Platinium Complexes
Eg. Cis-($Pt(II)Cl_2NH_3$)	Trans-($Pt(II)Cl_2NH_3$)
Have potential to exhibit antitumor activity, Many derivatives of cisplatin also inhibit growth, biological activity	*trans* isomer cannot have potential to exhibit antitumor activity, But other organic derivatives of complexes can show biological activity
Ecological open against cancer	Promising dare candidates
less selective	More selective
Soft ligand (less substituted ligands)	Soft ligand only teas /strong trans effect (more rapidly substituted than ligand in Cis
Focus on ecologic cal gent that disease	More focuses on compounds have found increasing interest
Prefer flat ligand rather than planar	Prefer Planar ligand and bulk size, aromatic heterocyclic ligands.
Thermodynamically more stable, slowly ligand exchange and stay stable	Thermodynamically less stable, highly rate of ligand exchange than cis

Finally, we will perform the Kurnakow test (scheme), a method developed in 1894 by Kurnakow that allows us to distinguish between the cis and trans-isomers of square planar complexes.



Scheme 3. Confirmatory Test of Cis and Trans-platinium (II) complexes (Kurnakow test)

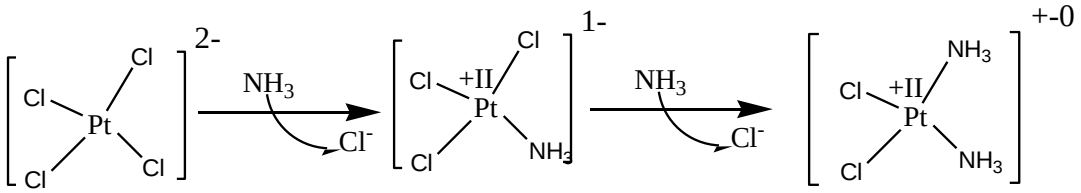
1.4 Kinetic effect of cis and transplastin from the view of co-ordination chemistry

The **Trans effect** can be defined as the effect of a ligand over rate of substitution of another ligand positioned trans to it in the square planar complexes. In general there are two factors contributing to trans direction of substitution as described in coordination chemistry. 1st factor **Trans influence:** This is a thermodynamic factor. Some ligands weaken the Metal-Ligand bond trans to them in the ground state and thus by facilitating the substitution. E.g. Strong σ- donors like H^-, I^-, Me^-, PR_3 etc., destabilize the M-L bond trans to themselves and thus by bringing the easy substitution of that ligand. 2nd factor, **Trans effect:** This is a kinetic factor and considered as true trans effect. It occurs by the stabilization of the transition state[28-30]. E.g. The strong π-acceptors like NO^+, C_2H_4, CO, CN^- etc., stabilize the transition state by accepting electron density that the incoming nucleophilic ligand donates to the metal through π-interaction. Most of the kinetic work is done on square planar

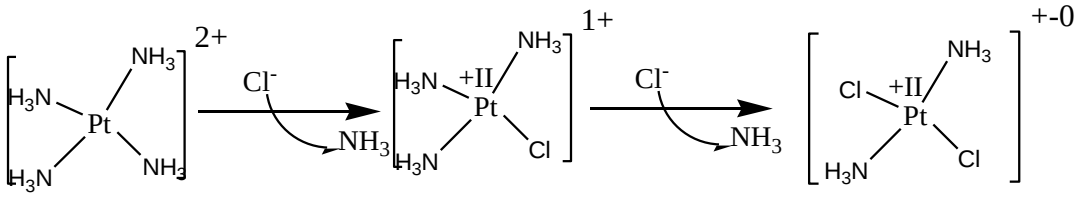
Pt(II) complexes to monitor the trans effect during the substitution reactions. Presence of bulky groups on the metal complexes decreases the rate of substitution. Infact of that, trans-platinium (II) of aromatic heterocyclic ligands show more stability and biological activity as cis geometry. When, consider coordination chemistry stabilization effect, the square planar substitution reactions occur slowly due to loss of CFSE during the formation of trigonal bipyramidal complex from square planar one. The loss of CFSE is increased down the group. Hence the square planar substitutions of 4d and 5d series are slower. This is why most of the square planar substitution kinetic studies are done on Pt(II) complexes[28].

The trans effect can dictate the product formed in the substitution reactions. The classic example of trans effect is the synthesis of **cisplatin**, cis-diamminedichloridoplatinum (II). It is prepared by substituting the two chloro groups of $PtCl_4^{2-}$ by ammonia molecules. In the first step, any of the chloro group is substituted by ammonia randomly. But in the second step, the ammonia group preferentially substitutes the chloro group cis to the first ammonia. This can be attributed to the fact that the Cl^- has a larger trans effect than NH_3. Whereas, the trans product is obtained by starting from $Pt(NH_3)_4^{2+}$. In this case the second Cl group is substituted preferentially at trans position to the first one[28].

In coordination Chemistry, the **trans effect** is the labilization (making unstable) of ligands that are trans to certain other ligands, which can thus be regarded as trans-directing ligands. It is attributed to electronic effects and it is most notable in square planar complexes, although it can also be observed for octahedral complexes [29]. The cis effect is most often observed in octahedral transition metal complexes. In addition to this kinetic trans effect, trans ligands also have an influence on the ground state of the molecule, the most notable ones being bond lengths and stability. Some authors prefer the term **trans influence** to distinguish it from the kinetic effect[30], while others use more specific terms such as **structural trans effect** or **thermodynamic trans effect**[29]. **Kinetic trans effect**: The intensity of the trans effect (as measured by the increase in rate of substitution of the trans ligand) follows this sequence: F^-, H_2O, OH^- < NH_3 < py < Cl^- < Br^- < I^-, SCN^-, NO_2^-, $SC(NH_2)_2$, Ph^- < SO_3^{2-} < PR_3, AsR_3, SR_2, CH_3^- < H^-, NO, CO, CN^-, C_2H_4. The classic example of the trans effect is the synthesis of cisplatin. Starting from $PtCl_4^{2-}$, the first NH_3 ligand is added to any of the four equivalent positions at random, but the second NH_3 is added *cis* to the first one, because Cl^- has a larger trans effect than NH_3.



If, on the other hand, one starts from $Pt(NH_3)_4^{2+}$, the *trans* product is obtained instead:



The trans effect in square complexes can be explained in terms of an addition/elimination mechanism that goes through a trigonal bipyramidal intermediate [30].

2. CURRENT AND FUTURE DEVELOPMENTS

Coordination chemistry in living systems is more than just a matter of metal-ligand bond formation and metal ligand stability. Control of metal binding to DNA, by simultaneous coordination and hydrogen bonding, especially the interest of platinium metal and it metal-ligand complexes isomers in biologically and drug discovery has been crucial to research. However, the attention of researchers toward trans-isomer platinium complexes used in medicinal chemistry and its discovery is not much developed as cis-isomers. It needs exceptionally, that the above presented highlights and outlook provide fascinating new possibilities for research for the coming

new generations. New techniques, which follow the reactions of Pt complexes and nucleic acids and proteins, will allow the detection of otherwise invisible intermediate products.

In generally, it is appreciated that vast progress has been made in the understanding of the mode of action of transplatin similar to cisplatin. Application of this knowledge in drug design is close, and it is generally expected that in the next generation improved antitumor drugs will be developed based on the knowledge of the trans-isomer Pt-DNA interactions (and their repair) and on the kinetics of binding of trans-Pt compounds to proteins and DNA. Although questions have been raised about whether the intrinsically weak metal-ligand coordination bond will ever lead to new drug applications, the kinetic control of stability is likely to overcome this.

The need for new transplatinium as cisplatin antitumor drugs was underscored by the usefulness of cisplatin and carboplatin in chemotherapy and the resistance of many tumors to these compounds. Coordination chemistry could aid in the search for cisplatin analogs if fast, high-throughput assays were available. The goal of review is to develop the knowledge and interest of researcher towards platinium isomers for rapid development of platinium complexes application in synthetic drug and medicinal Chemistry.

3. CONCLUSION

Recent advances in medicinal inorganic chemistry and discovery of synthetic drug in coordination chemistry; demonstrate significant prospects for the utilization of metal complexes as drugs, presenting flourishing stadium for inorganic chemistry. Significant progress in platinum based biological activity, like antimicrobial, antitumor, antibacterial, antioxidant and anticancer agents has been achieved, based in part on a mechanistic understanding of the DNA-binding and pharmacological effects of cisplatin. A lot of new cis-isomer platinium compounds with reduced toxicity and high specificity have been developed. The future development of medicinal inorganic chemistry requires to include the trans-isomer platinium based complexes consider for medicine purposes and an understanding of the physiological processing of metal complexes, to provide a rational basis for the design of new metal-based drugs. Application of new methodologies such as coordination chemistry, extensively used in organic drug discovery, will be beneficial for the development of inorganic compounds as therapeutics.

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