

Metal-Ligand Exchange Kinetics in Platinum and Ruthenium Complexes

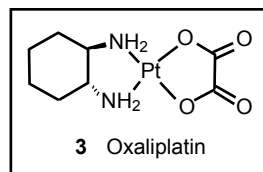
SIGNIFICANCE FOR EFFECTIVENESS AS ANTICANCER DRUGS

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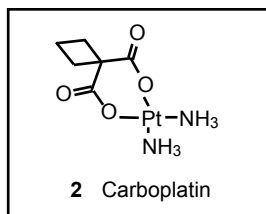
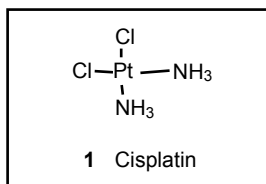
Metal coordination compounds with 'slow' metal-ligand exchange rates, comparable to those of cell division processes, often appear to be highly active in killing cancer cell lines. This is particularly marked in platinum and ruthenium complexes. Classical examples such as cisplatin, as well as very recent examples from the author's and other work, will be discussed in detail, and in the context of the current knowledge of the mechanism of antitumour action. It is shown that even though much is known about the molecular mechanism of action of cisplatin, many challenging questions are left for future research. For the ruthenium anticancer drugs molecular mechanistic studies are only at the beginning. Mechanistic studies on both platinum and ruthenium compounds have, however, opened many new avenues of research that may lead to the design of completely new drugs.

Since the appearance of the early review on *cis*-diamminedichloridoplatinum(II), commonly known as cisplatin, 1, in this Journal (1), and its early successes in the treatment of a variety of tumours, the topics of metal-DNA binding and platinum antitumour chemistry have attracted considerable interest from chemists, pharmacologists, biochemists, biologists and medical researchers (2). In fact cisplatin and the later compounds carboplatin, 2, and oxaliplatin, 3, enjoy the status of the world's best-selling anticancer drugs. This interest has stimulated much interdisciplinary scientific activity, which has already yielded quite detailed understanding of the mechanism of



action of cisplatin and related drugs. This knowledge has clearly resulted in much improved clinical administration protocols, as well as motivated research on other, related drugs containing transition metals, and their applications.

All chemotherapeutic drugs have drawbacks, including intrinsic or acquired resistance, toxicity, and consequent side effects. Cisplatin is no exception. Efforts to mitigate the drawbacks have prompted chemists to synthesise a variety of analogues, but only a handful of new drugs have resulted that have been shown to be suitable for clinical application. Improved understanding of the mechanism of action of cisplatin, resulting from the efforts of many research groups during the last two decades, has rationalised the design of new platinum drugs, and drugs based on other metals such as ruthenium (3–7). Nevertheless, many mechanistic questions remain, especially for the drugs containing metals other than platinum, and for the most recent derivatives of cisplatin (2, 8, 9).



This overview will begin with a brief introduction to the molecular, kinetic and thermodynamic details of the coordination chemistry of medicinally relevant metals, focusing on platinum, ruthenium and other noble metals that have been shown to possess important biological properties. The metal–ligand coordination bond appears to be particularly significant here. The bond is usually four to eight times weaker than a covalent bond, and there are large variations in ligand exchange kinetics for different metal–ligand pairs. This aspect will be introduced first, and will recur in later parts of the overview.

The central part of the overview will briefly summarise the state of the art in metal anticancer drugs and the current mechanistic insights, not only for cisplatin and related platinum drugs, but also for non-platinum drugs and candidate drugs.

Finally, an account will be given of the design, synthesis, structure and biological activities of new bifunctional and multifunctional platinum, ruthenium and mixed-platinum group metal (p gm) compounds with bridging ligands, and their possible development as anticancer drugs, or for other applications.

Ligand Exchange Kinetics in Coordination Compounds

To address such issues as structure, reactivity and (in)stability in the chemistry of metal coordination compounds, detailed knowledge of their thermodynamics and kinetics is important, in addition to proper knowledge of the geometric and electronic structures of the compounds.

Most chemists and many other scientists are fully conversant with classical covalent chemical bonds, such as C–H, C–C, O–H and N–H. These single bonds usually have a strength of some 250 to 500 kJ mol⁻¹ (in older units: 60 to 120 kcal mol⁻¹) (10). Double bonds as in C=O and C=N, and triple bonds as in dinitrogen (N≡N), have strengths up to 500 and 800 kJ mol⁻¹ respectively.

In addition to these covalent bonds, a large class of so-called non-covalent bonds is known. Here, much weaker interactions are found, the bonds are usually easily formed and broken, and so-called supramolecular structures may be generated. Examples of such bonds are:

- (a) Coordination bonds (50 to 150 kJ mol⁻¹)
- (b) Hydrogen bonds (20 to 60 kJ mol⁻¹)
- (c) Stacking of aromatic ring systems (10 to 40 kJ mol⁻¹)
- (d) Metal–metal bonds (50 to 150 kJ mol⁻¹)
- (e) Other hydrophobic interactions (below 50 kJ mol⁻¹)
- (f) Ionic bonds, as in lattices such as NaCl, where each Na⁺ ion is surrounded by six chloride ions; these bonds dissociate upon dissolution in water and may be compared in strength with coordination bonds.

Even though the bond strength values above are merely indicative of an order of magnitude, they clearly indicate that such bonds are weaker than classical covalent bonds. These weak interactions play an important role, for instance in protein structures (whether secondary, tertiary or quaternary), and in DNA structures (stacks within the helix, double helices). Many such bonds acting in concert, as in Watson-Crick base pairing, or over the range of several stacks along the DNA helix, may generate a rather strong interaction and hence a high thermodynamic stability.

In addition to the thermodynamic stability of molecules and aggregates, their kinetic stability must be considered. This parameter is far less discussed in the literature, and it was the late Professor Henry Taube (Nobel Prize in Chemistry, 1983), who developed this field (11). He explained why some metal ions exchange their water ligands as much as fourteen orders of magnitude faster than other metals, even when the M–OH₂ bonds have the same thermodynamic strength (e.g. 150 kJ mol⁻¹). The explanation for these differences is related to the electronic and geometrical structures, and their importance in the mechanism of action of cisplatin and other metal compounds that interfere with cell-division processes will be outlined. It has been known for several decades that the ligand-exchange processes of ions such as Mg(II), Ni(II), Ca(II), Na(I), are very fast indeed (up to 10⁹ sec⁻¹), whereas the ligand-exchange processes of Pt(II), Pt(IV), Ru(II), Os(II), Ir(III), Cr(III) are very slow; they may take hours (platinum, ruthenium) or even days (osmium, iridium) at ambient temperatures.

In the early literature, the metal–ligand bond in

cases of slow metal-ligand exchange was incorrectly termed 'covalent', or 'covalent-like'. A better classification for such bonds is in fact 'kinetically inert'. Most importantly, the 'slow' metal ions such as platinum and ruthenium, that exchange some of their ligands within the range of one to two hours, show high anticancer activity; these ligand exchange rates appear comparable to those of many cellular division processes (2).

The mechanism of ligand exchange reactions varies, depending on both the metal and the coordinated ligand. Square-planar Pt(II) compounds usually exchange their ligands *via* a so-called associative process, where the incoming ligand coordinates as a fifth ligand, after which one of the original ligands dissociates. Octahedral Ru(II) coordination compounds, on the other hand, tend to lose a ligand first (to generate a five-coordinate intermediate), after which the new ligand comes in. Details of ligand-exchange mechanism studies may be found in excellent overviews by Taube and Van Eldik (12–14).

A schematic presentation of ligand exchange rates for a variety of metal-aqua complexes is depicted in Figure 1; the figure is based on early results published by Taube (11).

History of Platinum Anticancer Drugs

The development of cisplatin will be discussed briefly, from its serendipitous discovery by Professor Barnett Rosenberg (15) and its reported

anticancer activity (16), up to the most recent papers on the discovery of new platinum compounds in the last decade. The focus will be on only the last few years and on some of the results from the author's laboratory, with appropriate references to excellent earlier published reviews in this field. After the early review in this Journal by Eve Wiltshaw (1), many highly informative reviews followed; those published before 1999 are referenced in Lippert's excellent monograph (17). References (2), (8) and (18–22) are post-1998 reviews on platinum anticancer drugs, and deal mainly with cisplatin. They are recommended for further reading.

The basic three compounds in worldwide clinical use at the time of writing (2007) are cisplatin, 1, carboplatin, 2, and oxaliplatin, 3. The orally administered drug, JM-216/satraplatin, 4, a Pt(IV) compound which is reduced *in vivo*, is promising in terms of treatment regime, since it can be administered without hospitalisation. However, careful control of the side effects requires frequent outpatient visits (23–24). A recent overview of the commonly used drugs from a patent point of view is available (25).

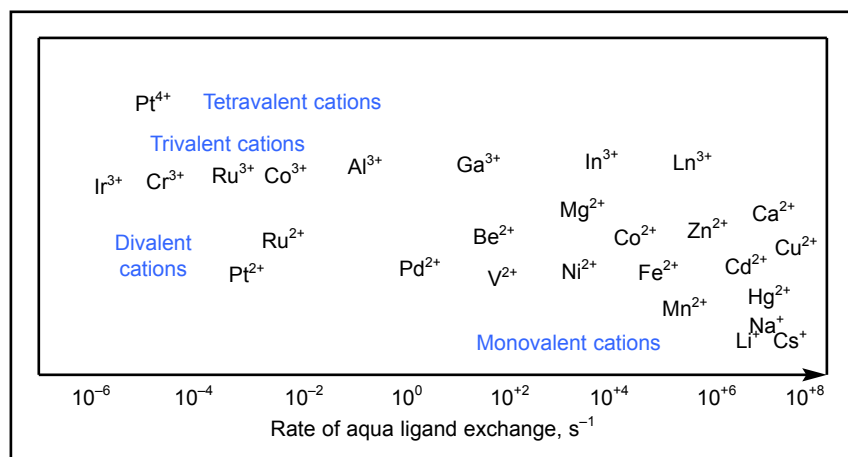
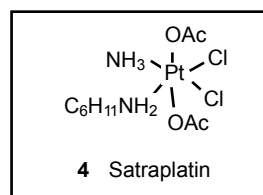


Fig. 1 Schematic, logarithmic presentation of relative kinetics of aqua (H₂O) ligand exchange, for a variety of metal ions

Mechanism of Action of Cisplatin

After cisplatin reaches the bloodstream (by injection or infusion), the drug is well known to be transported all over the body, while few ligand substitutions occur. Any exchange of the relatively mobile chloride ligands, on a timescale of a few hours, is largely compensated by the presence of the excess chloride in the blood (about 100 mM). The small fraction of the compound that does hydrolyse is held responsible for such acute toxicities as that causing kidney damage. Cisplatin eventually enters almost all types of cells, by means of passive or even active transport *via* specific receptors. Good evidence is now available that in addition to the passive process, the so-called constitutive triple response 1 (CTR1) receptor mechanism (by which copper is naturally transported), assists the platinum species to enter the cell; in the process of excretion, ATP (adenosine triphosphate) plays a role (2).

Upon entering the cells, temporary binding of cisplatin to one of the membrane components, i.e. phosphatidylserine, has been proposed on the basis of NMR analysis (26). A plausible structure for such a cisplatin-phosphatidylserine adduct is shown in 5.

At an early stage of mechanistic research on cis-

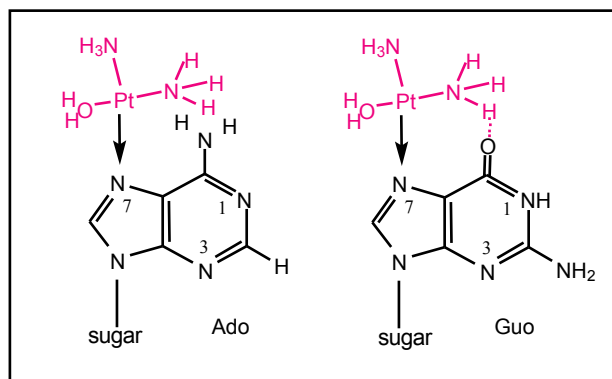
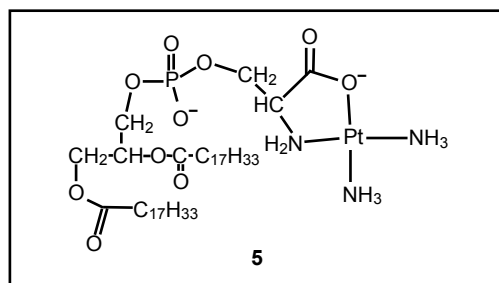


Fig. 2 Platinum binding at the N7 sites of adenosine (Ado) and guanosine (Guo), indicating that the kinetic approach to Guo is kinetically favoured due to hydrogen bonding with the O6

platin, attention was strongly focused on DNA and its fragments. It soon became clear that the guanosine (Guo) base binds more rapidly to platinum than do the other bases such as adenosine (Ado). This was explained by a higher basic pK_a and by simultaneous hydrogen bonding of the amine-NH to the O6 of guanosine, as indicated schematically in Figure 2. Careful analysis had already shown a much larger proportion of GuoGuo adducts than statistically expected (about two thirds of all platinum binds at GuoGuo (27)). This binding process has been studied on the mononuclear level (28, 29) and on the dinucleotide and trinucleotide levels (30, 31), including crystal structure determinations (32). When binding to double-stranded DNA, a clear kinked chelated structure is formed, as shown by several NMR and X-ray diffraction (XRD) structure determinations (33–36). Further work, particularly that of Lippard (37, 38), demonstrated that certain proteins in the body ‘recognise’ the kinked DNA, as a (direct or indirect) consequence of which the cell might be killed by apoptosis. A three-dimensional crystal structure of such a protein, bound to platinated DNA, has been determined recently (39). This shows that the overall kinked structure remains unchanged and that the protein more or less ‘embraces’ the platinated DNA. The link is possibly stabilised by a tryptophane side chain located between the two coordinated guanine bases.

From the outset of mechanistic studies on cisplatin and its derivatives, it was realised that other potential ligands, such as phosphate, carbonate, glutathione and peptides, are available in the cellular fluids, in addition to water and DNA. These ligands

may also bind to the platinum. Recently, preliminary *in vitro* experiments raised the suggestion (40) that carbonato-platinum species may generate DNA species different from those proven in earlier *in vivo* studies (27).

In early mechanistic studies considerable attention was given to the possibility of rapid S-donor ligand binding to the platinum species, perhaps as an intermediate (41–43) in transport to the DNA in the nucleus. Retardation of DNA binding has been proven (45), although to widely differing degrees for different S-donor ligands. Temporary binding to molecules such as glutathione and methionine is highly likely (21, 44). Visual evidence of the progress of intracellular platinum species through the cell was delivered by Moolenaar (46), using a *cis*-platinum diamine compound carrying a fluorescent label; the processes were followed in real time, from entering the cell, through entering the nucleus, to leaving the cell *via* the Golgi apparatus (46).

Other Platinum Compounds and Mechanistic Studies

The earliest variations on cisplatin were derived by substituting different amine and anionic ligands. These studies first produced carboplatin, 2, followed by compounds with different amine ligands such as oxaliplatin, 3, which is now in frequent use in the treatment of colon cancer. Further developments are shown schematically in Figure 3. In

general, ideas for new compounds arise from mechanistic findings on previous generations of drugs. Below a few important new developments are reviewed, that have recently led to or may lead to clinical applications of platinum drugs.

The obvious starting point for this account is oxaliplatin, 3 (proprietary name Eloxatin®). This was discovered over two decades ago by Kidani (47) and subsequently developed (48), but has only recently been in routine clinical use. This compound is especially interesting, as tumours which do not or hardly respond to cisplatin, for instance colorectal tumours, are sensitive to it. Nevertheless, almost the same Pt–DNA adducts have been reported as for cisplatin, including a three-dimensional adduct structure with a double-stranded section of DNA (49).

Like carboplatin, oxaliplatin and all other second- and third-generation platinum compounds with alternative amine and/or anionic ligands have at least one H-donor function available on one of the amine groups. Nevertheless, their steric and ligand-exchange characteristics are different, especially for the Pt(IV) compounds, as these react very slowly. The role of the NH group has been explained kinetically in terms of its approach to guanosine (Guo) (see Figure 2), in the additional stabilisation of the GuoGuo chelates which are formed, and also by hydrogen bonding to a DNA backbone phosphate (4, 50). This makes them less prone to

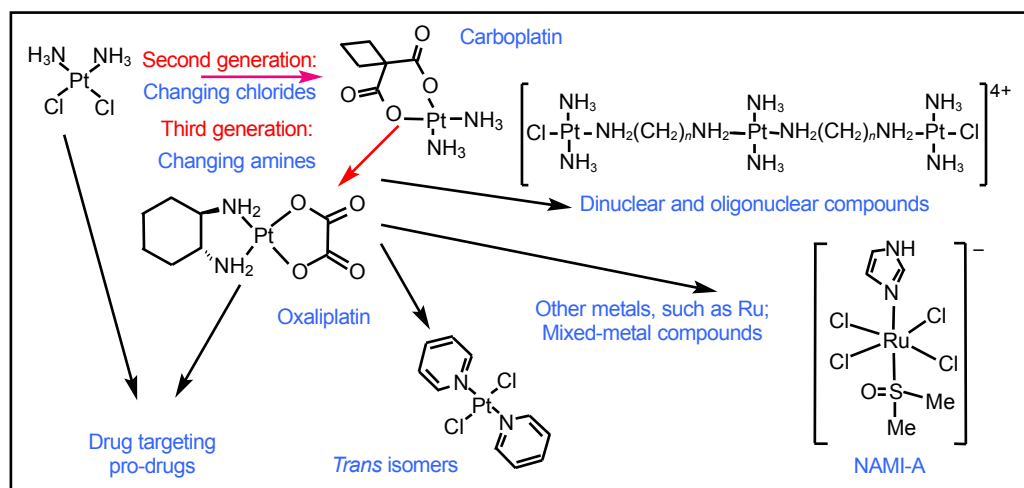


Fig. 3 Schematic history of the development of platinum drugs. Clinical use of cisplatin started in 1979, of carboplatin in 1989, and of oxaliplatin in 2004. The other compounds are not yet in routine clinical use

reversion by binding to the S-donor ligands in the cell.

The kinetically 'slow' Pt(IV) compounds that were found to be active against cancer were initially assumed to be reduced to Pt(II) *in vivo*, before binding to the DNA. Later studies have shown that some unreduced Pt(IV) compounds may react with DNA and DNA fragments (51), and that traces of Pt(II) catalyse this reaction (52–55). The mechanism of reduction also involves the phosphate groups, as proven for guanosine 5'-monophosphate (5'-GMP) (56).

Azido-platinum(IV) complexes have been reported as possible pro-drugs. Upon ultraviolet irradiation, dinitrogen is released by a redox reaction and more reactive Pt(II) amine complexes are formed (57, 58). These can react with DNA *in vitro* like the familiar Pt(II) compounds (59).

Initially all *trans*-Pt(II) compounds based on primary amines were found to be inactive; more recently, it was shown that Pt(IV) compounds were active both *in vitro* and *in vivo* (60, 61). It has also been shown that sterically hindered amine and imine groups, even when in *trans* positions, generate activity in the case of aromatic imines (62, 63) as ligands and in aliphatic amines and mixed imine-amine complexes (64–67).

A very important class of dinuclear and trinuclear compounds (see Figure 3) has been studied in detail by Brabec and Farrell (68–73). The flexible link between the platinum ions allows multiple binding on the DNA chain. This has resulted in interesting geometrical differences between isomers (74).

Another approach deals with more rigid bridges

between the platinum ions. After the first experiments by Kozelka (75), Komeda (76–78) focused on rigidly bridged dinuclear platinum compounds, containing either pyrazole or triazole bridges. Earlier attempts with imidazoles yielded mononuclear compounds upon binding to first-row transition metals (79), followed by platinum (80). These compounds proved to be rather inactive, but application in *trans* compounds (81), and with the azolato as a bridging ligand, showed very high *in vitro* cytostatic activities (76, 77, 82). The rationale for selecting and deploying the bridging azolato group is shown in Figure 4. The structural hypothesis appears to be valid, as shown by high anticancer activities (77).

More recent studies have proven the hypothesis by high-resolution NMR studies on double-stranded DNA with the (pyrazolato)Pt₂ unit bound (83), and further confirmed by calculations using density functional theory (DFT) (84).

Ruthenium Compounds

Medicinal ruthenium chemistry was reviewed in this Journal (85) in 2001 and the early work of Clarke was reviewed in 2003 (86). Recent excellent work from the Trieste groups on the NAMI-class compounds (87), and Keppler (88), has boosted the field of ruthenium anticancer research (6). Only the following interesting classes of compounds with high cytostatic activity are mentioned here:

- New antitumour metastasis inhibitor (NAMI)-type compounds (see Figure 3 for the structure of the ruthenium cation in NAMI-A).
- The so-called azpy (azopyridine) compounds, where different isomers show significantly

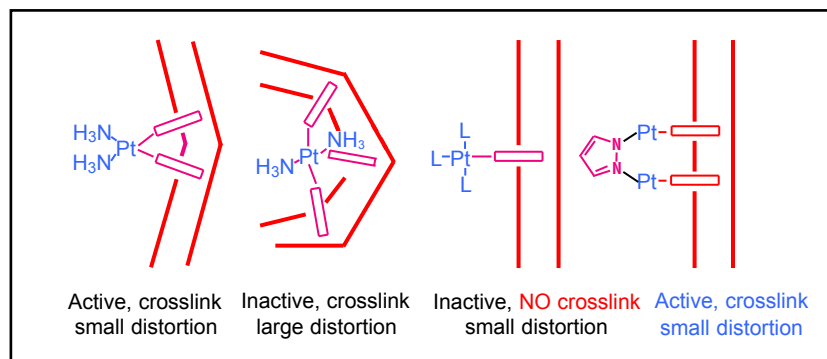


Fig. 4 Rationale behind the design of the azolato-bridged dinuclear platinum compounds, leading to a crosslink, and a very small DNA distortion

different cytostatic activity. The structures and activity indicators are given in Figure 5.

- (c) The organometallic half-sandwich compounds of formula $[\text{Ru}(\text{sandwich})(\text{diamine})\text{Cl}]$, where fine-tuning in the amine ligand is very important for the activity (89–91); again hydrogen bonding plays important roles here.

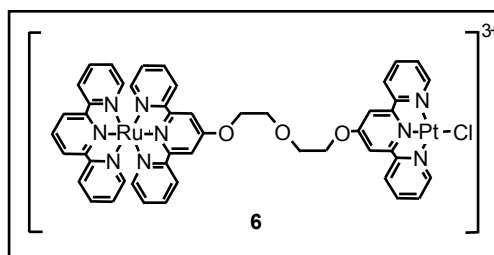
The NAMI-type compounds all contain Ru(III), and it is believed that prior to biological, cytostatic action, reduction to Ru(II) may take place.

The mechanism of action of the ruthenium compounds is hardly known, and even the fact that DNA is an important target is not sure as yet (92).

Mixed-PGM Compounds

Combination therapy using platinum and ruthenium compounds is of course possible (93). If two different metals can be linked, in a kinetically inert way, by a 'spacer' of variable length, then a wealth of new compounds is possible with a view to fine-tuning performance. For platinum and ruthenium, a few cases have already been reported (94, 95), including a three-dimensional structure determination, 6, a dinuclear cationic species containing Ru(II) and Pt(II), with a variable spacer.

Although the antitumour activity of this complex is limited, it has prompted new research on



related platinum-ruthenium compounds. Another possibility is to combine the 'slow' metal with a 'faster' metal, such as Cu(II). The latter is a well known DNA cleaving agent, when bound to phenanthroline-based ligands (96).

Concluding Remarks and Future Development

The work selected and summarised above has shown that the 'heavy metals' platinum and ruthenium, when coordinated to the appropriate ligands, may act as powerful anticancer drugs. The fact that these metals are 'slow' in ligand exchange reactions, and exchange many of their ligands within the same timescale as that of cellular division processes, indicates that these compounds are not dissociated before any of their biological targets are reached. The target for the platinum compounds is now accepted to be DNA, to which kinetically inert

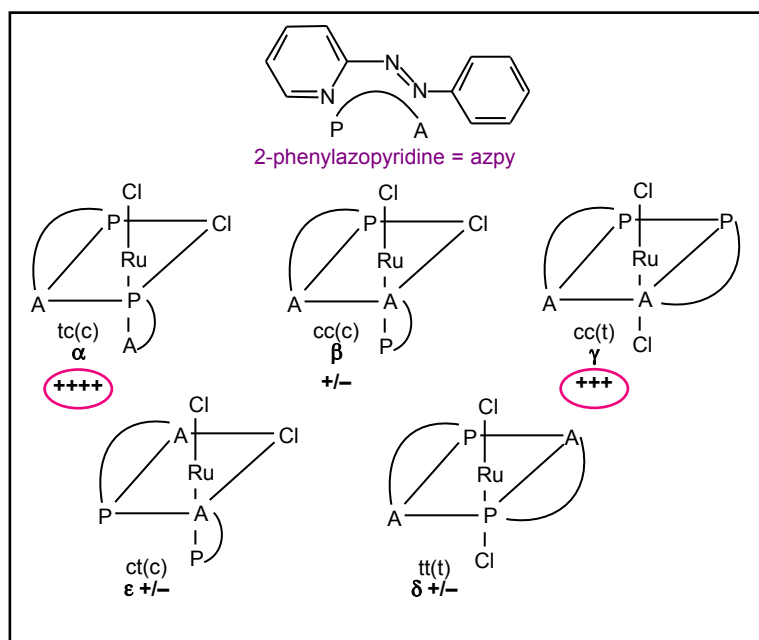


Fig. 5 Five different isomers of a bis(azpy)Ru(II) complex and their relative cytostatic activity (++++ = very active; t = trans; c = cis for each pair of ligand atoms (anions in parentheses))

attachment of the platinum compound allows the start of a cascade of reactions. The cascade eventually leads to apoptosis or necrosis of the tumour cells and repair of the non-tumour cells (2). It should be noted that DNA damage is sustainable in a non-replicating or resting cell, and that apoptosis will be induced only when the cell is growing and dividing.

Although the kinetics of ruthenium coordination chemistry are comparable to those of platinum, and even though a number of active ruthenium compounds do react with DNA and DNA fragments (97), the mechanism of action for the ruthenium compounds is currently far less understood. Targets other than DNA may play a role as well here (6, 92).

Future development in this field is likely to move towards bifunctional and trifunctional compounds, with other parameters such as intercalation, photosensitivity and redox properties coming into play.

Finally it should be noted that also other noble metals, such as gold and rhodium (98), are comparably slow in ligand exchange. The present brief overview is far from comprehensive; the focus has been on some issues of ligand exchange kinetics that platinum and ruthenium have in common, and also on topics not frequently reviewed. Finally, this review has been tuned to the general readership of this Journal, and less so to the specialists in the field of anticancer chemistry. The extensive reference list, including some specialist reviews, should help the interested reader to find more details. Reference (99) (citation added in proof) is a very recent overview of the field.

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