Half-Sandwich Organoruthenium and Organorhodium Complexes of Biologically Relevant Ligands.

Thesis submitted for the Degree of Doctor of Philosophy

by

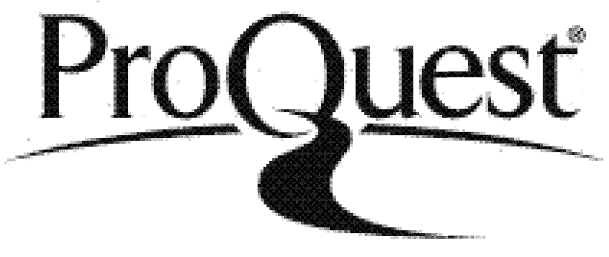
Glen Capper

in the

Department of Chemistry

at the University of Leicester.

SEPTEMBER 1995



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Title: **Half-Sandwich Organoruthenium and Organorhodium Complexes of Biologically Relevant Ligands.**

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ABSTRACT

This thesis describes some chemistry of $[(mes)RuCl_2]_2$, $[(Cp)RuCl(CO)_2]$ and $[(Cp^*)RhCl_2]_2$ complexes and in particular, the reactions with biologically relevant ligands.

Chapter one introduces the general chemistry of arene-ruthenium and pentamethylcyclopentadienyl-rhodium from early work described by Winkhaus and Singer in the preparation of half-sandwich arene-ruthenium complex $[(C_6H_6)RuCl_2(PPh_3)]$ and the contributions on the reactions of $[(Cp^*)RhCl_2]_2$ reported by Maitlis and co-workers. The second half of the introduction discusses the introduction and uses of inorganic complexes as anti-tumour agents.

Chapter two describes the reactions of amino acids with potentially co-ordinating side chains with $[(mes)RuCl_2]_2$ and the characterisation of the amino acidate complexes formed. The crystal structure of the complex [(mes)RuCl(phgly)] has been determined and a high temperature ^1H n.m.r. spectrum has been obtained.

Chapter three describes the preparation and characterisation of a number of pyranato and pyridinato complexes of arene-ruthenium and Cp^*-rhodium. A low temperature ^1H n.m.r. spectrum was obtained for the complex $[(Cp^*)RhCl(etmalt)]$ and conductivity experiments were obtained which indicate that the complexes exist in water as a mixture of water or chloride co-ordinated species.

Chapter four describes the reactions of a number of half-sandwich complexes of ruthenium and rhodium with nucleobases to determine the binding site(s) involved in co-ordination. A set of competition reactions were undertaken to determine any preference of the complex [(mes)RuCl(phgly)] for the various nucleobases. We have found that for this ruthenium complex, guanosine forms the most stable complexes with thymidine and uridine forming the least stable.

Statement.

This thesis is based upon work conducted by the author, in the Department of Chemistry of the University of Leicester, during the period between October 1991 and September 1994.

All the work described in this thesis is original unless otherwise stated in the text or in the references. This work is not being presented for any other degree.

Signed:_____ Date:_____

Glen Capper Esq.

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Acknowledgement is made to SERC for funding the research. Thanks to my family and friends for all their support and encouragement.

A very special mention must go to Herbs who has consistently been in the right place at the right time.

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Abbreviations.

aa	Amino acid anion
acacH	Pentane-2,4-dione
ado	Adenosine
alaH	Alanine
allylglyH	Allylglycine
aspH	Aspartic acid
β-alaH	β-alanine
bmik	Bis(N-methylimidazol-2-yl)ketone
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bipy	2,2'-bipyridyl
br	Broad
CH_2Cl_2	Dichloromethane
COD	Cyclo-octa-1,5-diene
Cp	η^5-Cyclopentadienyl anion
Cp^*	η^5-Pentamethylcyclopentadienyl anion
cyd	Cytidine
d	Doublet
dd	Doublet of doublets
dmppH	3-hydroxy-1,2-dimethyl-4-pyridinone
DMSO	Dimethylsulphoxide
dopaH	3,4-dihydroxy-phenylalanine
dppe	1,2-Bis(diphenylphosphino) ethane
eppH	3-hydroxy-2-ethyl-pyridin-4-one
Et	Ethyl
9-etguan	9-ethylguanine
etmaltH	Ethyl maltol, 3-hydroxy-2-ethylpyran-4-one
EtOH	Ethanol
glyH	Glycine
guo	Guanosine
hisH	Histidine
IR	Infrared

Abbreviations (continued).

KBr	Potassium Bromide disc
leuH	Leucine
m	Multiplet
Me	Methyl
9-meaden	9-methyladenine
1-mecyt	1-methylcytosine
MeOH	Methanol
memaltH	Methyl maltol, 3-hydroxy-2-methylpyran-4-one
mes	1,3,5-trimethylbenzene
nbd	Norbornadiene
n.m.r.	Nuclear magnetic resonance
NOBA	m-Nitrosylbenzylalcohol
Nu	Nucleophile
p	Para
p-cymene	4-methyl-isopropylbenzene
penH	Penicillamine
Ph	Phenyl
phalaH	Phenylalanine
phglyH	Phenylglycine
picH	Picolinic acid
proH	Proline
py	Pyridine
q	Quartet
serH	Serine
t	Triplet
theo	Theophylline
u.v.	Ultraviolet
valH	Valine

Chapter One

Introduction

Chapter 1 - General Introduction

1.1.1 - Introduction.

Ruthenium and rhodium both exhibit a wide range of oxidation states in their various complexes. For ruthenium, these oxidation states range between -II and VIII with the most common ones being 0, II and III for organometallic complexes. Similarly, for rhodium the oxidation states vary between -I and VI with those of I and III more commonly found. For both metals the oxidation states above III are usually found in inorganic rather than organometallic complexes, such as $[Ru^{IV}F_4]$, $[Ru^{VIII}O_4]$, $[Cs_2Rh^{IV}Cl_6]$ and $[RbRh^{V}F_6]$ where these higher oxidation states are stabilised by small hard donor ligands.[1]

Metal complexes of ruthenium and rhodium, in particular those containing phosphines such as $[RuClH(PPh_3)_3]$ or $[RhCl(PPh_3)_3]$, have found use as catalysts. Wilkinson's catalyst $[RhCl(PPh_3)_3]$ is one of the most well known catalysts and is used extensively in the hydrogenation of alkenes[2], whilst $[RuClH(PPh_3)_3]$ is also an extremely effective homogeneous catalyst for the highly selective hydrogenation of alk-1-enes.[3]

Conjugated alkenes such as benzene and the cyclopentadienyl anion have been shown to co-ordinate to transition metal centres.[4] One of the earliest benzene complexes prepared was $[(C_6H_6)Cr(CO)_3]$[5] which was shown by X-ray diffraction studies to have a half-sandwich structure. The benzene ring occupies three facial positions of the pseudo octahedral structure and the three carbonyl groups occupy the other three sites.[6] In 1965, Bailey and Dahl redetermined the crystal structure of the half-sandwich complex and found that the π-bonded ring showed no significant

distortion in terms of symmetry from that of free benzene which is indicative of a fully delocalised benzene-chromium interaction.[7] In 1967, Winkhaus and Singer reported the formation of a brown diamagnetic complex of empirical formula $[(C_6H_6)RuCl_2]_n$, from the reaction of ruthenium trichloride and cyclohexa-1,3-diene, which reacted with PBu_3 to give the mononuclear species $[(C_6H_6)RuCl_2(PBu_3)]$ and is the first example of a half-sandwich ruthenium complex.[8] Unconjugated dienes such as cyclo-1,5-diene (COD) and bicyclo-[2.2.1]-hepta-2,5-diene (norbornadiene) react with ruthenium(III) halides in ethanol forming complexes of the type $[(diene)RuX_2]_n$.[9] Rhodium(III) chloride reacts with a number of dienes (COD, cyclooctatetraene, norbornadiene, 1,5-hexadiene, and cyclohexa-1,3-diene) on heating to form the rhodium(I) dimers $[(diene)RhCl]_2$.[1] These chloride bridges are easily cleaved by a number of ligands and these are discussed later in this chapter.

Complexes of the cyclopentadienyl anion (Cp) with transition metals include the classic sandwich complexes "ferrocene"[10] and "manganocene"[11]. The complex $[(Cp)_2Ru]$ "ruthenocene" is similar to that of the well known iron analogue "ferrocene" $[(Cp)_2Fe]$ showing similar chemical reactivity, such as Friedel-Crafts substitution and metallation reactions.[12,13] The analogous rhodium sandwich cation $[(Cp)_2Rh]^+$ is prepared by the reaction of the Grignard reagent [(Cp)MgBr] with $[Rh(acac)_3]$.[14] Ruthenium and rhodium both form half-sandwich complexes $[(Cp)M(L)_2]$ (M = Rh) and $[(Cp)MX(L)_2]$ (M = Ru; X = Cl, Br) (L = CO, PMe_3, PPh_3, $P(OMe)_3$) respectively, whose chemistry has been reviewed previously.[15,16]

The chemistry of the half-sandwich complexes $[(Cp)RuCl(CO)_2]$[17] and the structurally related complex $[(Cp)RuCl(PPh_3)_2]$[18] differs markedly.[15] A feature of the chemistry of the complex $[(Cp)RuCl(PPh_3)_2]$ is the stepwise loss of the

triphenylphosphine ligand.[15] Comparison of the reactions of both complexes shows that with $[(Cp)RuCl(CO)_2]$ cationic complexes are not easily formed, whereas the chloride ion is easily ionised in the complex $[(Cp)RuCl(PPh_3)_2]$ in methanol according to Eqn. **1.1**, with the equilibrium lying well over to the right.[19]

$$[(Cp)RuCl(PPh_3)_2] \overset{MeOH}{\rightleftharpoons} [(Cp)Ru(MeOH)(PPh_3)_2]^+ Cl^-$$

Eqn 1.1

The analogous rhodium complex $[(C_5H_4R)Rh(CO)_2]$ (R = H or Me) is a valuable starting material for a range of organorhodium complexes.[16] The loss of one carbonyl group is reported in the reaction of the complex with I_2, giving rise to the complex $[(C_5H_4R)RhI_2(CO)]$.[16] The bis-phosphine complexes $[(Cp)Rh(PR_3)_2]$ are also known and can be prepared by the reaction of $[(Cp)RhI_2(PR_3)]$ (R = Me, Ph) with $MgBrPr^i$ in the presence of PPh_3[20], or more readily by the treatment of $[RhCl(PR_3)_2]_2$ with [(Cp)M] (M = Na, Tl).[16]

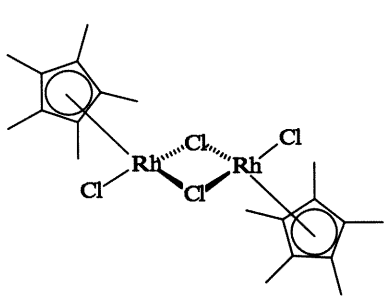
Arene ruthenium and pentamethylcyclopentadienyl (Cp^*) rhodium complexes play an important role in organometallic chemistry.[21,22] Both $[(\eta^5\text{-}Cp^*)RhCl_2]_2$[23,24] and $[(\eta^6\text{-p-cymene})RuCl_2]_2$[25] are readily synthesised from commercially available $RhCl_3.xH_2O$ and $RuCl_3.xH_2O$ respectively (scheme **1.2**). In the formation of the complex $[(p\text{-cymene})RuCl_2]_2$ the ruthenium is reduced from Ru(III) to Ru(II) whereas the rhodium metal remains in the +3 oxidation state.

$$RhCl_3.xH_2O + Cp^*H \xrightarrow[MeOH]{\text{reflux 3hrs}} [(Cp^*)RhCl_2]_2$$

$$RuCl_3.xH_2O + \alpha\text{- phellandrene} \xrightarrow[EtOH]{\text{reflux 4hrs}} [(p\text{-cymene})RuCl_2]_2$$

Scheme 1.2

The metal atoms in these dimeric complexes have an 18 electron configuration and the X-ray determination of the complex (**1.3**) has shown that the four-membered $[Rh\text{-}Cl]_2$ centre has a two-fold axis of symmetry.[26]



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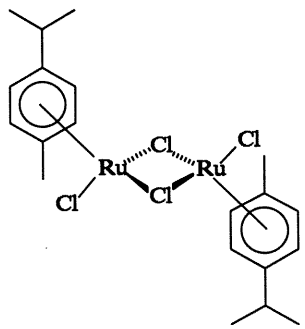
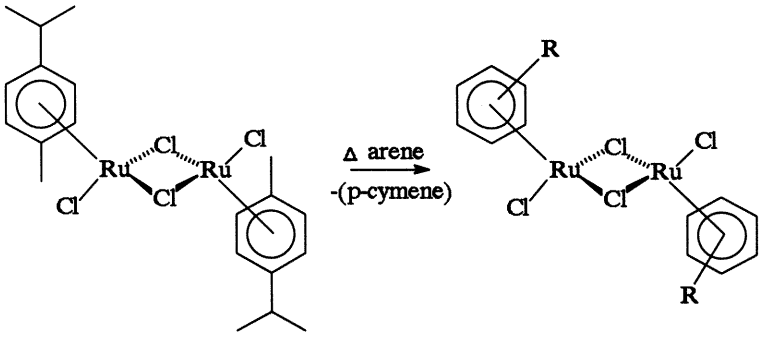


1.4

The original synthesis of the dimeric complex (**1.3**) by Maitlis *et al.*[23] was

achieved by refluxing rhodium trichloride with hexamethyl(Dewar benzene) in methanol. After initial incorrect formulation, the product was identified as the dimeric complex (1.3). The reaction proceeds through an acid catalysed ring contraction of the Dewar benzene giving rise to the pentamethylcyclopentadienyl derivative.[23,27] Complex (1.3) is more usually prepared by the reaction of $RhCl_3.xH_2O$ with Cp^*H.[24] Whereas complex (1.3) has been shown to be dimeric, the corresponding cyclopentadienyl complex $[(Cp)RhCl_2]_n$, which can be prepared in a similar manner by refluxing freshly distilled cyclopentadiene with rhodium trichloride, is polymeric.[21,27] The chemistry of both dimeric rhodium complexes is similar, specific examples of which have been reviewed.[16]

The p-cymene ligand of $[(p\text{-cymene})RuCl_2]_2$ (1.4) can, under certain conditions, exchange with other arene ligands. Thus heating $[(p\text{-cymene})RuCl_2]_2$ in a solid melt reaction with hexamethylbenzene produces $[(C_6Me_6)RuCl_2]_2$,[25] whilst refluxing it in neat arenes such as $1,2,4,5\text{-}Me_4C_6H_2$, $1,2,3,4\text{-}Me_4C_6H_2$, $1,3,5\text{-}Me_3C_6H_3$, $1,3,5\text{-}Et_3C_6H_3$ and $1,3,5\text{-}^iPr_3C_6H_3$ (Scheme 1.5) provides the corresponding $[(arene)RuCl_2]_2$ complexes.[28] Photochemical or thermal exchange of the p-cymene ring of $[(p\text{-cymene})RuCl_2(PBu_3)]$ with benzene or hexamethylbenzene has also been shown to take place, but only in moderate yields.[29] There are no reports of exchange of the pentamethylcyclopentadienyl ring in the rhodium complex (1.3).



Scheme 1.5

The two dimeric complexes (**1.3**) and (**1.4**) are isoelectronic and there are a number of reactions indicating the similarity between them. Both complexes undergo halide exchange with Br^-, I^- and with the pseudo halides SCN^-, NCO^- and N_3^- (Eqn. **1.6**).[15,23,30]

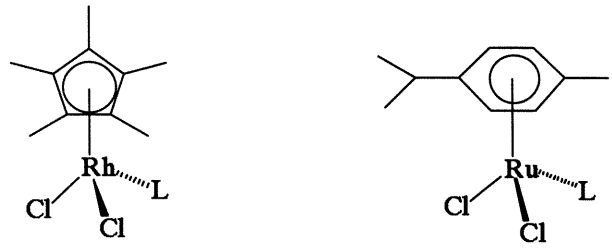
$$[(\text{ring})MCl_2]_2 + (\text{excess})Y^- \Rightarrow [(\text{ring})MY_2]_2 + 4Cl^-$$

(M = Rh, ring = Cp^*; M = Ru, ring = p-cymene; Y = Br^-, I^-, SCN^-, NCO^-, N_3^-).

Eqn. 1.6

The complex $[(C_6H_6)RuCl_2]_2$ when reacted with PBu_3 produces the complex $[(C_6H_6)RuCl_2(PBu_3)]$ as mentioned earlier.[8] A number of other neutral two-electron donor ligands L (L = py, CO, MeCN, DMSO, amines and other phosphines) react with

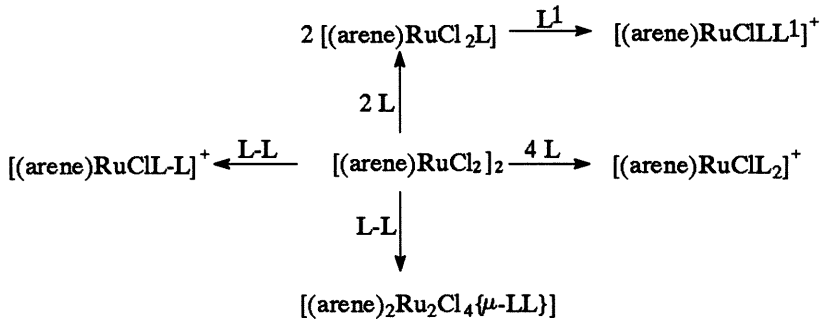
the dimers (**1.3**) and (**1.4**) to produce mononuclear half-sandwich complexes of the type $[(Cp^*)RhCl_2L]$[16,27] or $[(p\text{-cymene})RuCl_2L]$[15] (**1.7**) which have a piano stool structure. The reactions with amines can be used as simple models for the reactions of these dimers with nucleosides and nucleotides to establish whether the exocyclic amine groups are potential sites for co-ordination. (The reactions of nucleosides with ruthenium and rhodium complexes is further discussed in Chapter four).



1.7

The geometry of these complexes (**1.7**) is pseudooctahedral in which the π-ligand is considered to occupy three facial sites of an octahedron. In polar solvents the rhodium and ruthenium dimers can add two basic ligands to afford cationic derivatives $[(Cp^*)RhClL_2]^+$ or $[(arene)RuClL_2]^+$ (arene = p-cymene, C_6H_6) (Scheme **1.8**). Complexes (**1.3**) and (**1.4**) also react with bidentate ligands such as bipyridines, diamines and diphosphines cleaving the chloride bridges to produce two types of complex. The ligand can co-ordinate in a bridging fashion giving rise to complexes of the type $[(Cp^*)_2Rh_2Cl_4(\mu\text{-LL})]$ or $[(arene)_2Ru_2Cl_4(\mu\text{-LL})]$ (LL = diamines, diphosphines) or as a chelate in complexes of the type $[(ring)MCl(LL)]^+$ (ring = arene, M = Ru; ring

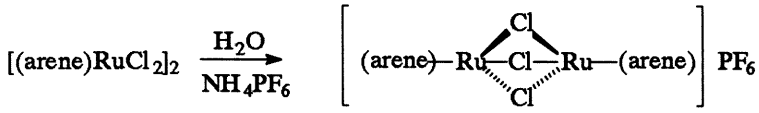
= Cp^*, M = Rh; LL = diamines, diphosphines, bipyridines) (Scheme **1.8**).[15,16]



Scheme 1.8

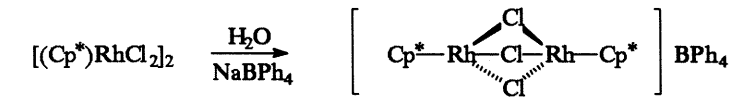
Anionic bidentate ligands can also be used to cleave the halide bridges. Thus, pyranones, 2,4-pentanedione and amino acids, when deprotonated, react with (**1.3**) and (**1.4**) to give the complexes [(ring)MCl(LL)] (ring = Cp^*, M = Rh; ring = p-cymene, M = Ru; LLH = amino acid, pyranones, 2,4-pentanedione).[31-36] The complex [(Cp^*)RhCl(acac)] reacts with $AgBF_4$ to produce the dimeric species [(Cp^*)Rh($acac_2$-)]$_2$(BF_4)$_2$ in which the acetylacetonato ligand bridges between two Cp^*-rhodium fragments through the deprotonated γ-carbon group, as determined by X-ray diffraction.[35]

The reaction of the dimeric complexes [(arene)$RuCl_2$]$_2$ with hot water, followed by treatment with ammonium hexafluorophosphate, affords the triply chloro-bridged ruthenium complexes [{(arene)Ru}$_2$(μ-Cl)$_3$](PF_6) (Eqn. **1.9**).[28]



Eqn 1.9

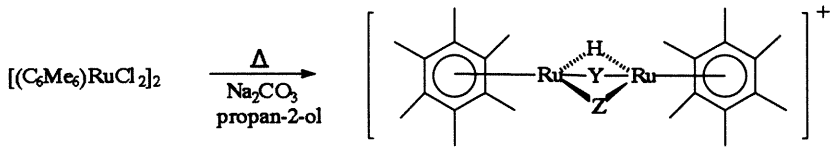
The same complexes can be more readily prepared in greater than 90% yield by shaking the dimers $[(arene)RuCl_2]_2$ with an excess of NH_4PF_6 in methanol.[37] $[(Cp^*)RhX_2]_2$ also forms triply bridged dinuclear cations $[(Cp^*)Rh(\mu\text{-}X)_3Rh(Cp^*)]^+$ (X = Cl, Br, I, N_3, NCO, SCN).[30,38] Kang and Maitlis reported the preparation of $[(Cp^*)Rh(\mu\text{-}Cl)_3Rh(Cp^*)]^+$ from the addition of $NaBPh_4$ to an aqueous solution containing $[(Cp^*)RhCl_2]_2$ (Eqn **1.10**), whereas the triply bridged hydroxyl species $[(Cp^*)Rh(\mu\text{-}OH)_3Rh(Cp^*)]^+$ was formed by the addition of excess NaOH to an aqueous solution of $[(Cp^*)RhCl_2]_2$.[38]



Eqn 1.10

Binuclear $[(arene)RuX_2]_2$ and $[(Cp^*)RhX_2]_2$ complexes are useful precursors for access to reactive alkyl or hydrido organometallic complexes.[39,40] The latter are key compounds for the formation of organometallic intermediates capable of C-H bond

activation leading to new hydrido and cyclometallated Cp^*-rhodium or arene-ruthenium derivatives. Treatment of $[(C_6Me_6)RuCl_2(PPh_3)]$ with aqueous sodium carbonate in propan-2-ol at 80 °C gives a high yield of $[(C_6Me_6)RuClH(PPh_3)]$ which has been reported to be a catalyst for the hydrogenation of benzene and alkenes.[39,41] In a similar manner, the dimeric complex $[(C_6Me_6)RuCl_2]_2$ undergoes a chloride-hydride exchange reaction with sodium carbonate in propan-2-ol to give the dinuclear, monohydrido cation $[\{(C_6Me_6)Ru\}_2Cl_2H]^+$ which on prolonged heating, gives rise to a mixture of the di-μ-hydrido (Y = H; Z = Cl) and tri-μ-hydrido (Y = Z = H) complexes (Eqn. **1.11**).[42,43]



Eqn 1.11

The complex $[(Cp^*)RhCl_2]_2$ is a catalyst for the hydrogenation of olefins under ambient conditions.[22] The reaction of $[(Cp^*)RhCl_2]_2$ with hydrogen gave the hydride complex $[\{(Cp^*)Rh\}_2HCl_3]$, which on the basis of IR and ^1H n.m.r. spectroscopy was proposed to contain one bridging hydride, one bridging chloride and two terminal chlorides. The ^1H n.m.r. shows a triplet at δ -11.54 due to the hydride coupled to two equivalent rhodium atoms. The observation of the triplet indicates that the hydride

bridges the two metal atoms. The IR spectrum showed no absorption due to a terminal M-H group.[22] The structure has been subsequently confirmed by X-ray diffraction studies by Churchill and Ni.[44]

Bennett and Smith have reported the preparation of the ruthenium-alkyl complexes [(arene)RuX(Y)L] (arene = C_6H_6, p-cymene; X = Cl, Y = Me; X = Y = Me; L = PR_3).[29] The complexes are prepared in very low yields, however, but yields are better when the arene is C_6Me_6 (Eqns. **1.12** & **1.13**).[45,46] It is reported that the monomethyl derivative $[(C_6Me_6)RuCl(CH_3)(PR_3)]$ (PR_3 = PMe_3, $PMePh_2$, PPh_3) can be prepared directly from the bis chloride complexes $[(C_6Me_6)RuCl_2(PR_3)]$. The cationic species $[(C_6Me_6)RuCl(PPh_3)_2]^+PF_6^-$ reacts with methyllithium to give the monomethyl complex $[(C_6Me_6)RuMe(PPh_3)_2]^+PF_6^-$ (Eqn. **1.14**).[45,46]

$$[(C_6Me_6)RuCl_2(PPh_3)] + 2LiCH_3 \rightarrow [(C_6Me_6)Ru(CH_3)_2(PPh_3)] \quad \text{Eqn } \mathbf{1.12}$$

$$[(C_6Me_6)RuCl_2(PPh_3)] + LiCH_3 \rightarrow [(C_6Me_6)RuCl(CH_3)PPh_3] \quad \text{Eqn } \mathbf{1.13}$$

$$[(C_6Me_6)RuCl(PPh_3)_2]^+PF_6^- + LiCH_3 \rightarrow [(C_6Me_6)RuCH_3(PPh_3)_2]^+PF_6^- \quad \text{Eqn } \mathbf{1.14}$$

An interesting reaction of the complex $[(C_6Me_6)RuMe_2(PR_3)]$ (PR_3 = PPh_3, PMe_3) is hydride abstraction on treatment with $(Ph_3C)PF_6$, which leads to the formation of the η^2-ethylene complex $[(C_6Me_6)RuH(C_2H_4)(PR_3)]^+PF_6^-$ which has been characterised by X-ray diffraction.[45,47] Cp^*-rhodium complexes containing rhodium-alkyl bonds have been synthesised by Maitlis *et al.* from $[(Cp^*)RhCl_2L]$ (L = pyridine, p-toluidine or triphenylphosphine) in a similar manner to those of the ruthenium

analogues.[27] An excess of methylmagnesium iodide reacts with $[(Cp^*)RhCl_2(PPh_3)]$ to produce the iodomethyl complex $[(Cp^*)RhIMe(PPh_3)]$ as the main product, due to halogen exchange, along with some dimethyl complex. In the corresponding reaction with $[(Cp^*)RhI_2(PPh_3)]$ only the dimethyl complex was isolated from the reaction.[27]

The dimers $[(Cp^*)RhCl_2]_2$ and $[(arene)RuCl_2]_2$ form the dicationic species $[(Cp^*)Rh(L)_3]^{2+}$ (L = acetone) or $[(arene)Ru(L_3)]^{2+}$ (L = acetone, arene = C_6Me_6, 1,3,5-trimethylbenzene; L = MeCN, arene = C_6H_6, p-cymene) in which the weakly bound solvent ligands can be displaced by other ligands such as tetramethylthiophene[48,49], DMSO, py or $P(OMe)_3$[50] giving a convenient route to other dicationic species. Bennett and Smith have shown that reaction of the dication $[(arene)Ru(NCMe)_3]^{2+}$ (arene = C_6H_6, p-cymene) with chloride ions converts the dication back to the dimeric starting material.[29]

The formation of half-sandwich complexes has prompted interest in chiral transition metal chemistry.[51] Many novel synthetic applications of organotransition-metal complexes have been reported which provide methods for transformations which may be otherwise difficult or impossible. For example, it is observed that reactions at organic ligands bound to the $[(C_5H_5)Fe(CO)PPh_3]$ fragment are highly stereoselective.[52] The reaction of PR_3 (R = Me, Ph, Bu) with either $[(C_6H_6)RuCl_2]_2$ or $[(Cp^*)RhCl_2]_2$ results in the formation of monomeric complexes.[15,27] In the presence of excess LiBr, the complex $[(C_6H_6)RuCl_2]_2$ reacts with PBu_3 forming two complexes, assigned as the dibromo and chlorobromo complexes $[(C_6H_6)RuBr_2(PBu_3)]$ and $[(C_6H_6)RuBrCl(PBu_3)]$ respectively, in which the chlorobromo complex exists as a pair of enantiomers.[29] The optically active complex $[(C_6H_6)RuClMe(Ph_2PNHCH(Me)Ph)]$, formed from the reaction of $[(C_6H_6)RuCl_2]_2$ with dimethyl mercury and the optically active phosphine

R-(+)-$Ph_2PNHCH(Me)Ph$, was reported by Brunner and Gastinger and exists as a pair of diastereomers which could be separated by a combination of column chromatography and fractional recrystallisation.[53,54] Recently, Bennett *et al.* have studied the planar chirality of arene ruthenium complexes[55] and have now extended this to the reactions of these complexes with chiral phosphines giving rise to diastereomeric complexes which were successfully separated.[56] If an unsymmetrical bidentate or tridentate ligand co-ordinates to the (Cp^*)Rh or (arene)Ru centre it results in the formation of enantiomeric complexes. Optically active bis(tertiary phosphines) are generally the most successful chiral auxiliaries in enantioselective catalysis.[57] Kawano *et al.* and James *et al.* have reported the preparation of several ruthenium complexes containing chiral phosphines.[58,59] It is noteworthy that one of the complexes $[(binap)_2Ru_2Cl_4(Et_3N)]$ prepared by Kawano *et al.* contains one five and one six co-ordinate ruthenium atom as complexes of this type have been shown to react easily with dihydrogen at the vacant site on the metal. Such unsaturation of these ruthenium centres is an important factor in their catalytic behaviour.[58] Another binap complex $[(C_6H_6)RuCl(binap)]Cl$ has been reported to be a highly efficient catalyst for the hydrogenation of acylaminoacrylic acids.[60]

The use of optically active bidentate ligands containing dissimilar donor groups is less well developed than those containing symmetric ligands. However, these ligands have important implications in the area of asymmetric synthesis, as they are capable of exercising stereo and electronic control over the reactions of co-ordinated substrates.[57,61] The complex $[(C_6H_6)RuCl(ala)]$ containing the anionic bidentate amino acidate ligand was initially reported by Dersnah and Baird with the ^1H and ^{13}C n.m.r. spectrum indicating the presence of both diastereomers and this suggests that

epimerisation at the ruthenium centre is slow on the n.m.r. timescale.[31] The complex has subsequently been characterised by X-ray determination, by Sheldrick and Heeb, and the crystal structure reveals the presence of both diastereomers ($R_{Ru}S_C$ and $S_{Ru}S_C$) in the unit cell.[62] Studies involving the formation of half-sandwich complexes containing arene-ruthenium and pentamethylcyclopentadienyl-rhodium complexes with amino acids are further reviewed in Chapter two.

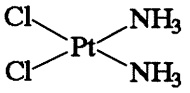
Rhodium and ruthenium complexes containing other N,O and N,N donors such as Schiff base ligands have been reported.[63-66] Kureshy and Khan have reported the preparation of $[RuL(H_2O)_2(PPh_3)]$ (L = Schiff base anion) complexes with the Schiff bases derived from amino acids such as phenylalanine and methionine.[67] One of the possible avenues of exploration in these types of complexes is in the possible interaction of the addition functional group of the Schiff base with the central metal or with an organic substrate. El-Hendawy *et al.* have recently reported the preparation of the complexes $[RuX_2(AsPh_3)_2(HL)]$ (X = Cl, Br; HL = Schiff base) and investigated their use as catalytic oxidants of both alcohols and catechols.[64]

Although there are several reports of complexes of rhodium and ruthenium with the O,O donor ligand $acac^-$ [68,69], there are few examples of complexes of pyranones or pyridinones with these metals.[70,71] The complex $[RuH(L)(PPh_3)_3]$ (L = memalt) prepared by El-Hendawy *et al.* shows similar results, as a catalyst for the selective oxidation of alcohols to aldehydes and ketones,[70] to those reported for the Schiff base complexes mentioned earlier. Complexes containing pyranones and pyridinones are discussed in Chapter three.

1.1.2 - Medicinal Applications of Ruthenium and Rhodium Complexes.

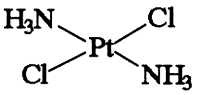
Metal complexes have been used as pharmaceutical agents since early history. The most important drugs from inorganic chemistry in routine medical use are those of auranofin (2,3,4,6-tetra-O-acetyl-1-thio-1-β-D-glucopyranosato)-(triethylphosphine)-gold(I) active against rheumatoid arthritis,[72] and disodiumpentacyanonitrosyl-ferrate(II)dihydrate, $Na_2[Fe(NO)(CN)_5].2H_2O$ which is used as an emergency drug in hyper-tension crises, and lithium salts are used in psychiatry[73].

In the field of cancer treatment, only one group of inorganic complexes are in routine use, those based on the complex cisplatin, *cis*-diamminedichloroplatinum(II), a complex that was initially synthesised in 1844 by Peyrone.[74] The tumour-inhibiting properties of this complex were not discovered until 1969 by Rosenberg. Rosenberg, while examining the influence of an electrical field on bacterial growth, observed filamentous growth of *escherichia coli* bacteria. He was later able to show that this effect was due to the presence of cisplatin.[75] A number of other platinum-amine complexes were prepared and their activity against several tumours were screened.[74] Application of *cis*-$[PtCl_4(NH_3)_2]$, *cis*-$[PtCl_2(NH_3)_2]$ (1.17), $[PtCl_2(en)]$ and $[PtCl_4(en)]$ resulted in a reduction of tumour weight and a prolongation of survival time of tumour-bearing animals.[73] However, the *trans* complexes (such as 1.18) were inactive against the same tumours except at very high concentrations.[76]



cis-platin

1.17

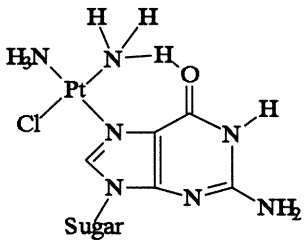


trans-platin

1.18

Although cisplatin is effective against a broad spectrum of tumours including bladder, lung, head, neck and cervical tumours it is primarily used in the treatment of testicular cancer where the cure rate is approaching 100%, especially if the early stages of testicular cancer are recognised.[77] Several unfavourable side effects accompany the use of cisplatin including liver failure, nephrotoxicity, nausea and vomiting which can be repressed by fractionated therapy and the use of diuretics.[74] Numerous examinations into the mechanisms of action of cisplatin have been carried out and are presented in several reviews.[74,76,78] The investigations have centred around the adducts that cisplatin forms with DNA. It is inferred that these adducts inhibit DNA replication and thus also directly affect tumour growth.[74,76,78] Cisplatin forms a number of intrastrand and interstrand chelates between DNA bases where these intrastrand chelates refer to the binding of two nucleobases within the same DNA strand, interstrand chelates to the binding to two nucleobases, one in each of two complementary DNA strands, intrabase chelates and DNA-protein crosslinks. Analysis of *in vitro* experiments show that the intrastrand *cis*-$[(NH_3)_2Pt(G)_2]^{2+}$ adducts are the most common (65% of the total complexed platinum) but adducts containing *cis*-

$[(NH_3)_2Pt(G)(A)]^{2+}$ adducts (25%) and *cis*-$[(NH_3)_2Pt(G)(protein)]^{2+}$ (1%) are also found.[79] Studies have concluded that cisplatin preferentially binds to the N(7) site of the guanine base *in vitro* and *in vivo*, with the N(7) site of the adenine base also reported as a potential co-ordination site.[73,76,78,79,80] No indications have yet been found to suggest that the N(1) site of the adenine nucleobase or the N(3) site of the cytidine nucleobase are involved in any adduct formation.[80] The preference of cisplatin for guanine nucleobases is reported to be due, in part to the secondary interaction with the neighbouring O(6) atom giving rise to indirect chelates from favourable hydrogen bonding interactions with either an amine or water group (**1.19**) (or repulsion with the $N(6)H_2$ group in the corresponding adenine complex)[80] (**1.20**). No evidence for direct chelation between the platinum atom and O(6) of the guanine nucleobase has been found which could account for the difference in reactivity of *cis* and *trans* $[PtCl_2(NH_3)_2]$.[81]



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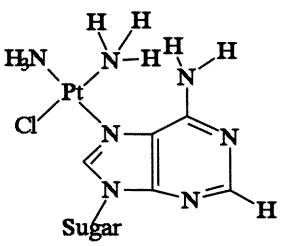


1.20

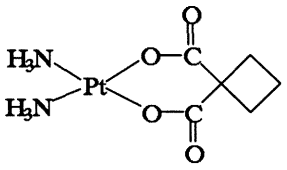
Interestingly, it has been reported that cisplatin inhibits the syntheses of proteins and RNA in tumour cells only to a very minor extent compared to that of

DNA, where incorporation of a radiolabeled isotope into DNA was suppressed over the period of time monitored.[76] These results suggest that selective inactivation of DNA synthesis is responsible for the drug's anti-tumour activity.[76] The search for new anti-tumour platinum drugs with higher activity and lower toxicity has resulted in many platinum complexes being screened for anti-tumour activity. The tests have identified a number of common features required for anti-tumour activity of simple platinum complexes[79]:-

1) Two cis amine groups seem to be necessary for activity (this geometric restriction is automatically answered for bidentate amines). The amine groups should possess at least one NH group (Complexes lacking this property are all inactive).

2) The complexes should possess good leaving groups, such as chloride. However, some readily soluble platinum complexes with strongly bound anions-citrate, oxalate, malonate or 1,1-cyclobutanedicarboxylate as leaving groups are also active, although they react much more slowly.

The most successful of the new platinum complexes are carboplatin (**1.21**) and iproplatin (**1.22**) which both show fewer of the side-effects that cisplatin shows. Although platinum drugs are highly active against some relatively rare tumours, they have little or no effect on other more common tumours.



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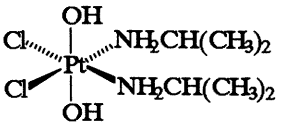
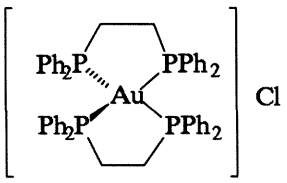


1.22

Approaches to discovering new anti-tumour active metal complexes, have in some instances centred on a change of the central metal atom which presents more variety in the type of complexes that can be tested due to the inevitable change in chemical properties.[73] Today, many non-platinum complexes are known that show anti-tumour activity in certain preclinical models[72] these include gold complexes such as potassium dicyanogold(I) and bis[1,2-bis(diphenylphosphinoethane)]-gold(I)chloride (**1.23**). Metallocenes complexes $[(Cp)_2MCl_2]$ (M = Ti, V, Nb, Zr, Hf) exhibit activity against several tumours.[82] For these complexes, it is proposed that the Cp_2-M fragment binds to DNA, and that this is responsible for the observed anti-tumour activity.[83,84] Other titanium complexes have also shown anti-tumour activity. Although $[Ti(acac)_2(OEt)_2]$ shows no anti-tumour activity, by replacing a methyl group with a phenyl group, the new complex $[Ti(phenylacetylacetonato)_2(OEt)_2]$ "Budotitane" (**1.24**) shows promising anti-tumour activity, particularly against Walker 256 carcinoma.[73] The complex (**1.24**) is currently undergoing further trials for colon cancer amongst others.[85]



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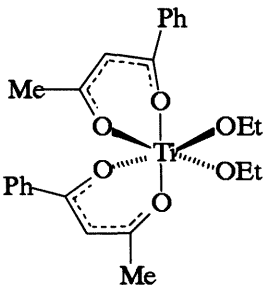
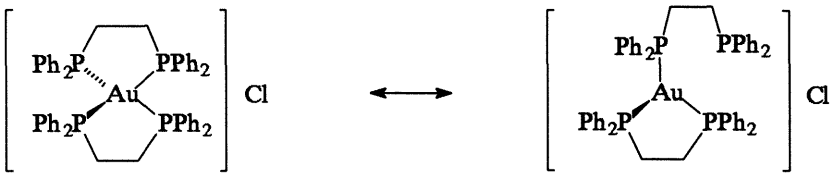


1.24

The anti-tumour activity of the tetrahedral gold(I) diphosphine complex (**1.23**) is reported to be due to a facile ring opening of the gold-phosphorus bond that allows the phosphine to undergo further interactions (scheme **1.25**).[86] This metal diphosphine complexes is reported to cause DNA strand breaks and DNA-protein crosslinks, which indicates that their mechanism of action is different from that of cisplatin.[86]



Scheme 1.25

With regard to rhodium and ruthenium complexes, it is evident that there are few reports in the literature on work to characterise their anti-tumour activity.[87] The complex *mer*-$[RhCl_3(NH_3)_3]$ has been reported to be the best rhodium-amine complex as regards anti-tumour activity, however, it is very insoluble in water.[88] During *in vitro* experiments, the derivative *trans*-$[RhCl_2(py)_4]^+$ induced filamentous growth in a similar manner to cisplatin.[89] However, this complex is more commonly discussed in terms of its anti-bacterial properties where it shows significant activity. The most well studied group of rhodium complexes that show anti-tumour activity are $[Rh_2(O_2CR)_4(L)_2]$ and [(diene)Rh(acac)] complexes.[73] Mestroni *et al.* have reported the effect of the rhodium and iridium derivatives [(L-L)M(chelate)] (L-L = 1,5-hexadiene,

1,5-cyclooctadiene or norbornadiene; M = Rh, Ir; chelate = acetylacetonate, pyridinalimine) on the Lewis lung carcinoma.[90] The conclusions that were drawn from the experiments were :-

1) The Rh(I) derivatives are more active than those of Ir(I).

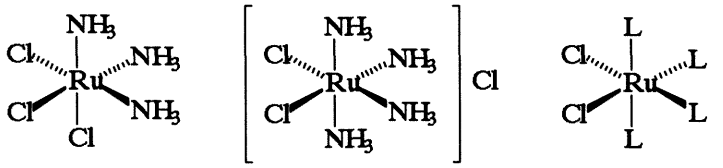
2) The two cyclic dienes gave results with similar activity observed.

3) Substitution of the pyridinalimine group with acetylacetonate increased the activity.

and this indicates that even within this small class of compounds studied, different degrees of activity can be identified.[90] The rhodium-carboxylate complexes $[Rh_2(O_2CR)_4(L)_2]$ have been the most studied of all the rhodium compounds. These complexes show their best activity against the Ehrlich ascites line but little activity against L1210 or B16 lines. The activity of these complexes is found to increase with the lipophilicity of the R group in the bridging carboxylate. The most important difference between these complexes and the platinum complexes is that these complexes do not bind to doubly stranded DNA.[90] Bear and co-workers have reported that their reactions with nucleic bases are specific with binding only occurring at the N(7) site of adenine bases.[91,92] The specificity of this interaction is attributed to a favourable hydrogen bonding interaction between the $N(6)H_2$ protons and the carboxylate group[91,92] analogous to that reported for the complex $[Co(acac)_2(NO_2)(ado)]$.[93] It must be noted however, that the acute toxicity of these rhodium-carboxylates complexes will probably limit further studies into the *in vitro* and *in vivo* activity of these complexes.[81]

For ruthenium complexes, there are several compounds in the literature

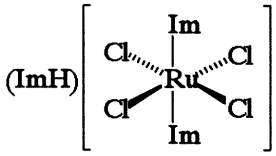
including *fac*-$[RuCl_3(NH_3)_3]$ (**1.26**), *cis*-$[RuCl_2(NH_3)_4]Cl$ (**1.27**) and $[RuCl_2(DMSO)_4]$ (**1.28**) that have been reported to show anti-tumour activity.[73]



1.26 **1.27** **1.28**

Interestingly, both the *cis* and *trans* isomers of $[RuCl_2(DMSO)_4]$ (**1.28**) exhibit anti-tumour activity and this illustrates a major difference between this compound and the platinum complexes (**1.17** & **1.18**). The complex *cis*-$[RuCl_2(DMSO)_4]$ is fairly soluble in water and although it shows only marginal activity against P388 leukaemia, it shows good inhibiting effects on other tumour systems, such as the Lewis lung tumour.[73] Mestroni *et al.* have reported a detailed study of the comparable reactions of *cis* and *trans*-$[RuCl_2(DMSO)_4]$ to determine anti-tumour activity.[94] The results indicate that DNA is the preferred site of attack *in vivo* and that the therapeutic potential of the ruthenium derivatives is higher than that of cisplatin based on the use of equitoxic doses.[94] The DMSO complex is noteworthy in that rhodium and platinum complexes with this ligand do not display any promising activity.[81] Keppler *et al.* have reported the study of the anti-tumour activity of ruthenium complexes with nitrogen donor ligands, such as $ImH[RuCl_4(Im)_2]$ (**1.29**) and $(ImH)_2[RuCl_5(Im)]$ (**1.30**) and found that these complexes show greater activity than either cisplatin or 5-fluorouracil in the

P388 leukaemia tumour model.[73]



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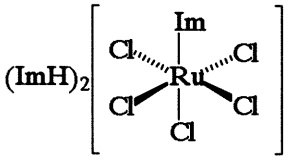

1.30

A recent report by Dale *et al.* stated that the ruthenium complex $[(C_6H_6)RuCl_2(metro)]$ shows good anti-tumour properties and a greater selective cytotoxicity than the free ligand metronidazole.[95] For this complex, it is proposed that the complex acts as a carrier for the metronidazole ligand. The use of metal complexes as carrier molecules can be highlighted by the gold complex which is highly cytotoxic *in vitro* due to the presence of the phosphine group which was discussed earlier.[86]

The indications are that the mode of action of ruthenium complexes is by direct binding to DNA. In contrast to platinum (II) complexes, strand breakage on DNA can occur due to the possibility of the ruthenium (III) / ruthenium (II) redox reactions. *In vivo* there are a number of possible reduction mechanisms to activate ruthenium (III) prodrugs to bind in the ruthenium (II) state.[96] The theory of the mechanisms have been investigated by Clarke *et al.* who report that tumour accumulation of simple ruthenium amines proceeds via two pathways.[97] In the first pathway, activation of the ruthenium (III) complexes is achieved by reduction inside the tumour due to the reducing environment. The second pathway is thought to occur through transferrin

transportation. Since ruthenium is immediately below iron in the periodic table it is not unsurprising that ruthenium is found to have a high affinity for this protein. The ruthenium is thought to be carried to the tumour by first binding to transferrin, and is transported through the cell wall after which it is subsequently released by intracellular reduction to ruthenium (II).[96,97]

It has been reported that the half-sandwich ruthenium complex $[(C_6H_6)RuCl(pro)]$ displays anti-tumour activity against P388 leukaemia *in vivo*.[98] The formation of protein-nucleobase complexes of cisplatin has already been suggested as one of the models for the *in vivo* activity observed.[77]

To conclude, many ruthenium and rhodium complexes have been shown to possess anti-tumour activity, but the number of studies detailing the mechanisms of their reactions is very limited in comparison to those of the various platinum complexes. It was decided to synthesise some complexes which show hydrophilic properties which makes oral administration possible and hydrophobic properties which would allow passage through cell membranes. Chapters two and three describe work relating to the formation of mesitylene-ruthenium and Cp^*-rhodium complexes of biologically important ligands such as amino acids and pyranones / pyridinones. Chapter four describes work on the reactions of half-sandwich complexes with nucleobase ligands in order to study the interactions of the metal complexes with these biological ligands and in particular, whether there is any selectivity for a specific nucleobase. Finally, a series of competition reactions were preformed to identify an order of preference of the amino acidate complex [(mes)RuCl(phgly)] for a particular nucleobase.

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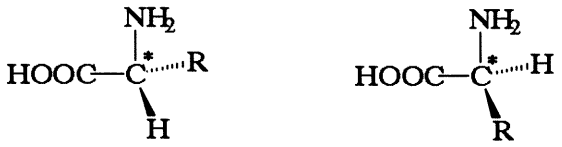
Chapter Two

The Synthesis and Characterisation of some Arene-Ruthenium Amino Acidate Complexes

Chapter 2 - The Synthesis and Characterisation of some Arene-Ruthenium Amino Acidate Complexes.

2.1.1 - Introduction.

Amino acids are naturally occurring molecules and are the building blocks from which all proteins are made. With the exception of glycine (R = H) all the naturally occurring amino acids contain a chiral centre (figure **2.1**) and thus two enantiomeric forms are possible.



[R] [S]

Figure 2.1

However, in nature only the "l-form" is found and this is assigned as the S enantiomer. In general, the amino acids are formulated as "$NH_2CH(R)CO_2H$" but in solution they exist primarily in the zwitterion form[1] (figure **2.2**).

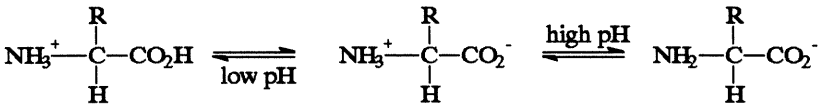


Figure 2.2

At low pH the amino acid is protonated and exists as a cation; at high pH, it is deprotonated and exists as an anion, therefore, at an intermediate pH, it must exist in a dipolar zwitterion form. This is known as the isoelectronic point.

The co-ordination of amino acids to metal centres has been well documented.[2] In general, these ligands are anionic bidentate ligands co-ordinating through the amine and deprotonated carboxylate group to form complexes of the type $M^{II}(aa)_2$, $M^{III}(aa)_3$ or $ML(aa)_2$ *etc.*[3-5] Examples of co-ordination through just the nitrogen donor are known *eg.* Cr^{III}, Pt^{II} metal ions and co-ordination through just the oxygen atom are also known in a few cases.[2] The co-ordination through both amine and deprotonated carboxylate group produces a thermodynamically stable 5-membered chelate around the metal centre (figure **2.3**) with bite angles $\angle H_2N\text{-}M\text{-}O_2C \approx 77\text{-}78°$. [6-8]

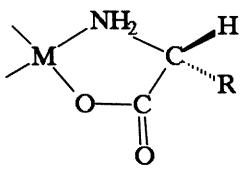


Figure 2.3

Co-ordination of a chiral amino acid ligand to a metal centre that is itself a chiral centre results in the formation of enantiomeric and diastereomeric complexes (figure **2.4**). Complexes of this type are now of great interest due to their possible application in enantioselective catalysis.[9]

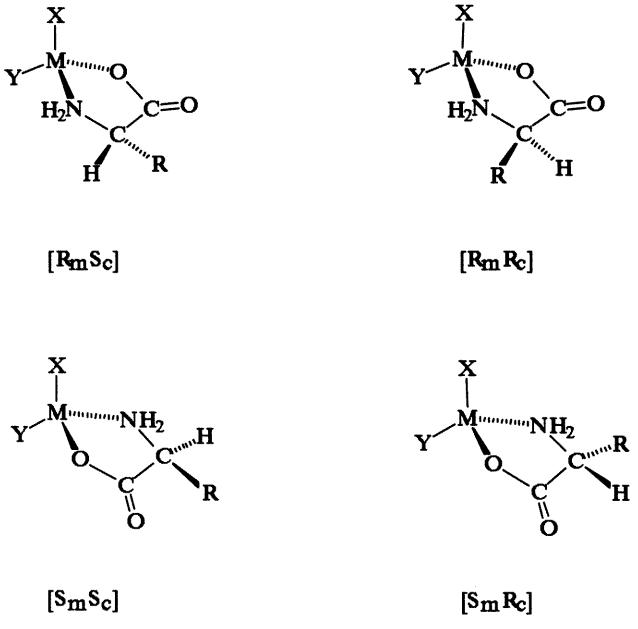


Figure 2.4

Of the 20 naturally occurring amino acids found in proteins, 15 have neutral side chains, 3 have basic side chains and 2 have acidic side chains. The presence of these side chains allows the possibility of co-ordination through a variety of donor atoms. Complexes of organomercury(II) containing cysteine ligands have been reported to co-

ordinate preferentially through the sulphur atom, whereas complexes containing Co(III) with cysteine ligands preferentially co-ordinate through the N,O or N,O and S atoms whereas Masoud *et al.* has determined the preference of Co(II) for O,S co-ordination in the complex $[Co(cysteinate)(H_2O)_4]$[10]. The metal ion, oxidation state of the metal and the structure of the amino acid all affect the co-ordination mode of the amino acid.

The first arene-ruthenium complex containing an amino acidate ligand $[(C_6H_6)RuCl(ala)]$ was prepared by Dersnah and Baird[11] and exists as a pair of diastereomers $R_{Ru}S_C$ and $S_{Ru}S_C$. Complexes of the type $[(C_6H_6)RuCl(aa)]$ containing other amino acidate ligands have been prepared mainly by Beck *et al.*[8] and Sheldrick *et al.*[12]. Many half-sandwich organometallic complexes have been prepared and reacted with amino acid ligands with a view to chiral synthesis, most recently by Beck *et al.* and Sheldrick *et al.*, including $[(Cp^*)Co(asp_2)]$[13], $[(Cp^*)MCl(aa)]$ (M = Rh, Ir, aa = gly, val, phala, phgly, trp, pro, his, asp and azetidine-2-carboxylate)[8], [(arene)RuCl(aa)] (arene = benzene, aa = pen, his[12]; arene = p-cymene, aa = pro, phala, p-NO_2phala, dopa, D-phgly[8]). Organometallic complexes with amino acidate ligands have also been reported such as $[MH(aa)(CO)(PPh_3)_2]$ (M = Ru, aa = phala, pro, leu, allylgly, ala, val; M = Os, aa = phala)[14] and [(diene)IrCl(aa)] (diene = COD, aa = ala, phala, val, leu, phgly and 1-aminocyclopropanecarboxylate)[8].

In the reported examples where the amino acidate ligands are alaninate[16], phenyl glycinate or prolinate[8], X-ray structural data indicates that the two diastereomers $S_{Ir}S_C$ and $R_{Ir}S_C$ (for prolinate $S_{Ir}S_CS_N$ and $R_{Ir}S_CS_N$) exist in the asymmetric cell. These diastereomers are found in a 50 / 50 ratio, (even though of the diastereomer ratio in solution is 60 : 40 , 92 : 8 for prolinate), implying that there is little difference in thermodynamic energy between the two diastereomers.

A recent publication by Beck and Krämer focused on the study of peptide synthesis, using amino acidate complexes as templates.[15] Of particular interest is the question whether optically active peptide ester complexes preferentially incorporate only one enantiomer of an α-amino acid ester present in a racemic mixture. From their report, they have found that the reactions of [(Cp*)RhCl(L-ala-gly-OMe{-H+})] with D,L-leu-OMe and D,L-ser-OMe indicate that the tripeptide esters L-leu-L-ala-gly-OMe and L-ser-L-ala-gly-OMe are formed somewhat faster at the complex than the corresponding diastereoisomers D-leu-L-ala-gly-OMe and D-ser-L-ala-gly-OMe respectively, indicating a degree of selectivity in the reaction.[15] A method is outlined in figure **2.7** to show how an organometallic fragment can be used in the synthesis of a tripeptide based on the authors report.[15]

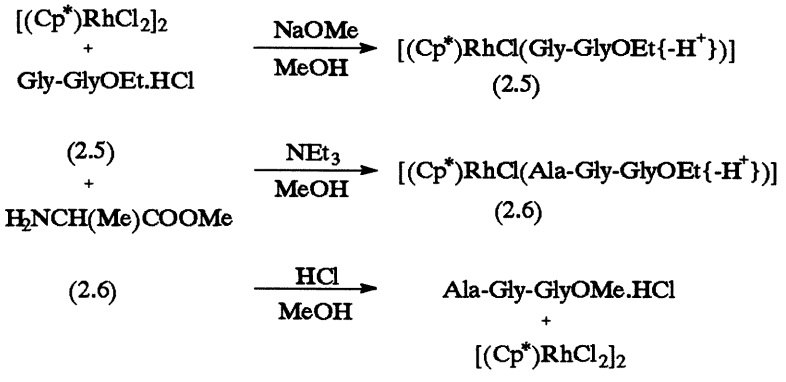
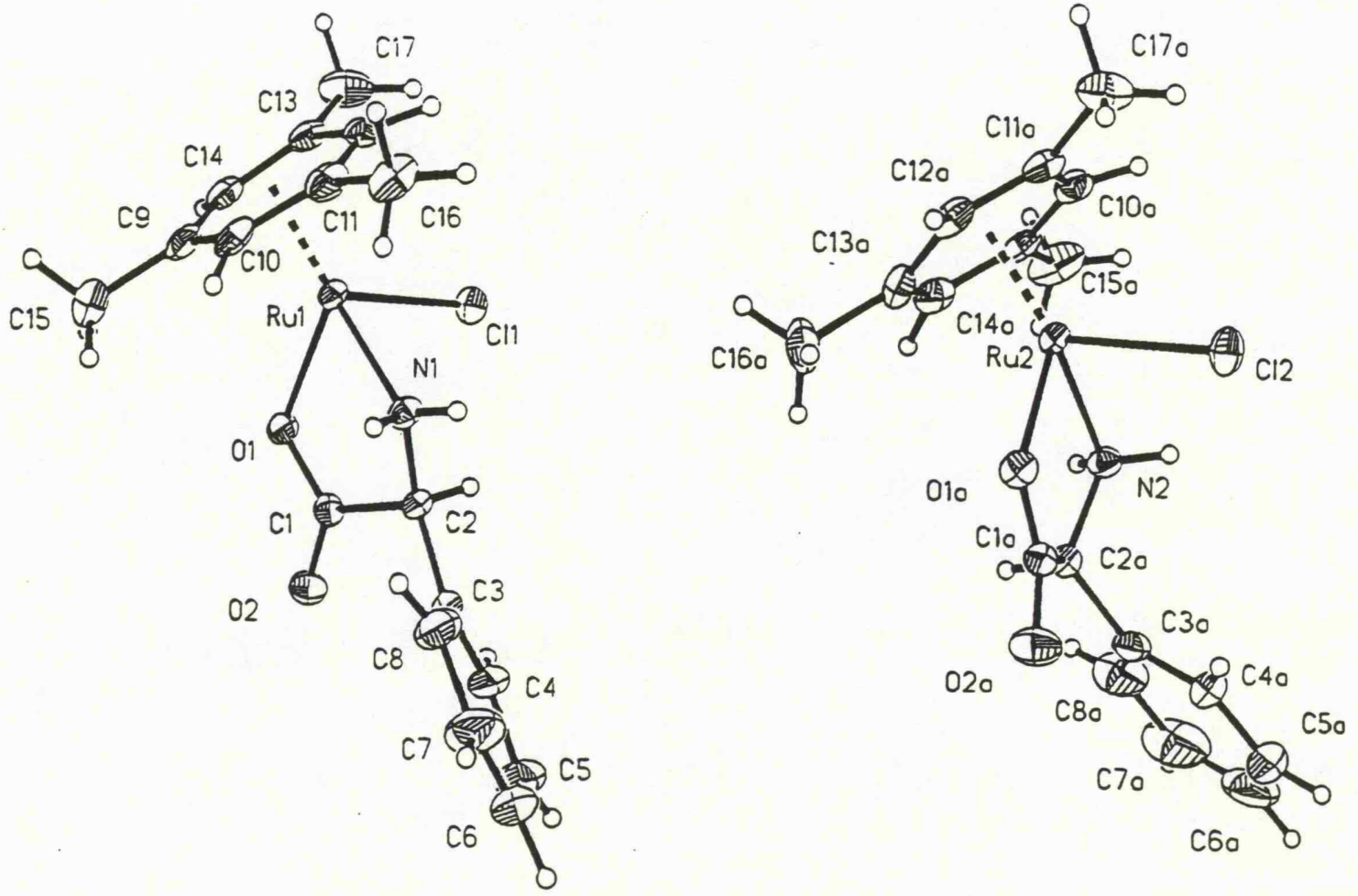


Figure 2.7

2.1.2 - Results and Discussion.

All the complexes in this chapter were prepared in a similar manner by the addition of the amino acid to $[(mes)RuCl_2]_2$ in a water / methanol mixture with an appropriate amount of base. Unlike the simple amino acidate complexes of the type [(mes)RuCl(aa)] (aa = gly, ala, phgly)[7], the complexes prepared in this chapter are not soluble in chlorinated organic solvents *eg.* dichloromethane. The L-form of the amino acid ligands were used with the exception of D-penicillamine. The complexes were characterised by ^1H n.m.r. (Table 2.AA), FAB mass spectroscopy and IR spectroscopy (Table 2.BB) and microanalysis (Table 2.CC) and in some cases X-ray structural analyses were obtained.

The complex [(mes)RuCl(phgly)] (2.8), was prepared in good yield as described by Carter.[7] The complex was prepared in order to study reactions with nucleobases (see Chapter four). However, from an n.m.r. sample in D_2O, crystals suitable for X-ray crystallography were obtained and hence the structure was determined and can be compared with that of [(mes)RuCl(ala)][16] which has been determined previously. The crystals were obtained as the dihydrate with the space group $P2_1$. Selected bond lengths and angles are presented in Table 2.DD. The X-ray structure (figure 2.9) confirms the expected N,O co-ordination mode of the phenyl glycinate ligand and also indicates the presence of both diastereomers in the unit cell $S_{Ru}S_C$ (2.8A) and $R_{Ru}S_C$ (2.8B) in a 50 : 50 ratio as was observed previously in [(mes)RuCl(ala)][16] and in related arene-ruthenium amino acidate complexes[8]. The mesitylene ring occupies three facial positions if the structure is assumed to be based on an octahedron.



2.8A **2.8B**

Figure 2.9 The Crystal Structure of [(mes)RuCl(phgly)].

Table 2.DD of Selected Bond Lengths (Å) and Bond Angles (°)

for Complex 2.8.

	[(mes)RuCl(phgly)] 2.8A	[(mes)RuCl(phgly)] 2.8B
Ru-N	2.108(4)	2.142(4)
Ru-O	2.117(3)	2.081(3)
Ru-Cl	2.425(2)	2.415(2)
O(1)-C(1)	1.292(5)	1.270(6)
O(2)-C(1)	1.235(6)	1.215(6)
N-Ru-O	76.3(1)	78.6(1)
N-Ru-Cl	84.6(1)	83.3(1)
O-Ru-Cl	88.6(1)	84.3(1)

For both diastereomers, the phenyl group points away from the arene ring as found for the alaninate methyl in [(mes)RuCl(ala)][16] and therefore interactions between the arene ring and the CHR group do not play a major role in determining the diastereomer ratios of the complexes. Subtle differences were noted between the two diastereomers in the unit cell. The Ru-N bond length for the diastereomer (**2.8A**) at 2.108(4) Å is shorter than that, 2.142(4) Å in diastereomer (**2.8B**). However, the Ru-O and Ru-Cl bond distances in diastereomer (**2.8A**) [2.117(3) and 2.425(2) Å respectively] are longer than those in (**2.8B**) [2.081(3) and 2.415(2) Å respectively]. The Ru-Cl bond lengths are shorter for the corresponding $S_{Ru}S_C$ and $R_{Ru}S_C$ diastereomers (**2.8A**) and (**2.8B**) than those observed of [(mes)RuCl(ala)][16] which are 2.439(3) and 2.428(3) Å for the diastereomers $S_{Ru}S_C$ and $R_{Ru}S_C$ respectively. The bite angle ∠N-Ru-O in diastereomer (**2.8A**) [76.3(1)°] is smaller than in diastereomer (**2.8B**) [78.6(1)°]. The bite angles follow a similar pattern to that

observed in the complex [(mes)RuCl(ala)] in which the angle ∠N-Ru-O in the $R_{Ru}S_C$ diastereomer 78.1(4)° is greater than in the $S_{Ru}S_C$ diastereomer 76.4(4)°.[16]

In water, the complex [(mes)RuCl(phgly)] exists with either a water or chloride co-ordinated ligand as determined from the ^1H n.m.r. spectrum (figure **2.10**).

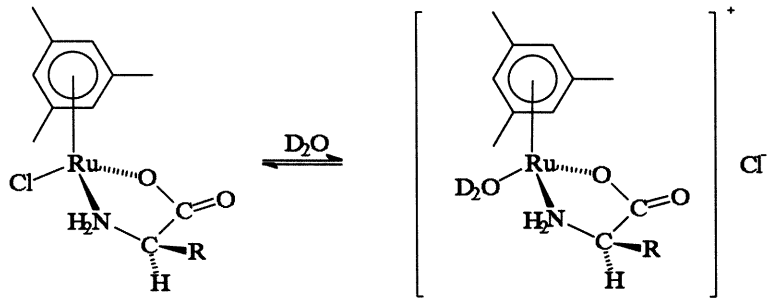


Figure 2.10

The existence of the equilibrium between water and chloride co-ordination has been well established.[7,8,11] This equilibrium can be displaced in favour of the chloride co-ordinated species by addition of a chloride salt *eg.* NaCl whereas the addition of a silver salt *eg.* $AgBF_4$ displaces the equilibrium in favour of the water co-ordinated species. The equilibrium is observed to be static on the n.m.r. timescale at room temperature which implies that the equilibrium is established within a few minutes. The effect of increased temperature on the complexes [(mes)RuCl(aa)] in solution has not been investigated to date. Thus, the complex [(mes)RuCl(phgly)] (**2.8**) was chosen in order to study this, and the effect was monitored by n.m.r. spectroscopy. The ^1H n.m.r. spectrum of

[(mes)RuCl(phgly)] (2.8) at room temperature in D_2O shows signals due to four co-ordinated [(mes)Ru(phgly)(L)] species (δ 2.10, 2.20 : 5.23, 5.34) corresponding to the chloride co-ordinated species and (δ 2.11, 2.21 : 5.29, 5.42) corresponding to the water co-ordinated species. As the signals corresponding to the mesitylene protons in these species are well separated, the region δ 5.20-5.80 was used to monitor any changes (figure 2.11). At 308 K (35 °C), both signals from the water and chloride co-ordinated species are still sharp. By 328 K (50 °C), both signals due to the water co-ordinated species have broadened. The signals observed for the chloride co-ordinated species have broadened slightly at 338 K (65 °C) whereas both the water co-ordinated resonances are observed to be extremely broad. In a separate experiment, a ten-fold excess of LiCl was added to [(mes)RuCl(phgly)] and the ^1H n.m.r. spectrum recorded at 333 K (60 °C). This resulted in the complete disappearance of the signals due to the water co-ordinated species, and showed that there was no significant broadening in the line widths of the chloride species. The conclusions from these experiments can be summarised by referring to scheme 2.12. At high temperatures, the water co-ordinated ligands are exchanging with other D_2O solvent molecules and thus the n.m.r. spectrum shows that the resonances associated with the water co-ordinated species are coalescing towards a central point (proportional to the ratio of each diastereomer) with a noticeable broadening of these signals. The coalescence of these signals is due to rapid interconversion of the diastereomers which results in inversion of configuration at the ruthenium.

High Temperature ^1H n.m.r. of [(mes)RuCl(phgly)] in D_2O at a) 35 °C, b) 50 °C and c) 65 °C.

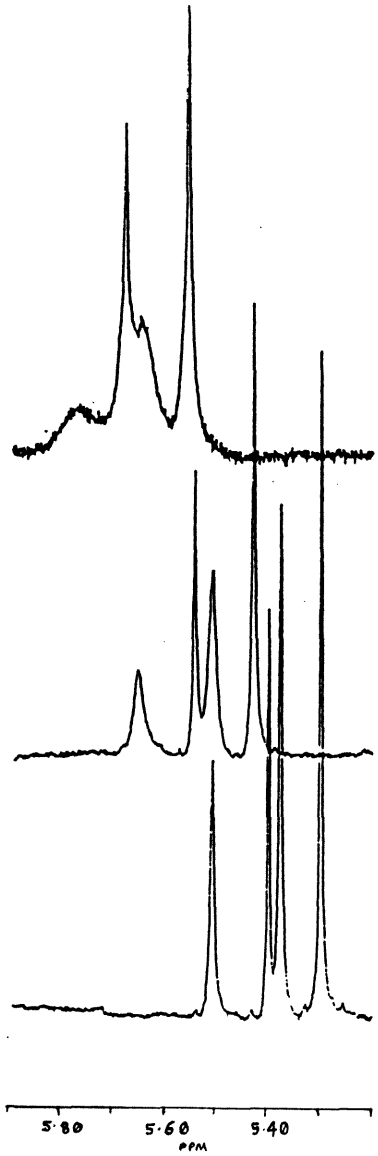
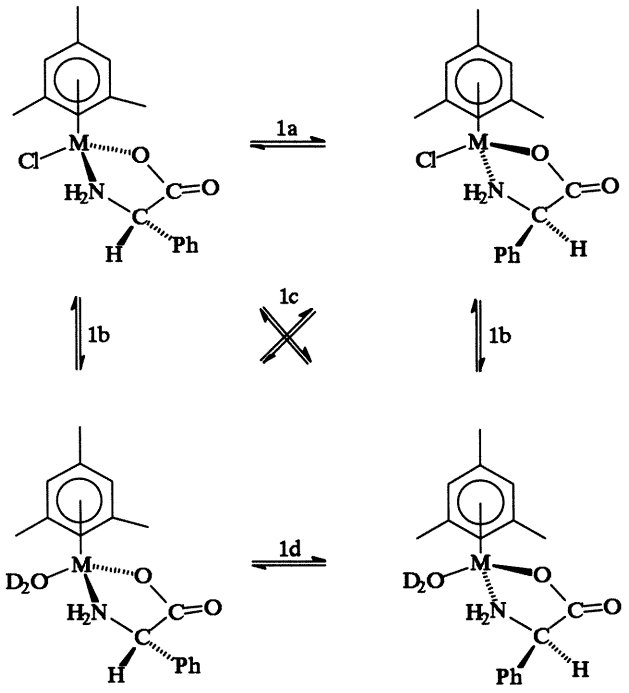


Figure 2.11



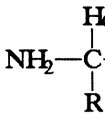
scheme 2.12

The ^{1}H n.m.r. data imply that the rate of exchange of the water ligands (**scheme 2.12** 1d) is faster than the other exchange processes in this experiment and that at a higher temperature complete coalescence of the water signals would be observed. It was observed that the diastereomer ratio measured from the integration of the signals did not change over the temperature range employed (although it must be noted that due to the broadening of the signals, the accuracy for the integration of the ^{1}H n.m.r. signals was affected). Beck *et al.* have reported the temperature dependency of the complex [(Cp*)IrCl(pheo)] in CD_3OD.[8] Between the temperature range -65 to 20 °C there are two

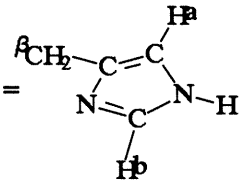
noticeable separated Cp^* peaks whereas at 52 °C it was observed that these signals collapse to one peak. It was proposed that the epimerization at the metal centre occurred through the dissociation of a weakly bound solvent molecule from the cationic complex $[(Cp^*)Ir(pheo)(CD_3OD)]^+$.[8] It has been reported by Oro *et al.* that for the complexes $[(Cp^*)MCl(pro)]$ (M = Rh, Ir) and [(p-cymene)RuCl(pro)], epimerization did not occur for these chloride species over a period of three days in $CDCl_3$ at room temperature.[6]

The Reaction of $[(mes)RuCl_2]_2$ with Amino Acids Containing Potentially Co-ordinating Side Chains.

(1) R = CMe_2SH



(2) R =

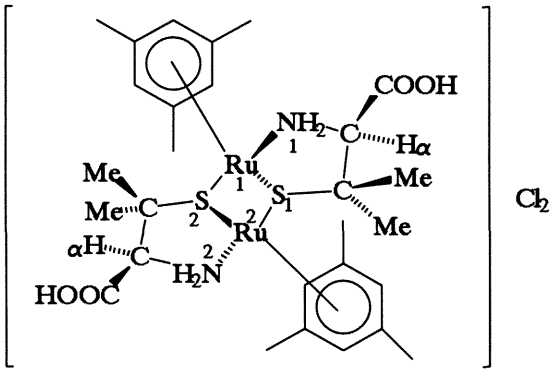


(3) R = $^{\beta}CH_2—COOH$

The reaction between two equivalents of penicillamine (1) with $[(mes)RuCl_2]_2$ in the presence of two equivalents of base gave, after work-up, an orange solid. Before work-up, the ^1H n.m.r. spectrum of the reaction mixture indicated the presence of several species containing penicillamine ligands co-ordinated to a mesitylene-ruthenium fragment. The ^1H n.m.r. after work-up, indicated the presence of only one species with singlets observed at δ 0.99(3H) and 1.46(3H) assigned to the methyl groups of the penicillamine ligand, and singlets at δ 2.17(9H) and 5.30(3H) due to the co-ordinated mesitylene ring

protons. A multiplet at δ 2.73(1H) is assigned as the proton Hα which is coupled to the two N-H protons, observed as broad signals at δ 5.07(1H) and 5.73(1H). The N-H protons are not always observed due to H / D exchange with D_2O and this would indicate that in this complex the amine group is co-ordinated to the metal. The addition of a ten-fold excess of LiCl has no effect on the number or position of the peaks observed in the ^1H n.m.r. spectrum indicating the absence of H_2O co-ordination.

The mass spectrum, in a NOBA matrix, indicates a cluster of peaks with a maximum at m/e 370 corresponding to $[(mes)Ru(pen\{-H\})]^+$. However, no cluster at m/e 405 corresponding to $[(mes)RuCl(pen\{-H\})]^+$ is observed but a cluster is observed at m/e 740 which corresponds to a dimeric species $[(mes)Ru(pen\{-H\})]_2^+$. In calculating possible formulae for mass spectra obtained, the results quoted are based on ^{102}Ru and ^{103}Rh as both ruthenium and rhodium have several isotopes and therefore the mass spectra always show clusters. The IR spectrum shows a stretch at 1735 cm^{-1} assigned to the C=O group of an unco-ordinated carboxylate suggesting that this group is not involved in co-ordination. Sheldrick and Heeb have reported the preparation of the complex $[(C_6H_6)Ru(pen\ N,S)]_2Cl_2$ and the structure has been determined by X-ray analysis.[12] The amino acidate is co-ordinated through the amine and sulphurs atoms.[12] The sulphur atoms bridge between ruthenium atoms giving rise to a four-membered $[Ru\text{-}S]_2$ ring and the carboxylate group is protonated as implied from the IR spectrum (C=O 1733 cm^{-1}) and observed in the crystal structure.[12] The spectroscopic data obtained from our work are consistent with that reported by Sheldrick and Heeb[12] and from this a possible structure of the complex is depicted (2.13) in which the complex exists as a dimeric species in which the amino acidate ligand co-ordinates through the amine and sulphur atoms with the sulphurs adopting a bridging position between two rutheniums.



2.13

A crystal suitable for X-ray determination was obtained from the n.m.r. sample in D_2O and selected bond lengths and angles are presented in Table **2.EE**. The structure (figure **2.14**) confirms the predictions made earlier and shows the presence of a dimeric species containing two [(mes)Ru(pen *N,S*)] fragments. The mesitylene rings are co-ordinated η^6 as expected whilst the amino acidates are co-ordinated through the amine groups and the deprotonated sulphur atoms with the sulphurs bridging between the two ruthenium atoms forming a four-membered [Ru-S-Ru-S] ring. The crystal structure (figure **2.14**) is very similar to that obtained by Sheldrick *et al.* for the corresponding complex $[(C_6H_6)Ru(pen\ N,S)]_2Cl_2$ (**2.15**)[12]. The major difference between the two crystal structures is that for (**2.13**) four waters of crystallisation are present in the unit cell, whereas in (**2.15**) only one water molecule exists in the unit cell[12].

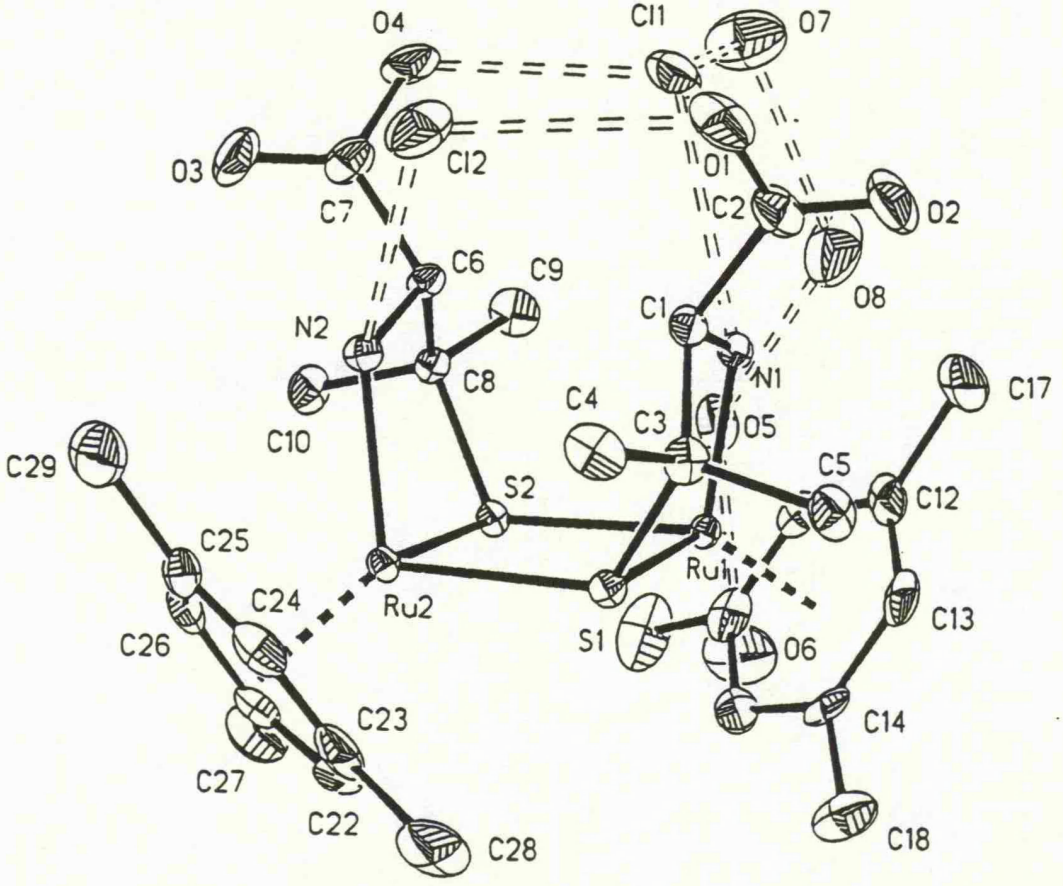


Figure 2.14 The Crystal Structure of $[(mes)Ru(pen)]_2Cl_2$.

Table 2.EE of Selected Bond Lengths (Å) and Bond Angles (°) for Complexes 2.13 and 2.15.

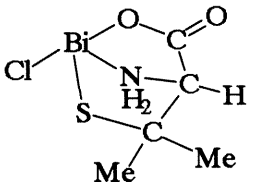
	[(mes)Ru(pen)]$_2$Cl$_2$ (**2.13**)	[(C_6H_6)Ru(pen)]$_2$Cl$_2$ (**2.15**)[12]
Ru(1)-N(1)	2.138(7)	2.169(4)
Ru(1)-S(1)	2.335(3)	2.346(4)
Ru(1)-S(2)	2.394(2)	2.416(4)
Ru(2)-N(2)	2.144(5)	2.164(4)
Ru(2)-S(2)	2.348(3)	2.345(4)
Ru(2)-S(1)	2.401(2)	2.398(4)
N(1)-Ru(1)-S(1)	81.4(2)	81.8(5)
Ru(1)-S(1)-Ru(2)	102.1(1)	101.0(5)
S(1)-Ru(1)-S(2)	78.1(1)	79.4(6)
N(2)-Ru(2)-S(1)	101.4(2)	101.4(5)

The average Ru-N bonds in complex (**2.13**) [2.141(8) Å] are observed to be shorter than in complex (**2.15**) 2.167(5) Å[12]. In (**2.13**) the bond lengths between the chelating sulphur atoms and the metal centres Ru(1)-S(1) 2.335(3) Å, Ru(2)-S(2) 2.348(3) Å are shorter than the bridging sulphur bonds Ru(1)-S(2) 2.394(2) Å, Ru(2)-S(1) 2.401(2) Å as found previously for (**2.15**)[12]. The four-membered [Ru-S-Ru-S] ring is essentially planar, again, as observed for (**2.15**)[12] and this type of four-membered ring centre has also been observed for the complex [(nbd)Ru(pen *N*,*S*)]$_2$[17]. The structure of complex (**2.13**) permits both chloride ions to form hydrogen bonds between the carboxylate group of one ligand and the amine group of the other. The O··Cl (2.874, 2.917 Å) and the N··Cl (3.249, 3.253 Å) distances are comparable with the distances found for the similar arrangement observed

in (**2.15**)[12]. The arrangement of the O atoms of the water molecules is consistent with a continuous hydrogen-bonded chain with O··O distances in the range 2.768-2.979 Å. The chloride ions have further hydrogen-bond contacts with water molecules. Hydrogen bonds between some water molecules and the carboxylate groups are also proposed on the basis of COOH··O distances of 2.825 and 2.798 Å. The ruthenium-ruthenium non-contact distance is 3.662 Å for the complex (**2.13**) whereas for the complex (**2.15**) this distance is 3.684 Å[12]. The bond angles in both complexes are similar with the ∠S(1)-Ru-N(1) bite angles being 81.4(2)° for (**2.13**) and 81.8(5)° [12] for (**2.15**) respectively.

As penicillamine has three possible co-ordination atoms N,O and S and has been reported previously to be ambidentate[2], it may be possible to preferentially select which co-ordination sites are used by the choice of either hard or soft metal centres. The Ru(II) ion has a tendency to prefer soft donor atoms and this is exemplified by the above complex (**2.13**) where N,S co-ordination is preferred to the more common N,O.[6-8,11]

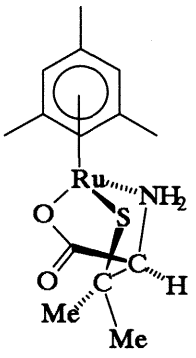
It has been reported recently by Herrmann *et al.*[18] that the penicillamine ligand can co-ordinate through all three sites when doubly deprotonated to produce a complex in which the ligand is tridentate (**2.16**).



2.16

Before work-up it was observed that the ^1H n.m.r. spectrum from the initial reaction of penicillamine with $[(mes)RuCl_2]_2$ contained several other peaks notably in the low frequency (δ 0.80-1.50) region of the spectrum. In an attempt to produce a complex in which the ligand is tridentate, the reaction of two equivalents of penicillamine with $[(mes)RuCl_2]_2$, was tried in the presence of four equivalents of base (NaOMe). A brown solid was obtained from the reaction upon evaporation of the solvents which was sparingly soluble in CH_2Cl_2 and therefore a CH_2Cl_2 extraction was used to separate any NaCl formed in the reaction. The ^1H n.m.r. in $CDCl_3$ was very broad and poorly resolved and therefore the ^1H n.m.r. was run in D_2O. The ^1H n.m.r. spectrum shows signals due to a co-ordinated mesitylene at δ 2.14(9H) and 5.01(3H) and singlets at δ 1.20(3H) and 1.24(3H) which are tentatively assigned as the methyl signals of a co-ordinated penicillamine ligand. At δ 3.16(1H) a multiplet is observed and assigned as the proton Hα. Broad resonances at δ 5.62 and 5.81 are tentatively assigned to N-H protons which suggests that the amine group is co-ordinated. The addition of LiCl had no effect on the number or position of the peaks observed in the ^1H n.m.r. spectrum indicating that there is no water molecule co-ordinated to the metal centre.

The mass spectrum shows the presence of a cluster at m/e 370 corresponding to $[(mes)Ru(pen\{+H\})]^+$. However, the mass spectrum also shows a number of other clusters that are unassigned. The IR spectrum (CH_2Cl_2 solution) shows an absorption peak at 1595 cm^{-1} which is assigned as a co-ordinated carboxylate group. The complex formed is tentatively assigned as the complex [(mes)Ru(pen_2. *N,S,O*)] (2.17) in which the amino acidate ligand is tridentate co-ordinating through all three donor atoms N,S and O. The spatial arrangement of the N,S and O atoms which is fixed by the R configuration at C suggests that the configuration at the metal centre would also be R.



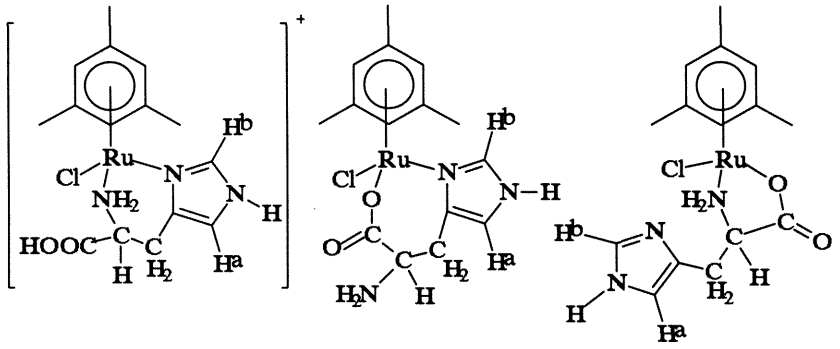
2.17

The ^{1}H n.m.r. spectrum also contained peaks corresponding to complex (**2.13**) and an additional set of peaks (**2.18**) are observed that are also present in the ^{1}H n.m.r. spectrum of the crude reaction mixture of complex (**2.13**) before work-up. The complex (**2.13**) may be formed from the protonation of the carboxylate group of (**2.17**) followed by the combination of two [(mes)Ru(pen *N,S*)] fragments. The additional peaks (**2.18**) give rise to the following resonances :- two singlets δ 1.09(3H) and 1.31(3H) are observed due to co-ordinated penicillamine methyl groups. Two sets of signals observed at δ 2.07(9H), 2.12(9H) and 5.16(3H), 5.24(3H) are assigned to co-ordinated mesitylene protons, a doublet at δ 3.38(1H), J = 7.5 Hz is assigned as the proton Hα and two broad multiplets at δ 5.62(1H) and 6.27(1H) attributed to amine protons. The same spectrum can be obtained independently by the reaction of $[(mes)RuCl_2]_2$ with one equivalent of penicillamine only. The integration of the ^{1}H n.m.r. spectrum indicates that this species contains two mesitylene-ruthenium fragments co-ordinated to one penicillaminato ligand.

The mass spectrum, obtained from a NOBA matrix, indicates ions at m/e 660 and

625 which correspond to $[((mes)RuCl)_2(pen_2.\{-H\})]^+$ and $[((mes)Ru)_2Cl(pen_2.\{-H\})]^+$ ions respectively. Further attempts to characterise this species (IR, microanalysis) have so far, failed to lead to a conclusive structure being proposed and attempts to grow crystals suitable for X-ray determination have also proved unsuccessful.

The reaction of histidine (2) with $[(mes)RuCl_2]_2$ proceeded to produce a yellow / green solid in high yield after work-up. It has been reported that histidine can co-ordinate through different combinations of the three donor atoms[2] giving rise to alternative binding modes. The three possible binding modes are illustrated in figure **2.19**, all of which have been reported previously.[8,12]



mode a mode b mode c

Figure **2.19**

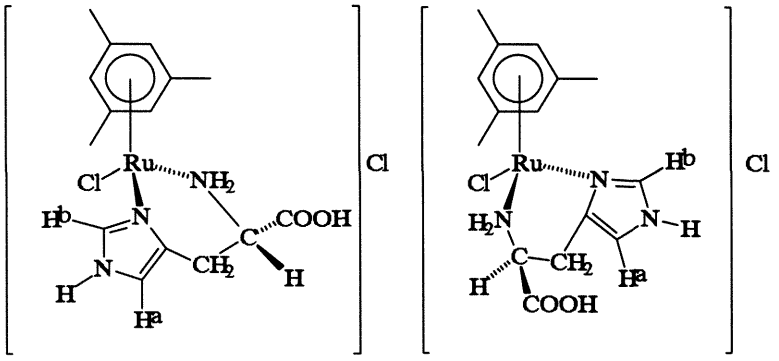
The ^1H n.m.r. spectrum in D_2O shows the presence of one major species with singlets observed at δ 2.21(9H) and 5.36(3H) respectively corresponding to co-ordinated mesitylene signals. Complex multiplets are observed at δ 3.84(1H) and 3.00(2H) assigned to the protons α-CH and β-CH_2 respectively and broad multiplets at δ 5.68 and 5.96 due to N-H protons. These amine protons do not exchange with D_2O over a period of days suggesting that the amine group is co-ordinated to the metal centre. A broad singlet at δ 6.95 and a doublet ^4J = 1.3 Hz at δ 8.40 are assigned to the protons H^a and H^b respectively. In the free ligand H^a is observed at δ 7.04 as a singlet whereas H^b occurs at δ 7.74 as a doublet ^4J = 1.1 Hz. The coupling of H^a to H^b was proved by decoupling experiments, whereupon irradiation of the signal for H^a resulted in the signal for H^b collapsing to a singlet. The shift to higher frequency of the proton H^b is indicative of co-ordination of the imidazole group. In the ^1H n.m.r. spectrum, a minor species was also observed with the mesitylene protons occurring as singlets at δ 2.16(9H) and 5.38(3H) and the α-CH and β-CH_2 protons giving rise to complex multiplets at δ 4.39(1H) and 3.47 (2H). The imidazole protons H^a and H^b are observed at higher frequency than in the major species with signals at δ 7.45(1H) and 8.70(1H) respectively. As for the major isomer, H^b is observed as a doublet ^4J = 1.3 Hz and H^a as a slightly broad singlet. Addition of a ten-fold excess of LiCl to this sample resulted in no change in the number or position of any existing peaks in the ^1H n.m.r. spectrum indicating that there is no co-ordinated water molecule.

From the ^1H n.m.r. spectrum data, it can be rationalised that the imidazole nitrogen is co-ordinated due to the large change in chemical shift of the proton H^b from that observed in the free ligand and the presence of amine protons suggests amine co-ordination as a co-ordinated amine slows the H / D exchange of the amine protons. From

these data, it would appear that the ligand co-ordinates through the two nitrogen sites as depicted in mode a (figure 2.18). The two species exist in a 10 : 1 ratio in solution. As has been observed in simple amino acidate complexes [(arene)RuCl(aa)] (arene = C_6H_6, mes; aa = pro, ala, gly)[7,8] there exists the possibility of diastereomers and / or water-chloride exchange. Koelle *et al.* have reported that the co-ordinated water molecule in the related complex $[(arene)Ru(bipy)(H_2O)]^{2+}$ (arene = benzene, p-cymene and hexamethylbenzene) is labile and is displaced by a variety of ligands including SCN^-, I^-, Br^-, N_3^- and N-methylimidazole.[19] It is assumed that as no change is observed on addition of LiCl to the ^1H n.m.r. spectrum, the second set of signals are due to the second diastereomer and that the difference in the ratio of the two species is a result of favourable hydrogen bonding and / or less steric crowding for one of the diastereomers. A spatial model was constructed to determine any possible favourable or unfavourable conditions that may be present in the two diastereomers. From the models it was found that in the $S_{Ru}S_C$ diastereomer, there exists the possibility of hydrogen bonding between the co-ordinated chloride and protonated carboxylate groups which is not present in the $R_{Ru}S_C$ diastereomer and this may account for the difference in diastereomer ratios observed.

The IR spectrum (KBr disc), shows a band at 1725 cm^{-1} due to the C=O stretching frequency and this is indicative of an unco-ordinated carboxylate group. The IR data indicate that the carboxylate is protonated and therefore not involved in co-ordination, therefore in agreement with the proposed co-ordination mode through the imidazole and amine donor atoms giving rise to the two diastereomers (2.20). The FAB-MS spectrum indicates the presence of ions at m/e 413 and 377 corresponding to $[M]^+$ and $[M\text{-}HCl]^+$ ions. The N,N bidentate co-ordination of the histidine in (2.20) has been reported

previously by Sheldrick and Heeb[12] in the complex $[(C_6H_6)RuCl(hisH\ N,N)]Cl$. The X-ray structure of the methyl ester derivative $[(C_6H_6)RuCl(hisMe\ N,N)]Cl$ was obtained and confirmed the N,N co-ordination mode of the ligand in that complex.[12] Interestingly, Sheldrick and Heeb report only one diastereomer in solution, the $S_{Ru}S_C$ diastereomer, and asssign this to favourable hydrogen bonding within that structure based on the crystal structure information.[12]



$S_{Ru}S_C$ $R_{Ru}S_C$

2.20

Beck *et al.* reported that the histidine ligand can co-ordinate through the imidazole and deprotonated carboxylate groups in the complex $[(Cp^*)IrCl(his\ N,O)]$ and through all three donor sites in the complex $[(C_6H_6)Ru(his\ N,N,O)]Cl$.[8] In an attempt to establish the effect of added base on the bonding of the histidine we carried out the reaction of $[(mes)RuCl_2]_2$ with histidine in the presence of base (NaOMe). The ^1H n.m.r. spectrum in D_2O, after work-up, showed the same peaks as observed in the reaction without base, and the mass spectrum shows the same peaks at m/e 413 and 377. This indicated that for

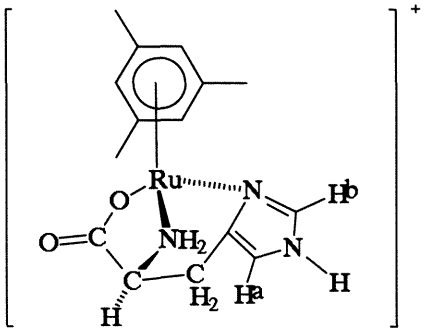
this reaction, the presence of base had no effect on the complex formed.

In an attempt to prepare a complex containing a tridentate histidinate ligand [(mes)RuCl(hisH *N,N*)]Cl (2.20) was treated with base and silver tetrafluoroborate. In the ^{1}H n.m.r. spectrum, the proton H^a is observed at δ 6.96(1H) as a broad singlet with H^b at δ 8.40(1H) as a doublet J = 1.3 Hz. As with (2.20), the shift of H^b to higher frequency is indicative of co-ordination of the imidazole group. The mesitylene protons are observed at δ 2.22(9H) and 5.37(3H) as singlets and the α-CH and β-CH_2 protons give rise to multiplets at δ 3.85(1H) and δ 2.97(2H) respectively. Only one broad signal is observed for the amine protons at δ 6.00(1H). The appearance of this proton suggests amine co-ordination. The addition of a ten-fold excess of LiCl to an n.m.r. sample had no effect on the number of peaks or position of the existing peaks in the spectrum indicating that there is no co-ordinated water molecule in the complex. There are only a few minor differences between the ^{1}H n.m.r. spectrum of the N,N bidentate complex and this complex, however, the appearance of only one set of peaks is consistent with only one diastereomer as expected for a tridentate co-ordination (see below). In the related complex [(C_6H_6)Ru(his *N,N,O*)]Cl the protons H^a and H^b are observed at δ 6.82 and 8.42 whereas the α-CH and β-CH_2 protons are observed at δ 3.66 and 2.84 respectively.[8] No resonances corresponding to amine protons are reported in the ^{1}H n.m.r. data. The IR spectrum indicates a band at 1644 cm^{-1} assigned as a co-ordinated carboxylate group.[8]

The mass spectrum, FAB-MS in a NOBA matrix, indicates the presence of an ion at m/e 376 corresponding to an $[(mes)Ru(his)]^+$ ion. No ion was observed at m/e 413 as is found for (2.20) and would be expected for a species of the type [(mes)RuCl(his *N,O*)] if the ligand co-ordinated through the imidazole and carboxylate groups. The IR spectrum shows a broad absorption band at 1620 cm^{-1} assigned to the co-ordinated carboxylate

group and this compares with a band at 1725 cm^{-1} corresponding to an unco-ordinated carboxylate group.

Although the ^1H n.m.r. spectrum data are inconclusive, the data do suggest that the complex formed contains a bound histidine in which the ligand is tridentate which gives rise to the proposed structure (**2.21**). Only one diastereomer is expected due to the fixed orientation of the chelating atoms N, N and O at the α-carbon and although we were unable to grow X-ray quality crystals, the spatial arrangement of the N,N and O atoms suggests that the configuration, fixed as S at the α-carbon, would be S at ruthenium.

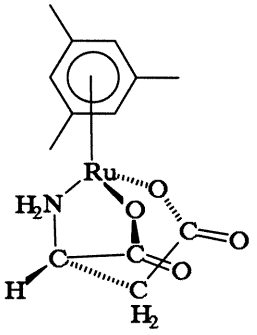


2.21

The reaction of two equivalents of aspartic acid (3) with $[(mes)RuCl_2]_2$ in the presence of four equivalents of base (NaOMe) to doubly deprotonate the amino acid proceeded to produce a complex in high yield. The ^1H n.m.r. spectrum in D_2O or d^4-methanol indicates the presence of only one species in solution with singlets at δ 2.17(9H)

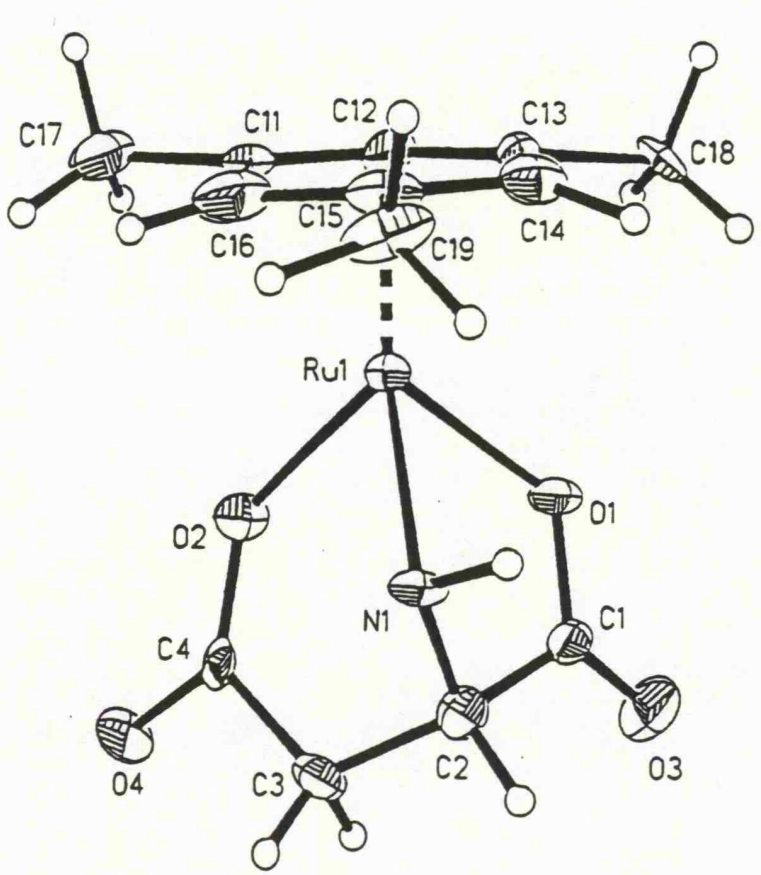
and 5.14(3H) due to the mesitylene ring. The α-CH and β-CH_2 protons are observed as multiplets centred at δ 3.59(1H) and 2.58(2H) respectively with coupling observed between the β-CH_2 protons and the N-H protons as determined by irradiation experiments. The N-H protons are observed as broad multiplets at δ 5.36(1H) and 6.06(1H) and did not disappear due to H / D exchange over a period of days as observed with the previous complexes (2.13), (2.20) and (2.21). This suggests that the amine group is co-ordinated to the metal centre. The addition of a ten-fold excess of LiCl to a D_2O solution of this complex resulted in no change in the number or position of any existing peaks in the spectrum indicating that there is no co-ordinated water molecule. The ^1H n.m.r. spectrum is consistent with the formation of a complex in which the ligand co-ordinates through the amine and both carboxylate groups.

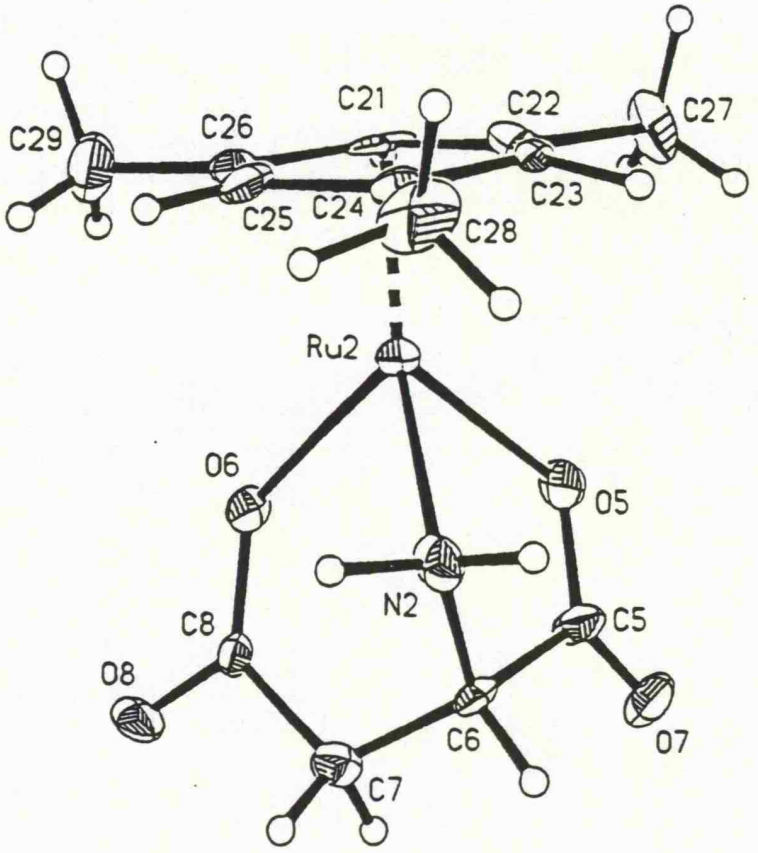
The IR spectrum shows the presence of a broad absorption at 1605 cm^{-1} indicative of a co-ordinated carboxylate group. No other band is observed in the carboxylate region 1800-1500 cm^{-1} suggesting that both C=O groups give rise to absorptions at similar frequencies. The mass spectrum indicates the presence of a cluster m/e 354 assigned to the molecular ion $[(mes)Ru(asp_2\text{-}N,O,O\ \{+H\})]^+$. From the data, a structure can be proposed for the complex in which the ligand is doubly deprotonated and co-ordinates to the metal centre in a tridentate mode through all three sites N, O and O $[(mes)Ru(asp_2\text{-}N,O,O)]$ (2.22).



2.22

An X-ray determination of a single crystal confirmed the tridentate co-ordination mode of the aspartic acidate ligand with the other three positions being occupied by the mesitylene ring. As for the tridentate histidinate complex, only one diastereomer is possible due to the fixed configuration at the α-carbon, this is expected to be $S_{Ru}S_C$ and this was confirmed by the crystal structure determination. The complex [(mes)Ru(asp_2-*N,O,O*)] (**2.22**) crystallised as the trihydrate in the space group P1 with two unique molecules in the unit cell. Selected bond lengths and angles are listed in Table **2.FF** and the molecular structure is shown (figure **2.23**). The tridentate co-ordination mode observed in this complex has been previously observed in the related complexes [(Cp^*)Co(asp_2-*N,O,O*)]·KI prepared by Beck *et al.*[13] and [(Cp^*)Co(asp_2-*N,O,O*)]·LiCl·$3H_2O$ prepared by Sheldrick *et al.*[20] and in both cases, the complexes crystallise as the $S_{Ru}S_C$ diastereomer only. From the X-ray data obtained, there are differences in terms of bond angles and lengths between the two molecules although the crystallographic determination indicates that the two molecules are approximately equal without inversion.





2.22A

2.22B

Figure 2.23 The Two Unique Molecules of [(mes)Ru(asp)].

Table 2.FF of Selected Bond Lengths (Å) and Bond Angles (°) for 2.22A and 2.22B.

	Molecule 2.22A	Molecule 2.22B
Ru-N	2.131(4)	2.097(5)
Ru-O(1)	2.095(3)	2.115(3)
Ru-O(2)	2.073(4)	2.104(5)
N-Ru-O(1)	79.1(2)	77.6(2)
O(1)-Ru-O(2)	85.3(2)	84.9(2)
N-Ru-O(2)	83.8(2)	83.2(2)

The Ru-N bond distance in molecule (**2.22A**) [2.131(4) Å] is longer than in the complex (**2.22B**) [2.097(5) Å], both Ru-O bond distances are shorter in molecule (**2.22A**) Ru-O(1) [2.095(3) Å] and Ru-O(2) [2.073(4) Å] than for complex (**2.22B**) Ru-O(1) [2.115(3) Å] and Ru-O(2) [2.104(5) Å]. The angle ∠N-Ru-O(1) is found to be smaller in complex (**2.22B**) 77.6(2)° than in (**2.22A**) 79.1(2)°. As only one species is observed in solution, it can be assumed that these differences are likely to be the result of packing forces between the molecules in the unit cell.

The Reaction of $HCl_{(aq)}$ with Complex 2.22.

The reaction of the aspartic acidate complex [(mes)Ru(asp_2- *N,O,O*)] with $HCl_{(aq)}$ was carried out to try to selectively protonate the β-carboxylate group and force the ligand to co-ordinate in a bidentate manner. It was observed by Carter[7] that the ligand β-alanine

could be displaced from the complex [(mes)RuCl(β-ala)] by alanine to form the complex [(mes)RuCl(ala)] exclusively, indicating a preference for the 5-membered chelate over the 6-membered chelate.

Following the addition of one equivalent of $HCl_{(aq)}$ to (2.22) in D_2O, the reaction was monitored by ^1H n.m.r. spectroscopy. The reaction proceeds with the ^1H n.m.r. spectrum showing signals due to four different (mes)Ru species (δ 2.15, 2.16, 2.17 and 2.19; 5.21, 5.26, 5.32 and 5.38) whereas only one co-ordinated mesitylene is observed in the starting complex (2.22). The signals for the protons α-CH and β-CH_2 are observed as complex multiplets in the regions δ 3.75-3.90(4H) and 2.75-2.92(8H) respectively. These new signals are due to the formation of a bidentate species containing either a co-ordinated chloride or water ligand. The addition of a five-fold excess of LiCl to the sample led to the simplification of the spectrum and only two [(mes)Ru(asp)] species being observed (δ 2.16, 2.18: 5.24, 5.29) though the α-CH and β-CH_2 groups still give rise to complex multiplets. Thus, it is assumed that the bidentate species has been formed [(mes)RuCl(asp *N,O*)] (2.24) and that the co-ordination is through the α-carboxylate group. These signals can also be reproduced by the reaction of $[(mes)RuCl_2]_2$ with two equivalents of aspartic acid and two equivalents of base, however, in this case the spectrum also shows substantial amounts of the tridentate species [(mes)Ru(asp_2. *N,O,O*)] (2.22).

The Stability of Amino Acidate Complexes at Low pH.

It was reported by Bennett *et al.*[21] that amines and phosphines could be displaced

from the complex [(arene)$RuCl_2L$] (arene = benzene, p-cymene) by a two-step process involving firstly, the addition of cyclo-octa-1,5-diene (COD) in the presence of a reducing agent (Na_2CO_3 in 2-propanol) followed by the addition of $HCl_{(aq)}$ to reform the parent dimer [(arene)$RuCl_2]_2$. Bennett *et al.* also reported that these amine or phosphine ligands could not be removed by the addition of hydrochloric acid only.[21] We have found, however, that the amines, pyridine and aniline could be removed from the complex [(mes)$RuCl_2$(amine)] by bubbling $HCl_{(g)}$ through a CH_2Cl_2 solution containing these complexes. Studies by Carter[7] indicated that the alaninate ligand could be displaced by bubbling $HCl_{(g)}$ through a solution of the amino acidate complex [(mes)RuCl(ala)] in CH_2Cl_2 at room temperature leading to the reformation of the parent complex [(mes)$RuCl_2]_2$. This observation was mirrored by bubbling $HCl_{(g)}$ through a solution of the complex [(mes)RuCl(phgly)] (2.8) in CH_2Cl_2 where reformation of the parent complex [(mes)$RuCl_2]_2$ was also observed. It was observed in the formation of complex (2.24) and established by Beck *et al.*[8] that the addition of one molar equivalent of $HCl_{(aq)}$ to a complex containing a tridentate aspartic acidate ligand results in the protonation of one of the carboxylate groups with the ligand now co-ordinating in the N,O bidentate mode. An experiment was attempted to determine whether the amino acidate ligand can be completely removed by protonation of the other co-ordinated groups. After addition of an excess of concentrated or dilute $HCl_{(aq)}$ to an aqueous solution of [(mes)RuCl(phgly)], [(mes)RuCl(ala)] or [(mes)Ru(asp_2. *N,O,O*)] it was observed that no precipitate was formed. The monitoring of such reactions by ^1H n.m.r. spectroscopy is difficult because of changes in chemical shifts caused by the addition of large excesses of acid and because of the large increase in the size of the HOD signal due to the inevitable presence of H_2O in $HCl_{(aq)}$ or $DCl_{(aq)}$ solutions. Therefore, monitoring of the progress of the reaction

between $HCl_{(aq)}$ and the complex [(mes)Ru(asp_2. *N,O,O*)] was achieved using a UV-VIS spectrophotometer by studying the changes in the absorption spectrum in the visible region. The complex (2.22) has strong absorptions at 308.0 and 379.0 nm in water. The free ligand, aspartic acid, has no absorption maximum at >300 nm in concentrated $HCl_{(aq)}$. After addition of a large excess of concentrated $HCl_{(aq)}$ to complex (2.22) the spectrum was monitored and any absorption changes recorded. From the graphs it is apparent that, with time, the absorption maxima have shifted (figure 2.25 (a-c)) indicating that the complex had reacted in solution. The new complex(es) has absorption maxima at 356 and 443 nm which increase steadily over a period of ≈1.5 hrs (figure 2.25 (b and c)) with a corresponding decrease in the peak at 317 nm over this period of time. As previously mentioned, the addition of $HCl_{(aq)}$ to (2.22) results in the proposed complex (2.24) and this would be expected to be the first product formed in the reaction and is tentatively assigned as graph (a) (figure 2.25). The protonation of the second carboxylate group would result would result in the formation of an intermediate in which only the amine group is co-ordinated in a complex analogous to the amine complexes. Carter has reported that in the reaction of $[(mes)RuCl_2]_2$ with amino acids (alaH, glyH), the ligands do not co-ordinate without the presence of base indicating that the amine group is a weak donor group.[7] From this it is postulated that the amine co-ordinate would be a short-lived intermediate. The visible spectra of $[(mes)RuCl_2]_2$ and the triply-bridged complex $[\{(mes)Ru\}_2Cl_3]PF_6$[7] were recorded in concentrated $HCl_{(aq)}$ and both show absorption maxima at 355 and 443 nm. From this, it is proposed that the species responsible for the absorptions in this reaction is the triply-bridged cation $[(mes)Ru\{\mu\text{-}Cl\}_3Ru(mes)]^+$.

Absorption Spectrum of [(mes)Ru(asp)] in Conc. HCl.

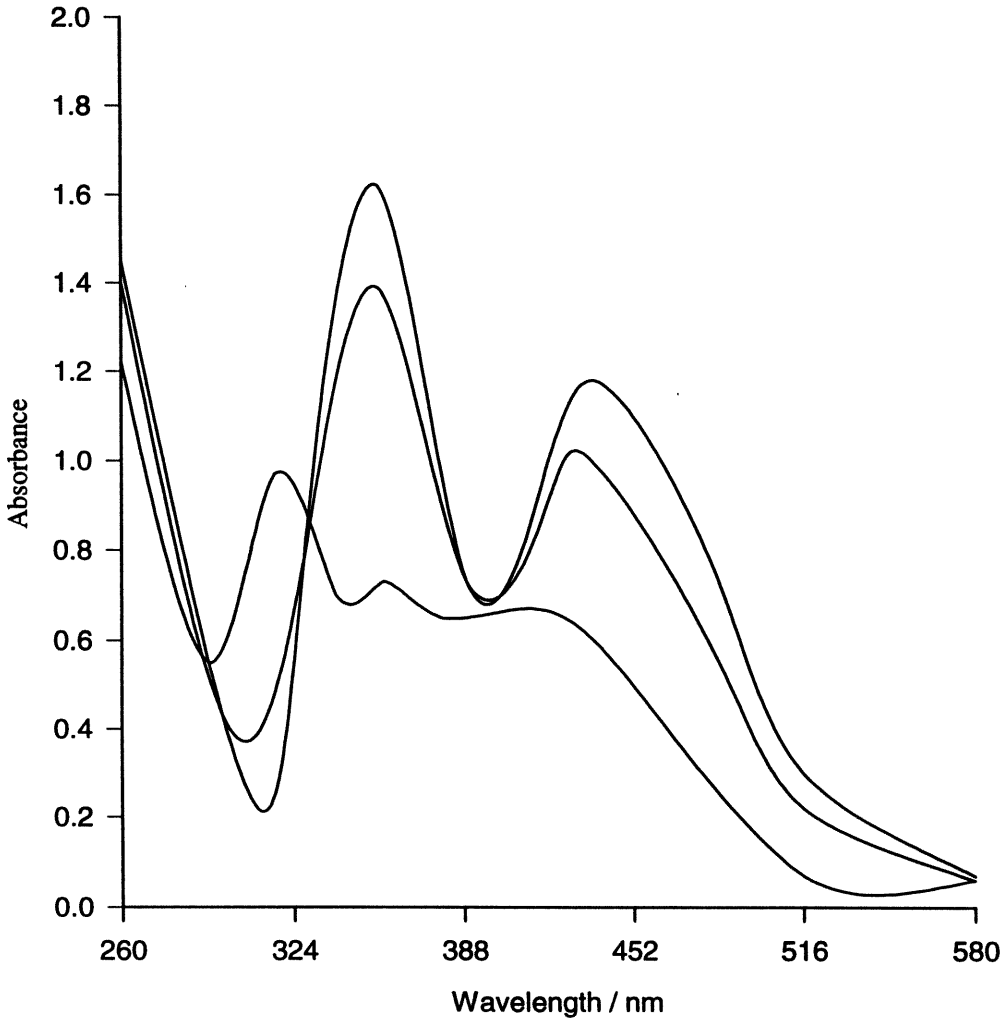


Figure 2.25

Cations of this type can be isolated by refluxing $[(arene)RuCl_2]_2$ (arene = C_6H_6, C_6Me_6, mes) in a methanol / water solution in the presence of NH_4PF_6.[22] The complexes [(mes)RuCl(aa)] (aa = ala[7], phgly), react with $HCl_{(g)}$ in CH_2Cl_2 to produce a brown precipitate, insoluble in D_2O or CH_2Cl_2 which in the FAB-MS shows a cluster of peaks at m/e 549 corresponding to a complex of the molecular formula $[(mes)_2Ru_2Cl_3]^+$. In water the ionic species $[(mes)_2Ru_2Cl_3]^+Cl^-$ is formed presumably due to favourable solvation effects whereas in CH_2Cl_2 the direct reformation of the parent dimer $[(mes)RuCl_2]_2$ occurs.

The results indicate that the amino acidate ligand can be removed from mesitylene-ruthenium amino acidate complexes by bubbling $HCl_{(g)}$ through a CH_2Cl_2 solution containing the complexes [(mes)RuCl(aa)] (aa = leu or ala[7]) or by the addition of concentrated $HCl_{(aq)}$ to an aqueous solution containing the complexes [(mes)RuCl(aa)] (aa = phgly, ala) or [(mes)Ru(asp_2. *N,O,O*)]. The results disagree from that reported by Bennett *et al.* although it must be noted that the reaction conditions were not stated in their report.[21] These results may have use in the application of asymmetric synthesis where there exists the possibility of removal of a co-ordinated chiral ligand such as amines or phosphines with the recovery of the organometallic fragment. The resolution of chiral arene-ruthenium complexes has been studied with a view to the production of enantiopure products.[23]

This chapter describes the preparation of some arene-ruthenium amino acidate complexes which are soluble in water. The chirality of the amino acid and metal centre gives rise to diastereomeric complexes. Dissolution in water of the simple amino acidate complexes leads to the formation of an equilibrium in which co-ordination of either a chloride or water ligand occurs. At high temperature, the co-ordinated water ligands

exchange rapidly with solvent molecules with a subsequent interconversion of the diastereomers. The functionalised side chain of amino acids has been shown to co-ordinate to the ruthenium metal allowing a variety of bonding modes including both bidentate and tridentate co-ordination. Bidentate co-ordination in the case of penicillamine through the sulphur and nitrogen atoms and tridentate co-ordination in the case of aspartic acid ligands have been shown by X-ray diffraction. In the case of aspartic acid, a single diastereomer ($S_{Ru}S_C$) was isolated. Both bidentate and tridentate amino acidate ligands could be displaced by the addition of $HCl_{(aq)}$ and $HCl_{(g)}$ with reformation of the parent dimer.

2.1.3 - Experimental.

All the reactions were performed under an inert atmosphere of dry nitrogen unless stated otherwise but the work-up was performed in air. Degassed solvents were used for the reactions and were dried by the appropriate literature method, as listed below:

a) Diethyl ether from sodium / benzophenone;

b) Dichloromethame from calcium hydride;

c) Methanol and ethanol from magnesium turnings and iodine and stored over 4 Å molecular sieves.

^1H n.m.r. spectra were recorded using a Varian EM390 or a Bruker AM300 spectrometer. Chemical shifts were recorded in ppm on the δ scale with tetramethylsilane ($CDCl_3$) or 2,2 dimethyl-2-silapentane-5-sulphonic acid sodium salt (CD_3OD and D_2O) as the internal standard, coupling constants J were measured in hertz and refer to ^3J coupling unless otherwise stated. $^{31}P-\{^1H\}$ n.m.r. spectra were recorded using a Joel FX90Q

spectrometer with $[P(OH)_4]^+$ in D_2O as an external standard, with positive δ values to high frequency. Fast atom bombardment (FAB) mass spectra with nitrosylbenzylalcohol (NOBA) as the matrix were obtained using a Kratos Concept double focusing Mass Spectrometer. Microanalyses were preformed by Butterworth Laboratories Ltd; 54-56, Waldegrave Road, Teddington, Middlesex. Infra-red spectra were recorded on a Perkin-Elmer 580B spectrometer as KBr discs unless stated otherwise. Visible spectra were recorded using a Beckmann DU-650 spectrophotometer.

All chemicals were obtained from Aldrich Chemical Co. Ltd and used as received, except ruthenium trichloride (Johnson Matthey p.l.c), sodium methoxide, L-histidine, L-aspartic acid and D-penicillamine (Lancaster Synthesis). $[(mes)RuCl_2]_2$[24] and [(mes)RuCl(aa)] (aa = ala[16], leu and phgly[7]) were prepared according to previous procedures.

The reaction of [(mes)RuCl(leu)] with $HCl_{(aq)}$ was preformed by A. Thompson as part of a third year undergraduate project.

Preparation of [(mes)RuCl(phgly)] (2.8).

$[(mes)RuCl_2]_2$ (200 mg, 0.34 mmol) was added to sodium methoxide (37 mg, 0.68 mmol) and phenylglycine (103 mg, 0.68 mmol) in water / methanol (1 : 1) (30 cm^3) and the mixture was refluxed for 3 hrs. After cooling, the solvents were evaporated to yield an orange / yellow solid which was extracted with CH_2Cl_2 (50 cm^3). The solution was filtered through celite and the filtrate collected. The solvent was evaporated to yield an orange-yellow solid [(mes)RuCl(phgly)] (2.8) (194 mg, 70%). Crystals suitable for X-ray were obtained from an n.m.r. sample in D_2O and were obtained as the dihydrate.

Preparation of [(mes)Ru(pen *N,S*)]$_2$Cl$_2$ (2.13).

[(mes)RuCl$_2$]$_2$ (250 mg, .425 mmol) was added to sodium methoxide (45 mg, 0.85 mmol) and D-penicillamine (128 mg, 0.85 mmol) in water / methanol (1 : 1) (40 cm^3) and the mixture was refluxed for 3 hrs. After cooling, the solution was filtered and the solvents removed under vacuum. The resulting solid was washed three times with ethanol (10 cm^3). The product was redissolved in the minimum amount of hot ethanol and after filtration, the solvent was removed under vacuum and the solid dissolved in methanol (20 cm^3) and diethyl ether layered upon the solution. After filtration through celite, the filtrate was evaporated to dryness to yield a brown-yellow solid [(mes)Ru(pen *N,S*)]$_2$Cl$_2$ (2.13) (198 mg, 53%). Crystals suitable for X-ray analysis were grown from D$_2$O and were obtained as the tetrahydrate. The complex was characterised by ^{1}H n.m.r., infrared and mass spectroscopy, and microanalysis (Tables 2.AA-2.CC).

Preparation of [(mes)Ru(pen$_2$. *N,S,O*)] (2.17).

[(mes)RuCl$_2$]$_2$ (100 mg, 0.17 mmol) was added to D-penicillamine (26 mg, 0.34 mmol) and sodium methoxide (19 mg, 0.72 mmol) in methanol (30 cm^3) and the suspension was refluxed for 3 hrs. After cooling, the solution was evaporated to dryness. The solid was dissolved in CH_2Cl_2 (40 cm^3), the brown solution was filtered and the solvent was removed under vacuum to yield a brown solid [(mes)Ru(pen$_2$. *N,S,O*)] (2.17) (52 mg, 41%). The complex was characterised by ^{1}H n.m.r., infrared and mass spectroscopy, and microanalysis (Tables 2.AA-2.CC).

Reaction of [(mes)RuCl$_2$]$_2$ with D-Penicillamine (2.18).

[(mes)RuCl$_2$]$_2$ (50 mg, 0.086 mmol) was added to D-penicillamine (13 mg, 0.086 mmol)

in water / methanol (1 : 1) (20 cm^3). This suspension was refluxed for 3 hrs and after cooling, the solution was filtered through kiesulguhr and the filtrate collected. The solvents were removed under vacuum to yield a brown solid (62 mg) and the ^1H n.m.r. spectrum was recorded. ^1H n.m.r. (D_2O):- δ 1.09 (s, 3H, Me); 1.31 (s, 3H, Me); 2.07 (s, 9H, C_6Me_3); 2.12 (s, 9H, C_6Me_3); 3.38 (d, 1H, Hα J = 7.5 Hz); 5.16 (s, 3H, C_6H_3); 5.24 (s, 3H, C_6H_3); 5.62 (b, 1H, N-H); 6.27 (b, 1H, N-H).

Preparation of [(mes)RuCl(hisH *N,N*)]Cl (2.20).

$[(mes)RuCl_2]_2$ (250 mg, 0.425 mmol) was added to histidine (128 mg, 0.85 mmol) in water / methanol (1 : 1) (30 cm^3). This suspension was refluxed for 3 hrs and after cooling, the solution was filtered the solvents removed under vacuum. The resulting yellow solid was redissolved in methanol (40 cm^3) and diethyl ether was slowly added until precipitation had just occurred. After filtration, the filtrate was collected and the solvents were removed under vacuum to yield a yellow-green solid [(mes)RuCl(hisH *N,N*)]Cl (2.20) (343 mg, 88%). The complex was characterised by ^1H n.m.r., infrared and mass spectroscopy, and microanalysis (Tables 2.AA-2.CC).

Preparation of [(mes)Ru(his *N,N,O*)]BF_4 (2.21).

$AgBF_4$ (44 mg, 0.22 mmol) was added to (2.20) (50 mg, 0.11 mmol) in a water / methanol mixture (1 : 1) (30 cm^3) and after precipitation of AgCl had occurred, NaOMe (6 mg, 0.11 mmol) was added. This suspension was stirred at room temperature for 1 hr after which, the yellow-green solution was filtered. The filtrate was collected and dissolved in the minimum amount of methanol after which, diethyl ether was layered upon the solution. The solution was subsequently filtered through kiesulguhr and the filtrate

was collected and the solvents removed under vacuum to yield a yellow-green solid [(mes)Ru(his *N,N,O*)]BF_4 (2.21) (35 mg, 69%). The complex was characterised by ^1H n.m.r., infrared and mass spectroscopy, and microanalysis (Tables 2.AA-2.CC).

Preparation of [(mes)Ru(asp$_2$. *N,O,O*)] (2.22).

$[(mes)RuCl_2]_2$ (150 mg, 0.26 mmol) was added to sodium methoxide (56 mg, 1.04 mmol) and aspartic acid (69 mg, 0.52 mmol) in water / methanol (1 : 1) (35 cm^3). This suspension was refluxed for 3 hrs and after cooling, the solution was filtered through celite and the solvents evaporated to dryness. The resulting solid was extracted with CH_2Cl_2 / methanol (2 : 1) (25 cm^3), and the resulting solution was filtered and the solvents evaporated to give a yellow-green solid [(mes)Ru(asp$_2$. *N,O,O*)] (2.22) (142 mg, 78%). A portion of the solid was recrystallised from slow evaporation of a water / methanol mixture (1 : 1) (5 cm^3) to yield yellow-green crystals which were filtered and dried under vacuum. The crystals obtained were suitable for X-ray analysis and were obtained as the trihydrate. The complex was characterised by ^1H n.m.r., infrared and mass spectroscopy, and microanalysis (Tables 2.AA-2.CC).

Reaction of [(mes)Ru(asp$_2$. *N,O,O*)] (2.22) with $HCl_{(aq)}$.

$HCl_{(aq)}$ (7 µl of a 12M sol^n, 0.084 mmol) was added to a solution of [(mes)Ru(asp$_2$. *N,O,O*)] (2.22) (30 mg, 0.084 mmol) in an n.m.r. tube and the ^1H n.m.r. spectrum was recorded. After addition of LiCl, the spectrum was recorded again. ^1H n.m.r. (D_2O / LiCl):- δ 2.16 (s, 9H, C_6Me_3); 2.18 (s, 9H, C_6Me_3); 3.24-3.30 (m, 2H, α-CH); 2.81-2.93 (m, 4H, β-CH_2); 5.23 (s, 3H, C_6H_3); 5.29 (s, 3H, C_6H_3). The complex is proposed to be [(mes)RuCl(asp *N,O*)] (2.24).

Reactions of excess $HCl_{(aq)}$ with [(mes)RuCl(aa)] (aa = phgly, ala).

$HCl_{(aq)}$ (10 cm^3 of a 12M sol^n, 120 mmol) was added to [(mes)RuCl(aa)] (≈15 mg, ≈0.37 mmol) dissolved in deionised water (3 cm^3). The solvent was removed under vacuum and the resulting solid washed with deionised water (15 cm^3) to leave an brown precipitate which was subsequently dried. The solids obtained were characterised by mass spectroscopy :- m/e = 549 and visible spectroscopy :-λ_{max} = 355, 442 nm indicating the presence of the cation $[(mes)_2Ru_2Cl_3]^+$.

Reaction of excess $HCl_{(aq)}$ with [(mes)Ru(asp$_2$. *N,O,O*)] (2.22).

$HCl_{(aq)}$ (2.5 cm^3 of a 12M sol^n, 30 mmol) was added to [(mes)Ru(asp$_2$. *N,O,O*)] (2.22) (2 mg, 0.006 mmol) and the solution obtained was monitored by visible spectroscopy :-λ_{max} = 355, 442 nm indicating the presence of the cation $[(mes)_2Ru_2Cl_3]^+$.

Reaction of $HCl_{(g)}$ with [(mes)RuCl(leu)].

[(mes)RuCl(leu)] (100 mg, 0.26 mmol) was dissolved in CH_2Cl_2 (35 cm^3) and $HCl_{(g)}$ was bubbled through the stirred solution for thirty minutes during which time a brown solid was formed. After the solvent was filtered off, the brown solid was washed with CH_2Cl_2 (40 cm^3) and then water (30 cm^3) and subsequently dried under vacuum. The solid was identified as the complex $[(mes)RuCl_2]_2$ by comparison to an authentic sample, mass spectroscopy :- m/e = 549.

Table 2.AA of ^1H n.m.r. Results in D_2O for the Amino Acidate Complexes.

Complex	C_6Me_3	C_6H_3	α-CH	Other Signals, ppm.
2.13	2.17	5.30	2.73 m	0.99 [s, 3H, **Me**1]; 1.46 [s, 3H, **Me**2]; 5.07 [b, 1H, **NH**] 5.73 [b, 1H, **NH**].
2.17	2.14	5.01	3.16 s	1.20 [s, 3H, **Me**1]; 1.24 [s, 3H, **Me**2]; 5.62 [b, 1H, **NH**]; 5.81 [b, 1H, **NH**].
2.20	2.21[a], 2.16[b]	5.36[a], 5.38[b]	3.84[a]m 4.39[b]m	Major 3.00 [m, 2H, β-CH_2]; 5.68 [b, 1H, **NH**]; 5.96 [b, 1H, **NH**]; 6.95 [b, 1H, H^a]; 8.40 [d, 1H, H^b $^4J(1.3)$] : Minor 3.47 [m, 2H, β-CH_2]; 5.68 [b, 1H, **NH**]; 5.96 [b, 1H, **NH**]; 7.45 [b, 1H, H^a]; 8.70 [d, 1H, H^b $^4J(1.3)$].
2.21	2.22[a]	5.37[a]	3.85[a]m	2.97 [m, 2H, β-CH_2]; 6.00 [b, 1H, **NH**]; 6.96 [b, 1H, H^a]; 8.40 [d, 1H, H^b $^4J(1.3)$].
2.22	2.17	5.14	3.59 m	2.37-2.70 [m, 2H, β-CH_2]; 5.36 [b, 1H, **NH**]; 6.06 [b, 1H, **NH**].
2.24[c]	2.16, 2.18	5.24, 5.29	3.87 m	2.75-2.92 [m, 2H, β-CH_2]; 5.09 [b, **NH**]; 5.69 [b, **NH**].

[a] Refers to the major species.

[b] Refers to the minor species.

[c] Refers to spectrum in D_2O + LiCl.

Table 2.BB of Mass Spectroscopy and IR Spectroscopy Results.

Complex	$[M]^+$	Other Clusters	C=O Stretch (cm^{-1})
2.13 [(mes)Ru(penH *N,S*)]$_2$Cl$_2$	740	370 $[M^{2+}]$ / 2	1735
2.17 [(mes)Ru(pen$_{2-}$ *N,S,O*)]	370[a]		1595[d]
2.20 [(mes)RuCl(hisH *N,N*)]Cl	413	377 $[M\text{-}HCl]^+$	1725
2.21 [(mes)Ru(his *N,N,O*)]BF_4	376		1620
2.22 [(mes)Ru(asp$_{2-}$ *N,O,O*)]	354[a]		1605
2.24 [(mes)RuCl(aspH *N,O*)]	388[b]	355[c] $[M\text{-}Cl]^+$	-

[a] Refers to the $[M+H]^+$ ion.

[b] Refers to the $[M-H]^+$ ion.

[c] Refers to the $[M+H-Cl]^+$ ion.

[d] Refers to CH_2Cl_2 solution IR spectrum.

Table 2.CC of Elemental Analyses.

Complex	Found (%)			Expected (%)		
	C	H	N	C	H	N
2.13 [(mes)Ru(pen *N,S*)]$_2$Cl$_2$[a]	38.30	5.67	3.09	38.22	5.73	3.18
2.17 [(mes)Ru(pen$_{2-}$ *N,S,O*)]	41.80	5.00	3.60	42.27	5.32	3.52
2.20 [(mes)RuCl(hisH *N,N*)]Cl[b]	38.66	4.97	8.96	38.71	4.98	9.03
2.21 [(mes)Ru(his *N,N,O*)]BF_4[c]	35.59	4.91	8.71	36.15	4.86	8.43
2.22 [(mes)Ru(asp$_{2-}$ *N,O,O*)][c]	40.34	5.00	3.25	40.20	5.45	3.61

[a] Complex crystallises with 4 moles of water.

[b] Complex crystallises with 1 mole of water.

[c] Complex crystallises with 2 moles of water.

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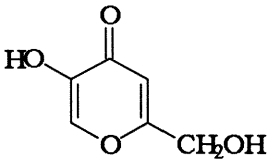
Chapter Three

The Synthesis of Arene-Ruthenium and Cp*-Rhodium Complexes with O,O Donor Ligands

Chapter 3 - The Synthesis of Arene-Ruthenium and Cp*-Rhodium Complexes with O,O Donor Ligands.

3.1.1 - Introduction.

The pyranones kojic acid (**3.1**) and methyl maltol (**3.2**) are naturally occurring ligands. Methyl maltol can be isolated from larch bark and kojic acid from fermentation of carbohydrates.[1] Both methyl maltol (**3.2**) and ethyl maltol (**3.3**) (R = Et) are food additives used in the baking industry.



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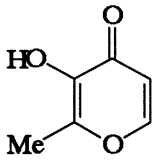
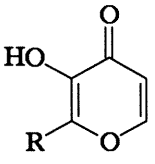
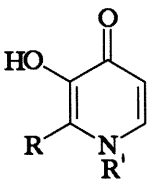


3.2



3.3

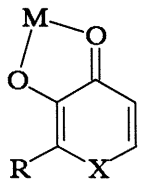


3.4

The pyridinones (**3.4**) (R = Me, Et; R' = H, Me, Et, Ph *etc.*) are prepared from the reaction of a pyranone with a primary amine, and hence a wide range of ligands can be produced which can be tailored specifically.[2,3] Pyranones and pyridinones have found

applications in the field of medicinal chemistry[4,5] where both types of ligand have found use in controlling metal ion concentrations inside the human body.[4-6] For example, iron overload is treated by the administration of desferrioxamine[7], but this treatment is expensive and has low iron excretion rates directly comparable to transfusion rates.[4,5] Desferrioxamine is orally inactive, but is a highly effective drug with low toxicity when used with care and this drug remains the yardstick by which all new chelators are compared.[4,5] The results of trials using pyranone and particularly pyridinone ligands for removal of iron look very promising.[8,9] By modifying the N-R' group of the pyridinone ligand it is possible to control the pharmacokinetics. Studies of these ligands with long organic and fluorinated alkyl chains have been reported recently.[2,3]

Pyranato and pyridinato ligands co-ordinate to many metal ions of biological interest, particularly Al^{III}, Fe^{III}, In^{III} and Ga^{III}.[10,11] Both pyranato and pyridinato ligands are anionic bidentate ligands that co-ordinate to metal ions through the keto and deprotonated hydroxyl groups. No examples of co-ordination through the heterocyclic oxygen or nitrogen atoms have been reported to date. Upon co-ordination to a metal centre they form five-membered chelate rings (**3.5**).[12]



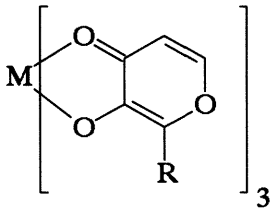
X = O, N-R'

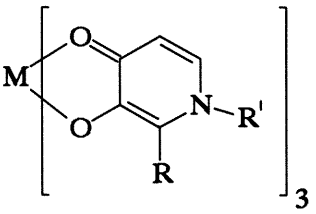
R = Me, Et

3.5

The majority of synthetic studies in the chemistry of pyranato and pyridinato ligands have focused on the formation of complexes of the type $M(L)_3$ (**3.6** & **3.7**) (M = Fe^{III}, Al^{III},

Co^{III} for example).[10,11]



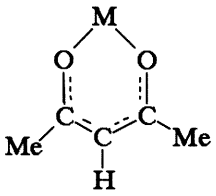


3.6 **3.7**

The co-ordination around the metal in these complexes is a slightly distorted octahedral arrangement[13] with either a *mer* or *fac* arrangement of the ligands.

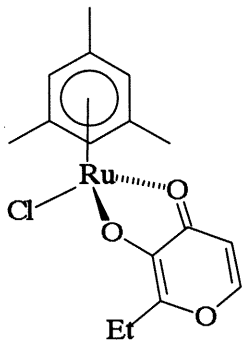
Structurally both pyranones and pyridinones are essentially flat molecules. The participation of the hetero atoms N or O into the delocalisation of electron density around the ring, has been proposed on the basis of crystal structure data.[14-17] All of the crystallised forms of both pyranones and pyridinones show some deformation from conventional single and double bond lengths. The keto and hydroxyl bonds in particular show significant deformation of bond length. In methyl maltol, the C-O bond lengths of the keto and hydroxyl groups are 1.242(12) Å and 1.347(12) Å respectively[18] whereas the standard bond lengths for C=O and C-O bonds are 1.21(1) Å and 1.43(1) Å respectively[19]. However, for the methyl maltol crystals, intermolecular hydrogen bonding is observed between the ligands and therefore, both this hydrogen bonding and electron delocalisation in the ring may be responsible for the observed bond distances.

Upon co-ordination, pyranato and pyridinato ligands closely resemble the $acac^-$ ligand which also co-ordinates through two oxygen donors in a bidentate manner (**3.8**).[20,21]

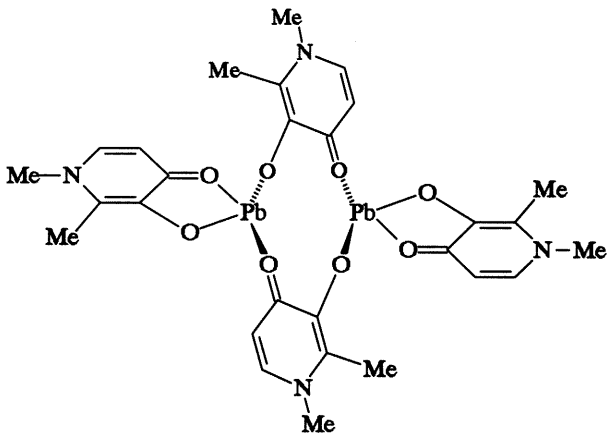


3.8

Pyranato and pyridinato ligands, having hard donor atoms, are both expected to form stable complexes with hard metal ions. Complexes of Al^{III}, Fe^{III}, Rh^{III} and Ir^{III} [22,23] with $acac^-$ have been reported as have the corresponding complexes with pyranones and pyridinones.[10,11] Complexes of pyranones and pyridinones with other metals ions such as Ru^{II} and Pb^{II} have also been reported (**3.9**, **3.10**).[24,25]



3.9



3.10

The complex (**3.10**) is the first example of a metal complex where a pyranato or pyridinato ligand has been shown crystallographically to co-ordinate in a bridging fashion. In this complex, each lead atom is co-ordinated to a pyridinato ligand in the usual chelate manner, and also co-ordinates to a second pyridinato ligand which bridges between the two metals.[25]

The crystal structures of $[M(acac)_3]$ (M = Al, Fe) show that the carbon-oxygen bond lengths are approximately equal[21-23] being intermediate between single and double bonds indicating a large degree of delocalisation around the co-ordinated ligand. Similar delocalisation has been reported by several authors[10,11,26] for pyranato and pyridinato complexes from crystal structure data where the keto (C=O) bond distance is observed to increase upon co-ordination to a metal centre whereas the carbon-oxygen single bond is observed to decrease. However, the degree of delocalisation around the pyranato or

pyridinato ligands is less than that of the acac$^-$ ligand. The extent of delocalisation in these ligands reflects the lack of favourable resonance forms (figure **3.11**).

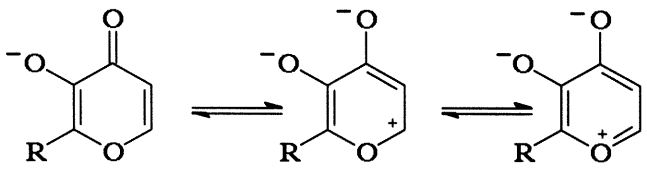
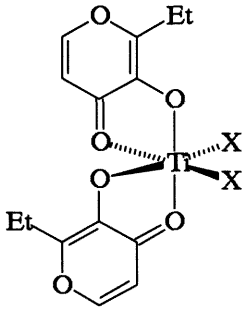
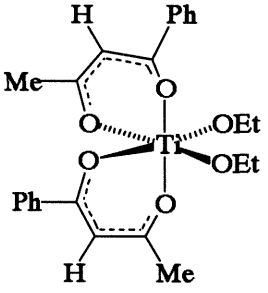


Figure 3.11

Studies involving the formation of complexes of the type $[MX_2(L)_2]$ (M = Sn, Ti, Si; L = pyranato, pyridinato; X = halide, RO^-, SCN^-, OH_2) have been undertaken.[25] These complexes are analogous to the complexes $[M(acac)_2X_2]$ (M = Ti, Sn; X = RO^-, halide) previously prepared.[27,28] The complexes $[TiCl_2(etmalt)_2]$ (**3.12**) and $[Ti(OEt)_2(etmalt)_2]$ (**3.13**) have been synthesised and their reactivity investigated.[25] The anti-tumour activity of both complexes was studied and the results show that they have good activity against tumours of the colon. Both these complexes bear a structural resemblance to the known anti-tumour complex budotitane (**3.14**), which has been shown to be active *in vitro* against colon tumour lines[29,30], therefore, it seems plausible that the mechanism of activity of these complexes is similar.



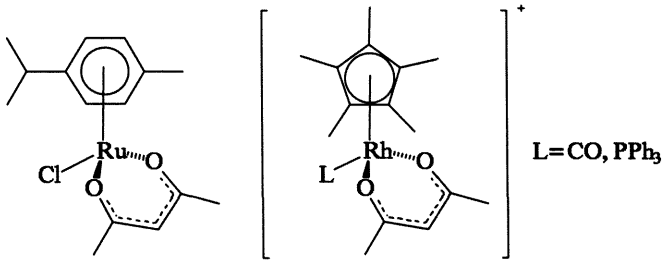


3.12 X = Cl

3.13 X = OEt

3.14

Few complexes containing either a pyranato or pyridinato ligand co-ordinated to an arene or Cp^*-metal fragment have been published.[24,31] In the case of $acac^-$, complexes such as $[(Cp)_2Ti(acac)](ClO_4)$[32], $[(Cp)_2MCl(acac)]$ (M = Ti, Zr)[33], $[(Cp)MX(acac)_2]$ (M = Zr, Hf; X = Cl, Br)[34], [(p-cymene)RuCl(acac)][35] (**3.15**), $[(Cp^*)Rh(acac)(L)]^+$ (L = CO, PPh_3)[36] (**3.16**) and $[(Cp^*)RhCl(acac)]$[37] have been synthesised.



L=CO, PPh_3

3.15 **3.16**

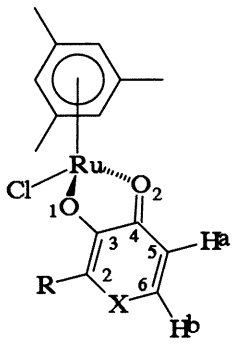
Complexes of the type [(arene)RuCl(L)] or [(Cp^*)RhCl(L)] (L = memalt, etmalt, dmpp or epp) contain a ligand which is asymmetric and therefore two enantiomers would be expected due to chirality at the metal centre. This is in contrast to the complexes [(mes)RuCl(aa)] (see Chapter two) in which both the ligand and metal centre are chiral, thus leading to the formation of both enantiomers and diastereomers. In solution, although both enantiomers of the pyranato or pyridinato complexes are present only one set of resonances would be expected as the two enantiomers are indistinguishable by n.m.r. spectroscopy.

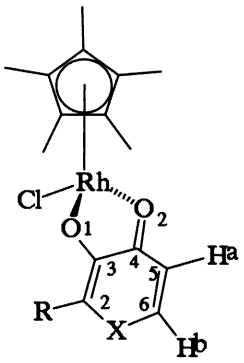
Pyranato and pyridinato metal complexes have been characterised by a range of spectroscopic techniques including n.m.r., infrared, ultraviolet and in certain cases X-ray crystallography.[3,10,11,25,26] In the ^1H n.m.r. spectra, all the complexes show a pair of doublets at high frequency >δ 6.00 with the coupling between the protons H^a and H^b observed to be J = 5 Hz in the pyranato complexes and J = 7 Hz in pyridinato complexes. Chapter three describes the synthesis and characterisation of some arene-ruthenium and Cp^*-rhodium complexes containing pyranato and pyridinato ligands. All these complexes are soluble in both polar organic solvents and water. This balance between solubility in polar organic solvents and water may be beneficial in any medicinal application. For example, the complex [TcCl(memalt)(PPh_3)$_2$] which is soluble in both water and polar organic solvents has been patented as a potential way of introducing the radioactive isotope ^{99m}Tc into the human body.[38]

3.1.2 - Results and Discussion.

All the complexes (3.17-3.23) were prepared in a similar manner by refluxing sodium methoxide, the appropriate pyranone or pyridinone ligand and either [(mes)$RuCl_2$]$_2$

or $[(Cp^*)RhCl_2]_2$, and were obtained in good yields.





3.17 X = O, R = Me

3.18 X = N-Me, R = Me

3.19 X = N-H, R = Et

3.20 X = O, R = Me

3.21 X = O, R = Et

3.22 X = N-Me, R = Me

3.23 X = N-H, R = Et

The ^{1}H n.m.r. spectra (Table **3.AA**) for the complexes [(mes)RuCl(L)] (L = memalt **3.17**, dmpp **3.18** or epp **3.19**) show the characteristic pair of doublets at $\delta \approx 6.3$-8.0 in $CDCl_3$ corresponding to the ring protons H^a and H^b where H^b is at the higher frequency. It has been reported by several authors[27,39,40] that upon co-ordination, the protons H^a and H^b are shifted to higher frequency from that of the unco-ordinated ligand[41]. The complexes prepared in this Chapter also show a shift of both H^a and H^b to higher frequency upon co-ordination. The mesitylene ring gives rise to two resonances at $\delta \approx 2.25$ and ≈ 4.90 corresponding to the methyl and aromatic proton signals respectively. In the ^{1}H n.m.r. spectra of the complexes (**3.17** and **3.18**) the heterocyclic methyl group

is observed at δ 2.40 and 2.39 respectively whilst the N-Me methyl group in complex (3.18) is observed at δ 3.56. The spectra of the corresponding rhodium complexes (3.20 & 3.22) are similar to those of the ruthenium complexes (Table 3.AA). The ^{1}H n.m.r. of the complex (3.21) is similar to that of the analogous ruthenium complex.[24] The maltol methyl group appears as a triplet (actually an overlapping doublet of doublets) at δ 1.21 J = 7.5 Hz. The olefinic protons H^a and H^b are observed at δ 6.46 and 7.58 as doublets, J = 5 Hz respectively with the Cp^* ring a singlet at δ 1.72. The methylene protons H^α and H^β are inequivalent giving rise to two multiplet patterns observed between the region δ 2.70-3.02. It was established, by ^{1}H n.m.r. simulations for the corresponding ruthenium complex [(mes)RuCl(etmalt)] that these line patterns were slightly second order.[31] The ^{1}H n.m.r. spectrum of complex (3.19) in $CDCl_3$ is complex with coupling between the N-H proton and the proton H^b and also between the methylene protons H^α and H^β with the methyl group. The N-H proton appears as a broad unresolved signal at δ 10.33 whilst H^b also appears as an unresolved signal at δ 6.90 whereas H^a is observed as a doublet δ 6.60 J = 7 Hz. The methylene protons H^α and H^β are observed as a very broad signal δ 2.60-2.85 and the methyl group appears as a triplet δ 1.05 J = 7 Hz. Adding a few drops of D_2O to the sample removes the resonance at δ 10.33 indicating an H / D exchange of the N-H proton with D_2O whilst the broad signal for H^b collapses to a doublet, J = 7 Hz. The signal for the methylene protons H^α and H^β remains unresolved. It is proposed that the observation of a broad signal for the methylene group of complex (3.19) occurs because there is a ligand exchange process at the metal centre at a rate comparable with the n.m.r. timescale due to the presence of trace amounts of water. The ^{1}H n.m.r. spectrum of the rhodium complex (3.23) is similar to that of the analogous ruthenium complex (Table 3.AA).

Mass spectra were obtained for all the complexes using FAB-MS, in a NOBA matrix and are listed in Table 3.CC. The fragmentation patterns observed in all cases indicate that the most stable ion is the $[M\text{-}Cl]^+$ ion. In all cases $[M]^+$ or $[M+H]^+$ ions are also observed but these tend to be very weak. Loss of the pyranato or pyridinato ligand is also observed in the mass spectra to leave the (mes)Ru or $(Cp^*)Rh$ fragment only. Elemental analysis of the complexes (3.17-3.23) gave satisfactory results and are presented in Table 3.DD.

The ^1H n.m.r. spectra in D_2O of the complexes (3.17, 3.18 and 3.19) indicate the presence of one species only (Table 3.BB). The mesitylene ring gives rise to two resonances at $\delta \approx 2.20$ and ≈ 5.20 corresponding to the methyl and aromatic proton signals respectively. The maltol methyl group is observed at δ 2.43 (3.17 and 3.18) with the N-Me group of (3.18) observed at δ 3.77. The protons H^a and H^b are observed as doublets for (3.17) at δ 6.71 and 7.96 J = 5 Hz and for (3.18) at δ 6.56 and 7.43 J = 7 Hz. The ^1H n.m.r. spectrum of complex (3.19) shows the characteristic pair of doublets for H^a and H^b at δ 6.65 and 7.40, J = 7 Hz respectively. The methylene protons H^α and H^β are observed as a quartet centred at δ 2.82, J = 7.5 Hz with the methyl group observed as a triplet δ 1.26, J = 7.5 Hz. No signal is observed for the N-H proton presumably due to H / D exchange. The methylene protons H^α and H^β are observed to be equivalent which could be due to either accidental equivalence or to fast ligand exchange at the metal centre. The proposed mechanism for this exchange and a more detailed investigation into this process is outlined later for the rhodium complex $[(Cp^*)RhCl(etmalt)]$ (3.21). The ^1H n.m.r. spectra in D_2O for the rhodium complexes (3.20, 3.22 and 3.23) show similar features to the analogous ruthenium complexes (3.17, 3.18 and 3.19) (all in Table 3.BB) with only one set of resonances being observed in each case. This would suggest that for

all these complexes only one species exists in solution. Exchange of water for chloride ligands in arene-ruthenium or Cp^*-M (M = rhodium or iridium) amino acidate complexes has been well established by several authors[42-44] and is observed for some complexes described in Chapter two. The exchange results in an equilibrium being established where two species exist, containing either a co-ordinated water or chloride. For the complexes (**3.17-3.23**) only one set of resonances is observed, suggesting either that for these complexes the equilibrium lies completely to one side or that the ligands exchange rapidly on the n.m.r. timescale. The addition of LiCl to a D_2O solution of complexes (**3.17-3.23**) resulted in no observed change to the number or position of the peaks in the ^1H n.m.r. spectra. To establish whether a water molecule was co-ordinated in these D_2O spectra, silver tetrafluoroborate was added to a sample of (**3.21**) or (**3.22**) in D_2O (figure **3.24**).

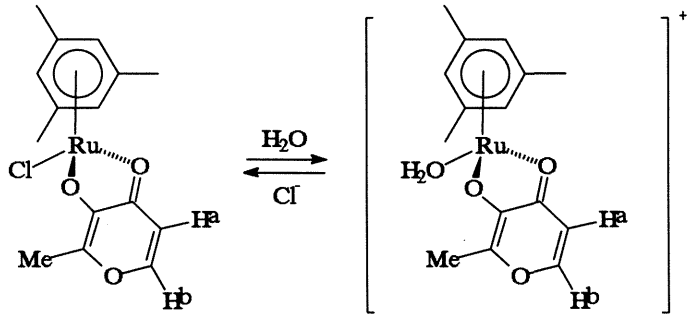
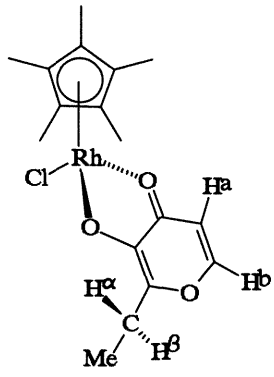


Figure 3.24

After filtration to remove AgCl, the ^1H n.m.r. spectrum for each of these reactions indicated a slight shift in the position of all the peaks in the spectra to higher frequency ($\Delta\delta$ +0.02) which suggests that when the chloride ligand is removed and only a water

molecule is co-ordinated to the metal centre, there is very little change in the n.m.r. spectra. When LiCl is subsequently added to these samples, the ^1H n.m.r. spectra indicate a return to the initial chemical shifts suggesting that the equilibrium has been re-established (figure **3.24**). Due to the very small changes in the ^1H n.m.r. spectra after addition of either Ag^+ or chloride it is difficult to determine whether these complexes exist solely with either a water or chloride co-ordinated upon dissolution in water or whether there is a fast exchange of the two ligands. Further studies on these complexes involving conductivity measurements are described later in this chapter.



3.21

The spectrum of complex (**3.21**) in D_2O or d^4-methanol indicates the presence of one species only, as observed for the other complexes (**3.17-3.23**), and that the methylene protons H^α and H^β are now equivalent, a quartet, J = 7.5 Hz, being observed at δ 2.83. An investigation of the n.m.r. spectra in d^4-methanol at low temperature was carried out to determine whether the quartet observed for the methylene protons was due to accidental co-incidence or whether they were becoming equivalent due to an exchange process.

Variable Temperature ^1H n.m.r. Spectrum of [(Cp^*)RhCl(etmalt)] in CD_3OD.

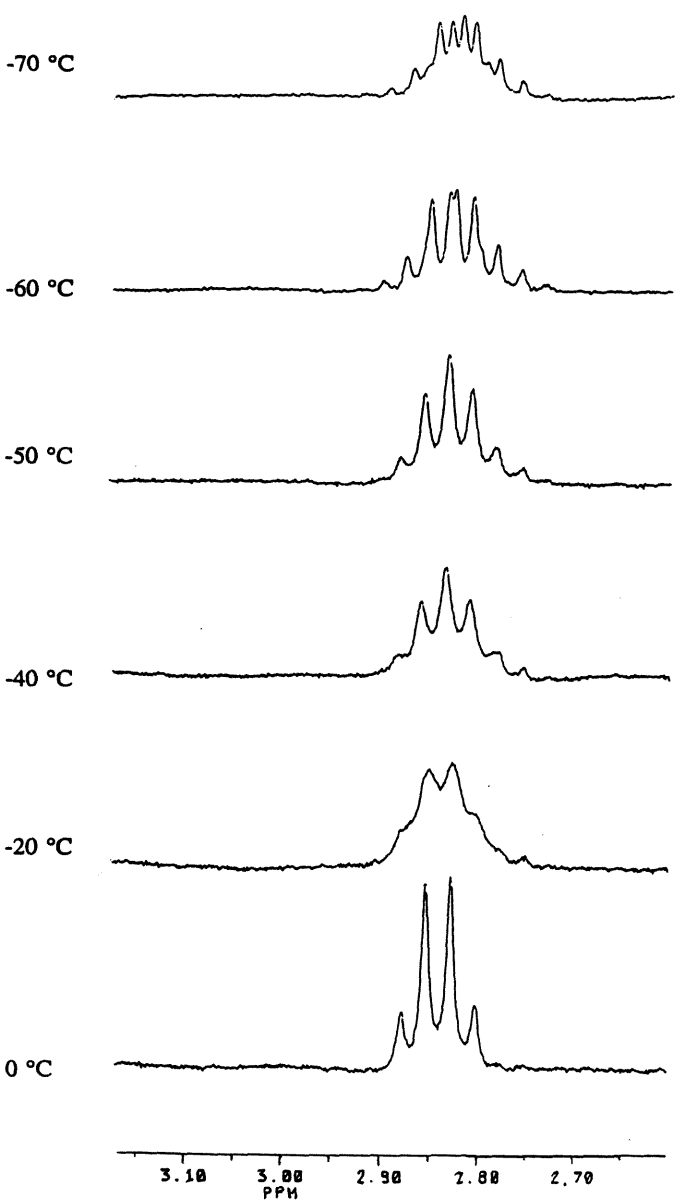
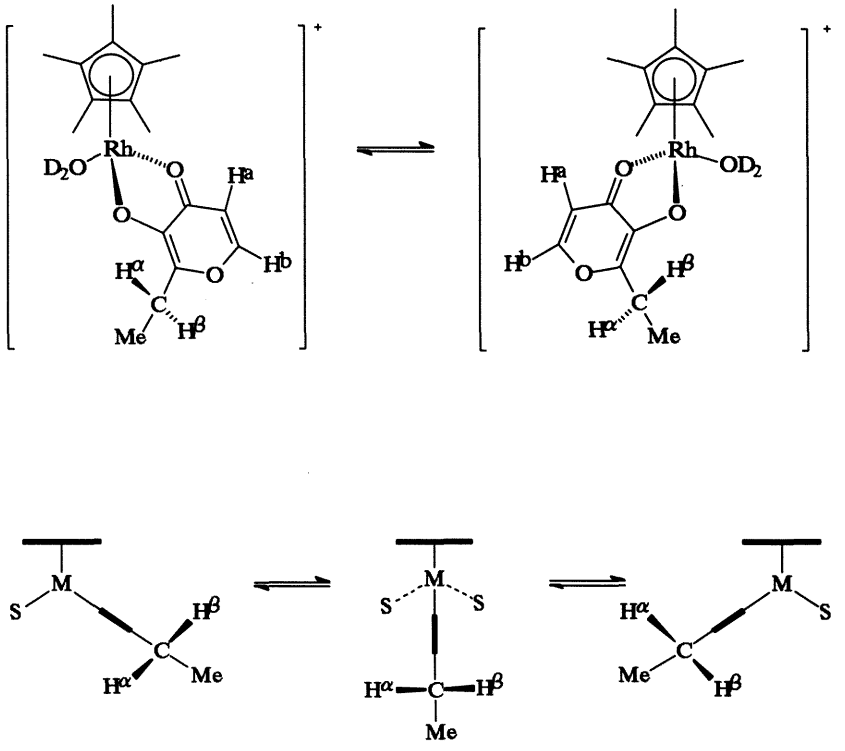


Figure 3.25

As is seen from (figure **3.25**) as the temperature decreases, the quartet signal broadens and splits giving rise to a more complex pattern. The two methylene protons are therefore not accidentally co-incident. The changes observed for the methylene protons are believed to be due to a decrease in the exchange rate of the co-ordinated water ligands at the metal centre (scheme **3.26**) and therefore we observe a time-averaged spectra at room temperature but not at lower temperatures.



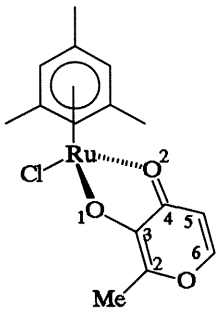
Scheme 3.26

[It must be noted that although the low temperature n.m.r. experiment was preformed in deuterated methanol, it was assumed that co-ordination of D_2O or methanol to the metal centre could occur due to the presence of water in the methanol].

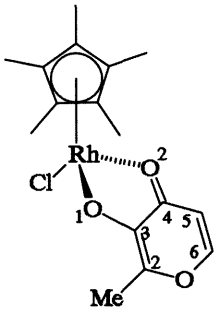
Conductivity measurements were recorded for the pyranato complexes [(mes)RuCl(etmalt)], [(Cp^*)RhCl(etmalt)] and for [(mes)RuCl(picolinic acidate)] to clarify whether a water or chloride ligand is co-ordinated to the ruthenium or rhodium metal in these pyranato and pyridinato complexes when the compounds are in aqueous solution. For the complex [(mes)RuCl(picolinic acidate)] the conductivity results ($\Lambda°_m$ = 88.3 Scm^2mol^{-1}) indicate partial ionisation in water as expected from the observation[24] of two species in the ^1H n.m.r. spectrum. The conductivity measurements for [(Cp^*)RhCl(etmalt)] and [(mes)RuCl(etmalt)], $\Lambda°_m$ = 101.4 and 68.5 Scm^2mol^{-1} respectively, also indicate partial ionisation in aqueous solution and this suggests that for each complex two species are present in aqueous solution with either water or chloride co-ordinated. The appearance of only one set of resonances in the ^1H n.m.r. spectrum must therefore be due to exchange between the two species which is fast on the n.m.r. timescale. The slight downfield shift of the protons of the complexes [(Cp^*)RhCl(etmalt)] and [(Cp^*)RhCl(dmpp)] in the ^1H n.m.r. spectra when Ag^+ is added is assumed to be due to the presence of the water co-ordinated species only or the equilibrium position if excess Cl^- is added. The low temperature spectra (figure 3.25) are in agreement with these results; as the temperature is reduced, the resulting ^1H n.m.r. spectra (figure 3.25) indicate that the methylene protons H^α and H^β become inequivalent and this must be due to a decrease in exchange rate at the metal centre. Elias *et al.* have recently reported the rates of exchange of water co-ordinated to (arene)Ru and (Cp^*)Rh half-sandwich complexes.[45] They suggest that the Cp^* ring increases the lability of the water ligand compared to the

arene ligands when comparing the rates of exchange of the water ligand in the complexes $[(Cp^*)Rh(bipy)H_2O]^+$ and $[(arene)Ru(bipy)H_2O]^+$ (arene = benzene, p-cymene, hexamethylbenzene) in which the rate of exchange for the $(Cp^*)Rh$ complex is 10^4 times faster than the (arene)Ru complexes.[45] The pyranato and pyridinato ligands also appear to have an effect on the exchange rate at the metal centre, and in this respect they differ from the complexes [(mes)RuCl(aa)] described in Chapter two where the water / chloride exchange rate appears to be slow on the n.m.r. timescale.

The Crystal Structures of the Complexes [(mes)RuCl(memalt)] 3.17 and [(Cp*)RhCl(memalt)] 3.20.

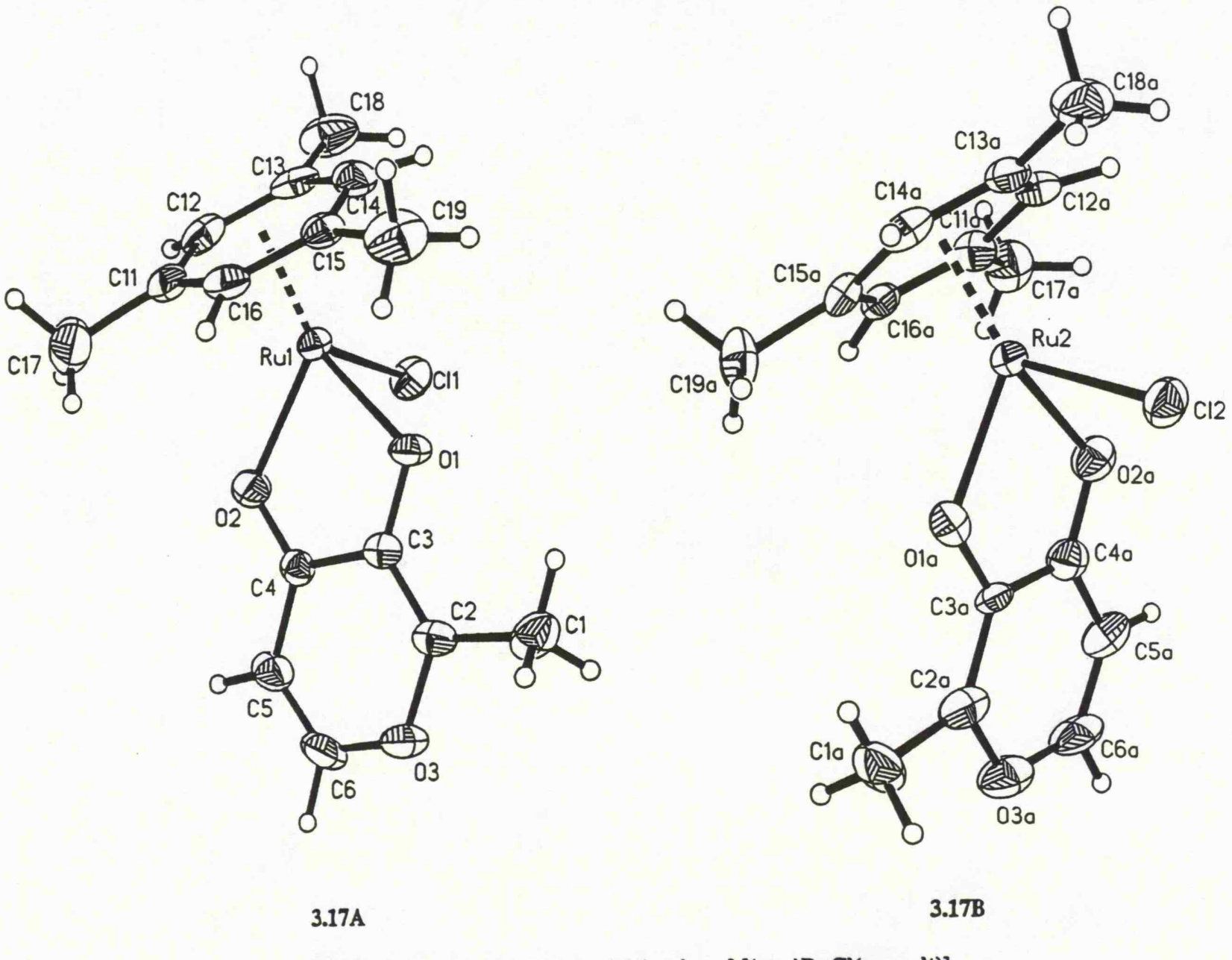


3.17



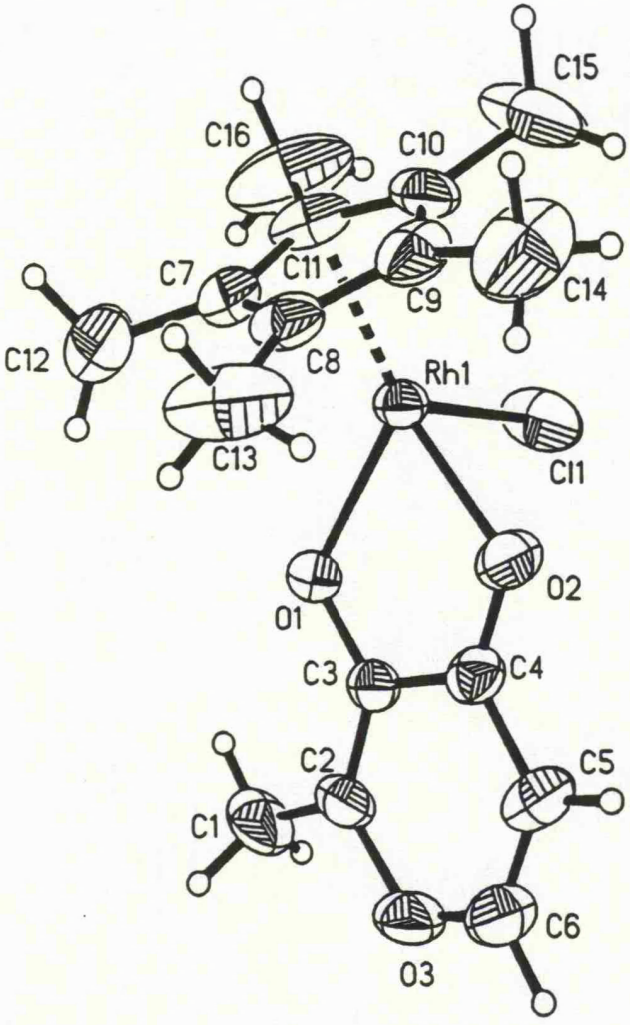
3.20

The complexes (**3.17**) and (**3.20**) were crystallised from petroleum ether / dichloromethane mixtures. The complex (**3.20**) crystallised in the space group $P\bar{1}$ with 1 molecule of water in the asymmetric cell whereas the isoelectronic complex (**3.17**) crystallised in the space group Pbca with no water molecules. Both crystal structures (figures **3.27** and **3.28**) indicate the presence of two unique molecules in the unit cell.

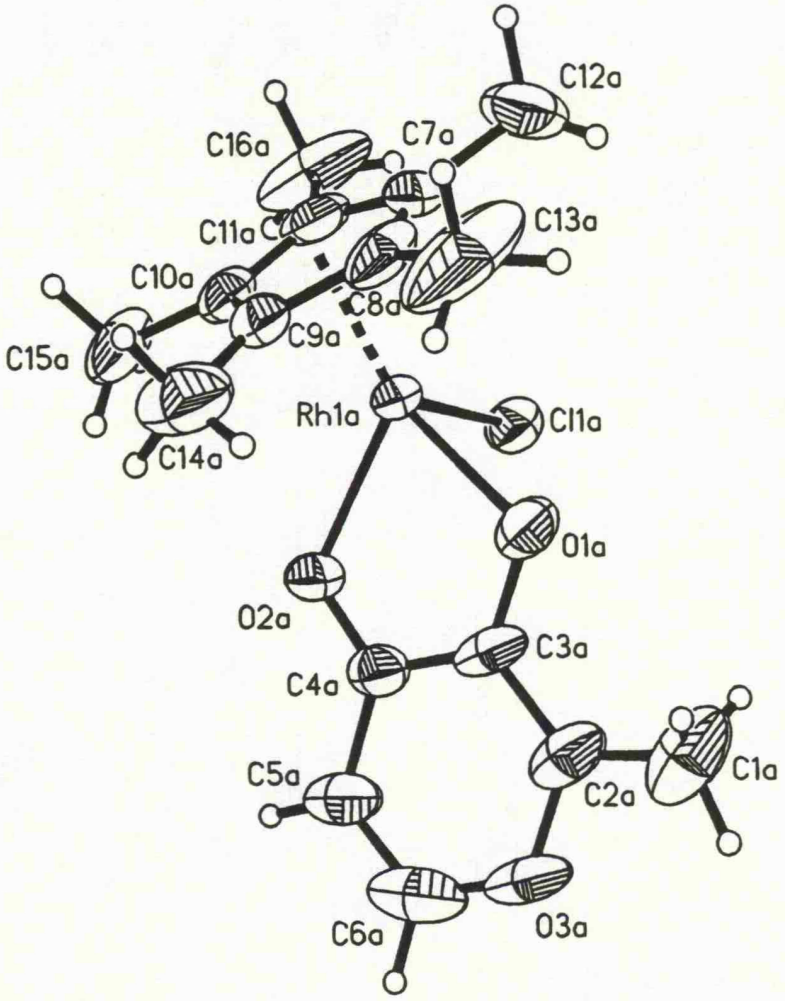


3.17A **3.17B**

Figure 3.27 The Two Unique Molecules of [(mes)RuCl(memalt)].



3.20A



3.20B

Figure 3.28 The Two Unique Molecules of [(Cp*)RhCl(memalt)].

Table 3.EE of Selected Bond Distances (Å) and Bond Angles (°) for Complexes 3.17 and 3.20.

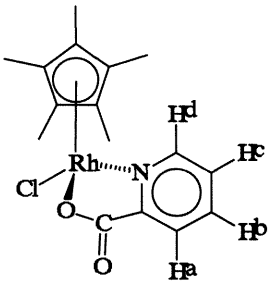
	3.17A	**3.17B**	**3.20A**	**3.20B**
M-O2	2.106(4)	2.117(5)	2.118(5)	2.133(5)
M-O1	2.091(4)	2.090(5)	2.116(3)	2.111(4)
M-Cl	2.420(2)	2.420(2)	2.409(2)	2.388(1)
O1-C3	1.306(8)	1.338(8)	1.326(7)	1.363(8)
O2-C4	1.276(8)	1.271(9)	1.250(6)	1.254(7)
O1-M-O2	79.2(2)	78.9(2)	78.3(2)	78.8(2)
O1-M-Cl	85.4(1)	85.5(1)	87.7(1)	86.7(1)
O2-M-Cl	83.6(1)	84.8(1)	88.2(1)	87.4(1)
O1-C3-C4	118.2(5)	118.9(6)	117.5(4)	121.3(5)

In both complexes (**3.17**) and (**3.20**) the metal atom sits at the centre of a slightly distorted octahedron with the conjugated rings occupying three facial sites on the metal. The deprotonated pyranato ligand chelates the metal centre through the O1 and O2 donor atoms with the chloride ligand occupying the sixth co-ordination site. For the two molecules (**3.17A**) and (**3.17B**) both the Ru-O bond distances are similar with Ru-O1 [2.091(4) Å and 2.090(5) Å] and Ru-O2 [2.106(4) Å and 2.117(5) Å]. The bond distance O1-C3 for molecule (**3.17A**) at 1.306(8) Å is shorter than for (**3.17B**) at 1.338(8) Å but the O2-C4 bond distances are statistically the same for both, (**3.17A**) 1.276(8) Å and (**3.17B**) 1.271(9) Å. The Ru-Cl bond lengths are the same, 2.420(2) Å, and are similar to those observed in amino acidate complexes where the average Ru-Cl bond lengths are found to be 2.434(3) Å and 2.420(2) Å for the complexes $[(C_6H_6)RuCl(ala)]$[46] and

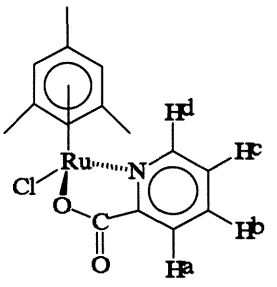
[(mes)RuCl(phgly)] respectively. For the rhodium molecules, the O1-C3 bond distance, 1.363(8) Å in (3.20B), is significantly longer than 1.326(7) Å for molecule (3.20A). The changes in the C-O and C=O bond lengths however, are far less substantial than those observed in the β-diketone complex $Co(acac)_3$, where upon co-ordination, both the carbon-oxygen bonds average 1.296(2) Å[21] indicating a large degree of delocalisation within this structure. The Rh-Cl bond lengths are significantly different at 2.409(2) Å and 2.388(1) Å for molecules (3.20A) and (3.20B) respectively with that of (3.20A) significantly closer to those of the Rh-Cl bond lengths for the functionalised amino acidate complexes [(Cp^*)RhCl(azetidine-2-carboxylate)][43] and [(Cp^*)RhCl(picolinic acidate)] (3.29) which are 2.403(2) Å[43] and 2.404(1) Å respectively. The ruthenium complex (3.17) shows a greater change in the carbon-oxygen bond lengths than its rhodium analogue (3.20) suggesting that there may be a greater degree of delocalisation around the chelate. There is found to be little difference between the chelate ∠O1-M-O2° in each of the molecules which are (3.17A) 79.2(2)° and (3.17B) 78.9(2)° whereas for the rhodium analogues they are (3.20A) 78.3(2)° and (3.20B) 78.8(2)°. From the crystal structure data, both the complexes (3.17) and (3.20) show slight variations of bond character in terms of bond distances and angles around the O1-M-O2 chelate ring compared to the unco-ordinated methyl maltol ligand.[18] However, the bond distances and angles around the co-ordinated pyranato ligand ring in each case show negligible changes from those of the free ligand suggesting that in these complexes, the pyranato ligand does not undergo significant delocalisation around the ring upon co-ordination.

In a further study, the reaction of picolinic acid with $[(Cp^*)RhCl_2]_2$ was performed in order to study the aquation of the complex which could then be compared to that of the ruthenium analogue.[24] The ligand is unsymmetrical but achiral, like those of the

pyranone and pyridinone ligands, and therefore two enantiomers of complex (**3.29**) exist which are not distinguishable by ^1H n.m.r. spectroscopy. Picolinic acid was added to $[(Cp^*)RhCl_2]_2$ in the presence of one equivalent of base (NaOMe) and proceeded to produce complex (**3.29**) as a brick red solid in high yield and it was characterised by ^1H n.m.r. (Table **3.BB**), mass spectroscopy (Table **3.CC**) and microanalysis (Table **3.DD**). Its' structure in the solid state was determined by X-ray diffraction and compared to that of the ruthenium analogue (**3.30**) reported previously.[24] The complex (**3.29**) is not soluble in CH_2Cl_2 or $CDCl_3$ unlike the complexes (**3.17-3.23**). The ^1H n.m.r. in D_2O shows broad signals with a singlet at δ 1.69 due to the Cp^* ring with the aromatic protons being observed in the region δ 7.85-8.87. The proton H^d is observed at highest frequency δ 8.87 as a broad signal. The protons H^b and H^c are observed as broad multiplets whereas H^a is observed as a broad doublet.



3.29



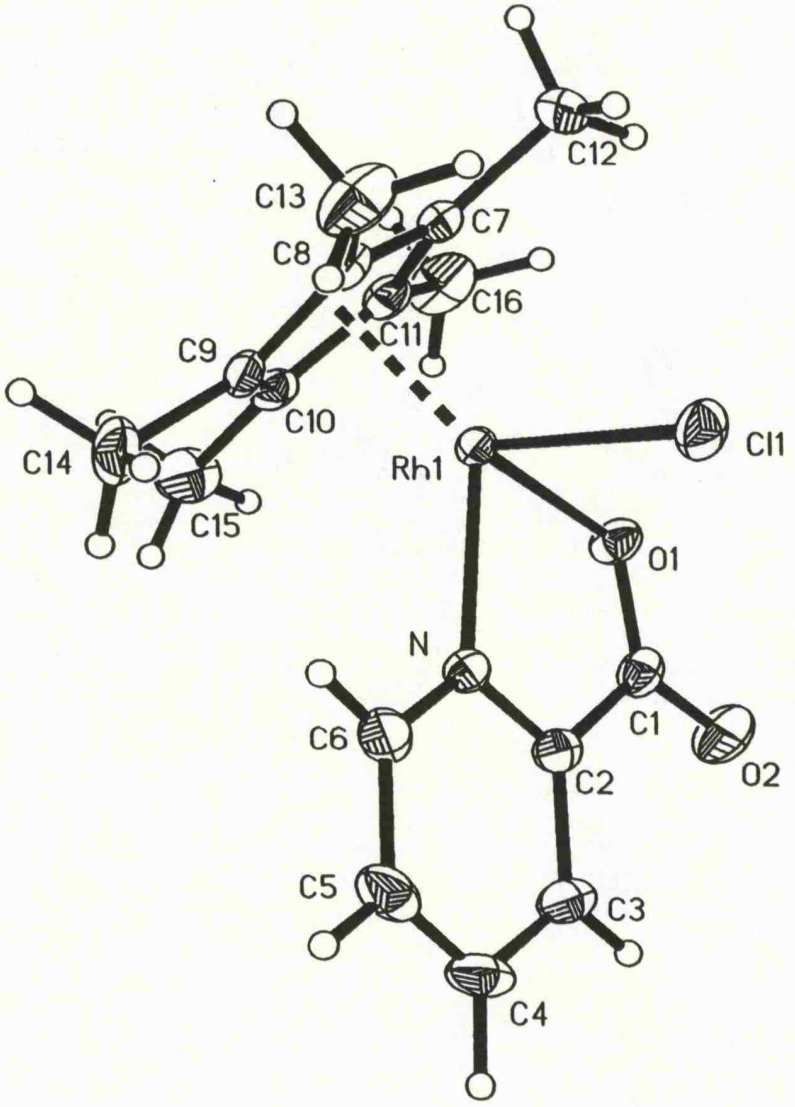
3.30

On addition of a ten-fold excess of LiCl, the spectrum is better resolved, with all the aromatic signals showing sharper peaks. The position of the proton H^d is observed at δ

8.86 as a doublet J = 5 Hz, whereas the positions of the protons H^a-H^c are assigned to the signals at δ 7.89 H^c, 8.03 H^a and 8.19 H^b. Alternatively, addition of $AgNO_3$ also results in the sharpening of the aromatic signals H^a-H^d. The proton H^d is observed to shift a long way to higher frequency δ 9.01 with the other aromatic protons H^a-H^c also observed to have shifted to higher frequency (Table 3.BB). In the presence of Ag^+ or excess chloride, only one resonance is observed for the Cp^* peak. From this evidence, it was proposed that the complex [(Cp^*)RhCl(picolinic acidate)] (3.29) exists in water as a mixture with either a chloride or water ligand co-ordinated. The addition of LiCl displaces the equilibrium in favour of the chloride co-ordinated species whereas the addition of $AgNO_3$ displaces the equilibrium in favour of the water co-ordinated species. The chemical shift of H^d in the water co-ordinated species is at δ 9.01 whereas in the equilibrium mixture it is at δ 8.87 and with excess chloride it is found in virtually the same position. This implies that for complex (3.29) the equilibrium in water between co-ordinated water and chloride ligands lies in favour of the chloride co-ordinated species. In the spectrum of complex [(Cp^*)RhCl(picolinic acidate)] (3.29) only one set of broad signals are observed for the protons of the ligand, whereas for the corresponding ruthenium complex resonances attributed to species containing either a co-ordinated water or chloride could be observed indicating the difference in exchange rate at the metal centre between these (Cp^*)Rh and (arene)Ru complexes.

The FAB mass spectrum indicates that the most stable ion is the $[M\text{-}Cl]^+$ ion m/e 360, as observed in many amino acidate complexes and also for complexes (3.17-3.23) as described earlier.

Crystals of (3.29) suitable for X-ray crystallography were grown from D_2O. The complex crystallised in the space group Pbca.



3.29

Figure 3.31 The Crystal Structure of [(Cp*)RhCl(pic)].

Table 3.FF of Selected Bond Distances (Å) and Bond Angles (°) for Complexes 3.29 and 3.30[24].

	[(Cp*)RhCl(pic)] (3.29)	[(mes)RuCl(pic)] (3.30)[24]
M-Cl	2.404(1)	2.420(1)
M-N	2.117(3)	2.102(4)
M-O1	2.108(2)	2.101(4)
C1-O1	1.283(4)	1.285(7)
C1-O2	1.231(4)	1.242(7)
C1-C2	1.498(5)	1.502(8)
N-M-Cl	85.9(1)	84.0(1)
N-M-O1	77.7(1)	77.9(2)
O1-C1-O2	124.5(3)	124.7(6)
O1-M-Cl	87.8(1)	83.6(1)
M-N-C2	113.6(2)	113.7(4)

The structure (figure **3.31**) confirmed the N,O co-ordination mode of the picolinic acidate ligand as observed in amino acidate complexes[31,43,46] and the structural similarity to the ruthenium analogue (**3.30**)[24] with the Cp^* ring co-ordinating η^5 as expected with the chloride and picolinic acidate ligand occupying the other three sites. Complex (**3.29**) crystallised in the anhydrous form, whereas the complex (**3.30**) crystallised as the tri-hydrate[24]. Some differences were noted between the two isoelectronic complexes. The Rh-Cl bond distance 2.404(1) Å is shorter than that observed for the Ru-Cl bond distance 2.420(1) Å[24]. The M-N and M-O bond distances are similar for the rhodium complex (**3.29**) [M-N 2.117(3) and M-O 2.108(2) Å] and the ruthenium complex (**3.30**) [M-N

2.102(4) and M-O 2.101(4) Å][24] which suggests that the arene and Cp^* rings affect the bond lengths of the picolinic acidate ligand, which is *trans* to them, to a similar extent. The bite angles in each molecule ∠N-M-O1° are the same 77.7(1) and 77.9(1)° [24] for the complexes 3.29 and 3.30 respectively and these values are similar to those observed by Beck *et al.*[43] and Carter *et al.*[31] in related amino acidate complexes.

This chapter has described the preparation and characterisation of some arene-ruthenium and Cp^*-rhodium complexes incorporating the O,O donor ligands pyranone and pyridinone as well as the related N,O ligand picolinic acid. All the pyranone and pyridinone complexes are soluble in water and polar organic solvents. Upon dissolution in water the co-ordinated chloride ligand exchanges rapidly with water molecules with a subsequent interconversion of the two enantiomers and the subsequent n.m.r. spectra show only one set of resonances indicating the equilibrium position of this exchange. This exchange is found to be slower at ruthenium than at rhodium highlighted by the two complexes of picolinic acid in which chloride or water co-ordinated species can be observed in the ^1H n.m.r. spectrum for the ruthenium complex whereas for the corresponding rhodium complex, a broad set of resonances are observed which indicates that the exchange rate is comparable to the n.m.r. timescale.

3.1.3 - Experimental.

General experimental techniques were as described in Chapter two. Conductivity measurements were performed by Dr. A.P. Abbott and K. Singh and obtained using a Solex model 4070 conductivity meter. $[(Cp^*)RhCl_2]_2$ and $[(mes)RuCl_2]_2$ were prepared by the literature methods.[47,48] Rhodium trichloride was obtained from Johnson Matthey, methyl maltol and N-methyl-3-hydroxy-2-methyl-4-pyridinone (dmpp) were obtained from

Sigma Chemicals, ethyl maltol from Pfizer Chemicals and 2-picolinic acid from Aldrich Chemicals Ltd., and all were used as received. 3-hydroxy-2-ethyl-4-pyridinone (eppH) was prepared by S. Parsons.[25]

Preparation of [(mes)RuCl(memalt)] (3.17).

$[(mes)RuCl_2]_2$ (100 mg, 0.17 mmol) was added to a solution of methyl maltol (43 mg, 0.34 mmol) and sodium methoxide (18 mg, 0.34 mmol) in a water / methanol mixture (1 : 1) (30 cm^3). This suspension was refluxed for 3 hrs and after cooling, the solution was evaporated to dryness. The resulting brown solid was extracted with CH_2Cl_2 and diethyl ether was added and after filtration through celite the solvents were removed under vacuum to yield a brown solid [(mes)RuCl(memalt)] (3.17) (yield 102 mg, 77%). A portion of the solid was recrystallised by layering petroleum ether onto a saturated CH_2Cl_2 solution of (3.17) to produce crystals suitable for X-ray analysis. The complex was characterised by ^1H n.m.r. and FAB mass spectroscopy, and microanalysis (Tables 3.AA-3.DD). $^{13}C-\{^1H\}$ n.m.r. (D_2O):- δ 16.9 Me; 20.8 arene Me; 75.1 arene ring C; 102.9 C2; 113.5 C5; 157.4 C6; 184.5 C4.

Preparation of [(mes)RuCl(dmpp)] (3.18).

$[(mes)RuCl_2]_2$ (50 mg, 0.086 mmol) was added to a solution of dmppH (24 mg, 0.17 mmol) and sodium methoxide (9 mg, 0.17 mmol) in a water / methanol mixture (1 : 1) (30 cm^3). The procedure followed that described for complex (3.17) and gave after work-up, a brown solid, [(mes)RuCl(dmpp)] (3.18) (yield 126 mg, 93%). The complex was characterised by ^1H n.m.r. and FAB mass spectroscopy, and microanalysis (Tables 3.AA-3.DD).

Preparation of [(mes)RuCl(epp)] (3.19).

$[(mes)RuCl_2]_2$ (50 mg, 0.086 mmol) was added to a solution of eppH (24 mg, 0.17 mmol) and sodium methoxide (9 mg, 0.17 mmol) in a water / methanol mixture (1 : 1) (30 cm^3). The procedure followed that described for complex (3.17) and gave after work-up, a brown solid [(mes)RuCl(epp)] (3.19) (yield 100 mg, 74%). The complex was characterised by ^1H n.m.r. and FAB mass spectroscopy, and microanalysis (Tables 3.AA-3.DD).

Preparation of [(Cp^*)RhCl(memalt)] (3.20).

$[(Cp^*)RhCl_2]_2$ (50 mg, 0.08 mmol) was added to solution of methyl maltol (20 mg, 0.16 mmol) and sodium methoxide (9 mg, 0.16 mmol) in methanol (20 cm^3). The procedure followed that described for complex (3.17) and gave after work-up, a red solid [(Cp^*)RhCl(memalt)] (3.20) (yield 61 mg, 90%). A portion of the red solid was recrystallised from a CH_2Cl_2 / petroleum ether solution to yield crystals suitable for X-ray analysis. The complex was characterised by ^1H n.m.r. and FAB mass spectroscopy, and microanalysis (Tables 3.AA-3.DD).

Preparation of [(Cp^*)RhCl(etmalt)] (3.21).

$[(Cp^*)RhCl_2]_2$ (50 mg, 0.080 mmol) was added to a solution of ethyl maltol (22 mg, 0.16 mmol) and sodium methoxide (9 mg, 0.17 mmol) in methanol (20 cm^3). The procedure followed that described for complex (3.17) and gave after work-up, a red solid [(Cp^*)RhCl(etmalt)] (3.21) (yield 63 mg, 96%). The complex was characterised by ^1H n.m.r. and FAB mass spectroscopy, and microanalysis (Tables 3.AA-3.DD).

Preparation of [(Cp*)RhCl(dmpp)] (3.22).

$[(Cp^*)RhCl_2]_2$ (50 mg, 0.08 mmol) was added to solution of dmppH (22 mg, 0.16 mmol) and sodium methoxide (9 mg, 0.16 mmol) in methanol (20 cm^3). The procedure followed that described for complex (3.17) and gave after work-up, a red solid [(Cp*)RhCl(dmpp)] (3.22) (yield 59 mg, 90%). The complex was characterised by ^1H n.m.r. and FAB mass spectroscopy, and microanalysis (Tables 3.AA-3.DD).

Preparation of [(Cp*)RhCl(epp)] (3.23).

$[(Cp^*)RhCl_2]_2$ (50 mg, 0.08 mmol) was added to solution of eppH (22 mg, 0.16 mmol) and sodium methoxide (9 mg, 0.16 mmol) in methanol (20 cm^3). The procedure followed that described for complex (3.17) and gave after work-up, a red solid [(Cp*)RhCl(epp)] (3.23) (yield 46 mg, 70%). The complex was characterised by ^1H n.m.r. and FAB mass spectroscopy, and microanalysis (Tables 3.AA-3.DD).

Preparation of [(Cp*)RhCl(pic)] (3.29).

$[(Cp^*)RhCl_2)_2$ (50 mg, 0.08 mmol) was added to sodium methoxide (9 mg, 0.16 mmol) and picolinic acid (20 mg, 0.16 mmol) in methanol (30 cm^3). This suspension was refluxed for 3 hrs and after cooling, the solution was filtered and dried. The resulting red solid was extracted with a CH_2Cl_2 / methanol mixture and the filtrate collected and dried. The solid was recrystallised from slow evaporation of a water / methanol solution to yield red crystals [(Cp*)RhCl(pic)] (3.29) (yield 52 mg, 81%) which were suitable for X-ray analysis. The complex was characterised by ^1H n.m.r. and FAB mass spectroscopy, and microanalysis (Tables 3.BB-3.DD)

Table 3.AA of ^{1}H n.m.r. Results in $CDCl_3$ for Complexes 3.17-3.23.

Complex	Ring Signal(s)	Other signals ppm.
3.17	2.25 C_6Me_3 ; 4.92 C_6H_3	2.40 [s, 3H, **Me**]; 6.48 [d, 1H, H^a J(5)]; 7.55 [d, 1H, H^b J(5)].
3.18	2.24 C_6Me_3 ; 4.85 C_6H_3	2.39 [s, 3H, **Me**]; 3.56 [s, 3H, N-**Me**]; 6.33 [d, 1H, H^a J(7)]; 6.90 [d, 1H, H^b J(7)].
3.19	2.20 C_6Me_3 ; 4.84 C_6H_3	1.05 [t, 3H, **Me** (X_3 part) J(7.5)]; 2.60-2.85 [b, 2H, CH_2 (AB part)]; 6.60 [d, 1H, H^a J(7)]; 6.90 [b, 1H, H^b]; 10.33 [b, 1H, N-**H**].
3.20	1.72 C_5Me_5	2.41 [s, 3H, **Me**]; 6.46 [d, 1H, H^a J(5)]; 7.55 [d, 1H, H^b J(5)].
3.21	1.72 C_5Me_5	1.21 [t, 3H, **Me** (X_3 part) J(7.5)]; 2.77[a] [m, 1H, **CH** (A part)]; 2.96[a] [m, 1H, **CH** (B part)]; 6.46 [d, 1H, H^a J(5)]; 7.58 [d, 1H, H^b J(5)].
3.22	1.72 C_5Me_5	2.39 [s, 3H, **Me**]; 3.58 [s, 3H, N-**Me**]; 6.33 [d, 1H, H^a J(7)]; 6.91 [d, 1H, H^b J(7)].
3.23	1.67 C_5Me_5	1.10 [t, 3H, **Me** (X_3 part) J(7.5)]; 2.45-2.55 [m, 2H, CH_2 (AB part)]; 6.20 [d, 1H, H^a J(7)]; 7.00 [b, 1H, H^b]; 10.65 [b, 1H, N-**H**].

[a] The chemical shifts are measured from first order principles.

Table 3.BB of ^{1}H n.m.r. Results in D_2O.

Complex	Ring Signal(s)	Other signals ppm.
3.17	2.19 C_6Me_3 ; 5.26 C_6H_3	2.43 [s, 3H, **Me**]; 6.71 [d, 1H, **H^a** J(5)]; 7.96 [d, 1H, **H^b** J(5)].
3.18	2.21 C_6Me_3 ; 5.23 C_6H_3	2.43 [s, 3H, **Me**]; 3.77 [s, 3H, **N-Me**]; 6.56 [d, 1H, **H^a** J(7)]; 7.43 [d, 1H, **H^b** J(7)].
3.19	2.23 C_6Me_3 ; 5.24 C_6H_3	1.26 [t, 3H, **Me** J(7.5)]; 2.82 [q, 2H, **CH_2** J(7.5)]; 6.65 [d, 1H, **H^a** J(7)]; 7.40 [d, 1H, **H^b** J(7)].
3.20	1.67 C_5Me_5	2.41 [s, 3H, **Me**]; 6.65 [d, 1H, **H^a** J(5)]; 7.96 [d, 1H, **H^b** J(5)].
3.21	1.68 C_5Me_5	1.22 [t, 3H, **Me** J(7.5)]; 2.83 [q, 2H, **CH_2** J(7.5)]; 6.66 [d, 1H, **H^a** J(5)]; 8.00 [d, 1H, **H^b** J(5)].
3.22	1.68 C_5Me_5	2.39 [s, 3H, **Me**]; 3.75 [s, 3H, **N-Me**]; 6.49 [d, 1H, **H^a** J(7)]; 7.41 [d, 1H, **H^b** J(7)].
3.23	1.69 C_5Me_5	1.23 [t, 3H, **Me** J(7.5)]; 2.79 [q, 2H, **CH_2** J(7.5)]; 6.59 [d, 1H, **H^a** J(7)]; 7.39 [d, 1H, **H^b** J(7)].
3.29[a]	1.69 C_5Me_5	8.03 [d, 1H, **H^a** J(7.5)]; 8.19 [t, 1H, **H^b** J_{a-b}(7.5) J_{b-c}(7)]; 7.89 [t, 1H, **H^c** J_{b-c}(7) J_{c-d}(5)]; 8.86 [d, 1H, **H^d** J(5)].
3.29[b]	1.72 C_5Me_5	8.08 [d, 1H, **H^a** J(7.5)]; 8.25 [t, 1H, **H^b** J_{a-b}(7.5) J_{b-c}(7)]; 7.93 [t, 1H, **H^c** J_{b-c}(7) J_{c-d}(5)]; 9.01 [d, 1H, **H^d** J(5)].

[a] Refers to the ^{1}H n.m.r. in D_2O with added LiCl.

[b] Refers to the ^{1}H n.m.r. in D_2O with added $AgNO_3$.

Tables 3.CC and 3.DD of Mass Spectrometry and Elemental Analyses.

Complex	$[M-Cl]^+$	$[M]^+$
[(mes)RuCl(memalt)] (3.17)	347	382
[(mes)RuCl(dmpp)] (3.18)	360	395
[(mes)RuCl(epp)] (3.19)	360	395
[(Cp^*)RhCl(memalt)] (3.20)	363	399[a]
[(Cp^*)RhCl(etmalt)] (3.21)	377	412
[(Cp^*)RhCl(dmpp)] (3.22)	376	411
[(Cp^*)RhCl(epp] (3.23)	376	411
[(Cp^*)RhCl(pic)] (3.29)	360	396[a]

[a] Refers to the molecular [M+H] ion.

Complex	Found (%)			Expected (%)		
	C	H	N	C	H	N
[(mes)RuCl(memalt)] (3.17)	46.62	4.53	-	47.18	4.49	-
[(mes)RuCl(dmpp)][a] (3.18)	45.95	4.43	3.57	45.30	4.83	3.20
[(mes)RuCl(epp)][b] (3.19)	43.65	4.97	3.58	43.68	5.73	3.18
[(Cp^*)RhCl(memalt)] (3.20)	48.08	5.11	-	48.20	5.06	-
[(Cp^*)RhCl(etmalt)][c] (3.21)	48.27	5.65	-	48.41	5.50	-
[(Cp^*)RhCl(dmpp)][a] (3.22)	48.31	6.08	3.06	48.52	5.75	3.33
[(Cp^*)RhCl(epp)][d] (3.23)	44.87	6.04	3.14	45.59	6.07	3.13
[(Cp^*)RhCl(pic)] (3.29)	45.90	4.69	3.34	45.53	4.84	3.54

[a] The calculated figures includes 0.5 moles of dichloromethane.

[b] The calculated figures includes 2.5 moles of water.

[c] The calculated figures includes 1 mole of water.

[d] The calculated figures includes 2 moles of water.

3.1.4 - References.

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Chapter Four

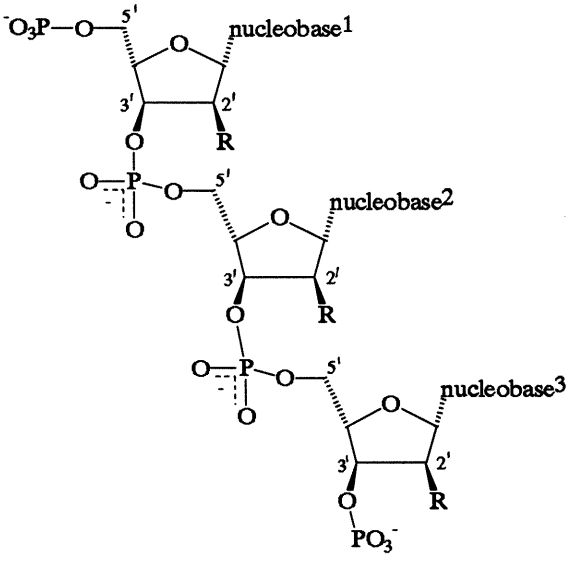
The Reactions of Half-Sandwich Arene-Ruthenium and Cp*-Rhodium Complexes with Nucleobases and Theophylline

Chapter 4 - The Reactions of Half-Sandwich Complexes with Nucleobases and Theophylline.

4.1.1 - Introduction.

Proteins are macromolecules built from amino acids by peptide bond formation. Similarly, nucleic acids are macromolecules built from nucleotides and the sequence of these nucleotides constitutes the genetic code. A nucleotide consists of a heterocyclic base attached to a sugar group, which is in turn attached to a phosphate group. If the phosphate group is removed the remaining fragment is called a nucleoside.

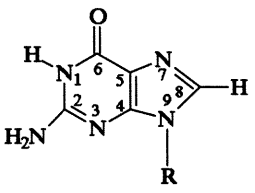
The construction of DNA / RNA strands occurs through a phosphate linkage between the 5' and 3' positions of neighbouring nucleosides (**4.1**).[1]



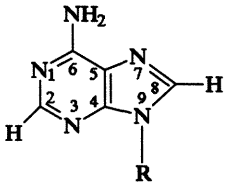
4.1

R = H Deoxyribonucleic acid strand (DNA); R = OH Ribonucleic acid strand (RNA).

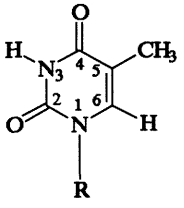
The four heterocyclic bases (R = H) found in ribonucleic acid (RNA) are adenine, guanine, cytosine and uracil. In deoxyribonucleic acid (DNA), thymine occurs in place of uracil (**4.2**) with H replacing OH at the sugar group in the 2' position.



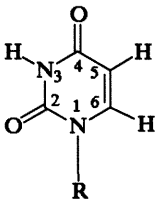
Guanine



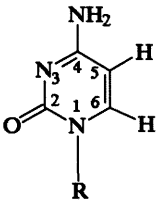
Adenine



Thymine

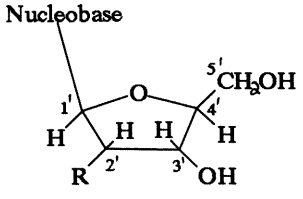


Uracil



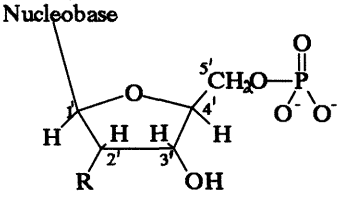
Cytosine

4.2



R = H Deoxyribonucleoside
R = OH Ribonucleoside

4.3

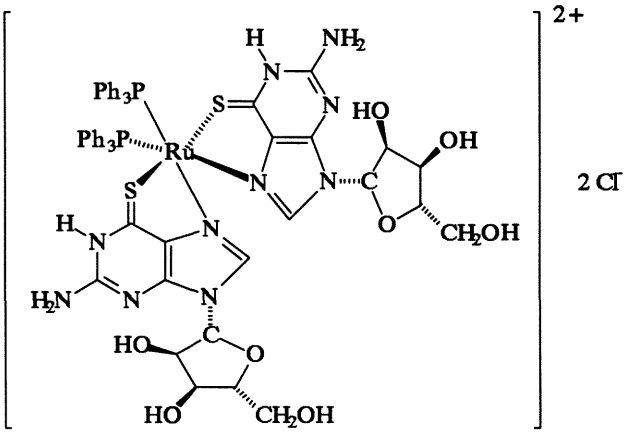


R = H Deoxyribonucleotide
R = OH Ribonucleotide

4.4

The heterocyclic bases (4.2) have both oxygen and nitrogen atoms which may co-ordinate to metal atoms. Although the ribose and deoxyribose groups (4.3) have possible sites for co-ordination to metal atoms, it is generally accepted that these have the weakest donor groups.[2] The participation of the phosphate group (4.4) in co-ordination to metal atoms has been well documented in previous reviews.[3,4] However, the co-ordination sites of the heterocyclic bases play the most important role in determining the interactions between metal atoms and nucleic acids. Studies involving the reactions and interactions of metal ions and metal complexes with nucleobases have been largely associated with the possibility of tumour-inhibiting activity being shown *in vitro* and these complexes were reviewed in Chapter one. The tumour-inhibiting properties of cisplatin were established by Rosenberg and these properties were also shown to be present in a number of other platinum complexes.[5,6] The mode of cisplatin binding to guanine bases was discovered at an early stage[3] and it was later proposed that GG and AG intrastrand crosslinks are responsible for the anti-tumour activity observed.[3,4] Further studies have shown that other bifunctional adducts of platinum complexes with protein-DNA crosslinks and interstrand crosslinks (Chapter one) are formed but the relevance of these to the anti-tumour activity are not yet fully established.[7] In figure 4.2, it is apparent that the heterocyclic bases have several potential co-ordination sites. For guanine, it has been established that the N(7) site is the preferred co-ordination site for several metals including Pd, Pt, Au.[8] The co-ordination of certain platinum complexes to the N(7) position of guanine bases is important in the field of anti-tumour drugs (reviewed in Chapter one). Although co-ordination has been shown to occur through N(9) in complexes like $[CuCl_2(guanine)]_2$[9] this site is unavailable in nucleosides and nucleotides and is therefore only of limited importance. Also, chelation of the ligand through both N(7) and O(6) has been proposed by several authors[10,11] on the basis of perturbation of the

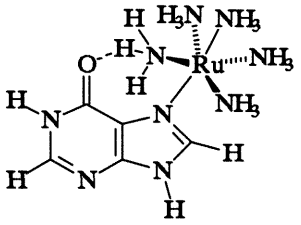
carbonyl stretch observed in the infra-red spectrum. There are several guanosine or 9-alkyl guanine (alkyl = Me, Et) (which can be viewed as a guanosine derivative as the N(9) position is blocked) complexes in the literature in which the N(7) site is implicated in the binding of the metal ion.[13-15] Few metal-nucleoside complexes have been characterised by single crystal X-ray diffraction. Cini and Hursthouse *et al.* have reported the crystal structure of the mercaptopurine complex $[Ru(HMPR)_2(PPh_3)_3]Cl_2 \cdot 2.75H_2O$ (**4.5**) in which the ruthenium ion is chelated by the N(7) and the S(6) atoms.[13]



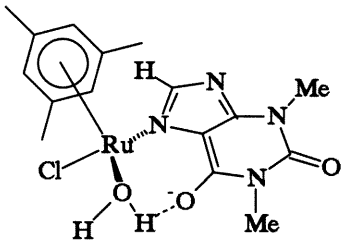
4.5

Chelation through both the N(7) and O(6) atoms has also been observed and characterised crystallographically in the titanium complex with the guanine derivative theophylline $[(Cp)_2Ti(theo)]$.[16] The possibility of intramolecular hydrogen bonding has been found for the complexes $[Ru^{III}(Hyp)(NH_3)_5]Cl_3$[17] and $[(mes)RuCl(theo)(H_2O)]$[18] (**4.6** and **4.7**) in which hydrogen bonding is observed between an ammonia or water ligand respectively and the O(6) atom of the purine base on the basis of the hydrogen-oxygen contact

distances which were found to be ≈2.0 Å.



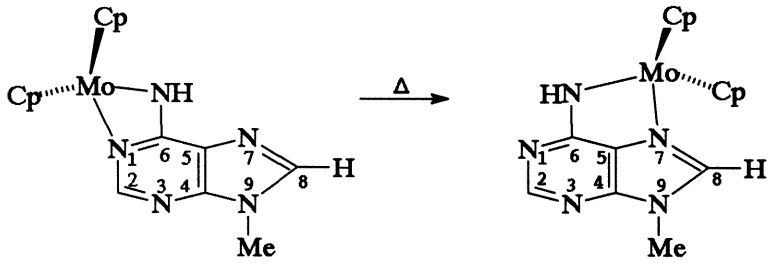
4.6



4.7

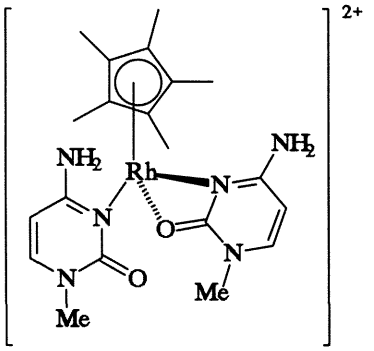
For adenine, both N(7) and N(1) which have similar basicities have been proposed as important sites for metal binding.[19] Although adenine complexes exist with N(9) and N(3) binding[20,21], both these sites are unavailable in nucleoside complexes due to sugar bond formation at N(9) and resultant steric hinderance at N(3). Metals binding at the N(7) and N(1) sites of 5'-methyladenosine include those of Mn, Fe, Ni and Zn in the adducts $[M(L)_2(ClO_4)_2].3EtOH$ (L = 5'-methyladenosine).[19] The formation of a 4 or 5-membered chelate ring involving either N(1) or N(7) with the exocyclic amine group N(6) has been reported.[22] Evidence for the co-ordination of the amine group can often be established by using ^1H n.m.r. spectroscopic techniques. The broadening of the amine proton resonances is attributed to chelation.[2] These spectra are generally observed in DMSO as nitrogen-bound protons are easily exchanged in water above 0 °C.[23] Co-ordination of a deprotonated amine group has been determined crystallographically in the complexes *cis*-$[(PMe_3)_2Pt(\mu\text{-}9\text{-etaden}\{-H^+\})]_2(NO_3)_2$ in which the nucleobase is co-ordinated through the deprotonated amine group N(6) and N(1)[24], whereas $[(Cp)_2Mo(9\text{-meaden}\{-H^+\})][PF_6]$ exists as two isomeric complexes with co-ordination observed through the deprotonated amine group and either N(1) or N(7).[25]

On heating the molybdenum complex, the N(1), N(6) isomer could be converted into the N(7), N(6) isomer (**4.8**).[25]

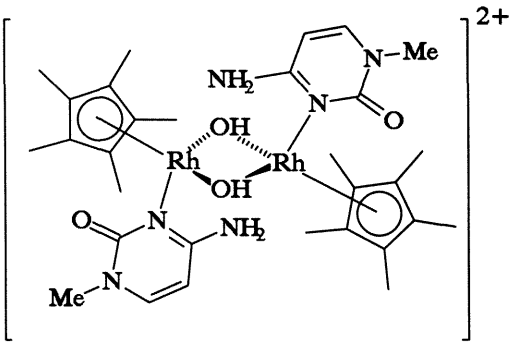


4.8

For cytosine complexes, binding invariably occurs at the N(3) position and this is mirrored in the nucleoside complexes where this site is still available for co-ordination. There are numerous publications indicating N(3) co-ordination to metal centres including the complexes $[Pt(bmik)(1\text{-mecyt})_2](ClO_4)_2 \cdot 1.5H_2O$[26] and $[(C_3H_5)PdCl(cytosine)]$[27]. The complex $[(Cp^*)Rh(N(3)\text{-}1\text{-mecyt})(O(2)N(3)\text{-}1\text{-mecyt})][OTf]_2$ (**4.9**) prepared by Fish *et al.* contains two methylated cytosine ligands (which can be viewed as an analogue of cytidine as the N(1) site is effectively blocked) which have been shown crystallographically to co-ordinate one through the N(3) position only and the other through the O(2) and N(3) positions giving rise to a four-membered ring.[28] The complex isolated depended on the solvent used for crystallisation. Thus, when the complex was crystallised from water instead of acetone a dimeric species $[(Cp^*)Rh(N(3)\text{-}1\text{-mecyt})(\mu\text{-}OH)]_2[OTf]_2$ (**4.10**) was formed which only contained monodentate methylcytosines co-ordinated through the N(3) position.



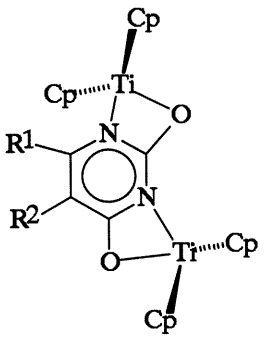
4.9



4.10

For both thymine and uracil, the other pyrimidines, the site N(3) is protonated in the free base and in the nucleoside making co-ordination at this site unfavourable. Deprotonation at this site (forming anions L^-) leads to a vacant site for metal co-

ordination and several complexes have been published in which a metal is co-ordinated at this site.[29,30] Hendrickson and Stucky *et al.*[31] have reported the preparation of the unusual complexes $[(Cp)_2Ti_2(L)]$ (**4.11**) in which two bis-cyclopentadienyl titanium fragments bind to one heterocycle which is deprotonated at both N(1) and N(3).



Complexes $[(Cp)_2Ti_2(L)]$.

a) R^1 = H R^2 = CH_3 L = thyminate.

b) R^1 = CH_3 R^2 = H L = 4-methyluracilate.

c) R^1 = CH_3 R^2 = CH_3 L = 4-methylthyminate.

d) R^1 = H R^2 = F L = 5-fluorouracilate.

4.11

The reaction of nucleosides and nucleotides with metal ions has been reported.[19,32,33] These reactions are used as simple models for the study of metal ions with DNA / RNA strands. There are several studies on the reactions of cisplatin with guanosine and guanosine derivatives.[4,7,34,35,36] The weight of evidence for N(7) co-ordination includes X-ray crystallography of isolated complexes.[36-38]

It has been mentioned previously (see Chapter one) that protein-DNA crosslinks may be important to the anti-tumour activity of metal complexes *in vivo*.[7] Gibson *et al.* have reported the preparation of several ternary Pt^{II} amino acid-nucleotide complexes.[15] The choice of the amino acids (methionine and histidine) reflects the constraint of the metal ion to bind to the amino acid side chain (as is more likely to happen with proteins) and not through the terminal groups. It has been reported by

Sheldrick and Heeb that the complex [(C_6H_6)RuCl(pro)] displays anti-tumour activity towards P388 leukaemia.[39] They have also reported the preparation of the complex [(C_6H_6)Ru(ala)(9-etguan)]Cl in which the 9-ethylguanine ligand co-ordinates through the N(7) position.[39] In the crystal structure, both diastereomers $S_{Ru}S_C$ and $R_{Ru}S_C$ are present in the unit cell in a 50 : 50 ratio. In the ^1H n.m.r. spectrum the equilibrium mixture indicates that the diastereomers exist in a 65 : 35 ratio. On the basis of this slight preference for one diastereomer, it was postulated that this was due to the favourable hydrogen bonding interactions between the amine protons and the O(6) group of the nucleobase in the $R_{Ru}S_C$ diastereomer.[39]

The formation of amino acid-nucleobase complexes has been studied by several authors to determine any selectivity that may be observed.[15,39,40-42] Carter has prepared the nucleoside complexes [(mes)Ru(ala)(nucleoside)]Cl (nucleoside = guanosine, cytidine) in which the complexes also exist as a pair of diastereomers in the ratios 75 : 25 and 70 : 30 respectively.[18] Pneumatikakis has reported the preparation of the complexes [PdCl(pro)(nucleobase)] (nucleobase = inosine, guanosine, cytidine or adenosine).[43] It was deduced from ^1H and ^{13}C n.m.r. data that the purine complexes of inosine and guanosine were co-ordinated through the N(7) atom, while the adenosine ligand co-ordinated through the N(7) and N(1) atoms in a bridging manner. Interestingly, the ^1H n.m.r. data revealed the presence of only one species in solution for each of these complexes even though they contain several chiral groups :- The α-carbon and nitrogen atoms of the prolinate ligand, the palladium metal and the sugar group protons of the nucleobases. It was also reported that these prolinate-nucleobase complexes were found to react further to give the complexes containing anionic nucleobases [Pd(pro)(nucleobase{-H^+})] (nucleobase = inosine, guanosine) for which it was established by IR spectroscopy that the nucleobases are co-ordinated through the

N(7) site and also through the O(6) group which shows a shift to lower frequency 1625 cm^{-1} compared to that of the parent complexes where the absorption appears at 1700 cm^{-1}.[43]

The reactions of amino acidate metal complexes with nucleosides are therefore of interest in terms of the selectivity shown by the complexes for the different nucleosides and for the specific binding sites within a given nucleoside. We have, therefore studied the reactivity of half-sandwich metal complexes with nucleosides and the results are described in this Chapter.

4.1.2 - Results and Discussion.

The complexes in this Chapter were all prepared in a similar manner by the addition of the appropriate nucleobase ligand to a methanol / water solution containing one of the half-sandwich ruthenium or rhodium complexes 1) [(mes)RuCl(phgly)][18] 2) [(mes)RuCl(ala)][44] 3) [(Cp^*)RhCl(ala)][45] 4) [(Cp)RuCl($CO)_2$][46] and 5) [(mes)RuCl(etmalt)][47], [(mes)RuCl(memalt)] and [(Cp^*)RhCl(etmalt)]. All the products prepared are found to be soluble in water but insoluble in chlorinated organic solvents, with the exception of the complex [(Cp)Ru($CO)_2$(theo)] (4.28).

Unfortunately, we were unable to grow crystals suitable for X-ray determination of the complexes formed in this Chapter of the type [(ring)M(nucleoside)(L)][anion] (L = amino acidate, pyranato or dicarbonyl) and therefore the characterisation relies heavily on spectroscopic methods particularly ^1H n.m.r and the change in chemical shifts of the protons of the ligands on co-ordination ($\Delta\delta$).

For the extensively studied co-ordination of platinum to nucleobases the

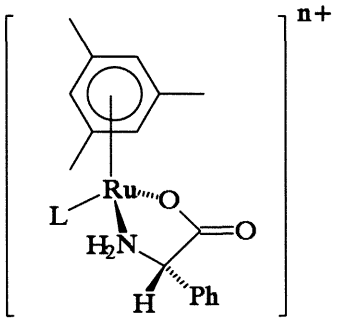
resonances of the proton H(8) in purines are strongly shifted to higher frequency (downfield) (+Δδ) compared to that of the free ligand.[3,4,48] For other metal nucleobase complexes, the shift to higher frequency (+Δδ) upon co-ordination is also reported.[49,50] The table of selected ^{1}H n.m.r. results for the unco-ordinated ligands are presented in Table **4.AA**.

Table 4.AA of Selected ^{1}H n.m.r. Data for the Unco-ordinated Ligands in D_2O.

Nucleobase	H(8)	H(6)	H(5)	H(2)	H(1)
Guanosine[a]	-	-	-	-	-
Guanosine 5'-monophosphate	8.13	-	-	-	5.85
Theophylline[b]	7.84	-	-	-	-
Theophylline	7.97	-	-	-	-
Adenosine	8.33	-	-	8.22	6.06
Cytidine	-	7.83	6.03	-	5.89
Uridine	-	7.87	5.90	-	5.91
Thymidine	-	7.64	6.27	-	6.27

[a] Not sufficiently soluble to obtain spectrum.

[b] Spectrum recorded in $CDCl_3$.



4.12 L = Cl, n = 0

4.13 L = guo, n = 1

4.14 L = 5'-GMP, n = 1

4.15 L = theo, n = 0

4.16 L = ado, n = 1

4.17 L = cyd, n = 1

The reactions of the half-sandwich amino acidate complex [(mes)RuCl(phgly)] (**4.12**)[18] with biological ligands such as nucleobases and the guanine derivative theophylline has been studied to determine the binding sites involved upon co-ordination of the metal to the ligands. In the ^{1}H n.m.r. spectra of these complexes the α-CH proton of the amino acidate ligand is not observed and is presumed to be under the HOD peak. The sugar group protons H(2')-H(5') are observed in similar positions δ 3.68-4.65 (Tables **4.CC** and **4.DD**) for the nucleobase complexes (**4.13**, **4.14**, **4.16** and **4.17**), with the phenyl group protons observed in the region δ 6.55-7.53 for all the complexes (**4.13-4.17**) (Tables **4.CC** and **4.DD**).

The ^{1}H n.m.r. spectrum of [(mes)Ru(phgly)(guo)]Cl (**4.13**) was recorded after work-up. For all these complexes (**4.13-4.17**) in this section, signals due to a minor isomer will be given in brackets following the corresponding signals for the major isomer. The co-ordinated mesitylene ring is observed at δ 2.01(1.98) and 5.22(5.24) as singlets while the proton H(1') occurs as a doublet at δ 5.88(6.02) J = 5 Hz and H(8) as a singlet at δ 8.29(8.32) [Δδ +0.28(+0.31)]. The shift of H(8) can be compared to the value in the unco-ordinated guanosine ligand of δ 8.01 reported by Marzilli and Miller.[34] This gives co-ordination shifts of the proton H(8) to higher frequency,

assigned to co-ordination at the N(7) site.[4,7,34,35,36,51] The two species are present in a 90 : 10 ratio, measured from the average values of the integration of the peaks corresponding to H(8), H(1') and the mesitylene protons which are all well separated on the ^{1}H n.m.r. spectrum. The presence of the two species is due to the presence of both diastereomers with differing chirality at the ruthenium centre (R_{Ru} and S_{Ru}). The reason for such a large preference for one diastereomer is unclear but possible explanations are discussed later.

The ^{1}H n.m.r. spectrum of the complex [(mes)Ru(phgly)(5'-GMP)]Cl (4.14) (Table 4.CC) shows similar resonances to that observed for complex (4.13). The major difference between the two spectra occurs for the H(5') proton of both isomers where coupling to the phosphorus nucleus in complex (4.14) alters the multiplicity observed, resulting in a broad unresolved signal δ 4.08 (2H for each isomer). The proton H(8) is observed at δ 8.25(8.36) [Δδ +0.12(+0.23)] which is a downfield shift from the unco-ordinated ligand indicative of co-ordination at the N(7) site.[4,34,52] A ^{31}P-{^{1}H} spectrum shows the resonance for the phosphorus nucleus is unchanged from that of the unco-ordinated nucleotide (δ 3.61) and this suggests that the phosphate group does not participate in co-ordination. Again, the diastereomer ratio was found to be 90 : 10 as observed in the guanosine complex (4.13).

The ^{1}H n.m.r. spectrum of the complex [(mes)Ru(phgly)(theo)] (4.15) (Table 4.CC) shows the presence of two diastereomers in the ratio 80 : 20, slightly less than that observed for the guanosine complex (4.13). The co-ordinated mesitylene ring and the phenyl group are observed in similar positions to those of complex (4.13). In addition, the two methyl groups of the theophylline occur at δ 3.20(3.33) and 3.45(3.58) whereas H(8) appears at δ 7.98(7.99) [Δδ -0.06(-0.05)]. The appearance of a small amount of unco-ordinated theophylline is observed with the proton H(8) at δ

8.04. An upfield shift of the proton H(8) has been observed in the complex [(mes)RuCl(theo)(H_2O)] [$\Delta\delta$ -0.06] in which the theophylline ligand was found by crystallography to be deprotonated at the N(9) position with the ruthenium bound at the N(7) position.[18] There are several examples in the literature in which the theophylline ligand co-ordinates through the N(7) site and is deprotonated at the N(9) position.[16,53-55] Buncel *et al.* reported the characterisation and crystal structure of the complex [Cd(theo)$_2$(H_2O)$_4$][56] in which the deprotonated theophylline co-ordinates through the N(7) position and hydrogen bonding occurs between the O(6) and co-ordinated water ligands. The ^{1}H n.m.r. spectrum of the cadmium complex indicates an upfield shift of the H(8) proton as expected for the co-ordinated deprotonated theophylline ligand.[56] From the data, it is tentatively assigned that in the complex (4.15) the ligand co-ordinates to the ruthenium centre through the N(7) site and that the ligand is deprotonated in solution.

The ^{1}H n.m.r. spectrum of the complex [(mes)Ru(phgly)(ado)]Cl (4.16) shows the presence of two major species which exist in a 3 : 2 mixture in solution, which due to the small difference in this ratio compared to the complexes previously described (4.13-4.15), suggests that they are not diastereomers. From the spectrum, it is evident that there are a number of other minor peaks, particularly in the co-ordinated mesitylene region and at high frequency (δ 8-9) which are not attributed to starting material and this also suggests that the metal co-ordinates to the nucleoside at more than one binding site. The assignments of the minor diastereomers for both the major species could not be achieved with any certainty due to the presence of unreacted starting complex and nucleoside. The presence of these unreacted starting materials is proposed to be due to an equilibrium between adenosine, water and chloride ligands for the sixth co-ordination site on the metal centre which, from ^{1}H n.m.r. integration

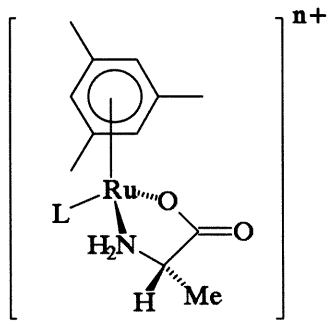
values, lies in favour of the co-ordinated adenosine complexes. This equilibrium suggests that the adenosine ligand forms less stable complexes with [(mes)RuCl(phgly)] than guanosine or theophylline. This observation is explored further in competition experiments later in the Chapter. For the most abundant complex, resonances are observed at the following positions with the values for the secondary species in brackets. Singlets at δ 1.88(1.95) and 5.31(5.35) correspond to the co-ordinated mesitylene ring. The protons H(2) and H(8) are tentatively assigned to the resonances at δ 8.33(8.37) [Δδ +0.11(+0.15)] and 8.97(8.36) [Δδ +0.64(+0.03)] respectively, which are shifted downfield with respect to those of the unco-ordinated adenosine. The H(1') proton is assigned to the doublet at δ 6.16(6.11) with J = 6 Hz. A downfield shift of the proton H(2) has been reported to be due to N(1) co-ordination and, by analogy, a downfield shift of H(8) is indicative of N(7) co-ordination.[43,50,57,58] Thus, for the major species, the large downfield shift of H(8) would suggest the metal is bound at the N(7) site, whilst for the minor species, the larger downfield shift of the H(2) proton and the very small downfield shift (Δδ +0.03) of the H(8) proton suggests that in this complex the metal is bound at the N(1) site. It was found that extending the reaction time had no effect on the resonances observed in the spectrum.

The ^{1}H n.m.r. spectrum from the reaction of cytidine with complex (4.12) indicates the presence of two co-ordinated [(mes)Ru(phgly)(cyd)]$^+$ species (4.17) in solution. The presence of both unco-ordinated starting materials is observed and although the reaction was repeated and the reaction time increased, there was no evidence from subsequent ^{1}H n.m.r. spectra that the ratio of co-ordinated cytidine increased with time as was also the case in the reaction with adenosine (4.16) mentioned above. Resonances due to [(mes)RuCl(phgly)] and [(mes)Ru(phgly)(D_2O)]$^+$ suggest that the cytidine ligand competes with water and chloride for the sixth co-

ordination site on the metal, and that from the ratio of the signals in solution, this equilibrium lies slightly in favour of the co-ordinated cytidine. The resonances for the co-ordinated mesitylene, phenyl and sugar group protons are listed in the experimental section (Table 4.DD). The protons H(6) and H(5) are observed as doublets at δ 7.93(7.97) [Δδ +0.10(+0.14)] and 6.13(6.20) [Δδ +0.10(+0.17)] J = 7.5 Hz for each. The major species is assigned to the complex [(mes)Ru(phgly)(cyd)]Cl in which the nucleoside is co-ordinated through the heterocyclic N(3) atom as the shift to higher frequency of the protons H(5) and H(6) is reported to be due to co-ordination of the metal to the N(3) site.[26,40,43,59-61] The ratio of major to minor species is small, (≈2 : 1), compared to those observed in the complexes $[(mes)Ru(phgly)(L)]^+$ (L = guo 9 : 1, L = 5'-GMP 9 : 1 and theo 8 : 2) and so the two species may not be diastereomers. An alternative explanation is that the two species may be rotational isomers. The occurrence of rotational isomers for 1-methylcytosine complexes has been reported previously by Lippert *et al.*[59], who found that the complex [Pd(gly-his)(1-mecyt)] exists as a pair of rotamers due to hindered rotation about the Pd-N(3) cytosine bond. Heating to 89 °C caused the two sets of resonances to collapse due to rapid nucleobase rotation. A high temperature (55 °C) ^{1}H n.m.r. spectrum of the complex (4.17) in D_2O showed no broadening of the signals for H(5) and H(6) which suggests that there was no interconversion of the two diastereomers at this temperature. The lack of any broadening in the spectrum suggests that the two sets of signals are due to the two diastereomers with differing chirality at the ruthenium and not to rotational isomers. It is observed from the ^{1}H n.m.r. spectrum of (4.17), that at high temperature the ratio of co-ordinated cytidine to unco-ordinated cytidine increases (1 : 1 at 25 °C to 14 : 9 at 55 °C) which indicates that the equilibrium between co-ordinated and unco-ordinated cytidine is displaced in favour of co-ordinated cytidine at higher temperatures.

The ^{1}H n.m.r. spectra from the reactions of either of the two pyrimidine ligands, uridine or thymidine, with [(mes)RuCl(phgly)] indicate the presence of only unreacted [(mes)RuCl(phgly)] and the free nucleoside. These nucleosides have been reported to co-ordinate through the deprotonated heterocyclic nitrogen N(3)[30], η^2 co-ordination from the π-bond of the heterocyclic ring[62] or from the heterocyclic oxygen O(4)[63]. In these reactions, the ^{1}H n.m.r. spectra indicate the presence of water or chloride co-ordinated species only. The reactions were not attempted in the presence of base.

The FAB mass spectra of the complexes (4.13-4.17) indicate the presence of the stable molecular ion corresponding to $[(mes)Ru(phgly)(nucleobase)]^+$. The presence of ions corresponding to $[(mes)Ru(nucleobase)]^+$ and $[(mes)Ru(phgly)]^+$ species due to loss of the amino acidate or nucleobase ligand respectively are also observed in all the spectra (Table 4.HH). Test samples containing mixtures of the complex [(mes)RuCl(phgly)] and the nucleobase ligands were also analysed by FAB mass spectroscopy. These spectra showed the presence of ions assigned as $[(mes)RuCl(phgly)]^+$ and $[(mes)Ru(phgly)]^+$ but there were no ions corresponding to $[(mes)Ru(phgly)(nucleobase)]^+$ which confirms that these amino acidate-nucleobase complexes are formed during the reaction stage and not in the mass spectrum experiment. The microanalyses of the complexes (4.13-4.15) are formulated with the presence of water molecules and for the complex (4.15) the results are consistent with a molecule of HCl present which suggests that the complex may be protonated in the solid state.



4.18 L = Cl, n = 0

4.19 L = theo, n = 0

4.20 L = ado, n = 1

4.21 L = 5'-GMP, n = 1

The reactions of [(mes)RuCl(ala)] (**4.18**)[44] with the ligands theophylline, adenosine and the nucleotide guanosine 5'-monophosphate (5'-GMP) were undertaken to determine any selectivity of these amino acidate complexes for the various nucleobases and the binding site(s) involved upon co-ordination to the metal centre. Comparisons could then be drawn to those of the previously prepared alaninate complexes [(mes)Ru(ala)(nucleoside)]Cl (nucleoside = guanosine, cytidine)[18] and to the corresponding phenyl glycinate complexes (**4.13-4.17**).

The ^{1}H n.m.r. spectrum from the reaction of [(mes)RuCl(ala)] with theophylline indicates the presence of two species in a ≈2 : 1 ratio assigned as co-ordinated [(mes)Ru(ala)(theo)] species (**4.19**). The co-ordinated mesitylene signals are observed at δ 2.02(2.01) and at δ 5.25 for both species. The co-ordinated theophylline signals are observed at δ 3.41(3.36) and 3.58 for the methyl groups although only one of the methyl groups of the minor species is observed, the other methyl signal is under a signal corresponding to unco-ordinated theophylline (δ 3.52). The H(8) proton occurs at δ 7.95(7.97) [Δδ -0.05(-0.03)] as a singlet with an upfield shift compared to that of unco-ordinated theophylline, observed at δ 8.00. The alaninate methyl group is

observed at δ 1.25(0.70) as a doublet J = 7 Hz; the α-CH is observed at δ 2.34 as a quartet J = 7 Hz for the major species, whereas the α-CH is not observed for the minor species and is assumed to be under the signals in the region δ 3.30-3.60. A large difference in chemical shift between the α-CH protons (δ 2.45 and 3.56) of the alaninate ligand has been reported previously by Sheldrick and Heeb[39] for the complex $[(C_6H_6)Ru(ala)(9\text{-etguan})]Cl$. They attributed this to hydrogen bonding between the O(6) and amine groups which restrains the five-membered ring from flipping rapidly giving rise to a distinct difference in the chemical shift of the α-CH proton in the two diastereomers. Their results are concluded from assessing crystal structure data which we have do not have, and so it is difficult to speculate about possible hydrogen bonding within the complex [(mes)Ru(ala)(theo)]. The diastereomer ratio for the two species is found to be ≈2 : 1 and is similar to that found for the corresponding complexes $[(mes)Ru(ala)(nucleoside)]^+$ (nucleoside = guo, cyd) which are 75 : 25 and 70 : 30.[18] From the data, the ruthenium complex is tentatively assigned to be co-ordinated at the N(7) site of the deprotonated theophylline ligand as proposed for the analogous complex [(mes)Ru(phgly)(theo)] (4.15).

The ^1H n.m.r. spectrum from the reaction of adenosine with [(mes)RuCl(ala)] shows the presence of two major species of formula $[(mes)Ru(ala)(ado)]^+$ (4.20). The spectrum also shows the presence of unco-ordinated adenosine and [(mes)RuCl(ala)]. The two major species exist in a ≈2.7 : 1 ratio with the major species assigned as follows with the minor species in brackets. The co-ordinated mesitylene ring is observed at δ 1.99(1.96) and 5.36(5.40) as singlets. The sugar group protons are observed in the region δ 3.84-4.44 with H(1'), a doublet, at δ 6.17(6.18) J = 6 Hz. The protons H(8) and H(2) are observed at δ 8.95(8.91) [Δδ +0.62(+0.58)] and 8.38(8.35) [Δδ +0.16(+0.13)] respectively. The methyl group of the amino acidate

ligand is observed as a doublet, δ 1.29(1.06) J = 7 Hz with the α-CH proton at δ 2.54 as a multiplet. The α-CH proton of the minor species is not observed and is presumed to be under the sugar group signals (δ 3.84-4.44). The ratio of the two species is found to be (73 : 27) and is similar to those of the guanosine and cytidine derivatives.[18] From the data, the large downfield shift of the H(8) signal and small shift of H(2) for both isomers suggests that, in this case, the metal centre is co-ordinated to the adenosine through N(7) in both isomers.[43,50,57] The isomers are, therefore, assigned as the two diastereomers differing in configuration at ruthenium. This is different to the related complex [(mes)Ru(phgly)(ado)]Cl (4.16) in which it was postulated that two species exist with either N(1) or N(7) bound to ruthenium.

The ^{1}H n.m.r. spectrum of [(mes)Ru(ala)(5'-GMP)]Cl (4.21) is similar to that observed for the related complex [(mes)Ru(ala)(guo)]Cl.[18] The mesitylene signals and sugar group protons are observed in the expected positions and are listed in the experimental section (Table 4.EE). The alaninate methyl group is observed as a doublet at δ 1.24(0.74) J = 7 Hz with the α-CH assigned as the multiplet at δ 2.37(3.50). The proton H(8) is observed at δ 8.36 [Δδ +0.23(+0.23)] as a singlet for both diastereomers with a downfield shift of H(8) as expected for N(7) co-ordination.[4,34,52] A $^{31}P-\{^{1}H\}$ spectrum shows the presence of only one resonance at δ 3.41 (Δδ -0.20) and, from the small change in the phosphorus chemical shift, it can be assumed that the phosphate group does not participate in co-ordination[25,34] as observed for the related complex [(mes)Ru(phgly)(5'-GMP)]Cl. The diastereomer ratio for [(mes)Ru(ala)(5'-GMP)]Cl is 80 : 20 which is similar to that found for [(mes)Ru(ala)(guo)]Cl[18], 75 : 25. Sheldrick and Heeb reported that the related complex $[(C_6H_6)Ru(ala)(9\text{-etguan})]Cl$ exists in solution with a diastereomer ratio of 65 : 35.[39]

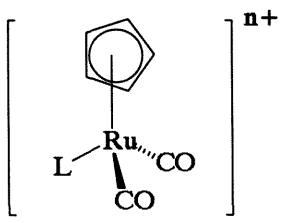
The ^{1}H n.m.r. spectrum from the reaction of complex (4.19)[18] with uridine reveals the presence of resonances assigned to unco-ordinated [(mes)RuCl(ala)] and unco-ordinated nucleoside (δ 7.86 H(6) and δ 5.89 H(5) doublets J = 8 Hz respectively) only, indicating that as observed for the reaction between uridine and [(mes)RuCl(phgly)], this ligand is too weak a donor to co-ordinate in these systems.

The FAB mass spectra of the complexes $[(mes)Ru(ala)(L)]^{n+}$ (L = theo n = 0, L = ado and 5'-GMP n = 1) indicate the presence of the stable molecular ions corresponding to $[(mes)Ru(ala)(nucleobase)]^+$ as is found for the related complexes $[(mes)Ru(phgly)(nucleobase)]^+$. The ions corresponding to $[(mes)Ru(nucleobase)]^+$ and $[(mes)Ru(ala)]^+$ due to loss of the amino acidate and nucleobase ligands respectively are also observed (Table 4.HH).

The complex $[(Cp^*)RhCl(ala)]$[45] (4.23), isoelectronic with [(mes)RuCl(ala)], was reacted with guanosine to compare the reactivity with that of the ruthenium complex. The ^{1}H n.m.r. spectrum of the complex $[(Cp^*)Rh(ala)(guo)]Cl$ (4.24) is similar to the ruthenium analogue [(mes)Ru(ala)(guo)]Cl. The spectrum indicated the presence of some unreacted $[(Cp^*)RhCl(ala)]$ and also some unassigned peaks in the low frequency region (δ 1.50-1.59). The pentamethylcyclopentadienyl signal is observed at δ 1.65(1.63) with the minor diastereomer in parentheses. The co-ordinated guanosine has resonances in the region δ 3.83-4.72 due to the sugar group, a doublet at δ 6.02(6.01) J = 5 Hz due to H(1') whilst the H(8) proton is observed as a singlet, shifted downfield, at δ 8.29(8.33) [Δδ +0.28(+0.32)][34], indicative of N(7) co-ordination.[4,7,34,35,36,51] For the alaninate ligand, the methyl group is observed as a doublet at δ 1.30(0.89) J = 7 Hz and the α-CH proton at δ 2.70(3.63) as an unresolved multiplet. Two broad peaks at δ 5.20 and 5.74 are tentatively assigned as amine protons and coupling between these amine protons and the α-CH proton could account

for the unresolved multiplets observed. It was reported for the ruthenium analogue that the two diastereomers exist in solution in a 75 : 25[18] ratio whereas for the rhodium complex this ratio is 60 : 40. Interestingly, at room temperature the ^{1}H n.m.r. spectrum in D_2O of the rhodium complex [(Cp*)RhCl(ala)] shows the presence of only one set of signals presumably due to a rapid exchange of water and chloride ligands at the rhodium centre which is fast on the n.m.r. timescale. For the corresponding ruthenium complex, water-chloride exchange is slower on the n.m.r. timescale and the respective diastereomers are observed. This difference has been observed previously and is discussed in Chapter three. Co-ordination of the guanosine ligand to either the rhodium or ruthenium complex results in the formation of two diastereomers both of which are observed in the ^{1}H n.m.r. spectra. The observation of both diastereomers suggests that exchange at the metal centre is slowed when the water or chloride ligands are replaced by the more strongly bound guanosine ligand.

The FAB mass spectrum of the complex [(Cp*)Rh(ala)(guo)]Cl (**4.24**) shows ions corresponding to [(Cp*)Rh(ala)(guo)]$^+$, as observed for [(mes)Ru(ala)(guo)]Cl, along with ions corresponding to [(Cp*)Rh(guo)]$^+$ and [(Cp*)Rh(ala)]$^+$ species formed by the loss of the amino acidate or nucleoside ligand respectively.



4.25 L =Cl, n = 0

4.26 L = guo, n = 1

4.27 L = theo, n = 0

4.28 L = ado, n = 1

4.29 L = cyd, n = 1

The half-sandwich complex [(Cp)Ru(CO)$_2$(L)] (**4.25**) originally prepared by

Stone *et al.*[46] is achiral and has been shown to undergo several reactions in which the chloride ligand is displaced by two electron donor ligands L giving rise to complexes of the type $[(Cp)Ru(CO)_2(L)]^+$.[36,46] The reaction of this complex (4.25) with the ligands guanosine, theophylline, adenosine and cytidine has been studied in order to determine the interactions of these biological ligands with the half-sandwich complex. The complexes were prepared by stirring stoichiometric amounts of the ruthenium complex and the individual nucleobases in a water / methanol mixture. After work-up, the reaction products were analysed by ^1H n.m.r., and mass spectroscopy.

The ^1H n.m.r. spectrum of reaction between $[(Cp)RuCl(CO)_2]$ and guanosine indicates the presence of only one species in solution assigned as the complex $[(Cp)Ru(CO)_2(guo)]Cl$ (4.26). The cyclopentadienyl ring is observed as a singlet at δ 5.62. The signals for the sugar protons are listed in the experimental section (Table 4.FF) with H(1') a doublet at δ 5.84, J = 5 Hz and H(8), a singlet at δ 8.39 (Δδ +0.38)[34] shifted downfield. The co-ordination is assumed to be at the N(7) site assigned on the basis of the large downfield shift of H(8).[4,7,34,35,36,51] The presence of only one species is expected for this complex as the ruthenium centre does not become chiral upon co-ordination of the guanosine ligand and all the chiral carbons of the sugar group have a fixed configuration.

The ^1H n.m.r. spectrum of complex $[(Cp)Ru(CO)_2(theo)]$ (4.27) in $CDCl_3$ shows singlets at δ 3.39 and 3.58 assigned to the methyl groups of the theophylline ligand with the proton H(8) observed at δ 7.30 (Δδ -0.54) as a singlet, whilst the cyclopentadienyl signal is observed at δ 5.52. The upfield shift of the proton H(8) is indicative of a shielding effect, which may arise from the deprotonation of the N(9) position of the theophylline ligand to form the anion which can then delocalise the negative charge over the ligand.[18,56] The deprotonation of the N(9) atom in metal

complexes has been observed previously.[16,53-55] The complex is therefore, tentatively assigned to co-ordinate to the N(7) position of theophylline which, from the upfield shift of the proton H(8), is assumed to be deprotonated.

The ^{1}H n.m.r. spectrum of the reaction between adenosine and [(Cp)RuCl(CO)$_2$] indicates the presence of two [(Cp)Ru(ado)(CO)$_2$] species (4.28) in solution in a ratio (8 : 5) which are assigned to the co-ordination of the metal centre to two different binding sites on the adenosine. Unco-ordinated adenosine is observed in the spectrum with the H(2) and H(8) signals shifted upfield at δ 8.16 and 8.32. The resonances for the prominent species are assigned as follows with the resonances for the secondary species in brackets. The cyclopentadienyl ring is observed at δ 5.77(5.78) as a singlet. The proton H(1') occurs as a doublet δ 6.00(6.03), J = 6 Hz for both species, with the remaining sugar group protons in the region δ 3.77-4.40. The signals corresponding to the H(2) and H(8) protons are tentatively assigned as singlets at δ 8.58 (Δδ +0.42) and 8.32 (Δδ 0) respectively for the major species and at 8.23 (Δδ +0.07) and 8.87 (Δδ +0.55) respectively for the minor species. The large downfield shift of either H(2) or H(8) in the two complexes compared to the free ligand is indicative of co-ordination at either the N(1) or N(7) site respectively.[43,50,57,58] For the two complexes formed the major species is assigned to the complex in which the ruthenium is bound at the N(1) position and in the minor species the ruthenium is bound at the N(7) position. The conclusion from these data is in disagreement with that of the adenosine complexes [(mes)Ru(aa)(ado)]Cl (aa = ala, phgly) described earlier in which it is postulated that N(7) is the major binding site.

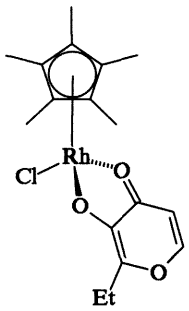
The reaction of cytidine with [(Cp)RuCl(CO)$_2$] gives rise to a complex assigned as [(Cp)Ru(CO)$_2$(cyd)]Cl (4.29) in which the ^{1}H n.m.r. spectrum indicates the presence of only one species in solution, initially. The reaction was monitored by ^{1}H n.m.r.

spectroscopy in which the proton H(6) is a convenient signal to monitor the co-ordination of the ligand. Cytidine was stirred in D_2O until all of the ligand had dissolved and then the complex $[(Cp)RuCl(CO)_2]$ was added. An initial ^1H n.m.r. spectrum after 0.5 hrs indicated the presence of a new doublet at high frequency δ 7.92 J = 7.5 Hz as well as a doublet at δ 7.83 due to the proton H(6) of the unco-ordinated cytidine ligand. The new resonance is attributed to H(6) from a co-ordinated cytidine complex in which the ligand co-ordinates through the heterocyclic N(3) site with new doublets at δ 6.16 J = 7.5 Hz, 5.85 J = 3.5 Hz and a singlet at δ 5.71 are also observed and assigned as the H(5), H(1') and cyclopentadienyl protons respectively. The downfield shift of both H(5) and H(6) has been reported previously as indicative of N(3) co-ordination.[26,40,43,59-61] The ratio of the protons H(6), free ligand to new complex are found to be 21 : 1. The reaction mixture was then recombined and ^1H n.m.r. spectrum was recorded after 2 days, 7 days, 16 days and 22 days. The increase in the size of the signal for the co-ordinated cytidine H(6) proton relative to that of the free ligand was monitored and shows a significant increase with time. In the ^1H n.m.r. spectrum recorded after 2 days, the ratio of free to co-ordinated ligand had changed to ($\approx$4 : 1). The protons corresponding to H(5), H(1') and the cyclopentadienyl ring of $[(Cp)Ru(CO)_2(cyd)]Cl$ are also observed to increase accordingly. After 7 days, the ratio is observed to be (2.75 : 1) and for the spectrum after 16 days the ratio is down to ($\approx$2 : 1). The final ^1H n.m.r. spectrum recorded after a further 6 days (22 days after initial addition) indicates that the new co-ordinated cytidine complex is the dominant species in solution, with the ratio of unco-ordinated to co-ordinated cytidine being 28 : 57 (1 : $\approx$2). The observation of unco-ordinated starting materials in the ^1H n.m.r. spectrum is probably due to the presence of water and chloride ligands competing for the sixth co-ordination site at the metal centre.

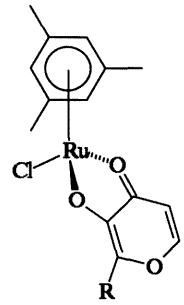
However, the presence of these starting materials may also be due to a slow rate of substitution at ruthenium centre resulting due to the protonation of the co-ordination site of the nucleobase. This may suggest that co-ordination in this system is pH dependant and therefore for these reactions to go to completion buffered solutions will be necessary.

The mass spectra of the complexes (**4.26-4.29**) indicate the presence of the molecular ions corresponding to $[(Cp)Ru(CO)_2(nucleobase)]^{n+}$. Successive loss of the carbonyl groups occur with ions corresponding to $[(Cp)Ru(CO)(nucleobase)]^+$ and $[(Cp)Ru(nucleobase)]^+$ observed (Table **4.HH**).

The corresponding reactions between $[(Cp)RuCl(PPh_3)_2]$ with the ligands guanosine and theophylline were attempted. There is no evidence from ^1H n.m.r., ^{31}P n.m.r. and mass spectral data to suggest the formation of any complex containing a co-ordinated ligand. The steric bulk of the phosphine groups in this ruthenium complex may prevent the ligands from co-ordinating and this represents a difference in the chemistry between the related complexes $[(Cp)RuCl(CO)_2]$ and $[(Cp)RuCl(PPh_3)_2]$.



4.30



4.31 R = Et

4.32 R = Me

The reactions of [(Cp*)RhCl(etmalt)] (4.30) and [(mes)RuCl(L)] (R = Et, L = etmalt (4.31)[47]; R = Me, L = memalt (4.32)) with guanosine were attempted. If the guanosine ligand displaces the chloride ligand the resulting complex formed will have chiral centres at the sugar group (C(1'), C(2'), C(3') and C(4')) and also at the metal centre leading to the formation of diastereomers.

The reaction of [(Cp*)RhCl(etmalt)] (4.30) with guanosine was attempted by stirring the reactants in methanol at room temperature. The pyranato complexes have already been shown in Chapter three to undergo water-chloride exchange indicating that the chloride ligand is labile. Upon preparation of the n.m.r. sample in D_2O a large amount of a white precipitate was observed with the ^1H n.m.r. spectrum of the resulting solution showing the same resonances as are observed for an authentic sample of [(Cp*)RhCl(etmalt)] in D_2O (Chapter three experimental section). The fact that the guanosine dissolves in methanol during the reaction suggests that although the ligand may have co-ordinated in solution initially, the co-ordination is unstable and the ligand is easily displaced.

The reaction between guanosine and the ruthenium analogue [(mes)RuCl(etmalt)][47] (4.31) was attempted, by stirring the reactants in a water / methanol solution at room temperature for three hours, which after filtration and evaporation of the solvents gave a brown solid. The ^1H n.m.r. spectrum showed a complex set of resonances with a singlet at δ 8.36 and a doublet at δ 6.60 J = 5 Hz assigned to co-ordinated guanosine protons H(8) and H(1') respectively. The ^1H n.m.r. spectrum also contained signals due to the starting complex [(mes)RuCl(etmalt)] plus numerous other peaks in the high frequency region (δ 7.8-8.4) that are, at present, unassigned. Attempts at recrystallisation from water / methanol and methanol / diethyl ether solution led to the precipitation of a white solid and a ^1H n.m.r. spectrum of the

brown solid obtained after work-up indicated the presence of signals in agreement with an authentic sample of [(mes)RuCl(etmalt)][47]. Further attempts to isolate a pure compound have proved ineffective.

A similar reaction of guanosine with [(mes)RuCl(memalt)] (4.32) resulted in the formation of a brown solid after work-up. Two isomers are observed in the ^1H n.m.r. spectrum which shows the presence of the co-ordinated mesitylene ring signals at δ 2.08(18H) and 5.22(6H) as singlets with the sugar group protons H(2')-H(5') in the region δ 3.72-4.54(10H) as a complex set of multiplets. The H(1') proton for each isomer is observed as a pair of doublets, δ 5.81(1H) and 5.84(1H) J = 5 Hz respectively, whereas H(8) is observed at δ 7.98(2H) as a singlet. The ring protons for the methyl maltol ligand are observed at δ 6.50(2H) as a doublet J = 5 Hz for H^a, and H^b at δ 7.75(2H) as two very closely spaced doublets, J = 5 Hz. The heterocyclic methyl group is observed at δ 2.36(3H) and 2.37(3H) for each isomer. Although crystals suitable for X-ray determination could not be grown there exists the possibility of "through space coupling" between the sugar group protons and the methyl maltol ring protons. A 2D COSY spectrum reveals that coupling exists between the methyl maltol protons H^a and H^b and between the protons of the sugar group as is expected, but no additional coupling was observed. A ^{13}C spectrum (proton decoupled) indicated the presence of two sets of signals in approximately equal proportions. From the data obtained, it was assumed that both diastereomers of the complex [(mes)Ru(memalt)(guo)]Cl (4.33) with differing configuration at the ruthenium are present with the ruthenium bound at the N(7) site. The observation of only one set of resonances for the co-ordinated mesitylene protons, H(8) and methyl maltol proton H^a are presumably due to co-incident chemical shifts of the protons.

The mass spectrum indicates the presence of ions at m/e 630, 540 and 347

assigned as [(mes)Ru(memalt)(guo)]$^+$, [(mes)RuCl(guo)]$^+$ and [(mes)Ru(memalt)]$^+$.

Diastereomer Ratios.

A table of diastereomer ratios for the half-sandwich amino acidate complexes with their guanosine adducts is presented to illustrate the difference between the complexes in solution when a guanosine ligand is co-ordinated in place of a chloride (Table **4.BB**).

Table 4.BB of Diastereomer Ratios of Related Guanosine and Chloride Complexes in D_2O.

Complex	Major Diastereomer	Minor Diastereomer
[(mes)RuCl(phgly)] (**4.12**)[a,b]	60	40
[(mes)RuCl(ala)] (**4.18**)[a,c]	60	40
[(Cp^*)RhCl(ala)] (**4.23**)[a,d]	50	50
[(mes)Ru(phgly)(guo)]Cl (**4.13**)	90	10
[(mes)Ru(ala)(guo)]Cl (**4.34**)[b]	75	25
[(Cp^*)Rh(ala)(guo)]Cl (**4.24**)	60	40

[a] Refers to the chloride diastereomers only.

[b] Reference 18.

[c] Reference 44.

[d] Reference 45.

From the table of data, it is clear that there is a change in the diastereomer ratios going from the chloride to the guanosine co-ordinated molecules. This change is most noticeable in the complexes [(mes)RuCl(phgly)][18] (**4.12**) and

[(mes)Ru(phgly)(guo)]Cl (4.13) where the diastereomer ratios are 60 : 40 and 90 : 10 respectively. The large difference between the two values may be attributed to a number of possibilities. Intramolecular attraction and repulsions may give rise to a preference for one diastereomer and although X-ray quality crystals could not be obtained for complex (4.13), simple molecular models suggest that in the $R_{Ru}S_C$ diastereomer there is the possibility of intramolecular hydrogen bonding between the O(6) atom of the heterocyclic base and one amine proton of the phenyl glycinate ligand. The phenyl group however, points towards the guanosine ligand in this model which may give rise to unfavourable steric interactions. A model of the $S_{Ru}S_C$ indicates that the phenyl group of the amino acidate ligand points away from the guanosine ligand with no possibility of steric interactions between these two ligands. There is, however, no evidence from the model for intramolecular hydrogen bonding between the O(6) and the amine group. In the report by Sheldrick and Heeb[39] they observe hydrogen bonding in the crystal structure of $[(C_6H_6)RuCl(ala)]$ between the chloride and amine atoms in the $S_{Ru}S_C$ diastereomer. Upon co-ordination of the nucleobase 9-ethylguanine to form $[(C_6H_6)Ru(ala)(9\text{-etguan})]Cl$ the configuration at the ruthenium is reversed and the structural determination indicates hydrogen bonding between the O(6) and amine atoms in the $R_{Ru}S_C$ diastereomer. Their diastereomer ratio in solution, 65 : 35 is assigned to a preference for this diastereomer on the basis of this crystal structure information. The crystal structures of our related complexes [(mes)RuCl(aa)] (aa = ala[44], phgly) indicate no presence of intramolecular hydrogen bonding within these complexes. The two diastereomers of these complexes are present in equal amounts in the crystal structure even though one diastereomer dominates in solution. The data we have is very limited and therefore, interpretation of the diastereomer ratios in solution may include other possibilities which have not

been discussed. We must conclude that, at the present, the factors that affect the diastereomer ratios are not fully understood.

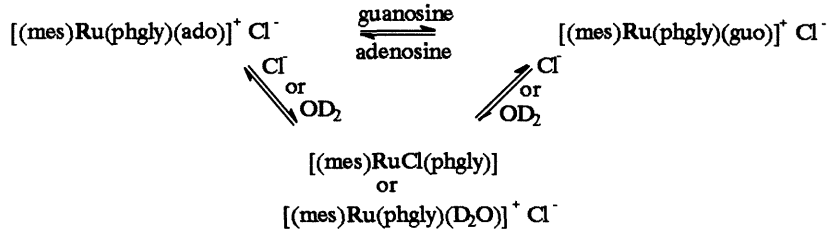
Competition reactions between the nucleobases.

A series of reactions was attempted to determine an order of stability for the nucleobase complexes. In the first set of experiments the complex [(mes)RuCl(phgly)] was introduced into an aqueous solution containing an equivalent amount of two of the ligands adenosine, cytidine, guanosine, theophylline or uridine. The solutions were stirred at room temperature for 3 hrs and ^{1}H n.m.r spectroscopy was used to determine the relative proportions of each complex formed. In each case, the ^{1}H n.m.r spectrum indicates that the guanosine ligand is the best donor and the complex [(mes)Ru(phgly)(guo)]Cl (4.13) is formed exclusively. The signals are the same as observed for an authentic sample of [(mes)Ru(phgly)(guo)]Cl (4.13) (together with signals due to the other unco-ordinated nucleoside). Theophylline is observed to be the next best donor and the exclusive formation of the complex [(mes)Ru(phgly)(theo)] (4.15) is observed when theophylline is in competition with either adenosine, cytidine or uridine. Adenosine is found to be a slightly better donor than cytidine as the ^{1}H n.m.r. spectrum of the competition reaction indicates the presence of co-ordinated adenosine and cytidine peaks in the ratio 2 : 1. However, as with the reactions of adenosine or cytidine with [(mes)RuCl(phgly)], resonances assigned to [(mes)RuCl(phgly)] and [(mes)Ru(phgly)(D_2O)]Cl are also observed, indicating that for both these nucleobases, water and chloride compete as donor ligands for the sixth co-ordination site on the ruthenium. The uridine ligand proved to be the weakest donor and as with the straightforward reaction of uridine with [(mes)RuCl(phgly)] no

complex containing a co-ordinated uridine ligand was observed.

In the second set of experiments the nucleobases (guanosine, theophylline, cytidine and uridine) were added to a D_2O solution of [(mes)Ru(phgly)(ado)]Cl (4.16) at 25 °C to determine whether the adenosine ligand could be displaced by the unco-ordinated nucleobase. The results from these experiments followed a similar pattern to those observed in the first set of experiments. On addition of one equivalent of guanosine, the suspension was stirred at constant temperature for 1 day. The ^1H n.m.r. spectrum of the solution indicates that complete displacement of the adenosine ligand has occurred. Resonances are observed at δ 8.22 and 8.33 due to free adenosine and a set of new resonances at δ 8.29, 5.88, 5.22 and 2.01 corresponding to the protons H(8), H(1') and the co-ordinated mesitylene ring which are in agreement with those of [(mes)Ru(phgly)(guo)]Cl (4.13). The minor guanosine diastereomer is also observed in the ^1H n.m.r. spectrum. From these two sets of experiments, it is evident that the guanosine complex [(mes)Ru(phgly)(guo)]Cl is thermodynamically more stable with respect to the others. The guanine derivative theophylline appears to form the next most stable complexes as on addition of this ligand to a solution containing the adenosine complex (4.16), the ^1H n.m.r. spectrum indicated the exclusive formation of the complex [(mes)Ru(phgly)(theo)] (4.15) with free adenosine also observed. The ^1H n.m.r. spectrum of the reaction between cytidine and the adenosine complex [(mes)Ru(phgly)(ado)]Cl (4.16) indicates a mixture of both co-ordinated adenosine and cytidine species, [(mes)Ru(phgly)(ado)]Cl and [(mes)Ru(phgly)(cyd)]Cl respectively with the integration showing a larger proportion of co-ordinated adenosine to cytidine (≈2 : 1). From this, it can be proposed that the adenosine complex is more stable than the cytidine complex. No evidence of co-ordination of either of the nucleosides thymidine or uridine was observed in the competition experiments as expected. The

^{1}H n.m.r. spectrum of the complexes [(mes)Ru(phgly)(nucleoside)]Cl (nucleoside = adenosine, cytidine) in D_2O reveals the presence of signals attributed to the species [(mes)RuCl(phgly)] and [(mes)Ru(phgly)(D_2O)]Cl which would indicate that there is an equilibrium between these complexes. It is assumed that the exchange of the nucleobases in solution occurs through a dissociative mechanism in which an intermediate species containing a co-ordinated water or chloride ligand exists (scheme **4.35**). These water or chloride ligands are displaced by the second nucleobase as opposed to direct displacement of the adenosine.



Scheme 4.35

The equilibrium for this (scheme **4.35**) appears to lie extensively in favour of the guanosine co-ordinated species. An order of stability can be ascertained from the two sets of data for the formation of nucleobase complexes [(mes)Ru(phgly)(L)] in which the nucleobases are co-ordinated in a monodentate fashion to an arene-ruthenium amino acidate complex which is :-

Guo ≫ Theo ≫ Ado > Cyd ≈ Chloride ≈ Water ≫ Uri ≈ Thy.

This order is in agreement with that found for the order of reactivity in competition experiments of the four nucleotides (GMP, AMP, CMP and UMP) with cisplatin and transplatin which is GMP > AMP > CMP > UMP.[64] This order, however, is different from that established by Lippert *et al.* for the complex [Pd(gly-his)Cl] for which nucleobase competition experiments indicate that the cytidine derivative 1-methylcyt forms more stable complexes than 9-meadenine.[59] The guanine derivative, 9-etguanine, formed the most stable complexes with [Pd(gly-his)Cl] and, as found in our studies, the 1-methyluracil complex was not observed in the ^1H n.m.r. spectrum in D_2O.[59]

For the complexes prepared in this chapter, it is found that guanosine and the guanine derivative theophylline form stable complexes with the complexes [(mes)RuCl(aa)] (aa = ala, phgly) or [(Cp)RuCl(CO)$_2$] with co-ordination occurring through the N(7) site. Co-ordination of [(mes)RuCl(aa)] (aa = ala, phgly) or [(Cp)RuCl(CO)$_2$] to adenosine or cytidine has also been shown to occur, with the N(1) or N(7) sites of adenosine and N(3) of cytidine implicated as the binding sites. From competition experiments it is found that the co-ordination of adenosine or cytidine is weaker than with guanosine or theophylline. From the observations in this chapter, it can be deduced that there is no difference in selectivity for the ancillary ligands and that the preference is governed by the metal. It can be concluded from these studies that DNA can be a possible site of co-ordination for these complexes.

4.1.3 - Experimental.

General experimental techniques were as described in Chapter two. The starting materials guanosine, 5'-guanosine monophosphate, adenosine, theophylline,

cytidine, adenine and tetramethyl ammonium chloride pentahydrate were obtained from Aldrich Chemical Co. Ltd., uridine and thymidine from Lancaster Synthesis Ltd. and all were used without further purification. The complexes [(mes)RuCl(aa)] (aa = phgly, ala)[18,44] and [(mes)RuCl(etmalt)][47] [(Cp^*)RhCl(ala)][45] and [(Cp)RuCl$(CO)_2$][46] were prepared according to the literature methods. [(mes)RuCl(memalt)] and [(Cp^*)RhCl(etmalt)] were synthesised as described in Chapter three.

Reaction of [(mes)RuCl(phgly)] with guanosine (4.13).

Guanosine (34 mg, 0.12 mmol) was added to a methanol / water solution (1 : 1) 30 cm^3 containing [(mes)RuCl(phgly)] (50 mg, 0.12 mmol) and the suspension stirred at room temperature for 2 hrs. The solution was filtered through kieselguhr and the filtrate collected. The solvents were then removed under vacuum to leave a yellow / orange solid [(mes)Ru(phgly)(guo)]Cl (4.13) (yield 82 mg, 89%). The complex was characterised by ^1H n.m.r., mass spectroscopy and microanalysis (Tables 4.CC, 4.GG and 4.HH). ^{13}C-{^1H} n.m.r. (major diastereomer only) :- δ 20.14 [C_6Me_3]; 61.20 [C(5')]; 72.50 [C(4')]; 76.82 [C(3')]; 78.10 [C_6Me_3]; 88.00 [C(2')]; 91.16 [αC-H]; 107.52 [C_6H_3]; 119.02 [C(1')]; 129.20-186.96 [C_6H_5 (Ph), C2, C4, C5, C6, C8, CO_2^-].

Reaction of [(mes)RuCl(phgly)] with guanosine 5'-monophosphate (4.14).

Guanosine 5'-monophosphate (55 mg, 0.12 mmol) was added to a methanol / water solution (1 : 1) 30 cm^3 containing [(mes)RuCl(phgly)] (50 mg, 0.12 mmol) and the suspension stirred at room temperature for 2 hrs. Work-up was as described for complex (4.13) and yielded an orange / yellow solid [(mes)Ru(phgly)(5'-GMP)]Cl (4.14) (yield 94 mg, 90%). The complex was characterised by ^1H n.m.r., mass spectroscopy and microanalysis (Tables 4.CC, 4.GG and 4.HH). ^{31}P-{^1H} (D_2O):- δ

3.06.

Reaction of [(mes)RuCl(phgly)] with theophylline (4.15).

Theophylline (22 mg, 0.12 mmol) was added to a methanol / water solution (1 : 1) 30 cm^3 containing [(mes)RuCl(phgly)] (50 mg, 0.12 mmol) and the suspension stirred at room temperature for 3 hrs. Work-up was as described for complex (4.13) and yielded an orange / yellow solid [(mes)Ru(phgly)(theo)] (4.15) (yield 61 mg, 86%). The complex was characterised by ^1H n.m.r., mass spectroscopy and microanalysis (Tables 4.CC, 4.GG and 4.HH).

Reaction of [(mes)RuCl(phgly)] with adenosine (4.16).

Adenosine (32 mg, 0.12 mmol) was added to a methanol / water solution (1 : 1) 30 cm^3 containing [(mes)RuCl(phgly) (50 mg, 0.12 mmol) and the suspension stirred at room temperature for 3 hrs. Work-up was as described for complex (4.13) and yielded an orange / yellow solid [(mes)Ru(phgly)(ado)]Cl (4.16). The complex was characterised by ^1H n.m.r. and mass spectroscopy (see Tables 4.DD and 4.GG).

Reaction of [(mes)RuCl(phgly)] with cytidine (4.17).

Cytidine (29 mg, 0.12 mmol) was added to a methanol / water solution containing (1 : 1) 30 cm^3 [(mes)RuCl(phgly)] (50 mg, 0.12 mmol) and the suspension stirred at room temperature for 3 hrs. Work-up was as described for complex (4.13) and yielded an orange / yellow [(mes)Ru(phgly)(cyd)]Cl (4.17). The complex was characterised by ^1H n.m.r. and mass spectroscopy (Tables 4.DD and 4.GG).

Reaction of [(mes)RuCl(phgly)] with uridine or thymidine.

Uridine (30 mg, 0.12 mmol) or thymidine (30 mg, 0.12 mmol) was added to a methanol / water solution (1 : 1) 30 cm^3 containing [(mes)RuCl(phgly)] (50 mg, 0.12 mmol) and the suspension refluxed for 2 hrs. After cooling, the solution was filtered through kieselguhr and the filtrate collected and the solvents were removed under vacuum. The ^1H n.m.r. spectra show starting materials only.

Reaction of [(mes)RuCl(ala)] with theophylline (4.19).

Theophylline (26 mg, 0.15 mmol) was added to a methanol / water solution (1 : 1) 30 cm^3 containing [(mes)RuCl(ala)] (50 mg, 0.15 mmol) and the suspension stirred at room temperature for 4 hrs. After filtration through kieselguhr the filtrate was collected and the solvents removed under vacuum. The solid was dissolved in methanol and filtered again through kieselguhr. The filtrate was collected and evaporation of the solvent yielded a brown solid [(mes)Ru(ala)(theo)] (4.19) (yield 69 mg, 91%). The complex was characterised by ^1H n.m.r., mass spectroscopy and microanalysis (Tables 4.EE, 4.GG and 4.HH).

Reaction of [(mes)RuCl(ala)] with adenosine (4.20).

Adenosine (39 mg, 0.15 mmol) was added to a methanol / water solution (1 : 1) 30 cm^3 containing [(mes)RuCl(ala)] (50 mg, 0.15 mmol) and the suspension stirred at room temperature for 3 hrs. Work-up was as described for complex (4.19) and yielded a brown solid [(mes)Ru(ala)(ado)]Cl (4.20). The complex was characterised by ^1H n.m.r. and mass spectroscopy (Tables 4.EE and 4.GG).

Reaction of [(mes)RuCl(ala)] with guanosine 5'-monophosphate (4.21).

Guanosine 5'-monophosphate (67 mg, 0.15 mmol) was added to a methanol / water solution (1 : 1) 30 cm^3 containing [(mes)RuCl(ala)] (50 mg, 0.15 mmol) and the suspension stirred at room temperature for 4.5 hrs. Work-up was as described for complex (4.19) to yield a yellow / green solid [(mes)Ru(ala)(5'-GMP)]Cl (4.21) (yield 106 mg, 91%). The complex was characterised by ^1H n.m.r., mass spectroscopy and microanalysis (Tables 4.EE, 4.GG and 4.HH). $^{31}P-\{^1H\}$ (D_2O):- δ 3.43

Reaction of [(Cp*)RhCl(ala)] with guanosine (4.24).

Guanosine (40 mg, 0.14 mmol) was added to [(Cp*)RhCl(ala)] (50 mg, 0.14 mmol) in of methanol 30 cm^3 and stirred at room temperature for 3 hrs. After filtration, the filtrate was collected and dried under vacuum. The orange solid was redissolved in water and washed twice with dichloromethane (10 cm^3). The aqueous layer was separated and the solvent removed under vacuum to yield an orange solid [(Cp*)Rh(ala)(guo)]Cl (4.24) (yield 81 mg, 90%). ^1H n.m.r. :- (major diastereomer) δ 1.30 [d, 3H, αC-Me J(7)]; 1.65 [s, 15H, Cp*]; 2.70 [q, 1H, α-CH J(7)]; 3.83-4.72 [m, 5H, H(2')-H(5')]; 5.20 [m, 1H, N-H]; 5.74 [m, 1H, N-H]; 6.02 [d, 1H, H(1') J(5)]; 8.29 [s, 1H, H(8)]; (minor diastereomer) δ 0.89 [d, 3H, αC-Me J(7)]; 1.63 [s, 15H, Cp*]; 3.63 [q, 1H, α-CH J(7)]; 3.83-4.72 [m, 5H, H(2')-H(5')]; 5.20 [m, 1H, N-H]; 5.74 [m, 1H, N-H]; 6.01 [d, 1H, H(1') J(5)]; 8.33 [s, 1H, H(8)].

Reaction of [(Cp)RuCl(CO)$_2$] with guanosine (4.26).

Guanosine (54 mg, 0.19 mmol) was added to [(Cp)RuCl(CO)$_2$] (50 mg, 0.19 mmol) to a methanol / water solution (1 : 1) 30 cm^3 and the suspension stirred at room temperature for 3 hrs. The solution was filtered through kieselguhr and the filtrate collected and the solvents removed under vacuum. The green solid was then

redissolved in water and extracted with dichloromethane. The aqueous layer was separated and the solvent removed under vacuum to yield a green solid [(Cp)Ru(CO)$_2$(guo)]Cl (4.26) (yield 87 mg, 84%). The complex was characterised by ^{1}H n.m.r., mass spectroscopy and microanalysis (Tables 4.FF, 4.GG and 4.HH). ^{13}C-{^{1}H} n.m.r. :- δ 63.13 [C(5')]; 72.10 [C(4')]; 76.45 [C(3')]; 87.72 [C(2')]; 91.04 [C_5H_5]; 91.34 [C(1')]; 119.36 [C5]; 146.75-198.43 [C2, C4, C6, C8, (CO)$_2$].

Reaction of [(Cp)RuCl(CO)$_2$] with theophylline (4.27).

Theophylline (34 mg, 0.19 mmol) was added to [(Cp)RuCl(CO)$_2$] (50 mg, 0.19 mmol) in a methanol / water solution (1 : 1) 30 cm^3 and the suspension stirred at room temperature for 3 hrs. Further work-up was as described for complex (4.26) and yielded a green solid was obtained [(Cp)Ru(CO)$_2$(theo)] (4.27) (yield 34 mg, 41%). The complex was characterised by ^{1}H n.m.r., mass spectroscopy and microanalysis (Tables 4.FF, 4.GG and 4.HH).

Reaction of [(Cp)RuCl(CO)$_2$] with adenosine (4.28).

Adenosine (240 mg, 0.9 mmol) was added to [(Cp)RuCl(CO)$_2$] (262 mg, 1.02 mmol) to a methanol / water solution (1 : 1) 30 cm^3 and the suspension stirred at room temperature for 4 hrs. Further work-up was as described for complex (4.26) and yielded a green solid was obtained [(Cp)Ru(CO)$_2$(ado)]Cl (4.28). The complex was characterised by ^{1}H n.m.r. and mass spectroscopy (Tables 4.FF and 4.GG).

Reaction of [(Cp)RuCl(CO)$_2$] with cytidine (4.29).

Cytidine (46 mg, 0.19 mmol) was added to [(Cp)RuCl(CO)$_2$] (50 mg, 0.19 mmol) in 10 cm^3 of D_2O and stirred at room temperature. The reaction was monitored by ^{1}H

n.m.r. spectroscopy (see results and discussion). The complex was characterised by ^1H n.m.r. and mass spectroscopy (Tables 4.FF and 4.GG).

Reaction of [(mes)RuCl(memalt)]with guanosine (4.33).

Guanosine (37 mg, 0.13 mmol) was added to [(mes)RuCl(memalt)] (50 mg, 0.13 mmol) in a methanol / water solution (1 : 1) 30 cm^3 and the suspension refluxed for 3 hrs. After cooling the orange / brown solution was filtered and the filtrate collected. The solvents were evaporated and the residual solid was washed with dichloromethane 10 cm^3. The solution was filtered and the filter collected by washing with methanol / water (1 : 1) 20 cm^3. The solvents were evaporated under vacuum to yield a brown solid [(mes)Ru(memalt)(guo)]Cl (4.33) (yield 69 mg, 80%). ^1H n.m.r. (D_2O) :- δ 2.08 [s, 18H, C_6Me_3]; 2.36 [s, 3H, Me]; 2.37 [s, 3H, Me]; 3.72-4.54 [m, 10H, H(2')-H(5')]; 5.22 [s, 6H, C_6H_3]; 5.81 [d, 1H, H(1') J(5)]; 5.84 [d, 1H, H(1') J(5.5)]; 6.50 [d, 2H, H^a J(4.5)]; 7.75 [m, 2H, H^b]; 7.98 [s, 2H, H(8)]. $^{13}C-\{^1H\}$ n.m.r. :- δ 16.70 [Me]; 16.79 [Me]; 20.27 [C_6Me_3]; 20.53 [C_6Me_3]; 63.55 [C(5')]; 63.68 [C(5')]; 72.63 [C(4')]; 72.88 [C(4')]; 75.03 [C(3')]; 76.68 [C_6H_3]; 76.78 [C_6H_3]; 88.00 [C(1')]; 88.19 [C(1')]; 90.45 [C-H^a]; 90.92 [C-H^a]; 105.37 [C_3Me_3]; 105.44 [C_3Me_3]; 112.95 [C-H^b]; 117.60 [C(5)]; [141.39-184.63 [(C2, C4, C6, C8 Guo), (C2, C3, C4 Memalt)].

Competition reactions between the nucleobases for the complex [(mes)RuCl(phgly)].

Two nucleobases were added to D_2O 5 cm^3, and stirred until all the ligands had dissolved (warmed if necessary) then a stoichiometric amount of the complex [(mes)RuCl(phgly)] was added and the solution stirred for 3 hrs, after which a sample 0.5 cm^3, was removed and the ^1H n.m.r. spectrum recorded.

Competition reactions of the nucleobases with adenosine for the complex [(mes)Ru(phgly)(aden)]Cl.

The complex [(mes)Ru(phgly)(ado)]Cl (4.16) and a stoichiometric amount of a second nucleobase were added to D_2O 3 cm^3 and the suspension degassed several times. The suspension was stirred for 24 hrs at 25 °C after which a sample ≈0.5 cm^3 was removed and the ^1H n.m.r. spectrum recorded.

Table 4.CC of ^{1}H n.m.r Spectroscopic Data in D_2O for complexes [(mes)Ru(phgly)(nucleobases)]Cl 4.13-4.15.

Complex	Species	Ring Protons (δ)		Other Signals (ppm) [multiplicity, assignment]
		C_6Me_3	C_6H_3	
[(mes)Ru(phgly)(guo)]Cl **4.13**	Major	2.01	5.22	3.85-4.65 [m, 5H, **H(2')-H(5')**]; 5.88 [d, 1H, **H(1')** J(5)]; 6.62-7.49 [m, 5H, **Ph**]; 8.29 [s, 1H, **H(8)**].
	Minor	1.98	5.24	3.85-4.65 [m, 5H, **H(2')-H(5')**]; 6.02 [d, 1H, **H(1')** J(5)]; 6.62-7.49 [m, 5H, **Ph**]; 8.32 [s, 1H, **H(8)**].
[(mes)Ru(phgly)(5'-GMP)]Cl **4.14**	Major	2.01	5.26	4.01-4.61 [m, 5H, **H(2')-H(5')**]; 5.85 [d, 1H, **H(1')** J(6)]; 6.57-7.45 [m, 5H, **Ph**]; 8.25 [s, 1H, **H(8)**].
	Minor	1.98	5.28	4.01-4.61 [m, 5H, **H(2')-H(5')**]; 5.98 [d, 1H, **H(1')** J(7)]; 6.57-7.45 [m, 5H, **Ph**]; 8.36 [s, 1H, **H(8)**].
[(mes)Ru(phgly)(theo)] **4.15**	Major	2.03	5.24	3.20 [s, 3H, CH_3]; 3.45 [s, 3H, CH_3]; 6.63-7.48 [m, 5H, **Ph**]; 7.98 [s, 1H, **H(8)**].
	Minor	1.98	5.22	3.33 [s, 3H, CH_3]; 3.58 [s, 3H, CH_3]; 6.63-7.48 [m, 5H, **Ph**]; 7.99 [s, 1H, **H(8)**].

Table 4.DD of ^{1}H n.m.r Spectroscopic Data for complexes 4.16-4.17.

Complex	Species	Ring Protons (δ)		Other Peaks (ppm) [multiplicity, assignment]
		C_6Me_3	C_6H_3	
[(mes)Ru(phgly)(ado)]Cl **4.16**	Major	1.88	5.31	3.68-4.44 [m, 5H, **H(2')-H(5')**]; 6.16 [d, 1H, **H(1')** J(5)]; 6.55-7.48 [m, 5H, **Ph**]; 8.33 [s, 1H, **H(2)**]; 8.97 [s, 1H, **H(8)**].
	Minor	1.95	5.35	3.68-4.44 [m, 5H, **H(2')-H(5')**]; 6.11 [d, 1H, **H(1')** J(6)]; 6.55-7.48 [m, 5H, **Ph**]; 8.37 [s, 1H, **H(2)**]; 8.36 [s, 1H, **H(8)**].
[(mes)Ru(phgly)(cyd)]Cl **4.17**	Major	2.11	5.32	3.76-4.32 [m, 5H, **H(2')-H(5')**]; 5.98 [d, 1H, **H(1')** J(4)]; 6.13 [d, 1H, **H(5)** J(7.5)]; 6.89-7.53 [m, 5H, **Ph**]; 7.93 [d, 1H, **H(6)** J(7.5)].
	Minor	2.05	5.27	3.76-4.32 [m, 5H, **H(2')-H(5')**]; 6.20 [d, 1H, **H(5)** J(7.5)]; 6.89-7.53 [m, 5H, **Ph**]; 7.97 [d, 1H, **H(6)** J(7.5)].

Table 4.EE of ^{1}H n.m.r. Spectroscopic Data in D_2O for complexes 4.19-4.21.

Complex	Species	Ring Protons (δ)		Other signals (ppm) [multiplicity, assignment].
		C_6Me_3	C_6H_3	
[(mes)Ru(ala)(theo)] **4.19**	Major	2.02	5.25	1.25 [d, 3H, αC-**Me** J(7)]; 2.34 [q, 1H, αC-**H** J(7)]; 3.41 [s, 3H, **Me**]; 3.58 [s, 3H, **Me**]; 7.95 [s, 1H, **H(8)**].
	Minor	2.01	5.25	0.72 [d, 3H, αC-**Me** J(7)]; 3.36 [s, 3H, **Me**]; 3.52 [s, 3H, **Me**]; 7.97 [s, 1H, **H(8)**].
[(mes)Ru(ala)(ado)]Cl **4.20**	Major	1.99	5.36	1.29 [d, 3H, αC-**Me** J(7)]; 2.54 [m, 1H, αC-**H**]; 3.84-4.44 [m, 5H, **H(2')-H(5')**]; 6.17 [d, 1H, **H(1')** J(5)]; 8.38 [s, 1H, **H(2)**] 8.95 [s, 1H, **H(8)**].
	Minor	1.96	5.40	1.06 [d, 3H, αC-**Me** J(7)]; 3.84-4.44 [m, 5H, **H(2')-H(5')**]; 6.18 [d, 1H, **H(1')** J(5)]; 8.35 [s, 1H, **H(2)**]; 8.91 [s, 1H, **H(8)**].
[(mes)Ru(ala)(5'-GMP)]Cl **4.21**	Major	2.02	5.29	1.24 [d, 3H, αC-**Me** J(7)]; 2.37 [m, 1H, αC-**H**]; 4.01-4.50 [m, 5H, **H(2')-H(5')**]; 5.95 [d, 1H, **H(1')** J(6.5)]; 8.36 [s, 1H, **H(8)**].
	Minor	2.01	5.28	0.74 [d, 3H, αC-**H** J(7)]; 3.50 [m, 1H, αC-**H**]; 4.01-4.50 [m, 5H, **H(2')-H(5')**]; 5.94 [d, 1H, **H(1')** J(6.5)]; 8.36 [s, 1H, **H(8)**].

Table 4.FF of ^{1}H n.m.r. Spectroscopic Data in D_2O for complexes 4.26-4.29.

Complex	Cp Signal	Other signals [multiplicity, assignment].
[(Cp)Ru(CO)$_2$(guo)]Cl	5.62	3.86 [d of q, 2H, **H(5')** $J_{H4'-H5'}$(3.5), $J_{H5'-H5'}$(13)]; 4.18 [m, 1H, **H(4')**]; 4.37 [t, 1H, **H(3')** $J_{H2'-H3'}$(5), $J_{H4'-H2'}$(5)]; 4.60 [t, 1H, **H(2')** $J_{H1'-H2'}$(4.5), $J_{H3'-H2'}$(5)]; 5.84 [d, 1H, **H(1')** J(4.5)]; 8.39 [s, 1H, **H(8)**].
[(Cp)Ru(CO)$_2$(theo)][a]	5.52	3.39 [s, 3H, **Me**]; 3.58 [s, 3H, **Me**]; 7.30 [s, 1H, **H(8)**].
[(Cp)Ru(CO)$_2$(ado)]Cl[b]	5.77	3.77-4.40 [m, 5H, **H(2')-H(5')**]; 6.00 [d, 1H, **H(1')** J(6)]; 8.58 [s, 1H, **H(2)**]; 8.32 [s, 1H, **H(8)**].
[(Cp)Ru(CO)$_2$(ado)]Cl[c]	5.78	3.77-4.40 [m, 5H, **H(2')-H(5')**]; 6.03 [d, 1H, **H(1')** J(5)]; 8.23 [s, 1H, **H(2)**]; 8.87 [s, 1H, **H(8)**].
[(Cp)Ru(CO)$_2$(cyd)]Cl	5.71	3.78-4.32 [m, 5H, **H(2')-H(5')**]; 5.85 [d, 1H, **H(1')** J(3.5)]; 6.16 [d, 1H, **H(5)** J(7.5)]; 7.92 [d, 1H, **H(6)** J(7.5)].

[a] refers to spectrum in $CDCl_3$.

[b] refers to the major species.

[c] refers to the minor species.

Table 4.GG of Mass Spectroscopy Results.

Complex	$[M]^+$	Other Peaks
4.13	655	$[M\text{-base}]^+$ 372; $[M\text{-phgly}\{-H\}]^+$ 504
4.14	734[a]	$[M\text{-Na-phgly}]^+$ 606; $[M\text{-base}]^+$ 372
4.15	552	$[M\text{-base}\{-H\}]^+$ 371; $[M\text{-phgly}\{-H\}]^+$ 401
4.16	639	$[M\text{-base}]^+$ 372; $[M\text{-phgly}\{-H\}]^+$ 488
4.17	615	$[M\text{-base}]^+$ 372; $[M\text{-phgly}\{-H\}]^+$ 464
4.19	490	$[M\text{-base}\{-3H\}]^+$ 307; $[M\text{-ala}\{-H\}]^+$ 401
4.20	577	$[M\text{-base}]^+$ 310; $[M\text{-ala}\{-H\}]^+$ 488
4.21	673[b]	$[M\text{-ala}]^+$ 584
4.24	609	$[M\text{-base}]^+$ 326; $[M\text{-ala}\{-H\}]^+$ 520
4.26	507[a]	$[M\text{-CO}\{+H\}]^+$ 479; $[M\text{-2CO}\{+H\}]^+$ 451
4.27	403	$[M\text{-CO}]^+$ 375; $[M\text{-2CO}]^+$ 347
4.28	490	$[M\text{-CO}]^+$ 462; $[M\text{-2CO}]^+$ 434
4.29	466	$[M\text{-CO}]^+$ 438; $[M\text{-2CO}]^+$ 410
4.33	630	$[M\text{-base}]^+$ 347; $[M\text{-memalt}]^+$ 505

[a] refers to $[M+H]^+$ molecular ion.

[b] refers to $[M+2H]^+$ molecular ion.

Table 4.HH of Elemental Analyses.

Complex	Expected (%)			Found (%)		
	C	H	N	C	H	N
4.13[a]	43.57	5.28	11.29	44.11	5.21	11.43
4.14[b]	38.10	4.38	9.87	37.68	3.71	9.43
4.15[c]	48.35	4.90	11.74	48.14	4.94	11.30
4.19[d]	43.55	4.81	13.37	42.96	4.90	13.19
4.21[e]	33.53	4.35	10.67	33.38	4.48	10.61
4.24[f]	41.11	5.55	12.51	40.72	5.62	12.37
4.26[g]	35.95	3.46	12.33	35.81	3.52	12.69
4.27[d]	38.41	2.99	12.80	38.61	2.55	12.89
4.33[a]	42.28	4.97	9.86	42.18	5.08	9.29

[a] includes 2.5 moles of water.

[b] includes 3 moles of water.

[c] includes 1 mole of HCl and 0.5 moles of water.

[d] includes 1 mole of HCl.

[e] includes 2 moles of water.

[f] includes 1.5 moles of water.

[g] includes 1 mole of water.

4.1.4 - References.

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