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**PHYSICOCHEMICAL AND STRUCTURAL STUDIES OF
FERROCENE SCHIFF BASE DERIVATIVES AND SOME
ASSOCIATED ADDUCTS**

133
60-9

A Thesis Presented in Partial Fulfilment of The Requirements For
The Degree of Master of Science at Massey University

**MASSEY UNIVERSITY
NEW ZEALAND**

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1995

DEDICATION

To my parents for keeping me looking towards the future.

And to the words that greeted me, just about every morning

“ have you got any crystals yet ? “

ABSTRACT

The results reported in this thesis are an investigation into the synthesis, characterisation, and coordination ability of some new Schiff base ferrocenyl derivatives.

Chapter One gives a brief overview of the practical applications that ferrocene based compounds have been put to, since ferrocenes first synthesis in 1951.

Chapter Two outlines the preparation and characterisation of six new Schiff base ferrocenyl derivatives, along with a new synthesis and full characterisation of a ferrocenyl thiosemicarbazide derivative which was first synthesised in 1968. The X-ray structure of bis-N-(*o*-hydroxybenzylidene) ferrocenylimine, (L11), was established, showing relatively strong intramolecular hydrogen bonding between the Schiff base nitrogen and the hydrogen of the hydroxy group on the phenol.

In Chapter three reduction attempts of the ferrocene derivatives in Chapter 2 are reported. The synthesis and characterisation of a borane adduct of the N-(*o*-hydrazonylpyridine) ferrocenimine ligand, (L2.BH₃), is studied. Its single crystal X-ray structure is determined and the adduct is compared to the parent L2 ligand.

Chapter Four contains the preparation and characterisation of the complex [Zn(L1)Cl]₂, which is based on the N-(*o*-hydroxybenzylidene) ferrocenylimine ligand, (L1). Five new metal complexes are reported, [Co(L2)Cl₂], [Ni(L2)Br₂], [Cu(L2)Cl₂], [Co(L2)Br₂] and [Zn(L2)Cl₂] based on the L2 ligand, and these are characterised by mass and infra-red spectroscopies.

In Chapter Five the ligands are studied by cyclic voltammetry and Mossbauer spectroscopies, with further cyclic voltammetry studies undertaken on the complexes. The electrochemical oxidation trends observed in the cyclic voltammetry studies on the Schiff base derivatives are in parallel with the Mossbauer studies, which have the results rationalised in terms of electron population movements within the ⁵⁷Fe d-orbitals and the p-orbitals of the cyclopentadienyl rings.

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ABBREVIATIONS

CDCl ₃	Deuterated chloroform
Cp	Cyclopentadiene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dmf	Dimethylformamide
dmsO	Dimethylsulphoxide
DNA	Deoxyribose Nucleic Acid
IR	Infra-red
NLO	Non-linear optical
NMR	Nuclear magnetic resonance
ppm	Parts per million
SCE	Saturated calomel electrode
Sod	Superoxide dismutase
T _c	Curie temperature
TCNE	Tetracyanoethylene
TCNQ	Tetracyanoquinodimethane
thf	Tetrahydrofuran
TMS	Tetramethylsilane
T _n	Neel temperature
ω	Frequency
red/ox	Reduction/oxidation

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CHAPTER 1

GENERAL INTRODUCTION

1.0 THE IMPORTANCE OF FERROCENE

The discovery of ferrocene in 1951 opened up a new spectacular branch of chemistry: that of organometallic chemistry [1]. This, at the time, unusual molecule, ferrocene, was the first recognized "cyclo-ene" π -bonded complex. It was Wilkinson and Fischer who first introduced the concept of the sandwich geometry involving bonding of the aromatic C_5H_5 ring to the vicinal iron atom. The wide variety of substitution patterns that are available for the ferrocenyl moiety [2] shows that the C_5H_5 ring in ferrocene is similar to other aromatic molecules such as benzene. But, unlike other aromatics, ferrocene does not survive certain vigorous reaction conditions, involved in many aromatic substitution and similar reactions, which benzene does. However, it does undergo Friedel-Crafts acylation, sulfonation and metallation by butyllithium. Its remarkable stability can be related to the fact that it obeys the 18 electron rule. Ferrocene and its derivatives have a wide range of applications in science, technology and medicine the following sections will review just two areas.

- 1.1) Applications to material science
- 1.2) Applications to medical science

1.1 APPLICATIONS TO MATERIAL SCIENCE

Interactions between metal atoms in molecules have aroused much interest particularly when they take place between two or more different metals. Such studies have been performed on molecules containing donor ligands linked to ferrocene [3-6]. This is because the ferrocene moiety has an inherent ability to act as a redox centre, and it has been found that such centres are sensitive in their response toward other host metals if the ligand donors are appropriately linked to the C_5H_5 ring. The Schiff base reaction is

one that may be utilised to bring the redox-active ferrocene unit nearby a site that can detect host metal ions but there are others. Suitable complexes must allow communication between the two metals to occur, e.g. via a conjugated pathway. Understanding of these sorts of interactions is of importance in the field of materials science. A range of compounds have been investigated for the following applications:

- a) As molecular switches in controlling supermolecular assemblies [7]
- b) As non-linear optical materials [14]
- c) As molecular sensors [16]
- d) As molecular magnetic materials (ferrocenium salts). [20]

1.1.1 SUPERMOLECULAR ASSEMBLIES

The interest in connecting ferrocene into a supermolecular assembly, such as a porphyrin ring, is to construct macrocycles containing multiple redox-active centres. These may serve as new types of electron relay catalysts for redox photochemical reactions which, in the near future, may lead to more efficient light harvesting devices. Such molecules are currently under investigation by many groups. One of the more recent examples [7] is a new porphyrin-ferrocene-quinone linked molecule (**Fig 1.1**).

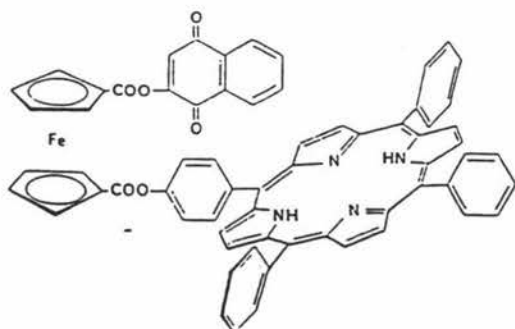


Fig 1.1

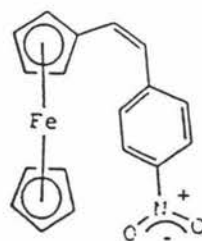


Fig 1.2

1.1.2 NON-LINEAR OPTICAL (NLO) MATERIALS

One of the second order non-linear optical effects of practical importance is the process of second harmonic generation (SHG). Second harmonic generation is a process by which light of frequency w is converted to frequency $2w$ upon interaction with the non-linear medium. A more important application of this effect is in the laser industry where the limited frequencies available from a laser can be extended thus reducing costs by avoiding the use of multiple lasers.

The development of new materials with large optical non-linearity is an exciting discipline with applications in telecommunications, optical information processing and optical computing [8]. It is now well established that molecular structures that possess both large differences between ground state and excited state dipole moments will have large second-order optical non-linearity. The strategy for some of the organometallic NLO compounds has been to link up an electron-donating metallocene and an electron-withdrawing organic group by a conjugated system.

Molecules with π donor-acceptor interactions therefore are promising candidates to fulfil these requirements. While the criteria will ensure large molecular second-order non-linearity it is imperative that the molecular dipole resides in a non-centrosymmetric environment if the molecular non-linear polarisation is to lead to an observable effect in the bulk compound.

Over the past twenty years large efforts have focussed on the synthesis of organic compounds with large SHG efficiencies, whereas the organometallic compounds have received little attention, and up until 1992 there were only a few reports of compounds exhibiting second-order optical non-linearity [9-13]. One of the more famous is (Z) - [1-ferrocenyl-2-(4-nitrophenyl)ethylene] [14] (**Fig 1.2**). This exhibits a SGH with an efficiency 62 times that of the urea reference standard at 1907nm.

Other NLO materials which also produce significant SGH from 1907nm have been synthesized by linking $[\text{Mo}(\text{NO})\text{L}(\text{X})]^+$ (**Fig 1.3**) (where $\text{X} = \text{Cl}$ or I and $\text{L} = \text{tris}(3,5\text{-dimethylpyrazol-1-yl})\text{hydroborate}$) to a ferrocene moiety via an aryl or with better effect, diarylazo groups [15]. With this series of NLO materials, only the use of the

ferrocenyl groups to produce active materials has been attributed to the packing arrangement of the crystal lattice to allow phase-matched SHG.

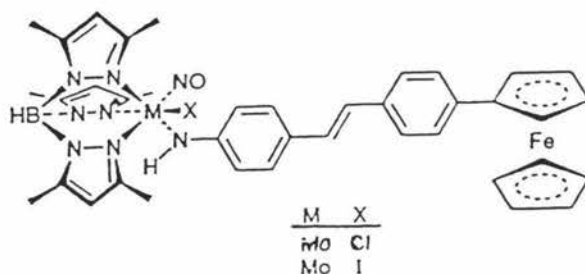
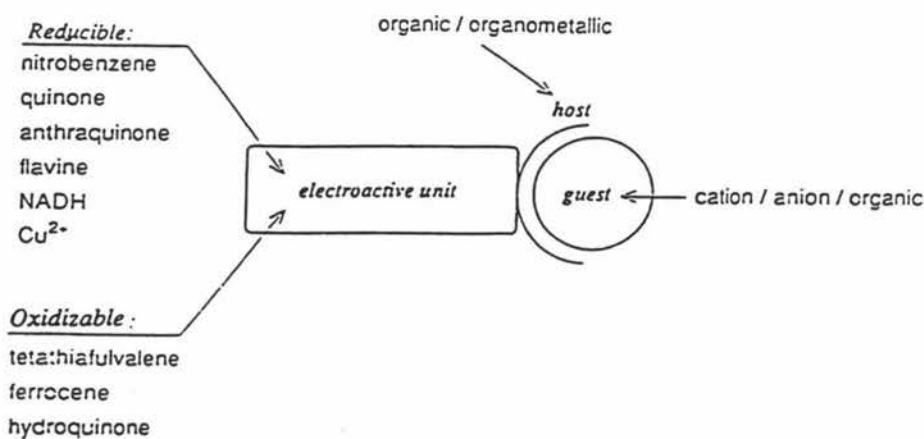


Fig 1.3

1.1.3 MOLECULAR SENSORS

The area of molecular sensors is one of the fastest growing areas of organometallic chemistry. This is because cyclic voltammetry provides a useful technique to study the presence of an electroactive centre. Ferrocene itself has long been used as a calibrant for this electrochemical technique because of the fully reversible voltammogram that results ($E^{1/2} = 435\text{mv}$ vs SCE) [$E^{1/2}$ conditions are 0.01 mol dm^{-3} in MeCN on a platinum disc].

There have been many reports of studies of heterobimetallic compounds because of their unique chemical character. A large variety of electrochemical responsive units have been synthesised and these can be divided into those containing reducible and those containing oxidizable centres. Both categories have been built into organic and organometallic receptor-host assemblies to provide specific binding sites for cations, anions or neutral organic guest species. A schematic model is shown below.

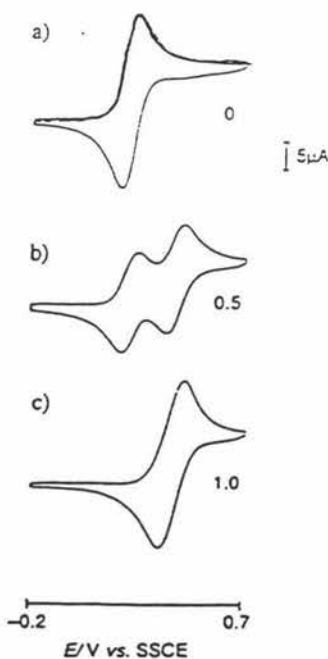


1.1.3 (a) Reducible Electroactive Units

Of the reducible electroactive units, the nitrobenzene and quinone-based systems have been used extensively [16]. During reduction, such systems become negatively charged. As a consequence, sensor models possessing reducible electroactive sites often show enhanced cation-binding after reduction. With the presence of a positively charged cation in the host compartment, a system will usually exhibit an anodic shift in the reduction potentials. The magnitude of the anodic shifts is often strongly dependent on the charge/radius ratio of the alkali metal ions. The shifts generally decrease in order $\text{Li}^+ > \text{Na}^+ > \text{K}^+$, reflecting the fact that cation/electroactive unit interaction is strongest for small cations which possess a higher polarising power.

1.1.3 (b) Oxidizable Electroactive Units

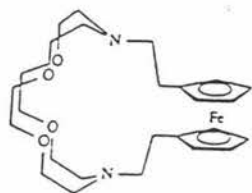
Oxidizable electroactive units such as ferrocene and tetrathiafulvalene have been used since 1989. Gokel *et al.* [17], linked a ferrocene moiety to a 18-crown N_2O_4 macrocycle (**Fig 1.4**) forming a cryptand structure which proved to be an efficient sodium and potassium ion responsive assembly. The cyclic voltammograms of this compound can be seen in diagram 1.1



Cyclic voltammograms of Gokel's ferrocene cryptand system, after addition of (a) 0 equivalents, (b) 0.5 equivalents, and (c) 1.0 equivalent of NaClO_4 .

Diagram 1.1

Other examples include several polyoxa- (Fig 1.5) and polyoxathiaferrocenophanes [18]. These have been used for redox driven sodium ion transport across a membrane. Ratajczak *et al.* [19] developed a methodology using high dilution techniques that is still used today to synthesise dithio pyridinyl ferrocenyl dimers (Fig 1.6).



Gokel 1991

Fig 1.4

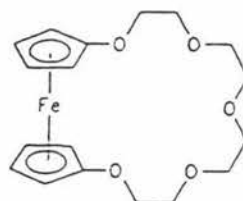


Fig 1.5

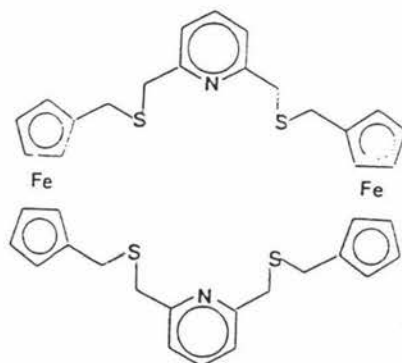


Fig 1.6

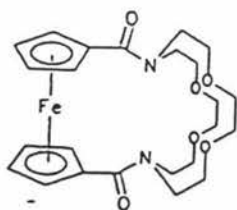


Fig 1.7

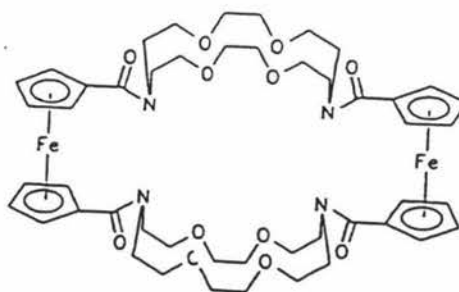


Fig 1.8

The ferrocene cryptand [Fc 2,2] (**Fig 1.7**) has been prepared by a reaction of 1,1'-bis(chlorocarbonyl)ferrocene with diaza-18-crown-6-ether and was reported to be an ion selective binding agent as is the dimer [Fc(2,2);(2,2)Fc] (**Fig 1.8**).

1.1.4 FERRICINIUM SALTS

Highly magnetic materials are essential for frictionless bearings, switches, motors and the recording of sound and pictures on optical disc. Powerful electromagnets are also used to store energy and are used in superconductors.

The following terms are defined before continuation:

paramagnetism	possessed by atoms or an ions with one or more unpaired electrons in random orientation; occurs when in a magnetic field.
ferromagnetism	the magnetic moments on the separate molecules or ions all align in the same way.
antiferromagnetism	paramagnetic molecules or ions that have as many magnetic moments aligned in one direction as in the other direction giving a net magnetism of zero.
Ferrimagnetism	paramagnetic molecules or ions that have as many magnetic moments aligned in one direction as in the other direction, with the resultant moment, being greater than zero.

For all the spins in a solid to align, either ferromagnetically or antiferromagnetically, the interaction among spins must be stronger than the thermal energies that affect individual electrons by making their spins jostle and disorder each other throwing their spins out of alignment. Thermal energies increase with temperature, whereas the interactions among spins are usually independent of temperature. This

means that above a certain critical temperature, called the Curie temperature (T_c) for ferromagnets and Neel temperature (T_n) for antiferromagnets, the thermal energies overcome the spin interactions and the material becomes paramagnetic. A diagram simulating the electron spins for each of the different forms of magnetism is shown in diagram 1.2

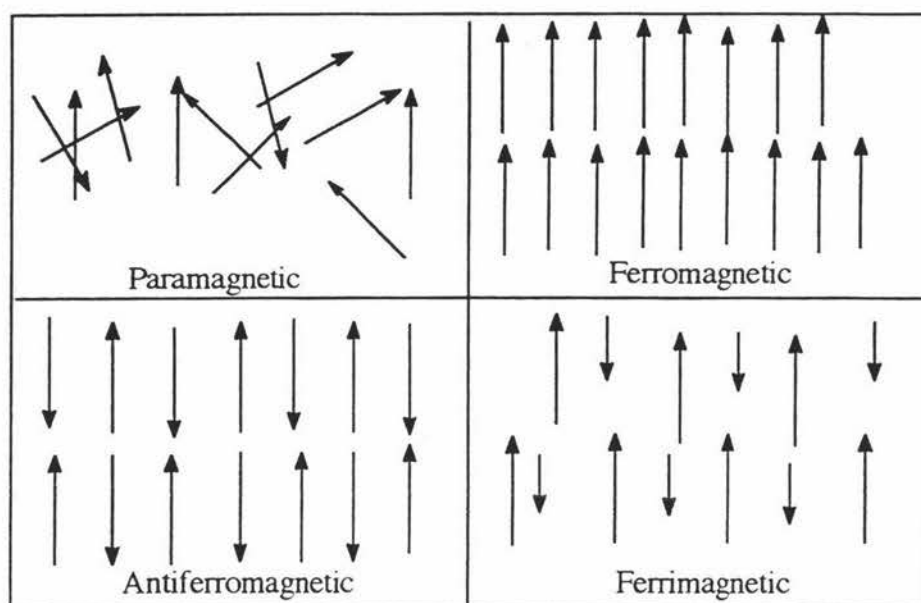


Diagram 1.2

In order to design an organomagnet containing a 3-dimensional array of atoms, molecules or ions must contain uncoupled electrons which have the electrons close enough to have co-operative interactions among them. Partial occupation of a band brought about by electron transfer [21] is also required. Miller *et al.* [20] discovered the first organometallic bulk ferromagnet, $[\{Fe^{III}[C_5(CH_3)_5]_2\}^+[TCNE]^-]$ ($FeCp_2^*TCNE$) where TCNE is tetracyanoethylene (**Fig 1.9**). It appears the highly symmetric pentamethylated ferrocene is important in allowing for co-operative magnetic coupling which gives the ferromagnetic behaviour below the T_c value of 4.8 K.

The ferricinium salts with planar radical anions, such as TCNE, contain chains of alternating donors and acceptors and the difference in magnetic properties depends on the presence of the iron atom, which determines the spin on the cation and the nature of the anion. There is also a requirement that the neighbouring chains be displaced by half a unit along the X-Y diagonal plane, so that the distance between donors in one layer and

the acceptors in an adjacent layer is about the same as the distance between donors and acceptors in the same layer. The salt therefore has a true three dimensional structure and bulk magnetism becomes a possibility.

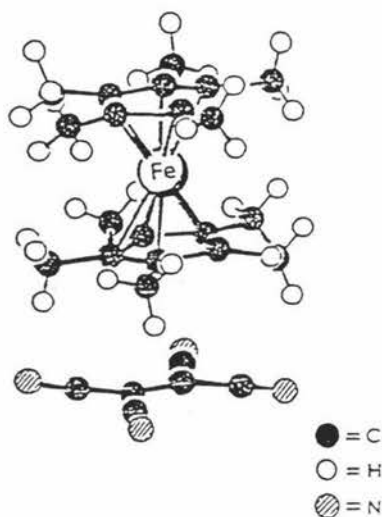


Fig 1.9

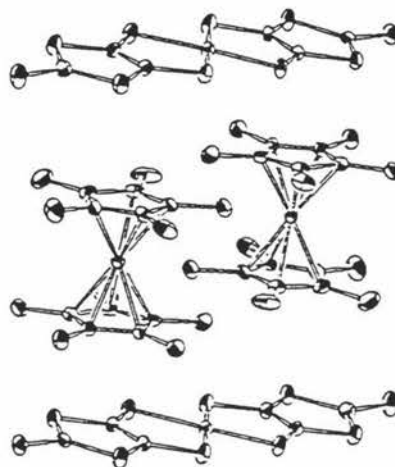


Fig 1.10

Since the first organic magnet, $\text{FeCp}_2^+ \text{TCNE}$, was synthesised there have been numerous others including those containing the counter ion TCNQ (TCNQ = tetracyanoquinodimethane). It was observed that the length of the counter ion influences the structure and hence the intermolecular interactions, and that T_c appears to increase with increasing length of the anion. This has led to work on synthesising longer counter anions [21]. In an alternative approach, hetero-bimetallic ferromagnetically-ordered molecular assemblies have been studied by Hoffman [22] using a molecular series of charge transfer salts of the type $[\text{Fe}(\text{C}_5\text{Me}_5)_2][\text{Ni}(\text{X}_2\text{R})_2]$ (Fig 1.10) where X_2R represents one of a series of dichalcogolene ligands (2-thioxo-1,3-dithiole-4,5-dithiolate or 1,2-benzenediselenolate). This system was modelled for the stabilization of ferromagnetism by virtual charge transfer between donor and acceptor, with the X_2R unit playing the same role as the planar structure of TCNE. Miller in 1989 investigated the octamethyl ferrocene salts, $[\text{Fe}(\text{C}_5\text{Me}_4\text{H})_2]^+[\text{A}]^-$ ($[\text{A}] = \text{TCNE}$ or TCNQ) to observe

the effect symmetry of the ferrocene moiety had on the T_c value. He concluded that the lack of magnetic ordering may be due to poorer interionic overlap within and between the chains which lead to the substantially weaker magnetic coupling compared with that of the $[\text{Fe}(\text{C}_5\text{Me}_5)]^+[\text{A}]^-$ system.

1.2 APPLICATIONS IN MEDICAL SCIENCE

1.2.1 ANTICANCER DRUGS

Rosenberg's [29] wonder drug discovery of diamminedichloroplatinum(II) (cis-platin) (**Fig 1.11**) in 1969 opened up a new and beneficial area in cancer therapy. However the induced side effects of this drug are severe with kidney toxicity, nausea and vomiting, neurotoxicity and a drop in red blood cell reproduction resulting in anaemia, being a problem. For this reason second, and more recently third generation drugs are being synthesised and tested .

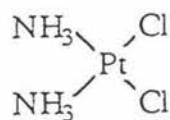
The criteria for a second generation drug are:

- a) Highly soluble (for potential oral administration)
- b) Less kidney toxicity
- c) Less nausea and vomiting
- d) A better penetration of the blood-brain barrier
- e) An improved therapeutic index
- f) Different mechanism of action
- g) Can act synergistically in combination chemotherapy.

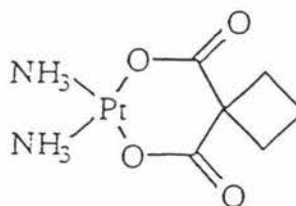
For third generation drugs, the criteria also include higher activity per dose compared with carboplatin (**Fig 1.12**), the best known second generation drug.

Kopf-Maier [30] divides the transition metal complexes, other than platinum group metals into three groups early, medium or late. Metallocene complexes of the general formulation $\text{M}(\text{C}_5\text{H}_5)_2\text{X}_2$ (where $\text{M} = \text{Ti}, \text{V}, \text{Nb}, \text{Mo}$) and $\text{X} = \text{Cl}^-$ for example), fall into the early transition metal category. The medium transition metal compounds are

also metallocinium complexes but are salt like rather than neutral in contrast with the early transition metal complexes. They have the general formulation $M(cp)_2X$ (where $M = Fe, Co$ and $X^- = FeCl_4^-$). The late transition metals form compounds containing for example copper and ligands such as thiosemicarbazide.



Cisplatin

Fig 1.11

Carboplatin (JM-8)

Fig 1.12

The mechanisms by which the anti-tumour complexes function are not well understood, but their interactions with DNA are important and may be generally summarized as:

- a) Intercalation
- b) Covalent and non-covalent outersphere binding
- c) Covalent inner-sphere binding
- d) Strand breakage
- e) Indirect methods.

The only mechanism that is thought to be important for ferrocene based drugs is the outersphere binding (b). However the other mechanisms will be very briefly reviewed for comparison. Diagram 1.3 summarises the different modes of interaction with the DNA.

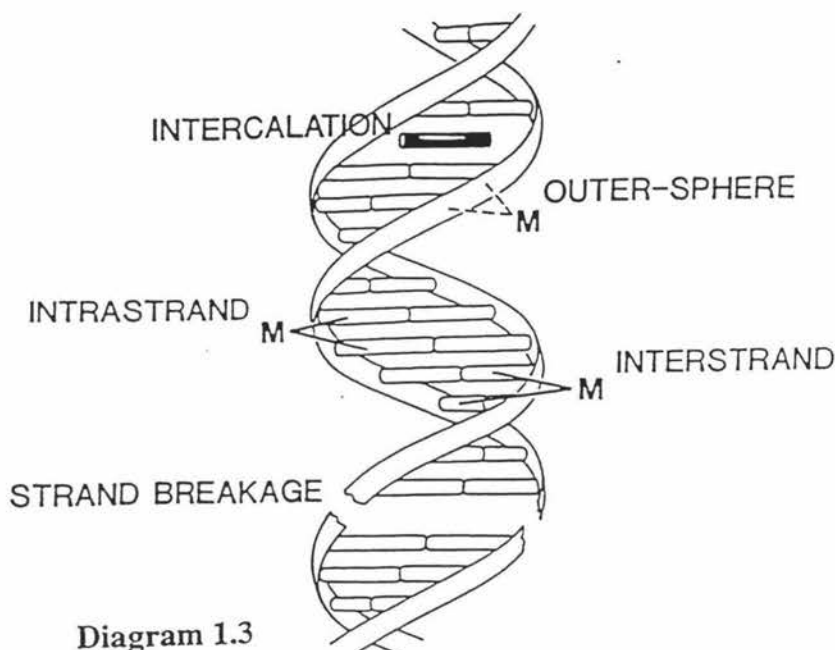


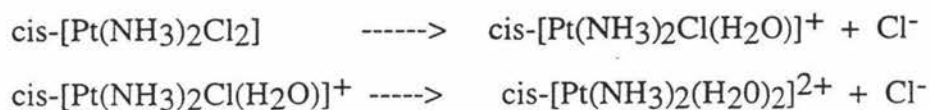
Diagram 1.3

Schematic presentation of the modes of interaction of metal complexes with DNA.

1.2.1 (a) INTERCALATION

This interaction was originally proposed by Lerman [31] to explain the binding of planar aromatic drugs such as proflavine. Classical intercalation involves the insertion of the planar molecule between two neighbouring base pairs of DNA to which it is held by van der Waals forces, though electrostatic type interactions may also be present. A non-classical intercalation model has also been proposed, which involves changing the angle of the DNA strand. In this model the presence of an intercalater requires that the helix be extended and locally unwound by the binding reaction. This affects the hydrodynamic properties with an increase in viscosity and results in a stiffening of the double helix, or in simpler terminology it prevents the DNA from dividing, thus stopping replication. Cisplatin provides an example of this mechanism of action. It has been postulated that after the first rate-determining hydrolysis step, the resulting aquachloroplatinum(II) complex co-ordinates preferentially to guanine bases of the DNA [32]. The subsequent reaction with an adjacent nucleotide base leads to damage of the DNA.

On the other hand, it has been suggested that the reaction with other binucleophiles, especially S-containing nucleophiles, proceeds by a direct nucleophilic substitution of the chloride ligand without prior formation of the aquachloroplatinum(II) species [32] as occurs in the reaction below.



Since reactions of the above type are important for the activation of the drug on transport to the tumor and for toxic side effects, the labile Cl^- leaving groups were exchanged by less labile leaving groups, such as cyclobutane-1,1-dicarboxylate, in carboplatin. Carboplatin indeed possesses reduced toxicity but also lower antitumour activity due to its low hydrolysis rate [33]. Many groups have tried to reduce the side effects of cisplatin by variations of the neutral ligand.

1.2.1 (b) OUTERSPHERE BINDING

The negatively charged backbone of the DNA helix may interact with a variety of positively charged molecules such that, either through columbic interactions or phosphate-oxygen binding, the overall charge is reduced with subsequent effects on the stability of DNA and its conformation.

It has been postulated that ferrocene based drugs function not by the cisplatin method of intercalation but by groove binding to the DNA. It must be noted that only the ferricinium ions have anti-tumour activity whereas the parent ferrocene does not [27]. This suggests that ionic interactions may play an important role in this mechanism. It is postulated that the π cloud of the cyclopentadienyl ring interacts with π acceptors on the DNA back bone. This stabilizes the ferricinium ions within the groove of the DNA and results in it becoming a blocking group to prevent DNA replication.

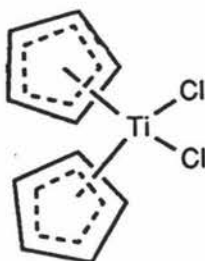


Fig 1.13

Another metallocene complex which has been tested against lung and gastrointestinal carcinomas (1990) is a titanocene complex $(C_5H_5)_2 TiCl_2$ (Fig 1.13). It is believed that the first stage of the mechanism of activation of this drug is similar to that of cisplatin, with fast hydrolysis in an aqueous media giving rise to oxobridged and aqua complexes. These species unlike cisplatin, however, may have high affinity for PO_4^{3-} ions rather than the nitrogen atoms of the nucleotide bases of DNA. It has also been postulated that titanium-amino acid interactions may also take place .

1.2.1 (c) COVALENT INNERSPHERE BINDING

A number of metal-aquo ions bind covalently to the bases of DNA such as mercury and causes the DNA structure to be stabilized. The mercury ions bind to the thymine bases substituting for hydrogen bonds and thus forms strong cross links which stabilize the helix [34]. Like the intercalator binding, this effects the hydrodynamic properties of the DNA.

1.2.1 (d) STRAND BREAKAGE

Strand breakage involves covalent bond cleavage of the helix backbone and may be either singly stranded or doubly stranded. This again can cause changes in the hydrodynamic properties. Radiation products, especially the hydroxyl radical, are particularly effective in this respect and much of the work on strand breaks centres on this aspect.

1.2.1 (e) INDIRECT METHODS

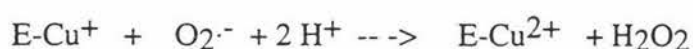
The modes of interaction of these drugs do not function on the tumour cells directly but suppress replication of the tumour by deactivating an enzyme that is required for replication.

i) Deactivation of the ribonucleoside diphosphate reductase (rdr)

Cupric thiosemicarbazones are used in the deactivation of this key enzyme, which is needed in the synthesis of precursors for DNA replication. It can be deactivated by either complexation of the free ligand by iron at the active site or by coordination of the copper to the free thiols in the enzyme. The subsequent reduction of the coordinated complex results in the release of its thiosemicarbazone [35].

ii) Superoxide dismutase (Sod) mimetic activity

Sod is a copper/zinc containing enzyme which catalyses the dismutation of the superoxide radical as follows ;



A deficiency of intracellular Sod in malignant cells can result in an accumulation of superoxide which may attack cellular structure and initiate neoplasia. Other cellular pro-oxidant states (increase concentrations of active oxygen compounds including organic peroxides and oxy-radicals) could also promote the conversion of cells to neoplastic states [36]. It has been shown that Cu (II) salicylates scavenge superoxide and may act as antineoplastic agents.

1.2.2 ANTIBIOTIC DRUGS

The formation of stable coordination compounds with heavy metals and aroylhydrazone ligands have shown promise as specific reagents in analytical and extractive chemistry. These types of compounds possess strong biological activity and can inhibit many vital enzymatic reactions that are catalysed by heavy metal ions. It has

been reported that the replacement of aromatic groups by the ferrocenyl moiety in penicillin (**Fig 1.14**) and cephalosporin (**Fig 1.15**) improves their antibiotic activity [37]. In these molecules, ferrocene has two aromatic rings that can undergo substitution. Thus the antibiotic molecules may be modified in three dimensions without changing the profile required for biological activity.

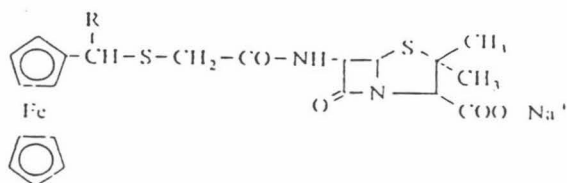


Fig 1.14

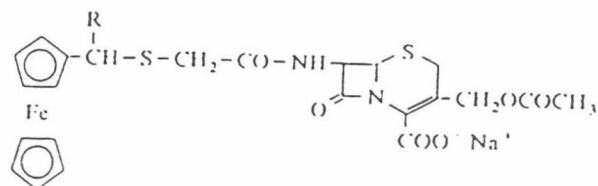


Fig 1.15