

*Arene-Ruthenium(II) Complexes of
Amines and some Biologically
Important Ligands.*

Thesis submitted for the Degree of
Doctor of Philosophy

by

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in the
Department of Chemistry
of the
Faculty of Science
at the
University of Leicester



January 1994

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For My Parents

TITLE: Arene-Ruthenium(II) Complexes of Amines and Some Biologically Important Ligands

AUTHOR: Lee C. Carter

ABSTRACT

This thesis describes some chemistry of [(arene)RuCl₂]₂ complexes and their derivatives, in particular their reactions with biologically important ligands such as amino acids and nucleosides.

Chapter 1 reviews the general chemistry of arene-ruthenium compounds from early work by Zelonka and Bennett, to the more recent use of such complexes as catalysts in carbamate reactions. The second part contains a discussion of inorganic complexes as anti-cancer agents, in particular those of ruthenium.

Chapter 2 describes the preparation and characterisation of a number of arene-ruthenium amine complexes. As previously reported we find that primary amines coordinate whereas tertiary ones do not. However, we report the first examples of secondary amine coordination and the X-ray determination of [(mes)RuCl₂(pip)] is described.

The reactions of some amino-acids with [(mes)RuCl₂]₂ are presented in Chapter 3. The resulting complexes, [(mes)RuCl(aa)], are soluble in both water and organic solvents and exist as a pair of diastereomers. A study of the factors influencing the diastereomer ratios was undertaken, including substituting the chloride ligand in the complex [(mes)RuCl(ala)], with a number of other ligands. However, no clear patterns were found for predicting diastereomer ratios.

In Chapter 4 the reactions of complexes [(mes)RuCl(L-L)]ⁿ⁺ (L-L = Etmal, Pyr, ala, n=0; L-L = bipy, n = 1) with carbon monoxide in the presence of AgBF₄ are described, and the X-ray structure of [(mes)Ru(CO)(Etmal)]BF₄ is reported. The reactions of [(mes)Ru(CO)(Etmal)]BF₄ with water and other nucleophiles are described.

The final Chapter describes the reactions of [(mes)RuCl₂]₂ with some nucleobases and theophylline. The molecular structure of the theophylline adduct [(mes)RuCl(H₂O)(C₇H₇N₄O₂)] is described and it establishes the presence of N(7) coordination. We find the stabilities of the nucleobase complexes to be the same as other metal complexes, with guanosine complexes being the most stable and cytidine ones the least.

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 1989 and September 1992.

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: 
Lee C Carter Esq.

Date: 30/3/94

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ABBREVIATIONS

acacH	Pentane-2,4-dione
Aden	Adenosine
alaH	<i>l</i> -Alanine
AmphosH	1-Aminoethylphosphonous acid
AscH	Ascorbic acid
AspH	Aspartic acid
bipy	2,2'-bipyridine
br	Broad
ⁿ Bu	<i>n</i> -Butyl
^t Bu	<i>t</i> -Butyl
chpt	Cycloheptatriene
cod	Cyclo-octa-1,5-diene
Cp	Cyclopentadienyl anion
Cp*	Pentamethylcyclopentadienyl anion
Cyt	Cytidine
d	Doublet
dGMP	Deoxyguanosine monophosphate
dmsO	Dimethylsulphoxide
dpae	1,2-Bis(diphenylarsino) ethane
dppb	1,4-Bis(diphenylphosphino) butane
dppe	1,2-Bis(diphenylphosphino) ethane
dppp	1,2-Bis(diphenylphosphino) propane
dq	Doublet of quartets
dt	Doublets of triplets
edtaH ₄	Ethylenediamine tetraacetic acid
Et	Ethyl
9Etgua	9-Ethylguanine
EtmalH	Ethylmaltol
GluH	Glutamic acid
glyH	Glycine
Guan	Guanosine
HisH	Histidine
Hyp	Hypoxanthine (purine-6-one)
Im	Imidazole
In	Indazole

ABBREVIATIONS (continued)

IR	Infra red
leucH	<i>l</i> -leucine
<i>m</i>	Meta
Me	Methyl
1-MecytH	1-Methylcytosine
Me ₂ Hpz	3,5-Dimethylpyrazole
mes	Mesitylene (1,3,5-Me ₃ C ₆ H ₃)
metro	Metronidazole
NADH	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
<i>o</i>	Ortho
<i>p</i>	Para
Ph	Phenyl
PhalaH	<i>l</i> -Phenylalanine
phen	1,10-Phenanthroline
PhglyH	<i>l</i> -Phenylglycine
picH	Picolinic acid
pip	Piperidine
iPr	iso-Propyl
proH	<i>l</i> -Proline
py	Pyridine
PyrH	N-methyl-3-hydroxy-2-ethyl-4-pyridinone
q	Quartet
sarcH	Sarcosine (N-methylglycine)
t	Triplet
TheoH	Theophylline
u.v.	Ultraviolet

Chapter One

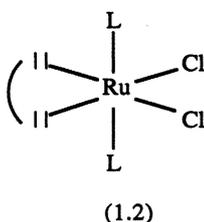
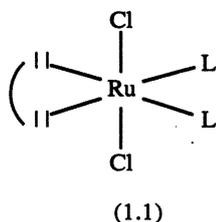
Introduction

CHAPTER 1 - INTRODUCTION

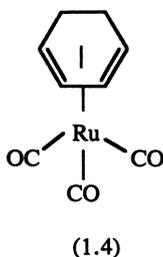
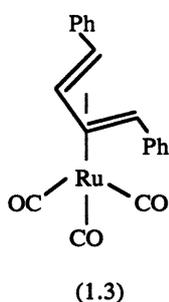
1.1 - Arene-Ruthenium Chemistry.

The organometallic chemistry of ruthenium centres on Ru⁰, Ru^{II} and Ru^{III}, occasionally higher oxidation states of IV, V, VI and VIII occur, but these are mostly seen in the inorganic chemistry of ruthenium. The use of π -bonded ligands in organometallic chemistry has, and is still being extensively studied.^{1,2} For ruthenium, the majority of complexes of such ligands contain ruthenium in oxidation state II, which is easily reached by oxidative addition to Ru⁰ or by reduction of Ru^{III} species.

Unconjugated dienes such as cyclo-octa-1,5-diene and bicyclo-[2.2.1]-hepta-2,5-diene react with ethanolic ruthenium(III) halides to form insoluble complexes $[(\text{diene})\text{RuX}_2]_n$ which are thought to have polymeric halide-bridged structures.³ These compounds are good precursors to a variety of ruthenium(II) complexes, owing to the ease with which the halide bridges are cleaved. For example, a number of amines react at room temperature to give monomeric complexes $[(\text{diene})\text{RuCl}_2\text{L}_2]$ ³ for which two isomers can be identified.



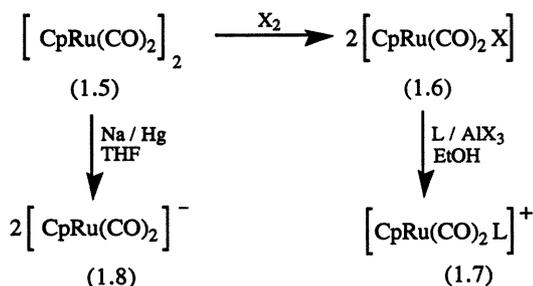
The aniline⁴ and piperidine⁵ complexes adopt structure (1.1) whereas the *n*-hexylamine product has structure (1.2). Conjugated π -complexes have also been well documented,¹ Ru₃(CO)₁₂ reacts with *trans*-1,4-diphenylbuta-1,3-diene to give the monomeric complex (1.3),¹ Ru₃(CO)₁₂ also reacts with cyclo-hexa-1,3-diene to give the half - sandwich compound (1.4).⁶



The reaction of ethanolic ruthenium trichloride with cycloheptatriene gives a complex which, was initially proposed to contain bidentate 1,2 : 4,5- η^4 -chpt, although the NMR spectra were also consistent with a dimeric structure analogous to $[(\eta^6\text{-arene})\text{RuCl}_2]_2$.⁷ Reaction of $[(\eta^6\text{-chpt})\text{RuCl}_2]_2$ with Lewis bases affords the monomeric complexes $[(\eta^6\text{-chpt})\text{RuCl}_2\text{L}]$ (L = PBu_3 , PPh_3 , P(OPh)_3 , AsPh_3),⁸ this is consistent with the starting complex being dimeric and containing an η^6 -ligand.

Conjugated π -complexes often undergo nucleophilic attack which usually occurs at the ring, for example, $[(\eta^5\text{-C}_6\text{H}_7)\text{Ru}(\text{CO})_3]\text{BF}_4$ reacts with nucleophiles to give the substituted $[(\eta^4\text{-C}_6\text{H}_7\text{Nu})\text{Ru}(\text{CO})_3]$.⁹ When the nucleophile is MeO^- the initial product is $[(\eta^5\text{-C}_6\text{H}_7)\text{Ru}(\text{CO})_2\text{CO}_2\text{Me}]$, which shows that in this case the nucleophile adds first to the carbonyl group, then migrates to the ring.⁹

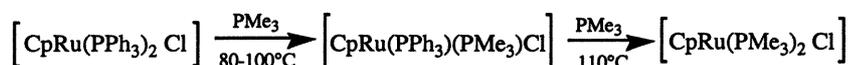
A special case of an η^5 -conjugated ligand is the cyclopentadienyl anion, Fischer *et al.* in 1962 prepared $[\text{CpRu}(\text{CO})_2]_2$ (1.5).¹⁰ Complex (1.5) can undergo a number of reactions which have been extensively reviewed,¹¹ some of which are shown below, Scheme 1.1.



Scheme 1.1

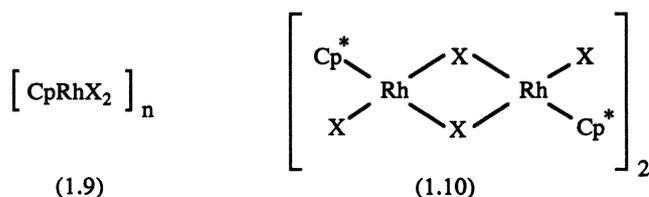
Complex (1.5) can be broken down into monomeric half-sandwich units using sodium amalgam in THF to give complex (1.8), complex (1.5) also reacts directly with halogens in halogenated solvents to give the monomeric compounds (1.6) (X = Cl, Br). The halogens in turn can be easily displaced by various ligands in the presence of a Lewis acid to form cations (1.7) (L = MeCN, MeNC, NH₃, PEt₃, PPh₃, 1/2 dppe). Alkenes also displace the chloride ion in the presence of AlCl₃ to give complexes (1.7) (L = C₂H₄, CH₂=CHMe, cyclohexene).^{10,12}

Although [CpRu(PPh₃)₂Cl] has a structure related to the dicarbonyl analogue, its chemistry is quite different,¹¹ an interesting feature is the stepwise loss of the triphenylphosphine ligand,¹³ Scheme 1.2.

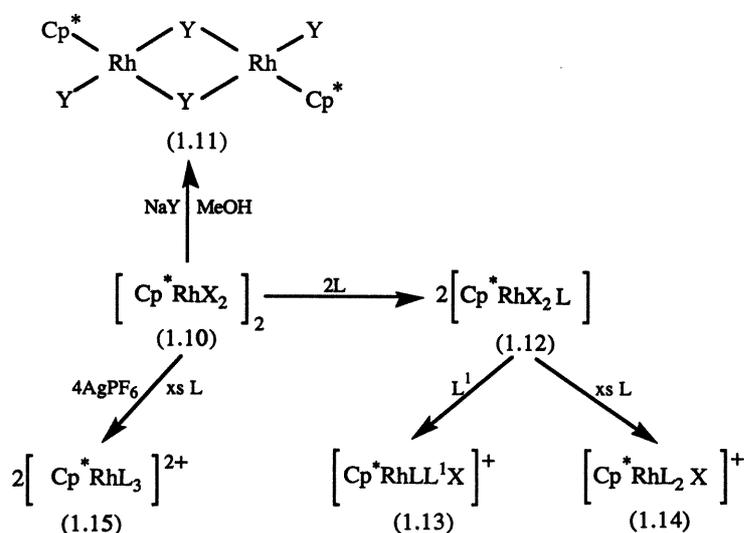


Scheme 1.2

The break down of dimeric compounds into half-sandwich monomers is further exemplified in the chemistry of cyclopentadienyl rhodium complexes. The reaction between rhodium trichloride and cyclopentadiene in methanol gives the polymeric complex (1.9) (X = Cl).¹⁴ The analogous compound (1.10) (X = Cl), which is dimeric, can be made by similar methods using pentamethylcyclopentadiene.^{14,15} The chemistry of both complexes is similar and has been extensively reviewed.¹⁶



Some reactions of complex (1.10) are detailed below in Scheme 1.3, these are very similar to those of the isoelectronic compounds [(η⁶-arene)RuCl₂]₂, discussed later.



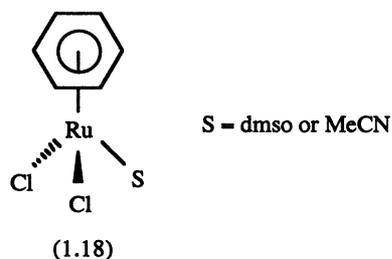
Scheme 1.3

The chloride ligand in complex (1.10) ($X = \text{Cl}$) can be replaced by Br^- , I^- , N_3^- to give the dimeric compounds (1.11) ($Y = \text{Br}$, I , or N_3). Alternatively, the halide bridges can be cleaved to give a number of monomeric adducts (1.12).¹⁶ The reaction of complexes (1.10) with donor ligands gives the compounds (1.12) ($X = \text{Cl}$, $L = \text{PPh}_3$, MeCN , py ; $X = \text{I}$, $L = \text{PPh}_3$; $X = \text{N}_3$, $L = \text{PPh}_3$, $\text{P}(\text{OMe})_3$, py). The addition of excess ligand results in further displacement of the halide to yield the cationic complexes (1.14). Similarly, treatment of complex (1.12) with another ligand L^1 affords the mixed ligand compounds (1.13). AgPF_6 reacts with the dimer in a coordinating solvent to produce the dicationic complexes (1.15) ($L = \text{py}$, dmsO , MeCN).¹⁶

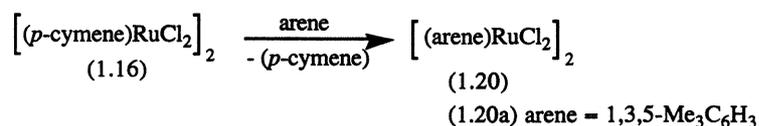
The chemistry of the arene-ruthenium complexes is very similar to that of the isoelectronic cyclopentadienyl rhodium species. In 1967 Winkhaus and Singer⁷ first reported the preparation of an insoluble, brown, diamagnetic benzene complex of empirical formula $[(\text{C}_6\text{H}_6)\text{RuCl}_2]$, which when reacted with PBu_3 gave the complex $[(\text{C}_6\text{H}_6)\text{RuCl}_2(\text{PBu}_3)]$. Arene-ruthenium complexes have been extensively studied since this discovery.¹⁷⁻¹⁹ Interest was further generated when the catalytic potential of many π -arene metal complexes was

realised.^{20,21} They are good starting materials for access to the highly reactive arene-metal hydrides, these have in turn been used for carbon-hydrogen bond activation. Arene-ruthenium compounds are also potential precursors of organometallic polymers.

The complexes of $[(p\text{-cymene})\text{RuCl}_2]_2$ (1.16) and $[(\text{C}_6\text{H}_6)\text{RuCl}_2]_2$ (1.17) are prepared by reacting ethanolic ruthenium trichloride with the appropriate cyclohexadiene, although insoluble in most organic solvents, these dimers are broken down by coordinating solvents such as dmsO and MeCN to form monomeric piano-stool complexes (1.18).^{17,18} The dimers are also soluble in water, but an equilibrium is established involving $[(\text{arene})\text{RuCl}_2(\text{H}_2\text{O})]$, $[(\text{arene})\text{RuCl}(\text{H}_2\text{O})_2]\text{Cl}$ and $[(\text{arene})\text{Ru}(\text{H}_2\text{O})_3]\text{Cl}_2$; $[(\text{arene})_2\text{Ru}_2\text{Cl}_3]\text{Cl}$ also exists in solution.¹⁷

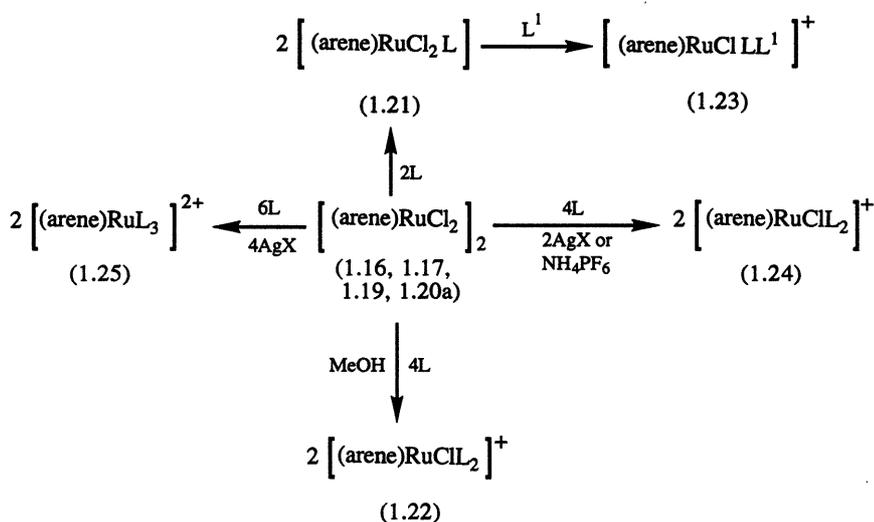


Although the dimers are stable and the metals have an 18 electron configuration, the arene rings can be displaced under certain conditions. Harsh conditions such as solid melts and high temperature reflux can cause the rings of the dimers to exchange with free arenes.²² The preferred starting complex for these arene exchange reactions is complex (1.16), as the *p*-cymene ligand is the most labile arene. This complex is made by refluxing ethanolic ruthenium trichloride with commercially available α -phellandrene.²³ Heating complex (1.16) with hexamethylbenzene as a solid melt gives the complex $[(\text{C}_6\text{Me}_6)\text{RuCl}_2]_2$ (1.19).²³ Refluxing complex (1.16) with neat ligands, 1,2,3,4-Me₄C₆H₂, 1,3,5-Me₃C₆H₃, 1,3,5-Et₃C₆H₃ or 1,3,5-ⁱPr₃C₆H₃ also leads to arene exchange giving complexes (1.20) in good yields.²²



U.v. irradiation also causes arene exchange, photochemical (and thermal) exchange of the *p*-cymene ligand in the complex [(*p*-cymene)RuCl₂(PBU₃)] with benzene or hexamethylbenzene has been shown to take place, however this only occurs in moderate yields.¹⁷ The coordinated arene is less susceptible to electrophilic substitution than free arene because some of the electrons in coordinated arenes are used in ligand-metal bonding, for example [(C₆H₆)RuCl₂(PMe₂Ph)] is inert to acetic anhydride at 60°C, conditions under which free benzene is readily acetylated.²⁴

Whilst we have discussed arene ligand exchange in the dimeric complexes it is also interesting to note that the chloride ligand can also be replaced by bromide and iodide to form the analogous complexes [(arene)RuX₂]₂ (X = Br, I). The reaction of ruthenium trichloride with cyclo-hexa-1,3-diene, in the presence of a four fold excess of LiBr gave two species attributed to the dibromo and chlorobromo complexes.¹⁷ Indeed, when the mixture was reacted with PBU₃ two phosphine complexes were formed in a 2:1 ratio, the dibromo and chlorobromo species respectively. However, when LiI was used and a similar experiment carried out only one species was formed, the diiodo complex (this also reacts with PBU₃ to form [(C₆H₆)RuI₂(PBU₃)]).¹⁷ The [(arene)RuCl₂]₂ complexes undergo a number of reactions, Scheme 1.4.

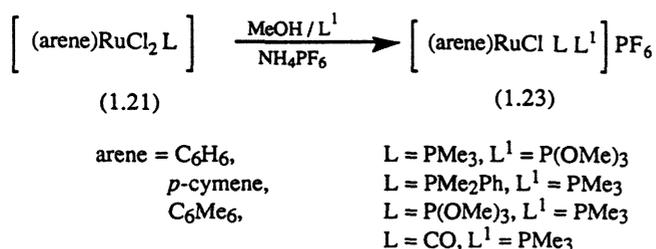


Scheme 1.4

Cleavage of the halide bridges is achieved by the addition of a variety of two electron donor ligands (L) such as, phosphines, phosphites, arsines, stibines, pyridine,^{17,18} isonitrile,²⁵ carbon monoxide^{18,26} and dmsO²⁷ to give complexes (1.21). These half-sandwich compounds have a piano-stool structure, analogous to that of [(arene)Cr(CO)₃], as confirmed by X-ray studies.²⁸ For soft donor ligands such as phosphines, phosphites and arsines, the reactions were carried out by refluxing the dimers in benzene for complex (1.17) or *n*-hexane for complexes (1.16, 1.19 and 1.20a) with equimolar amounts of ligand. In some cases the ligand itself can be used as a solvent, e.g., pyridine, dmsO and acetonitrile. Excess ligands may displace the arene ring, dimethylphenylphosphine when used in stoichiometric amounts gives the complex [(arene)RuCl₂(PMe₂Ph)], however, when used in excess under the same conditions arene displacement occurs to give [(PMe₂Ph)₆Ru₂Cl₃]Cl.¹⁷ Complex (1.21) (L = CO, arene = C₆H₆) was prepared by Zelonka and Baird,¹⁸ however the complex was very unstable and was characterised only by ¹H NMR and IR spectroscopy. Thiol complexes were also synthesised, early work by Stephenson *et al.*²⁷ centred on such compounds as [(C₆H₆)RuCl₂(Et₂S)] and [(C₆H₆)RuCl(Et₂S)₂]PF₆. However, more recently Dixneuf *et al.* have prepared [(mes)RuCl₂(Et₂S)]²⁹ with a view to activation of terminal alkynes by utilising the labile Ru-S bond, as a way of coordinating such alkynes.

There are two types of cationic species involved in arene-ruthenium chemistry, monocationic complexes (1.22 - 1.24) and the dicationic complexes (1.25). There are three general pathways to monocations (Scheme 1.4), in polar solvents complexes (1.16, 1.17, 1.19) can add two basic ligands per ruthenium atom to afford the complexes (1.22) (L = PMe₃, PPh₃, PMe₂Ph, P(OMe)₃).^{27,30,31} Alternatively, the use of silver salts to remove the chloride ion or, NH₄PF₆ to precipitate out the ruthenium cation gives the complexes (1.24) (L = PPh₃, PMePh₂, PMe₂Ph).³¹ Stephenson reported that [(C₆H₆)RuCl(py)₂]PF₆ could be prepared by refluxing pyridine in ethanol with the triply bridged cation [(C₆H₆)₂Ru₂Cl₃]PF₆,²⁷ however, a second product [(py)₄RuCl₂] was also isolated. Related complexes (1.24) (L = NH₃, SEt₂) were also synthesised using this method.²⁷ The synthesis of mixed ligand cations (1.23) is very similar, leading to a wider variety of

complexes,^{26,30,31} these are prepared using the neutral monomeric adducts (1.21) as starting material, as shown in Scheme 1.5.



Scheme 1.5

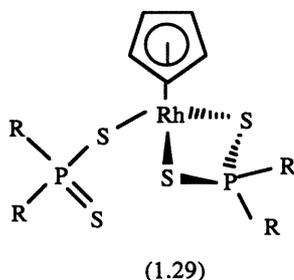
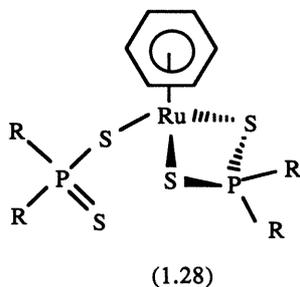
The dicationic complexes are prepared by reacting the dimeric [(arene)RuCl₂]₂ with a coordinating solvent, in the presence of silver salts to give the complexes [(arene)Ru(OCMe₂)₃]²⁺ (1.25a) (arene = C₆Me₆, 1,3,5-Me₃C₆H₃)³² and [(arene)Ru(NCMe)₃]²⁺ (1.25b) (arene = C₆H₆, *p*-cymene).¹⁷ Other dications have also been prepared using ligands such as N₂H₄, NH₂NMe₂,³³ NH₃,³⁴ and dmsO.³⁵ The easily formed [(arene)Ru(OCMe₂)₃]²⁺ (arene = C₆Me₆, 1,3,5-Me₃C₆H₃) readily undergoes displacement reactions, this property gives a convenient route to other dications [(arene)RuL₃]²⁺ (L = dmsO, py, P(OMe)₃) and also another preparative pathway to [(arene)Ru(NCMe)₃]²⁺.³² Interestingly, the treatment of [(arene)Ru(NCMe)₃]²⁺ (arene = C₆H₆, *p*-cymene) with chloride ions converts the dication back to the dimeric starting material.¹⁷ Bennett and Pertici³⁶ reported an alternative method for converting the monomeric adducts (1.21) (arene = C₆H₆, *p*-cymene; L = PPh₃, PMePh₂, PBu₃, PhCH(Me)NH₂, *sec*-BuNH₂), back to their dimeric starting materials, which involved reacting the adducts with cyclo-octa-1,5-diene in the presence of a reducing agent (Na₂CO₃ in 2-propanol) and then reacting these ruthenium(0) species with HCl to give [(arene)RuCl₂]₂.

Bidentate ligands can be utilised in two ways, they can be used to bond one ruthenium atom, thus forming a chelated complex [(arene)RuCl(L-L)]⁺ (1.26) or, they can be used as bridging ligands to form binuclear compounds [(arene)RuCl₂]₂(μ-L-L) (1.27). Complexes (1.26) are prepared by similar methods employed in the formation of complexes (1.22),

reacting $[(C_6H_6)RuCl_2]_2$ in a polar solvent such as methanol or ethanol with the appropriate ligand (LL) (LL = dppe, dppp, dppb, dpae) gives the solids $[(C_6H_6)RuCl(LL)]Cl$.³⁷

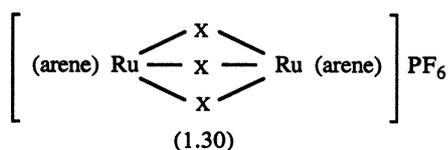
Faraone *et al.* described the synthesis of bridged and chelated arene-ruthenium complexes using ligands such as $Ph_2P(CH_2)_nPPh_2$ and $Ph_2As(CH_2)_nAsPh_2$. However, he found that using a 1:2 molar ratio of dimer:ligand, gave the mononuclear species $[(C_6H_6)RuClPh_2E(CH_2)_nEPh_2]Cl$ (E = P, As; n = 1,2,3,4), but when a 1:1 molar ratio was employed, a binuclear complex $[(C_6H_6)RuCl]_2(\mu-LL)$ was isolated, reacting these further with more of the same ligand results in the formation of the aforementioned species $[(C_6H_6)RuClPh_2E(CH_2)_nEPh_2]Cl$ (E = P, As; n = 2,3,4).³⁷

Bidentate ligands containing nitrogen or sulphur also react with the complexes $[(arene)RuCl_2]_2$ to form chelated compounds (1.26) (arene = C_6H_6 , 1,3,5- $Me_3C_6H_3$, LL = phen; arene = C_6H_6 , LL = bipy).³⁸ Sulphur ligands in the form of dithio acids form the neutral complexes (1.28) (arene = C_6H_6 , 1,3,5- $Me_3C_6H_3$; R = Me, Ph, OMe, OPh), which contain one unidentate and one bidentate ligand.³⁹ Similarly the isoelectronic cyclopentadienyl rhodium complex (1.29) has also been synthesised.³⁹ Other bidentate ligands such as $NH_2CHR_2COO^-$ (R = H, Me, Ph) and $NH_2CH(CH_3)PO_2^-H$ are discussed in Chapter 3.



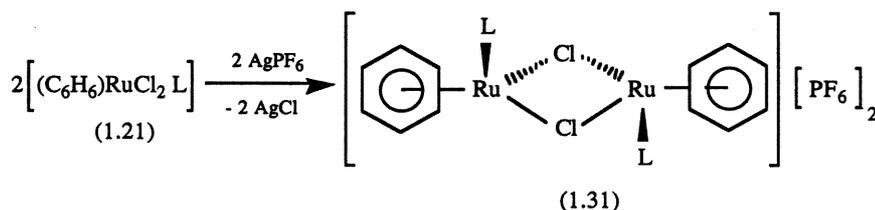
Dinuclear arene-ruthenium complexes can be prepared with a variety of bridging atoms and ligands. The chloro-bridged complexes $[(arene)_2RuCl_3]PF_6$ (arene = C_6H_6 , *p*-cymene) have been prepared by Stephenson *et al.*, by refluxing the appropriate dimers in hot water and precipitating out the solid with NH_4PF_6 .⁴⁰ Similarly, the hydroxy and alkoxy bridged complexes (1.30) have also been prepared using excess sodium hydroxide⁴¹ and various

sodium alkoxides^{41,42} in alcoholic solvents to give the desired complexes. Interestingly, the complex $[(C_6H_6)_2Ru_2(OH)_3]^+$ is not known, although early work by Stephenson *et al.*⁴³ reported a species of this formulation, subsequent studies showed the structure to be that of the tetranuclear complex $[(C_6H_6)_4Ru_4(\mu_2-OH)_4(\mu_4-O)][BPh_4]_2$.⁴⁴



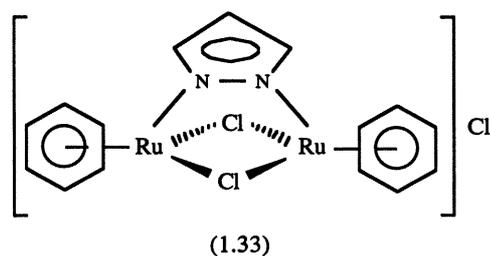
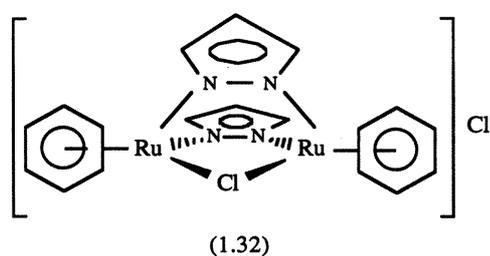
arene = C₆H₆; X = OMe, OEt, OPh
 arene = 1,3,5-Me₃C₆H₃; X = OH, OMe
 arene = *p*-cymene; X = OH

The above compounds have three bridging atoms, however, Werner and Werner synthesised other similar species (1.31) with two bridging atoms using the monomeric complexes (1.21) (arene = C₆H₆) as starting materials.³¹

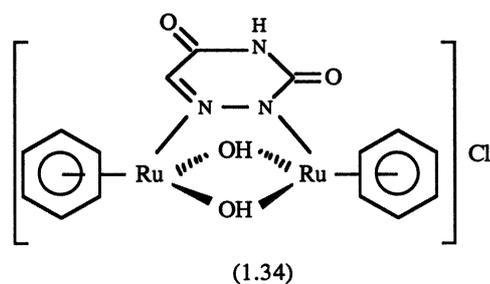


L = P(OMe)₃, PMe₃, PMe₂Ph, PPh₃

The use of bidentate phosphines as bridging ligands has already been mentioned (where Faraone prepared complexes $[(C_6H_6)RuCl_2]_2(\mu-L-L)$).³⁷ However, nitrogen donor ligands in the form of pyrazoles⁴⁵ and amino pyrazoles⁴⁶ can also form bridges between two ruthenium centres. When $[(C_6H_6)RuCl_2]_2$ reacts with pyrazole in a 1:2 molar ratio in a methanol/water mixture the complex (1.32) is formed, however, when a 1:1 molar ratio was used a different complex (1.33) was isolated.⁴⁵ It was previously reported that when benzene was used as the solvent in the above reactions, only the monomeric species $[(C_6H_6)RuCl_2(\text{pyrazole})]$ was formed.⁴⁷

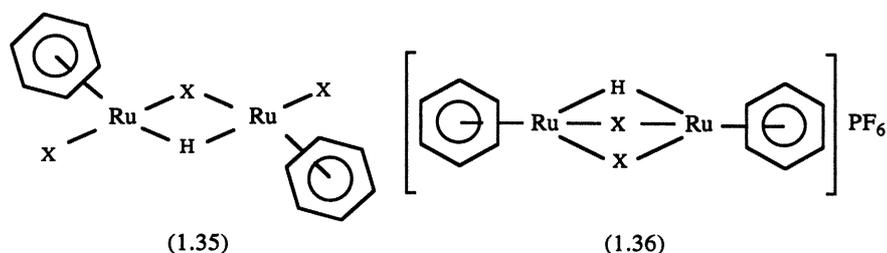


Sheldrick *et al.* also reported that the chloride atoms in complexes (1.32) and (1.33) could be replaced by hydroxide ions at temperatures over 321K to form analogous hydroxy-bridged complexes. A similar complex (1.34) was also prepared by Sheldrick,⁴⁵ but could only be isolated with two hydroxy ligands, with chloride bridges the Ru-N-N bond angles were energetically unfavourable.

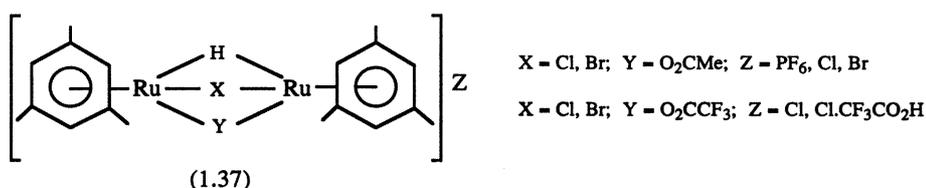


Hydrides can also act as bridging atoms to give some interesting dinuclear compounds.⁴⁸ For example, reacting $[(\text{arene})\text{RuCl}_2]_2$ with hydrogen at 4 atmospheres pressure, in the presence of triethylamine gives complexes (1.35) (arene = C_6Me_6 , 1,2,4,5- $\text{Me}_4\text{C}_6\text{H}_2$, 1,3,5- $\text{Me}_3\text{C}_6\text{H}_3$, X = Cl, Br; arene = *p*-cymene, C_6H_6 , X = Cl).

The triply-bridged complexes (1.36) have also been isolated (arene = C₆Me₆, 1,3,5-Me₃C₆H₃, X = Cl, O₂CMe).⁴⁸



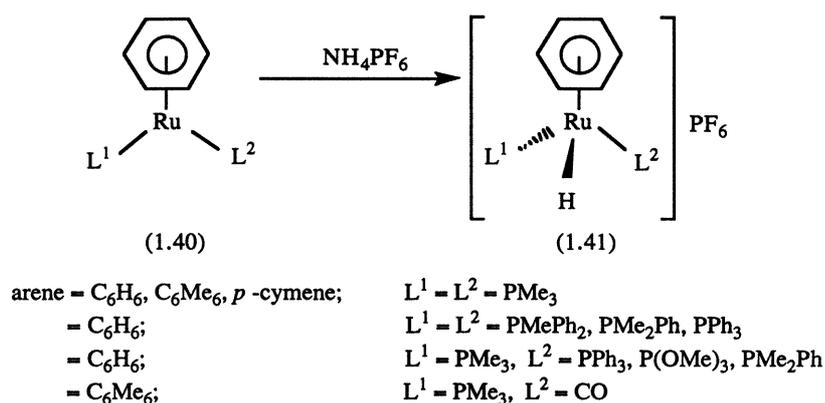
Going one step further, complexes (1.37) containing three different bridging ligands can be synthesised.⁴⁸



Mononuclear arene-ruthenium hydride complexes are useful derivatives for access to arene-ruthenium(0) complexes and as catalysts for C-H bond activation.⁴⁹ The majority of such compounds are made by selective reduction of arene-ruthenium(II) complexes or by protonation of arene-ruthenium(0) species to give monohydride or dihydride ruthenium complexes.

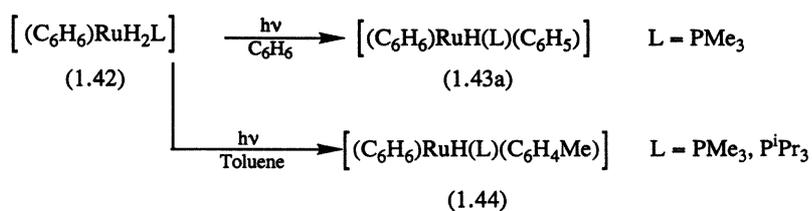
The mononuclear complex [(C₆Me₆)RuClH(PPh₃)] (1.38) is a well known hydrogenation catalyst,⁴⁹ it can be prepared by reduction of [(C₆Me₆)RuCl₂]₂ with Na₂CO₃ in 2-propanol in the presence of PPh₃, or by reduction of [(C₆Me₆)RuCl₂(PPh₃)]. The related complexes with different phosphines (PMe₃, PMe₂Ph, PMe^tBu₂) have also been prepared.⁵⁰ The dihydride compounds [(C₆Me₆)RuH₂(PR₃)] (1.39) (PR₃ = PMe₃, PPh₃, PMe₂Ph) are prepared from [(C₆Me₆)Ru(O₂CCF₃)₂(PR₃)] by reduction with "Red-Al" [NaAlH₂(OCH₂CH₂OMe)₂].^{51a} Reaction of the dihydride complexes (1.39) with HBF₄ gives the trihydride complexes [(C₆Me₆)RuH₃(PR₃)]BF₄.^{51b}

Another synthetic route to arene-ruthenium hydrides is by protonation of arene-ruthenium(0) complexes. Complexes (1.40) are easily protonated using NH_4PF_6 to give the cationic hydrides (1.41),^{26,30,52} as shown in Scheme 1.6.



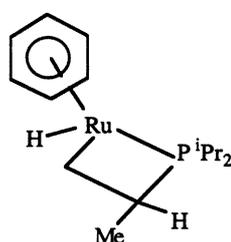
Scheme 1.6

Hydrides undergo many reactions, the most important being C-H bond activation. This is illustrated by the photolysis of the dihydride complexes (1.42), which in benzene and toluene results in the elimination of hydrogen and C-H bond activation to form compounds (1.43a and 1.44),⁵³ Scheme 1.7.



Scheme 1.7

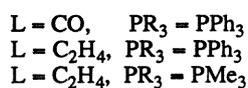
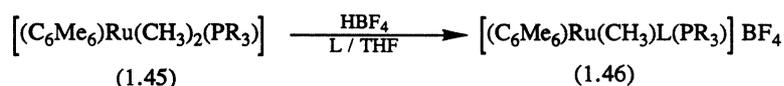
In contrast, photolysis of complex (1.42) ($\text{L} = \text{P}^i\text{Pr}_3$) in cyclohexane gave a different species, that of a cyclometallated product (1.43b).⁵³



(1.43b)

The use of alkyls and other hydrocarbon ligands in arene-ruthenium chemistry is well documented,⁵⁴ these compounds also show C-H bond activation in a similar way to the hydride complexes. The alkyl compounds are easily prepared, for example, $[(C_6H_6)RuCl_2]_2$ reacts with $HgMe_2$ or $HgPh_2$ in acetonitrile, subsequent addition of triphenylphosphine leads to monoalkylation or arylation to form the compounds $[(C_6H_6)RuClR(PPh_3)]$ ($R = Me, Ph$).⁵⁵ Methyl lithium and methylmagnesium iodide were used by Bennett and Smith as alkylating agents, but only small amounts of $[(C_6H_6)Ru(CH_3)_2L]$ and $[(C_6H_6)RuX(CH_3)L]$ ($X = Cl, L = PMe_2Ph, PPh_3$) were isolated.¹⁷ However, complexes of hexamethylbenzene when treated with methyl lithium gave improved yields of $[(C_6Me_6)Ru(CH_3)_2(PR_3)]$ (1.45) ($PR_3 = PMe_3, PPh_3, PMe_2Ph$).⁵⁶ Reaction with one equivalent of methyl lithium produced the complex $[(C_6Me_6)RuCl(CH_3)(PMe_3)]$ in 46% yield.⁵⁷

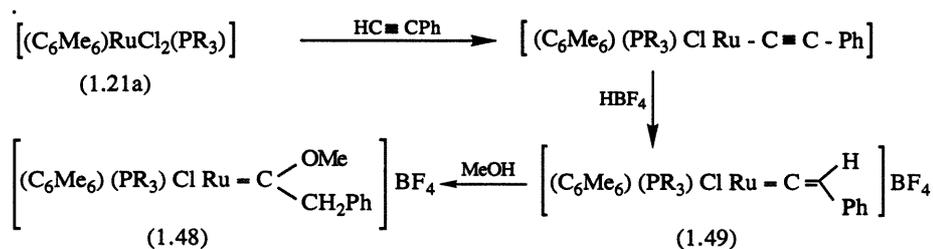
The cleavage of the Ru-CH₃ bonds by acid has been used by Werner and Kletzin.⁵⁸ Addition of HBf_4 to complexes (1.45) in the presence of carbon monoxide or ethylene allows coordination of these molecules to give compounds (1.46), Scheme 1.8.



Scheme 1.8

We have seen previously with the arene-ruthenium hydride compounds that ruthenium(0) complexes are good precursors for ruthenium(II) hydrides, ruthenium(0) compounds are also

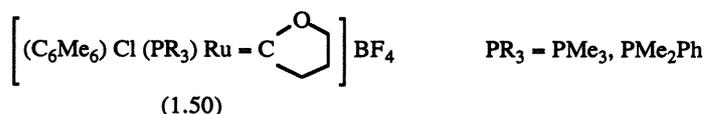
Arene-ruthenium complexes containing carbene ligands have also been reported.^{54,62} Complexes (1.21a) react at room temperature with a variety of terminal alkynes in alcohols, in the presence of HBF₄ to produce stable alkoxy alkyl carbene ruthenium derivatives (1.48).



PR₃ = PMe₃, PMe₂Ph

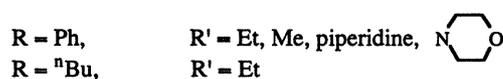
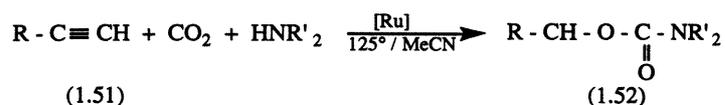
Scheme 1.11

The formation of such complexes proceeds via a vinylidene intermediate (1.49),^{62b} Scheme 1.11. Similarly, the cyclic carbene (1.50) was also prepared by reacting complexes (1.21a) with 4-hydroxy-1-butyne in methanol and in the presence of HBF₄.^{62b}



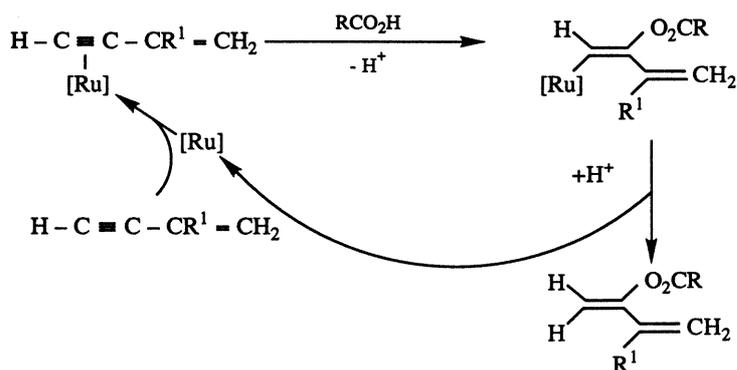
Arene-ruthenium complexes have found applications as hydrogenation catalysts.^{20,21,49,63} In 1973 Iwata *et al.* showed that the complex [(arene)RuCl₂]₂ (arene = C₆H₆, 1,3,5-Ph₃C₆H₃ or 1,3,5-Me₃C₆H₃) could catalyse hydrogenation reactions.^{20a} Hinze around the same time published similar results using [(C₆H₆)RuCl₂]₂.^{20b} Although the use of these dimers is well documented, it was not until 1978 that Bennett *et al.* showed that the monomeric complex [(C₆Me₆)RuClH(PPh₃)] was a long lived homogeneous catalyst for the hydrogenation of benzene and alkenes.⁴⁹ Analogous compounds which also contain phosphine ligands are the most active catalysts, indeed, [(C₆Me₆)RuCl₂(PPh₃)] shows the same activity as the above hydride complex.⁴⁹ Bennett also reported a year later that the bridged complex [(C₆Me₆)Ru(μ-H)₂(μ-Cl)Ru(C₆Me₆)]Cl showed similar catalytic activity.²¹

More recently, Dixneuf *et al.* have discovered a new catalytic synthesis of vinyl carbamates from terminal alkynes, using arene-ruthenium complexes as catalysts.⁶⁴ Vinyl carbamates are important intermediates for access to agricultural chemicals and to transparent polymers.⁶⁵ The most useful complex in the catalytic synthesis of vinyl carbamates was $[(C_6Me_6)RuCl_2(PMe_3)]$, which transformed the alkyne (1.51) into the carbamate (1.52) in 67% yield,^{64a} Scheme 1.12.



Scheme 1.12

Other ruthenium complexes such as $[(p\text{-cymene})RuCl_2(NCMe)]$ and $[(p\text{-cymene})RuCl(NCMe)_2]BF_4$ also show catalytic activity but with reduced yield of the carbamate (1.52).^{64a} The complex $[(p\text{-cymene})RuCl_2(PMe_3)]$ has also been used as a catalyst in the regioselective synthesis of 2-acyloxy-1,3-dienyl carboxylates from carboxylic acids or N-protected amino acids and 2-methyl-1-buten-3-yne, Scheme 1.13. These reactions were carried out in toluene in an autoclave at 80°C for 24 hours, with carboxylic acid (10 mmol), the enyne (12 mmol) and the catalyst $[(p\text{-cymene})RuCl_2(PMe_3)]$, where acid/catalyst = 100.⁶⁶

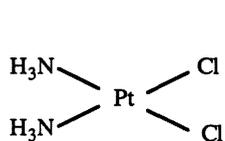


Scheme 1.13

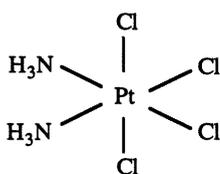
1.2 - Ruthenium Complexes as Anti-Cancer Agents

Metal complexes have been used as pharmaceutical agents for many centuries, although it was not until the early twentieth century that their therapeutic value was realised. Today “Auranofin”, which is active against primary chronic polyarthritis,⁶⁷ and sodium nitroprusside, which is used as an emergency drug in hyper-tension crises,⁶⁸ are two of the most commonly administered inorganic drugs.

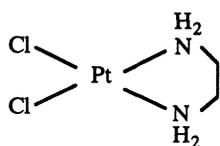
In cancer therapy only one family of inorganic drugs are under routine clinical use, that is those based on cisplatin (1.53). It was first discovered by Michele Peyrone in 1844⁶⁹ but it was not until 1969, that Rosenberg, whilst investigating the effect of an electric field on bacterial growth, noticed that the platinum electrode stopped cell division and caused filamentous growth of *e-coli* bacteria.⁷⁰ He subsequently showed that this effect was due to the presence of very small amounts of cisplatin (1.53). This gave rise to the idea that such compounds may be capable of inhibiting tumour growth. Rosenberg then went on to synthesise some simple platinum-ammine complexes, and screened them against sarcoma 180 and the murine L1210 leukaemia. The application of complexes (1.53 - 1.56) each produced a reduction in tumour weight and a prolonged survival time in tumour-bearing animals.^{70,71} In contrast, the corresponding *trans*-complexes of compounds (1.53 and 1.54) were found to be inactive.



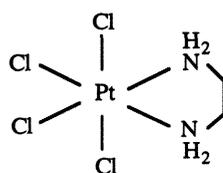
(1.53)



(1.54)



(1.55)



(1.56)

Cisplatin has been successful in the treatment of bladder, lung, head and neck, cervical, and especially testicular and ovarian cancers.^{72,73} The mechanism by which it is thought to act against such tumours is that of cross-linking, Fig 1.1. It is supposed that cisplatin-DNA adducts inhibit DNA replication, and thus affect cell growth. The most frequent adduct is the intrastrand crosslink between neighbouring guanine bases, via complexation at N(7). Many studies of this reaction have been carried out and are reviewed by Lippard and Sherman.⁷⁴

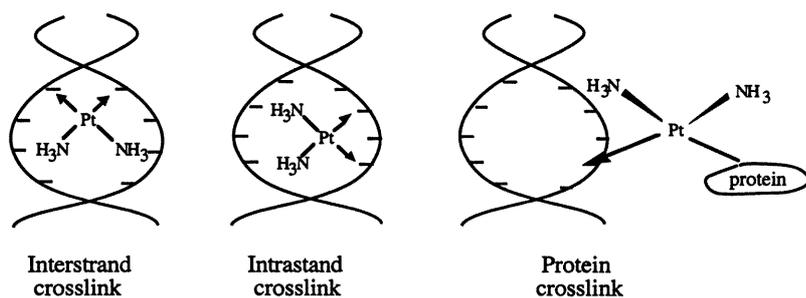


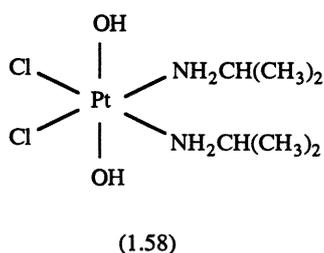
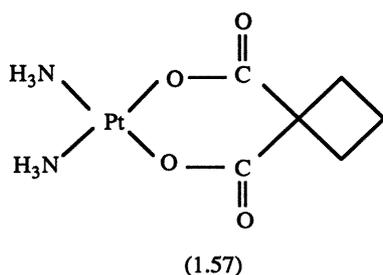
Fig 1.1

It is not easy to understand how the DNA-adducts, shown in Figure 1.1, and this unspecific crosslinking can control the effect of cisplatin, which is directed only at specific tumours e.g. testicular carcinoma. The suggestion of 'selective accumulation' in tissues is frequently used; however, it has been shown that there is no real correlation between concentration and effectiveness of cisplatin in specific organs. High concentrations are found in the skin and liver, whilst there is no significant activity against tumours of corresponding localisation.^{75,76} Unfortunately, severe side effects accompany cisplatin and often limit its clinical applications, these effects include liver failure, nephrotoxicity, nausea and vomiting.

The development of new anti-tumour metal complexes can be summarised by the three following procedures:

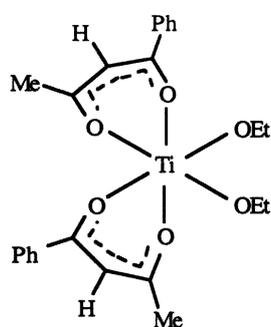
- (i) Synthesis and activity of direct cisplatin analogues.
- (ii) The linking of cancer-toxic platinum compounds or other tumour inhibiting complexes with carrier molecules or systems in order to achieve selective accumulation.
- (iii) Trials with new metal complexes that do not contain platinum as their central atom.

The first of these procedures is likely to give compounds similar to cisplatin in both activity and mechanism of action. The most successful of these compounds are carboplatin (1.57) and iproplatin (1.58) which show fewer side-effects than cisplatin. For example, nephrotoxicity was reduced, as were some of the nausea problems normally associated with cisplatin chemotherapy. Carboplatin is now in routine clinical use in many countries.⁷⁷

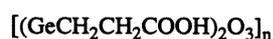


The second possibility, of linking platinum compounds to carrier molecules is illustrated on the basis of osteotropic platinum compounds containing phosphate ligands, other examples include hormone linked platinum derivatives with an affinity to hormone receptor-positive tumours, which have been developed by Schöenberger *et al.*⁷⁸

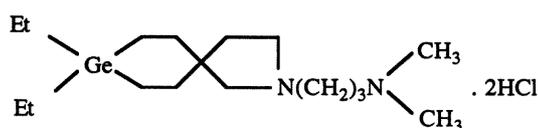
Although platinum drugs are highly active against some relatively rare tumours, they have little or no effect on other more common tumours. The third approach which involves changing the central metal atom presents more opportunities for finding complexes which may be active against different cancers. The anti-tumour properties of tin, gold, rhodium and ruthenium complexes have been extensively reviewed,^{79,80} as have metallocene dichlorides such as $[(Cp)_2MCl_2]$ ($M = Ti, V, Nb, Zr, Hf$).^{80,81} Only a few metal complexes are currently undergoing clinical trials, including budotitan (1.59), germanium 132 (1.60) and spirogermanium (1.61). Some simple gallium salts have also been screened.^{72,82}



(1.59)



(1.60)

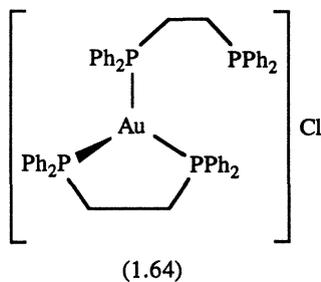
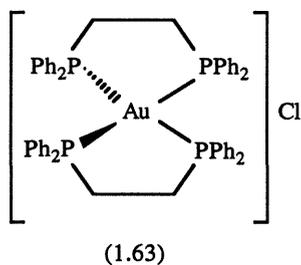
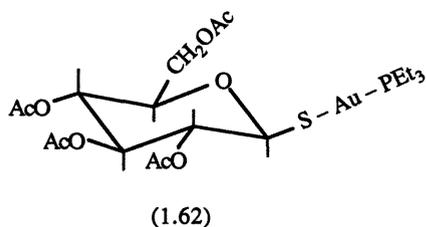


(1.61)

Of these compounds, budotitane has shown the most promising anti-tumour activity, similar activity can be observed with the related complexes in which F, Cl, and Br replace the ethoxy ligand. These compounds caused a doubling, and even trebling, of survival times of animals with Walker 256 carcinoma, and also in a transplantable murine leukaemia.⁷⁹ Budotitane is currently undergoing further trials for colon cancer, amongst others.⁸³ Similarly other $[\text{Ti}(\text{acac})_2(\text{OEt})_2]$ compounds also exhibit anti-tumour activity. Although $[\text{Ti}(\text{acac})_2(\text{OEt})_2]$ shows no anti-tumour activity itself, by changing a methyl group for a tertiary butyl, the activity is increased enormously, replacing one of the methyl groups with a phenyl gives the aforementioned budotitane.

Metallocene complexes, such as titanocene dichloride $[(\text{Cp})_2\text{TiCl}_2]$, together with $[(\text{Cp})_2\text{VX}_2]$ and $[(\text{Cp})_2\text{Fe}]X$ ($X = \text{Halide}$) exhibit systematic activity against other experimental tumours.⁸⁴ It was originally postulated by Doppert⁸⁵ that the metal acted simply as a carrier for the highly reactive cyclopentadienyl ligand. However, cyclopentadiene and dicyclopentadiene exhibit only random cytotoxicity, and do not affect the growth of solid tumours.⁸⁶ It is now more realistically known that the "Metal-Cp" fragment binds to DNA, and it is thought that this is responsible for the observed anti-tumour activity.⁸¹ Most of the complexes discussed have a similar method of action, in which the metal actively takes part by binding to DNA, in much the same way as for cisplatin. Although many factors affect the compounds activity towards tumours few of these are understood mechanistically.

Organogermanium compounds are thought to have a slightly different mechanism, which is apparently not based on direct cytotoxic effects, but on host mediated, immunopotentiating mechanisms.⁸⁷ However, there are other mechanisms of anti-tumour action, for example when the metal merely acts as a carrier for a cytotoxic ligand. Examples of such compounds are described below; Auranofin (1.62), although highly cytotoxic to cells in culture, is active against only one tumour model-P388 leukaemia.⁸⁸ The high cytotoxicity *in vitro* of auranofin is attributed to the presence of the phosphine ligand; however, its low potency *in vivo* makes it a poor anti-cancer agent. In contrast to this, the tetrahedral gold(I) diphosphine complexes such as $[\text{Au}(\text{dppe})_2]\text{Cl}$ (1.63) are much less reactive to ligand exchange, and thus exhibit a wider spectrum of anti-cancer activity.⁸⁴ Silver(I) and copper(I) phosphine complexes also use the same mechanism of action. There are facile mechanisms for ring openings that allow the ligand (in intermediate (1.64)) to act as an attacking agent. These metal diphosphine complexes appear to cause DNA strand breaks and DNA-protein crosslinks, showing their mechanism of action is different to that of cisplatin.⁸⁴

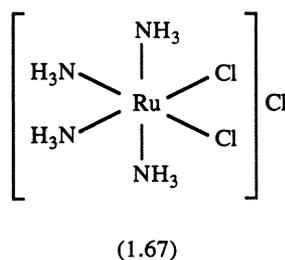
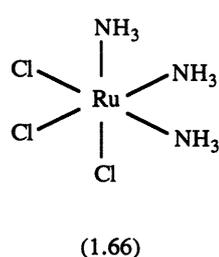
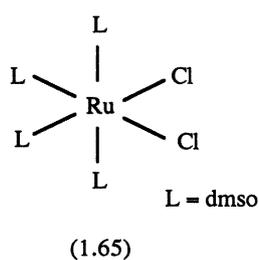


These complexes have yet to be tested clinically due to the severe side-effects on the heart and lungs. Attempts at reducing these effects by increasing the aqueous solubility via ligand

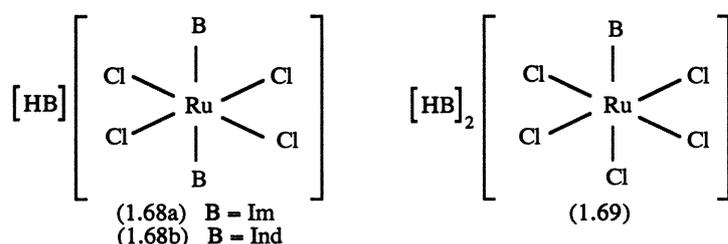
substitution, substitution of phosphorus by arsenic or preparing analogous $[\text{Ni}(\text{dppe})\text{Cl}_2]$ complexes that may be more labile, are all currently under investigation.^{84,89} The promising nature of the metal complexes and their mechanisms discussed above highlights the point that other types of cancer may be cured by these new compounds.

Ruthenium compounds show promise in the development of new anti-cancer drugs, of particular interest is the accessibility of two oxidation states, which may both be active *in vivo*. In 1965 Dwyer and his co-workers suggested that chelates of ruthenium might function as oncostatic and viruscidal agents.⁹⁰ It was not until the late 1970's and early 1980's that a more concentrated effort to the design of ruthenium compounds as anti-cancer pharmaceuticals was made. The development has centred on complexes which are likely to bind to DNA.

The most well known ruthenium tumour-inhibiting compound is *cis*- $[\text{RuCl}_2(\text{dmsO})_4]$ (1.65). This is water soluble, and although it only exhibits marginal activity against P388 leukaemia, it is highly active in some other tumour systems, such as Lewis lung carcinoma.⁹¹ Both the *cis* and *trans* isomers of complex (1.65) show anti-tumour activity against several murine tumour models,⁹¹ this illustrates a major difference between this compound and the platinum complexes (1.53 and 1.54), of which only the *cis*-isomers are active against tumours. Mestroni concludes that the mutagenic activity of *cis*- $[\text{RuCl}_2(\text{dmsO})_4]$ suggests that DNA is the preferred target *in vivo*. The *in vitro* experiments show that both the *cis* and *trans* isomers react easily with DNA and more recent *in vitro* results suggest *cis*- $[\text{RuCl}_2(\text{dmsO})_4]$ also possesses a differential cytotoxicity towards some human cell lines.⁹²



Ruthenium compounds with nitrogen-donor ligands, such as complexes (1.66) and (1.67), have also shown good anti-tumour activity, and many also localise in tumour tissue.^{79,93,94} Ruthenium(II) complexes with amines or imine ligands are capable of binding to specific sites on protein surfaces, and altering their activity,^{94,95} causing them to have other biological effects, and thus possibly affecting DNA replication. Keppler and co-workers have made water soluble compounds such as $[\text{HB}][\text{RuB}_2\text{Cl}_4]$ (1.68) and $[\text{HB}]_2[\text{RuBCl}_5]$ (1.69) (B = heterocycle).⁷⁹



The two most promising of these are $[\text{HIm}][\text{RuIm}_2\text{Cl}_4]$ (1.68a) and $[\text{HInd}][\text{RuInd}_2\text{Cl}_4]$ (1.68b). They have both shown activity greater than that of cisplatin and fluorouracil (which are both clinically established drugs) in the P388 leukaemia tumour model.⁷⁹ Complex (1.68a) has shown high activity against transplantable tumour models such as, Walker 256 carcinoma, Stockholm ascitic tumour, MAC 15A colon adenocarcinoma and also intramuscularly transplanted sarcoma 180.⁹⁶ These tumours, and in particular colon adenocarcinoma are unaffected by cisplatin. This highlights the versatility of compounds with different metal centres. The complex (1.68b) shows remarkable activity in the autochthonous colon tumours, but not in any other models. It is less toxic in chronic application than (1.68a) and thus higher doses can be administered. When the complex was tested in an autochthonous colorectal tumour of a rat, the result was a decrease in tumour volume to 5%. Final evaluation showed that in the group of animals tested, one third were found to be tumour free. The activities of some other compounds which have been tested are listed below, Table 1.2.1. The T/C values are expressed as 100 times the ratio of the lifetime of the animals treated with the ruthenium drug, to that for untreated animals. The values listed are for the most common initial screens ie:

P388 leukaemia, L1210 carcinoma or sarcoma 180. In some cases the values on other screens were considerably higher or lower.⁹⁵ The ascorbate complex shows only slight anti-tumour activity, however the similar squarate complex proved to be very effective against the mouse P388 lymphocytic leukaemia tumour. This complex also showed promise against a melanoma, with all the animals tested surviving. No activity was seen when the complex was screened against an MXI, transplantable human mammary tumour.

Table 1.2.1 The Anti-Tumour Activity of Some Ruthenium Complexes

Compound	Dose mg/kg	T/C
<i>fac</i> -[Ru ^{III} Cl ₃ (NH ₃) ₃]	50	189
[Ru ^{III} Cl ₃ (1,5-dimethyltetrazole) ₃]	80	179
[HIm][RuCl ₄ Im ₂]	72.8	162.5
[Ru ^{III} Cl(NH ₃) ₅]Cl ₂	1.5	116
[Ru ^{III} (Asc)(NH ₃) ₅]CF ₃ SO ₃	10	96
[Ru ^{III} (C ₄ O ₄)(NH ₃) ₅]CF ₃ SO ₃	21.2	140
[Ru ^{III} Cl ₂ (phen) ₂]ClO ₄	6.25	90

Although having the same charge and overall structure the difference in activities of the ascorbate and squarate complexes is somewhat surprising. Assuming the target site is chromatin nucleic acids, neither of these compounds would bind without ligand loss, thus opening a coordination position. Electrochemical results actually show that this is the case and both ascorbate and squarate are lost upon reduction at the ruthenium centre, however, to be active *in vivo* the complexes must have a biologically accessible reduction potential; for the squarate the potential is accessible, but for the ascorbate it is not. Consequently the squarate complex will produce a much greater quantity of [Ru^{II}(H₂O)(NH₃)₅]²⁺ to actively bind to nucleic acids and other molecules.⁹⁵ It was reported recently that the ruthenium-metronidazole complex [(C₆H₆)RuCl₂(metro)] showed good anti-tumour properties and a greater selective cytotoxicity than the free ligand,⁹⁷ itself a cytotoxic compound. In this case, it is thought the

ruthenium acts as carrier of the metronidazole compound, thus increasing its local concentration at the DNA target. The use of other metal complexes as possible carries of cytotoxic ligands has been discussed earlier.

The mechanism of action of many anti-tumour compounds is largely unknown, however, one theory for the mechanism of ruthenium-pentaammine complexes has been postulated by Clarke.⁹⁵ The tumour accumulation of simple ruthenium ammines is thought to proceed by two pathways. First rapid tumour uptake proceeds through activation of ruthenium(III) compounds towards binding by reduction in the tumour. Since small ions are excreted fairly readily by the kidneys, this mode of binding should decrease with time. A second slower mode of tumour binding which may occur for many days following injection is probably mediated by transferrin. This second mode of binding, which is thought to occur via transferrin transportation, is poorly understood. The ruthenium is thought to be carried to the tumour by first binding to transferrin, in much the same way as iron does, and hence is carried through the cell membrane to the tumour tissue, where it is then presumably released by the intracellular reduction to ruthenium(II). It is then thought to separate and bind to cellular structures, whilst the transferrin is free to migrate out of the cell. If transferrin does transport ruthenium complexes to the tumour sites it is likely that the ligands of the complex will be displaced upon attachment of ruthenium to the binding sites of transferrin.

The fact that different complexes have varying degrees of anti-tumour activity suggests that the transferrin mechanism is not the major contributor to activity since this ought to introduce the same ruthenium species to the cell independent of the initial ligands coordinated. Few ruthenium compounds have undergone clinical trials, due to the fact that ruthenium complexes have generally not been investigated in realistic and sufficiently sophisticated tumour models. Also, these compounds are invariably tested in comparison with cisplatin in the P388 leukaemia model and fail to show better activity. However, there is no real need for active ruthenium complexes, which qualify for clinical evaluation to surpass cisplatin in this particular model, because it is extremely sensitive to cisplatin.

In conclusion, many ruthenium complexes have been shown to possess anti-tumour activity, however, these are still some way away from clinical use. It is now necessary to

synthesise complexes which show hydrophilic properties (which makes administration to patients easier). Their reactions with DNA bases, DNA fragments, proteins and enzymes also needs to be investigated further, to provide an insight as to what interactions occur when these complexes are tested on real tumours. In particular, whether there is any selectivity for a particular nucleobase. Chapters 3, 4 and 5 will describe work on arene-ruthenium complexes of some biologically important molecules.

Chapter Two

The Synthesis of some Arene-Ruthenium

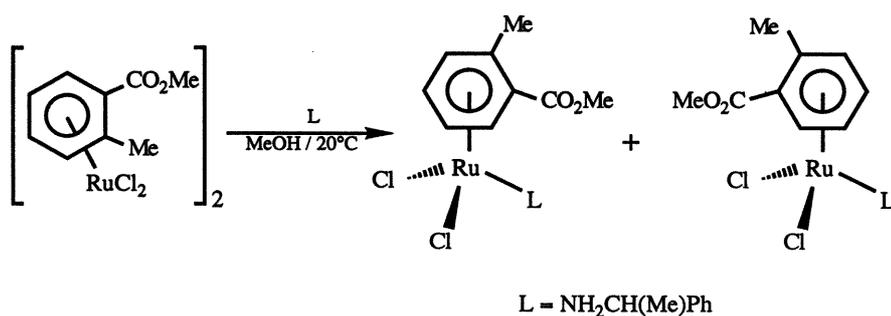
Amine Complexes

CHAPTER 2 - THE SYNTHESIS OF SOME ARENE-RUTHENIUM
AMINE COMPLEXES

2.1- Introduction

The reactions of the dimers $[(\text{arene})\text{RuCl}_2]_2$ with a number of two electron donor ligands such as phosphines, phosphites and nitrogen bases (including pyridine, hydrazine and ammonia) were discussed in Chapter 1. However, the use of simple amines as ligands is much less documented, and is limited to complexes with primary amines.^{98,99}

In 1988, Bennett *et al.* described the reaction of $[(\eta^6\text{-}o\text{-MeC}_6\text{H}_4\text{CO}_2\text{Me})\text{RuCl}_2]_2$ with (-)(S)-1-phenylethylamine which afforded the complex $[(\eta^6\text{-}o\text{-MeC}_6\text{H}_4\text{CO}_2\text{Me})\text{RuCl}_2(\text{NH}_2\text{CH}(\text{Me})\text{Ph})]$,⁹⁸ which was used as a probe of chirality, as described in Section 3.1. The chemistry of these particular arene-ruthenium amine complexes was not examined further.



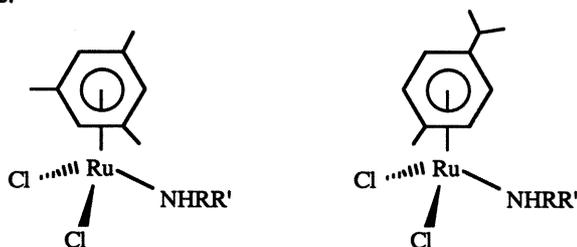
More recently, Wright *et al.* studied the ultrasound promoted reactions of arene-ruthenium dimers with amines.⁹⁹ The complexes $[(\text{C}_6\text{H}_6)\text{RuCl}_2(\text{NH}_2\text{R})]$ ($\text{R} = \text{Et}, \text{C}_6\text{H}_4\text{Me}, \text{CMe}_3$) and $[(p\text{-cymene})\text{RuCl}_2(\text{NH}_2\text{CMe}_3)]$ were prepared by reacting $[(\text{C}_6\text{H}_6)\text{RuCl}_2]_2$ or $[(p\text{-cymene})\text{RuCl}_2]_2$ with the appropriate amine in a THF solution. It was reported that neither secondary nor tertiary amines would react, and it was suggested that this was due to unfavourable steric interactions. The cationic complex $[(\text{C}_6\text{H}_6)\text{RuCl}(\text{NH}_2\text{C}_6\text{H}_4\text{Me})_2]\text{PF}_6$ was

also isolated from the reaction mixture of $[(C_6H_6)RuCl_2]_2$ with $NH_2C_6H_4Me$ when excess ligand was used, this halide substitution was only observed with an aromatic amine ligand.

In this Chapter we report the thermal reactions of $[(mes)RuCl_2]_2$ and $[(p\text{-cymene})RuCl_2]_2$ with a variety of primary and secondary amines, and try to assess the contribution of steric factors towards the stability of these amine complexes. We also describe the formation of two cationic complexes, each containing two amine ligands.

2.2 - Results and Discussion

Heating a suspension of $[(mes)RuCl_2]_2$ with a slight excess of various primary and secondary amines in CH_2Cl_2 or $CHCl_3$ leads to the formation of the complexes (2.1). Similarly, the analogous product (2.2) can be isolated from a solution of $[(p\text{-cymene})RuCl_2]_2$ and diethylamine.



	R	R'
2.1a	H	Ph
2.1b	H	CH ₂ Ph
2.1c	Et	Et
2.1d	ⁿ Bu	ⁿ Bu
2.1e	RR'NH = piperidine	

2.2 R = Et, R' = Et

The complexes were characterised by 1H NMR and mass spectroscopy, and microanalysis, Tables 2.3.1 - 2.3.3. In most cases molecular ions were observed in the FAB mass spectra, though in a number of samples, ions due to dimeric species are observed. These may have formed in the matrix, or possibly by reactions within the spectrometer.

All the complexes show the expected signals due to coordinated arene and the amine in their 1H NMR spectra. The coordinated mesitylene signals occur in the regions δ 2.0 - 2.26

and δ 4.8 - 5.0 due to the methyls and aromatic protons respectively. In addition to the mesitylene peaks complex (2.1a) exhibits a multiplet at δ 7.25 due to the phenyl protons, while a signal due to the NH_2 group is not visible. However, the NH_2 protons are observed in the ^1H NMR spectrum of the benzylamine complex (2.1b), as a broad signal at δ 3.22; the spectrum also displays a multiplet due to the phenyl protons at δ 7.30 and a singlet at δ 4.21, which is assigned to the methylene group. These methylene protons are equivalent because a plane of symmetry is present through the ligand which coincides with the $\text{N}-\text{CH}_2$ bond (Fig 2.2.1(a)).

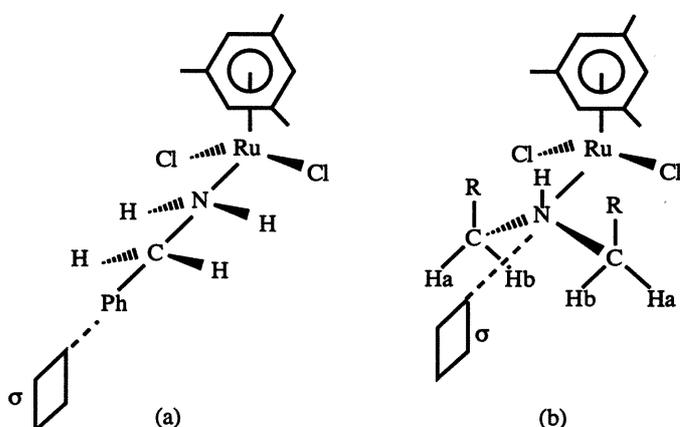
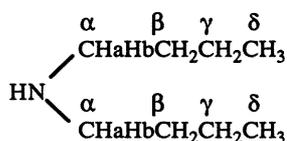


Fig. 2.2.1

It is noticeable that for complexes (2.1c-e) and (2.2) the methylene groups attached to the nitrogen contain inequivalent hydrogens i.e. NCHaHb . In these cases the plane of symmetry does not coincide with the $\text{N}-\text{CH}_2$ bond and thus the protons are no longer equivalent (Fig 2.2.1(b)). The ^1H NMR spectrum of complex (2.1c) exhibits multiplets at δ 3.13 and 3.63 for the inequivalent protons Ha and Hb while the methyl groups are observed as a triplet (6H) at δ 1.22 ($J = 7$). Similarly, for complex (2.1d) the inequivalent α -methylene protons are observed as multiplets at δ 3.01 and 3.47.



The ^1H NMR spectrum of the complex (2.1d) also displays multiplets at δ 1.28 and 1.55 which correspond to the β and γ protons, the methyl groups are assigned to the triplet (6H) at δ 0.90 ($J = 7$). The observation of inequivalent methylene hydrogens in these complexes shows that the dissociation of amine is slow, at least on the NMR timescale because in the free amine the protons are equivalent.

The complexes (2.1c) and (2.1d) are unstable in solution with some loss of ligand occurring. Thus free diethylamine or dibutylamine is always observed in the ^1H NMR of the products (2.1c) and (2.1d) respectively. Complex (2.1c) also decomposes in the solid state over a period of several days and hence the analysis results are inaccurate. Inequivalent methylene protons are also observed in the piperidine adduct (2.1e), as shown in Fig 2.2.2.

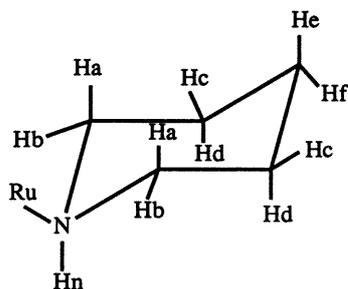
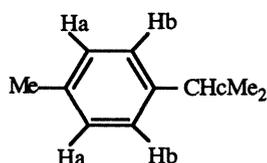


Fig 2.2.2

One of the protons (Hb) is observed as a doublet at δ 3.75 ($^2J_{\text{ab}} = 12$) with coupling to Ha only, whereas Ha gives rise to a pseudo-quartet at δ 2.93 which is actually a doublet of doublet of doublets with coupling to Hb, Hd and also to the N-H all with the same coupling constants, where $J_{\text{ad}} = J_{\text{an}} = 12$ and $^2J_{\text{ab}} = 12$. The remaining protons are assigned to the complex signals between δ 1.35 and 1.90.

In the ^1H NMR spectrum of $[(p\text{-cymene})\text{RuCl}_2(\text{NHEt}_2)]$ (2.2) the cymene ring protons are assigned as follows:



A doublet at δ 1.31 ($J = 7$) is observed for the two methyl groups of the isopropyl group with the corresponding Hc proton being observed as a septet at δ 3.03 ($J = 7$). The remaining methyl group is assigned to the singlet at δ 2.23 while Ha and Hb are seen as an $(\text{AB})_2$ pattern at δ 5.33 and 5.37 ($J(\text{AB}) = 6$). The amine ligand contains inequivalent methylene protons, as seen for complex (2.1c), which are observed as multiplets at δ 3.16 and 3.50; the adjacent methyl groups are assigned to the triplet at δ 1.22 ($J = 7$) while the NH proton is not visible.

In the reactions with benzylamine, two products could be formed, depending on the reaction time or the solvent used. The neutral adduct $[(\text{mes})\text{RuCl}_2(\text{NH}_2\text{CH}_2\text{Ph})]$ (2.1b) is the sole product when $[(\text{mes})\text{RuCl}_2]_2$ is refluxed in hexane with excess benzylamine or when refluxing in CH_2Cl_2 with one equivalent of amine per ruthenium atom. If excess benzylamine is used in either CHCl_3 or CH_2Cl_2 then a mixture of the complex (2.1b) and its corresponding cationic adduct $[(\text{mes})\text{RuCl}(\text{NH}_2\text{CH}_2\text{Ph})_2]\text{Cl}$ are formed which cannot be separated easily. This solvent dependence has been observed previously in the reaction of 3,5-dimethylpyrazole with $[(\text{C}_6\text{H}_6)\text{RuCl}_2]_2$.⁴⁷ In benzene, the neutral adduct $[(\text{C}_6\text{H}_6)\text{RuCl}_2(\text{Me}_2\text{Hpz})]$ was isolated, whereas in methanol the cationic species $[(\text{C}_6\text{H}_6)\text{RuCl}(\text{Me}_2\text{Hpz})_2]\text{Cl}$ was formed. In the latter case the increased polarity of the solvent favours the ionic product. Wright *et al.*,⁹⁹ whilst studying the ultrasonic reactions of arene-ruthenium dimers also observed coordination of a second amine to give a cationic product when *p*-toluidine was used in excess. In addition, we found cationic formation with benzylamine, however, we did not see any evidence of cationic formation with excess aniline. The reason for this observation is not clear.

A variety of mesitylene-ruthenium complexes have been prepared with both primary and secondary amines coordinated, however, we were not able to prepare the complex [(mes)RuCl₂(NH₂^tBu)]. The reaction was attempted using excess ligand in hexane, CHCl₃ and CH₂Cl₂, which all proved unsuccessful. The analogous complex [(*p*-cymene)RuCl₂(NH₂^tBu)] has been prepared by Wright using ultrasound.⁹⁹ We also synthesised the same complex by the thermal reaction of [(*p*-cymene)RuCl₂]₂ with NH₂^tBu in refluxing CH₂Cl₂. The ¹H NMR spectrum of the product was identical to that reported by Wright. This apparent difference in reactivity between the mesitylene and *p*-cymene dimers towards NH₂^tBu may be due an increased amount of steric hindrance between the mesitylene ligand and the amine.

Although NH₂^tBu was the only primary amine not to react with [(mes)RuCl₂]₂, secondary amine adduct formation was possible with diethylamine, dibutylamine and piperidine, with the piperidine complex being most stable. No reaction was seen with diphenylamine or triethylamine. Steric factors are probably the reason that triethylamine does not react, whereas with diphenylamine the major factor is more likely to be related to the poor electron donating power of the phenyl groups.

In order to try and assess the degree of steric crowding in these complexes we determined the crystal structure of the piperidine adduct (2.1e), as shown in Fig 2.2.3. For comparison purposes the structure of the complex [(mes)RuCl₂(py)], which has been made previously,¹⁷ was also determined (Fig 2.2.4). Selected bond lengths and angles are listed in Table 2.2.1 for complex (2.1e) and Table 2.2.2 for the pyridine adduct. The crystals of [(mes)RuCl₂(pip)] (2.1e) were grown from a dichloromethane/mesitylene mixture while those of [(mes)RuCl₂(py)] were obtained from a dichloromethane/diethylether mixture.

The Ru–N bond distance in complex (2.1e), 2.153(4) Å, is longer than in the pyridine complex, 2.127(7) Å, as expected. The Ru–Cl bond lengths are slightly different in complex (2.1e), 2.409(2) and 2.422(1) Å, while the corresponding distances are the same for the pyridine complex, 2.419(2) and 2.415(2) Å. The Cl–Ru–Cl bond angles are the same in both complexes at 88.4(1)°. A notable feature in the structure of complex (2.1e) is the orientation of the piperidine, with the N–H pointing away from the mesitylene and the more sterically

demanding CH₂ groups pointing towards the mesitylene. This may be due to attractive forces between the piperidine ring and the methyl groups on the mesitylene and also the possibility of hydrogen bonding between the N–H and the two chlorine atoms. The N⋯Cl separations of 2.95 and 3.02 Å and the N–Ru–Cl bond angles of 80.4(1) and 82.4(1)° are smaller than the corresponding distances (3.15 and 3.09 Å) and angles [87.4(2) and 85.4(2)°] observed for the pyridine complex, and are consistent with there being some hydrogen bonding between the N–H and the chlorine atoms. However, these differences may also be the result of increased steric hindrance between the piperidine and the mesitylene thus forcing the piperidine to be closer to the chlorines. Given that the N–H proton was not found in the difference Fourier map and has been included in a calculated position, it is difficult to determine which of the above factors has the greatest effect on the orientation of the piperidine ring.

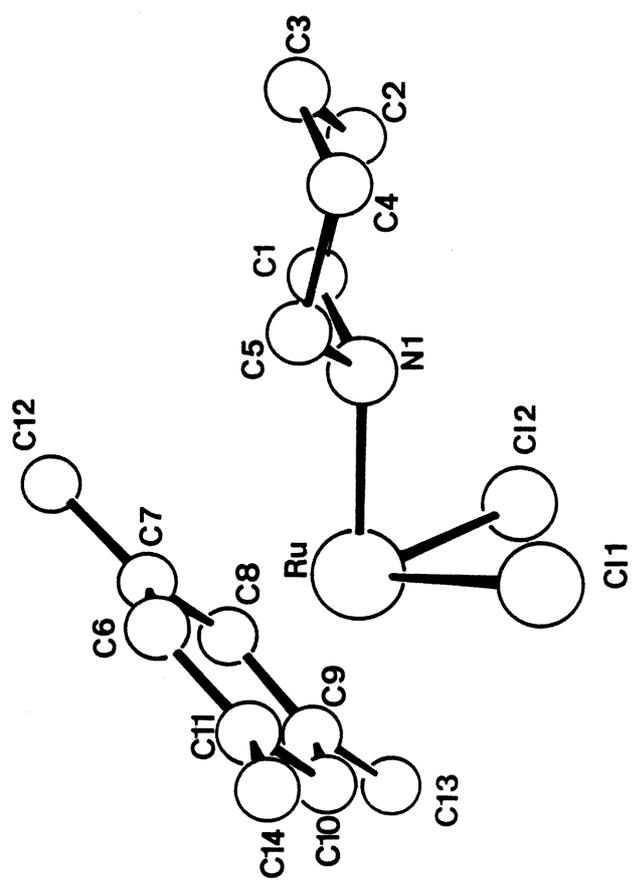


Fig. 2.2.3. Molecular Structure of [(mes)RuCl₂(pip)] (2.1e).

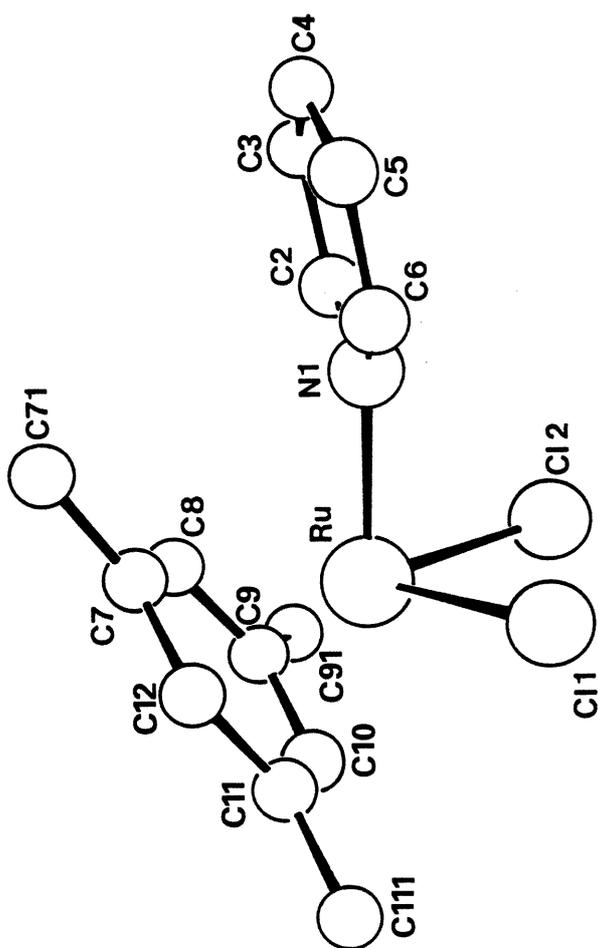


Fig. 2.2.4. Molecular Structure of $[(\text{mes})\text{RuCl}_2(\text{py})]$.

Table 2.2.1 Selected Bond Distances and Angles of [(mes)RuCl₂(pip)] (2.1e)

BOND DISTANCES (Å)			
Ru – Cl(1)	2.409(2)	Ru – C(8)	2.182(5)
Ru – Cl(2)	2.422(1)	Ru – C(9)	2.213(5)
Ru – N(1)	2.153(4)	Ru – C(10)	2.172(5)
Ru – C(6)	2.183(5)	Ru – C(11)	2.182(5)
Ru – C(7)	2.204(5)		
BOND ANGLES (°)			
Cl(1) – Ru – Cl(2)	88.4(1)	N(1) – Ru – Cl(2)	82.4(1)
N(1) – Ru – Cl(1)	80.4(1)	C(5) – N(1) – C(1)	110.1(5)

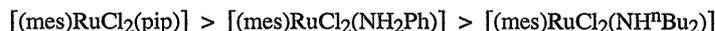
Table 2.2.2 Selected Bond Distances and Angles of [(mes)RuCl₂(pv)]

BOND DISTANCES (Å)			
Ru – Cl(1)	2.419(2)	Ru – N(1)	2.127(7)
Ru – Cl(2)	2.415(2)		
BOND ANGLES (°)			
Cl(1) – Ru – Cl(2)	88.4(1)	N(1) – Ru – Cl(2)	85.4(2)
N(1) – Ru – Cl(1)	87.4(2)		

In our attempts to determine the role of steric factors and their effects on the relative stability of the amine complexes, we attempted some amine exchange reactions.



No reaction occurred between aniline and $[(\text{mes})\text{RuCl}_2(\text{pip})]$, however, when $[(\text{mes})\text{RuCl}_2(\text{NH}^n\text{Bu}_2)]$ was reacted with aniline, the dibutylamine was displaced and after work up the complex $[(\text{mes})\text{RuCl}_2(\text{NH}_2\text{Ph})]$ was isolated. The aniline ligand itself can be displaced by reacting $[(\text{mes})\text{RuCl}_2(\text{NH}_2\text{Ph})]$ and piperidine giving the complex $[(\text{mes})\text{RuCl}_2(\text{pip})]$ (2.1e). These results lead to the following series of stability;

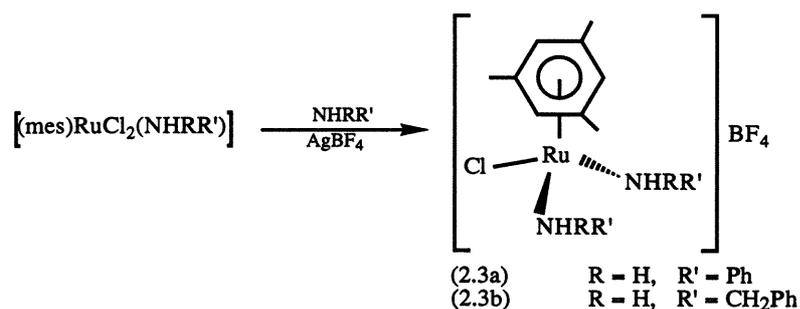


Qualitatively we have observed that primary amine complexes are more stable than secondary ones, however the piperidine complex seems to be a special case. The use of this amine exchange reaction is limited by the occurrence of competing side reactions in certain cases. For example, the reaction between the piperidine complex (2.1e) and one equivalent of benzylamine when monitored by ^1H NMR shows the presence of the starting complex (2.1e), some of the benzylamine adduct (2.1b), and some other species, which judging by the chemical shift of the mesitylene protons is due to a cationic species containing two amines.

From our work we conclude that the stability of the amine complexes is dependent on both steric and electronic factors. Steric factors are emphasised most by the fact that triethylamine does not react with $[(\text{mes})\text{RuCl}_2]_2$. The secondary piperidine complex (2.1e) is more stable than the primary adduct (2.1b) implying here that electronic factors are more important. During the course of our work a report has been published on amine exchange reactions of the complex cations $[(\text{dppe})\text{PdMe}(\text{NRR}'\text{R}'')]^+$ which concluded that both steric and electronic factors were important in determining the relative stability of the various cations.¹⁰⁰

As mentioned previously, with benzylamine it is possible to form the cation $[(\text{mes})\text{RuCl}(\text{NH}_2\text{CH}_2\text{Ph})_2]\text{Cl}$ by direct reaction of $[(\text{mes})\text{RuCl}_2]_2$ with benzylamine, however,

isolation of this complex was difficult. An alternative procedure is to react the amine adducts [(mes)RuCl₂(NHRR')] with one equivalent of amine and AgBF₄. Using this method we have isolated the complexes (2.3a) and (2.3b), which are characterised by ¹H NMR spectroscopy and microanalysis, Tables 2.3.1 and 2.3.3. Complex (2.3b) was also identified on the basis of its FAB mass spectrum (Table 2.3.2).



The ¹H NMR spectrum of complex (2.3a) shows the mesitylene signals are shifted to higher field than for complex (2.1a), being observed at δ 1.69 and 4.76, compared to δ 2.00 and 4.83 for the neutral adduct. The NH₂ protons are assigned to the broad peaks at δ 4.48 and 5.83 while the phenyl groups are observed as a multiplet at δ 7.35. For complex (2.3b) the mesitylene resonances are at lower field (δ 2.30 and 5.10) than those of the corresponding neutral adduct (2.1b) (δ 2.21 and 4.92), the methylene protons of both amine ligands are observed as a multiplet at δ 4.01 and the NH₂ groups are assigned to broad signals at δ 2.50 and 4.42. A multiplet at δ 7.34 is observed for the phenyl protons.

Since complexes (2.3) contain cationic ruthenium fragments one might expect a shift to lower field, as is observed with complex (2.3b). Thus, the upfield shift for the complex (2.3a) may be due to ring current effects of the phenyl rings. It is also noteworthy that for complex (2.1a) the methyl groups of the methylene ring are about 0.2 ppm upfield from the other adducts (2.1b-e), this may also be a consequence of a ring current effect.¹⁰¹

The complexes prepared in this Chapter are also stable to ultrasound with no decomposition occurring. We were able to form the phosphine complex [(mes)RuCl₂(PPh₃)] (2.4) by ultrasonic and thermal methods, however, none of the amine complexes described here

could be synthesised using the ultrasound technique. We have shown both steric and electronic factors are responsible for the stability of the amine complexes, while in certain cases no reactions occur. It is interesting that only with benzylamine does excess ligand result in cation formation, while cationic species were not observed with any other amine. The isolation of the cations was made easier by employing AgBF_4 to remove the chloride ligand.

2.3 - Experimental

All reactions were performed under an inert atmosphere though the work-up of reactions was done in air. Degassed solvents were used for the reactions and were dried over the appropriate drying agent, as listed below:

- (i) Dichloromethane from calcium hydride;
- (ii) Diethylether from sodium/benzophenone;
- (iii) Methanol from magnesium turnings and iodine, stored over Linde type 4Å molecular sieves.

^1H NMR spectra were recorded using a Varian EM390 (operating at 90MHz) or a Bruker AM300 (operating at 300.13 MHz) 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 an internal reference, coupling constants J were measured in hertz and refer to 3J coupling unless otherwise stated. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra were recorded using a Jeol FX90Q spectrometer operating at 36.21MHz, $[\text{P}(\text{OH})_4]^+$ in D_2O was used as an external reference, with positive values to high frequency (low field). Jeol FX90Q and Bruker AM300 spectrometers were operated in the Fourier transform mode. Fast atom bombardment (FAB) mass spectra with nitrobenzylalcohol (NOBA) as the matrix were obtained using the SERC Mass Spectroscopy Service Centre at University College, Swansea or recorded on a Kratos Concept double focussing Mass Spectrometer here in Leicester. Microanalyses were performed by Butterworth Laboratories Ltd; 54-56, Waldegrave Road, Teddington, Middlesex. Ultrasound reactions were carried out using a Sonicator Ultrasonic Liquid Processor (Model W385).

All chemicals were obtained from Aldrich Chemical Co. Ltd; and used as received, except Ruthenium trichloride (Johnson Matthey p.l.c), [(mes)RuCl₂]₂²² and [(*p*-cymene)RuCl₂]₂²³ were prepared by literature methods.

Preparation of [(mes)RuCl₂(NH₂Ph)] (2.1a)

Aniline (114 mg, 1.55 mmol) was added to a suspension of [(mes)RuCl₂]₂ (301 mg, 0.52 mmol) in dichloromethane (50 cm³) and the mixture was refluxed for 2.5 hours. The solvent was removed and the solid washed with petroleum ether. Recrystallisation from dichloromethane/diethylether gave [(mes)RuCl₂(NH₂Ph)] (2.1a) as a yellow solid (338 mg, 85%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 2.3.1 - 2.3.3.

Preparation of [(mes)RuCl₂(NH₂CH₂Ph)] (2.1b)

Using the same procedure as for complex (2.1a), benzylamine (90 mg, 0.84 mmol) and [(mes)RuCl₂]₂ (245 mg, 0.42 mmol) were reacted in dichloromethane (50 cm³) to give, after work-up, [(mes)RuCl₂(NH₂CH₂Ph)] (2.1b) as orange crystals (287 mg, 87%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 2.3.1 - 2.3.3.

Preparation of [(mes)RuCl₂(NHEt₂)] (2.1c)

Diethylamine (94 mg, 1.2 mmol) was added to a suspension of [(mes)RuCl₂]₂ (251 mg, 0.43 mmol) in chloroform (50 cm³) and the mixture was refluxed for 2 hours. The solvent was removed and the solid washed with petroleum ether to leave [(mes)RuCl₂(NHEt₂)] (2.1c) as a yellow solid (232 mg, 74%). The compound was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 2.3.1 - 2.3.3.

Preparation of [(mes)RuCl₂(NHⁿBu₂)] (2.1d)

Using the same procedure as for complex (2.1c), dibutylamine (278 mg, 2.15 mmol) and [(mes)RuCl₂]₂ (252 mg, 0.43 mmol) were refluxed in chloroform (75 cm³) for 1.5 hours to give, after work-up, [(mes)RuCl₂(NHⁿBu₂)] (2.1d) as a yellow solid (363 mg, 90%). The compound was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 2.3.1 - 2.3.3.

Preparation of [(mes)RuCl₂(pip)] (2.1e)

Using the same procedure as for complex (2.1a), piperidine (183 mg, 2.15 mmol) and [(mes)RuCl₂]₂ (252 mg, 0.43 mmol) were refluxed in chloroform (50 cm³) for 3 hours, to give after work-up, [(mes)RuCl₂(pip)] (2.1e) as an orange solid (281 mg, 86%). The compound was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 2.3.1 - 2.3.3.

Preparation of [(*p*-cymene)RuCl₂(NHEt₂)] (2.2)

Using the same procedure as for complex (2.1a), diethylamine (39 mg, 0.53 mmol) and [(*p*-cymene)RuCl₂]₂ (108 mg, 0.176 mmol) were refluxed in chloroform (50 cm³) for 3 hours to give, after work-up, [(*p*-cymene)RuCl₂(NHEt₂)] (2.2) as a bright yellow solid (66 mg, 50%). The compound was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 2.3.1 - 2.3.3.

Preparation of [(*p*-cymene)RuCl₂(NH₂^tBu)]

tert-butylamine (148 mg, 2.03 mmol) was added to a solution of [(*p*-cymene)RuCl₂]₂ (155 mg, 0.25 mmol) in dichloromethane (50 cm³) and refluxed for 20 hours, after which time the colour changed from orange to red. The solvent was removed and the residue recrystallised from dichloromethane/diethylether to give [(*p*-cymene)RuCl₂(NH₂^tBu)] as red crystals (156 mg, 81%). The complex was characterised by ¹H NMR spectroscopy, with data being the same as previously reported.⁹⁹

Amine exchange reactions

Complex (2.1d) (250 mg, 0.59 mmol) and aniline (166 mg, 1.78 mmol) were refluxed in chloroform (50 cm³) for 2.5 hours. The solvent was removed and the oily solid was washed with petroleum ether to give a yellow solid identified as complex (2.1a) on the basis of its ¹H NMR spectrum (157 mg, 70%).

The same general procedure was used for the reaction of complex (2.1a) with piperidine in equimolar amounts to give complex (2.1e) in 71% yield. Using the same method refluxing of complex (2.1e) with aniline gave no reaction.

Preparation of [(mes)RuCl(NH₂Ph)₂]BF₄ (2.3a)

Aniline (48 mg, 0.52 mmol), followed by AgBF₄ (101 mg, 0.52 mmol) were added to a solution of [(mes)RuCl₂(NH₂Ph)] (2.1a) (200 mg, 0.52 mmol) in dichloromethane (50 cm³) and the mixture was stirred for 0.5 hours. The solid AgCl formed was removed by filtration through Celite and the solvent was removed by rotary evaporation. Recrystallisation from dichloromethane/diethylether gave [(mes)RuCl(NH₂Ph)₂]BF₄ (2.3a) as an orange crystalline solid (259 mg, 94%). The compound was characterised by ¹H NMR and microanalysis, Tables 2.3.1 and 2.3.3.

Preparation of [(mes)RuCl(NH₂CH₂Ph)₂]BF₄ (2.3b)

Using the same procedure as for complex (2.3a), benzylamine (47 mg, 0.44 mmol), AgBF₄ (86 mg, 0.44 mmol) and [(mes)RuCl₂(NH₂CH₂Ph)] (2.1b) (177 mg, 0.44 mmol) were reacted in dichloromethane (60 cm³) for 0.5 hours to give, after work-up, [(mes)RuCl(NH₂CH₂Ph)₂]BF₄ (2.3b) as an orange crystalline solid (170 mg, 68%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 2.3.1 - 2.3.3.

Preparation of [(mes)RuCl₂(PPh₃)] (2.4)

Method (a)

Triphenylphosphine (283 mg, 1.08 mmol) was added to a suspension of [(mes)RuCl₂]₂ (252 mg, 0.43 mmol) in chloroform (30 cm³) and subjected to ultrasound for 1 hour using a sonic horn, after which time a red solution was observed. The solvent was removed and the residue recrystallised from dichloromethane/diethylether to give [(mes)RuCl₂(PPh₃)] as a red crystalline solid (365 mg, 76%). The complex was identified by ³¹P{¹H} and ¹H NMR spectroscopy. ³¹P{¹H}: δ +31.88. ¹H NMR (CDCl₃): δ 1.97 (s, 9H, C₆Me₃), δ 4.63 (s, 3H, C₆H₃), δ 7.30 (m, 7H, PPh₃), δ 7.70 (m, 8H, PPh₃).

Method (b)

Triphenylphosphine (284 mg, 1.08 mmol) was added to a suspension of [(mes)RuCl₂]₂ (252 mg, 0.43 mmol) in chloroform (50 cm³) and refluxed for 3 hours. The solvent was removed and the residue recrystallised from dichloromethane/diethylether to give [(mes)RuCl₂(PPh₃)] as a red solid (382 mg, 79%). The complex was identified by ³¹P{¹H} and ¹H NMR spectroscopy with identical data to that above.

Table 2.3.1 ^1H NMR data for complexes (2.1 - 2.3) in CDCl_3 ^a

Complex	Arene Protons (δ)		Amine Protons (δ)
	C_6Me_3	C_6H_3	
2.1a	2.00	4.83	7.25 (m, 5H, Ph)
2.1b	2.21	4.92	3.22 (br, 2H, NH), 4.21 (s, 2H, CH_2), 7.30 (m, 5H, Ph)
2.1c	2.26	4.91	1.22 [t, 6H, CH_3 , J(7)], 3.13 (m, 2H, CHaHb), 3.63 (m, 2H, CHaHb)
2.1d	2.26	4.90	0.90 [t, 6H, CH_3 , J(7)] 1.28 (m, 4H, CH_2), 1.55 (m, 4H, CH_2), 3.01 (m, 2H, CHaHb), 3.47 (m, 2H, CHaHb)
2.1e	2.26	4.97	1.35 - 1.90 (m, 6H, various pip), 2.93 [q, 2H, CHaHb , $^2\text{J}(12)$], J(12)], 3.75 [d, 2H, CHaHb , $^2\text{J}(12)$]
2.2 ^b	-	-	1.22 [t, 6H, CH_3 , J(7)], 3.16 (m, 2H, CHH), 3.50 (m, 2H, CHH)
2.3a	1.69	4.76	4.48 (br, 2H, NH), 5.83 (br, 2H, NH), 7.35 (m, 10H, Ph)
2.3b ^c	2.30	5.10	2.50 (br, 2H, NH), 4.01 (m, 4H, CH_2), 4.42 (br, 2H, NH), 7.34 (m, 10H, Ph)

^a All J values refer to ^3J coupling unless otherwise stated.

^b The (*p*-cymene) assignments are as follows:

δ 1.31 [d, 6H, CHcMe_2 , J(7)], 2.23 (s, 3H, $\text{C}_6\text{H}_4\text{Me}$), 3.03 [sep. 1H, CHcMe_2 , J(7)], 5.33, 5.37 [(AB)₂, 4H, C_6H_4 , J(AB)6].

^c in CD_2Cl_2 .

Table 2.3.2 Mass spectroscopy data for complexes (2.1b-e) and (2.3b)^a

Complex	[M+H] ⁺	Other Peaks
[(mes)RuCl ₂ (NH ₂ CH ₂ Ph)] (2.1b)	399 ^b	364 [M-Cl] ⁺
[(mes)RuCl ₂ (NHEt ₂)] (2.1c)	366 ^b	
[(mes)RuCl ₂ (NH ^t Bu ₂)] (2.1d)	422 ^c	
[(mes)RuCl ₂ (pip)] (2.1e)	378 ^c	342 [M-Cl] ⁺
[(mes)RuCl(NH ₂ CH ₂ Ph) ₂]BF ₄ (2.3b)	471 ^{cd}	364 [M-NH ₂ CH ₂ Ph] ⁺

^a Mass spectra for complexes (2.1a), (2.2) and (2.3a) are not available.

^b Only the [M]⁺ ion is observed.

^c The [M]⁺ ion is also observed.

^d M refers to the complex cation.

Table 2.3.3 Elemental analyses of complexes (2.1 - 2.3)

Complex	Found (%)			Calculated (%)		
	C	H	N	C	H	N
[(mes)RuCl ₂ (NH ₂ Ph)] (2.1a)	47.18	4.83	3.55	46.77	4.97	3.64
[(mes)RuCl ₂ (NH ₂ CH ₂ Ph)] (2.1b)	48.25	5.59	3.37	48.13	5.30	3.51
[(mes)RuCl ₂ (NHEt ₂)] (2.1c)	33.37	4.32	1.26	42.74	6.35	3.83
[(mes)RuCl ₂ (NH ^t Bu ₂)] (2.1d)	48.58	7.64	3.61	48.44	7.42	3.32
[(mes)RuCl ₂ (pip)] (2.1e)	44.54	5.95	3.71	44.50	6.14	3.71
[(<i>p</i> -cymene)RuCl ₂ (NHEt ₂)] (2.2)	43.65	6.55	3.55	44.33	6.64	3.69
[(mes)RuCl(NH ₂ Ph) ₂][BF ₄] (2.3a)	47.23	4.88	4.96	47.61	4.95	5.29
[(mes)RuCl(NH ₂ CH ₂ Ph) ₂][BF ₄] (2.3b)	49.68	5.43	4.90	49.52	5.42	5.02

Chapter Three

The Synthesis and Reactions of Arene-Ruthenium

Complexes with Amino Acids

and other N_2O Donor Ligands

CHAPTER 3 - THE SYNTHESIS AND REACTIONS OF ARENE-RUTHENIUM
COMPLEXES WITH AMINO ACIDS AND
OTHER N, O DONOR LIGANDS

3.1 - Introduction

Amino acids are the building blocks of peptides and proteins, and as such they are a major constituent of living cells. They have the general formula "NH₂CH(R)CO₂H", however in aqueous media they exist in the 'Zwitterionic' form, which is pH dependent.



Consequently, depending upon the pH, the amino acids can coordinate through either or both of the amino (NH₂) or carboxylate (CO₂⁻) groups. The coordination chemistry of amino acids has been extensively reviewed by Laurie.¹⁰² Monodentate coordination occurs through the nitrogen atom with metal ions such as Cr^{III}, Co^{III}, Ir^{III}, Pt^{II} and Rh^{III}, monodentate coordination through the weaker field oxygen atom is seldom seen, but has been observed with Co^{III} and Pt^{II}. More common is bidentate coordination through both the nitrogen and oxygen atoms, which gives rise to a thermodynamically stable 5-membered ring for α-amino acids (6-membered for β-alanine), Fig 3.1.1. This chelate formation is well established for metal ions such as Co^{III}, Rh^{III}, Ru^{III} and Pt^{II} to give complexes of the types: [M^{II}(aa)₂], [M^{III}(aa)₃], [ML(aa)₂] etc. Amino acids with coordinating side chains such as histidine or cysteine can also react to form bidentate complexes. However, coordination can also occur through the side chain group to give tridentate compounds. These are discussed further by Laurie.¹⁰²

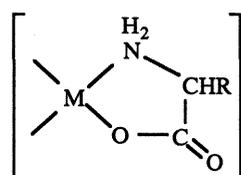


Fig 3.1.1

Amino acids, except for glycine ($R = H$) contain a chiral carbon atom and can thus exist as two enantiomeric forms, Fig 3.1.2. However, naturally occurring acids exist as the *l*-enantiomer only (which have the [S] configuration).

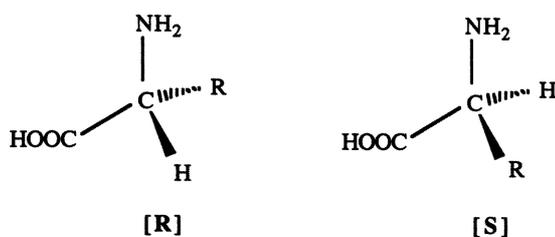


Fig 3.1.2

If a chiral ligand such as an amino acid is attached to a metal which itself contains a chiral centre, it results in enantiomeric and diastereomeric complexes (a-d), as shown below, Fig 3.1.3.

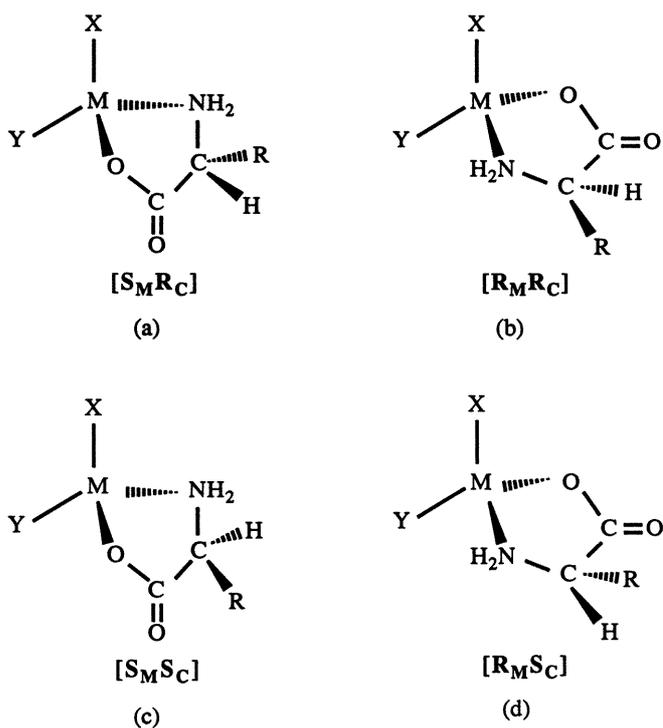
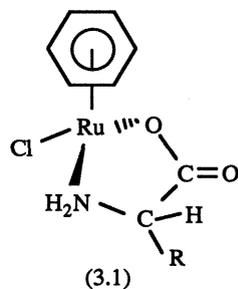


Fig 3.1.3

The chiral centres are assigned [R] and [S] according to Baird¹⁰³ and Sloan's¹⁰⁴ proposals, where the order of priority of the ligands reads X > Y > O > N. The resolution of racemic mixtures via coordination to a metal has been well documented,^{105,106} [Cu(*l*-aa)₂] complexes can be used to resolve *d,l*-Asp, *d,l*-Glu and *d,l*-His.^{105,106} Schiff base complexes of both Co^{III} and Ni^{II} have also been used to resolve amino acids.^{107,108}

Organometallic compounds containing a chiral metal centre have been the subject of recent interest because they can offer a possibility of highly enantioselective catalytic or stoichiometric reactions.¹⁰⁹⁻¹¹² Dersnah and Baird reported the first chiral arene-ruthenium complex in 1977,¹¹³ they prepared the complex [(C₆H₆)RuCl(NH₂CHRCOO)] (R = Me) (3.1) as a pair of diastereomers which were not separated.



A year later, Brunner and Gastinger synthesised the optically active complexes (3.2), shown in Fig 3.1.4, by employing the phosphine ligand [R-(+)-Ph₂PNHCH(Me)Ph] and reacting it with [(C₆H₆)RuCl₂]₂ in the presence of HgMe₂ to afford a pair of diastereomers which were then separated by chromatography.^{114,115}

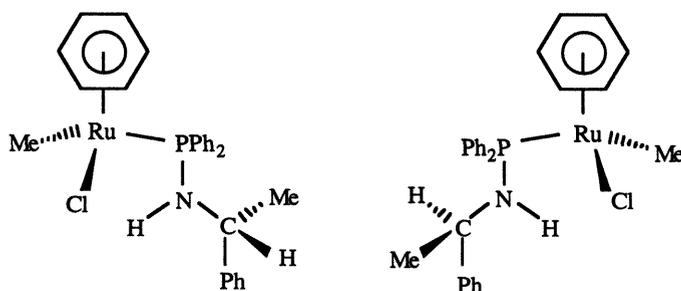
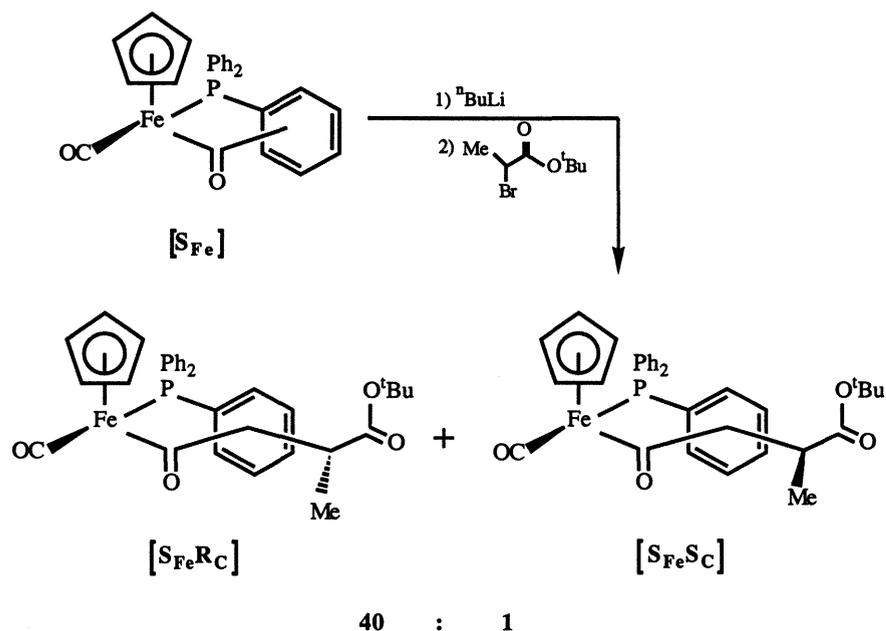


Fig 3.1.4

A different kind of chirality was reported by Bennett *et al.*,⁹⁸ they described the synthesis of $[(\eta^6\text{-}o\text{-MeC}_6\text{H}_4\text{CO}_2\text{Me})\text{RuCl}_2]_2$, which was the first example of an arene-ruthenium complex having planar chirality. This molecule has two different substituents on the arene ring, which generate a planar chirality in the coordination to the metal with respect to the face of the coordinated arene. The complex $[(\eta^6\text{-}o\text{-MeC}_6\text{H}_4\text{CO}_2\text{Me})\text{RuCl}_2]_2$, was reacted with various amines and phosphines to give diastereomers which could be separated by physical methods.⁹⁸

The importance of chiral complexes was seen more recently, where Davies *et al.*¹¹⁶ used a cyclopentadienyl complex to show enhanced enantioselectivity in organic syntheses. They found that the lithium enolate derived from the homochiral iron-acetyl complex $S\text{-}[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})(\text{PPh}_2)\text{COCH}_3]$ reacted preferentially in a 40:1 ratio with the [R] enantiomer of racemic *t*-butyl-2-bromopropionate to give an iron-3-methyl-succinoyl complex of high diastereomeric purity, as can be seen in Scheme 3.1.1.



Scheme 3.1.1

The use of amino acids as ligands is of current interest because of their biological importance and the variety of coordination modes they can display.¹⁰² Although Dersnah and Baird reported the first arene-ruthenium amino acidate complex, it was not until the late 1980's that the subject was studied in greater depth.

Complexes of the types [(diene)RuCl(aa)₂],¹¹⁷ [(diene)IrCl(aa)]¹¹⁸ (diene = cyclo-octa-1,5-diene or norbornadiene), [CpMCl(aa)] (M = Rh, Ir),^{118,119} [(η⁶-arene)Os(PR₃)(aa)]X (R₃ = ⁱPr₃, Me^tBu₂; X = SbF₆, PF₆)¹²⁰ and [(η⁶-arene)RuCl(aa)]¹¹⁸ have been prepared using a variety of amino acids which include alanine, valine, phenylglycine and proline which coordinate through both the nitrogen and oxygen atoms. A pair of diastereomers were observed for most of the complexes and could be detected by spectroscopic, and in some cases X-ray methods. However, these diastereomers were not separated. Further work involving the preparation of some other arene-ruthenium amino acid complexes has been carried out by Sheldrick *et al.* and Oro *et al.*^{119,121}

Peptides and amino acids with coordinating side chains can also be used as ligands in organometallic chemistry.¹²²⁻¹²⁴ In particular, Sheldrick and Heeb have prepared some arene-ruthenium complexes using *l*-histidine and triglycine.¹²⁴ When *l*-histidine reacts with [(C₆H₆)RuCl₂]₂ a chelate complex (3.3) is formed in which coordination occurs via the amino (NH₂) and imidazole groups, Fig 3.1.5. Similarly, triglycine forms a bidentate product (3.4) when reacted with [(C₆H₆)RuCl₂]₂, which is also depicted in Fig 3.1.5. As with the histidine complex the carboxylate group does not participate in metal coordination because ruthenium(II) species prefer nitrogen donor ligands.

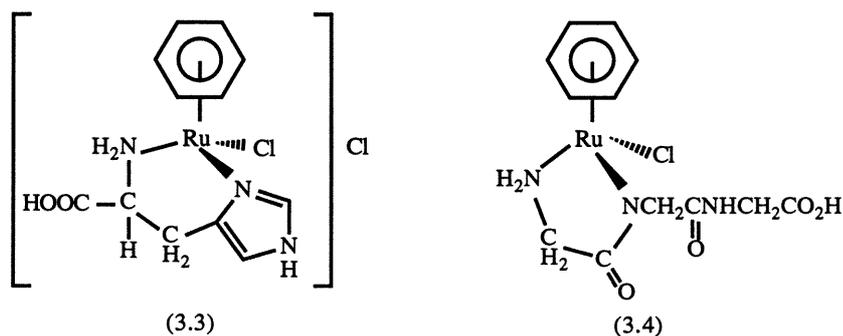


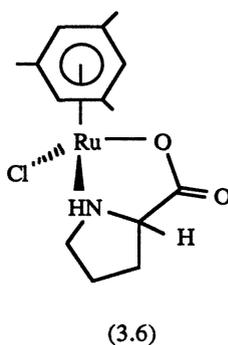
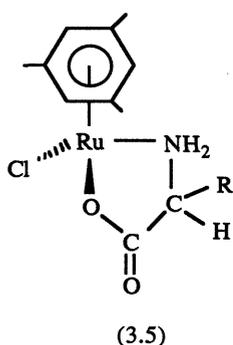
Fig 3.1.5

This chapter will look at the reactions of $[(\text{mes})\text{RuCl}_2]_2$ with various amino acids and other ligands which coordinate through the amino and carboxylate groups. We will also discuss the diastereomeric ratios of such complexes and factors which influence them.

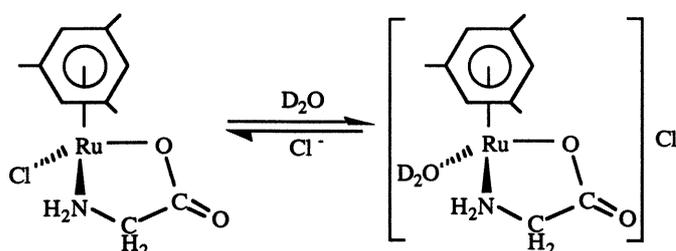
3.2 - Results and Discussion

3.2.1 - Amino Acid Complexes

Complexes (3.5) ($R = \text{H, Me, Ph, CH}_2\text{Ph}$ and CH_2CHMe_2) and (3.6) can be prepared in good to moderate yields by refluxing $[(\text{mes})\text{RuCl}_2]_2$ in a water/methanol mixture, with sodium methoxide and the appropriate amino acid. The sodium chloride formed in the reaction is removed by extraction of the complexes with dichloromethane. The compounds are characterised by microanalysis, ^1H NMR and mass spectroscopy, Tables 3.3.1 - 3.3.4.



In CDCl_3 the ^1H NMR spectra are not well resolved, however, in D_2O sharper peaks and better resolved multiplets are observed. The ^1H NMR spectrum of $[(\text{mes})\text{RuCl}(\text{gly})]$ (3.5; $R = \text{H}$) in D_2O shows two species are present in the solution, due to the substitution of the chloride ligand by D_2O , which results in an equilibrium being established, as shown in Scheme 3.2.1.



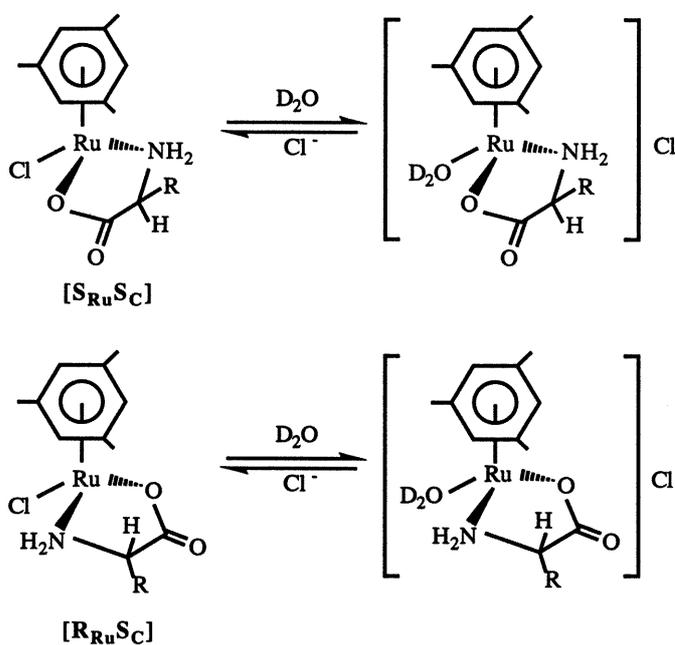
Scheme 3.2.1

The existence of such an equilibrium was first reported by Dersnah and Baird in 1977,¹¹³ for the analogous $[(C_6H_6)RuCl(gly)]$ complex. The three methyl groups of the mesitylene ligand are equivalent, due to rapid rotation of the ring on the NMR timescale, and hence, give rise to a singlet observed at δ 2.14 for the chloride complex, and δ 2.19 for the corresponding aquated species. The three aromatic protons are also observed as singlets at δ 5.19 and 5.31, for the chloride complex and the aquated species respectively. With both the chloro and the aquated species present the glycine protons are difficult to assign, the inequivalent α -protons are observed as two multiplets at δ 3.04 and 3.21 as an AB spin system with coupling to the amino protons, however, signals due to the two amino protons are not visible. Addition of a 10 fold excess of potassium chloride to the NMR sample causes the equilibrium to be displaced in favour of the chloride complex, resulting in a significant decrease in the intensity of the peaks due to the aquated species, making spectral assignments much easier.

Complexes (3.5) ($R = Me, Ph, CH_2Ph, CH_2CHMe_2$) contain two chiral centres, the ruthenium atom and the α -carbon of the amino acidate ligands. In each case the *l*-amino acid, which has the [S] configuration at the α -carbon (*d*-amino acids are assigned [R]), was employed as the ligand. The ruthenium atom can have an [R] or [S] configuration, therefore there are two possible diastereomers $[R_{Ru}S_C]$ and $[S_{Ru}S_C]$ for each complex, which are both observed by 1H NMR spectroscopy. The 1H NMR spectra in D_2O show the existence of four species which are attributed to the two diastereomers mentioned above, and the two corresponding diastereomers of the aquated species, as shown in Scheme 3.2.2.

As explained above, addition of excess potassium chloride displaces the equilibrium in favour of the chloride complex. It is also possible to displace the equilibrium towards the

aquated species, by addition of silver nitrate to the sample. Silver chloride was precipitated and filtered, leaving the aquated cation in solution. Although they can be observed in the ^1H NMR spectra, the spectra are usually very weak and therefore not easy to assign fully, we will focus our attention on the ^1H NMR spectra in D_2O and those with added KCl. The difference between the spectrum in D_2O and that with KCl added is highlighted for the complex $[(\text{mes})\text{RuCl}(\text{ala})]$ (3.5; $\text{R} = \text{Me}$), in Fig. 3.2.1.



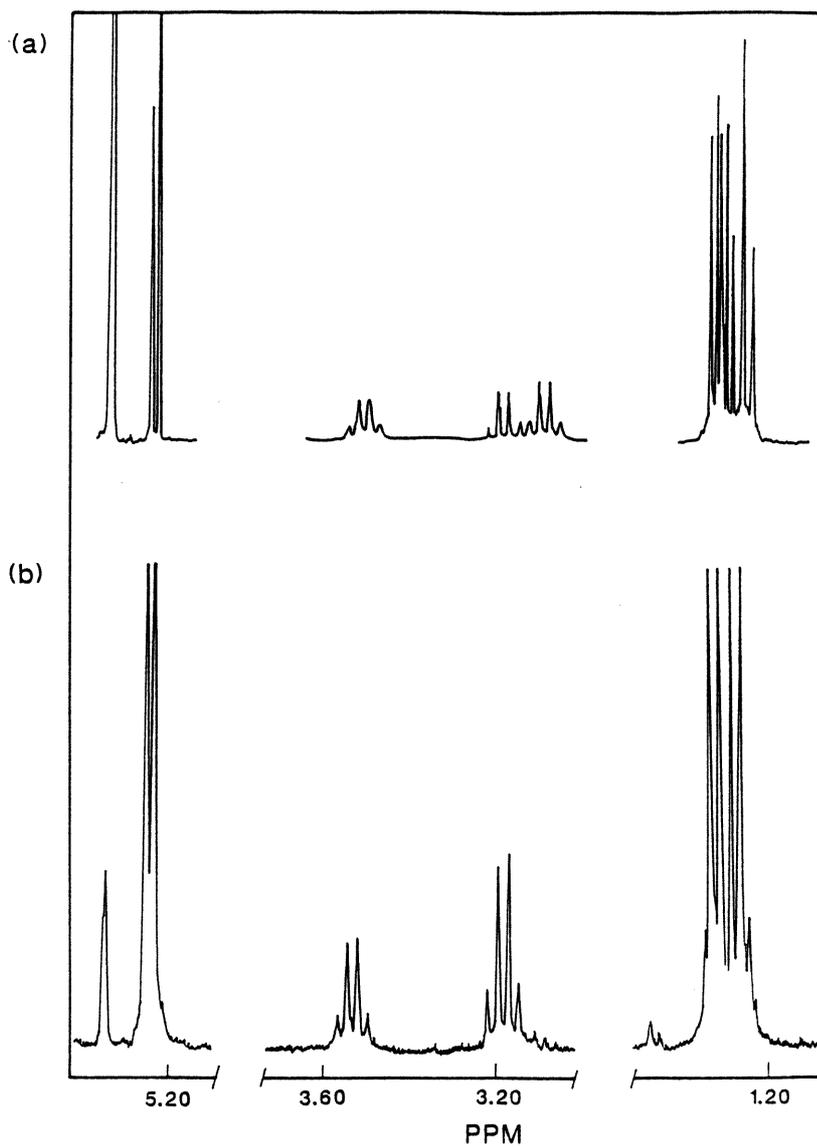
Scheme 3.2.2

Note: on replacement of Cl by D_2O the configuration at the ruthenium centre does actually change, this is not due to a physical rearrangement of other bonds in space, but due to the method used to assign the configuration.^{103,104} The CO_2 group has higher priority than the D_2O group, but lower than Cl, therefore the ruthenium metal changes to the opposite configuration upon D_2O substitution.

Fig. 3.2.1. Selected Regions of ^1H NMR Spectra of;

a) $[(\text{mes})\text{RuCl}(\text{ala})]$ in D_2O .

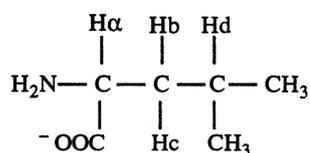
b) $[(\text{mes})\text{RuCl}(\text{ala})]$ in D_2O with added KCl.



In the ^1H NMR spectrum of $[(\text{mes})\text{RuCl}(\text{ala})]$ (3.5; $\text{R} = \text{Me}$) in D_2O , the aromatic protons are observed as four singlets at δ 5.24 (5.26) for the chloride complex, and δ 5.33 (5.34) for the aquated species, the minor diastereomer is shown in parentheses. The methyl groups of the mesitylene only give rise to two peaks at δ 2.15 and 2.18 due to the chloride coordinated and aquated species respectively. Thus, the separate signals are resolved for the aromatic protons of the different diastereomers but not for those of the methyl groups, presumably because they are further from the ruthenium centre. The alaninate protons are observed as a quartet at δ 3.18 (3.53) ($J = 7$) and a doublet at δ 1.33 (1.27) ($J = 7$) due to the α -proton and methyl group respectively of the chloride complex; with the analogous signals at δ 3.09 (3.53) ($J = 7$) and δ 1.31 (1.25) ($J = 7$) for the aquated species, in each case the corresponding signals for the minor diastereomer are shown in parentheses. The NH_2 protons become inequivalent upon coordination to the ruthenium centre, however they are not observed in this case possibly because they are broad and/or H-D exchange may have taken place. An identical spectrum is observed when *d*-alanine is used as the ligand, although the configuration at the α -carbon is different, the observed diastereomers are $[\text{R}_{\text{Ru}}\text{R}_{\text{C}}]$ and $[\text{S}_{\text{Ru}}\text{R}_{\text{C}}]$ which are enantiomeric with $[\text{S}_{\text{Ru}}\text{S}_{\text{C}}]$ and $[\text{R}_{\text{Ru}}\text{S}_{\text{C}}]$, and therefore give rise to an identical ^1H NMR spectrum.

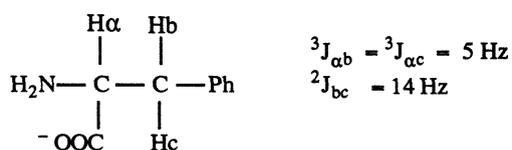
In general, for complexes (3.5) and (3.6) the signals due to the methyl groups of the mesitylene are observed between δ 2.10 and 2.20 for chloride complex, and between δ 2.11 and 2.21 for the corresponding aquated species. Signals for the aromatic protons are observed further downfield between δ 5.19 and 5.34 for the chloride complex, and between δ 5.29 and 5.42 for the aquated species. For the remaining amino acidate complexes, four species are always observed in the ^1H NMR spectra in D_2O .

The ^1H NMR spectrum of $[(\text{mes})\text{RuCl}(\text{leuc})]$ (3.5; $\text{R} = \text{CH}_2\text{CHMe}_2$) shows peaks due to the mesitylene in the expected regions, Table 3.3.1. The ligand protons are assigned as follows:



The two inequivalent methyl groups are observed as doublets at δ 0.96 ($J = 6$) and 0.87 ($J = 6$), for the major diastereomer and at δ 0.92 ($J = 6$) and 0.87 ($J = 6$) for the minor one. The lowest field multiplets at δ 3.45 and 3.09 are assigned to the α -proton of the minor and major diastereomers respectively, while the multiplets at δ 1.76 (1H) and 1.54 (2H) are assigned to the remaining protons (Hb, Hc and Hd). A broad signal at δ 5.79 (2H) is assigned to the NH_2 group of one diastereomer, though the two hydrogens are nominally inequivalent only one signal is observed.

The complex [(mes)RuCl(Phgly)] (3.5; R = Ph) shows the expected signals for the mesitylene (Table 3.3.1). The α -protons are observed as two singlets at δ 4.27 and 4.58 for the major and minor diastereomers respectively, while the phenyl group appears as a complex signal in the region δ 7.10 - 7.55. Uncharacteristic mesitylene shifts are observed for the major diastereomers of complex [(mes)RuCl(Phala)] (3.5; R = CH_2Ph). Signals at δ 1.99 and 4.84, and δ 2.03 and 4.95 are assigned to the mesitylene ring of the major diastereomer, of the chloride and aquated species respectively. The corresponding signals for the minor diastereomer are observed at δ 2.09 and 5.20 for the chloride complex, and δ 2.11 and 5.29 for the aquated species. The considerable shift to lower frequency for the major diastereomer may be caused by an interaction of the mesitylene ring and the other phenyl ring. In the [S_{Ru}SC] diastereomer, the two rings are reasonably close to each other and the ring current of the phenyl ring may, thus affect the shifts of the mesitylene. The benzylic protons are inequivalent since there is no mirror plane through the group thus an ABX spin system occurs which is only slightly second order (ascertained from the slight perturbation in line intensities) and can be assigned by first order principles. For the major diastereomer two partially overlapping AB quartets at δ 3.04 (${}^2J = 14$, $J = 5$) and 3.17 (${}^2J = 14$, $J = 5$) are observed, corresponding to Hb and Hc which couple to each other and to H α , while H α is observed as a triplet at δ 3.37 ($J = 5$).



The signals due to the H_b and H_c protons of the minor diastereomer were not assigned because the peaks appeared underneath those of the major diastereomer, however, H_α is observed as a doublet of doublets at δ 3.83 ($J = 8, J = 5$). The phenyl group of both diastereomers appears as a complex signal between δ 7.20 - 7.55.

The complex [(mes)RuCl(pro)] (3.6) contains three chiral centres, the carbon atom which has the fixed [S] configuration, the ruthenium, and the nitrogen which becomes chiral upon coordination to the ruthenium centre (it is strongly bonded and cannot easily be displaced). Therefore, four diastereomers are possible, however of these only two are sterically favourable i.e. [R_{Ru}S_CS_N] and [S_{Ru}S_CS_N], as found by Beck *et al.*¹¹⁸ for the analogous [(C₆H₆)RuCl(pro)] complex, Fig 3.2.2. In both diastereomers, the nitrogen has the [S] configuration, since when it has an [R] arrangement, a large degree of strain is caused within the proline ring system. This strain is apparent on constructing a model.

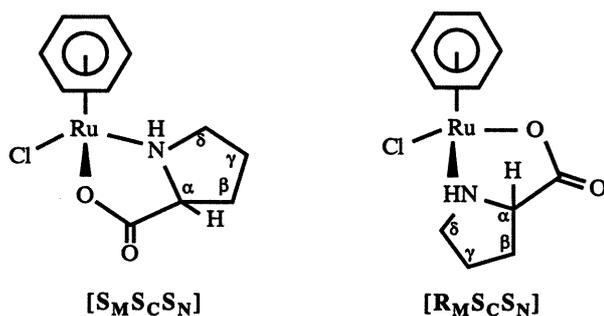


Fig 3.2.2

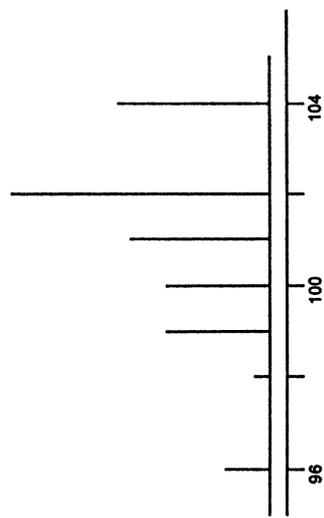
The ¹H NMR spectrum shows the expected signals for the mesitylene ring for both diastereomers, Table 3.3.2. The protons of the proline are observed as doublets of doublets at δ 4.01 and 3.73, and as multiplets at δ 3.44, 3.20, 3.06, and also complex signals between δ 1.56 and 2.25. From chemical shift considerations, the α -proton would be expected to be at lowest field (δ 4.01), owing to its close proximity to the nitrogen atom and the carboxylate group. The two different δ protons being near the nitrogen atom would also be expected at lower field, possibly being assigned to the multiplets between δ 3.06 and 3.44. However, decoupling experiments show that the signals observed at δ 3.06 and 4.01 are coupled, irradiation at δ 3.06 results in the doublet of doublets at δ 4.01 becoming a doublet, while

irradiation at δ 4.01 results in simplification of the multiplet at δ 3.06. The proline protons are thus assigned as follows; the doublet of doublets at δ 4.01 (${}^2J = 11$, $J = 5$) and the multiplet at δ 3.06 are assigned to the δ -protons of the major diastereomer, while the corresponding δ -protons for the minor diastereomer are observed as a doublet of doublets at δ 3.73 (${}^2J = 10$, $J = 8$) and a multiplet at δ 3.20. The signal observed at δ 3.44 is assigned to the α -proton of both diastereomers, while the remaining β - and γ -protons are observed as a complex signal between δ 1.56 and 2.25.

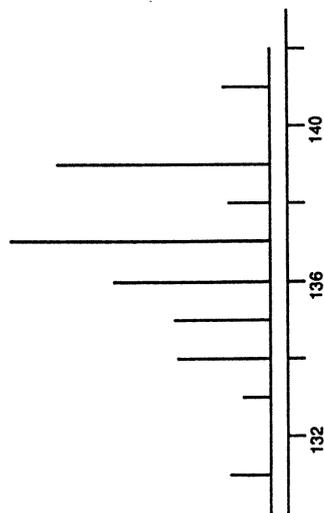
In contrast, results published by Beck *et al.*¹¹⁸ suggested an alternative assignment for the $[(C_6H_6)RuCl(pro)]$ complex, in which the lowest field multiplet was assigned to the α -proton, presumably on considerations of chemical shift. One possible explanation for the difference is that Beck's assignment was not confirmed by decoupling experiments.

The FAB mass spectra of complexes (3.5) and (3.6) were carried out using a NOBA matrix, and all have similar characteristics, Table 3.3.3. The ions are observed as clusters of peaks, because ruthenium has seven isotopes, with ${}^{102}Ru$ being the most naturally abundant (31.6%) and chlorine contains two isotopes of mass 35 and 37, with natural abundances of 76% and 24% respectively. These isotopes combine to give characteristic patterns; the pattern for the $[RuCl]^+$ fragment, and that of ruthenium alone are shown in Fig 3.2.3. These can be compared with those from an actual mass spectrum of $[(mes)RuCl(ala)]$ (3.5; $R = Me$), the $[M]^+/[M+H]^+$ and $[M-Cl]^+$ fragments are illustrated.

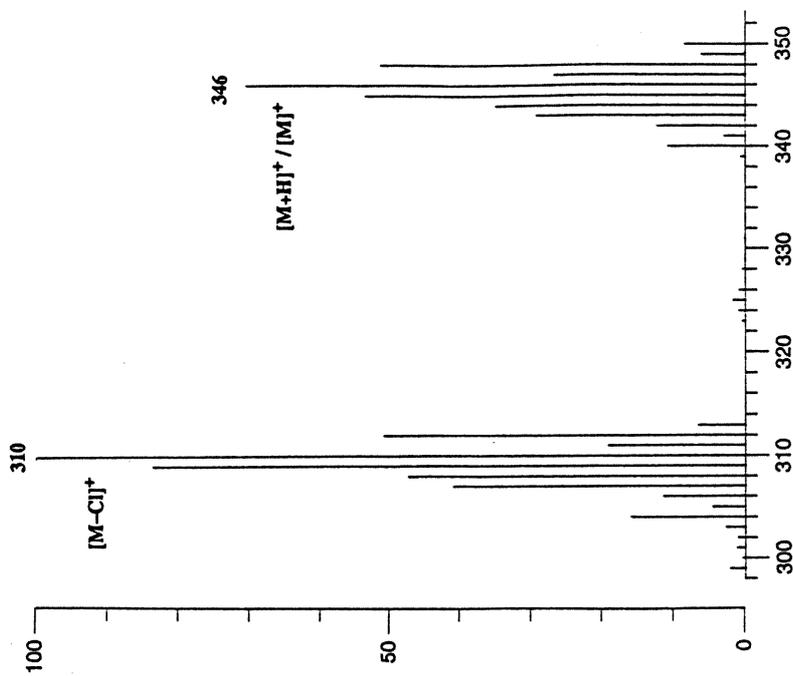
All the complexes show clusters due to the molecular ion (and in most cases the protonated molecular ion also) and the loss of the chlorine atom from these ions. For example, the spectrum of $[(mes)RuCl(Phgly)]$ shows ions at m/e 408 and 372 which correspond to the $[M+H]^+$ and $[M-Cl]^+$ and fragments respectively. There are also clusters observed at m/e 257 due to the $[(mes)RuCl]^+$ fragment, and at m/e 221, corresponding to $[(mes)Ru]^+$. Clusters higher than the molecular ion are also observed for complexes (3.5) and (3.6). For example, for $[(mes)RuCl(Phgly)]$, ions are observed at m/e 664 and m/e 779, which are tentatively assigned to the bimetallic species $[(mes)_2Ru_2Cl_2(Phgly)]^+$ and $[(mes)_2Ru_2Cl(Phgly)_2]^+$ respectively. The reason for their formation is unclear, it may depend upon conditions used within the spectrometer, or as a consequence of reactions in the matrix.



i) The isotopic pattern for $[Ru]^+$.



ii) The isotopic pattern for the $[RuCl]^+$ fragment.



iii) $[M+H]^+ / [M]^+$ and $[M-CI]^+$ Fragments of $[(mes)RuCl(ala)] (3.5; R=Me)$.

Fig. 3.2.3.

The structure of complex [(mes)RuCl(ala)] (3.5; R = Me) was determined by X-ray diffraction, suitable crystals were obtained by recrystallisation from a CH₂Cl₂/mesitylene mixture and the complex crystallised as a 50:50 mixture of the two diastereomers. Diagrams of both diastereomers are shown in Fig 3.2.4, with selected bond lengths (Å) and bond angles (°) shown in Table 3.2.1. In the following discussion the diastereomers will be referred to by their configuration at ruthenium. The Ru–N bond lengths of both diastereomers are statistically the same, 2.112(9) and 2.123(10) Å for the [S_{Ru}] and [R_{Ru}] configurations respectively, as are the Ru–O bond lengths of 2.085(8) and 2.093(9) Å for the [S_{Ru}] and [R_{Ru}] configurations. However, the Ru–Cl bond distances differ slightly, the distance in the [S_{Ru}] diastereomer is 2.439(3) Å compared to the slightly smaller value of 2.428(3) Å observed for the [R_{Ru}] diastereomer. The bite angle N–Ru–O, 76.4(4)°, for the [S_{Ru}] isomer is smaller than that observed for the [R_{Ru}] isomer, 78.1(4)°. The H···Cl distance (2.277 Å) between N–H of the [S_{Ru}] isomer and the chloride of the [R_{Ru}] diastereomer, is evidence of a weak intermolecular hydrogen bond.

Sheldrick and Heeb have reported the structure of [(C₆H₆)RuCl(ala)]¹²¹ (Fig 3.2.5). It is important to note that in this paper the diastereomers are assigned incorrectly. The isomer labelled [S_{Ru}SC] is in fact [R_{Ru}SC], and the configuration assigned [R_{Ru}SC] should read [S_{Ru}SC]. In this and future discussions we will refer to these diastereomers by their correctly assigned configurations and not as Sheldrick does. It is proposed that, in this complex intramolecular hydrogen bonding exists in the [S_{Ru}] isomer, between the N–H and chlorine atoms, with N···Cl and H···Cl distances of 2.84 and 2.42 Å respectively. The corresponding distances in the [R_{Ru}] isomer are 3.24 and 2.90 Å, hence intramolecular hydrogen bonding is not present. Further comparisons between the benzene and mesitylene complexes reveal that the [R_{Ru}] diastereomers have very similar bond lengths (Tables 3.2.1 and 3.2.2). For example, the Ru–N bond lengths are 2.123(10) and 2.130(12) Å for the mesitylene and benzene [R_{Ru}] diastereomers respectively. The Ru–O bond lengths of 2.085(8) and 2.079(11) Å for the [S_{Ru}] diastereomer of the mesitylene and benzene complexes respectively, are also the same within experimental error. However, there are more noticeable differences between the corresponding Ru–Cl and Ru–N bond distances of the [S_{Ru}] diastereomer.

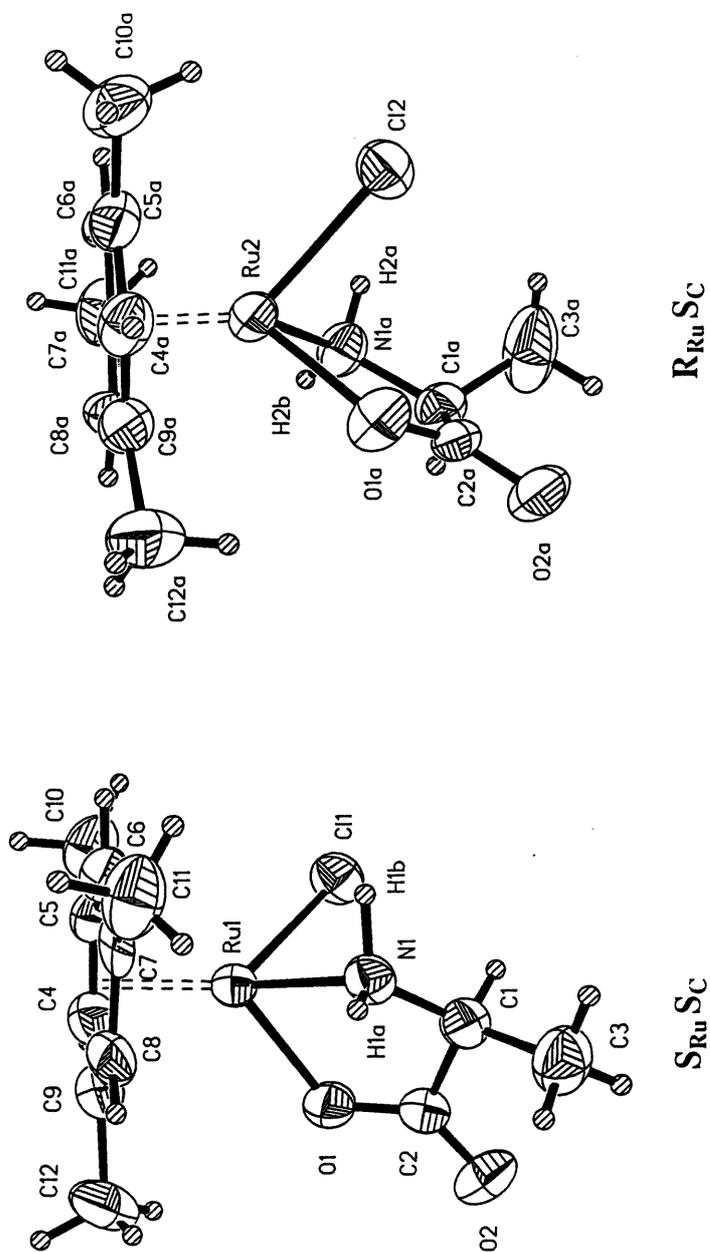


Fig. 3.2.4. The Diastereomers of [(mes)RuCl(ala)] (3.5; R = Me).

**Table 3.2.1 Selected Bond Distances and Angles
of [(mes)RuCl(ala)] (3.5: R = Me)**

BOND DISTANCES (Å)			
[SRuSc]		[RRuSc]	
Ru(1) – N(1)	2.112(9)	Ru(2) – N(1a)	2.123(10)
Ru(1) – Cl(1)	2.439(3)	Ru(2) – Cl(2)	2.428(3)
Ru(1) – O(1)	2.085(8)	Ru(2) – O(1a)	2.093(9)
C(2) – O(1)	1.263(13)	C(2a) – O(1a)	1.273(14)
C(2) – O(2)	1.232(15)	C(2a) – O(2a)	1.234(14)
BOND ANGLES (°)			
[SRuSc]		[RRuSc]	
O(1) – Ru(1) – Cl(1)	86.6(3)	O(1a) – Ru(2) – Cl(2)	85.1(3)
N(1) – Ru(1) – Cl(1)	85.2(3)	N(1a) – Ru(2) – Cl(2)	85.9(4)
N(1) – Ru(1) – O(1)	76.4(4)	N(1a) – Ru(2) – O(1a)	78.1(4)
C(2) – O(1) – Ru(1)	119.1(7)	C(2a) – O(1a) – Ru(2)	118.3(7)
C(1) – N(1) – Ru(1)	111.2(7)	C(1a) – N(1a) – O(1a)	113.5(7)
C(1) – C(2) – O(1)	115.3(10)	C(1a) – C(2a) – O(1a)	118.4(10)
O(2) – C(2) – O(1)	124.9(11)	O(2a) – C(2a) – O(1a)	122.4(10)

Table 3.2.2 Selected Bond Distances (Å) of [(C₆H₆)RuCl(ala)]

[SRuSc]		[RRuSc]	
Ru – N(2)	2.152(11)	Ru – N(2)	2.130(12)
Ru – O(12)	2.079(11)	Ru – O(12)	2.066(12)
Ru – Cl	2.392(7)	Ru – Cl	2.408(7)

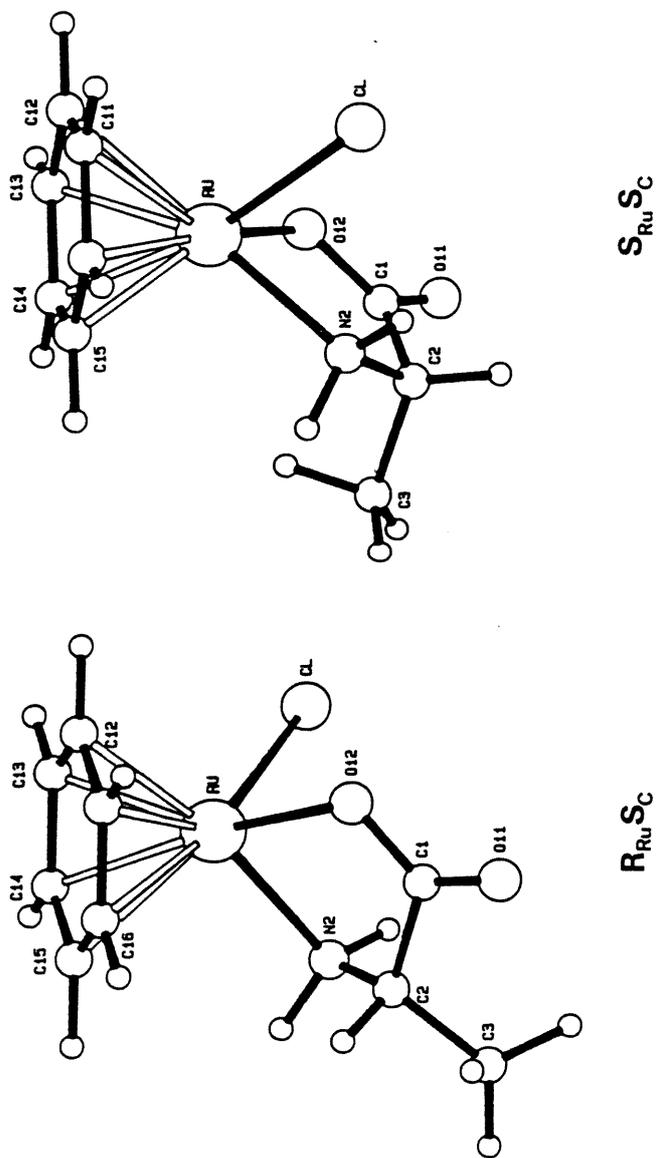


Fig. 3.2.5. The Diastereomers of $[(C_6H_6)RuCl(ala)]$.

The Ru–Cl bond length is 2.439(3) Å in the mesitylene [S_{Ru}] diastereomer whereas for the corresponding benzene species it is significantly smaller at 2.392(7) Å. Conversely, in the benzene [S_{Ru}] diastereomer the Ru–N bond is slightly larger at 2.152(11) Å, compared to 2.112(9) Å for the corresponding mesitylene isomer.

3.2.2 - Diastereomer Ratios

Examination of the crystal structure of complex (3.5) (R = Me) and its analogue [(C₆H₆)RuCl(ala)],¹²¹ show that the substituent on the α -carbon of the amino acid does not point directly towards the arene ring in either diastereomer (Figs 3.2.4 and 3.2.5). Therefore, steric interactions between the substituent and the ring should not be very different for the two diastereomers and might not be expected to play a major role in determining the diastereomer ratio. However, if the difference in energy between the two diastereomers is only small, then even relatively small differences in steric interactions may have a significant effect on the diastereomer ratio. The diastereomer ratios of the complexes in this discussion are measured from the integrations in their ¹H NMR spectra, for the mesitylene complexes these ratios are accurate to $\pm 2\%$.

In previous work, the proline complexes [(C₆H₆)RuCl(pro)]¹¹⁸ and [(*p*-cymene)RuCl(pro)]¹¹⁹ have both given the largest diastereomer ratios, [S_{Ru}]:[R_{Ru}] of 90:10. However, for the mesitylene complexes the phenylalaninate complex (ratio 75:25) has a greater ratio than the proline compound (70:30). It may be that there is greater steric repulsion between the mesitylene ligand and the proline than with benzene or *p*-cymene. Alternatively, there may be an electronic interaction between the mesitylene and the phenyl group, which results in an increased stability of the [S_{Ru}] diastereomer in the phenylalaninate complex. The highest preference for a particular pair of enantiomers is observed for the complex [(mes)RuCl(sarc)] (3.7) (> 95:5), described later, in which a methyl group is attached to the nitrogen atom. This suggests that steric factors are much more important for N-substituted ligands.

As has been mentioned previously for the benzene complex, there is evidence of intramolecular hydrogen bonding occurring between the chloride ligand and an amino (NH₂)

proton in the [S_{Ru}] isomer, and as a result it was proposed that this is the major diastereomer.¹²¹ However, this intramolecular interaction is not observed for the corresponding mesitylene complex (3.5; R = Me). In this case the structural data shows evidence of intermolecular hydrogen bonding occurring between both diastereomers in the solid state. This conflicting evidence makes it unclear what the precise effect of intramolecular hydrogen bonding has on the diastereomer ratios.

An attempt was made to assess the contribution of hydrogen bonding to the diastereomer ratio, by changing the halide ion in the complex [(mes)RuCl(ala)]. A ten-fold excess of NaBr was added to a solution of [(mes)RuCl(ala)] in D₂O, forming the complex [(mes)RuBr(ala)] which was identified by ¹H NMR spectroscopy. The methyl groups of the mesitylene are observed at δ 2.16 for both diastereomers, while the corresponding aromatic protons are observed at δ 5.25 and 5.27 for the major and minor diastereomers respectively. The methyl signals are assigned to the doublets at δ 1.30 (major) and 1.26 (minor), while the α -protons are observed as quartets at δ 3.21 and 3.55 for the major and minor diastereomers respectively. The diastereomer ratio is 65:35, showing only a slight change from that of the chloride complex. The similar complex [(mes)RuF(ala)] is prepared by reacting complex (3.5; R = Me) with AgNO₃, followed by NH₄F. The ¹H NMR spectrum exhibits a peak at δ 2.11 which is assigned to the methyl groups of the mesitylenes of both diastereomers, while the aromatic protons of the diastereomers are observed as singlets at δ 5.21 and 5.24. Quartets due to the α -protons are observed at δ 3.67 and 3.25 for both diastereomers and doublets at δ 1.41 and 1.27 are assigned to the methyl groups; the diastereomer ratio is 50:50. The difference between this ratio, and that of the chloride complex may be due to different amounts of hydrogen bonding within the molecules.

The chloride ligand of complex (3.5; R = Me) has also been replaced by the N-donor ligands pyridine, cytidine and guanosine (Chapter 5) with diastereomer ratios of 65:35, 70:30 and 75:25 respectively, here the ratios increase with the size of the coordinated ligand. However, for the corresponding complexes [(*p*-cymene)Ru(PPh₃)(ala)]BF₄¹¹⁹ and [(C₆H₆)Ru(9Etgua)(ala)]Cl¹²¹ which have ratios of 64:36 and 65:35 respectively, there is only a slight difference between these ratios and those of the analogous chloride complexes.

Overall there appears to be no significant correlation between the size of the ligand and the diastereomer ratio. Interestingly, for the proline complex [(mes)RuCl(pro)] (3.6), the aquated species [(mes)Ru(D₂O)(pro)]Cl has a diastereomer ratio of 50:50, compared to 70:30 for the chloride complex. One possible explanation is that the extent of hydrogen bonding to D₂O rather than chlorine may be different here. This is the only case in which the aquated species has a noticeably different diastereomer ratio to the parent complex.

It is very difficult to determine which factors have the greatest effect on the diastereomer ratios, it is most probably a combination of intramolecular hydrogen bonding and other intramolecular interactions. Steric factors appear to be most relevant for N-substituted ligands, as shown for the sarcosine complex. The diastereomer ratios of some arene-ruthenium complexes are listed in Table 3.2.3.

Several investigations into ways of separating the individual diastereomers were carried out. Flash column chromatography was attempted using silica gel as the column adsorbant with a variety of solvent mixtures (methanol/diethylether, dichloromethane/diethylether, dichloromethane/ethylacetate/diethylether, etc.), all of which resulted in only one band coming off the column containing both diastereomers, with no evidence of separation occurring.

We also attempted to separate the diastereomers by fractional recrystallisation, slow diffusion of diethylether into methanol and methanol/dichloromethane solutions of the complexes proved unsuccessful and both diastereomers were observed upon analysis of the products by ¹H NMR spectroscopy. Similarly, in the case of [(mes)RuCl(ala)] the slow diffusion of mesitylene into a methanol solution of the complex yielded crystals suitable for X-ray diffraction, the crystal structure of one such crystal showed both diastereomers were present in a 50:50 ratio. Attempts at crystallising a single diastereomer using vapour diffusion techniques with similar solvent mixtures also proved unsuccessful. Finally, addition of LiCl to aqueous solutions of the complexes was also attempted, however, as with previous experiments both diastereomers crystallised together.

In all cases the products of the various crystallisations were identifiable on the basis of their ¹H NMR spectra in D₂O. Although epimerisation may occur upon dissolution this has

Table 3.2.3 Diastereomer Ratios of Some Amino Acid Complexes^a

Complex	Ratio
[(mes)RuCl(ala)] (3.5; R = Me)	60:40
[(mes)RuCl(leuc)] (3.5; R = CH ₂ CHMe ₂)	66:34
[(mes)RuCl(Phgly)] (3.5; R = Ph)	60:40
[(mes)RuCl(Phala)] (3.5; R = CH ₂ Ph)	75:25
[(mes)RuCl(pro)] (3.6)	70:30 / 50:50 ^b
[(mes)RuBr(ala)]	65:35
[(mes)RuF(ala)]	50:50
[(C ₆ H ₆)RuCl(ala)] ^c	62:38
[(<i>p</i> -cymene)RuCl(ala)] ^d	68:32
[(mes)Ru(py)(ala)]Cl (5.4) ^e	65:35
[(mes)Ru(Guan)(ala)]Cl (5.6) ^e	75:25
[(mes)Ru(Cyt)(ala)]Cl (5.7) ^e	70:30
[(C ₆ H ₆)Ru(9Etgua)(ala)]Cl ^c	65:35
[(<i>p</i> -cymene)Ru(PPh ₃)(ala)]BF ₄ ^d	64:36
[(C ₆ H ₆)RuCl(pro)] ^f	90:10
[(<i>p</i> -cymene)RuCl(pro)] ^d	90:10

^a The ratios of the mesitylene complexes are accurate to $\pm 2\%$

^b Refers to the aquated species

^c From Ref 121

^d From Ref 119

^e Prepared in Chapter 5

^f From Ref 118

previously been reported to be slow on the NMR timescale for the analogous complex $[(C_6H_6)RuCl(ala)]$.¹²¹ More recently, Mandal *et al.* have reported that for the Schiff base complex $[(p\text{-cymene})Ru(OH_2)(L)]ClO_4$ (where $LH = 2\text{-HOC}_6\text{H}_4\text{CH}=\text{NCH}(\text{Me})\text{Ph}$) epimerisation did not occur in solution and only one diastereomer was observed in the ^1H NMR spectrum.¹²⁵ The complex $[Cp^*IrCl(\text{pro})]$ has been prepared by Carmona *et al.*¹¹⁹ and the X-ray structure showed both diastereomers in a 50:50 mixture even though from the ^1H NMR evidence the ratio was 95:5. More recent work by this group involving the formation of the alkynyl complex $[Cp^*Ir(\text{pro})C\equiv C\text{-CMe}_3]$ has shown it is possible to isolate one diastereomer from the original solution containing two diastereomers.¹²⁶ This suggests that with the right choice of ligand separation of the diastereomers of the arene-ruthenium amino acidate complexes may also be possible.

The synthesis of complexes $[(\text{mes})RuCl(\text{aa})]$ (3.5) and (3.6) were carried out in the presence of base. In contrast, in the preparation of the analogous complex $[(C_6H_6)RuCl(ala)]$ by Sheldrick and Heeb,¹²¹ no base was used, $[(C_6H_6)RuCl_2]_2$ was dissolved in water and the ligand added to afford the complex $[(C_6H_6)RuCl(ala)]$. Similar compounds prepared by Beck *et al.*¹¹⁸ employed *t*-butoxide as a base, while Dersnah and Baird, who synthesised the first arene-ruthenium amino acidate complexes, used the amino acid anions (K^+aa^-) as the starting material.¹¹³ The complex $[(\text{mes})RuCl_2]_2$ is poorly soluble in water and therefore Sheldrick's procedure is difficult to implement. Furthermore, when a mixture of $[(\text{mes})RuCl_2]_2$ and *l*-alanine were refluxed in water in the absence of base, no reaction occurred. Presumably base is required to deprotonate the amino acid allowing attack of the amine at the metal. It is not clear why base was required in our preparations, but not by Sheldrick and Heeb, for the analogous benzene complexes.

3.2.3 - Reactions of Amino Acid Complexes

As a result of the amine exchange reactions, discussed in Chapter 2, two experiments were carried out to establish an order of stability for the amino acidate complexes. The complex $[(\text{mes})RuCl(\text{pro})]$ (3.6) was dissolved in a water/methanol mixture, *l*-alanine was added and the mixture was refluxed for three hours, after which time the solvent was removed and the

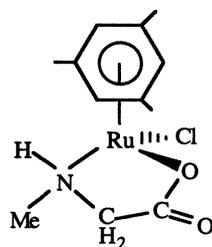
products dissolved in CH_2Cl_2 and filtered to remove any uncoordinated amino acids. The ^1H NMR spectrum of the worked up product showed that the complex $[(\text{mes})\text{RuCl}(\text{ala})]$ had formed, with the proline being displaced. This result is similar to those found for the amine complexes, in that a secondary amino acid can be displaced by a primary acid. A similar reaction was carried out between the complex $[(\text{mes})\text{RuCl}(\text{Phgly})]$ (3.5; $\text{R} = \text{Ph}$) and *l*-alanine. However, in this case, the isolated product was a mixture of both complexes $[(\text{mes})\text{RuCl}(\text{Phgly})]$ and $[(\text{mes})\text{RuCl}(\text{ala})]$. Thus, only partial displacement had taken place. These results are not as conclusive as for the amines, and no further work was carried out.

In an attempt to force the amino acid to become monodentate, we decided to react the complex $[(\text{mes})\text{RuCl}(\text{ala})]$ (3.5; $\text{R} = \text{Me}$) with hydrochloric acid. Thus, bubbling HCl gas through a solution of $[(\text{mes})\text{RuCl}(\text{ala})]$ in CH_2Cl_2 was carried out. However, the reaction was unsuccessful, the HCl gas totally displaced the ligand, which led to the formation of a red-orange precipitate identified as $[(\text{mes})\text{RuCl}_2]_2$.

In contrast, Bennett *et al.*³⁶ reported that amines and phosphines could not be removed from $[(\text{mes})\text{RuCl}_2\text{L}]$ by treatment of the complexes with hydrochloric acid (see Chapter 1). It is not clear why in our experiment the ligand is so easily removed, it may be a solvent effect, HCl gas in CH_2Cl_2 as opposed to $\text{H}^+(\text{aq})$ as is present in hydrochloric acid used by Bennett.³⁶ It is also important to note that, the conditions employed by Bennett are not stated in the report.

3.2.4 - Complexes with other N,O Donor Ligands

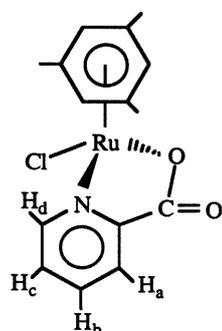
The complex $[(\text{mes})\text{RuCl}(\text{sarc})]$ (3.7) was prepared in the same way as for complexes (3.5) and (3.6) and characterised by microanalysis, ^1H NMR and mass spectroscopy (Tables 3.3.2 - 3.3.4).



(3.7)

The ligand is similar to proline, in that it contains a secondary nitrogen atom whose configuration is not fixed, until it is attached to the ruthenium centre, which results in it becoming chiral. Since there are two chiral centres (Ru and N) there are four possible configurations. However, only two are likely on steric grounds, because when the methyl group points towards the mesitylene ring there is considerable steric hindrance. The favoured configurations are $[R_{Ru}S_N]$ and $[S_{Ru}R_N]$, these are enantiomeric hence, only one series of peaks is clearly observed in the 1H NMR spectrum in D_2O/KCl . There is evidence of a second species in the mesitylene regions of the spectrum which could be tentatively assigned to the minor diastereomer, thus giving a diastereomer ratio of $> 95:5$. However, these peaks are small and may be due to a small amount of impurity. The mesitylene protons of the major species are observed at δ 2.18 and 5.18, the inequivalent α -protons appear as doublet of doublets at δ 2.78 ($J = 10$ and $^2J = 16$) and 3.16 ($J = 6$ and $^2J = 16$), due to the protons coupling to each other and to the N-H, the N-Me is observed as a doublet at δ 2.75 ($J = 6$) also coupling to the N-H. A broad signal observed at δ 6.47 is assigned to the N-H proton.

The complex $[(mes)RuCl(pic)]$ (3.8) was prepared from $[(mes)RuCl_2]_2$, NaOMe and picolinic acid, and was characterised by microanalysis, 1H NMR and mass spectroscopy, Tables 3.3.2 - 3.3.4, and its structure was determined by X-ray diffraction.



(3.8)

The ligand has no chiral centre, thus two enantiomeric species exist, which are not distinguishable by 1H NMR spectroscopy. Signals at δ 2.18 and 5.18, and δ 2.20 and 5.27 are assigned to the mesitylene ring of the chloride coordinated species and the aquated complex

respectively. The ligand protons for the chloride complex are assigned as follows: two triplets (actually overlapping doublets of doublets) at δ 8.14 ($J = 7$) and 7.84 ($J = 6$) are assigned to Hb and Hc respectively. Doublets observed at δ 7.92 ($J = 7$) and 9.20 ($J = 5$) are assigned to Ha and Hd. The corresponding signals are also observed for the aquated species at δ 9.40 (Hd), δ 8.25 (Hb), δ 8.00 (Ha) and δ 7.93 (Hc).

The molecular structure of [(mes)RuCl(pic)] (3.8) is illustrated in Fig 3.2.10, with a summary of selected bond angles ($^\circ$) and distances (\AA) given in Table 3.2.4. The ligand has a planar arrangement with chelation through the oxygen and nitrogen atoms. The Ru–N bond length is 2.102(4) \AA , which is comparable with the Ru–N bond distances of 2.112(9) and 2.123(10) \AA observed for the [S_{Ru}] and [R_{Ru}] configurations of [(mes)RuCl(ala)] respectively. The Ru–O bond distance of 2.101(4) \AA is also similar to the corresponding distances [2.085(8) and 2.093(9) \AA] found for the diastereomers of [(mes)RuCl(ala)].

The bite angle N–Ru–O(1), 77.9(2) $^\circ$, is the same as the bite angle in the [R_{Ru}] isomer of [(mes)RuCl(ala)], 78.1(4) $^\circ$, and slightly larger than the corresponding angle in the [S_{Ru}] isomer, 76.4(4) $^\circ$. The O(1)–Ru–Cl angle, 83.6(1) $^\circ$, is smaller than the corresponding angles in both diastereomers of [(mes)RuCl(ala)], where the angles are 86.6(3) and 85.1(3) $^\circ$ for the [S_{Ru}] and [R_{Ru}] diastereomers respectively. The complex co-crystallised with three molecules of water, which form a layer between the complex molecules. The hydrogen atoms of the water molecules were not located, but the O \cdots O separations of 2.78 and 2.85 \AA , suggest that hydrogen bonding occurs between these water molecules. There are also close contacts between a water molecule and the chlorine (3.236 \AA) and also between the two remaining water molecules and the two carboxylate oxygen atoms (2.898 and 2.931 \AA).

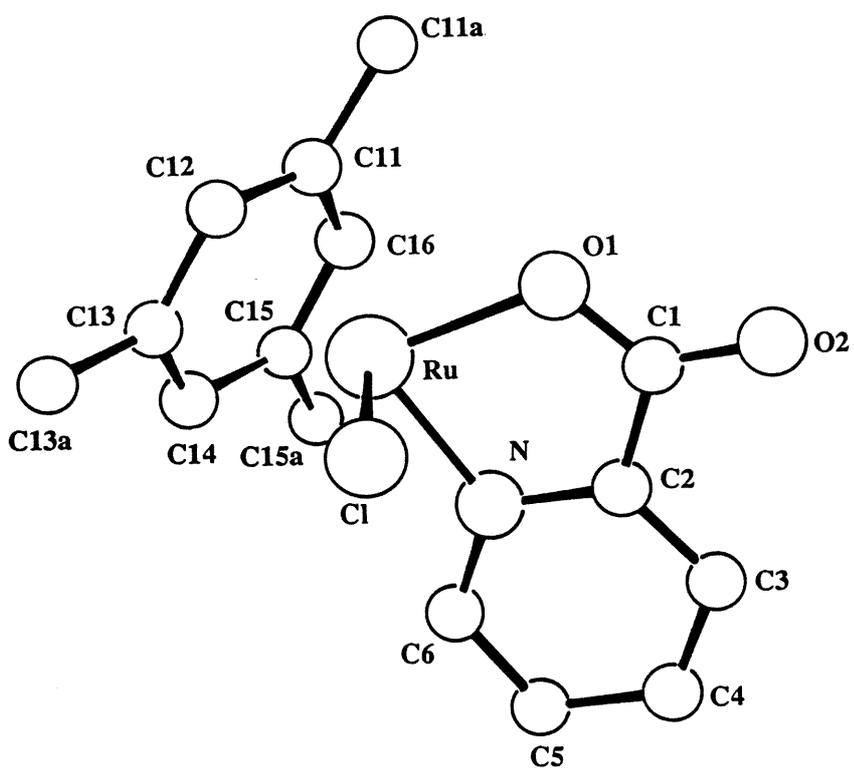


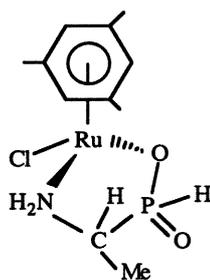
Fig. 3.2.10. The Molecular Structure of [(mes)RuCl(pic)] (3.8).

Table 3.2.4. Selected Bond Lengths (Å) and Angles (°) of [(mes)RuCl(pic)] (3.8).

Bond Distances			
Ru-Cl	2.420(1)	C(1)-O(1)	1.285(7)
Ru-N	2.102(4)	C(1)-O(2)	1.242(7)
Ru-O(1)	2.101(4)	C(1)-C(2)	1.502(8)
Ru-C(11)	2.185(5)	C(11)-C(12)	1.410(8)
Ru-C(12)	2.203(5)	C(12)-C(13)	1.436(10)
Ru-C(13)	2.220(6)	C(13)-C(14)	1.410(9)
Ru-C(14)	2.203(6)	C(14)-C(15)	1.438(8)
Ru-C(15)	2.206(5)	C(15)-C(16)	1.403(8)
Ru-C(16)	2.176(5)	C(16)-C(11)	1.419(8)

Bond Angles			
N-Ru-Cl	84.0(1)	O(2)-C(1)-O(1)	124.7(6)
O(1)-Ru-Cl	83.6(1)	C(2)-C(1)-O(1)	115.1(5)
O(1)-Ru-N	77.9(2)	C(2)-N-C(6)	119.3(5)

The complex [(mes)RuCl(Amphos)] (3.9) was synthesised from 1-aminoethylphosphonous acid, NaOMe and [(mes)RuCl₂]₂. It was characterised by microanalysis (Table 3.3.4), ³¹P{¹H}, ¹H NMR and mass spectroscopy (Table 3.3.3).



(3.9)

The ¹H NMR spectrum of the complex in D₂O is very complicated, because the molecule contains three chiral centres (Ru, C, and P) giving rise to a mixture of diastereomers. Three major species are observed with mesitylene signals at δ 2.12, 2.13 and 2.16, and at δ 5.22, 5.24 and 5.33. Two overlapping doublets of doublets which are observed at δ 6.56 (¹J_{PH} = 525, ³J_{HH} = 4.5) and a third at δ 6.48 (¹J_{PH} = 540, ³J_{HH} = 4) are assigned to the P-H group. The methyl signals are observed as a number of overlapping doublets between δ 1.18 and 1.44, while signals for the α -protons are not clearly visible. Addition of LiCl to the sample results in some precipitation, thus the ¹H NMR spectrum in D₂O/LiCl was weak and poorly resolved, hence no further information was obtained. The diastereomers are more clearly seen in the ³¹P{¹H} NMR spectrum in CD₃OD, where signals are observed at δ 40.52, 48.56 and 48.72. It is not clear why only three of the four possible diastereomers are observed.

The poor solubility of the complex in CH₂Cl₂ meant that the removal of NaCl from the reaction mixture was attempted by dissolving the solid in a mixture of CH₂Cl₂ and methanol, which proved unsuccessful. The microanalysis results show the presence of one mole of NaCl. In the FAB mass spectrum a cluster is observed at m/e 389 corresponding to [M+H+Na]⁺, in this case, the Na⁺ is possibly ionically bonded to the phosphate group.

Evidence of this has previously been seen in some of the early preparations of the amino acidate complexes, where the removal of NaCl was not complete and the mass spectra also showed $[M+Na]^+$ peaks.

This Chapter has described arene-ruthenium complexes incorporating amino acids and some related N,O donor ligands. If the ligand is chiral the complexes exist as a pair of diastereomers and a variety of factors were found to influence the diastereomer ratios. All the complexes are soluble in water and polar organic solvents. Dissolution in water leads to substitution of chloride by water, this can be reversed to some extent by addition of excess chloride ions.

3.3 - Experimental

Experimental conditions were as described in Chapter 2. 1-aminoethylphosphonous acid was prepared by the literature method,¹²⁷ while all other chemicals were used as supplied (Aldrich).

Preparation of [(mes)RuCl(gly)] (3.5; R = H)

Sodium methoxide (56 mg, 1.03 mmol) and glycine (78 mg, 1.03 mmol) were added to a suspension of [(mes)RuCl₂]₂ (302 mg, 0.517 mmol) in methanol/water (1:1) (70 cm³) and the mixture was refluxed for 3 hours. The solvent was removed and the residue dissolved in dichloromethane (150 cm³) and filtered through Celite to remove the NaCl formed. Evaporation of the solvent gave [(mes)RuCl(gly)] (3.5; R = H) (144 mg, 43%) as a yellow solid. The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 3.3.1, 3.3.3 and 3.3.4.

Preparation of [(mes)RuCl(ala)] (3.5; R = Me)

Sodium methoxide (37 mg, 0.685 mmol) and *l*-alanine (61 mg, 0.685 mmol) were added to a suspension of [(mes)RuCl₂]₂ (200 mg, 0.34 mmol) in methanol/water (1:1) (70 cm³) and the mixture was refluxed for 2.5 hours. The solvent was removed and the residue dissolved in dichloromethane (100 cm³) and filtered through Celite. Evaporation of the solvent

gave a yellow solid and recrystallisation of this from methanol/diethylether afforded [(mes)RuCl(ala)] (3.5; R = Me) (193 mg, 83%) as a yellow solid. The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 3.3.1, 3.3.3 and 3.3.4. A small portion of the complex was recrystallised from dichloromethane/mesitylene which afforded orange crystals suitable for an X-ray structure determination.

Preparation of [(mes)RuCl(leuc)] (3.5; R = CH₂CHMe₂)

The compound was prepared in a similar way to complex (3.5; R = Me) using sodium methoxide (55 mg, 1.02 mmol), *l*-leucine (134 mg, 1.02 mmol) and [(mes)RuCl₂]₂ (299 mg, 0.512 mmol) in methanol/water (1:1) (70 cm³) to give, after work-up, [(mes)RuCl(leuc)] (3.5; R = CH₂CHMe₂) as a yellow crystalline solid (262 mg, 66%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 3.3.1, 3.3.3 and 3.3.4.

Preparation of [(mes)RuCl(Phgly)] (3.5; R = Ph)

Using the same procedure as for complex (3.5; R = Me), sodium methoxide (35 mg, 0.65 mmol), *l*-phenylglycine (104 mg, 0.685 mmol) and [(mes)RuCl₂]₂ (200 mg, 0.34 mmol) were reacted in methanol/water (1:1) (70 cm³) to give, after work-up, [(mes)RuCl(Phgly)] (3.5; R = Ph) as a yellow crystalline solid (222 mg, 78%). The compound was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 3.3.1, 3.3.3 and 3.3.4.

Preparation of [(mes)RuCl(Phala)] (3.5; R = CH₂Ph)

Using the same procedure as for complex (3.5; R = Me), sodium methoxide (55 mg, 1.02 mmol), *l*-phenylalanine (168 mg, 1.02 mmol) and [(mes)RuCl₂]₂ (297 mg, 0.51 mmol) in methanol/water (1:1) (60 cm³) were refluxed to give, after work-up, [(mes)RuCl(Phala)] (3.5; R = CH₂Ph) as a yellow solid (372 mg, 87%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 3.3.1, 3.3.3 and 3.3.4.

Preparation of [(mes)RuCl(pro)] (3.6)

Using the same procedure as for complex (3.5; R = Me), sodium methoxide (36 mg, 0.66 mmol), *l*-proline (82 mg, 0.712 mmol) and [(mes)RuCl₂]₂ (208 mg, 0.36 mmol) were reacted in methanol/water (1:1) (60 cm³) to give, after work-up, [(mes)RuCl(pro)] (3.6) as a yellow solid (231 mg, 87%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 3.3.2 - 3.3.4.

Preparation of [(mes)RuF(ala)]

AgNO₃ (30 mg, 0.18 mmol) was added to a solution of [(mes)RuCl(ala)] (3.5; R = Me) (61 mg, 0.18 mmol) in water (30 cm³). The mixture was stirred for 3 minutes and then a solution of NH₄F (10 mg, 0.27 mmol) in water (3 cm³) was added dropwise, the mixture was stirred for a further 30 minutes and filtered to remove the AgCl formed. Evaporation of the solvent gave [(mes)RuF(ala)] as a yellow solid (42 mg, 72%) which was identified by ¹H NMR spectroscopy. ¹H NMR (D₂O/NaF): δ 1.27 [d, 3H, Me, J(7)], δ 1.41 [d, 3H, Me, J(7)], δ 2.11 (s, 9H, C₆Me₃), δ 3.25 [q, 1H, H α , J(7)], δ 3.67 [q, 1H, H α , J(7)], δ 5.21 (s, 3H, C₆H₃), δ 5.24 (s, 3H, C₆H₃).

Amino-acid exchange reactions.

l-alanine (66 mg, 0.74 mmol) was added to a solution of [(mes)RuCl(pro)] (91 mg, 0.25 mmol) in methanol/water (1:1) (40 cm³) and the solution was refluxed for 3 hours. The solvent was removed and the residue dissolved in dichloromethane (100 cm³) and filtered through Celite. Evaporation of the solvent gave a yellow solid identified as complex [(mes)RuCl(ala)] (3.5; R = Me) on the basis of its ¹H NMR spectrum (yield 65 mg, 77%).

The same procedure was also used for the reaction of complex [(mes)RuCl(Phgly)] (3.5; R = Ph) (130 mg, 0.32 mmol) with *l*-alanine (57 mg, 0.64 mmol) to give a yellow solid identified as a mixture of the complexes [(mes)RuCl(ala)] (3.5; R = Me) and [(mes)RuCl(Phgly)] (3.5; R = Ph).

Reaction of [(mes)RuCl(ala)] (3.5; R = Me) with HCl gas

[(mes)RuCl(ala)] (100 mg, 0.29 mmol) was dissolved in dichloromethane (40 cm³) and filtered. HCl gas was bubbled through this solution for 5 minutes, after which time a brown solid was formed and identified as [(mes)RuCl₂]₂ by comparison with an authentic sample.

Preparation of [(mes)RuCl(sarc)] (3.7)

Using the same procedure as for complex (3.5; R = Me), sarcosine (66 mg, 0.74 mmol), sodium methoxide (40 mg, 0.74 mmol), and [(mes)RuCl₂]₂ (216 mg, 0.37 mmol) were refluxed in methanol/water (1:1) (70 cm³) to give, after work-up, [(mes)RuCl(sarc)] (3.7) as a yellow solid (190 mg, 75%). The compound was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 3.3.2 - 3.3.4.

Preparation of [(mes)RuCl(pic)] (3.8)

Sodium methoxide (40 mg, 0.74 mmol) and picolinic acid (106 mg, 0.86 mmol) were added to a suspension of [(mes)RuCl₂]₂ (251 mg, 0.43 mmol) in methanol/water (1:1) (70 cm³) and the mixture refluxed for 3 hours. The solvent was removed and the residue dissolved in dichloromethane (100 cm³) and filtered. Evaporation of the solvent gave [(mes)RuCl(pic)] (3.8) as a yellow solid (267 mg, 82%). The compound was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 3.3.2 - 3.3.4.

A small portion of the complex was recrystallised from D₂O/LiCl which afforded red crystals suitable for X-ray structure analysis.

Preparation of [(mes)RuCl(Amphos)] (3.9)

Sodium methoxide (34 mg, 0.74 mmol) and 1-aminoethylphosphonous acid (81 mg, 0.74 mmol) were added to a suspension of [(mes)RuCl₂]₂ (217 mg, 0.37 mmol) in methanol/water (1:1) (70 cm³) and the mixture refluxed for 3 hours. The solvent was removed and the residue dissolved in a dichloromethane/methanol mixture (15 cm³: 2 cm³) and diethylether (3 cm³) added. A pale orange solid was removed by filtration and the remaining solution was evaporated to dryness to give [(mes)RuCl(Amphos)] (3.9) as an orange solid (100

mg, 35%). The complex was characterised by ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR and FAB mass spectroscopy, and microanalysis. $^{31}\text{P}\{^1\text{H}\}$ (MeOD): δ 40.52, 48.56, 48.72. $^{31}\text{P}\{^1\text{H}\}$ (D_2O): δ 42.38, 43.71, 49.79, 50.17, 51.08, 51.64. $^{31}\text{P}\{^1\text{H}\}$ ($\text{D}_2\text{O}/\text{LiCl}$): δ 42.83, 50.27, 50.61. ^1H NMR (D_2O): δ 1.18 - 1.44 (m, 9H, Me), δ 2.12, 2.13, 2.16 (s, 9H, C_6H_3), δ 5.22, 5.24, 5.33 (s, 3H, C_6H_3), δ 6.48 [dd, 1H, PH, $^1\text{J}_{\text{PH}}(540)$, $^3\text{J}_{\text{HH}}(4)$], δ 6.56 [dd, 1H, PH, $^1\text{J}_{\text{PH}}(525)$, $^3\text{J}_{\text{HH}}(4.5)$]. Other signals were also observed but not assigned.

Table 3.3.1. ¹H NMR data for complexes (3.5) in D₂O / KCl.^a

R	I ^b	Arene Protons (δ) ^c		Ligand Protons (δ)
		C ₆ Me ₃	C ₆ H ₃	
H	-	2.14 (2.16)	5.19 (5.31)	3.04 and 3.21 [m, 2H, CH ₂ , (AB part)]
Me	M	2.15 (2.18)	5.24 (5.33)	1.33 [d, 3H, Me, J(7)], 3.18 [(q, 1H, Hα, J(7)]
	m	2.15 (2.18)	5.26 (5.34)	1.27 [d, 3H, Me, J(7)], 3.53 [q, 1H, Hα, J(7)]
CH ₂ CHMe ₂	M	2.15 (2.17)	5.24 (5.33)	0.87 [d, 3H, Me, J(6)], 0.96 [d, 3H, Me, J(6)], 1.54 (m, 2H), 1.76 (m, 1H, Hα)
	m	2.16 (2.18)	5.26 (5.35)	0.87 [d, 3H, Me, J(6)], 0.92 [d, 3H, Me, J(6)], 1.54 (m, 2H), 1.76 (m, 1H, Hα)
Ph	M	2.10 (2.11)	5.23 (5.29)	4.27 (s, 1H, Hα), 7.10 - 7.55 (m, 5H, Ph)
	m	2.20 (2.21)	5.34 (5.42)	4.58 (s, 1H, Hα), 7.10 - 7.55 (m, 5H, Ph)
CH ₂ Ph	M	1.99 (2.03)	4.84 (4.95)	{3.03 [dd, 1H, Hb, ² J(14), J(5)], 3.17 [dd, 1H, Hc, ² J(14), J(5)], 3.37 [t, 1H, Hα, J(5)]} ^d , 7.20 - 7.55 (m, 5H, Ph)
	m	2.09 (2.11)	5.20 (5.29)	3.83 [dd, 1H, Hα, J(8,5)], 7.20 - 7.55 (m, 5H, Ph)

^a All J values refer to ²J coupling unless otherwise stated.

^b I refers to the major (M) or minor (m) diastereomer.

^c Mesitylene shifts due to the aquated species are given in parentheses.

^d The chemical shifts are measured from first order principles for the ABX system.

Table 3.3.2. ¹H NMR data for complexes (3.6 - 3.8) in D₂O / KCl.^a

Complex	I ^b	Arene Protons (δ) ^c		Ligand Protons (δ)
		C ₆ Me ₃	C ₆ H ₃	
3.6	M	2.19 (2.20)	5.32 (5.33)	1.56 - 2.25 (m, 4H, CH ₂), 3.06 (m, 1H, Hδ), 3.44 (m, 1H, Hα), 4.01[dd, 1H, Hδ, ² J(11), J(5)]
	m	2.17 (2.21)	5.34 (5.40)	1.56 - 2.25 (m, 4H, CH ₂), 3.20 (m, 1H, Hδ), 3.44 (m, 1H, Hα) 3.73 [dd, 1H, Hδ, ² J(10), J(8)]
3.7	-	2.18 (2.18)	5.18 (5.29)	2.75 [d, 3H, NMe, J(6)], 2.78 [dd, 1H, Hα, ² J(16), J(10)], 3.16 [dd, 1H, Hα, ² J(16), J(6)], 6.47 (br, 1H, NH)
3.8	-	2.18 (2.20)	5.18 (5.27)	7.84 [t, 1H, Hc, J(6)], 7.92 [d, 1H, Ha, J(7)], 8.14 [t, 1H, Hb, J(7)], 9.20 [d, 1H, Hd, J(5)]

^a All J values refer to ³J coupling unless otherwise stated.

^b I refers to the major (M) or minor (m) diastereomer.

^c Mesitylene shifts due to the corresponding aquated species are given in parentheses.

Table 3.3.3 Mass spectroscopy data for complexes (3.5 - 3.9)

Complex	[M+H] ⁺ a	[M-Cl] ⁺	Other Peaks
[(mes)RuCl(gly)] (3.5; R = H)	332	296	627 [2M-Cl] ⁺ ; 590 [2M-gly] ⁺
[(mes)RuCl(ala)] (3.5; R = Me)	346	310	655 [2M-Cl] ⁺ ; 601 [2M-ala] ⁺
[(mes)RuCl(leuc)] (3.5; R = CH ₂ CHMe ₂)	388	352	739 [2M-Cl] ⁺ ; 644 [2M-leuc] ⁺
[(mes)RuCl(Phgly)] (3.5; R = Ph)	408	372	779 [2M-Cl] ⁺ ; 664 [2M-Phgly] ⁺
[(mes)RuCl(Phala)] (3.5; R = CH ₂ Ph)	422	386	807 [2M-Cl] ⁺ ; 678 [2M-Phala] ⁺
[(mes)RuCl(pro)] (3.6)	372	336	709 [2M-Cl] ⁺ ; 628 [2M-pro] ⁺
[(mes)RuCl(sarc)] (3.7)	346	310	-
[(mes)RuCl(pic)] (3.8)	379 ^b	344	-
[(mes)RuCl(Amphos)] (3.9)	366	330	389 [M + H + Na] ⁺

^a In all cases the [M]⁺ ion is also observed.

^b Only the [M]⁺ ion is observed.

Table 3.3.4 Elemental analyses of complexes (3.5 - 3.9)

Complex	Found (%)			Calculated (%)		
	C	H	N	C	H	N
[(mes)RuCl(gly)] (3.5; R = H)	39.47	4.78	4.08	39.94	4.88	4.23
[(mes)RuCl(ala)] (3.5; R = Me)	42.24	5.40	3.96	41.80	5.26	4.06
[(mes)RuCl(leuc)] (3.5; R = CH ₂ CHMe) ^a	44.01	6.45	2.93	44.49	6.47	3.46
[(mes)RuCl(Phgly)] (3.5; R = Ph) ^b	49.34	5.06	3.21	49.09	5.09	3.37
[(mes)RuCl(Phala)] (3.5; R = CH ₂ Ph)	51.41	5.29	3.23	51.36	5.27	3.33
[(mes)RuCl(pro)] (3.6)	44.41	5.37	3.50	44.28	5.57	3.69
[(mes)RuCl(sarc)] (3.7)	41.57	5.30	4.03	41.80	5.26	4.06
[(mes)RuCl(pic)] (3.8) ^a	45.97	4.36	3.44	45.34	4.56	3.52
[(mes)RuCl(Amphos)] (3.9) ^c	30.91	4.45	3.15	31.22	4.52	3.31

^a Complex crystallises with one mole of water.

^b Complex crystallises with 0.5 moles of water.

^c Complex crystallises with one mole of NaCl.

Chapter Four

The Synthesis and Reactions of Arene-Ruthenium

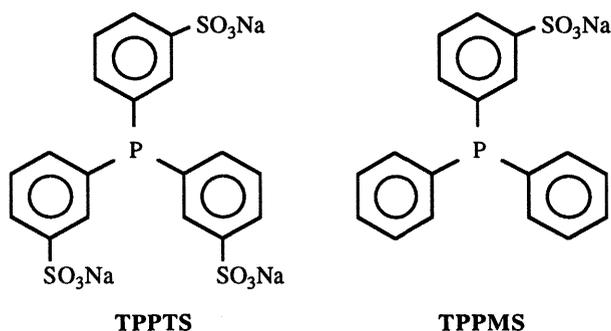
Complexes with N,N and O,O Donor Ligands

CHAPTER 4 - THE SYNTHESIS AND REACTIONS OF ARENE-
RUTHENIUM COMPLEXES WITH N,N
AND O,O DONOR LIGANDS

4.1 - Introduction

Organometallic complexes have been used as homogeneous catalysts for a number of organic reactions.¹²⁸ However, most of these catalysts are insoluble in aqueous media, owing to the hydrophobic nature of the attached ligands. From an industrial stand-point, homogeneous catalysts of this type are difficult to use, because they are not readily separable from the products, which are usually formed in the same phase. Water soluble catalysts used in two phase systems make the separation of the catalysts from the products much easier. A lot of interest has been focused in this field recently,¹²⁹⁻¹³⁰ due to the potential benefits to industry of easily recovered catalysts. Many catalytic processes including hydroformylation, hydrogenation and sulphur removal have been reported using biphasic systems or transition metal phase transfer techniques.¹³¹

Most water-soluble catalysts contain sulphonated phosphine ligands, the most widely investigated being tris-(*m*-sulphophenyl)phosphine (TPPTS) and *m*-sulphophenyl diphenylphosphine (TPPMS),¹³² coordinated to metals such as rhodium, ruthenium, iridium and palladium.

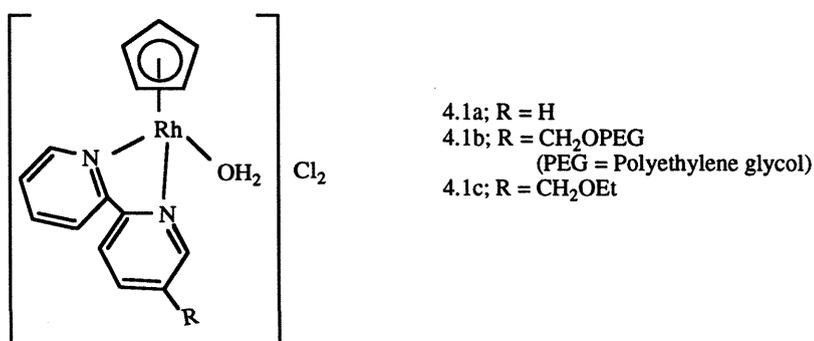


Numerous catalytic applications of rhodium and ruthenium complexes have been reported.¹³²⁻¹³⁵ For example, [RhCl(TPPMS)₃] and [HRuCl(TPPMS)₃] are catalysts for the

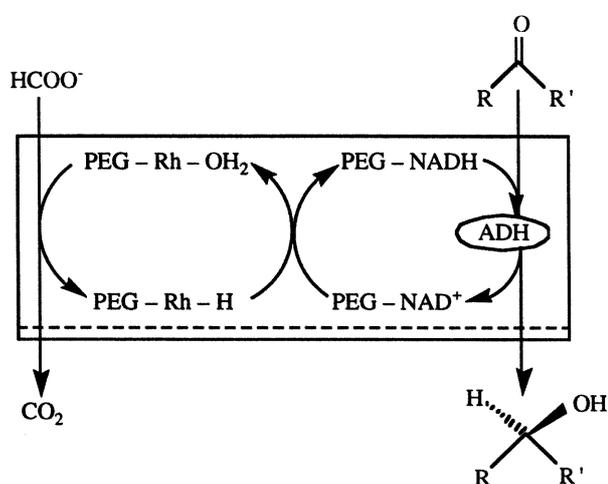
hydrogenation of alkenes;^{132,134} the hydroformylation of 1-hexene has been achieved using the bimetallic complex $[\text{Rh}_2(\mu\text{-S}^t\text{Bu})_2(\text{CO})_2(\text{TPPTS})_2]$ as the catalyst;¹³⁵ and the ruthenium complex $[\text{RuCl}_2(\text{TPPMS})_2]$ is a catalyst for the reduction of $\text{RCH}=\text{CHCHO}$ to $\text{RCH}=\text{CHCH}_2\text{OH}$.¹³⁶

A wide variety of water soluble complexes have recently been synthesised by Darensbourg, incorporating the ligand 1,3,5-triaza-7-phosphaadamantane (PTA). One such complex is $[\text{RuCl}_2(\text{PTA})_4]$.¹³⁷ Although in solution the catalytic activity of $[\text{RuCl}_2(\text{PTA})_4]$ towards hydrogenation is 30 times less than for the TPPTS complexes, it is much more stable in air, and is therefore more attractive for use in biphasic catalysis. Furthermore, the PTA ligand is not a pronounced surfactant, as are other water soluble phosphines, thus providing better phase separation.

Water soluble complexes containing ligands other than phosphines also display interesting catalytic properties. Steckhan *et al.*¹³⁸ synthesised the rhodium complexes (4.1).



Complex (4.1a) was reported as being an effective homogeneous catalyst for the regeneration of the enzyme co-substrates NADH and NADPH.¹³⁸ Binding complex (4.1a) to polyethylene glycol gave complex (4.1b), which exhibits the same catalytic activity as complex (4.1a); however, it is water soluble and can be retained by ultrafiltration. Complex (4.1b) has been used for the continuous regeneration of NADH, itself being used as a catalyst for the reduction of aldehydes to alcohols. A schematic diagram of the reaction is shown in Scheme 4.1.1.



Scheme 4.1.1

A recent publication by the same group describes how a similar catalytic system was used for asymmetric catalysis.¹³⁹ It is noteworthy that cyclopentadienyl-rhodium compounds are isoelectronic with the corresponding arene-ruthenium complexes. Some arene-ruthenium complexes have been used as catalysts (see Chapter 1) though not, as yet, in aqueous systems.

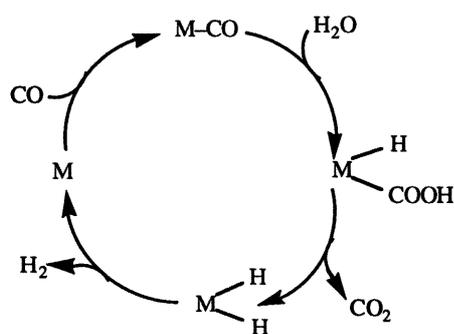
Another important catalytic reaction is the Water-Gas Shift Reaction (WGSR) (Scheme 4.1.2), which is the principle method used to obtain H₂ for the Haber-Bosch synthesis of NH₃.



Scheme 4.1.2

The conventional heterogeneous catalysts for the reaction consist of chromium activated iron oxide (Fe₃O₄ / Cr₂O₃) or cobalt-molybdenum oxides (CoO / MoO₂); the reaction is carried out at 400-460°C and 200 atm of CO or CO + H₂. Attempts have been made to discover a more suitable catalyst, which would lessen the harsh conditions currently used industrially. Homogeneous catalysts such as, [Rh(CO)₂I₂]⁻ and Ru₃(CO)₁₂ have previously been examined.¹⁴⁰ Kaspar *et al.*, in 1981, studied the use of [Ir(COD)L₂]⁺ (L = PPh₃, PMePh₂, phen, Ph₂P(CH₂)₂PPh₂) as catalysts and showed that the ligands were easily displaced by

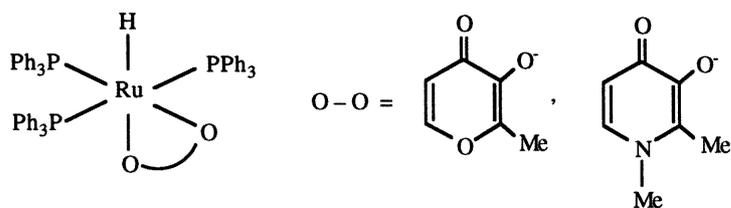
carbon monoxide to form metal-carbonyl complexes, which subsequently proved to be active catalysts in the WGSR.¹⁴¹ The proposed mechanism for such reactions is shown below (Scheme 4.1.4).



Scheme 4.1.4

More recently, Khan *et al.* demonstrated the use of the complex $K[Ru^{II}(Hedta)(CO)]$ as a catalyst for the WGSR.¹⁴² The experimental conditions were much less severe than those used industrially, using a temperature of 20-80°C and a CO pressure of 1-35 atmospheres.

Hydroxy-pyrone and hydroxy-pyridinone ligands have been, and are still currently being tested for control of iron and aluminium levels in the body.¹⁴³ These ligands and some of their complexes can be soluble in lipophilic and hydrophilic solvents.¹⁴⁴



(4.2)

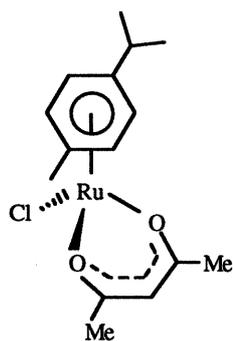
Ruthenium complexes containing such ligands have been prepared by El - Hendawy *et al.*¹⁴⁵ The complexes (4.2) showed promising results as catalysts for the selective oxidation of alcohols to aldehydes and ketones.^{145c} However, these complexes are only soluble in organic

media. Chapter 4 describes the synthesis of some arene-ruthenium complexes containing maltol, bipyridyl and pyridinone ligands, which are soluble in water. Their reactions with carbon monoxide are discussed as are some of the reactions of the resultant carbonyl complexes with various nucleophiles.

4.2 - Results and Discussion

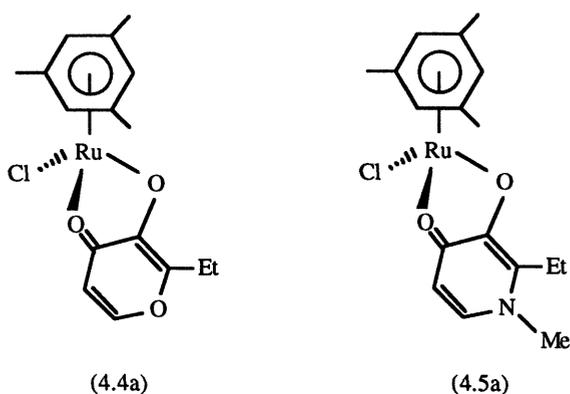
4.2.1 - Ethylmaltol, Pyridinone and Bipyridine Complexes

Although maltol and pyridinone ligands form complexes with ruthenium-phosphine compounds, there are no reports of their chelation to arene-ruthenium species. However, the use of other O,O donor ligands as chelates for arene-ruthenium complexes was reported by Carmona *et al.* in 1990.¹⁴⁶ The reaction between $[(p\text{-cymene})\text{RuCl}_2]_2$ and sodium acetylacetonate in acetone affords complex (4.3).



(4.3)

We prepared two analogous complexes (4.4a) and (4.5a) which contain deprotonated ethylmaltol or a hydroxy-pyridinone as the chelating ligand. The complex $[(\text{mes})\text{RuCl}(\text{Etmal})]$ (4.4a) and $[(\text{mes})\text{RuCl}(\text{Pyr})]$ (4.5a) were prepared by reacting $[(\text{mes})\text{RuCl}_2]_2$ and NaOMe with the α -hydroxyketone; 3-hydroxy-2-ethyl-4-pyrone (ethylmaltol) or N-methyl-3-hydroxy-2-ethyl-4-pyridinone respectively.



The complexes were obtained in good yields, and were characterised by ^1H NMR and mass spectroscopy, and microanalysis, Tables 4.3.1 - 4.3.3. Both the complexes are soluble in water and polar organic solvents.

The ^1H NMR spectrum of complex (4.4a) in CDCl_3 displays singlets at δ 2.25 for the methyl groups, and at δ 4.91 for the aromatic protons of the mesitylene. The ethylmaltol protons are assigned as follows; according to Fig 4.2.1.

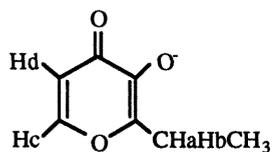


Fig 4.2.1

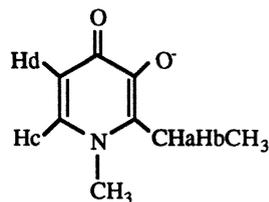


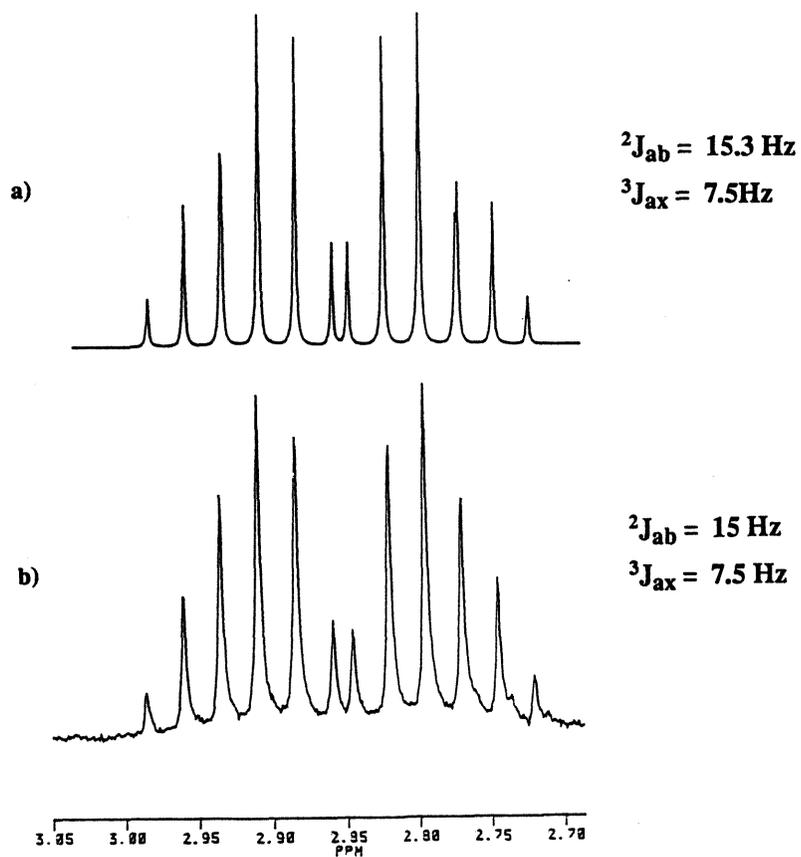
Fig 4.2.3

Doublets observed at δ 7.57 and 6.48 are assigned to Hc and Hd respectively, the ethyl group of the ligand is observed as an ABX_3 pattern with the inequivalent methylene protons (AB part) being assigned to the multiplets between δ 2.72 and 2.99, while the triplet at δ 1.21 corresponds to the methyl group (X_3 part). First and second order simulations of an ABX_3 spin system were carried out and a comparison between the AB parts of the actual and simulated spectra are shown in Fig 4.2.2. The second order simulation gave the chemical shifts of the AB multiplets at δ 2.79 and 2.92 and the coupling constants as $^2J = 15.3$ and

Fig. 4.2.2. Comparison of the simulated and the actual spectra of the AB part of the ABX₃ spin system for the complex [(mes)RuCl(Etma)] (4.4a).

a) Simulated spectrum.

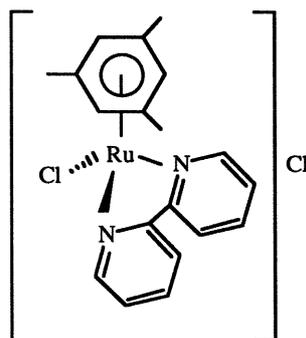
b) Actual spectrum.



$^3J = 7.5$. The chemical shifts (δ 2.78 and 2.92) measured from the spectrum assuming it is first order were almost identical as the simulated values, the coupling constants of $^2J = 15$ and $^3J = 7.5$ were also almost identical, as expected. The first order simulation gave a very similar result in terms of line positions to the second order one, however, the intensities of the inner lines were noticeably different. For second order spectra, perturbation of line intensities occurs before significant changes from first order chemical shifts and hence the spectrum is only slightly second order.

In the ^1H NMR spectrum of complex (4.5a) in CDCl_3 the mesitylene protons are observed as singlets at δ 2.21 and 4.82. The ligand protons (Fig 4.2.3) are observed as doublets at δ 6.83 ($J = 7$) and 6.30 ($J = 7$) for Hc and Hd respectively, while the N-methyl group is observed as a singlet at δ 3.58. The inequivalent protons Ha and Hb are observed as multiplets at δ 3.00 and 2.62, with the adjacent methyl group being assigned to the triplet at δ 1.17 ($J = 7.5$).

Arene-ruthenium complexes with the N,N chelates 2,2'-bipyridine and 1,10 phenanthroline were mentioned in Chapter 1. The formation of the complex $[(\text{mes})\text{RuCl}(\text{bipy})]\text{Cl}$ was cited in a communication by Robertson and Stephenson,^{38a} however no data was reported in the corresponding full paper.^{38b} Here we report details of the preparation of $[(\text{mes})\text{RuCl}(\text{bipy})]\text{Cl}$ (4.6a) and its full characterisation by ^1H NMR and mass spectroscopy, and microanalysis, Tables 4.3.1 - 4.3.3. The complex is soluble in water and methanol, but only sparingly soluble in chlorinated hydrocarbons.



(4.6a)

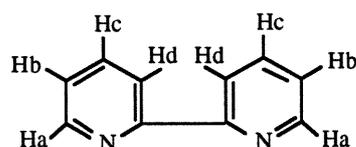


Fig 4.2.4

The ^1H NMR spectrum of complex (4.6a) in CD_3OD exhibits signals at δ 2.20 and 5.53 which are assigned to the mesitylene protons. Doublets observed at δ 9.48 ($J = 6$) and 8.50 ($J = 7$) are assigned to protons Ha and Hd respectively, as shown in Fig 4.2.4, while the signals due to Hb and Hc are observed as multiplets at δ 8.23 and 7.77 respectively.

The ^1H NMR spectrum of complex (4.4a) in D_2O initially displays evidence of two species in a 1:1 ratio. In particular, two signals are observed at δ 2.06 and 2.20 which are assigned to the methyl groups of the mesitylene ligand. After a period of 15 minutes the signal at δ 2.06 disappears indicating only one species now exists in solution. Signals for this complex are observed as singlets at δ 2.20 and 5.27 for the mesitylene protons, and doublets at δ 8.00 ($J = 5$) and 6.63 ($J = 5$) assigned to Hc and Hd of the ethylmaltol ligand. The methyl group is observed as a triplet at δ 1.23 ($J = 7.5$), while a quartet at δ 2.85 ($J = 7.5$) is assigned to the adjacent methylene protons Ha and Hb, which are now coincident.

In contrast, the ^1H NMR spectrum of complex (4.5a) in D_2O shows evidence of only one species, with signals being observed at δ 2.17 and 5.17 for the mesitylene protons. Doublets at δ 6.51 ($J = 6$) and 7.33 ($J = 6$) correspond to Hd and Hc of the pyridinone, while the N-methyl is observed as a singlet at δ 3.74. The ethyl group is observed as a triplet at δ 1.15 ($J = 7.5$) due to the CH_3 and the adjacent methylene protons Ha and Hb are assigned to the multiplet at δ 2.95. Similarly, the ^1H NMR spectrum of the complex (4.6a) in D_2O also shows evidence for only one species being present in solution. The mesitylene protons are observed at δ 2.17 and 5.56, while the bipyridyl protons are assigned to the multiplets at δ 8.30 (Hb and Hd) and 7.82 (Hc), and a doublet at δ 9.46 ($J = 6$) (Ha).

This NMR data is consistent with displacement of the chloride ligand by D_2O to form an aquated species, as shown in Fig 4.2.5. The displacement is slower for complex (4.4a), and therefore both complexes (4.4a) and (4.4b) are observed. However, in complexes (4.5a) and (4.6a) the chloride is displaced rapidly, and only the aquated complexes (4.5b) and (4.6b) are observed in the ^1H NMR spectra in D_2O . The equilibrium which occurs for the amino acidate complexes (see Chapter 3) is not observed here, furthermore addition of a five fold excess of LiCl fails to displace the D_2O from the ruthenium centre. The large excess of D_2O coupled with the apparent stability of the aquated species may make the displacement of D_2O very difficult.

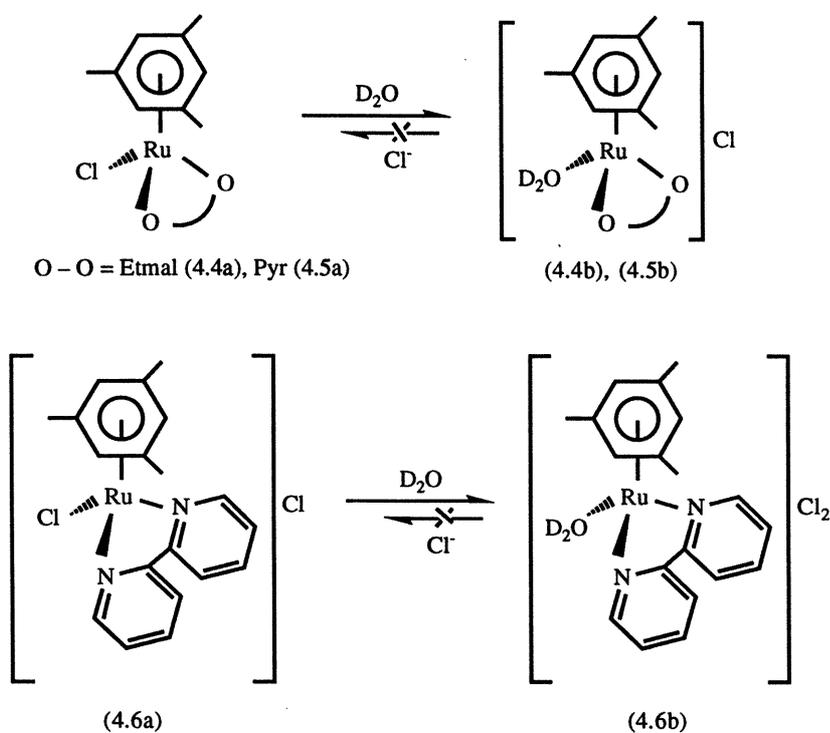


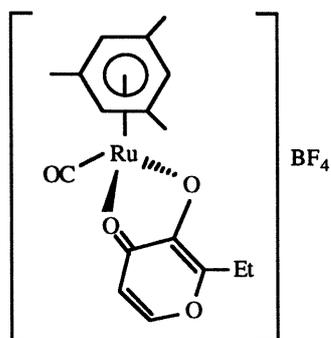
Fig 4.2.5

4.2.2 - Reactions with Carbon Monoxide

The reaction of $[(\text{mes})\text{RuCl}(\text{Etmal})]$ (4.4a) with carbon monoxide, in the presence of AgBF_4 affords the complex $[(\text{mes})\text{Ru}(\text{CO})(\text{Etmal})]\text{BF}_4$ (4.4c), which has been characterised by ^1H NMR, IR and mass spectroscopy and microanalysis, Tables 4.3.1 - 4.3.3. Its structure has been determined by X-ray diffraction.

The ^1H NMR spectrum exhibits resonances at δ 2.26 and 5.68, which are assigned to the mesitylene ligand, and doublets at δ 6.67 ($J = 5$) and 7.85 ($J = 5$) which correspond to Hd and Hc (as assigned in Fig 4.2.1) respectively. The methyl group is observed as a triplet at δ 1.23 ($J = 7.5$), while the methylene protons Ha and Hb though formally inequivalent are seen as a coincident quartet at δ 2.83. The IR spectrum of the complex exhibits an absorption at 2050 cm^{-1} , which is characteristic of a terminal $\text{RuC}\equiv\text{O}$ bond. The FAB mass spectrum

exhibits a weak signal at m/e 389 for the molecular ion, with the strongest peak being the $[M-CO]^+$ fragment at m/e 361.



An X-ray structure determination was carried out on complex (4.4c), and the molecular structure is illustrated in Fig 4.2.6, together with the crystallographic numbering system. Two molecules are observed in the asymmetric unit, with selected bond lengths and angles for both molecules listed in Table 4.2.1. The Ru–CO bond distance of 1.906(12) Å for molecule (a) is similar to that of molecule (b), 1.870(12) Å, and both values are comparable to the literature value of 1.896 Å,^{147a} which is an average Ru–CO distance for a number of ruthenium carbonyl complexes. The Ru–O bond distances of 2.085(7) and 2.105(7) Å in molecule (b) are marginally larger than those of molecule (a) which are 2.059(7) and 2.079(7) Å. As regards the bond angles, the angles C(8)–Ru–O(1) and C(8)–Ru–O(2) are almost identical for molecule (a) [90.4(4) and 89.1(4)°], while there is a small difference in the second molecule where the corresponding angles are 92.4(4) and 89.5(4)° respectively. Also, a small deviation from linearity of the O(4)–C(8)–Ru bond is observed for molecule (b) [174.1(10)°], which is not seen for molecule (a), where the corresponding angle is 177.6(10)°. In solution only one species is observed and therefore these differences are most likely a result of packing forces between the molecules in the unit cell.

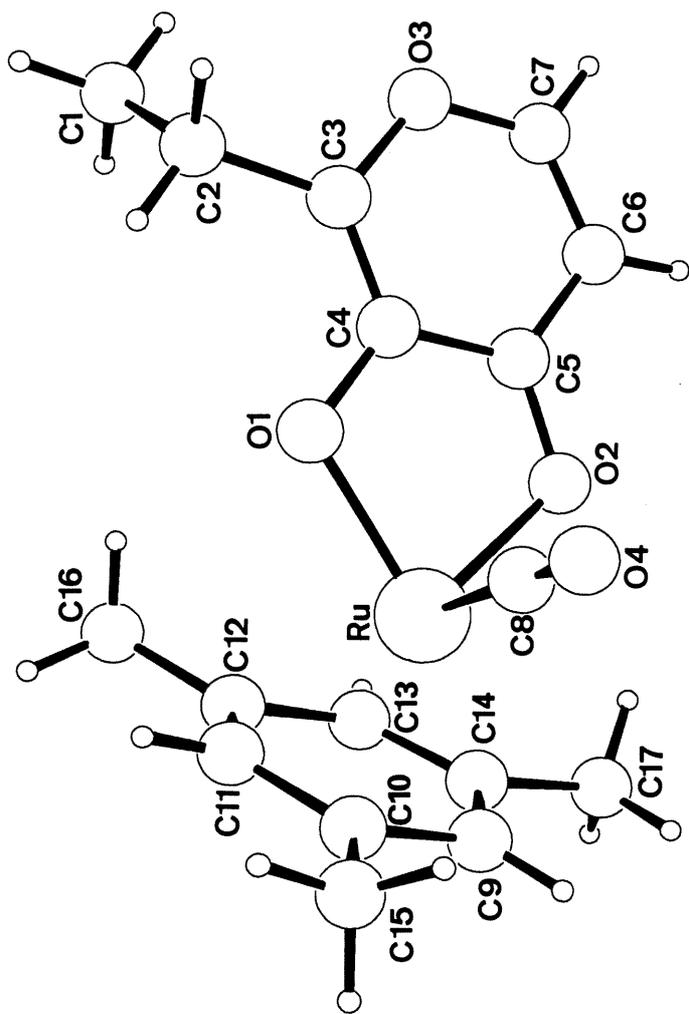


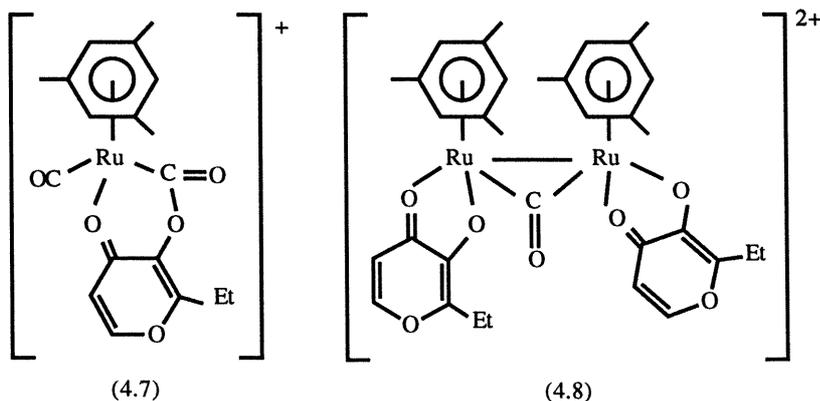
Fig. 4.2.6. The Molecular Structure of One of the Molecules of [(mes)Ru(CO)(Etmal)]BF₄ (4.4c).

**Table 4.2.1- Selected Bond Distances and Angles
of [(mes)Ru(CO)(Etmal)]BF₄ (4.4c)**

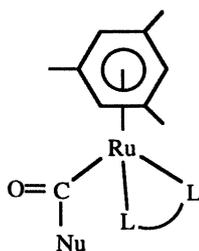
BOND DISTANCES (Å)		
	Molecule (a)	Molecule (b)
Ru – C(8)	1.906(12)	1.870(12)
Ru – O(1)	2.059(7)	2.085(7)
Ru – O(2)	2.079(7)	2.105(7)
C(8) – O(4)	1.156(16)	1.138(15)
C(5) – O(2)	1.296(12)	1.278(12)
C(4) – O(1)	1.338(12)	1.330(13)
C(5) – C(4)	1.418(14)	1.433(15)
BOND ANGLES (°)		
	Molecule (a)	Molecule (b)
O(2) – Ru – O(1)	79.7(3)	80.5(3)
C(8) – Ru – O(1)	90.4(4)	92.4(4)
C(8) – Ru – O(2)	89.1(4)	89.5(4)
O(4) – C(8) – Ru	177.6(10)	174.1(10)

The C(5)–O(2) bond distance in molecule (a) [1.296(12) Å] is slightly larger than the corresponding C=O bond length of 1.243(2) Å in the free ligand, whereas for molecule (b) the distance is 1.278(12) Å which is similar to that observed in the free ligand.^{147b} The C(4)–O(1) bond distances [1.338(12) and 1.330(13) Å] and the C(5)–C(4) distances [1.418(14) and 1.433(15) Å] are statistically the same as those found in free ethylmaltol, where the corresponding bond lengths are 1.350(2) and 1.442(2) Å respectively. These bond lengths are consistent with a small amount of electron delocalisation occurring around the O(1)–C(4)–C(5)–O(2) bonds. The O(1)–Ru–O(2) bite angles of molecules (a) and (b) are 79.7(3) and 80.5(3)° respectively which are marginally larger than the N–Ru–O bite angle of 77.9(2)° for the complex [(mes)RuCl(pic)] (3.8).

Although complex (4.4c) is the only complex isolated from the reaction mixture, there is evidence of another carbonyl species existing before work-up. A sharp absorption is observed at 1720 cm⁻¹ in the IR spectrum, while the ¹H NMR spectrum (CDCl₃) also indicates the presence of a second species with resonances at δ 2.16 and 5.00, corresponding to the mesitylene protons. Signals at δ 7.61 and 6.50 are assigned to the Hc and Hd protons of an ethylmaltol ligand, while a broad multiplet at δ 0.83 can be tentatively assigned to the methyl protons. All attempts to isolate this complex in a pure state were unsuccessful. The absorption at 1720 cm⁻¹ is typical of an acyl carbonyl or a bridging carbonyl group. An acyl complex could result from insertion of carbon monoxide into the Ru–O bond to give complex (4.7).



The IR spectrum of this species would be expected to show two absorptions, one for the terminal carbonyl group and another for the acyl carbonyl. An alternative is complex (4.8) which might be formed by reaction of the carbonyl complex (4.4c) with the reaction intermediate $[(\text{mes})\text{Ru}(\text{Etmal})(\text{solvent})]^+$. A third alternative is attack of a nucleophile on the carbonyl group to form a complex of type (4.9).

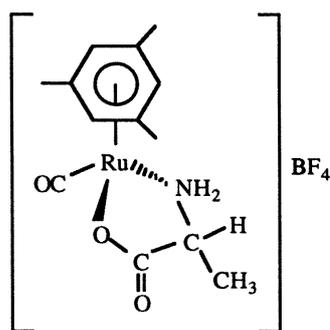


(4.9)

However, this possibility was ruled out by subsequent experiments (see later). A further experiment was carried out in order to try and identify the second species. Carbon monoxide was bubbled through a reaction mixture containing both species, after three hours no change in the reaction composition had occurred as monitored by IR spectroscopy. This suggests that complex (4.4c) does not react with carbon monoxide and thus acyl formation is unlikely. We do not expect (4.8) to react with excess carbon monoxide and this is perhaps a more likely second species.

The complex $[(\text{mes})\text{Ru}(\text{CO})(\text{ala})]\text{BF}_4$ (4.10a) was prepared in the same way as complex (4.4c), and characterised on the basis of ^1H NMR and IR spectroscopy. The ^1H NMR spectrum of the complex in CD_3OD exhibits a singlet due to the methyl groups of the mesitylene at δ 2.32 for both diastereomers, the corresponding aromatic protons for both diastereomers are observed as a singlet at δ 5.29. Doublets at δ 1.28 ($J = 7$) (major) and δ 1.54 ($J = 7$) (minor) are assigned to the alaninate methyl groups, while a multiplet observed at δ 2.58 is due to the α -proton of one diastereomer, the signal for the second diastereomer is not visible. The IR spectrum of the reaction mixture exhibits two absorptions at 2050 cm^{-1} and 1740 cm^{-1} .

The absorption at 2050 cm^{-1} is typical for a terminal carbonyl ligand, while the second absorption at 1740 cm^{-1} may be due to a product formed from a side reaction, similar to that observed for complex (4.4c).



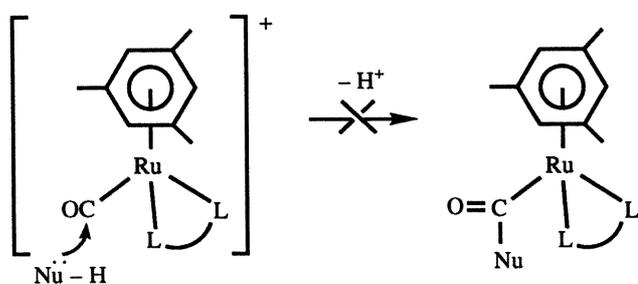
(4.10a)

Carbon monoxide was also reacted with the complexes $[(\text{mes})\text{RuCl}(\text{Pyr})]$ (4.5a) and $[(\text{mes})\text{RuCl}(\text{bipy})]\text{Cl}$ (4.6a). The IR spectra of both reaction mixtures exhibit two absorptions. The bipyridyl complex displays absorptions at 2025 and 1720 cm^{-1} , while for the pyridinone complex absorptions are observed at 2040 and 1725 cm^{-1} . Although these absorptions suggest the presence of a terminal carbonyl ligand, and perhaps an acyl or bridging carbonyl group, none of these products were isolated. The ^1H NMR spectra from both reactions showed the presence of two species, with signals due to the mesitylene and the attached ligands being observed, however any further assignment was not possible.

4.2.3 - Reactions of Carbonyl Complexes with Nucleophiles

The subject of nucleophilic activation of carbon monoxide ligands has been extensively reviewed by Ford *et al.*,¹⁴⁸ in particular, the employment of oxygen and nitrogen bases as the nucleophiles. The expected products of nucleophilic attack at the carbonyl ligand of complexes (4.4c) and (4.10a) are the acyl complexes (4.9). Both complexes (4.4c) and (4.10a) were reacted with water which resulted in carbonyl displacement and the formation of the aquated

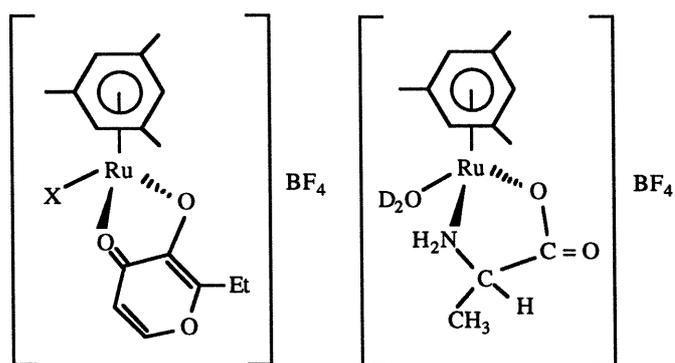
species (4.4d) and (4.10b) respectively, with no evidence of nucleophilic attack at the carbonyl group being observed.



(4.4c) L - L = Etmal

(4.9)

(4.10a) L - L = ala



(4.4d) X = D₂O

(4.10b)

(4.4e) X = PhCH₂NH₂

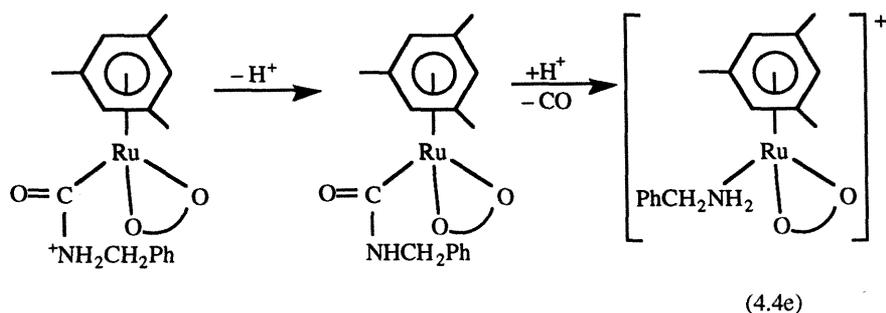
The displacement of the carbonyl group is best illustrated in the ¹H NMR spectrum of complex (4.4c) in D₂O. Immediately after the complex was dissolved in D₂O two species were observed in a 1:1 ratio, corresponding to the carbonyl complex (4.4c) and the aquated species (4.4d). The mesitylene signals for the aquated complex are observed at δ 2.20 and 5.29, while the carbonyl complex exhibits mesitylene signals at δ 2.29 and 5.83. After a period of two

hours, the ratio had changed from 1:1 to 1:2 in favour of the aquated complex (4.4d), after two days only complex (4.4d) was observed. The chemical shifts for complex (4.4d) are listed in Table 4.3.1. In contrast, the ^1H NMR spectrum of complex (4.10a) in D_2O displays one set of signals, which are attributed to the aquated complex (4.10b) (Table 4.3.1), where the carbonyl ligand has been rapidly displaced. In this case, the gradual displacement of the carbonyl ligand can be observed by obtaining a ^1H NMR spectrum in CD_3OD , in which only the carbonyl complex (4.10a) is observed. D_2O was then added in portions, after each addition the ^1H NMR spectrum was taken. As the amount of D_2O added increased, a second set of signals were observed, corresponding to the aquated species (4.10b) being formed, while resonances due to complex (4.10a) decrease, until eventually only the aquated complex is observed in the spectrum.

To see if this substitution reaction was a general phenomenon or specific to water, the reaction of complex (4.4c) with benzylamine was attempted. The IR spectrum showed no absorption in the terminal carbonyl or acyl regions, suggesting that the carbon monoxide ligand had been displaced. The ^1H NMR spectrum of the product displays signals due to the mesitylene protons at δ 2.02 and 4.70, a triplet is observed at δ 1.27 ($J = 7.5$) due to the methyl group of an ethylmaltol ligand, while a multiplet at δ 2.90 is assigned to the adjacent methylene protons Ha and Hb which are the AB part of an ABX_3 spin system. Doublets at δ 7.81 ($J = 5$) and 6.65 ($J = 5$) are assigned to the protons Hc and Hd respectively. The multiplet observed at δ 3.45 is assigned to an NH proton and the methylene group of the attached benzylamine ligand with the phenyl protons being observed as a complex signal between δ 7.30 and 7.52. The FAB mass spectrum exhibits a peak at m/e 468 which corresponds to the molecular ion of $[(\text{mes})\text{Ru}(\text{NH}_2\text{CH}_2\text{Ph})(\text{Etmal})]^+$. This evidence shows that the carbonyl ligand has been replaced by the amine to form a complex of the form $[(\text{mes})\text{Ru}(\text{NH}_2\text{CH}_2\text{Ph})(\text{Etmal})]\text{BF}_4$ (4.4e). The microanalysis of the product agrees with this formulation (Table 4.3.3). The identity of the product as $[(\text{mes})\text{Ru}(\text{NH}_2\text{CH}_2\text{Ph})(\text{Etmal})]\text{BF}_4$ was confirmed by preparing the complex via an alternative pathway. $[(\text{mes})\text{RuCl}(\text{Etmal})]$ was reacted with benzylamine and AgBF_4 . The ^1H NMR spectrum of the product was identical to that for complex (4.4e) described above.

The displacement of the carbonyl ligands of complexes (4.4c) and (4.10a) by various nucleophiles is in contrast to predictions made by Angelici *et al.*, where a relationship between the carbonyl stretching frequency and the susceptibility of that carbonyl ligand to nucleophilic attack was reported.¹⁴⁹ Carbonyl complexes which have C≡O stretching absorptions above 2000 cm⁻¹ were found to react with nucleophiles such as amines, whereas those with stretching frequencies below 2000 cm⁻¹ did not react, and this was found to be the case for a large number of carbonyl complexes. However, the fact that complex (4.4c) does not react with various nucleophiles, even though the carbonyl stretching frequency is 2050 cm⁻¹, suggests in this instance other factors are influencing the susceptibility of the ligand to nucleophilic attack.

One possible mechanism for this reaction is direct attack at the ruthenium centre which causes displacement of the carbon monoxide. An alternative mechanism could be nucleophilic attack by the amine at the carbonyl with subsequent deprotonation to form the amide. There must then be elimination of the carbon monoxide followed by reprotonation of the nitrogen to form complex (4.4e), as shown in Scheme 4.2.1. However, this mechanism is unlikely because both deprotonation and protonation must occur while the reaction conditions remain the same.



Scheme 4.2.1

This Chapter has described arene-ruthenium complexes incorporating the O,O donor ligands; ethylmaltol and an N-substituted pyridinone, and the N,N chelate 2,2'-bipyridine. The versatility of the arene-ruthenium ethylmaltol complex (4.4a) is demonstrated by its ability to coordinate to such ligands as benzylamine, water, carbon monoxide and also pyridine

(Chapter 5). Complexes (4.4) have the advantage of being soluble in both water and polar organic solvents. In particular, this advantage is emphasised in the reactions with carbon monoxide. It is possible to isolate the complex [(mes)Ru(CO)(Etmal)]BF₄ (4.4c), whereas it proved difficult to isolate one product in similar reactions with complexes (4.5a) and (4.6a), as the products are poorly soluble in CH₂Cl₂ and react with water. The solubility of complexes (4.4) in both aqueous and organic media may prove useful if they are to be used as catalysts.

Unfortunately, the carbonyl ligand was easily displaced by water and benzylamine, however, it may be possible to directly attack the carbonyl ligand itself by using other nucleophiles, such as carbon based nucleophiles, or by using different reaction conditions. Carrying out the reactions under a pressure of carbon monoxide may result in nucleophilic attack as opposed to displacement.

4.3 - Experimental

General experimental techniques were as described in Chapter 2. Ethylmaltol was obtained from Pfizer Chemicals and carbon monoxide was obtained from B.O.C. Ltd. N-methyl-3-hydroxy-2-ethyl-4-pyridinone was prepared following the procedure outlined by Orvig *et al.*¹⁵⁰ and amended by Patel¹⁵¹ while [(mes)RuCl₂]₂ was prepared as stated in Chapter 2. All other reagents were obtained from the Aldrich Chemical Company Ltd. and used without further purification. IR spectra were recorded in dichloromethane solution on a Perkin-Elmer 580 spectrophotometer.

Preparation of [(mes)RuCl(Etmal)] (4.4a)

Sodium methoxide (68 mg, 1.32 mmol) and ethylmaltol (186 mg, 1.32 mmol) were added to a suspension of [(mes)RuCl₂]₂ (387 mg, 0.66 mmol) in methanol/water (1:1) (60 cm³) and the mixture was refluxed for 2 hours. The solvent was removed and the residue dissolved in dichloromethane (80 cm³) and filtered through Celite. The solvent was evaporated and the resultant orange solid was recrystallised from dichloromethane/diethylether to give [(mes)RuCl(Etmal)] (4.4a) as orange crystals (421 mg, 80%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 4.3.1 - 4.3.3.

Preparation of [(mes)RuCl(Pyr)] (4.5a)

Sodium methoxide (60 mg, 1.16 mmol) and N-methyl-3-hydroxy-2-ethyl-4-pyridinone (177 mg, 1.16 mmol) were added to a suspension of [(mes)RuCl₂]₂ (338 mg, 0.58 mmol) in methanol/water (1:1) (60 cm³) and the mixture was refluxed for 2.5 hours. The solvent was removed, the residue dissolved in dichloromethane (80 cm³) and filtered through Celite. The solvent was evaporated to give a brown solid which was recrystallised from dichloromethane/diethylether to give [(mes)RuCl(Pyr)] (4.5a) as red crystals (320 mg, 68%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 4.3.1 - 4.3.3.

Preparation of [(mes)RuCl(bipy)]Cl (4.6a)

2,2'-bipyridine (160 mg, 1.02 mmol) was added to a suspension of [(mes)RuCl₂]₂ (300 mg, 0.51 mmol) in chloroform (50 cm³) and the mixture was refluxed for 2 hours. The solvent was removed and the residue was recrystallised from methanol/diethylether to give [(mes)RuCl(bipy)]Cl (4.6a) as an orange solid (340 mg, 74%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 4.3.1 - 4.3.3.

Preparation of [(mes)Ru(CO)(Etmal)]BF₄ (4.4c)

A solution of [(mes)RuCl(Etmal)] (4.4a) (252 mg, 0.64 mmol) in dichloromethane (50 cm³) was cooled to -78°C and purged with carbon monoxide for 15 minutes. AgBF₄ (124 mg, 0.64 mmol) was then added to the solution with carbon monoxide still bubbling through, the mixture was allowed to warm to room temperature and stirred for a further 2 hours. The mixture was filtered and the solvent was removed, the residue was recrystallised from dichloromethane/diethylether to give [(mes)Ru(CO)(Etmal)]BF₄ (4.4c) as red crystals (251 mg, 88%). IR spectrum: ν (C=O) 2050 cm⁻¹. The complex was also characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 4.3.1 - 4.3.3.

Preparation of [(mes)Ru(CO)(ala)]BF₄ (4.10a)

A solution of [(mes)RuCl(ala)] (3.5; R = Me) (120 mg, 0.35 mmol) in dichloromethane (50 cm³) was cooled to -78°C and purged with carbon monoxide for 10 minutes. AgBF₄ (68 mg, 0.35 mmol) was then added to the solution and with continuous bubbling of carbon monoxide through the mixture, it was slowly heated to room temperature and stirred for a further 2 hours. The mixture was filtered and the IR spectrum taken. The solvent was removed to give [(mes)Ru(CO)(ala)]BF₄ (4.10a) as a yellow solid (87 mg, 59%). The complex was characterised by IR spectroscopy: ν (C=O) 2050 cm⁻¹ and ¹H NMR spectroscopy, Table 4.3.1.

Reaction of [(mes)RuCl(Pyr)] (4.5a) with carbon monoxide and AgBF₄

Using the same procedure as for complex (4.10a), [(mes)RuCl(Pyr)] (4.5a) (152 mg, 0.37 mmol) and AgBF₄ (73 mg, 0.37 mmol) were reacted with carbon monoxide in dichloromethane (50 cm³) to give, after work-up, a brown solid. IR spectrum: ν (C=O) 2040 cm⁻¹.

Reaction of [(mes)RuCl(bipy)]Cl (4.6a) with carbon monoxide and AgBF₄

Using the same procedure as for complex (4.10a), [(mes)RuCl(bipy)]Cl (4.6a) (110 mg, 0.25 mmol) and AgBF₄ (96 mg, 0.49 mmol) were reacted with carbon monoxide in dichloromethane/methanol (60 cm³: 7 cm³) to give, after work-up, a brown solid. IR spectrum: ν (C=O) 2025 cm⁻¹.

Reaction of [(mes)Ru(CO)(Etmal)]BF₄ (4.4c) with benzylamine

Benzylamine (23 mg, 0.21 mmol) was added to a stirred solution of [(mes)Ru(CO)(Etmal)]BF₄ (4.4c) (102 mg, 0.21 mmol) in dichloromethane (50 cm³), Na₂CO₃ (32 mg, 0.21 mmol) was then added and the mixture stirred for one hour. The mixture was filtered, the solvent removed and the residue recrystallised from methanol/diethylether to give [(mes)Ru(NH₂CH₂Ph)(Etmal)]BF₄ (4.4e) as an orange crystalline solid (86 mg, 72%). The

complex was characterised by ^1H NMR and FAB mass spectroscopy, and microanalysis, Tables 4.3.1 - 4.3.3.

Preparation of [(mes)Ru(NH₂CH₂Ph)(Etmal)]BF₄ (4.4e)

AgBF₄ (51 mg, 0.26 mmol) was added to a stirred solution of [(mes)RuCl(Etmal)] (4.4a) (103 mg, 0.26 mmol) in dichloromethane (50 cm³), followed by the addition of benzylamine (28 mg, 0.26 mmol). The mixture was stirred for 0.5 hours and filtered, the solvent was removed to afford [(mes)Ru(NH₂CH₂Ph)(Etmal)]BF₄ (4.4e) as an orange solid (117 mg, 90%). In this case, the complex was characterised by ^1H NMR spectroscopy.

Table 4.3.1 ¹H NMR data for complexes (4.4 - 4.6) and (4.10a)^a

Complex	Arene Protons (δ)		Ligand Protons (δ)
	C ₆ Me ₃	C ₆ H ₃	
4.4a ^b	2.25	4.91	{1.21 [t, 3H, Me (X ₃ part), J(7.5)], 2.79 and 2.92[m, 2H, CH ₂ (AB part), ² J(15.3), J(7.5)]] ^c , 6.48 [d, 1H, Hd, J(5)], 7.57 [d, 1H, Hc, J(5)]
4.4b ^d	2.20	5.27	1.23 [t, 3H, Me, J(7.5)], 2.85 [q, 2H, CH ₂ , J(7.5)], 6.63 [d, 1H, Hd, J(5)], 8.00 [d, 1H, Hc, J(5)]
4.5a ^b	2.21	4.82	1.17 [t, 3H, Me, J(7.5)], 2.62 [m, 1H, CHaHb], 3.00 [m, 1H, CHaHb], 3.58 (s, 3H, NMe), 6.30 [d, 1H, Hd, J(7)], 6.83 [d, 1H, Hc, J(7)]
4.5b ^d	2.17	5.17	1.15 [t, 3H, Me, J(7.5)], 2.95 (m, 2H, CH ₂), 3.74 (s, 3H, NMe), 6.51 [d, 1H, Hd, J(6)], 7.33 [d, 1H, Hc, J(6)]
4.6a ^e	2.20	5.53	7.77 (m, 2H, Hc), 8.23 (m, 2H, Hb), 8.50 [d, 2H, Hd, J(7)], 9.48 [d, 2H, Ha, J(6)]
4.6b ^d	2.17	5.56	7.82 (m, 2H, Hc), 8.30 (m, 4H, Hb, Hd), 9.46 [d, 2H, Ha, J(6)]
4.4c ^b	2.26	5.68	1.23 [t, 3H, Me, J(7.5)], 2.83 [q, 2H, CH ₂ , J(7.5)], 6.67 [d, 1H, Hd, J(5)], 7.85 [d, 1H, Hc, J(5)]
4.4d ^d	2.20	5.29	1.25 [t, 3H, Me, J(7.5)], 2.87 [q, 2H, CH ₂ , J(7.5)], 6.63 [d, 1H, Hd, J(5)], 8.03 [d, 1H, Hc, J(5)]
4.10a ^e	{2.32	5.29	1.28 [d, 3H, Me, J(7)]] ^f , 2.58 (m, 1H, Hα)
	{2.32	5.29	1.54 [d, 3H, Me, J(7)]] ^g

Table 4.3.1 (continued)

Complex	Arene Protons (δ)		Ligand Protons (δ)
	C ₆ Me ₃	C ₆ H ₃	
4.10b ^d	2.17	5.33	1.33 [d, 3H, Me, J(7)], 3.10 (q, 1H, H α)] ^f
4.4e ^b	2.17	5.34	1.54 [d, 3H, Me, J(6)], 3.51 (q, 1H, H α)] ^g
	2.02	4.70	1.27 [t, 3H, Me (X ₃ part), J(7.5)], 2.90 [m, 2H, CH ₂ (AB part)], 3.45 (m, 3H, CH ₂ /NH), 6.65 [d, 1H, Hd, J(5)] 7.30 - 7.52 (m, 5H, Ph), 7.81 [d, 1H, Hc, J(5)]

^a All J values refer to ³J coupling unless otherwise stated.

^b In CDCl₃.

^c Data obtained from a simulated second order spectrum.

^d In D₂O, ^e In CD₃OD, ^f Major diastereomer, ^g Minor diastereomer.

Table 4.3.2 Mass spectroscopy data for complexes (4.4 - 4.6)

Complex	[M] ⁺	Other Peaks
[(mes)RuCl(Etmal)] (4.4a)	396 ^a	361 [M-Cl] ⁺
[(mes)RuCl(Pyr)] (4.5a)	409 ^a	374 [M-Cl] ⁺
[(mes)RuCl(bipy)]Cl (4.6a)	413 ^{ab}	378 [M-Cl] ⁺
[(mes)Ru(CO)(Etmal)]BE ₄ (4.4c)	389 ^b	361 [M-CO] ⁺
[(mes)Ru(NH ₂ CH ₂ Ph)(Etmal)]BE ₄ (4.4e)	468 ^b	361 [M-PhCH ₂ NH ₂] ⁺

^a The [M+H]⁺ ion is also observed.

^b M refers to the complex cation.

Table 4.3.3 Elemental analyses of complexes (4.4), (4.5) and (4.6)

Complex	Found (%)			Calculated (%)		
	C	H	N	C	H	N
[(mes)RuCl(Etma)] (4.4a) ^a	47.95	4.79	–	47.46	4.98	–
[(mes)RuCl(Pyrr)] (4.5a)	50.08	5.47	3.54	49.93	5.42	3.42
[(mes)RuCl(bipy)] Cl (4.6a) ^b	49.01	4.92	5.92	48.93	4.76	6.01
[(mes)Ru(CO)(Etma)]BF ₄ (4.4c)	42.66	3.66	–	42.97	4.03	–
[(mes)Ru(NH ₂ CH ₂ Ph)(Etma)]BF ₄ (4.4c)	49.54	5.20	2.73	49.82	5.09	2.52

^a Complex crystallises with 0.5 moles of water.

^b Complex crystallises with one mole of water.

Chapter Five

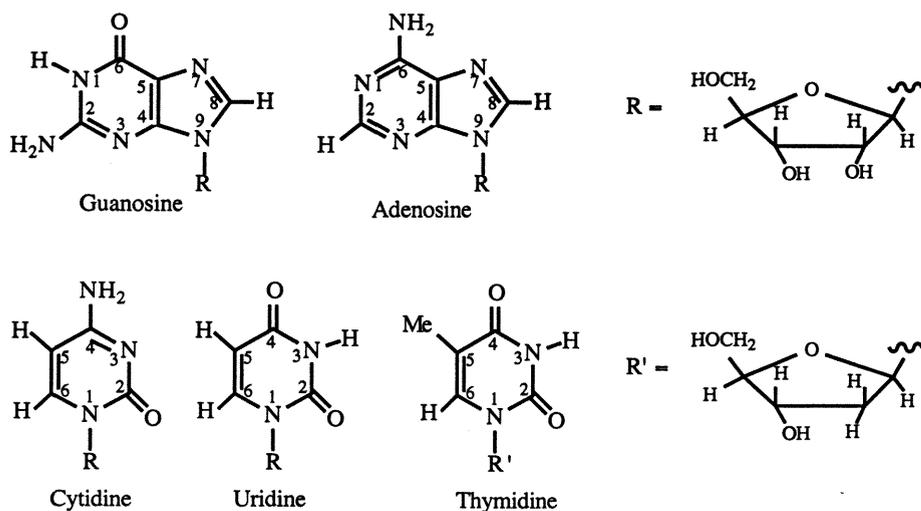
Reactions of Arene-Ruthenium Complexes

with Nucleobases, Theophylline and Pyridine

CHAPTER 5 - REACTIONS OF ARENE-RUTHENIUM COMPLEXES
WITH NUCLEOBASES, THEOPHYLLINE
AND PYRIDINE

5.1 - Introduction

Numerous metal complexes have been investigated as anti-tumour drugs, some of which are described in Chapter 1. However, the mechanism by which these drugs work is generally not well understood. Identification of the chemical interactions of these drugs in biological systems should provide important clues to their mechanisms of action. The phenomenon of cisplatin binding to guanine was recognised at an early stage,¹⁵² and later it was proposed that GG and AG crosslinks are responsible for anti-tumour activity (for a review see ref. 74), though other bifunctional platinum adducts may also be important.¹⁵³ In view of this it is generally accepted that the study of reactions of metal complexes, particularly those that show anti-tumour properties, with the nucleobases guanosine, adenosine, cytidine, uridine and thymidine, and similar related compounds such as imidazoles and xanthines, may lead to an improved understanding of the mechanism by which such complexes work.



The X-ray structure of the complex $cis\text{-}[(\text{NH}_3)_2\text{Pt}(\text{9Etgua})_2]\text{Cl}_2 \cdot 3\text{H}_2\text{O}$ shows coordination via the N(7) position, with a 'head to head' arrangement of the guanine ligands.¹⁵⁴ Similarly, the structure of $cis\text{-}\{(\text{NH}_3)_2\text{Pt}[\text{d}(\text{pGpG})]\}$, reported by Sherman *et al.* in 1988¹⁵⁵ showed N(7) coordination and confirmed the 'head to head' arrangement of the guanine ligands, this structure provided the first detailed study of the effects of cisplatin binding to a dinucleotide segment of DNA. A large number of adenosine and cytidine platinum complexes have also been prepared and investigated, these are described in detail in a review by Lippert.¹⁵⁶

There has also been considerable research into the nucleobase chemistry of other transition metals.^{80,157} In particular, ruthenium where the reaction of $[\text{Ru}^{\text{III}}\text{Cl}(\text{NH}_3)_5]^{2+}$ with a series of nucleoside bases or methylated modifications has been carefully studied by Taube and Clarke.^{95,158-163} The coordination of guanine and guanosine to the pentaammine complexes occurs via the N(7) site,¹⁶¹⁻¹⁶³ and if the sugar group is removed coordination can also occur through the N(3) and N(9) positions.¹⁶³ Favourable hydrogen bonds are formed between coordinated ammonia molecules and the carbonyl group of the guanine, which provides some additional stabilisation in the case of N(7) coordination of guanine and the related xanthine and hypoxanthine complexes, as shown by the X-ray structure of the hypoxanthine complex $[\text{Ru}^{\text{III}}(\text{Hyp})(\text{NH}_3)_5]\text{Cl}_3$, Fig 5.1.1.^{95,163}

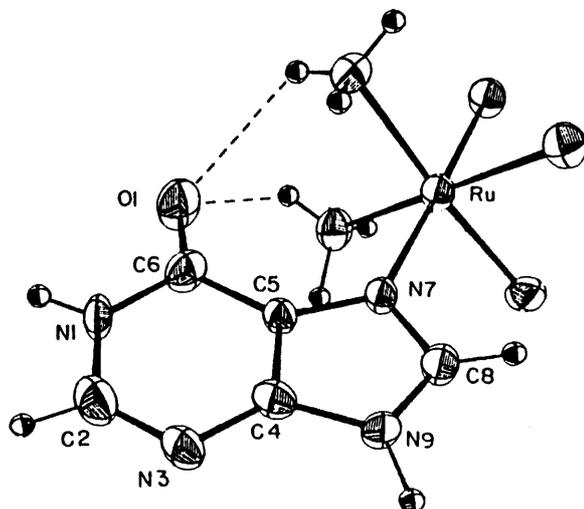


Fig 5.1.1 Structure of N(7) $[\text{Ru}^{\text{III}}(\text{Hyp})(\text{NH}_3)_5]\text{Cl}_3$

Pentaammineruthenium complexes of adenosine and cytidine have also been synthesised by Clarke.¹⁶⁴ In the case of adenosine, of the three ring nitrogens available for coordination N(3) is sterically hindered to attack by the ribose group, leaving the N(1) and N(7) sites available for coordination. In cases where favourable steric and hydrogen bonding interactions occur between a coordinating ligand and the exocyclic amine, N(7) coordination is more likely.^{95,165} In the absence of these interactions N(1) coordination may be expected as it is the most basic towards coordination and the least sterically hindered by the exocyclic amine. Coordination through an exocyclic amine group has been verified by X-ray studies for the analogous methylcytosine complex $[\text{Ru}^{\text{III}}(1\text{-MeCyt}^{\ominus})(\text{NH}_3)_5][\text{PF}_6]_2$,^{164,166} Fig 5.1.2.

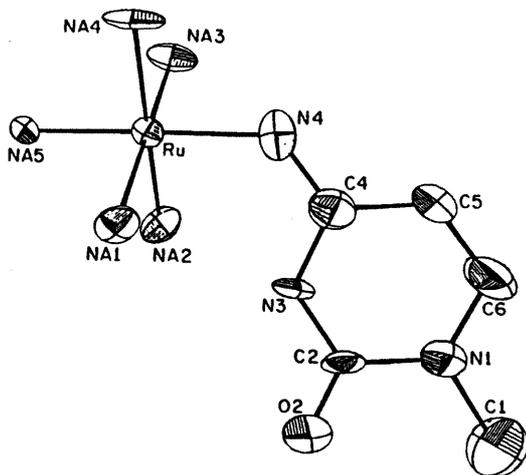


Fig 5.1.2 Structure of $[\text{Ru}^{\text{III}}(1\text{-MeCyt}^{\ominus})(\text{NH}_3)_5][\text{PF}_6]_2$

Exocyclic binding of cytosine to platinum has also been reported.¹⁶⁷ It is generally accepted that metal coordination to an exocyclic nitrogen occurs only when the NH_2 group is deprotonated.^{164,168} In general, N(3) is the preferred coordination site as it is the most electron rich and the most basic towards protonation,¹⁶⁹ and also because additional

interactions are possible with the metal through the exocyclic oxygen and nitrogen atoms,^{170,171} Fig 5.1.3.

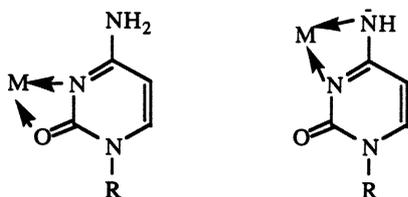


Fig 5.1.3

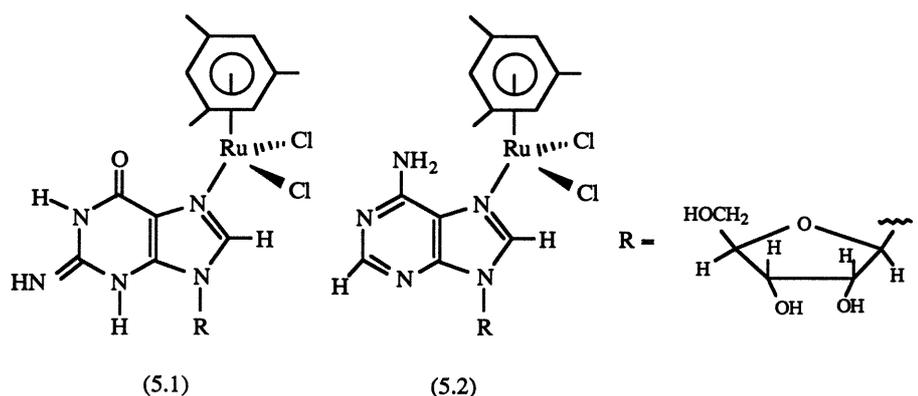
Direct metal binding to the exocyclic oxygen has also been shown in the cases of Ag(I)¹⁶⁵ and Pt(II).¹⁷² Interestingly, it has been suggested that the complexes $[\text{Ru}(\text{Hedta})(\text{H}_2\text{O})]^-$ and $[\text{Ru}(\text{edta})(\text{H}_2\text{O})]^{2-}$ react with cytidine and uridine to form complexes in which the bases are bound via the C(5)–C(6) bond.¹⁷¹ The complexes were identified on the basis of ^1H NMR and ^{13}C NMR spectroscopies, and electrochemical measurements, however, there was no X-ray data available.

The anti-tumour complexes *cis* and *trans*- $[\text{RuCl}_2(\text{dmsO})_4]$ have been shown to react *in vivo* and *in vitro* with DNA.⁹¹ Subsequently, Alessio *et al.*¹⁷³ reported the reactions of *trans*- $[\text{RuCl}_2(\text{dmsO})_4]$ with guanosine monophosphate (5'-dGMP), coordination occurred via N(7) and the α -phosphate oxygen, forming two diastereomers with opposite chiralities at the ruthenium centre. Perhaps the most interesting finding is that *trans*- $[\text{RuCl}_2(\text{dmsO})_4]$ does not readily bind to two 5'-dGMP molecules at neutral pH. Thus, in addition to the stereochemical differences between octahedral Ru(II) and square planar Pt(II) drugs, the Ru(II) compounds may not easily form the N(7)–N(7) GpG crosslinks, characteristic of the DNA adducts formed by platinum anti-cancer drugs. Thus, a different mechanism of action against tumours may occur with ruthenium(II) complexes. It has also been reported recently that the complex $[(\text{C}_6\text{H}_6)\text{RuCl}(\text{pro})]$ has shown significant anti-tumour activity towards P388 leukaemia.¹²¹

In this Chapter we report the reactions of some arene-ruthenium complexes with the nucleobases guanosine, adenosine and cytidine, and also with theophylline and pyridine.

5.2 - Results and Discussion

It was shown in Chapter 2 that nitrogen donor ligands can coordinate to $[(\text{mes})\text{RuCl}_2]_2$. In view of this, and of the current interest in understanding the reactions of nucleobases with metal complexes, we attempted the reactions of $[(\text{mes})\text{RuCl}_2]_2$ with guanosine, adenosine and cytidine. The reactions were carried out by refluxing $[(\text{mes})\text{RuCl}_2]_2$ with the appropriate nucleobase in a methanol/water mixture (1:1) for 3 hours, after which time an orange solution was observed. Evaporation of the solvent gave the products as orange solids. The complexes $[(\text{mes})\text{RuCl}_2(\text{Guan})]$ (5.1) and $[(\text{mes})\text{RuCl}_2(\text{Aden})]$ (5.2) were obtained in good yields and characterised by ^1H NMR and FAB mass spectroscopy, and microanalysis, Tables 5.3.1 - 5.3.3.



The ^1H NMR spectrum of complex (5.1) in D_2O is quite complex, the chlorine ligands are easily displaced by the water, forming an equilibrium which results in three species being observed. These are attributed to $[(\text{mes})\text{RuCl}_2(\text{Guan})]$ (5.1a), $[(\text{mes})\text{RuCl}(\text{D}_2\text{O})(\text{Guan})]\text{Cl}$ (5.1b) and $[(\text{mes})\text{Ru}(\text{D}_2\text{O})_2(\text{Guan})]\text{Cl}_2$ (5.1c), as shown in Fig 5.2.1.

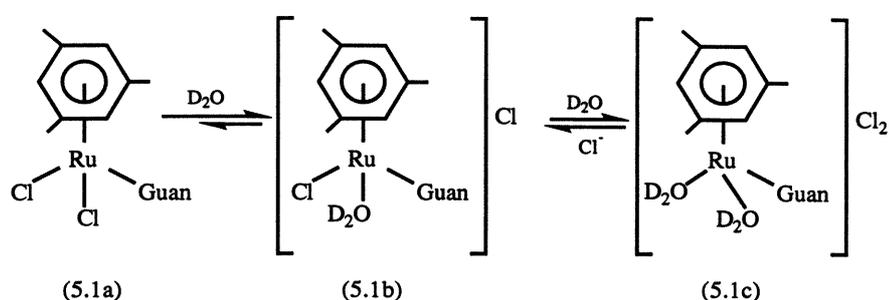
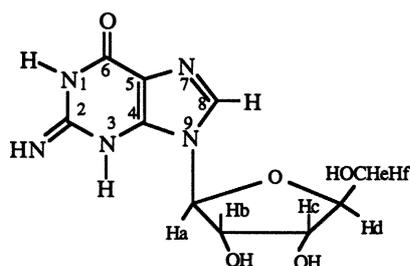


Fig 5.2.1

Three singlets are observed at δ 1.98, 1.99 and 2.04 due to the methyl protons of the mesitylene of complexes (5.1a), (5.1b), and (5.1c) respectively, while the corresponding aromatic protons are seen at δ 5.25, 5.26 and 5.39 respectively.

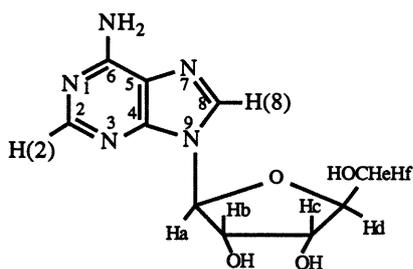


For the guanosine ligand, H(8) is the only clearly assignable proton with signals being observed at δ 8.43 (5.1c), 8.29 (5.1b) and 7.87 (5.1a), whereas in free guanosine the H(8) proton is observed at δ 7.68. Although guanosine can bind through a number of positions,^{74,156} there is a large amount of evidence to show that the downfield shifts of H(8) in coordinated guanosine correlate to N(7) binding.^{95,173,174} Thus, the observed downfield shift of H(8) in complex (5.1) is consistent with N(7) coordination. A doublet at δ 5.60 corresponds to Ha of species (5.1a), while a broad multiplet at δ 5.95 is assigned to Ha of the other two species. The remaining protons Hb - Hf are assigned to complex multiplets between δ 3.75 and 4.70. Addition of a five-fold excess of LiCl resulted in the removal of peaks due to the aquated species (5.1c), however, it failed to provide any further information towards the assignments of (5.1a) and (5.1b). When the ^1H NMR spectrum is run in d_6 -dmso the

guanosine ligand is rapidly displaced, with free ligand and the complex [(mes)RuCl₂(d₆-dmsO)] being observed. The mesitylene peaks of the dmsO complex are seen at δ 2.14 and 5.46.

The H(8) protons of complex (5.1) in D₂O are observed at similar shifts to those of the analogous complex [(C₆H₆)RuCl₂(9Etgua)] (δ 8.10, 8.20, 8.38) the structure of which has been determined by X-ray crystallography¹²¹ and shows coordination via the N(7) position. Thus, adding further weight to our supposition that in complex (5.1) guanosine is also bound via the N(7) position.

The ¹H NMR spectrum of the adenosine complex (5.2) in D₂O shows a number of species, including free adenosine, which makes the assignment very difficult. However, the ¹H NMR spectrum in CD₃OD is much simpler with only one set of resonances being observed for the complex, though a small amount of free adenosine is also present. Singlets due to the mesitylene protons are observed at δ 1.94 and 5.15, while the adenosine protons are assigned as follows:



Two singlets observed at δ 8.84 and 8.27 are assigned to H(8) and H(2) respectively, while the corresponding signals in free adenosine are observed at δ 8.36 [H(8)] and 8.20 [H(2)]. Ha in complex (5.2) is observed as doublet at δ 6.07 ($J = 5$) while Hb is assigned to the triplet at δ 4.66 ($J = 5$). Multiplets at δ 4.32 and 4.18 correspond to Hc and Hd respectively with a large multiplet at δ 3.82 being observed for He and Hf. As described in Section 5.1, adenosine can coordinate through a number of positions. In the case of [(mes)RuCl₂(Aden)] (5.2) the large downfield shift of H(8) from its value in free adenosine compared to the relatively small change observed for H(2) is indicative of coordination via N(7), as has previously been shown in other platinum¹⁷⁵ and metallocene¹⁷⁶ adenosine complexes. The ¹H NMR spectrum in d₆-dmsO is

similar to that for complex (5.1), the adenosine is rapidly displaced, with the free ligand and the complex [(mes)RuCl₂(d₆-dmsd)] being observed.

The FAB mass spectrum of complex (5.2) displays the molecular ion at m/e 559 while clusters are also observed at m/e 524 and 488, corresponding to the [M-Cl]⁺ and [M-Cl-HCl]⁺ fragments respectively. The molecular ion of complex (5.1) is not observed in the mass spectrum, however, the [M-Cl]⁺ fragment is seen at m/e 540. The [M-2Cl-Sugar]⁺ fragment is seen in both spectra with peaks at m/e 356 for complex (5.2) and m/e 372 for complex (5.1).

The reaction between [(mes)RuCl₂]₂ and cytidine was attempted, and as with complexes (5.1) and (5.2) all the starting dimer dissolves to give an orange solution after three hours, with evaporation of the solvent giving an orange/brown solid. However, attempts to redissolve this solid always led to formation of some insoluble orange precipitate. The ¹H NMR in D₂O displayed resonances which are attributed to free cytidine and another species which contains a ruthenium-mesitylene fragment, possibly the triply-bridged complex [(mes)₂Ru₂Cl₃]Cl which leads to the dimer on evaporation of the solvent. Thus, although cytidine may coordinate, work-up of the complex results in easy displacement of the ligand. Refluxing [(mes)RuCl₂]₂ with excess guanosine or adenosine in a methanol/water mixture (1:1) for three hours results in the formation of the mono-adducts (5.1) and (5.2) only, there is no evidence to suggest that a second ligand was attached, this may be due to unfavourable steric interactions between the two ligands. The reaction was not attempted in the presence of Ag⁺.

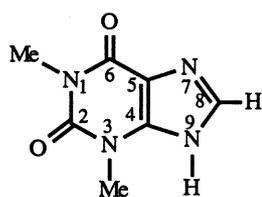
In the ¹H NMR spectrum of complex (5.1) in D₂O no free guanosine is observed, whereas free adenosine is evident in both the D₂O and CD₃OD ¹H NMR spectra of complex (5.2), suggesting that the solvents can displace some adenosine. In the case of cytidine, the product formed from the reaction with [(mes)RuCl₂]₂ is so unstable it is not possible to isolate the coordinated complex. Thus the order of stability of the complexes reads:



It has been shown previously that ruthenium guanosine complexes are more stable than the corresponding ruthenium-adenosine complexes.¹⁷⁷

The reaction between the oxopurine theophylline, a guanosine analogue, with [(mes)RuCl₂]₂ was also carried out, using the same procedure as for complexes (5.1) and (5.2)

to give an orange/brown solid. The FAB mass spectrum of the solid (Table 5.3.2) exhibits a cluster of peaks at m/e 437 which is consistent with the $[M-Cl]^+$ fragment from a complex of formula $[(mes)RuCl_2(TheoH)]$, a large cluster at m/e 401 corresponds to the $[M-Cl-HCl]^+$ fragment. The microanalysis result (Table 5.3.3) is also consistent with the formula $[(mes)RuCl_2(TheoH)]$.



Theophylline (TheoH)

The 1H NMR of the solid in D_2O shows the existence of free theophylline and two other species in a 1:1 ratio. The methyl groups of the mesitylene ligand give rise to singlets at δ 2.01 and 2.03 with the corresponding aromatic protons being observed at δ 5.29 and 5.38. There are also two sets of theophylline resonances; singlets at δ 7.99 and 7.90 are assigned to H(8), while the corresponding signal due to free theophylline is observed at δ 8.01. Resonances at δ 3.58 and 3.57 are assigned to the N(1) methyl protons and the N(3) methyl protons are observed at δ 3.43 and 3.44, while signals due to the N(1) and N(3) methyl protons of uncoordinated theophylline are observed at δ 3.56 and 3.36 respectively. Addition of a five-fold excess of LiCl results in the removal of one set of peaks, however, while the resonances at δ 7.99 and 5.38 disappear it is difficult to pin-point which of the N-methyl and mesitylene methyl signals are removed because the signals of the two species are very close, and addition of LiCl alters the chemical shifts slightly. It is interesting that only two species are observed in the 1H NMR spectrum, whereas for the guanosine complex, three are seen. In the case of the theophylline complex we were fortunate enough to get X-ray quality crystals and hence were able to determine the structure, as shown in Fig 5.2.2. Selected bond lengths (\AA) and angles ($^\circ$) are listed in Tables 5.2.1 and 5.2.2.

The X-ray structure confirms the presence of N(7) coordination of the deprotonated theophylline ligand, the coordination sphere of the ruthenium also contains a chloride ligand

and a water molecule which hydrogen bonds to the O(6) atom of theophylline. The Ru–N bond distance, 2.086(3) Å is shorter than that [2.101(4) Å] observed for [(C₆H₆)RuCl₂(9Etgua)],¹²¹ while the Ru–Cl bond length, 2.382(1) Å is also shorter than those in the 9-Ethylguanine complex, 2.416(1) and 2.420(1) Å. The N(7)–Ru–Cl bond angle is 86.1(1)°, while the O(1)–Ru–Cl and N(7)–Ru–O(1) angles are the same, 84.4(1)°.

In solution there exists a tautomeric equilibrium between the N(7)–H and N(9)–H forms of neutral theophylline, however, in the solid state the weakly acidic proton is bound via the N(7) position.^{178,179} In the following discussion free theophylline refers to the average values of 14 structures of uncoordinated neutral theophylline derivatives containing an N(7)–H or an N(7)–C bond.¹⁷⁸ In our complex, the C(4)–N(9)–C(8) bond angle, 102.1(3)° is statistically the same as in free theophylline, 103.4(8), while the N(7)–C(8) and C(8)–N(9) distances which are the same in free theophylline [1.346(18) and 1.337(12) Å respectively], become different upon coordination to the ruthenium, 1.322(4) and 1.351(4) Å respectively, suggesting here that the double bond is more localised along the N(7)–C(8) bond when the ligand is coordinated. This phenomenon is not observed in the complex [Cd(H₂O)₄(Theo)₂],¹⁷⁹ where the deprotonated theophylline is also bound via the N(7) site, in which the N(7)–C(8) and C(8)–N(9) bond lengths are the same within experimental error, 1.365(9) and 1.362(9) Å respectively. In the case of [(Cp)₂Ti(Theo)], where the deprotonated theophylline ligand is bound bidentately via the N(7) and O(6) positions, the N(7)–C(8) and C(8)–N(9) bond lengths are 1.346(5) and 1.360(5) Å respectively.¹⁷⁸ In these cases the evidence suggests that the negative charge is delocalised about the N(7)–C(8)–N(9) bonds.

The C(4)–N(9) and C(5)–N(7) bond lengths [1.337(4) and 1.386(4) Å respectively] differ slightly in complex (5.3b), this difference is also observed in the cadmium complex where the corresponding distances are 1.345(9) and 1.398(9) Å, indicating in both cases that some electron redistribution has occurred, resulting in the C(4)–N(9) bond displaying some double bond character.

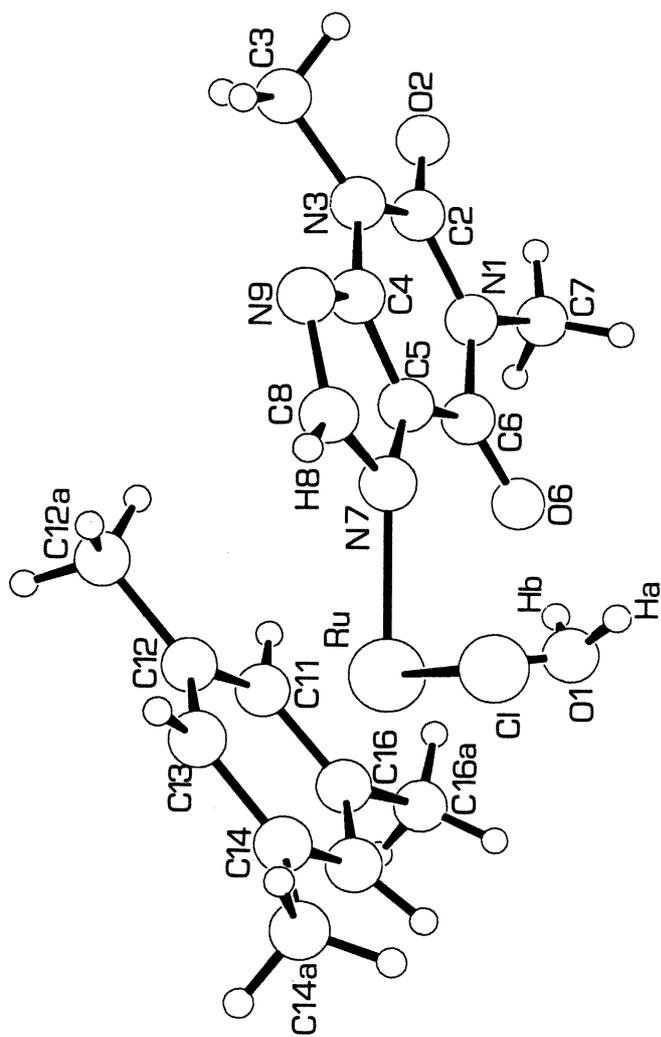


Fig. 5.2.2. Molecular Structure of [(mes)RuCl(H₂O)(C₇H₇N₄O₂)] (5.3b).

Table 5.2.1. Selected Bond Distances (Å) of [(mes)RuCl(H₂O)(C₇H₇N₄O₂)₁](5.3b).

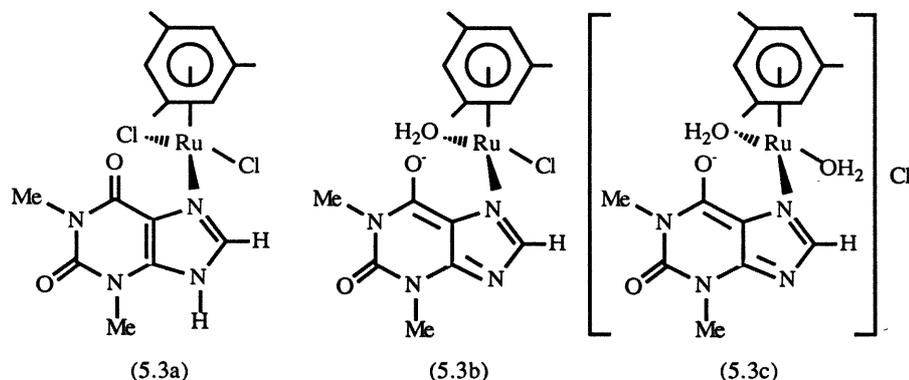
Ha-O(1)	0.80(5)	C(7)-N(1)	1.464(4)
Hb-O(1)	0.71(5)	C(6)-N(1)	1.386(4)
C(8)-N(7)	1.322(4)	O(6)-C(6)	1.227(4)
C(5)-N(7)	1.386(4)	C(5)-C(6)	1.406(4)
H8-C(8)	0.95(5)	Cl-Ru	2.382(1)
N(9)-C(8)	1.351(4)	O(1)-Ru	2.122(3)
C(4)-N(9)	1.337(4)	N(7)-Ru	2.086(3)
N(3)-C(4)	1.369(4)	C(11)-Ru	2.169(3)
C(5)-C(4)	1.370(4)	C(12)-Ru	2.167(3)
C(3)-N(3)	1.456(4)	C(13)-Ru	2.155(3)
C(2)-N(3)	1.364(5)	C(14)-Ru	2.181(3)
O(2)-C(2)	1.207(4)	C(15)-Ru	2.192(3)
N(1)-C(2)	1.395(4)	C(16)-Ru	2.168(4)

Table 5.2.2. Selected Bond Angles (°) of [(mes)RuCl(H₂O)(C₇H₇N₄O₂)₁](5.3b).

Hb-O(1)-Ha	107(5)	C(6)-N(1)-C(2)	127.1(3)
C(5)-N(7)-C(8)	103.7(3)	C(6)-N(1)-C(7)	118.1(3)
H(8)-C(8)-N(7)	121(3)	O(6)-C(6)-N(1)	119.3(3)
N(9)-C(8)-N(7)	115.8(3)	C(5)-C(6)-N(1)	112.8(3)
N(9)-C(8)-H(8)	124(3)	C(5)-C(6)-O(6)	127.8(3)
C(4)-N(9)-C(8)	102.1(3)	C(4)-C(5)-N(7)	106.7(3)
N(3)-C(4)-N(9)	126.0(3)	C(6)-C(5)-N(7)	131.6(3)
C(5)-C(4)-N(9)	111.7(3)	C(6)-C(5)-C(4)	121.4(3)
C(5)-C(4)-N(3)	122.2(3)	O(1)-Ru-Cl	84.4(1)
C(3)-N(3)-C(4)	120.7(3)	N(7)-Ru-Cl	86.1(1)
C(2)-N(3)-C(4)	119.8(3)	N(7)-Ru-O(1)	84.4(1)
C(2)-N(3)-C(3)	119.3(3)	Ha-O(1)-Ru	111(4)
O(2)-C(2)-N(3)	122.3(3)	Hb-O(1)-Ru	100(5)
N(1)-C(2)-N(3)	116.2(3)	C(8)-N(7)-Ru	122.7(2)
N(1)-C(2)-O(2)	121.6(4)	C(5)-N(7)-Ru	130.8(2)
C(7)-N(1)-C(2)	114.6(3)		

There is evidence of hydrogen bonding between the O(6) atom of theophylline and Hb of the coordinated water molecule, with O(6)⋯Hb and O(6)⋯O(1) distances of 1.913 and 2.623 Å respectively. Similar interactions have also been reported for other complexes,¹⁸⁰ including the aforementioned complex $[\text{Cd}(\text{H}_2\text{O})_4(\text{Theo})_2]$,¹⁷⁹ where the O(6)⋯H-O and O(6)⋯O distances are 1.891(6) and 2.689(3) Å respectively.

In conclusion we can see that in the original solid (5.3a) neutral theophylline is bound to the ruthenium centre via the N(7) position.

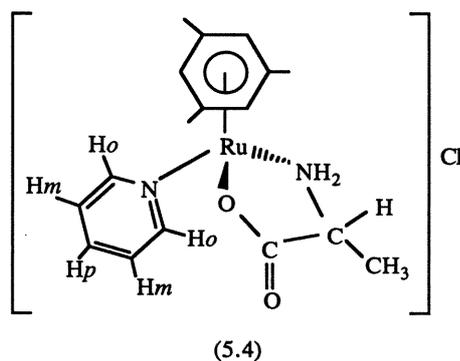


As previously mentioned, two species are observed in the ^1H NMR spectra in D_2O , the upfield shift of the H(8) resonances, compared to free theophylline which have also been observed in similar systems, are consistent with deprotonated theophylline binding via the N(7) position, as confirmed by the X-ray structure of one of the species (5.3b). Thus, we propose the second species observed in ^1H NMR spectrum is the cationic complex (5.3c), also containing deprotonated theophylline. In both cases where theophylline is deprotonated, the negative charge is delocalised around the whole ligand.

The anti-tumour activity of $[(\text{C}_6\text{H}_6)\text{RuCl}(\text{pro})]$ has recently been reported, in addition, the related complex $[(\text{C}_6\text{H}_6)\text{RuCl}(\text{ala})]$ was shown to react with 9-Ethylguanine to give $[(\text{C}_6\text{H}_6)\text{Ru}(\text{9Etgua})(\text{ala})]\text{Cl}$.¹²¹ We attempted to investigate the generality and specificity of the reactions of nucleobases with $[(\text{mes})\text{RuCl}(\text{ala})]$ (3.5; R = Me) by reacting this complex with

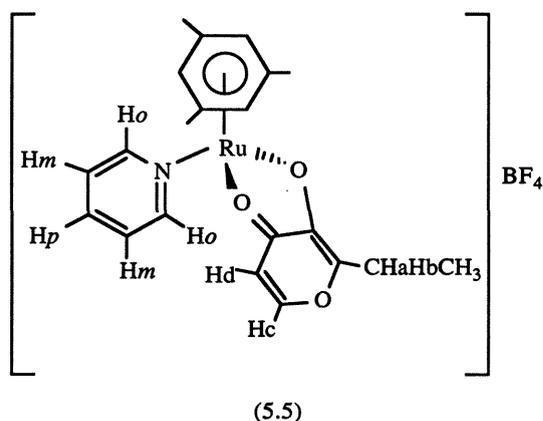
cytidine, guanosine and pyridine. The reaction between [(mes)RuCl(Etmal)] (4.4a) and pyridine was also carried out.

One molar equivalent of pyridine was added to a stirred aqueous solution of [(mes)RuCl(ala)], which afforded the complex [(mes)Ru(py)(ala)]Cl (5.4) in good yield. The complex was characterised by ^1H NMR and FAB mass spectroscopy, and microanalysis, Tables 5.3.1 - 5.3.3.



Observation of two singlets at δ 5.30 and 5.32 suggested the presence of two diastereomers, as expected (see Chapter 3). These signals correspond to the mesitylene aromatic protons of the major and minor diastereomers respectively, the mesitylene methyl protons are observed as a singlet at δ 1.99, for both diastereomers. Doublets at δ 1.22 ($J = 7$) (major) and δ 0.72 ($J = 7$) (minor) are assigned to the alaninate methyl groups while the α -proton of the major diastereomer is observed as a quartet at δ 3.65, the corresponding signal for the minor diastereomer was not visible. The diastereomers are not resolved in the pyridine region, thus a broad doublet at δ 8.58 ($J = 5$) is assigned to both *ortho*-protons (*Ho*), a multiplet at δ 7.60 corresponds to the *meta*-protons (*Hm*) and a broad triplet at δ 8.04 is observed for the *para*-proton (*Hp*). The diastereomer ratio is 65:35 and this is discussed with the other alaninate complexes in Chapter 3. The FAB mass spectrum displays a cluster of peaks at m/e 389 which corresponds to the molecular ion [(mes)Ru(py)(ala)] $^+$, a cluster is also observed at m/e 310 due to the [(mes)Ru(ala)] $^+$ fragment.

A similar reaction between [(mes)RuCl(Etmal)] (4.4a) and pyridine was carried out to determine whether pyridine coordination is dependent upon an amino acidate ligand being present. One equivalent of pyridine was added to a solution of [(mes)RuCl(Etmal)] in water, in this case no evidence for pyridine coordination was observed. However, when the reaction was performed in CH₂Cl₂ in the presence of AgBF₄, the complex [(mes)Ru(py)(Etmal)]BF₄ (5.5) was formed, and characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 5.3.1-5.3.3.

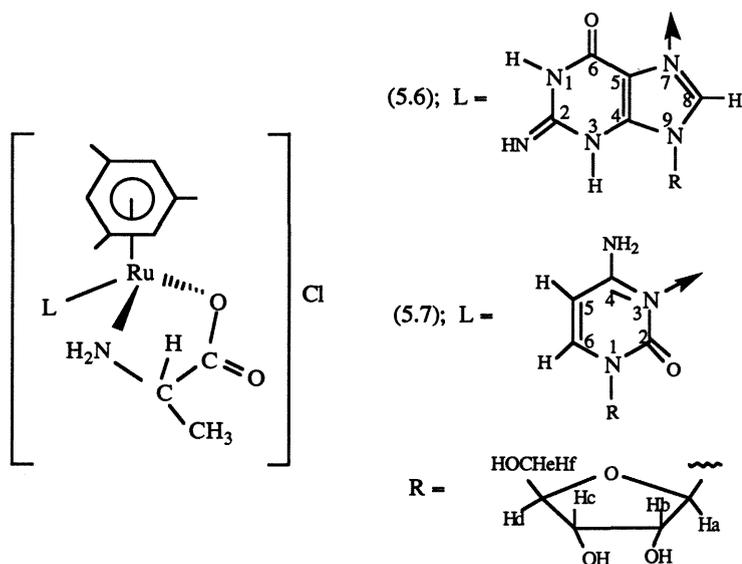


In the ¹H NMR spectrum in CDCl₃, the mesitylene signals are observed at δ 2.06 and 5.03, while for the ethylmaltol ligand the inequivalent methylene protons overlap coincidentally and are observed as a quartet at δ 2.76 while the methyl group is assigned to the triplet at δ 1.17 ($J = 7.5$). The remaining protons Hc and Hd are assigned to the doublets at δ 7.58 ($J = 5$) and 6.45 ($J = 5$) respectively. Signals due to the pyridine are seen as a doublet for the *ortho*-protons (Ho) at δ 8.53, a triplet at δ 7.79 (1H) corresponds to the *para* proton (Hp) while the *meta* protons (Hm) are observed as a multiplet at δ 7.41 (2H). The molecular ion [(mes)Ru(py)(Etmal)]⁺ is observed at m/e 440 in the FAB mass spectrum.

The reason no reaction occurs between pyridine and [(mes)RuCl(Etmal)] in water is presumably due to the fact that when the ethylmaltol complex is dissolved in water, the aquated complex [(mes)Ru(H₂O)(Etmal)]Cl (4.4b) is formed, and is particularly stable (see Chapter 4).

Thus, it is difficult to displace the coordinated water by such a relatively small amount of pyridine. However, when AgBF_4 is used to remove the chloride ligand in a weakly coordinating solvent the reaction can proceed and thus pyridine coordinates to form complex (5.5).

Guanosine and cytosine can also be reacted with $[(\text{mes})\text{RuCl}(\text{ala})]$ in a similar way to pyridine. The alanine complex was dissolved in a methanol/water mixture and one molar equivalents of guanosine or cytosine were added to afford the complexes $[(\text{mes})\text{Ru}(\text{Guan})(\text{ala})]\text{Cl}$ (5.6) or $[(\text{mes})\text{Ru}(\text{Cyt})(\text{ala})]\text{Cl}$ (5.7) respectively. Both complexes were characterised by ^1H NMR and FAB mass spectroscopy, and microanalysis, Tables 5.3.1 - 5.3.3.



The ^1H NMR spectrum of complex (5.6) in D_2O displays a singlet due to the mesitylene methyl protons of both diastereomers at δ 2.03, and similarly a singlet is observed at δ 5.26 for the aromatic protons of both diastereomers. The alaninate methyl protons are observed as doublets at δ 1.25 ($J = 7$) and 0.75 ($J = 7$) for the major and minor diastereomers respectively, while the α -protons are assigned to multiplets at δ 2.38 (major) and 3.53 (minor). The guanosine protons are assigned as follows, the J values are the same for both diastereomers and

signals due to the minor diastereomer are given in parentheses: The H(8) proton is observed as a singlet at δ 8.25 (8.27) and Ha is assigned to the doublet at δ 5.99 (5.98) ($J = 5$), Hb and Hc are observed as triplets at δ 4.63 (4.73) ($J = 5$) and δ 4.36 (4.43) ($J = 5$) respectively. The remaining protons of both diastereomers are observed as multiplets at δ 4.26 for Hd and δ 3.90 for He and Hf. Two broad signals at δ 5.56 (major) and 6.27 (minor) can be assigned to one N–H of the alanine ligands.

The ^1H NMR spectrum of complex (5.7) is equally complicated; as for complex (5.6), the diastereomers are not resolved in the mesitylene resonances with two singlets being observed at δ 2.12 and 5.31 for the methyl and aromatic protons respectively. Doublets at δ 1.32 ($J = 7$) (major) and δ 1.10 ($J = 7$) (minor) correspond to the alaninate methyl protons, while the α -protons are observed as quartets at δ 2.84 ($J = 7$) (major) and 3.64 ($J = 7$) (minor). The cytidine protons H(5) and H(6) are observed as doublets (due to coupling with each other) at δ 6.16 ($J = 7.5$) and 7.94 ($J = 7.5$) for the major diastereomer and at δ 6.03 ($J = 7.5$) and 7.83 ($J = 7.5$) for the minor diastereomer. The doublet at δ 5.95 ($J = 4$) corresponds to Ha of the minor diastereomer while the major diastereomer displays a triplet at δ 5.88 ($J = 3.5$), with coupling to Hb and possibly Hc. The remaining sugar protons of both diastereomers are observed as complex multiplets at δ 4.22 for Hb, Hc and Hd, and at δ 3.88 for He and Hf. No N–H signals were seen, presumably because they are broad or H–D exchange has taken place. The diastereomer ratios of both complexes (5.6) and (5.7) are 75:25 and 70:30 respectively, these are discussed with the other alaninate complexes in Chapter 3. The FAB mass spectra of both complexes (5.6) and (5.7) display peaks due to the molecular ions at m/e 593 and 553 respectively, as well as peaks due to $[\text{M-ala}]^+$ at m/e 504 and 464 and $[\text{M-base}]^+$ at m/e 310 for both complexes. The microanalyses are consistent with one mole of water present in both cases.

It is interesting that the alaninate α -protons are observed as quartets in the cytidine complex, but appear as a more complex signal in the guanosine spectrum. The ^1H NMR spectrum of the analogous complex $[(\text{C}_6\text{H}_6)\text{Ru}(\text{9Etgua})(\text{ala})]\text{Cl}$ displays two overlapping quartets for the α -protons of the minor diastereomer at δ 3.56 while the major diastereomer is assigned to a quartet at δ 2.45. It was proposed by Sheldrick and Heeb,¹²¹ that the

overlapping quartets were observed due to two possible orientations of the alaninate ring in the minor diastereomer (with $[S_{Ru}]$ configuration) caused by a favourable hydrogen bonding interaction between the N–H of the alaninate ring and O(6) of 9-Ethylguanine, as suggested by the X-ray structure. As we do not have any structural data for complexes (5.6) and (5.7), it is difficult to speculate about possible hydrogen bonding within these molecules. However, in the 1H NMR spectrum of complex (5.6) the appearance of multiplets for α -protons is probably due to the α -protons coupling to an N–H, especially as two N–H signals are observed in the spectrum. It is also noticeable that for complex (5.7) no N–H signals are observed, and the α -protons are seen as simple quartets.

Both complexes (5.6) and (5.7) are stable in water and methanol, however, this is not the case in dmsO. When monitored by 1H NMR spectroscopy it can be seen that the cytidine ligand is rapidly displaced by d_6 -dmsO. Whereas for the guanosine complex after four days a 50:50 mixture of $[(mes)Ru(Guan)(ala)]Cl$ and the substituted complex $[(mes)Ru(d_6-dmsO)(ala)]Cl$ was observed. In neither case was there any evidence to suggest alanine displacement and in both cases free ligand is observed in the spectrum. In both spectra the complex $[(mes)Ru(d_6-dmsO)(ala)]Cl$ exhibits resonances at δ 2.05 for the methyl mesitylene protons of both diastereomers while the aromatic protons are observed at δ 4.98 (major) and 5.07 (minor). Both methyl alaninate groups are assigned to overlapping doublets at δ 1.12 and the α -protons are not visible. From the above observations we can see that complex (5.6) is less susceptible to attack by dmsO than complex (5.7) which emphasises further that guanosine complexes are more stable than cytidine ones, agreeing with the generally accepted order of stability of nucleobase complexes^{156,177} i.e. $G > A > C$.

Our investigations have shown that guanosine, adenosine and theophylline react with $[(mes)RuCl_2]_2$ to form adducts with coordination occurring through the N(7) position. We have also seen that the nucleobase complexes $[(mes)Ru(Guan)(ala)]Cl$ (5.6) and $[(mes)Ru(Cyt)(ala)]Cl$ (5.7) are more stable than the analogous complexes $[(mes)RuCl_2(Guan)]$ and $[(mes)RuCl_2(Cyt)]$ as the cytidine is very easily displaced in $[(mes)RuCl_2(Cyt)]$ but more strongly coordinated in $[(mes)Ru(Cyt)(ala)]Cl$, as shown by the reactions with dmsO.

5.3 - Experimental

General experimental techniques were as described in Chapter 2. All starting materials were obtained from Aldrich Chemical Co. Ltd. and used without further purification. $[(\text{mes})\text{RuCl}_2]_2$ was prepared as stated in Chapter 2 and the complexes $[(\text{mes})\text{RuCl}(\text{ala})]$ (3.5; R = Me) and $[(\text{mes})\text{RuCl}(\text{Etmal})]$ (4.4a) were synthesised as described in Chapters 3 and 4 respectively.

Preparation of $[(\text{mes})\text{RuCl}_2(\text{Guan})]$ (5.1)

Guanosine hydrate (266 mg, 0.94 mmol) was added to a suspension of $[(\text{mes})\text{RuCl}_2]_2$ (275 mg, 0.47 mmol) in methanol/water (1:1) (70 cm³) and refluxed for 3 hours, after which time an orange solution was formed. The solvent was removed to give $[(\text{mes})\text{RuCl}_2(\text{Guan})]$ (5.1) as a brown crystalline solid (452 mg, 83%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 5.3.1 - 5.3.3.

Preparation of $[(\text{mes})\text{RuCl}_2(\text{Aden})]$ (5.2)

The same procedure was used as for complex (5.1) using adenosine (197 mg, 0.74 mmol) and $[(\text{mes})\text{RuCl}_2]_2$ (215 mg, 0.37 mmol) in methanol/water (1:1) (70 cm³) to give, after work-up, $[(\text{mes})\text{RuCl}_2(\text{Aden})]$ (5.2) as a brown solid (313 mg, 76%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 5.3.1 - 5.3.3.

Reaction of $[(\text{mes})\text{RuCl}_2]_2$ with cytidine

Cytidine (246 mg, 1.01 mmol) was added to a suspension of $[(\text{mes})\text{RuCl}_2]_2$ (295 mg, 0.51 mmol) in methanol/water (1:1) (70 cm³) and refluxed for 3 hours, after which time an orange solution was formed. Evaporation of the solvent gave a brown solid, the FAB mass spectrum of the solid suggested the presence of $[(\text{mes})_2\text{Ru}_2\text{Cl}_3]\text{Cl}$ with the molecular ion $[(\text{mes})_2\text{Ru}_2\text{Cl}_3]^+$ being observed as a cluster at m/e 548. The ¹H NMR spectrum exhibits peaks due to free cytidine.

Reaction of [(mes)RuCl₂]₂ with theophylline (C₇H₈N₄O₂)

The same procedure was used as for complex (5.1) using theophylline (128 mg, 0.72 mmol) and [(mes)RuCl₂]₂ (208 mg, 0.36 mmol) in methanol/water (1:1) (70 cm³) to give, after work-up, a brown solid. The microanalysis (Table 5.3.3) and FAB mass spectrum (Table 5.3.2) are consistent with a complex of formulation [(mes)RuCl₂(C₇H₈N₄O₂)] (5.3a). Recrystallisation of the solid from D₂O gave orange crystals of formula [(mes)RuCl(H₂O)(C₇H₇N₄O₂)] (5.3b) as determined by X-ray diffraction. The ¹H NMR of the original solid shows the presence of two species, Table 5.3.1.

Reaction of [(mes)RuCl(ala)] (3.5; R = Me) with pyridine

Pyridine (45 mg, 0.57 mmol) was added to a solution of [(mes)RuCl(ala)] (197 mg, 0.57 mmol) in water (50 cm³) and stirred for 0.5 hours at room temperature. The solvent was removed to afford [(mes)Ru(py)(ala)]Cl (5.4) as a yellow solid (225 mg, 92%). The complex was characterised by ¹H NMR and FAB mass spectroscopy, and microanalysis, Tables 5.3.1 - 5.3.3.

Reaction of [(mes)RuCl(Etmal)] (4.4a) with pyridine

Pyridine (28 mg, 0.35 mmol) was added to a stirred solution of [(mes)RuCl(Etmal)] (120 mg, 0.35 mmol) in water (50 cm³) and stirred at room temperature for 2 hours. The solvent was removed to give an orange solid, identified as the starting material [(mes)RuCl(Etmal)] from its ¹H NMR spectrum in CDCl₃.

Reaction of [(mes)RuCl(Etmal)] (4.4a) with pyridine and AgBF₄

AgBF₄ (81 mg, 0.42 mmol) was added to a stirred solution, cooled to -78°C, of [(mes)RuCl(Etmal)] (150 mg, 0.38 mmol) in dichloromethane (40 cm³). Pyridine (30 mg, 0.38 mmol) was then added and the mixture was slowly heated to room temperature and stirred for a further 2 hours. The mixture was filtered and the solvent removed to give [(mes)Ru(py)(Etmal)]BF₄ (5.5) as an orange solid (168 mg, 84%). The complex was

characterised by ^1H NMR and FAB mass spectroscopy, and microanalysis, Tables 5.3.1 - 5.3.3.

Reaction of [(mes)RuCl(ala)] (3.5; R = Me) with guanosine hydrate

Guanosine hydrate (138 mg, 0.49 mmol) was added to a stirred solution of [(mes)RuCl(ala)] (167 mg, 0.49 mmol) in water (50 cm³) and stirred at room temperature for 2 hours. The solvent was removed to afford [(mes)Ru(Guan)(ala)]Cl (5.6) as a pale yellow crystalline solid (217 mg, 72%). The complex was characterised by ^1H NMR and FAB mass spectroscopy, and microanalysis, Tables 5.3.1 - 5.3.3.

Reaction of [(mes)RuCl(ala)] (3.5; R = Me) with cytidine

Cytidine (86 mg, 0.35 mmol) was added to a solution of [(mes)RuCl(ala)] (122 mg, 0.35 mmol) in water (40 cm³) and stirred at room temperature for 2 hours. The solvent was removed to yield [(mes)Ru(Cyt)(ala)]Cl (5.7) as a yellow solid (172 mg, 88%). The complex was characterised by ^1H NMR and FAB mass spectroscopy, and microanalysis, Tables 5.3.1 - 5.3.3.

Table 5.3.1. ¹H NMR data for complexes (5.1 - 5.7)^a

Complex	Arene Protons (δ)		Ligand Protons (δ)
	C ₆ Me ₃	C ₆ H ₃	
5.1 ^e	{ 1.98	5.25	3.75 - 4.70 (m, 5H, Hb - Hf), 5.60 [d, 1H, Ha, J(3)], 7.87 [s, 1H, H(8)] ^b
	{ 1.99	5.26	3.75 - 4.70 (m, 5H, Hb - Hf), 5.95 (m, 1H, Ha), 8.29 [s, 1H, H(8)] ^c
	{ 2.04	5.39	3.75 - 4.70 (m, 5H, Hb - Hf), 5.95 (m, 1H, Ha), 8.43 [s, 1H, H(8)] ^d
	1.94	5.15	3.82 (m, 2H, He/ Hf), 4.18 (m, 1H, Hd), 4.32 (m, 1H, Hc), 4.66 [t, 1H, Hb, J(5)], 6.07 [d, 1H, Ha, J(5)], 8.27 [s, 1H, H(2)], 8.84 [s, 1H, H(8)]
5.3 ^e	{ 2.01	5.29] ^g	{ 3.43 (s, 3H, N(3)-Me), 3.44 (s, 3H, N(3)-Me), 3.57 (s, 3H, N(1)-Me), 3.58 (s, 3H, N(1)-Me)] ⁱ
	{ 2.03	5.38] ^h	7.90 [s, 1H, H(8)] ^g , 7.99 [s, 1H, H(8)] ^h
5.4 ^e	{ 1.99	5.30	1.22 [d, 3H, Me, J(7)], 3.65 [q, 1H, Hα, J(7)], 7.60 [m, 2H, Hm,], 8.04 [t, 1H, Hp,], 8.58 [d, 1H, Ho, J(5)] ^j
	{ 1.99	5.32	0.72 [d, 3H, Me, J(7)], 7.60 [m, 2H, Hm,], 8.04 [t, 1H, Hp,], 8.58 [d, 2H, Ho, J(5)] ^k
5.5 ^l	2.06	5.03	1.17 [t, 3H, Me, J(7.5)], 2.76 [q, 2H, CH ₂], 6.45 [d, 1H, Hd, J(5)], 7.41(m, 2H, Hm), 7.58 [d, 1H, Hc, J(5)], 7.79 (t, 1H, Hp), 8.53 [d, 2H, Ho, J(6)]

Table 5.3.1 (continued)

Complex	Arene Protons (δ)		Ligand Protons (δ)
	C ₆ Me ₃	C ₆ H ₃	
5.6 ^e	{2.03	5.26	1.25 [d, 3H, Me, J(7)], 2.38 (m, 1H, H α), 3.90 (m, 2H, He/Hf), 4.26 (m, 1H, Hd), 4.36 [t, 1H, Hc, J(5)], 4.63 [t, 1H, Hb, J(5)], 5.56 (br, 1H, NH), 5.99 [d, 1H, Ha, J(5)], 8.25 [s, 1H, H(8)] ^j
		5.26	0.75 [d, 3H, Me, J(7)], 3.53 (m, 1H, H α), 3.90 (m, 2H, He/Hf), 4.26 (m, 1H, Hd), 4.43 [t, 1H, Hc, J(5)], 4.73 [t, 1H, Hb, J(5)], 5.98 [d, 1H, Ha, J(5)], 6.27 (br, 1H, NH), 8.27 [s, 1H, H(8)] ^k
	{2.12	5.31	1.32 [d, 3H, Me, J(7)], 2.84 [q, 1H, H α , J(7)], 3.88 (m, 2H, He/Hf), 4.22 (m, 3H, Hb/Hc/Hd), 5.88 [t, 1H, Ha, J(3.5)], 6.16 [d, 1H, H(5), J(7.5)], 7.94 [d, 1H, H(6), J(7.5)] ^j
	{2.12	5.31	1.10 [d, 3H, Me, J(7)], 3.64 [q, 1H, H α , J(7)], 3.88 (m, 2H, He/Hf), 4.22 (m, 3H, Hb/Hc/Hd), 5.95 [d, 1H, Ha, J(4)], 6.03 [d, 1H, H(5), J(7.5)], 7.83 [d, 1H, H(6), J(7.5)] ^k

^a All J values refer to ³J coupling unless otherwise stated.

^b Refers to [(mes)RuCl₂(Guan)] (5.1a), ^c [(mes)RuCl(D₂O)(Guan)]Cl (5.1b), ^d [(mes)Ru(D₂O)₂(Guan)]Cl₂ (5.1c).

^e In D₂O, ^f In CD₃OD.

^g Refers to [(mes)RuCl(H₂O)(C₇H₇N₄O₂)] (5.3b), ^h [(mes)Ru(H₂O)₂(C₇H₇N₄O₂)]Cl (5.3c).

ⁱ The detailed assignment of these signals to (5.3b) and (5.3c) is not possible.

^j denotes the major diastereomer, ^k minor diastereomer.

^l In CDCl₃.

Table 5.3.2 Mass spectroscopy data for complexes (5.1 - 5.7)

Complex	[M] ⁺ ^a	Other Peaks
[(mes)RuCl ₂ (Guan)] (5.1)	Not observed	540 [M-Cl] ⁺ , 372 [M-2Cl-Sugar] ⁺
[(mes)RuCl ₂ (Aden)] (5.2)	559	524 [M-Cl] ⁺ , 488 [M-Cl-HCl] ⁺ , 356 [M-2Cl-Sugar] ⁺
[(mes)RuCl ₂ (TheoH)] (5.3a)	Not observed	437 [M-Cl] ⁺ , 401 [M-Cl-HCl] ⁺
[(mes)Ru(py)(ala)]Cl (5.4)	389 ^b	310 [M-py] ⁺
[(mes)Ru(py)(Etmal)]BF ₄ (5.5)	440 ^b	361 [M-py] ⁺
[(mes)Ru(Guan)(ala)]Cl (5.6)	593 ^b	504 [M-ala] ⁺ , 310 [M-Guan] ⁺
[(mes)Ru(Cyr)(ala)]Cl (5.7)	553 ^b	464 [M-ala] ⁺ , 310 [M-Cyt] ⁺

^a In all cases the [M+H]⁺ ion is also observed.

^b M refers to the complex cation.

Table 5.3.3 Elemental analyses of complexes (5.1 -5.7)

Complex	Found (%)			Calculated (%)		
	C	H	N	C	H	N
[(mes)RuCl ₂ (Guan)] (5.1) ^a	38.85	4.59	11.13	38.45	4.59	11.80
[(mes)RuCl ₂ (Aden)] (5.2) ^a	39.37	4.59	10.69	39.51	4.71	12.13
[(mes)RuCl ₂ (TheoH)] (5.3a)	40.92	4.48	11.12	40.69	4.26	11.86
[(mes)Ru(py)(ala)]Cl (5.4)	48.42	5.42	6.71	48.16	5.47	6.61
[(mes)Ru(py)(Etmal)]BF ₄ (5.5)	47.59	4.31	2.67	47.84	4.59	2.66
[(mes)Ru(Guan)(ala)]Cl (5.6) ^a	40.88	4.96	12.90	40.86	5.15	13.01
[(mes)Ru(Cyt)(ala)]Cl (5.7) ^a	41.93	5.26	9.41	41.62	5.49	9.25

^a Complex crystallises with one mole of water.

Conclusions
and
Further Work

CONCLUSIONS AND FURTHER WORK

Conclusions

Our initial studies concentrated on the preparation and reactivity of a variety of arene-ruthenium amine complexes. We have synthesised the first secondary amine arene-ruthenium complexes [(mes)RuCl₂(L)] (L = NHEt₂, NHⁿBu₂, and piperidine) whose formation was previously thought impossible.⁹⁹ We have shown that the stability of these amine compounds is dependent on both steric and electronic factors, and that although the piperidine complex [(mes)RuCl₂(pip)] (2.1e) contains a secondary amine ligand, it is more stable than some of the less sterically hindered primary amine complexes.

Recent interest in chiral organometallic complexes and their potential use in asymmetric synthesis prompted us to extend our study of amine complexes to investigate a series of arene-ruthenium amino acidate complexes. One such complex, [(C₆H₆)RuCl(pro)], had also recently been reported to show significant anti-tumour activity against P388 leukaemia.¹²¹ The complexes [(mes)RuCl(NH₂CHR₂COO)] (3.5; R = H, Me, Ph, CH₂Ph), [(mes)RuCl(pro)] (3.6) and also [(mes)RuCl(sarc)] (3.7) were prepared in good to moderate yields by refluxing [(mes)RuCl₂]₂, sodium methoxide and the appropriate ligand in water/methanol mixtures. The complexes are soluble in both water and polar organic solvents. In aqueous solution the chloride ligand is displaced by a water molecule resulting in an equilibrium being formed between the chloride complex and the aquated species.

The use of enantiopure *l*-amino acids and the presence of a second chiral centre, i.e. the ruthenium, in each complex means that such complexes exist as a pair of diastereomers, the ratios of which were found to be dependent on a number of factors. Steric interactions between the mesitylene ring and the chelated ligand are thought to be most important for N-substituted ligands e.g. the sarcosine complex [(mes)RuCl(sarc)] (3.7), where only one diastereomer could be clearly identified in the ¹H NMR spectrum and thus a ratio of > 95:5 is assumed. In the case of the α -substituted amino acidate complexes the α -substituent does not point towards the arene

ring, as shown by the crystal structures of [(mes)RuCl(ala)] (3.5; R = Me) and [(C₆H₆)RuCl(ala)]¹²¹ and therefore any interaction between these would probably be small.

In a previous study it has been suggested that intramolecular hydrogen bonding may affect the diastereomer ratios. In the complex [(C₆H₆)RuCl(ala)], prepared by Sheldrick and Heeb,¹²¹ there is evidence of intramolecular hydrogen bonding between the chlorine atom and an amino proton in one of the diastereomers. In contrast, we found no evidence for intramolecular hydrogen bonding in our analogous complex [(mes)RuCl(ala)] (3.5; R = Me), in this case we observed an intermolecular interaction between an amino proton of one diastereomer and the chloride of the other. In an attempt to probe the role of hydrogen bonding further we prepared the complexes [(mes)RuX(ala)] (X = Br, F) by substituting the chloride ligand with fluoride and bromide, in the bromide case the diastereomer ratio 65:35 was similar to that of the chloride complex, however upon fluoride coordination the ratio was reduced to 50:50. Without further crystallographic data it is difficult to determine the extent of hydrogen bonding in the complexes and the exact role it plays in influencing the diastereomer ratios.

Replacement of the chloride ligand in the complex [(mes)RuCl(ala)] (3.5; R = Me) with the N-donor ligands pyridine, cytidine and guanosine caused the diastereomer ratio to increase with the size of ligand. This effect was not observed when the chloride ligand of the complex [(*p*-cymene)RuCl(ala)] was replaced by triphenylphosphine giving [(*p*-cymene)Ru(PPh₃)(ala)]BF₄,¹¹⁹ the diastereomer ratios of these two complexes were very similar, and thus there is no simple correlation between the size of the ligand and the effect it has on the diastereomer ratio.

The synthesis of some arene-ruthenium complexes containing the N,N ligand 2,2'-bipyridine and O,O donor ligands ethylmaltol and an N-substituted pyridinone is described in Chapter 4. The complexes [(mes)RuCl(Etmal)] (4.4a) and [(mes)RuCl(Pyr)] (4.5a) are both soluble in aqueous and polar organic solvents, while [(mes)RuCl(bipy)]Cl (4.6a) is soluble in water and methanol, but only sparingly soluble in chlorinated hydrocarbons. For the above compounds dissolution in water leads to the chloride ligand being displaced, however, unlike the amino acidate complexes described earlier, an equilibrium between the chloride adducts and

the aquated species is not observed with only the aquated species existing in solution. Addition of LiCl did not result in reformation of the chloride adducts.

The ethylmaltol, pyridinone and bipyridyl complexes were reacted with carbon monoxide in the presence of AgBF_4 , the most promising result coming from the ethylmaltol complex where we were able to isolate and obtain a crystal structure of the complex $[(\text{mes})\text{Ru}(\text{CO})(\text{Etmal})]\text{BF}_4$ (4.4c). Although there was evidence of carbonyl formation with the bipyridyl and pyridinone complexes, all attempts to isolate these products in a pure state were unsuccessful. The carbonyl ligand of the complex $[(\text{mes})\text{Ru}(\text{CO})(\text{Etmal})]\text{BF}_4$ (4.4c) was subjected to attack by the nucleophiles benzylamine and water. It had previously been reported that if the stretching frequency of a carbonyl ligand was greater than 2000 cm^{-1} , the ligand would be susceptible to nucleophilic attack.¹⁴⁹ However, although the carbonyl ligand in complex (4.4c) has a stretching frequency of 2050 cm^{-1} , it was displaced by water and benzylamine with no evidence of nucleophilic attack being observed.

Many ruthenium complexes have shown promise as anti-tumour agents, some of which are discussed in Chapter 1. The complex $[(\text{C}_6\text{H}_6)\text{RuCl}(\text{pro})]$ has also been reported to show anti-cancer activity.¹²¹ However, the mechanisms by which such complexes operate are poorly understood, the complexes are thought to bind to DNA and thus inhibit replication. We have studied the reactions of various arene-ruthenium complexes with nucleosides in an attempt to understand how such complexes have the ability to bind to DNA.

The reactions between $[(\text{mes})\text{RuCl}_2]_2$ and guanosine, adenosine and theophylline gave the complexes $[(\text{mes})\text{RuCl}_2(\text{Guan})]$ (5.1), $[(\text{mes})\text{RuCl}_2(\text{Aden})]$ (5.2) and $[(\text{mes})\text{RuCl}_2(\text{TheoH})]$ (5.3a) respectively, all of which showed the ligands binding through the N(7) position. A similar reaction between cytidine and $[(\text{mes})\text{RuCl}_2]_2$ gave an unstable complex thought to be $[(\text{mes})\text{RuCl}_2(\text{Cyt})]$. The order of stability of the above complexes follows the well established order of: $\text{G} > \text{A} > \text{C}$. Recrystallisation of complex $[(\text{mes})\text{RuCl}_2(\text{TheoH})]$ (5.3a) from water gave X-ray quality crystals of a slightly different product. The structure of one such crystal confirmed N(7) coordination of the theophylline ligand, but also showed deprotonation at the N(9) position and replacement of one of the chlorides by a water molecule, thus giving the complex $[(\text{mes})\text{RuCl}(\text{H}_2\text{O})(\text{C}_7\text{H}_7\text{N}_4\text{O}_2)]$ (5.3b).

The reactions of guanosine and cytidine with [(mes)RuCl(ala)] (3.5; R = Me) in water gave the complexes [(mes)Ru(Guan)(ala)]Cl (5.6) and [(mes)Ru(Cyt)(ala)]Cl (5.7). The cytidine-alanine complex (5.7) is more stable than [(mes)RuCl₂(Cyt)], indicating that the alanine ligand enhances the cytidine coordination, this may prove useful when studying possible interactions within the body as the ancillary ligand appears to have an effect on the coordination of the nucleobases. The guanosine-alanine complex (5.6) was more stable than its cytidine counterpart as shown by reactions with dmsO.

Further Work

The investigation into the reactivity and synthesis of the arene-ruthenium amine complexes was satisfactorily concluded and no further work is planned. Some of the complexes prepared in Chapter 4 have potential as water-soluble catalysts, further work could investigate this and also ways of modifying the reactions involving nucleophilic attack at the carbonyl group in the complex [(mes)Ru(CO)(Etmal)]BF₄ (4.4c). The arene-ruthenium amino acidate complexes may have uses in asymmetric syntheses, since the reaction between the isoelectronic complex [Cp*IrCl(pro)] and an alkyne has been reported,¹²⁷ and that the related complex [CpFe(CO)(PPh₃)COCH₃] shows enhanced stereoselectivity in its reaction with a lithium enolate.¹¹⁶ However, I feel the most promising lines for further research would be further investigations into the complexes formed in Chapters 3 and 5.

Some of our complexes have shown some activity in *in vitro* tests against the murine tumours L1210 leukaemia and ADJ/PC6 plasmacytoma as well as the human ovarian cell line CH1.¹⁸¹ A significant advantage of these complexes, should any of them make clinical trials is that their administration to the patient would be made easier by their solubility in aqueous media. It is generally accepted that two labile groups are required for platinum based complexes to exhibit anti-tumour activity, however, this is not necessarily the case for other metal anti-cancer complexes, for example, the complex [(C₆H₆)RuCl(pro)] has only one labile site (assuming the proline and benzene ligands are not displaced) and is active against tumours. Therefore, an investigation into the coordination of this and other amino acidate complexes with various nucleotides may improve our knowledge of the mechanisms of the anti-tumour activity

of these complexes, and indicate whether nucleoside or nucleotide binding is any indication of potential anti-tumour activity. Furthermore, the structure of arene-ruthenium complexes with an η^6 - arene ligand occupying one face of an octahedron may also be used as models for the *fac*-isomers of octahedral ruthenium complexes, especially as *fac*- $[(\text{NH}_3)_3\text{RuCl}_3]$ is reported as being very active against tumours.⁹⁵

Initially, we could react various mononucleotides with the amino acidate complexes, presumably the chloride ligand would be displaced by the base and we could then investigate whether the phosphate group interacts with the amino acidate ligand, possibly via hydrogen bonding. Following this we could observe how a dinucleotide might interact, one of the bases would presumably coordinate by displacing the labile chloride ligand and again the phosphate might interact with the amino acidate ligand. Continuing further, oligonucleotides and their possible modes of coordination could also be investigated.

Although our initial attempts to coordinate a second nucleoside ligand to $[(\text{mes})\text{RuCl}_2(\text{Guan})]$ (5.1) were unsuccessful it may be possible to coordinate two nucleosides to the ruthenium centre by performing the reaction in the presence of a chloride scavenger, such as a silver salt. If coordination of two nucleosides is possible, it may also be possible to coordinate two nucleobases from the same dinucleotide fragment or even from a DNA strand. Thus reactions between $[(\text{mes})\text{RuCl}_2]_2$ and various mononucleotides and dinucleotides could also be attempted. For mononucleotides the purine bases would presumably coordinate via the N(7) position and in this case the phosphate group can have two possible modes of interaction, either by direct binding of an oxygen atom to the ruthenium by displacement of a chloride ligand, or alternatively since we know the chloride can exchange with water in aqueous solution, the phosphate group may interact with a coordinated water molecule via hydrogen bonding. We have seen that coordinating two nucleosides to the same ruthenium centre has proved difficult, however, coordination of a dinucleotide may be easier because in this case the second nucleobase will be held in close proximity to the ruthenium centre and thus promote chelation more readily. A number of interactions are theoretically possible. After initial coordination of one of the nucleobases, the second base could coordinate by displacing a chloride ligand, alternatively the phosphate group attached to the second nucleobase could also

coordinate to the ruthenium via an oxygen atom, perhaps in competition with the second base group. There is also the possibility of this phosphate group interacting with a coordinated water molecule via hydrogen bonding. Structural characterisation of these ruthenium nucleobase and nucleotide complexes would show which particular coordination sites of the ligands are used in binding to the ruthenium centre, and also if any intramolecular interactions occur (such as hydrogen bonding). The information gained may provide further evidence of how ruthenium complexes bind to actual DNA and thus exhibit anti-tumour activity

Finally, further *in vitro* testing of more arene-ruthenium complexes against various tumours could be carried out, in order to assess if any correlation can be made between positive anti-cancer activity and their reactions with nucleoside or nucleotide ligands, and if any particular reaction is indicative of anti-tumour activity.

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