THE STUDY OF SYNTHESIS IN Ru(III) COMPLEXES WITH DONOR LIGANDS

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Abstract

This observation led to cis-diamminadichloroplatinum(II), commonly known as cisplatin, being approved by the American Food and Drugs Adimintration (FDA) for cancer therapy in 1978. It has since become the most widely used anticancer drug, with an estimated 70% of patients receiving the compound as part of their treatment.

Introduction

Whilst the chemotherapeutic success of platinum is undeniable, it by no means the perfect drug. It is by no means the perfect drug. It is not effective against many common types of cancer, drug resistance is common and it has a deplorable range of side effects, which can include nerve damage, hair loss and nausea.

To overcome these limitations some compounds based on ruthenium have been developed and tested against cancer cell lines. These compounds tend to cause fewer (and less severe) side effects compared to platinum drugs.

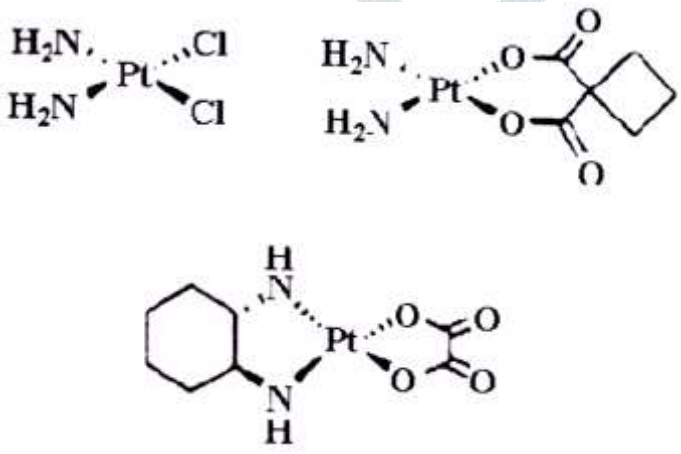

Fig :- The chemical structures of cisplatin, carboplatin and oxaliplatin

Ruhenium's properties are well suited towards pharmacological applications. It can access range of oxidation states (II, III and IV) under physiologically relevant conditions. Also, the energy barrier to interconversion between these oxidation states is relatively low, allowing for ready oxidation state changes when inside the cell. In spite of this flexibility in oxidation state, ruthenium coplexes display relatively slow ligand exchange rates in water - its kinetics are on the timescale of cellular reproduction ion does bind to something in the cell, it is likely to remain bound for the

remainder of that cell's lifetime. Furthermore, ruthenium tends to form octahedral complexes, which gives the chemist tow more ligands to exploit compared with platinum(II) complexes, which adopt a square planar geometry. Ruthenium can also form strong chemical bonds with a range of different elements verying chemical 'hardness' and electronegativities, 01 meaning that ruthenium can bind to a range of bimoleculars, not just DNA.

Why is ruthenium less toxic?

One hypothesis as to why ruthenium compounds are less toxic in general than platinum drugs is Activation by Reduction'. This theory is based on the observation that ruthenium(III) complexes are more inert than ruthenium(II), which can partially by attributed to its higher effective nuclear charge(Z_{eff}). Also cancerous cells tend to have a more chemically reducing environment than healthy cells, owing to their lower concentration of molecular oxygen (due to their higher metabolic rate and remoteness from the blood supply). These two factors taken in parallel mean that compounds of ruthenium can be administered in the (relatively inert)III oxidation state causing minimal damage to healthy cells, but being reduced to the (active)ll oxidation state in cancer cell'. Recently, however, this theory has come under considerable criticism and even the question of how ruthenium compounds enter cells has been the subject of some literature debate.

Can ruthenium impersonate iron?

Ruthenium is a transition metal in group 8 - the same chemical group as iron. Iron, in spite of its potential reactivity and biological toxicity, is a key element without which most cells connot survive. In fact, nature has developed considerable machinery to sequester, transport and make use of iron. The fact that iron and ruthenium are in the same chemical group has led to

some chemists postulating that it is capable of taking iron's place in some proteins, most notably in the chaperone and uptake protein transferring". However, others remain skeptical that the two metals are similar enough to be interchangeable; specifically, ruthenium binds tighter and more slowly than iron and has a preference for 'softer' ligands. Nature has also developed extremely high affinity iron binding stites (e.g. transferring holds iron with a binding constant of 10^{23} M), and it has been questioned whether ruthenium can outcompete iron in these contexts. Another suggestion is that ruthenium can bind to other sites on transferring, and 'piggy- back' into the cell when iron is taken into the cell.

Key molecules

Two ruthenium compounds are currently undergoing clinical evaluation anticancer drugs NAMI-A and as KP1019(fig).

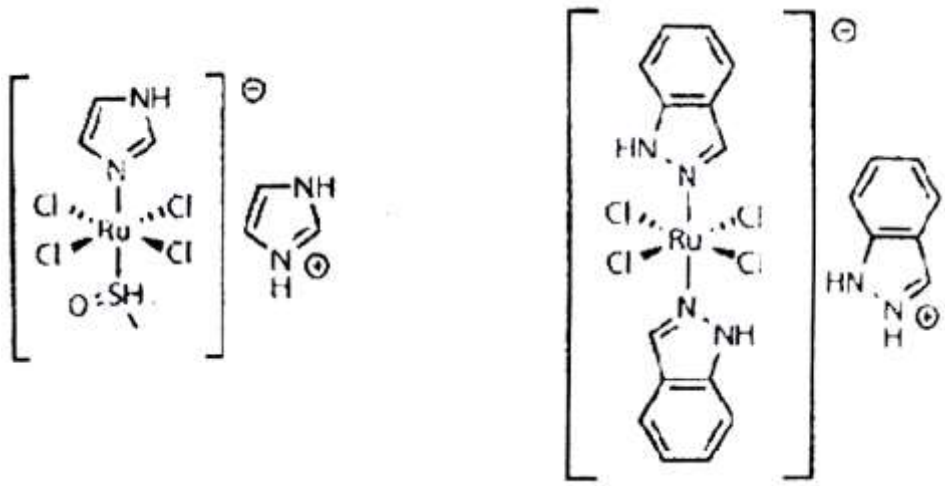

Fig: - Chemical structure of (left to right) NAMI – A and KP1019, the first ruthenium anticancer compounds to enter clinical trials

KP1019 and NAMI-A Appear to be quite similar structurally (both are Ru(III)" complexes with chloride and heterocyclic ligands and a heterocyclic counterion) yet they display remarkably different types of anticancer activity; KP1019 is active against secondary tumour cells (ie the main tumour mass which forms first in a patient). Whereas NAMI-A is active against secondary tumour cells (ie the metastases which form after cells from the primary tumour have moved to a different organ, eg via the bloodstream). Currently there are very few treatment

options for secondary (metastatic) cancers and the prognosis for patients who develop this form of the disease is much worse.

Arguably the most successful ruthenium organometallic anticancer complexes have been the so-called RAPTA' complexes (fig-1.3). RAPTA complexes are characterized by the presence of a facially-coordinated aromatic ring. Oddly, RAPTA complexes display a similar spectrum of activity to the coordination complex NAMI-A, in spite of their apparent differences in oxidation state, ligands, charge and geometry.

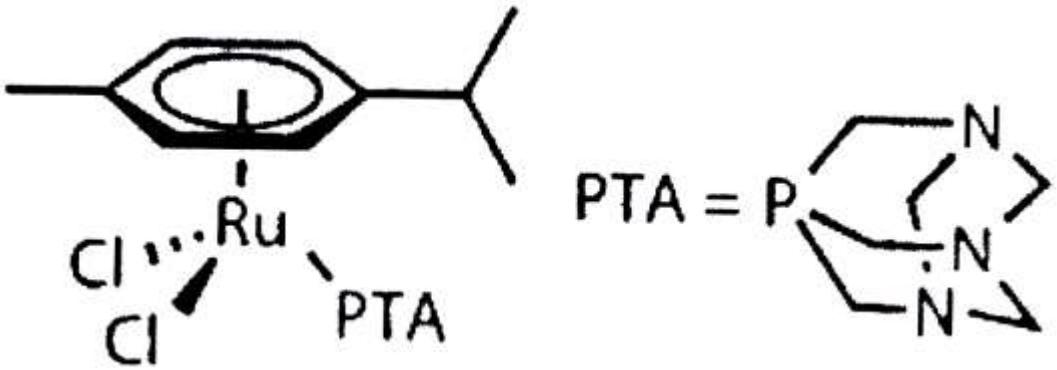

Fig :- An example of a RAPTA complex

The ability of ruthenium species to form multinuclear and supramolecular architectures has been known for some time, but their application to medicinal chemistry has only been explored recently.

Some particularly interesting strategies include ruthenium- platinum mixed-metal compounds, ruthenium cluster com plexes, ruthenium DNA intercalators, and supramolecular 'Trojan Horses', which contain a cytotoxic payload that is released upon entry to the cancer cell (fig).

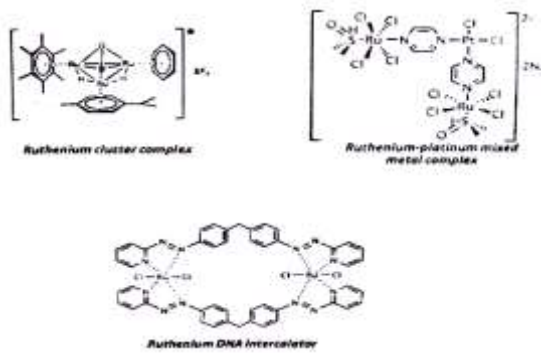

Fig :- Selected multinuclear ruthenium anticancer complexes

Directed therapies

Recently, chemists have developed compounds where a precious metal is chemically linked to an 'organic directing molecule' (ODM), which has a known biological target -eg a drug molecule. It has been speculated that the organic molecule can lead' the metal into the cell and to a specific target. If the metal then binds directly to the cellular target, it could massively increase the potency of the drug. The main difference between this strategy and the above work is that here the biological target of the molecule is known, making this strategy a more rational form of drug design.

Biological target of ruthenium drugs

A recent trend in medicinal chemistry has been a trend away from high- throughput approaches to drug discovery (i.e. those where vast databases of molecules are screened against a biological target) towards structure-based drug discovery (i.e. those where drug design is based on specific structural information about a biological target) which recent research estimates can save around 50% of the cost associated with discovering a drug". However, a major limitation in the field is 01 the lack of an agreed biological target. Currently, the two main theories are that ruthenium compounds target DNA or (as yet unknown) proteins. To date, a great deal of research has been directed at generating novel complexes for testing with relatively little rational design or work aimed at elucidating the modes of action of these complexes.

Future ruthenium drugs

In conclusion, ruthenium compounds have shown highly promising anticancer activity in cell, animals and humans. To date, two compounds are being evaluated in phase II clinical trials. However a major limitation in ruthenium drug discovery is their unknown mode of action. This leads to three possible strategies for future ruthenium drug design.

Chemists could continue the current approach, without a clear biological target for their compounds, but instead generating large numbers of different compounds to screen against different targets and cell lines. This approach could include structure-activity relationships (SARS) in order to determine how altering different functional groups on the molecule affect its anticancer activity. This strategy has the advantage of simplicity, but it would be inefficient and

a lack of information about the physiological target of the resultant complexes could complicate regulatory approval.

Alternatively, more research could be directed at eliciting the mode of action of existing ruthenium compounds. Then, armed with detailed information about how media - what it prefers to bind to how it gets into cells etc chemists can begin to design ruthenium drugs which have a high affinity for cancer targets, with far less server side effects. This strategy could be highly advantageous if a target can be identified.

The final and most recent approach to ruthenium drug design would be the generation of further ruthenium-ODM complexes, in which an organic molecule binds to the active site of an enzyme and the attached ruthenium ion binds to a nearby residue of the same protein. The high-energy interaction set up between the metal and the target offers medicinal chemists a high-energy mode of bonding which isn't available to 'traditional organic medicines. The advantage to this approach is that the compound has a known (or, at least, desired) biological target against which enzymological studies can be performed - such as enzyme inhibition studies and protein crystallography.

Of course, in reality, it is likely that all three of these approaches will be followed to a greater or lesser degree, as more and more chemists enter the newly emerging field of ruthenium anticancer drugs. the continued progress of ruthenium compounds in elinical trial, and the frequent and exciting reports of new ruthenium-containing drug candidates in the literature point towards future where medicinal chemists look beyond the classical biological' elements of carbon, hydrogen, nitrogen and oxygen, and begin to consider the potential of the less explored regions of the periodic table to generate powerful and effective drugs.

Under the present scenario of ruthenium(III) coordination chemistry, we in the present programme, propose synthesis and characterization of two series of Ru(III) complexes of the type $[Ru(CI)_2\ L^{1-6}\ (P\varphi_3)_2]$ and $[Ru(CI)(\ L^{1-6})_2(P\varphi_3)]$.

Where ligands L^{1-6} have been obtained by Schiff base condensation between para-(N,N'-dimethylamino) aniline and salicylaldehyde as well as substituted salicylaldehydes.

RUTHENIUM(III) COMPLEXES

1. Nitrogen-donor Ligands

1.1. Monodentate ligands

The water exchange in $[Ru(NH_3)_2(H_2O)]^{3+}$ has been studied using quantum chemical methods, with both free and hydrated ions being investigated. EPR spectroscopic data have been reported for $[M(NH_3)_5H_2O)][CF_3SO_3]$ (M=Ru, Os) over a range of temperatures for solid powers and frozen solutions; variable-temperature H NMR spectra of $[M(NH_3)_5H_2O)][CF_3SO_3]$ in propane-1, 2-diol carbonate, and resonances for the axial and equatorial NH, ligands and for the H.O ligands have been assigned. The complexes are useful precursors to a variety of disubstituted Ru(III) and Ru(II) complexes. Related Ru(II) and mixed valence complexes have also been studied.

By using [RUCL2(PPh3)2(bpy)JCI as a precursor, the complexes $(RuCl_3(PPh_3)L_2]4H_20$ (L= im, Meim) have beer prepared; crystallographic data for $(RUCI_3(PPh_3)(Meim)]$- $4H_20$ confirm mer-Cl and cis-imidazole ligands.

Theory

Synthesis of Rutheniumcun Schiff base complexes- $[Ru(CI)_2(P\varphi_3)_2L^1]$

A solution of $[Ru(CI)_2(P\varphi_3)_2L^1]$ (0.1 mmol, 99.342 mg) in CHCI; (10 cm^3) were mixed together, colour change was noticed on the addition of the ligand due to the formation o complexes. The contents were refluxed for 4-5 h. The resulting solution was concentrated to small volume (3 cm') on a rotary evaporator and the product was separated by the addition o small amount of pet-ether (60-80°C). The compound tha separated was filtered, washed with benzene followed by ether dried in vacuo over anhydrous CaCl2, then recrystallised form 1:2 (v:v) chloroform-pet ether (60-80°C) mixture. The purity o the complex was checked by TLC.

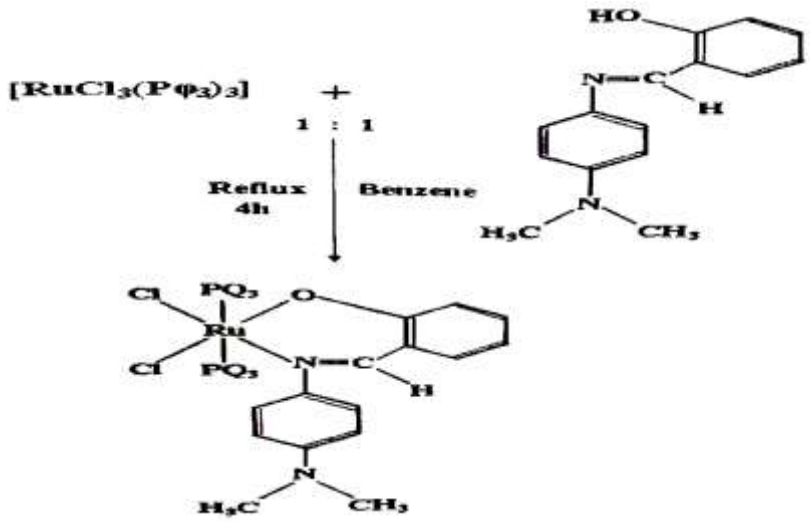

Fig :- Synthesis of Ruthenium (III) Schiffbase complexes $[Ru(CI)_2(P\varphi_3)_2L^1]$

Result and Discussion

Cyelic Voltammetry

The electron transfer properties of the new Ru(III) complexes were examined by cylic voltammetry with DMSO solutions using 0.1 M TBAP as supporting electrolyte. The redox potentials were measured relative to Ag/AGCI electrode at a scan rate of 0.1V/s. All the complexes were electroactive in the sweep range +1.5 V and displayed well-defined one- III II electron reversible/quasi-reversible reduction Ru"/Ru" wave in the range -0.647 to -0.724 V with peak-to-peak separation 70- AI II 292 mV, one electron reversible oxidation Ru /Ru" wave in the range 0.226 to 0.247 V (AEp= 24-115 mV) for 2,3,5&6, an irreversible oxidation at 0.422 V (AEp = 684 mV) for 1 and quasi-reversible oxidation at 0.308 V (AEp = 212 mV) for 4. The difference in oxidation behavior of 1&4 may be due to the absence of electron withdrawing groups like halogens in the Schiff bases used. Also these complexes showed ligand-based reduction at less negative potentials with cathodic peak potential (Epc) ranges between -0.39 to 0-639 V.

Antibacterial Screening of the complexes

Antibacterial activities of legends and the ruthenium (III) complexes have been carried out against the Gram +ve bacteria Staphylococcus aurous and Gram -ve bacteria Proteus mirabilis by well diffusion method. The test solutions were prepared in dimethyl sulfoxide. Blank experiments with RuCl,.3H2O and the Ru(III) precursors were carried out under identical

experimental conditions and show the inability of these complexes to inhibit the bacterial growth. The effectiveness of an antimicrobial agent in sensitivity is based on the zones of inhibition. The diameter of the zone is measured to the nearest millimetre (mm). In general, it has been observed that ruthenium chelates have high antibacterial activity than that of the respective free ligand lagainst the same microorganism under identical experimental conditions .

- The following observations have been made V The complexes are more active than that of the parent ligand. Such an increased activity for the metal chelates as compared to the free ligands can be explained on the basis of Tweedy's chelation theory.
- The activity increases with increase in the concentration of the test solution containing the new complexes.
- All the complexes exhibited significant activity against both the organisms which is comparable with the reported literature.
- The variation in the effectiveness of the different compounds against different organisms depends on the impermeability of the microbial cells or on the difference in the ribosome of the microbial cells.

Reference

1. Alves, J.J.F.; Franco, D.W.Polyhedron 1996, 15, 3299- 3307.
2. Alves, J.J.F.; Plepis, A.M.D.; Davanzo, C.U.; Franco, D.W. Polyhedron 1993, 12, 2215-2219.
3. Ando, I.; Fujimoto, H.; Nakayama, K.; Ujimoto, K.; Kurihara, H. Polyhedron 1991, 10, 1139-1141.
4. Ando, I.; Ishimura, D.; Mitsumi, M.; Ujimoto, K.; Kurihara, H. Polyhedron 1992, 11, 2335-2340.
5. Ando, I.; Ishimura, D.; Ujimoto, K.; Kurihara, H.Inorg.Chem. 1994, 33, 5010-5014.
6. Chou, M.H.; Szalda, D.J.; Creutz, C.; Sutin, N.Inorg.Chem. 1994, 33, 1674-1684.
7. Derezende, N.M.S.; Martins, S.D.; Marinho, L.A.; Dossantos, J.A.V.; Tabak, M.; Perussi, J.R; Franco, D.W. Inorg.Chem.Acta. 1991,182, 87-92.

8. Mazzetto, S.E.; Rodrigues, E.; Franco, D.W.Polyhedron 1993,12, 971-975.

9. Anderson, C,; Beauchamp, A.L.Can. J. Chem. 1995, 73, 471-482.

10. Chatlas, J.; Vaneldik. R.; Keppler, B.K.Inorg. Chim. Acta. 1995, 233, 59-63.

11. Anderson, C.; Beauchamp, A, Linorg. Chem.1995, 34, 6065-6073.

12. Anderson, C; Bewauchamp, A. L Inorg Chem. heta. 1995, 233, 33-41.

13. Hartmann, M; Einhauser, TJ Keppler, BK.Chem. Commun. 1996, 1741-1742, 28. Peti, W.; Pieper, T; Sommer, M, Keppler, B.K, Giester, G.Eur.J.Inorg Chem.1999, 1551-1555,

14. Pieper, T; Sommer, M; Galanski, M, Keppler. B.K giester, G.Z. Anort, Allg Chem.2001, 627, 261-265,

15. La Chance-Galang, K. J, Doan, P.E Clarke, M.J; Rao, U.; Yamano, A, Hoffman, BM. Jam. Chem. Soc 1995, 117, 3529-3538.