Oxidative Addition of Amino Acids to Iridium(I) Metal Centers

by

Lisa Ann Huff

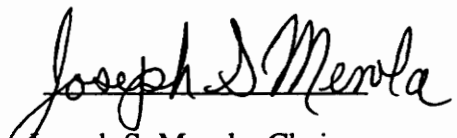
Thesis submitted to the Faculty of the Virginia Polytechnic Institute and State University in partial fulfillment of the requirements for the degree of

Master of Science

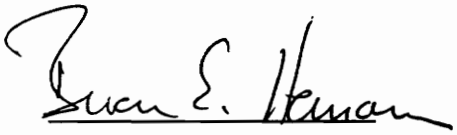
in

Chemistry

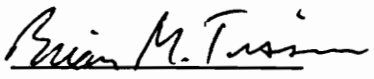
APPROVED:



Joseph S. Merola, Chairman



Brian E. Hanson



Brian Tissue

September, 1996

Blacksburg, VA

Keywords: Iridium, Amino Acid Complexes, Metal Hydrides, Organoiridium Chemistry

Oxidative Additions of Amino Acids to Iridium(I) Metal Centers

By

Lisa Ann Huff

Joseph S. Merola, Committee Chairman

Department of Chemistry

(ABSTRACT)

The oxidative addition of both monosubstituted and disubstituted α-amino acids to $[Ir(COD)(PMe_3)_3]Cl$ (COD = cyclooctadiene) was studied and the reactivity of the resulting complexes was examined. The reaction of $[Ir(COD)(PMe_3)_3]Cl$ with the disubstituted amino acids, diphenylglycine and methylphenylalanine, led to an almost exclusive facial product. Monosubstituted amino acid complexes were observed to be mixtures of the meridional and facial isomers with the meridional isomer largely predominating. The meridional isomer was found to convert to the facial isomer when heated for several days at 100°C. In fact, a predominantly meridional mixture was found to convert to a predominantly facial mixture upon heating. The facial isomer was therefore shown to be the thermodynamic product from the mixture. Small amounts of other isomers were observed in the hydride region of the proton NMR spectrum. One resonance at -23.75 ppm disappeared upon heating t-butyl acetylene with the amino acid complex. The disappearance of this hydride resonance may indicate the insertion of the unsaturate into the Ir-H bond, or alternatively, the conversion of this isomer to a more thermodynamically stable isomer. Reactions of these complexes with methylpropiolate and acrylamide were attempted but evidence of an insertion product was not found.

Oxidative addition of amino acids to the coordinatively unsaturated [Ir(DEPE)(COD)]Cl (DEPE = bisdiethylphosphinoethane) gave a mixture of isomers of the type HIr(aa)(DEPE)Cl and [HIr(aa)(DEPE)($H_2$0)]Cl (aa = amino acid). The equilibrium mixture of six isomers was elucidated based on chemical shifts of the hydride resonances. The addition of excess chloride ion produced only those resonances in the hydride region corresponding to chloride-bound species. Alternatively, the removal of chloride ion from the solution by $AgPF_6$ addition produced only those hydride resonances corresponding to water-bound species. Reaction with unsaturates was identified based on the disappearance of the hydride resonances immediately after addition of methyl propiolate. In addition, ^{13}C NMR spectra indicated the presence of vinyl carbons, and the ^{1}H NMR spectra indicated the presence of vinylic protons. The addition of excess phosphine in aqueous solution also resulted in the formation of complexes of the type [HIr(aa)((DEPE)(PR_3)$_3$]Cl (R = Methyl or Ethyl).

This thesis is dedicated to my Mother

Thanks for the strength and encouragement

that you have given me throughout my life.

Acknowledgments:

I would first like to thank my committee members for all their help in doing all the things that committee members do. I would like to thank my advisor, Dr. Merola, for providing the humor that managed to get me through my dreaded public speaking ordeals last semester. I learned some valuable lessons from the experience. Next time, I will definitely remember to put down the microphone and pointer before returning to my seat! I would like to say though that I am very grateful for the experience of being at that meeting. Thanks also go to my other committee members, Dr. Brian Hanson and Dr. Brian Tissue, for their time and help. Thanks to the Hanson and Brewer groups for all the "loans" over the years and in general for help and support. Acknowledgment also goes to the National Science Foundation for funding.

I'd like to thank Robert (Otis) Clark for all his help in showing me the ropes when I first joined the group. Gina and Margaret, I am very glad that you joined the group and brought some seriously needed civility and good humor to the lab. If you find the time, please "react a peptide" in my name. Sophie, all I can say is hang in there! Mitra, thanks for discussing your trials and tribulations with me and thanks for listening to mine. I'm glad I could add one more name to the list of graduates who spent their last days at your apartment. A special thanks to Jan for helping me put everything into perspective and for helping me maintain my sanity through some difficult times. A special thanks also goes to my father figure, Pete, for all your help. Remember the car ride up here to look for an apartment?!? Thanks for the laughs, the support, and the unselfish love that you have given me throughout the years.

Table of Amino Acid Abbreviations*

Ala = Alanine

Diphenylgly = Diphenylglycine

Gly = Glycine

His = Histidine

Homophenylala = Homophenylalanine

Leu = Leucine

Met = Methionine

Methylphenylala= Methylphenylalanine

Phenylgly = Phenylglycine

Pro = Proline

Tyr = Tyrosine

Val = Valine

* These abbreviations will be used to refer to the amino acidate ligands resulting from the deprotonation of the amino acid zwitterion.

Table of Contents

Table of Contents

List of Figures

List of Schemes

List of Equations

List of Tables

Chapter 1. Introduction and Literature Review

1.1 Intent of Thesis

The complexes discussed in this thesis have the potential to add either the O-H or the N-H functionality of amino acids to unsaturates. In addition, these chiral complexes have the potential for asymmetric catalysis. Very few examples of C-O and C-N bond formation assisted by transition metals have been reported in the literature. In these cases, the transition metal is usually used to activate the unsaturate towards nucleophilic attack. An alternative scheme can be imagined in which the amino acid is oxidatively added to the Ir(I) complex, an unsaturate coordinates to the metal and inserts into the Ir-H bond, and finally reductive elimination takes place to yield the functionalized product (Figure 1.1.1).

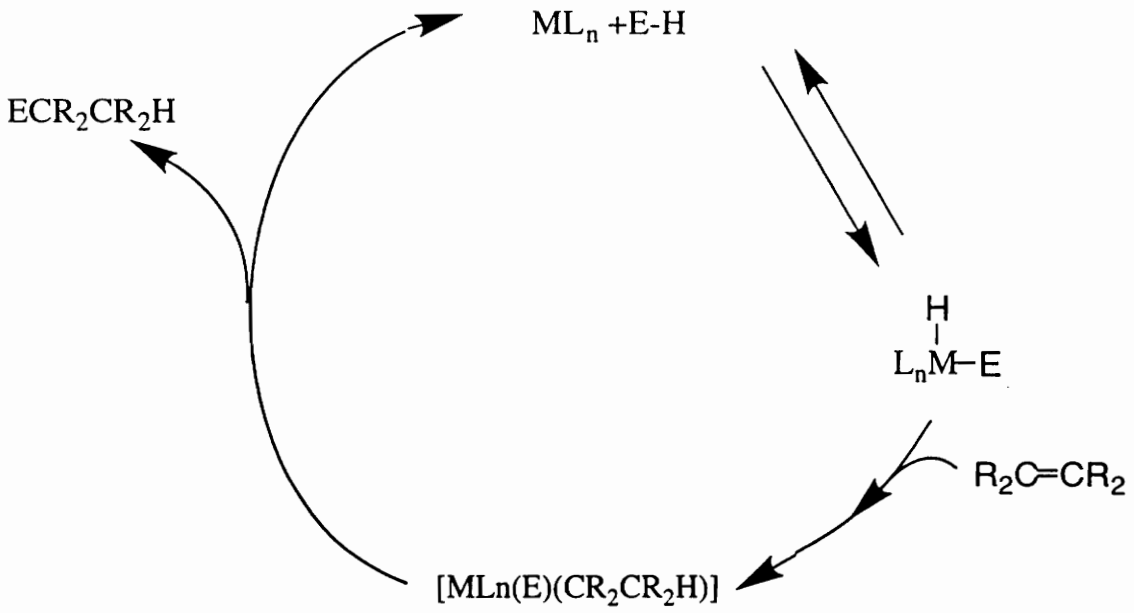


Figure 1.1.1 Addition of E-H (E = N, O) to unsaturates using oxidative addition/ reductive elimination mechanism

This oxidative addition/ reductive elimination scheme has been utilized extensively for C-C bond formation. The intent of this research is therefore to explore the possibility of this oxidative addition/ reductive elimination mechanism of C-O bond formation with amino acids. If the amino acid ligand proves to be stable enough to disfavor reductive elimination, the complexes may alternatively have the potential for oligomer or polymer formation by successive insertions of an unsaturate (Figure 1.1.2). These complexes may also find important biological applications.

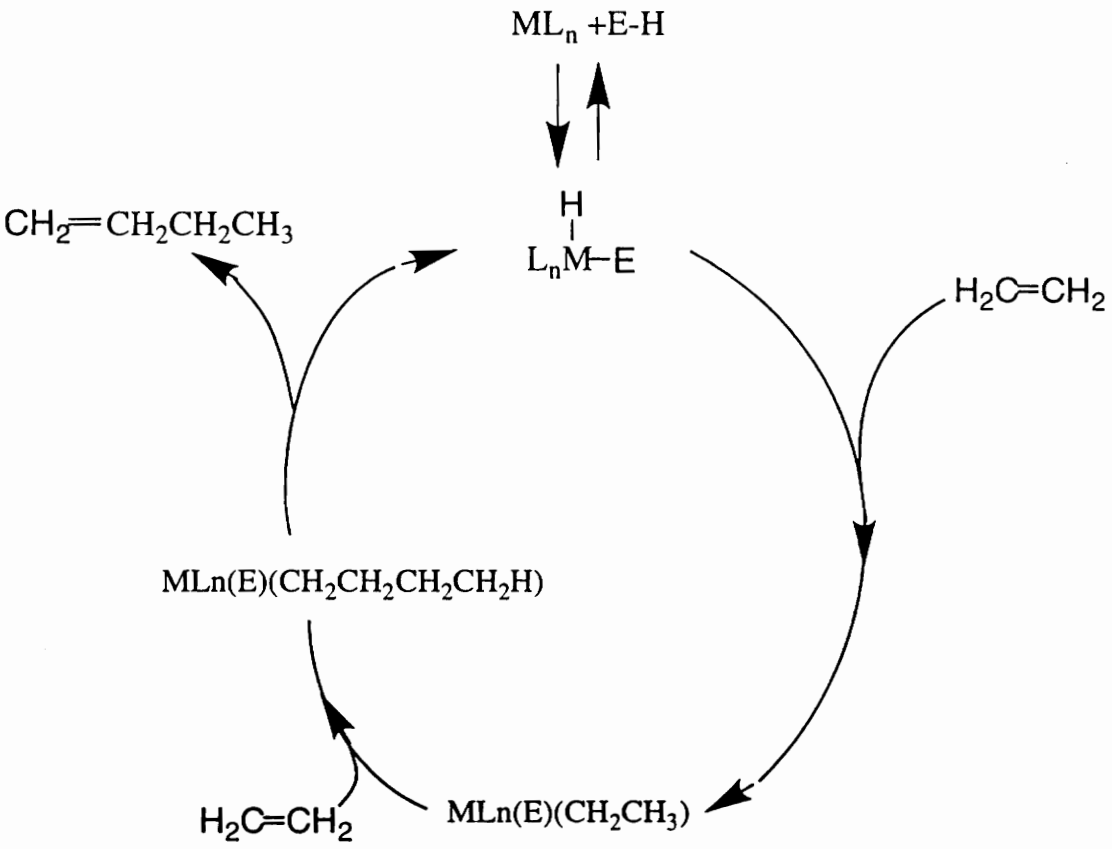


Figure 1.1.2 Oligomer formation

1.2 Biological Importance of Platinum Group Metals

The first row transition metals play important roles in biological systems including oxygen transport, oxygen storage, and electron transfer.[1] The second and third row transition metals are alternatively noted for their toxic effects on organisms. Molybdenum, utilized in nitrogenase, is the only known second or third row transition metal utilized by nature in biological processes.[2] The large amount of research on platinum metals and their therapeutic effect began about 25 years ago with the discovery by Rosenberg, et al.[3] that cisplatin, $Pt(NH_3)_2(Cl)_2$ (Figure 1.2.1), acts as an anti-tumor agent.

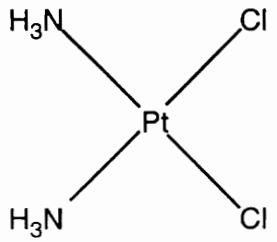


Figure 1.2.1 Cisplatin

Certain side effects associated with cisplatin such as severe nausea and vomiting have caused a tremendous amount of research to be devoted to producing effective and less toxic anti-cancer drugs. The high requirement and uptake of nutrients, such as amino acids, by tumor cells was hoped to be exploited by developing amino acid complexes in which the amino acid ligand serves as a carrier for the platinum drug.[4,5] Amino acid ligands also increase the effectiveness of the drug by imparting water solubility to the complex. It was also hoped that amino acid complexes of the platinum metals would be less toxic and more target specific than cisplatin. Many of the amino acid complexes of platinum have been shown to have biological activity, but these complexes have so far been less target specific and less active than cisplatin.

Ruthenium (II) complexes such as [$RuCl_2$(DMSO)Cl] (Dimethylsulfoxide) have shown activity towards lung cancer.[6] In the case of B16 melanoma and MCa mammary cancer, Ru(II) derivatives actually exhibit greater activity than cisplatin.[6,7] Sheldrick, et al. have prepared amino acid complexes of the type [(η^6-C_6H_6)Ru(aa)Cl].[8] The labile Ru-Cl bond was expected to make these complexes succeptible to DNA binding. In fact, studies have confirmed that the chloride of [(η^6-C_6H_6)Ru(L-alanine)Cl] is replaced by the nucleotide, 9 ethylguanine, to form [(η^6-C_6H_6)Ru(L-alanine)(9 ethylguanine)]Cl and the unidentately N-bound L-alanine methyl ester of [(η^6-C_6H_6)Ru(L-alanine methyl ester)Cl] is completely displaced by the same nucleotide to form [(η^6-C_6H_6)Ru(9 ethylguanine)Cl_2].[8] These [(η^6-C_6H_6)Ru(aa)Cl] complexes, in particular [(η^6-C_6H_6)Ru(pro)Cl] (Figure 1.2.2), have been shown to have significant effects against p388 form of leukemia.[8]

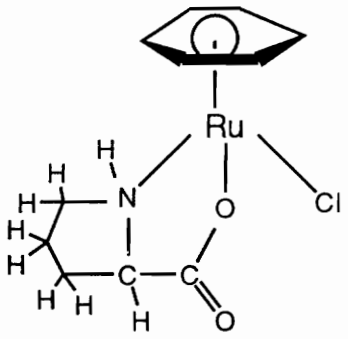


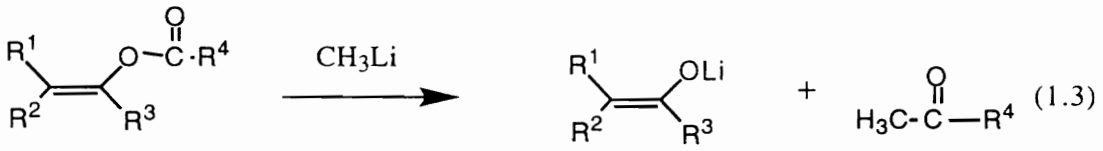
Figure 1.2.2 [η^6-C_6H_6Ru(pro)Cl]

Very little is known about the therapeutic effect of the platinum metals rhodium and iridium. Christopher Roy[9] discovered that [Ir(L-phenylala)(PMe_3)$_3$]Cl has moderate activity against HIV while the similar complex [Ir(L-tyr)(PMe_3)$_3$]Cl demonstrates no

activity. It is an interesting observation that the hydroxy group on tyrosine causes the complex to lose all activity against HIV infected cells. This loss of activity may result from either the electron withdrawing properties or the hydrophilicity of the hydroxy substituent.

1.3 O-H Additions to Unsaturates

The asymmetric addition of O-H bonds to unsaturates to create enol esters and esters is a highly desirable process. Enol esters have important applications in organic chemistry as intermediates and have also been widely used as polymer precursors.[10] Enol esters may be used to generate regio- and stereospecific lithium enolates through the addition of methyl lithium (Figure 1.3.1).[11]



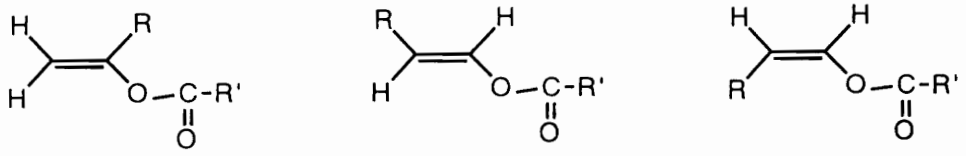
(1.3)

Equation 1.3.1 Generation of enolates from enol esters through the addition of methyl lithium

Enolates are subject to electrophilic attack not only by protons but also by halogens, alkylating agents, and the positively polarized carbon of other carbonyl compounds.[12] The latter two reactions result in the highly desirable process of C-C bond formations.

Three major methods are available for the synthesis of enol esters. The first consists of the treatment of the aldehyde or ketone under either acidic or basic conditions with the appropriate acid anhydride or chloride.[13] Secondly, $Pd(OAc)_2$ salts have been used to promote the acetoxylation of olefins in acetic acid.[14] The catalyzed addition of carboxyllic acids to alkynes has also been acheived using an electrophile or a transition

metal complex. Mercury salts, where organomercurials serve as intermediates, have been found to be useful catalysts.[11,15] However, the requirement of stoichiometric quantities of hazardous mercury salts has led to a large amount of research into safer alternatives. A transition metal complex offers the potential for the selective formation of the G, E, or Z isomers (Figure 1.3.2) through fine adjustments of the ligands.



G E Z

Figure 1.3.2 Geminal (G), Trans (E), and Cis (Z)

A number of the transition metal catalyst systems[16,17,18,19,20,21] have been reported in which the metal activates the unsaturate towards nucleophilic attack. Ladipo[22] has shown that $Ir(O_2CC_6H_5)_2(PMe_3)_3Cl$ catalyzes the addition of benzoic acid to acetylenes (Figure 1.3.3). The following mechanism was proposed for this enol ester formation: (i) dissociation of the benzoate ligand (ii) π-coordination of the acetylene (iii) external attack of benzoate anion on the coordinated acetylene (iv) direct protonation of the vinyl ligand to yield the enol ester.

The oxidative addition/ reductive elimination mechanism of C-O bond formation (Figure 1.1.1) has been much less studied than the external attack of an electrophile on an activated unsaturate. In fact, an example of the reductive elimination of an ester from an (alkyl)(carboxylate)metal complex could not be found in the literature. Alternatively, the formation of esters from the reductive elimination of (acyl)(aryloxy) nickel(II) and palladium(II) complexes has been reported.[23] Atwood has also reported that the Ir(III)

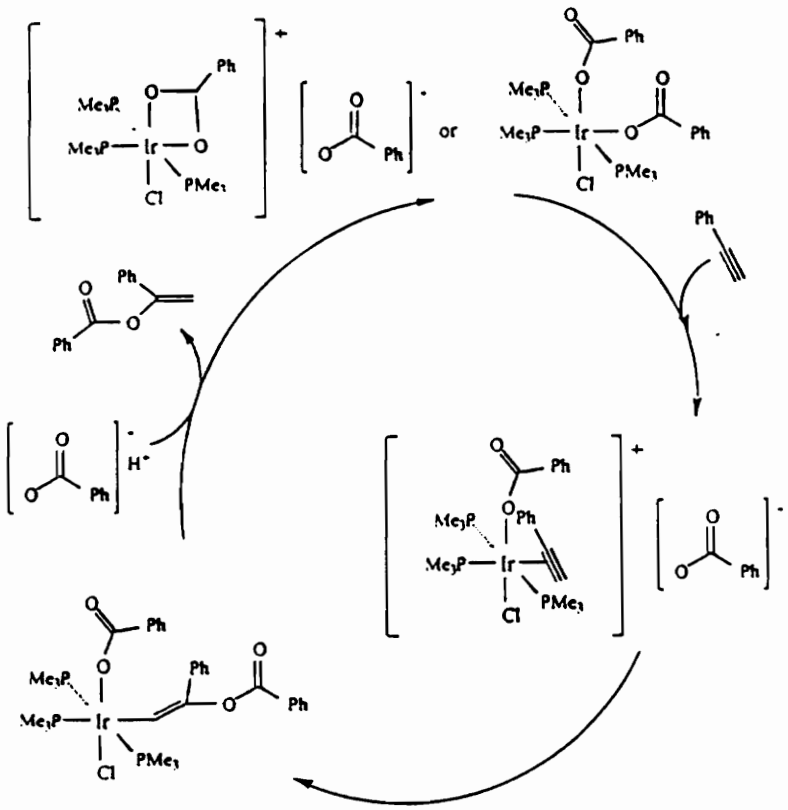


Figure 1.3.3 Fola's catalytic addition of benzoic acid to acetylenes

complex $RIr(OMe)(CO)(PPh_3)_2Cl$ reductively eliminates an ester forming $Ir(CO)(PPh_3)_2Cl$.[24] The formation of C-O bonds from the reductive elimination of a late transition metal complex containing a carboxylate and an alkyl substituent is thought to be possible due to the relatively weak Ir-O bond. Late transition metal complexes containing alkoxy and carboxylate ligands have only recently been reported in the literature since the the hard carboxylate and alkoxy groups were thought to be a poor match for these soft metals. Recently research has focused on exploiting this poor mismatch in order to produce an active catalyst.

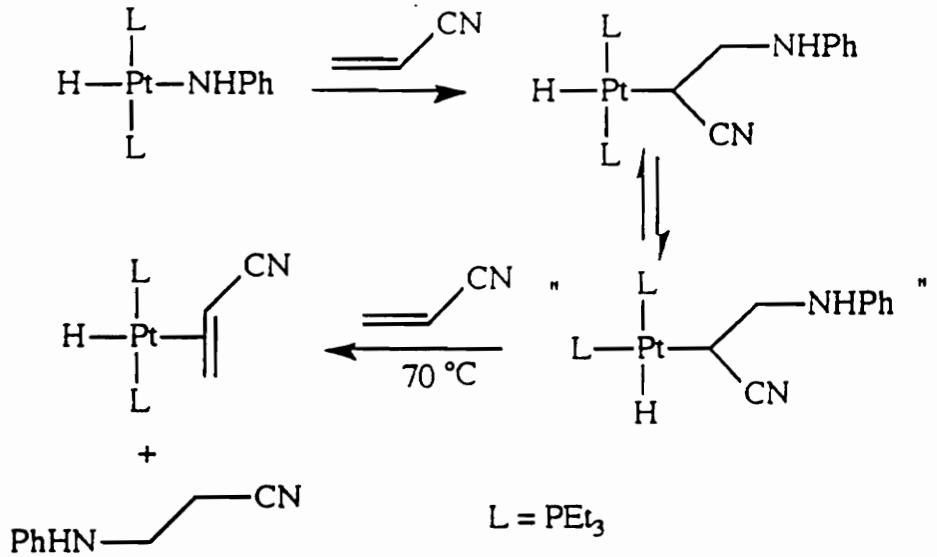
1.4 N-H Additions to Unsaturates

It is difficult to predict the exact mechanism of a catalytic reaction and therefore the possibility of N-H formation must also be considered. For example, it is possible that

deprotonation of the amine terminus may occur followed by insertion of an unsaturate into the Ir-H bond and subsequent reductive elimination to yield the amination product.

A general procedure for generating olefin amination has not been acheived. Current methods to effect amination include Ritter reactions, reductive amination of ketones or aldehydes, reduction of nitriles, and Hoffamn degradation of amides.[25,26] The direct amination of ethylene and propene with ammonia has been reported,[27] but the catalytic amination of olefins has yet to be fully realized. Transition metals are usually used to activate the amine towards electrophilic attack. Recently, the alternative oxidative addition/reductive elimination mechanism has been reported to effect catalytic amination of unsaturates.

In 1987, Trogler and Cowen[28] demonstrated the feasibility of an insertion-reductive elimination sequence for the reaction of a hydrido amido complex with an olefin (Scheme 1.4.1).



Scheme 1.4.1 First demonstrated insertion reductive elimination of a hydrido amido complex

Acrylonitrile was found to insert into the metal-nitrogen bond of trans-$(PEt_3)_2Pt(H)NHPh$ in benzene at 20°C. By heating to 70°C in the presence of free acrylonitrile they were able

to show that the complexes would undergo rearrangement and subsequent reductive elimination of 3-anilinopropionitrile. This reaction was not catalytic, but Milstein, et al.[29] have since demonstrated the catalytic amination of norbornylene based on the oxidative addition of a N-H bond followed by insertion - reductive elimination sequence.

1.5 Literature Review of Amino Acids and Platinum Metals

1.5.1 Introduction

An intense amount of research has been devoted to the development of amino acid complexes of the platinum metals since the discovery of the antitumor properties of cisplatin in 1969.[3] Platinum and palladium have been the most intensely studied and several amino acid complexes of these metals have also diplayed anticancer properties.[30] Ruthenium amino acid complexes have also demonstrated biological activity against the p388 form of leukemia.[8] Certain ruthenium complexes have also been studied as radiopharmaceuticals and imaging agents[31, 32] and have been used for the study of kinetic and thermodynamic properties of long-range electron transfer.[33-36] Ruthenium amino acid complexes have also been used as catalysts in the promotion of hydrolysis of amino acid esters, amino acid amides, and peptides.[37-40] Osmium complexes have also been prepared, but the complexes are often unstable and therefore difficult to characterize. The electroanalytical studies conducted by Farooq in 1974 established that amino acid complexes of Rhodium are stable.[25] Several rhodium amino acid complexes have since been synthesized with the aim of exploiting the amino acid stereogenic center for the development of chiral catalysts. Iridium amino acid complexes have essentially been neglected until recently. Two independent reports of the synthesis of several types of amino acid complexes of iridium appeared in the literature in 1990 by Beck, et al.[42] and

Carmona, et al.[43] A great deal of research has since been devoted to understanding the properties of amino acid complexes of iridium by Beck[44,45] and Carmona[46] and also recently by Grotjahn[47,48] and Merola[9].

1.5.2 Ruthenium and Osmium Amino Acid Complexes

Dersnah and Baird reported the first fully characterized ruthenium(II) complexes of α-amino acids in 1977.[49] Reactions of $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ with glycine and D,L-alanine in methanol were found to give the bidentate {N,O} chelation complexes of the type $[(\eta^6\text{-}C_6H_6)RuCl(aa)]$ (Figure 1.5.1). Beck et al. later reported a similar synthesis of other amino acid η^6-arene ruthenium complexes of the type shown in Figure 1.5.1.[42]

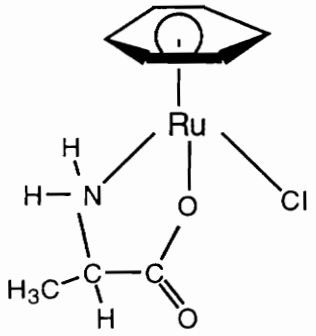


Figure 1.5.1 $[(\eta^6\text{-}C_6H_6)RuCl(ala)]$

Sheldrick, et al. reported a mondentate binding of the alanine methyl ester through the amine nitrogen in the $[(\eta^6\text{-}C_6H_6)Ru(L\text{-}alaMe)Cl_2]$ complex.[8] Sheldrick et al. also reported the reaction of $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ with the amino acids l-penicillamine (l-pen), l-histidine, l-histidine methyl ester (l-hisMe) which all contain side chains with donor atoms capable of coordinating to the metal.[8] The crystal structure analysis established a tridentate amino acidate ligand in $[(\eta^6\text{-}C_6H_6)Ru(l\text{-}pen)]_2Cl_2$ with the deprotonated sulfur atom adopting a

bridging position between the two ruthenium atoms leading to a four membered RuSRuS ring (Figure 1.5.2). The crystal structure analysis of $[(\eta^6\text{-}C_6H_6)Ru(l\text{-}hisMe)Cl]Cl$ established a bidentate coordination of the amino acid through the amino nitrogen and the imidazole nitrogen (Figure 1.5.3). Identical bidentate coordination of the amino acid through the amino nitrogen and the imidazole nitrogen for both the l-histidine and the l-histidine methyl ester was established by the similarity of the ^1H NMR spectra for the two complexes.

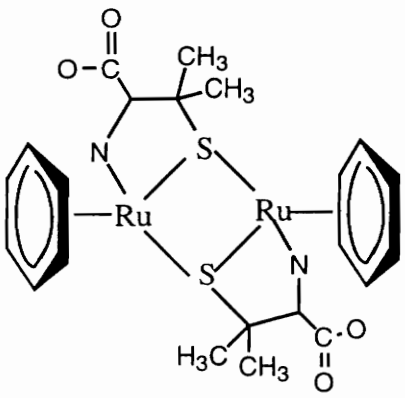


Figure 1.5.2 Tridentate binding of amino acid ligand in $[(\eta^6\text{-}C_6H_6)Ru(l\text{-}pen)]_2Cl_2$

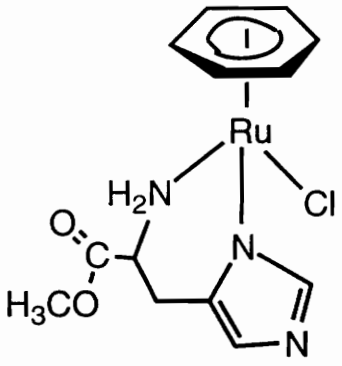


Figure 1.5.3 $[(\eta^6\text{-}C_6H_6)Ru(l\text{-}hisMe)Cl]Cl$

Sheldrick, et al. have prepared other half sandwich complexes of the type [Cp*Ru(aa)Cl] (Cp* = pentamethylcyclopentadiene, aa= L-ala, L-met).[50] A room temperature reaction of $[Cp^*RuCl_2]_2$ with L-alanine in methanol in the presence of NaOMe with the solvent acting as a reducing agent yielded complexes with a five membered {N,O} chelate ring (Figure 1.5.4) as observed for the arene complexes (Figure 1.5.1). The sulfur containing amino acid, L-methionine, formed neutral complexes with {N,O,S} chelation about the ruthenium (Figure 1.5.5) under the same reaction conditions.

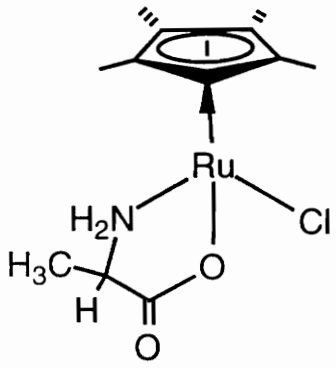


Figure 1.5.4 Na[Cp*Ru(L-ala)Cl]

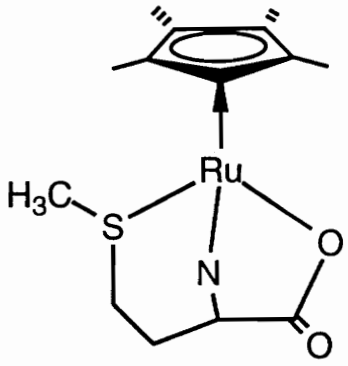


Figure 1.5.5 [Cp*Ru(L-met)Cl]

Over the years there has been much research dedicated to the development of half-sandwich complexes of amino acids containing an aromatic ring. This reasearch interest stems from the potential use of ruthenocene and its derivatives as radiopharmaceuticals.[31] In fact, radiolabled ruthenocenylalanine has been studied as a pancreating imaging agent.[32] Sheldrick, et al. have prepared three such Cp* Ruthenium (III) complexes of L-phenylalanine, L-tyrosine, and L-tryptophan.[50] The {N,O} chelate complex, Na[Cp*RuCl(L-phenylala)], was synthesized by the reaction of L-phenylalanine and $[Cp^*RuCl_2]_2$ in CH_3OH/CH_3ONa at a temperature of O°C. In contrast, a mixture of both the {N,O} chelate complex as well as the sandwich complex, [Cp*Ru(η^6-L-phenylala)]Cl (Figure 1.5.6), was obtained when the reaction was carried out at room temperature. When the reaction was carried out under reflux in methanol, an 88% yield of the sandwich complex was obtained. Additionally, the relative yields of the sandwich complexes were found to be affected by the electron withdrawing properties of the substituents on the aromatic ring. The maximum yield (40%) of the para-chlorophenylalanine complex was half that of the yield (80%) of the phenylalanine complex. Sandwich complexes of L-tryptophan and its derivative 5-hydroxy tryptophan were also prepared (Figure 1.5.7).

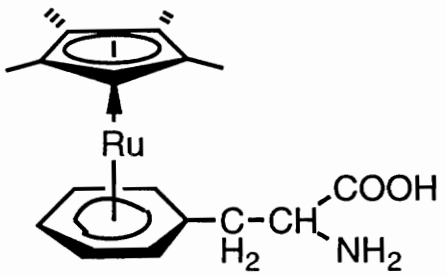


Figure 1.5.6 [Cp*Ru(η^6-L-phenylala)]Cl

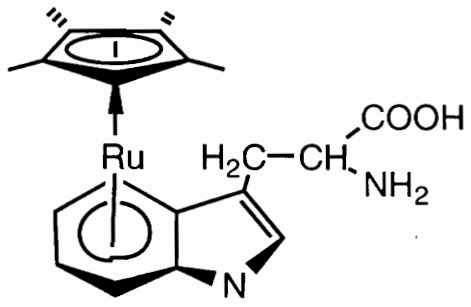
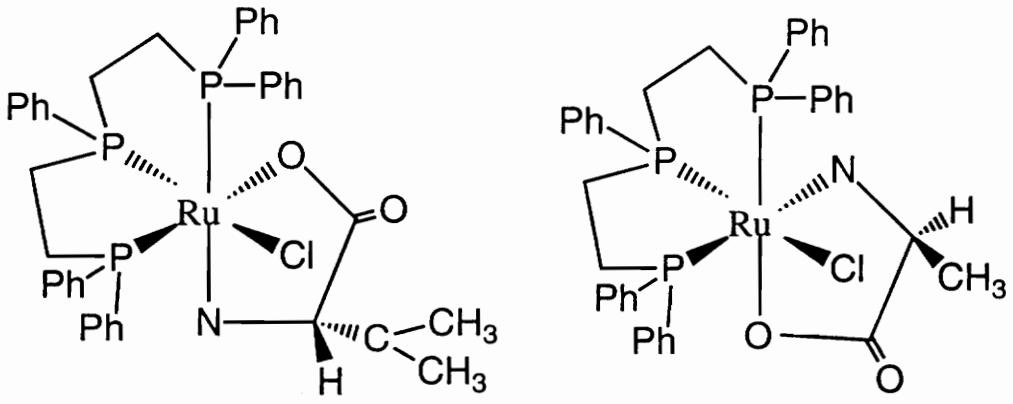


Figure 1.5.7 [Cp*Ru(η^6-L-tryptophan)]Cl

The triphos ligand, $PhP(CH_2CH_2PPh_2)_2$, has been suggested by Sheldrick, et al. as a potential alternative to the facially coordinating η^6-C_6H_6 and Cp* ligands.[51] Complexes of the type [RuCl(aa)(triphos)] (Figure 1.5.8) were prepared by the reaction of $[Ru_2(\mu\text{-}Cl)_3(triphos)_2]Cl$ with the amino acids L-valine and L-alanine in the presence of base (KOH and CH_3ONa). The valine complex exhibited only one set of resonances in the ^1H and ^{31}P NMR spectra and the diaestereomer $R_{Ru}S_C$ was identified by crystal structure analysis. The alanine complex alternatively favored the $S_{Ru}S_C$ diaestereomer in a ratio of 14:1.



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

(a) (b)

Figure 1.5.8 (a) [RuCl(L-val)(triphos)] and (b) [RuCl(L-ala)(triphos)]

Sheldrick, et al. prepared complexes of the type $[(diene)RuCl(aa)]_n$ (diene= norbornadiene nbd and 1,5-cyclooctadiene cod, aa= glycine, D,L-alanine, D,L-valine) from the reaction of polymeric $[(diene)RuCl_2]_n$ with the amino acid in methanol at reflux.[52] Alternatively, complexes of the type $[(diene)Ru(L\text{-}aa)_2]$ with {N,O} chelation of the amino acids were formed when water was used as the solvent. The $[(nbd)Ru(L\text{-}phenylala)_2]$ was shown to crystallize as the Δ isomer with the N of the first amino acid trans to the O of the second amino acid (Figure 1.5.9). Crystal structure analysis of the tetrameric $[(COD)Ru(D,L\text{-}phe)Cl]_4$ established that the amino acidate ligands have an unusual

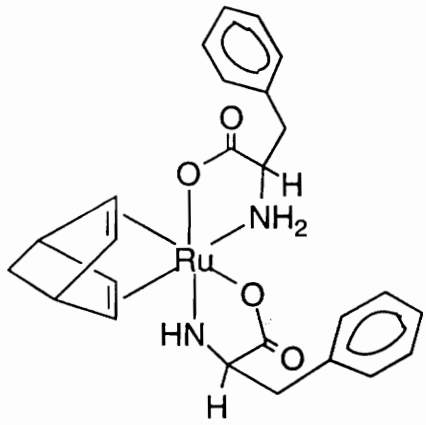


Figure 1.5.9 Δ-[(nbd)Ru(L-Phenylala)2]

tridentate binding mode with symmetrical carboxyl bridges between the individual ruthenium atoms. Reaction of nitrogen bases with $[(diene)RuCl(aa)]_n$ gave the monomeric species [(diene)RuCl(aa)B]. The amino acid chelate ring was assumed to remain intact while the Ru-O bond to the bridging carboxylate was replaced by a Ru-N bond to the base.

Saito, et al.[53] have reported square pyramidial complexes of the type $[Ru(aa)Cl(PPh_3)_2]$ (aa = glycine, l-serine, l-hydroxyproline, l-allohydroxyproline) formed from a fourfold excess of amino acid ligand and $[RuCl_2(PPh_3)_3]$ in acetone, but very little

analytical data was reported to support the conclusion. Furthermore, the formation of this product seemed unlikely since such reaction conditions would be expected to yield an 18 e$^-$ complex of the type $[Ru(aa)_2(PPh_3)_2]$. Sheldrick and Exner[52] have repeated Saito's work and have determined that $[Ru(aa)_2(PPh_3)_2]$ is indeed the product formed by refluxing $[RuCl_2(PPh_3)_2]$ with the respective amino acid (aa = gly, L-ala, L-val) in methanol in the presence of $NaHCO_3$. Crystal structure analysis of the L-alanine complex established cis-positioned triphenylphosphine ligands and a trans arrangement of the carboxyl oxygen of the first and the amine nitrogen of the second amino acid. The Δ isomer was the single isomer formed in the solid state, but the presence of two AB quartets in the $^{31}P\{^1H\}$ NMR suggested that both the Δ (Figure 1.5.10) and Λ (Figure 1.5.11) isomers were present in methanol solution. In contrast, the $^{31}P\{^1H\}$ NMR spectrum of the glycine complex displayed a single line indicative of magnetically equivalent phosphorous atoms. Based on chemical shifts, this complex was assumed to be arranged with cis phosphines with the N atoms trans to one another (Figure 1.5.12).

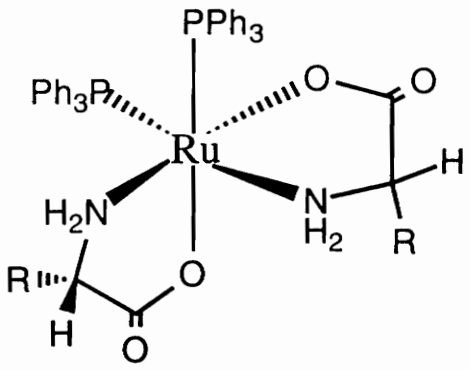


Figure 1.5.10 Δ configuration of $[Ru(aa)_2(PPh_3)_2]$ (aa = L-ala, L-val) determined from crystal structure analysis

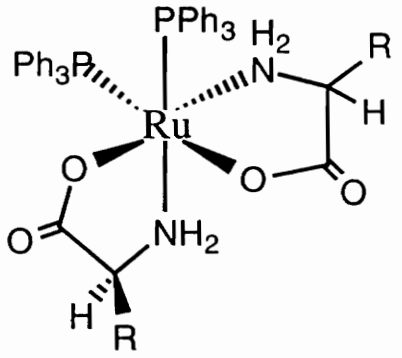


Figure 1.5.11 Λ configuration of $[Ru(aa)_2(PPh_3)_2]$ (aa = L-ala, L-val) present in methanol solution

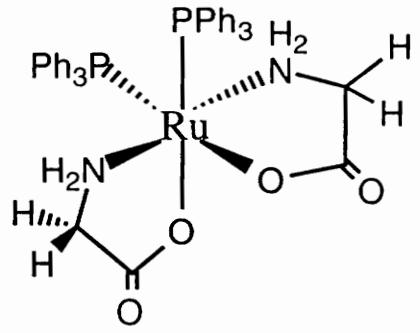


Figure 1.5.12 $[Ru(glycine)_2(PPh_3)_2]$

The reaction of $[RuCl_2(PPh_3)_3]$ with glycine or L-alanine in acetone leads to the Schiff base complexes $\{Ru[(CH_3)_2C{:}NCH(R)COO]_2(PPh_3)_2\}$ (R = H, CH_3). Crystal structure analysis established that the Schiff base of the glycine complex contained trans phosphines while the Schiff base of the alanine complex contained cis phosphines (Figure 1.5.13).

In contrast, the reaction of L-valine and serine with $[RuCl_2(PPh_3)_2]$ in acetone resulted in the same product obtained from the methanol solution, $[Ru(aa)_2(PPh_3)_2]$. Schiff base formation in acetone was therefore proposed to be less favored with longer side chains and kinetic factors were thought to control the type of complex, $[Ru(aa)_2(PPh_3)_2]$ or $\{Ru[(CH_3)_2C{:}NCH(R)COO]_2(PPh_3)_2\}$, that was formed in acetone.

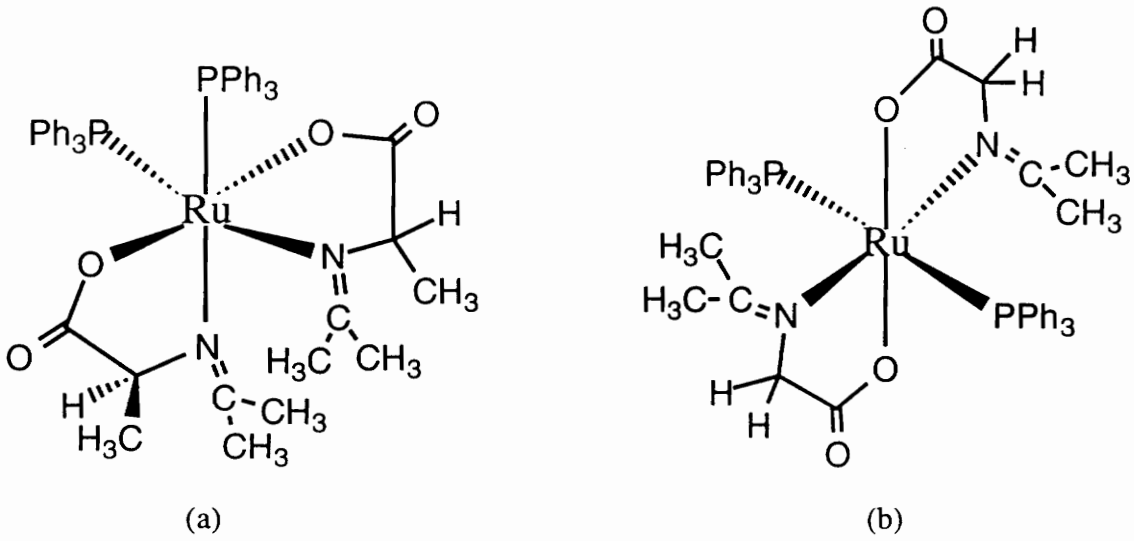


Figure 1.5.13 Schiff base complexes $\{Ru[(CH_3)_2C{:}NCH(R)COO]_2(PPh_3)_2\}$ (a) R = CH_3 (b) R = H

Beck, et al. have reported one of very few examples of hydrido platinum metal complexes in the literature.[45] Hydrido-N,O-chelate amino acid complexes, $HM(CO)(aa)(PPh_3)_2$ (M=Ru, Os, aa= L-phenylala, L-pro, L-leu, D,L-allylgly, L-ala, L-val) (Figure 1.5.14), have been prepared by the reaction of the hydrido $HMCL(CO)(PPh_3)_3$ complex with salts of α-amino acids. Meyer, et al.[54] have also reported a similar reaction of $[HMCl(CO)(PMe^tBu_2)_2]$ (M=Ru, Os) with glycine and D/L-phenylalanine to give octahedral $[HM(aa)(CO)(PMetBu_2)_2]$ complexes. Beck, et al.[45] have also prepared these hydrido complexes through an oxidative addition reaction of the

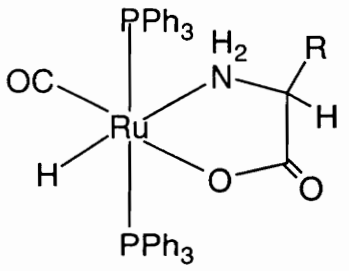


Figure 1.5.14 $HM(CO)(aa)(PPh_3)_2$

appropriate α-amino acid to $Ru(CO)_3(PPh_3)_2$. This oxidative addition of an amino acid to a platinum metal is only one of two such reactions reported in the literature. The oxidative addition of amino acids to $[(COD)Ir(PMe_3)_3]Cl$ was reported by Roy.[9] Beck found that the leucinato complex, $HRu(CO)(leu)(PPh_3)_2$, was an effective catalyst for the decomposition of formic acid. Reactions of $HRuCl(CO)(PPh_3)_3$ with amino acids gave the chloro-N,O-chelate complexes $RuCl(CO)(NH_2CHRCOO)(PPh_3)_2$. These complexes were found to catalyze the decomposition of amino acids to imines and CO_2 (Figure 1.5.15).

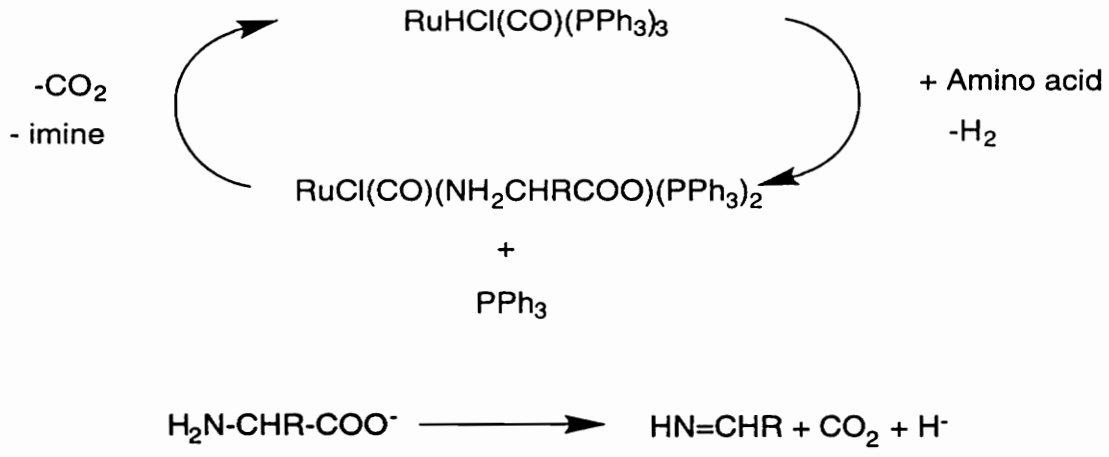


Figure 1.5.15 The decomposition of amino acids catalyzed by $RuCl(CO)(aa)(PPh_3)_2$

Ruthenium(III) amino acid complexes have also been used to promote the hydrolysis of amino acid esters, amino acid amides, and peptides.[37-40] Unlike labile metal ions, Cu(II), Zn(II), Ni(II), Cd(II), Hg(II), and Pb(II), amino acid complexes of Cobalt(III) and Ruthenium(III) are kinetically inert and allow for structural determination of the starting materials as well as intermediates and mechanisms involved in the hydrolysis process. Chelation of esters, amides, and peptides of amino acids to Co(III) complexes enhances their hydrolysis under basic conditions. In acidic conditions, hydrolysis of Co(III)-chelated amino acid esters is also enhanced significantly. In contrast, Co(III)-chelated amino acid amides and peptides are stable toward hydrolysis at low pH. The effect of other metal centers on the hydrolysis of amino acid amides and peptides in acid solution is also small, and elevated temperatures are needed in order to study it. Contrary to the stability of other metal glycinamide chelated complexes in acidic pH, Ru(III)-chelated glycinamide easily undergoes parallel hydrolysis and aquation in acidic solution (Figure 1.5.16).[37-39]

Ru(III)-chelated glycinamide undergoes hydrolysis about 5 orders of magnitude faster than Co(III)-chelated glycinamide.[40] This indicates a much stronger interaction of the carbonyl oxygen with Ru(III) than with Co(III) which can be explained by a significant ligand to metal charge transfer from the oxygen to the half-filled t_{2g} orbital of Ru(III). Similar interactions are well known for known for Ru(III) metal center, but impossible for the d^6 Co(III) ion.

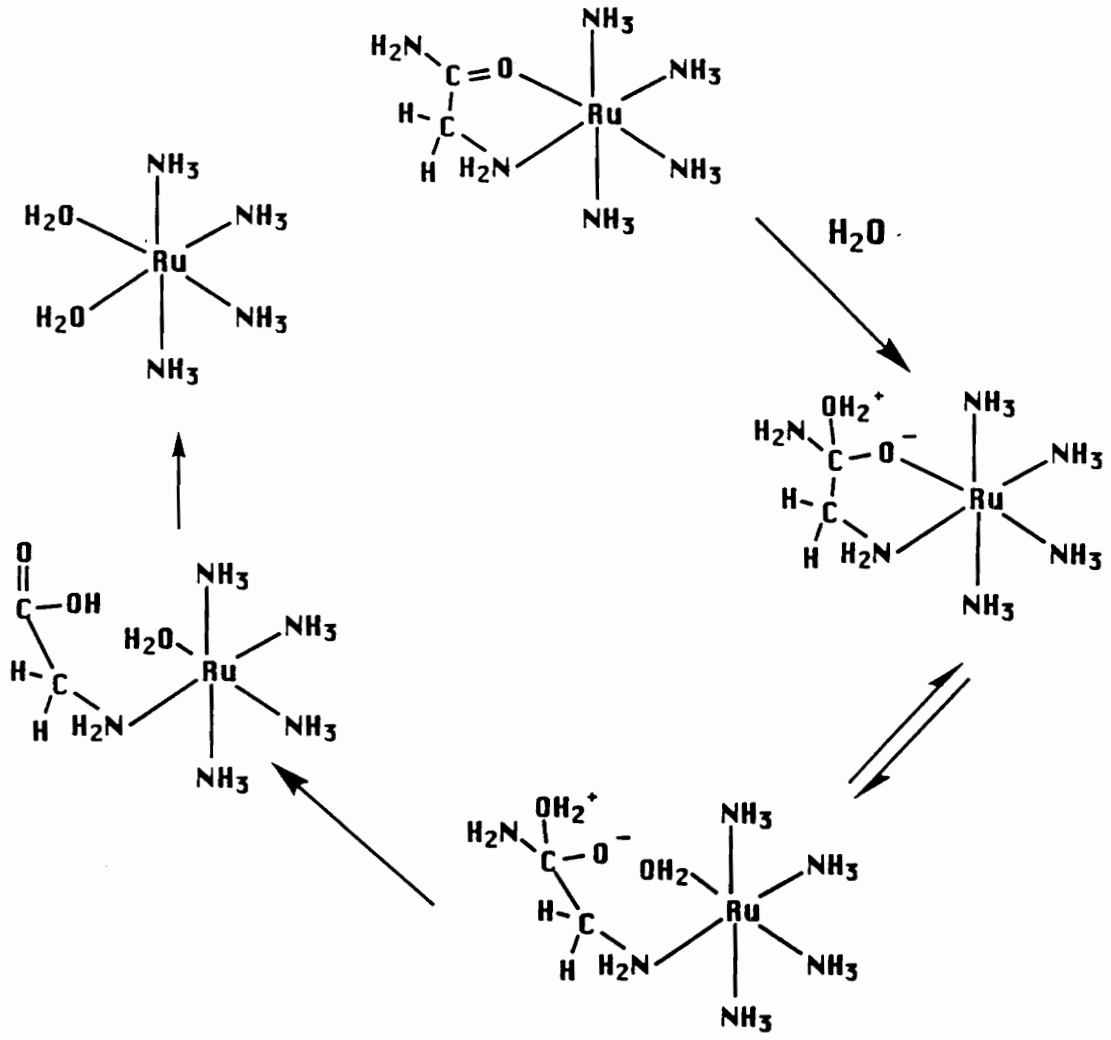


Figure 1.5.16 Hydrolysis of an amino acid promote by the chelation of the amino acid to a ruthenium (III) metal

Pentaammine Ru(III) metalloproteins in which the imidazole group of histidine is bound to the metal have been used to study the role of redox-site separation distance on metalloprotein electron transfer rates. In these well characterized semisynthetic systems, the electron transfer distances are fixed and known. These probes are used to facilitate the kinetic and thermodynamic studies of long-range electron transfer in cytochrome c[33,34],

azurin[35], and myoglobin[36]. Schuger et al have demonstrated that a monodentate mode of binding of l-histidine occurs with Ru(III) at N3 of the imidazole ring (Figure 1.5.17).[55]

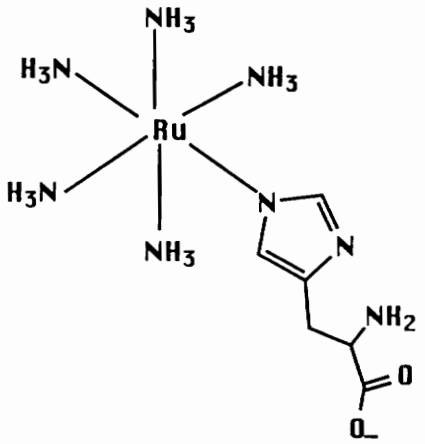


Figure 1.5.17 Binding of l-histidine to Ru(III)

Amino acid complexes of osmium are usually too unstable to allow isolation of solid complexes and therefore very few complexes have been fully characterized. The facile reduction of osmium tetroxide by amino groups has made the preparation of amino acid complexes of osmium difficult, but some amino acid complexes in which the amino groups are protected have been prepared.[56] The unreactive amide bond promotes the reaction of the side chain polar groups with osmium tetroxide. The solutions are too unstable to allow the isolation of solid compounds, but the evidence shows that they contain adducts with side chain nitrogen (lysine) or sulfur (methionine) atoms acting as donors.[56] Hinckley et al reported the synthesis of the first stable and well characterized amino acid complexes of osmium (VI) in 1980.[24] $OsO_2(gly)_2$ was prepared by the reaction of OsO_4 and glycine in water. The two nitrogens are trans to each other and the molecule has a center of symmetry. Meyer, et al. have been able to prepare, isolate, and characterize the osmium (II) complexes $[(C_6H_6)Os(aa)(P^iPr_3)]I$ and $[(C_6H_6)Os(aa)(PMe^tBu_2)]I$ with {N,O} chelation of the amino acid from the reaction of $[C_6H_6Os(PR_3)I_2]$

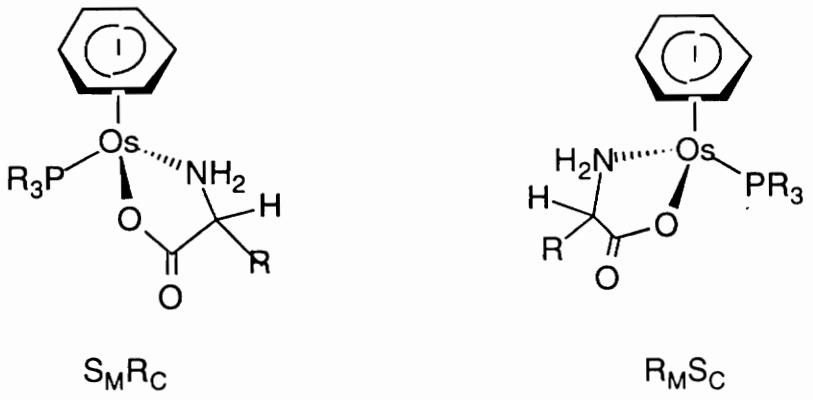


Figure 1.5.18 Enantiomers of $[(C_6H_6)Os(D,L\text{-Phenylala})(PR_3)]I$

and α-aminocarboxylates.[54] NMR spectroscopic and crystal structure data of $[(C_6H_6)Os(L\text{-ala})(PMe^tBu_2)]$ established that the R_MS_C diaestereomer was the exclusive product from the reaction. The similar D/L-phenylalanine was found to preferentially form the S_MR_C and R_MS_C pair of enantiomers (Figure 1.5.18).

1.6.3 Platinum and Palladium Amino Acid Complexes

An intense amount of research has been devoted to the amino acid complexes of palladium and platinum since the discovery of the anti-tumor properties of cisplatin.[23] Reviews of amino acid complexes of palladium and platinum have been written by Pettit and Kozlowski[57] and Pettit and Bezer.[58] Only an overview of this vast area of research will be presented.

Research has mostly focused on sulfur containing amino acid complexes of palladium and platinum due to the preferential binding of these metals by soft donors. Ackerfeldt and Lovgren conducted the earliest work on palladium and amino acids and

demonstrated that Pd(II) ions could be used for the quantitative estimation of cysteine and related thiols in solution.[59]

Amino acids which contain sulfur have been shown to have a strong preference for coordination to palladium through both the S and N centers. McAuliffe, et al.[60] used IR evidence to demonstrate that the amino acid in [$PdCl_2$Methionine] binds to the metal through both the S and N centers to form a six membered ring (Figure 1.5.19). This

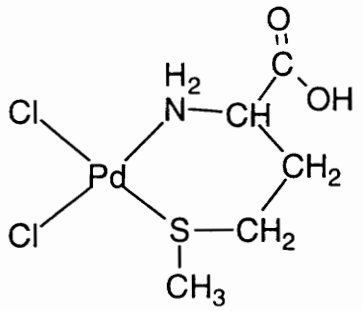


Figure 1.5.19 [$PdCl_2$Methionine]

prediction was confirmed later by crystallographic studies performed by Stephenson, et al.[61] S-methyl-L-cysteine, having one less methylene group in the side chain than methionine, forms stable 5-membered {N,S} chelate rings with both platinum and palladium.[58] The coordination of a thioether sulphur results in the formation of a new chiral center on the sulphur donor atom. In [$PdCl_2$(S-Me-L-cysteine methyl ester)] both asymmetric centers, the the coordinated sulphur and the α-carbon atom, have the same R-configuration[63] while two configurations of [$PdCl_2$(S-Me-L-cysteine)] in which the S atoms have opposite chirality have been determined through crystallographic analysis.[64] In solution both complexes with opposite chiralities of coordinated sulphur atoms are usually observed.[65] The concentration ratio between different diaestereomers has been shown to be markedly influenced by the S-substituent.[66-68] For small substituents such as methyl or

ethyl groups the major diaestereomer (70%) has α-C(R)-S(S) configurations while in the case of S-benzyl derivatives the predominant isomer has α-C(R)-S(R) absolute configurations.

Less research has been done on palladium and platinum complexes that contain amino acids that do not contain sulfur. Bidentate {N,O} coordination of amino acids was first suggested by Wilson and Martin based on the CD spectra of a number of l-amino acid complexes with Pd(II).[69] X-ray crystal structures of numerous amino acid complexes have proven that bidentate coordination through N and O is possible.[57] The bis(aa)-complexes have the potential for either cis or trans isomers. The cis coordination has been observed more frequently than trans (Figure 1.5.20).[57] Monodentate coordination through the

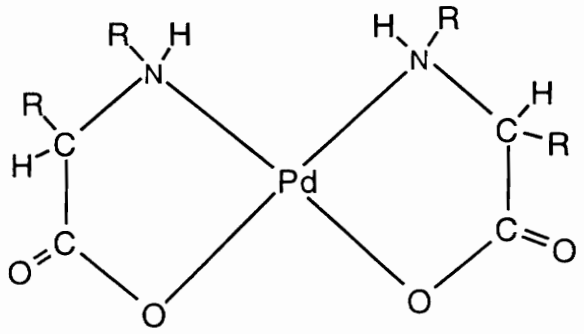


Figure 1.5.20 Cis configuration of bis(amino acid) complexes of Pd(II) and Pt(II)

nitrogen atom of the amino acid is also frequently observed.[57] X- ray structures have shown that the nitrogens of two amino acids bound unidentately can be trans[62] or cis[73] to each other while the carboxyl groups remain protonated.

Appleton has used ^{15}N and ^{31}Pt NMR spectroscopy to show that amino acids such as glycine initially bind unidentately to platinum through the oxygen.[70] The chelate ring will close if the solution is allowed to stand for several hours, heated, or if the pH is

increased. The preference of the hard oxygen atom for the soft platinum metal must be the result of kinetic factors. Longer chain amino acids were found to form kinetically stable products with monodentate O-coordination, but the {N,O} chelation product was found to be thermodynamically favored.

Recently Appleton has conducted similar studies with palladium and has found that the monodentate O-carboxylate species is not only the kinetic product but also exists in equilibrium with the {N,O} chelate species.[71] The greater thermodynamic stability of monodentate O-carboxylate complexes of palladium verses platinum may be attributed to the smaller preference that palladium has for N donors verses O donors compared with platinum. It was once assumed that Pd (II) chemistry are the same as Pt (II) chemistry execpt that the reactions are faster. Appleton's results show that this assumption is not entirely true. Appleton also noted that the stability of the N, O chelate palladium complexes decreased relative to the nonchelate complexes as the ring size increased from 5 to 6 to 7 which mirrors the differences in the kinetics of chelate ring closure with the platinum complexes.[72]

Wilson and Martin[74] have also conducted studies on complexes containing orthionine, $H_2N(CH_2)_3CH(NH_2)COOH$, which has three potential donor sites. Bidentate binding of the amino acid was observed and equal amounts of 5 and 7 membered rings were formed. The formation of the larger seven membered ring is competitive with the smaller five membered ring due to the preference of Pd(II) for nitrogen donors.

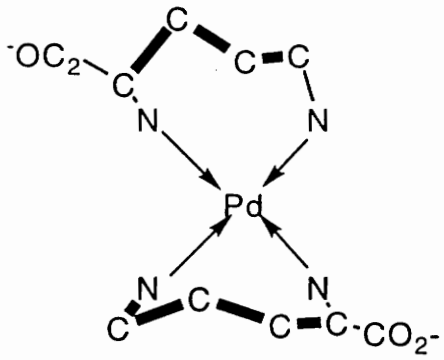


Figure 1.5.21 [Pd(l-orn)$_2$]

Nakayama, et al.[75] solved the crystal structure of [Pd(l-orn)$_2$] and found that the two seven membered rings were arranged around the metal with the chelates in a twisted chair conformation (Figure 1.5.21). The formation of Pt (IV) amino acid complexes has been achieved by reacting $[PtCl_6]^{2-}$ with amino acids, but the reaction is very slow and the products are insoluble.[76] The reaction of $[(Me)_3Pt(H_2O)_3]SO_4$ with sodium amino acidate salts produced octahedral Pt (IV) complexes with a facial arrangement of phosphines.[77] The different forms of this complex consist of $[(Me)_3Pt(aa)]_2$, $[(Me)_3Pt(aa)H_2O]$, and bis-aa and tris-aa complexes. The amino acids bind unidentately through the N donor or bidentately {N,O} (Figure 1.5.22).

A variety of isomeric forms of methionine complexes with Pt (IV) have also been isolated in which chelation is through the nitrogen and sulfur donors.[78,79] These complexes were prepared through the oxidation of $[PtCl_2(Met)]$ with chlorine in the presence of HCl. In all of the isomeric species {N,S} chelation was suggested.

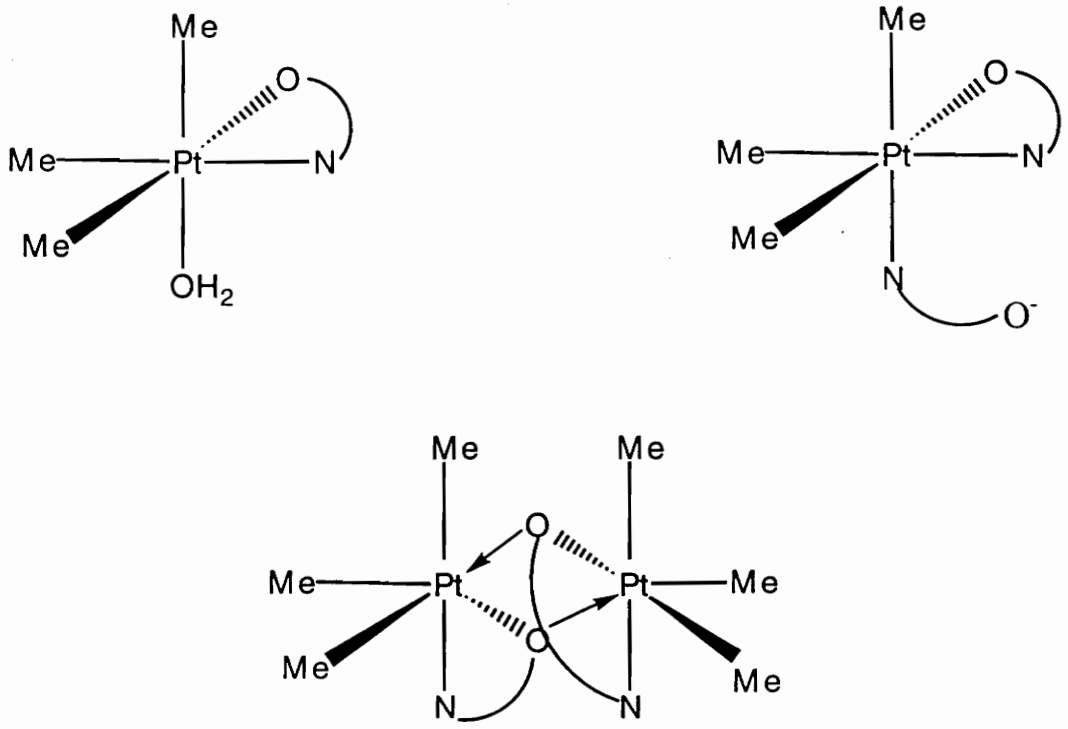


Figure 1.5.22 The facial Pt (IV) amino acid complexes

1.6.4 Rhodium and Iridium Amino Acid Complexes

Although research into palladium and platinum amino acid complexes is quite extensive, relatively little research has been conducted on iridium and rhodium. Electroanalytical studies by Farooq suggest that Rh(III) complexes with amino acids were stable.[41] The binding of N and O donors to form chelates with no involvement of side chain donors is suggested for most amino acid complexes of rhodium and iridium contrasting with the commonly observed sulfur and nitrogen donation of amino acid side chains to palladium and platinum.[57]

The earliest of these studies involve the reaction of amino acids with $RhCl_3$ in H_2O/ethanol solution to form $H[Rh_2(aa)_2Cl]$ complexes with {N,O} chelation. Rajca,

et al.[80] found that these compounds were efficient homogeneous hydrogenation catalysts for some aromatic compounds.

Although most of the research has focused on amino acid complexes of Rh(I), Ir(I), and Ir(III), several amino acid complexes of Rh(II) have also been prepared. Chaterjee demonstrated the possibility for monodentate carboxylate coordination with the $[(NH_3)_5(gly)Rh]^{3+}$ ion (Figure 1.5.23).[81] This complex was prepared by heating $[(NH_3)_5Rh(III)ClO_4]$ in an aqueous solution with a five fold excess of glycine to 90°C for three hours. Crystals of the glycine complex were formed upon reduction of volume of the solution. The stable tetrakis-μ-aceto dirhodium (II) complex, $[Rh_2(O_2CCH_3)_4]$, also reacts with amino acids containing sulfur, cysteine and peniciliamine, to form monomeric square planar Rh(II) complexes that have {S,N} chelation (Figure 1.5.24).[82]

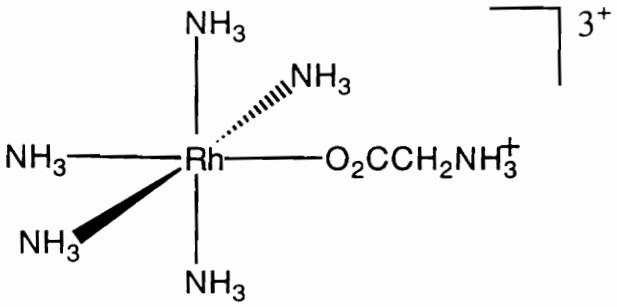


Figure 1.5.23 $[(NH_3)_5(gly)Rh]^{3+}$

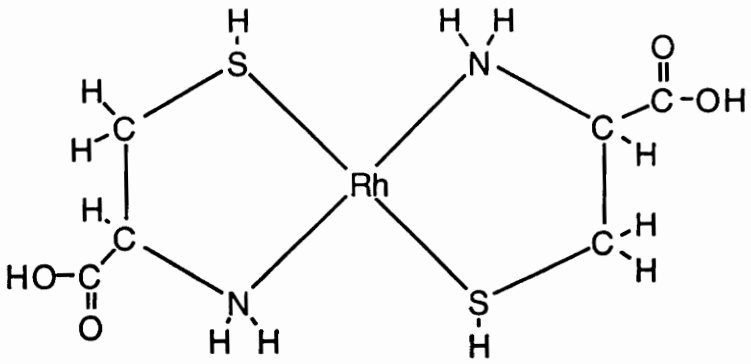


Figure 1.5.24 {S, N} chelation with Rh(II)

Singh, et al.[83] have prepared Rh(I) amino acid complexes stabilized by carbonyl ligands by reacting $[(OC)_2Rh(n\text{-}Cl)_2Rh(CO)_2]$ with an excess of amino acid ion in a benzene solution. The following amino acids were used to prepare these $(aa)Rh(CO)_2$ complexes: glycine, l-alanine, β-alanine, l-leucine, l-histidine, l-tryptophan, l-phenylalanine, and sarcosine. These complexes are dimeric in the solid state (Figure 1.5.25), but in solution they are monomeric and the amino acid chelates to the metal center (Figure 1.5.26). The carbonyl complexes are reactive and the CO ligands can be exchanged with PPh_3 or $AsPh_3$.

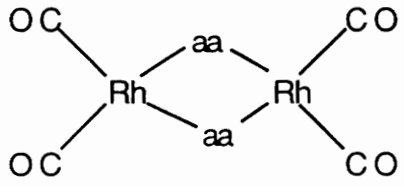


Figure 1.5.25 Dimeric rhodium carbonyl complex

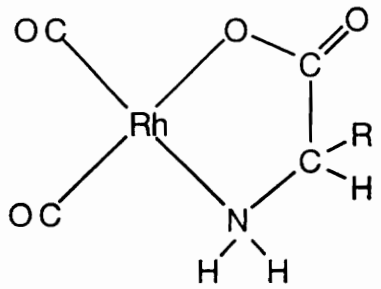
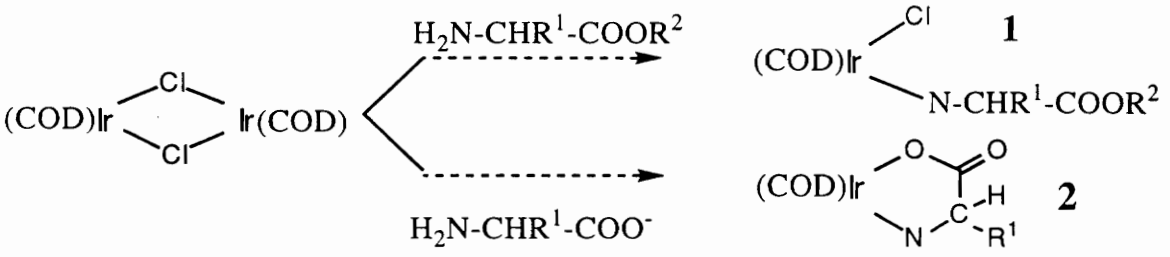


Figure 1.5.26 Monomeric rhodium carbonyl complex

Marko, et al.[84] have also prepared dicarbonylrhodium(I) complexes of eleven amino acids from the reaction of $[AcORh(COD)]_2$ and the appropriate amino acid by

carboxylato ligand exchange followed by treatment with CO. The (aa)Rh(CO)$_2$ complexes had square planar geometry and cis-carbonyl ligands as shown in Figure 1.5.26.

Beck, et al. have conducted one of the first studies on iridium and amino acids.[42] Ir(I) complexes were prepared by reacting [(COD)IrCl]$_2$ with an amino acid anion and the product was shown to be a 5-membered chelate compound. Alternatively, if the amino acid was in its ester form then the amino acid was unidentately bound to iridium through the amine terminus (Figure 1.5.27). Ir(III) complexes, [Cp*Ir(Cl)(aa)], were prepared by reacting [Cp*(Cl)Ir(μ-Cl)$_2$(Cl)Cp*] with the amino acid in a methanol solution at a ratio of two equivalents of amino acid to one equivalent of dimer (Figure 1.5.28). A report by Carmona, et al. of this same reaction with various amino acid ligands entered the literature at about the same time and the two independent studies were in agreement.[43]



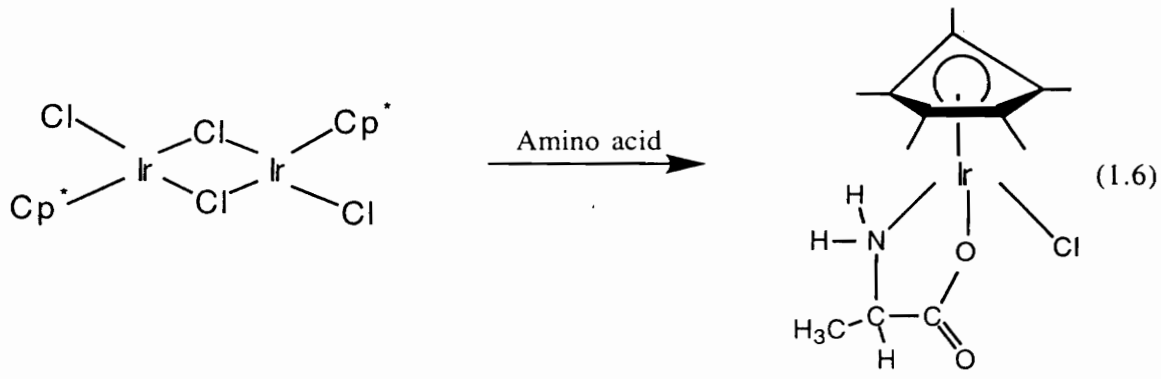
1

R^1	R^2
H	$-CH_2CH_3$
$-CH_3$	$-CH_3$
$-CH(CH_3)_2$	$-CH_3$

2

R^1
$-CH_3$
$-CH_2Ph$
$-CH(CH_3)_2$
$-CH_2CH(CH_3)_2$
$-Ph$

Figure 1.5.27 Formation of Unidentate verses Bidentate amino acid Complexes of Ir (I)



(1.6)

Figure 1.5.28 [Cp*Ir(Cl)(aa)]

Carmona, et al.[85] also reported the synthesis of [(η^5-C_5Me_5)Ir(L-pro)(C≡C-CMe_3)] from the reaction of [(η^5-C_5Me_5)Ir(L-pro)Cl] with t-butylacetylene and triethylamine in methanol. A mixture of diaestereomers was formed but after leaving the less stable diaestereomer (S_{Ir},S_N,S_C) in a methanolic solution for 24 hours the thermodynamically more stable diaestereomer (R_{Ir},S_N,S_C)-[(η^5-C_5Me_5)Ir(L-pro)(C≡C-CMe_3)] was formed exclusively with the Cp* and amino acid side chain substituent trans to one another (Figure 1.5.29).

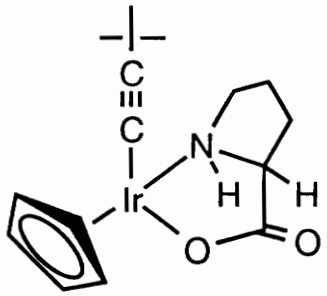


Figure 1.5.29 (R_{Ir},S_N,S_C)-[(η^5-C_5Me_5)Ir(L-pro)(C≡C-CMe_3)]

Beck, et al. have also prepared unusual trinuclear [Cp*Rh(η-L-phenylala)]$_3$[BF_4]$_3$ complexes from the treatment of Cp*Rh(L-phenylala)Cl with $AgBF_4$.[44] In this complex

the amino acid ligand acts as an (N,O)-chelating ligand and as a carboxylate bridging ligand according to the X-ray structural analysis (Figure 1.5.30).

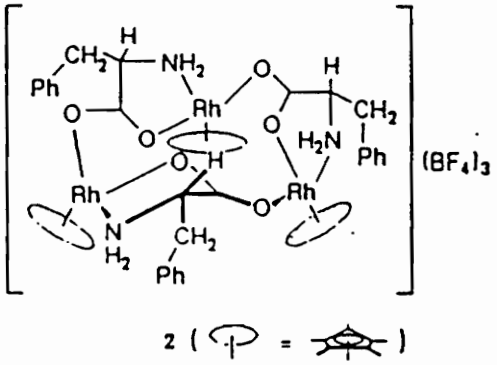


Figure 1.5.30 $[Cp^*Rh(\eta\text{-L-phenylala})]_3[BF_4]_3$

It is interesting to note that in the crystal only diastereomers with the same configuration at the three chiral rhodium atoms ($R_{Rh}R_{Rh}R_{Rh}$ and $S_{Rh}S_{Rh}S_{Rh}$) are formed. These compounds have potential as chiral catalysts since cleavage of the ligand bridges provides a coordination site suitable for substrate binding. In fact, the ester exchange reaction of N,N-dimethylglycine ethylester with the solvent CD_3OD was effectively catalyzed by $[Cp^*Rh(\eta\text{-L-phenylala})]_3[BF_4]_3$ while the monomeric Cp*Rh(L-phenylala)Cl showed very low catalytic activity.

Grotjahn, et al.[47b] have recently prepared one of the only coordinatively unsaturated metal amino acid complexes aside from the $(CO)_2Rh(aa)$ complexes reported by Singh et al and Marko et al. The Cp*Ir-Amino Acid complexes (Figure 1.5.31) were prepared in THF by the reaction of $[Cp^*IrCl(\mu\text{-Cl})]_2$ with one equivalent of amino acid per iridium center and an excess of K_2CO_3. Electron withdrawing groups (tosyl, CO_2CH_2Ph, or $COCH_3$) were used to facilitate the deprotonation at N and thus strongly increase the

binding of N to the metal center. The relatively short Ir-N and Ir-O bonds calculated from crystal structure analysis are consistent with stabilization of unsaturated Ir by π-donation.

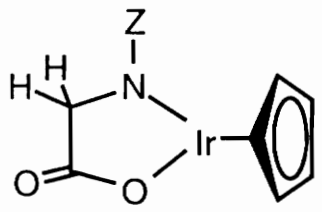


Figure 1.5.31 Coordinatively unsaturated Cp*Ir(aa) complexes

Z = tosyl, CO_2CH_2Ph, or $COCH_3$

The enantiomeric purity was determined by liberating the amino acid ligand with the addition of two moles of HCl and coupling with (S)-α-methyl benzylamine to give diastereomeric amides.[48] The enantiomeric purity of the phenylglycine complex was determined to be >95% based on ratio of >20 to 1 for the diastereomeric amides. A more convienent method of determining enantiomeric purity was acheived by the direct complexation reaction of (S)-α-methyl benzylamine with Cp*Ir(aa) complexes.[48] The alanine complex was determined to have an e.e. of at least 99% while the phenylglycine complex was determined to have an e.e. of at least 96%. This method was devised based on previous complexation reactions of with red Cp*Ir(aa) compounds and CO and phosphines to produce yellow, coordinatively saturated complexes. Undemanding phosphines (PMe_3 and PMe_2Ph) and CO were added to the chiral complexes to give diaestereoselectivity of at least 25 or 50 to 1. NOE experimements established a cis arrangement of amino acid side chains R and Cp* (Figure 1.5.32) and this addition was shown to be the result of both kinetic control (room temperature) and thermodynamic control (after equilibration at 80°C). The kinetic preference for cis addition of the

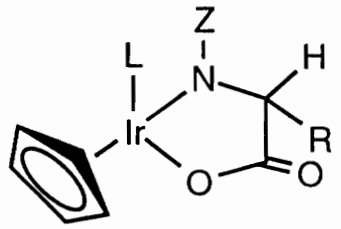


Figure 1.5.32 Cis arrangement of amino acid side chains R and Cp*

unsaturate to the less hindered side of the complex is easily understood. The thermodynamic preference of the cis arrangement is less obvious and was reasoned to be due to the octahedral coordination environment about Ir that makes the effective size of the ligand greater than that of the Cp* ligand which is oriented away from the stereogenic carbon. The steric strain is thus lessened by directing the ligand away from the α-amino acid group. The addition of the achiral primary amine, $PhCH_2NH_2$, to the alanine complex also was shown to take place with the larger metallacycle groups, R and Cp*, cis to each other.

Grotjahn and Hubbard, et al. have also studied the highly stereoselective formation of Cp*IrCl complexes of N,N-dimethylamino acids.[86] Reactions of N-unsubstituted amino acids with $[Cp^*IrCl(\mu\text{-}Cl)]_2$ to give $[(\eta^5\text{-}C_5Me_5)M(aa)Cl]$ were previously shown by Carmona, et al. to have essentially no diaestereomeric excess while proline, an N-monosubstituted amino acid, produced an 84% diastereoselective.[46] The α-side chains of N, N-dimethylamino acids were shown to have a strong preference for cis interaction with the Cp* ligand. This high diaestereoselectivity (> 50:1) was determined to be the result of N,N-dialkyl substitution rather than the bulk of the amino acid side chain. It should be noticed that these results contrast with the thermodynamically favored trans product resulting from the addition of t-butyl acetylene and triethylamine (Figure 1.5.29).

References For Chapter 1:

1. Cotton, F.A.; Wilkinson, G.; *Advanced Inorganic Chemistry,* 5th Ed., John Wiley and Sons, New York, 1988.
2. Stryer, L.; *Biochemistry,* 3rd Ed., W.H. Freeman and Company, New York, 1988.
3. Rosenberg, B.; Van Camp, L.; Trosko, J.E.; Mansour, V.H. *Nature* **(1969)** 222, 385
4. Wallach, D.F.; *J. Mol. Med.* **(1976)** 1, 97
5. Williams, D.R.; *Chem. Rev.* **(1972)** 72, 203.
6. James, B.R.; Ochiai, E.; Rempel, G.L. *Inorg. Nucl. Chem. Lett.* **(1971)** 7, 781.
7. Mestroni, G.; Zassinovich, G., Alessio, E. *Bontempi Inorg. Chim. Acta* **(1987)** 137, 63.
8. Sheldrick, W.S.; Heeb, S. *Inorganica Chimica Acta* **(1990)** 168, 93.
9. Roy, C.P. Ph. D. thesis, **1993**, VPI&SU.
10. Wiessermal, K.; Arpe, H. *J. Chim. Org. Ind.* **(1981)** 210.
11. Larock, R. C.; Oertle, K.; Beatty, K. M. *J. Am. Chem. Soc.* **(1980)** 102, 1966.
12. Volhardt, K.P. *Organic Chemistry*, W. H. Freeman and Company, New York, 1987.
13. Bedoukian, P.Z. *J. Am. Chem. Soc.* **(1944)** 66, 1325.
14. Kitching, W.; Rapport, Z.; Winstein, S.; Young, W.G.; *J. Am. Chem. Soc.* **(1966)** 88, 2054.
15. Bach, R. D.; Woodward, R. A.; Anderson, T. J.; Glick, M.D. *J. Org. Chem.*, **(1982)** 47, 3707.
16. Shvo, Y. Rotem, M. *Organometal.* **(1983)** 2, 1689.
17. Shvo, Y.; Rotem, M.; Goldberg, I.; Shmueli, U. *Organomet* . **(1984)** 3, 1758 .
18. Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Wantabe, Y. *Tetrahedron Lett.* **(1986)** 27, 2125 .

19. Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Wantabe, Y. *J. Org. Chem.* **(1987)** 52, 2230.

20. Dixneuf, P.H.; Ruppin, C. *Tetrahedron Lett.* **(1986)** 27, 6323.

21. Dixneuf, P.H.; Lecolier, S.; Ruppin, C. *Tetrahedron Lett.* **(1988)** 29, 5365.

22. Ladipo, Fola Ph.D. thesis, July **1991**

23. Yamamoto, Akio; Yamamoto, Takakazu *Organometallics* **(1985)** 1130.

24. Atwood, J.; Bernard, K. *Organometallics* **(1987)** 6, 1134.

25. Patais, S. *The Chemistry of the Amino Group*, Interscience Publishing Co., New York, New York, 1968.

26. Barton, D. Ollis, W.D.*Comprehensive Organic Chemistry*, Interscience Publishing Co., New York, New York, 1982.

27. Stull, D. R.; Westrum, E. F.; Sinke, G. C. *The Chemical Thermaodynamics of Organic Compounds* Wiley; New York, New York, 1969, 632.

28. Trogler, W.C.; Cowan, R.L. *Organometallics* **(1987)** 6, 2451.

29. Casalnnovo, A.L.; Calabrese, J.C.; Mistein, D. *J. Am. Chem. Soc.* **(1989)** 11, 4108.

30. Pasini, Alessandro; Columbo, Anna; Di Gioia, Rita *Inorganica Chimica Acta*; **(1986)** 125, L1-L3.

31. Wenzel, M.; Asindraza, P.; Schachschneider, G. *J. Labelled Compd. Radiopharm.*, **(1983)** 20, 1061

32. Soine, A.H.; Guyer, C.E.; Knapp, F.F. *Journal of Medicinal Chemistry*, **(1984)** 27, 803.

33. Nocera, D.G.; Winkler, J.R.; Yocum, K.M.; Bordignon, E.; Gray, H.B. *Journal of the American Chemical Society* **(1984)** 106, 5145.

34. Isied, S.S.; Kuehn, C.; Worosila, G.J. *Journal of the American Chemical Society* **(1984)** 106, 1722.

35. Gray, H.B.; *Chemical Society Reviews* **(1986)** 106, 17.

36.37. Yeh, A.; Taube, H.; *J. Am. Chem. Soc.* **(1980)** 102, 4725.

38. Diamond, S.E.; Taube, H. *J. Am. Chem. Soc.* **(1975)** 97, 5921.

39. (a) Ilian, Y.; Taube, H *Inorg. Chem.* **(1983)** 22, 1655 (b) Ilan, Y.; Taube, H. *Inorg. Chem.* **(1983)** 22, 1655 (c) Ilan, Y.; Kapon, M. *Inorg. Chem.* **(1986)** 25, 2350.

40. Kfir, Ariela; Ilan, Yigal *Inorg. Chem.* **(1987)** 26, 2872 .

41. Farooq, O.; Ahmad, N. *J.Electroanal. Chem.*, **(1974)** 53, 2037.

42. Beck, W.; Kramer, L; Polborn, K; Wanjek, H.; Zahn, I. *Chem. Ber.* **(1990)** 123, 767 .

43. Carmona, D.; Oro, L.A.; Mendoza, A.; Lahoz, F.J. *Journal of Organometallic Chemistry* **(1990)** 396, C17-C21.

44. Beck, W.; Kramer, R.; Polborn, K.; Robl, C. *Inorganica Chimica Acta* **(1992)** 198-200, 415.

45. Beck, W.; Severin, K.; Sunkel, K. *Chem. Ber.* **(1994)** 127, 615

46. Carmona, D.; Lahoz, F. J.; Atencio, R.; Oro, L.A. *Tetrahedron: Asymmetry* **(1993)** Vol. 4, No. 7, 1425.

47. (a) Grotjahn, D.B.; Groy, T.L. *J. Am. Chem. Soc.* **(1994)** 116, 6969. (b) Grotjahn, D.B.; Groy, T.L. *Organometallics* **(1995)** 14, 3669.

48. Grotjahn, D.B. *Tetrahedron: Asymmetry* **(1995)** Vol. 6, No. 3, 745.

49. Dersnah, D.F.; Baird, M.C. *Journal of Organometallic Chemistry* **(1977)** 127, C55.

50. Sheldrick, W. S.; Gleichmann, A. *Journal of Organometallic Chemistry* **(1994)** 470, 183.

51. Sheldrick, W.S.; Brandt, K. *Inorganica Chimica Acta* **(1994)** 217, 51.

52. Sheldrick, S.; Exner, R. Inrorganica Chimica Acta **(1989)** 166, 213.

53. Saito, Y.; Takita, K.; Inoue, N.; Shinoda, S. *Inorg. Chem. Acta.* **(1982)** 65, L21.

54. Meyer, U.; Werner, H.; Daniel, T.; Nurnberg, O.; Knaup, W. *Journal of Organometallic Chemistry* **(1993)** 445, 229.

55. Schuger, H.J.; Krogh-Jespersen, K.; Westbrook, J.D.; Potenza, J.A. *Journal of the American Chemical Society* **(1987)** 109, 7025.

56. Lim, M. C. *Inorg. Chem.* **(1981)** 20, 1377.

57. Kozlowski, Henryk; Pettit, Leslie D., *Stud. Inorg. Chem.* **(1991)** 11,530.

58. Petitt, L. D.; Bezer, M. *Coord. Chem Rev.* **(1985)** 61, 97.

59. Ackerfeldt, S.; Lovgren, G.; *Anal. Biochem.* **(1964)** 8, 233.

60. McAullife, C. A.; *J. Chem. Soc. A* **(1967)** 641.

61. Stephenson, N.C.; McConnell, J.T.; Warren, Z.; *Inorg. Nucl.Chem. Lett.* **(1967)** 5, 553.

62. I.A. Baidina and S.V. Borisov, *Zh. Strukt. Khim.* **(1981)** 22,183.

63. M. Kubiac, A. Allian, B. Jezowska-Trzebiatowska, T. Glowiak and H. Kozlowski, *Acta Crystallogr.* **(1980)** B36, 2246.

64. L. P. Battaglia, A.B. Corradi, C. G. Palmeri, N. Nardelli and E. V. Tani, *Acta Crystallogr.* **(1973)** B29, 762.

65. B. Decock-Le Reverend and H. Kozlowski, *J. Chim. Phys.* **(1985)** 82, 883.

66. H. Kozlowski, Z. Siatecki and B. Jezowska-Trzebiatowska, *Inorg. Chim. Acta* **(1980)** 46, L25.

67. B. Decock-Le Reverend, C. Loucheux, T. Kowalick and H. Kozlowski, *Inorg. Chim. Acta.* **(1982)** 66, 205.

68. H. Kozlowski, B. Decock-Le Reverend, J. L. Delaruelle, C. Loucheux, and B. Ancian , *Inorg. Chim. Acta.* **(1983)** 78, 31.

69. E. W. Wilson and R. B. Martin, *Inorg. Chem.* **(1970)** 9, 528, and **(1971)** 10, 1197.

70. Appleton, T.G.; Hall, J.R.; Ralph, S.F. *Inorganic Chemistry* **(1985)** 24, 673.

71. Appleton, T.G.; Bailey, A.J., Bedgood, D.R., Hall, J.R. *Inorganic Chemistry* **(1994)** 33, 217.

72. Appleton, T.G.; Hall, J.R.; Ralph, S.F. *Aust. J. Chem.* **(1986)** 39, 1347.

73. I. A. Baidina, N.V. Podberezskaya and S.V. Borisov, *Zh. Strukt. Khim* **(1980)** 21, 185.

74. Wilson, E.W.; Martin, R. B., *Inorg. Chem.* **(1971)** 10, 1197.

75. Nakayama, Y.; Matsuko, K.; Ooi, Kuroya, H., *J. Chem. Soc. Chem. Comm.* **(1970)** 170.

76. Volstein, L.; *Koord. Khim.*, 1, **(1975)** 595.

77. Appleton, T. G.; Hall, J. R.; Lampart, L., *Inorg. Chim. Acta* **(1978)** 29.

78. Mogolevina, M. F.et al, *Koord. Khim.* **(1979)** 5,1866.

79. Mogolevina, M. F. et al, *Koord. Khim.* **(1985)** 11, 1381.

80. Rajca, I., *Pol. J. Chem.* **(1981)** 55, 775.

81. Chatterejee, C.; Bali, *A. Bull. Chem. Soc. Jpn.* **(1987)** 60, 1210.

82. Pneumatkakis, G.; Psaroulis, P. Inorg. Chim. Acta **(1980)** 46, 97.

83. Dowerah, P.; Sing, M. *J. Chem. Res.* **(1979)** 13, 38.

84. Marko, L.; Nagy-Magos, Z.; Kvintovics, P. *Transition Metal Chemistry*, **(1980)** 5, 186.

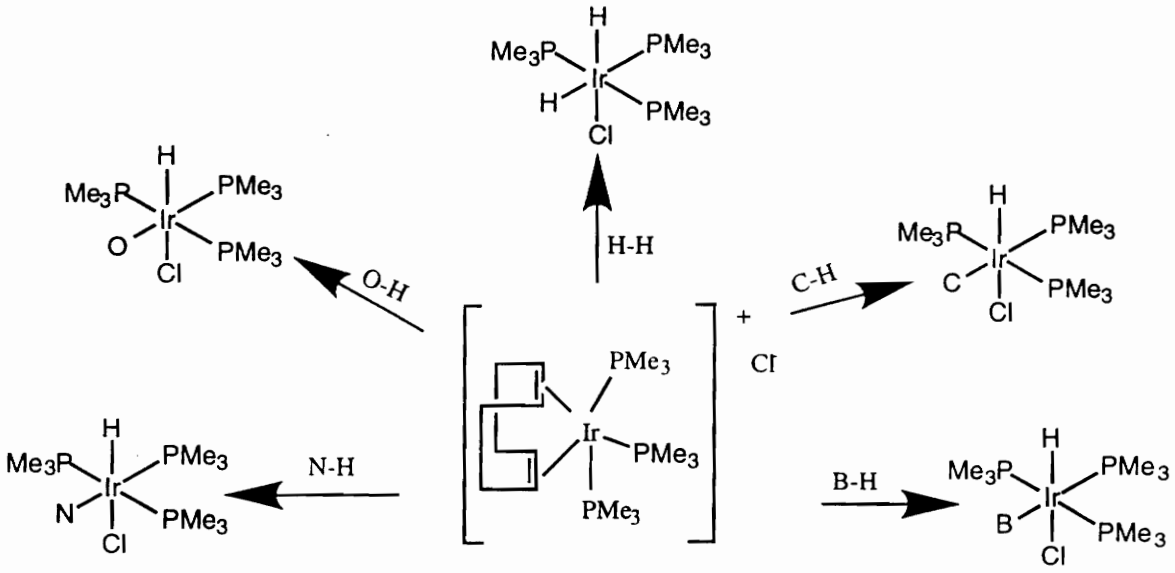
85. Carmona, D.; Oro, L.A.; Fernando, J. L., Reinaldo, A.*Tetrahedron:Asymmetry*, **(1993)** Vol. 4, No. 7, 1425.

86. Hubbard, J.L.; Grotjahn, D.B. *Organometallics* 13, **(1996)** 15, 1230.

Chapter 2. The Meridional and Facial Isomers of [HIr(aa)(PMe3)3]Cl

2.1 Introduction

Merola et al have demonstrated that C-H[1], B-H[2], N-H[3], O-H[4], and H-H[5] bonds could be oxidatively added to the iridium center, [Ir(COD)(PMe3)3]Cl, to form hydridoiridium complexes (Scheme 2.1.1).

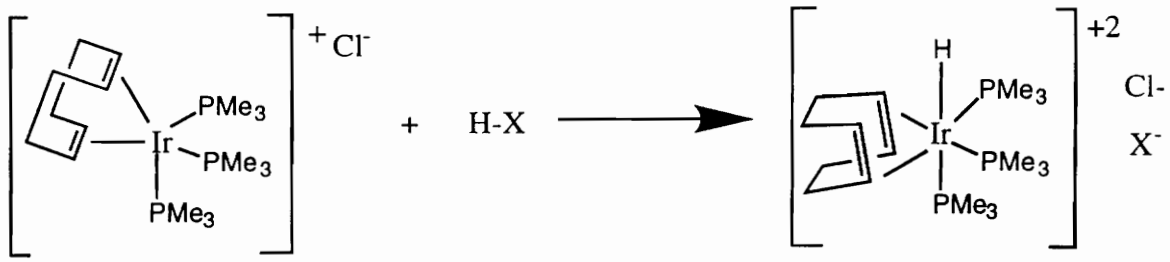


Scheme 2.1.1 C-H, B-H, O-H, N-H, and H-H additions to [Ir(COD)(PMe3)3]Cl

Folami Ladipo demonstrated that pyrrole and aniline could be oxidatively added to [Ir(COD)(PMe3)3]Cl to form amino-hydrido complexes.[6] The protons on the nitrogen are made more acidic by the electron withdrawing properties of the phenyl ring in aniline and the heterocyclic nitrogen in pyrrole. Ladipo also demostrated that carboxylic acids and phenols readily undergo oxidative addition reactions while decomposition products were observed from the reaction of primary, secondary, and tertiary alcohols with the iridium(I) center.[4b] Although an initial oxidative addition probably occurred with the aliphatic

alcohols, the product quickly rearranged to give the β-hydride elimination product for alcohols having hydrogens on the β carbon and the dehydration product in the case of *tert* - butyl alcohol. Robert Clark demonstrated that carboxylic amides, in close analogy to carboxylic acids, could also be activated towards oxidative addition.[7]

The acidity of the O-H and N-H protons appears to play an important role in the oxidative addition reaction. Salycillic acid reacts via addition of the carboxylic acid O-H bond rather than the the phenolic O-H bond.[4b] The protonation of the Ir(I) center may well be the first step in the oxidative addition reaction. Support for this comes from the isolation of the protonated dication resulting from the reaction of $[Ir(COD)(PMe_3)_3]Cl$ and strong acids (Equation 2.1.1).[8]



X= Cl, $CF_3C(O)O$, $PhC(O)O$

Equation 2.1.1 Protonation of $[Ir(COD)(PMe_3)_3]Cl$

The relative acidity of amino acids has likewise been exploited for oxidative addition reactions. Very few oxidative addition reactions involving amino acids have been reported in the literature. In 1994, Beck et al[9] reported the oxidative addition reaction of α-amino acids to $Ru(CO)_3(PPh_3)_2$ to form complexes of the type $RuH(CO)(aa)(PPh_3)_2$. Roy[10] reported the first hydrido platinum metal complex of an amino acid in 1993. Roy reported mer-$[HIr(aa)(PMe_3)_3]Cl$ as the exclusive isomer from the oxidative addition of

monosubstituted amino acids to [Ir(COD)(PMe_3)$_3$]Cl. The crystal structure of this complex was solved and the single isomer formed from the reaction was shown to be the meridional isomer with the hydride trans to the nitrogen of the amino acid (Figure 2.1.1).

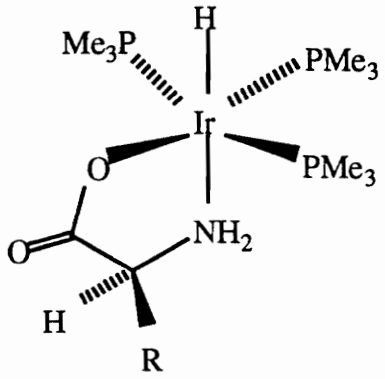
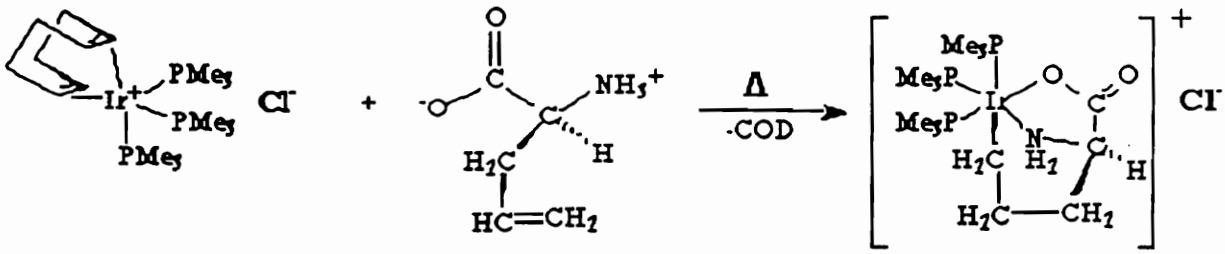


Figure 2.1.1 Exclusive isomer of the oxidative addition of amino acids to [(COD)(PMe_3)$_3$Ir]Cl reported by Roy

Nearly all of the naturally occuring amino acids were studied and all produced the product shown in figure 2.1.1 except for the sulfur containing amino acids methionine and cysteine. These two amino acids formed mixtures of products presumably from the binding of the sulfur atom to the metal.

Roy was unable to observe any intermolecular reactions of monsubstituted amino acid complexes with unsaturates. However, the intramolecular insertion of the tethered



Equation 2.1.2 Intramolecular insertion of the tethered olefin of 2-amino-4-pentenoic acid

olefin of 2-amino-4-pentenoic acid was observed (Figure 2.1.2). N-methyl substituted amino acid complexes were also synthesized in an attempt to weaken the Ir-N bond, but the complexes were still found to be unreactive towards unsaturates. Amino acid complexes were observed to exchange with free amino acids. When the amino acid complexes were heated with excess free amino acid at 100°C an equilibrium mixture of the original amino acid complex and the substitution product was observed. The product containing the least demanding amino acid (smaller side chain) was always found to be the major product. This lability of the amino acid combined with the observed intramolecular insertion of the tethered olefin of 2-amino-4-pentenoic acid demonstrate that these complexes and similar complexes may be able to produce esters and enol esters of amino acids through the desired oxidative addition/ reductive elimination method.

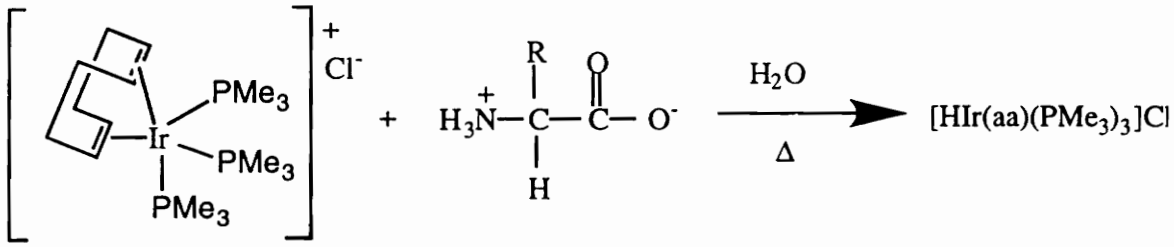
The biological activity of these complexes was also investigated. [Ir(L-Phenylala)(PMe_3)$_3$]Cl was found to be moderately active against HIV while a similar complex [Ir(L-tyrosine)(PMe_3)$_3$]Cl was found to be completely inactive. Tyrosine differs from phenylalanine only by the hydrophylic hydroxy group present on the phenyl ring. Either the hydrophilic property or the electron withdrawing property of the hydroxy substituent appears to limit the activity against HIV infected cells. This discovery prompted the synthesis of complexes of amino acids with hydrophobic side chains similar to phenylalanine. Methylphenylalanine, homophenylalanine, diphenylglycine, and phenylglycine were chosen for this investigation.

2.2 Results and Discussion

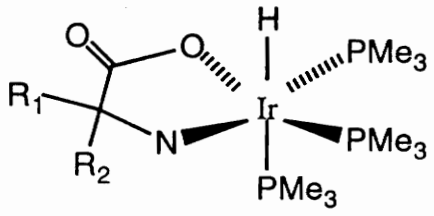
The general reaction of the oxidative addition of amino acids to [Ir(COD)(PMe_3)$_3$]Cl is shown in Equation 2.2.1 and the two diastereomers of the facial complex and the two geometric isomers of the meridional complex are shown in Figure 2.2.1. The facial isomer may be formed with R_1 pointed towards the hydride or R_2

pointed towards the hydride depending on how the amino acid adds to the complex. The meridional isomer may be formed with the hydride trans to the nitrogen or the hydride trans to the oxygen. Roy only observed one quartet in the hydride region of the proton NMR spectrum around -20 ppm corresponding to the hydride being split by the three meridional phosphines. The crystal structure of this product was solved and established to be the meridional isomer with the hydride trans to nitrogen.

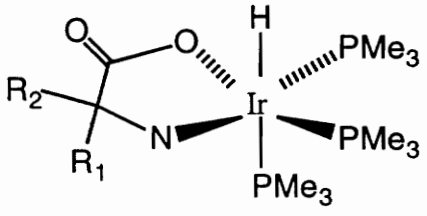
Contrasting results were found for phenylglycine, methylphenylalanine, homophenylalanine, and diphenylglycine. Amino acid complexes of these four amino acids produced a mixture of both the meridional and facial isomers. Roy's synthesis of the valine and glycine complexes was repeated and a mixture of the meridional and facial isomers was also determined to be present with these two complexes. The fact that the facial isomer was not observed by Roy may have to do with differences in reaction time and temperature. It should be noted that deuterium exchange with the hydride occurs within hours for the meridional complex while the facial isomer does not appear to exchange with deuterium when these complexes are heated in D_2O.



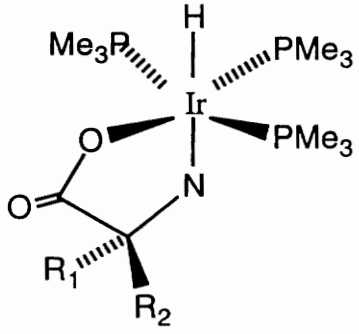
Equation 2.2.1 Oxidative addition of amino acids to $[HIr(aa)(PMe_3)_3]Cl$



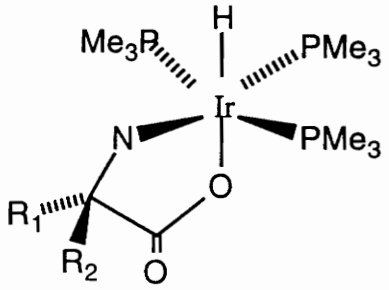
fac (I)



fac (II)



mer (I)



mer (II)

Figure 2.2.1 The two diastereomers of the fac-[HIr(aa)(PMe_3)$_3$]Cl and the two geometrical isomers of mer-[HIr(aa)(PMe_3)$_3$]Cl

The identification of the isomers was easily made using the hydride region of the ^{1}H NMR spectrum. The quartet observed around -20 ppm agrees with the hydride resonances established for the meridional isomer observed by Roy with the hydride positioned trans to the nitrogen of the amino acid. Resonances corresponding to the facial isomer appeared around -10 ppm as two overlapping doublet of triplets split in such away as to resemble a doublet of quartets. These resonances correspond to the splitting of the hydride by the trans phosphine and then again by the two cis phosphines. If R_1 and R_2 are equivalent only one possible facial isomer is formed and a clear doublet of triplets is

observed (Figure 2.2.2 (a)). Figure 2.2. (b) shows the overlap of the two hydride resonances correponding to the two facial diaestereomers of the homophenylalanine complex. The resonances of the two facial diastereomers of the methylphenylalanine complex are separated enough to distinctly see the two separate doublets of triplets (Figure 2.2.2 (c)).

The resonance arising from protons on the trimethylphosphine of the facial isomer are split into a doublet by the phosphine attached to the methyl groups. Three doublets should be observed correlating to three inequivalent phosphines. The resonance arising from the protons on the cis trimethylphosphine of the meridional isomer are split into a doublet by the phosphine directly attached to the methyl group, while resonances arising from the protons on the trans phosphines are split not only by the phosphine directly attached to the methyl group but also by the trans phosphine. This splitting of the resonances arising from the methyl protons by the trans phosphine results in what is known as a virtual triplet. Since a mixture of both facial and meridional isomers is formed, the phosphine methyl proton region consists of overlapping peaks that do not provide a means of measuring the relative amounts of each isomer in solution. The hydride region of the proton NMR spectrum is the best way to measure the relative amounts of facial and meridional isomers because the resonances are widely separated (-10 and -20 ppm respectively) and therefore do not overlap.

The meridional and facial products were the major isomers, but other minor products were also detected in the hydride region of the proton NMR spectra. A doublet of quartets was detected in the -10 ppm region which could correspond to the hydride resonance being split by a trans phosphine and again by three cis phosphines. This arrangement corresponds to a tetrakistrimethylphosphine complex as shown in Figure 2.2.3. The remaining ligand, labelled X in Figure 2.2.3, could be water, chloride, or the

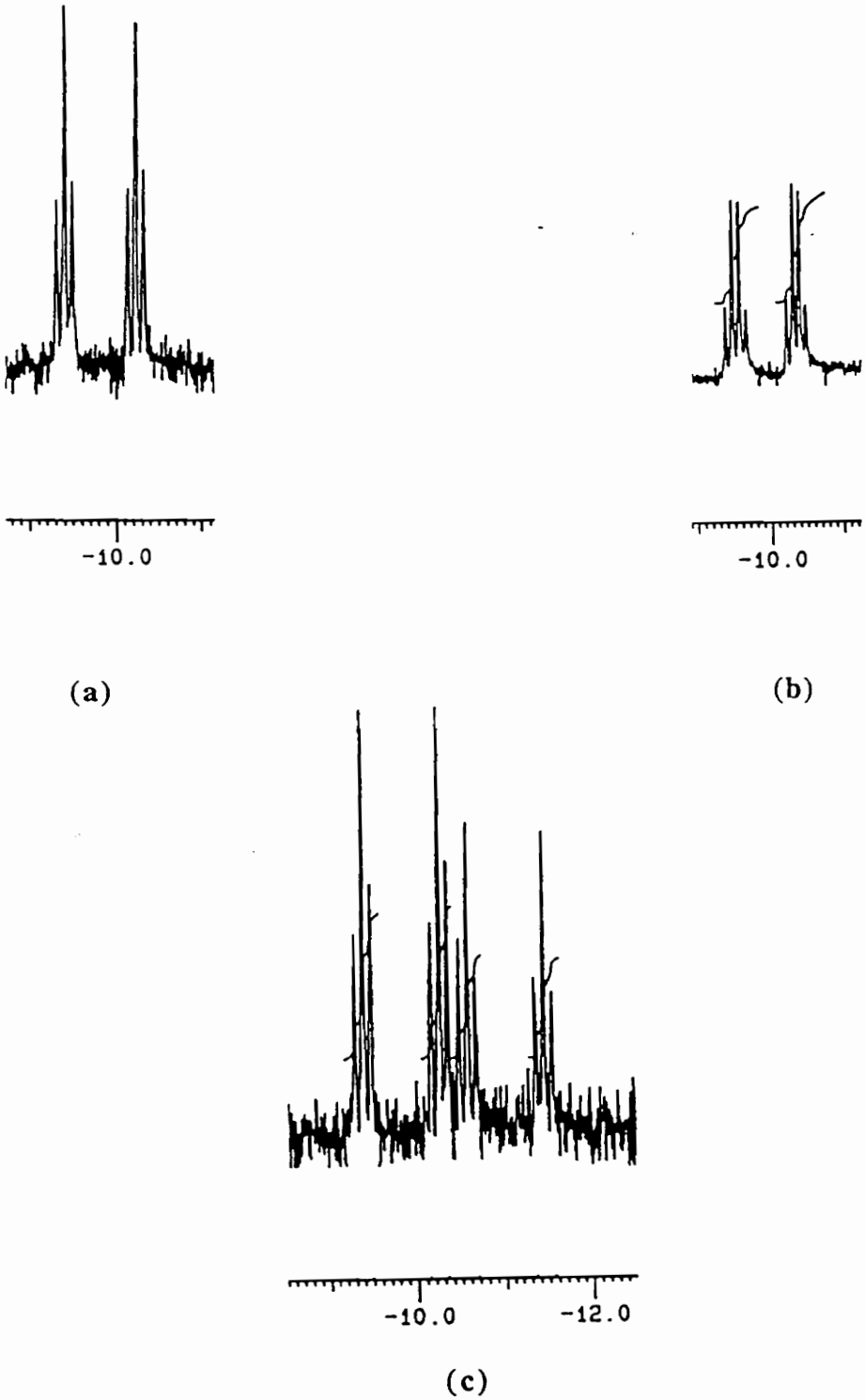
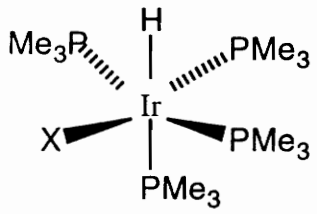


Figure 2.2.2 The Hydride region of the ^1H NMR spectrum of fac-[HIr(aa)$(PMe_3)_3$]Cl.

(a) aa = diphenylgly, (b) aa = homophenylala (c) methylphenylala



X = Cl, OH_2, -$OC(O)CH_2NH_2$, -$NH_2CH_2(O)CO$

Figure 2.2.3 tetrakistrimethylphosphine complex

unidentately bound amino acid. Two triplets were also observed around -23 ppm and -24 ppm consistent with complexes containing only two phosphines. Hydride resonances appearing near -24 ppm are known to correspond to hydrides trans to chloride.[11] The addition of excess phosphine to the solution caused the peak near -24 ppm to disappear which is consistent with the chloride ligand being displaced by the phosphine ligand to form the trisphosphine complex. The complex shown in Figure 2.2.4 is consistent with these observations.

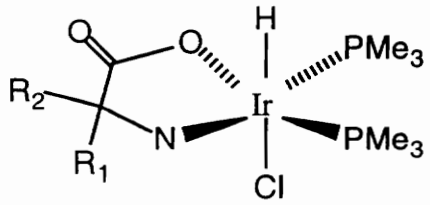


Figure 2.2.4 Bisphosphine complex tenatatively identified as the isomer corresponding to the hydride resonance at -24 ppm

All other peaks were present after the addition of excess phosphine, which may indicate that the chloride is more tightly bound in the other complexes. At this point it is impossible

to conclusively identify these minor isomers, but it is important to note that phosphine substitution was possible for one isomer and may indicate that this complex contains a labile ligand capable of undergoing reactions with unsaturates.

The product distributions after refluxing the appropriate amino acid with $[Ir(COD)(PMe_3)_3]Cl$ in water are shown in Table 2.2.1. A few general conclusions may be drawn from these data. First, monosubstituted amino acids appear to form predominantly the meridional isomer while the disubstituted amino acids appear to form predominantly the facial isomer. For instance, the product mixture of the glycine complex contains a 91% abundance of the meridional isomer while the product mixture of the methylphenylalanine complex contains only a 5% abundance of the meridional isomer . This difference was attributed to the fact that both R_1 and R_2 are forced into close proximity with the phosphines in the meridional conformation. If both of these R groups are bulky (not H) then enough steric strain is created to promote the dissociation of a ligand and

Table 2.2.1 Isomer Distributions of $[HIr(aa)(PMe_3)_3]Cl$

(ϕ= phenyl)

Amino Acid	R_1	R_2	%mer	%fac	%other
Homophenylala	H	$CH_2CH_2\phi$	86	14	0
Phenylala	H	$CH_2\phi$	86	14	0
Phenylgly*	H	ϕ	76	20	4
Methylphenylala	CH_3	$CH_2\phi$	5	93	2
Diphenylgly*	ϕ	ϕ	3	73	24
Valine	H	$CH(CH_3)_2$	72	18	10
Glycine	H	H	91	4	5

* Isomer distributions were calculated from the average of several reactions

subsequent conversion to the facial isomer. The monosubstituted amino acid complexes require more energy to effect this conversion since less steric strain is present in this isomer.

The synthesis of the phenylglycine complex was repeated several times and the product distributions for each reaction are listed in Table 2.2.2. The percentage of the meridional isomer varied from 73% to 82%. Different product distributions, 82 % and 75% meridional, were obtained even when both reactions were refluxed for the same amount of time (22 hours). The length of time that the reaction was refluxed therefore did not appear to be the reason for the different product distributions. However, the temperature was not carefully controlled, and although the reaction time is probably significant, it is difficult to determine the effect of the temperature verses the effect of the reaction time on the product distributions.

The synthesis of the diphenylglycine complex was also repeated and in one case a small amount of the meridional (7%) was formed and in the other case the meridional isomer was not detected to be in the product mixture. This difference in product distributions is probably also due to a difference in the reaction time and temperature.

Table 2.2.2 Reproducibility of the Isomer Distributions of [Ir(Phenylgly)(PMe_3)$_3$]Cl

Amino Acid	% fac	% mer	% other	Reflux time(hrs)
L-Phenylglycine(31)	25	75	0	23
L-Phenylglycine(167)	17	73	10	20
R-Phenylgycine(265)	12	82	6	22
D-Phenylglycine(35)	25	75	0	22

Table 2.2.3 Reproducibility of the Isomer Distributions for [Ir(Diphenylgly)(PMe_3)$_3$]Cl

Amino Acid	% fac	% mer	% other	Reflux time(hrs)
Diphenylgly(129)	67	7	26	?
Diphenylgly(267)	78	0	22	22

The product distributions of the meridional and facial isomers were thought to depend on the steric factors created by the R groups of the amino acids. The two R groups of disubstituted amino acids appeared to cause a relatively facile conversion of these complexes to the facial isomer through the dissociation of a ligand. It was therefore predicted that the favored diastereomer of the facial isomer would also be the one in which the larger R group is oriented away from the sterically demanding phophine. It was not possible to measure the relative amounts of these two diastereomers for most of the complexes since the corresponding hydride resonances nearly always overlapped. The relative amounts of the two diastereomers could only be measured for complexes of methylphenylalanine and phenylalanine. The methylphenylalanine complex contained a 56% (-9.6 ppm) and 44% (-10.7 ppm) mixure while the phenylalanine complex contained a 54% (-9.6 ppm) and 46% (-10.4 ppm) mixture of the two facial isomers. It was expected that the benzyl group would be oriented away from the phosphine for both the methylphenylalanine and the phenylalanine complexes, but the size of the R groups surprisingly did not appear to influence the product distributions of these two isomers. This finding contradicts with the belief that the steric interactions of the R groups and the phosphines promotes dissociation of a ligand for disubstituted amino acid complexes and increases the conversion rate of the meridional isomer to the facial isomer. Alternatively,

the slower conversion of monosubstituted amino acids to the facial isomer may be attributed to the deprotonation of the relatively acidic proton on these α-amino acids.

Complexes of valine, homophenylalanine, and phenylglycine were heated at 100°C for several days in a pressure tube and the mostly meridional mixture was found to convert to a mostly facial mixture (Table 2.2.4). In fact, the facial isomer was determined to be the the exclusive product after heating the phenylglycine complex for 12 days. The mostly facial mixture (85%) of the complex of methylphenylalanine remained a mostly facial (95%) mixture after heating for 6 days at 100°C. Complete conversion of the meridional isomer and some conversion of the other isomers were observed for this methylphenylalanine complex. The facial isomer is therefore the thermodynamic product for both monosubstituted and disubstituted amino acid complexes.

Table 2.2.4 Effect of Heating on Isomer Distributions (H_2O, 100°C)

(I) Valine

Hours	% mer	% fac	% other
0	72	18	10
74	55.3	30.1	14.58
174	32.9	67.1	0

(II) Homophenylalanine

Hours	% mer	% fac	% other
0	85	15	0
74	56.1	41.2	2.69
174	27.8	72.2	0

Table 2.2.4 Effect of Heating on Isomer Distributions (H_2O, 100°C)

(III) Phenylglycine

Hours	% mer	% fac	% other
0	81.7	12.4	5.86
74	27.5	72.5	0
174	10.3	89.7	0
298	0	100	0

(IV) Methylphenylalanine

Hours	% mer	%fac	% other
0	4	85	11
144	0	95	5

Section 2.3 The Addition of Unsaturates to [HIr(aa)(PMe_3)$_3$]Cl

Roy was unable to observe any intermolecular reactions of monsubstituted amino acid complexes with unsaturates. However, the intramolecular insertion of the tethered olefin of pentenoic acid was observed. This observation indicated that these complexes had the potential for insertion reactions if an open coordination site for the unsaturate could be obtained. The disubstituted amino acid complexes were thought to be more sterically strained and therefore potentially more reactive with unsaturates. The reactivity of both the disubstituted amino acid complexes and the monosubstituted amino acid complexes is described below.

Potential evidence for the reaction of t-butylacetylene with the diphenylglycine complex after heating an aqueous solution at 75°C overnight was given by the disappearance of the hydride resonance at -24 ppm in the ^1H NMR spectrum. The other resonances in the hydride region were not found to diminish in intensity after the addition of the unsaturate. The disapearance of the peak at -24 ppm upon phosphine addition previously suggested that the complex contained a labile chloride ligand. Chloride ligands are known to be displaced by softer unsaturate ligands. Alternatively, a reaction may not have taken place and the dissapearance of the peak at -24 ppm may correspond with the conversion of the isomer to the facial complex. Reactions with methylpropiolate, acrylamide, and t-butylacetylene at elevated temperatures (Figure 2.3.1) were attempted for several of the amino acid complexes in H_2O but no evidence of an insertion product was found.

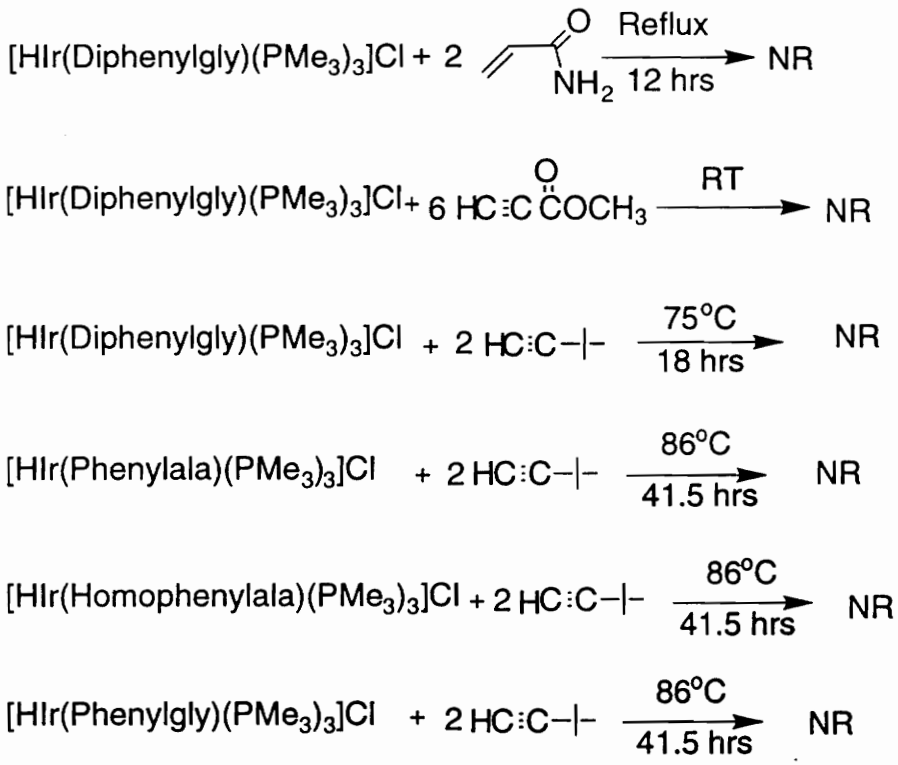


Figure 2.3.1 Reactions of $[Ir(aa)(PMe_3)_3]Cl$ with unsaturates

Section 2.4 Experimental

General Considerations

Unless otherwise specified, the following procedures were conducted under an inert atmosphere of argon or nitrogen using Schlenk techniques and a glove box purchased from M. Braun, Germany. The amino acids were purchased from Aldrich Chemical Co. and were used as received. Ether and pentane were purchased from Fisher Scientific and distilled from Na/K alloy/benzophenone under nitrogen. Methylene chloride was purified by passing through a column of activated grade I basic alumina under argon. Deionized water was used when water was required as a solvent. Deuterated water and deuterated methylene chloride were purchased from Cambridge Isotope Laboratories and stored under argon. Iridium trichloride was puchased from Johnson Matthey and hexachloroiridic acid, H_2IrCl_6, was purchased from PGM chemicals, Inc. Both were used as received. $[Ir(COD)Cl]_2$[12] and $[Ir(COD)(PMe_3)_3]Cl$[13] were prepared according to previously reported literature procedures.

^1H and ^{31}P NMR spectra were obtained using a Bruker WP-200 NMR spectrometer. ^{13}C NMR were obtained using a Varian UN-400 MHz NMR spectrometer. Chemical shifts are reported in δ(ppm) and are referenced to the solvent peak. Elemental Analyses were performed by Atlantic Microlabs, Norcross, Georgia.

Synthesis of $[Ir(diphenylgly)(H)(PMe_3)_3]Cl$ (LAH I 129)

A 100 mL flask equipped with a stir bar and septum was charged with 296.3 mg (1.34 mmol) of diphenylglycine. The flask was then charged with 350 mg (0.620 mmol) of $[Ir(COD)(PMe_3)_3]Cl$ under N_2 in the drybox. The flask was then connected to a double manifold (vacuum/nitrogen) Schlenk line and 25 mL of distilled water was added to the flask via syringe. The solution was stirred magnetically and heated to reflux. After 21 hours at reflux the reaction was allowed to cool and the solvent was removed in vacuo.

The white solid residue was treated with distilled methylene chloride (3 x 10 mLs) to extract the product from the excess amino acid. The solution was filtered from the solid using cannula techniques. The methylene chloride was removed in vacuo and the solids were dried under reduced pressure to yield 200 mg (0.293 mmol), 47.2 % of [Ir(diphenylgly)(H)(PMe_3)$_3$]Cl. The facial product was determined to be the nearly excusive product based on NMR data. The fac-[Ir(diphenylgly)(H)(PMe_3)$_3$]Cl was identified on the basis of the following data:

C,H analysis: Calculated for $C_{23}H_{40}NO_2P_3IrCl$ C, 40.44% H, 5.90% Found: C, 40.50% H, 5.95% ^{1}H NMR (CD_2Cl_2): δ 6.8 - 8.1 (m, 10 H, aromatic), δ 4.76 (br s, 2H, N-H), δ 1.46 (d, 9 H, J_{H-P} = 7.7 Hz, PMe_3 trans to hydride), δ 1.66 (d, 9H, J_{H-P} = 10.7 Hz, PMe_3), δ 1.85 (d, 9H, J_{P-H} = 10.4 Hz, PMe_3), δ -8.4 (dt, $J_{H-P(trans)}$ = 174.5 Hz, $J_{H-P(cis)}$ = 19.9 Hz, Ir-H) ^{31}P NMR (D_2O): δ -38.0 (dd, PMe_3 trans to H), δ -40.8 (dd, PMe_3), δ -44.4 (dd, PMe_3) ^{13}C NMR (D_2O): δ 183.04 (s, -COO), δ 142.37 (s, ipso phenyl), δ 138.28 (s, ipso phenyl), δ 129.04 (s, aromatic carbon), δ 128.90 (s, aromatic carbon), δ 128.82 (s, aromatic carbon), δ 128.79 (s, aromatic carbon), δ 128.01 (s, aromatic carbon), δ 126.94 (s, aromatic carbon), δ 73.12 (s, quarternary carbon of diphenylgly), δ 18.96 (dd, J_{C-P} = 42.2 Hz, J_{P-P} = 3Hz, PMe_3 cis to hydride), δ 17.8 (dd, J_{C-P} = 42.2 Hz, J_{P-P} = 3 Hz, PMe_3 cis to hydride), δ 13.2 (d, J_{C-P} = 30.2 Hz, PMe_3 trans to hydride). IR: 2040 cm^{-1} (fac hydride), 1648 cm^{-1} (-COO), 947 cm^{-1} (PMe_3)

Synthesis of [Ir(D-phenylgly)(H)(PMe_3)$_3$]Cl (LAH I 35)

A 100 mL flask equipped with a stir bar and septum was charged with 188.3 mg (1.25 mmol) of D-phenylglycine. The flask was then charged with 349 mg (0.619 mmol) of [Ir(COD)(PMe_3)$_3$]Cl under N_2 in the drybox. The flask was then connected to a double manifold (vacuum/nitrogen) Schlenk line and 25 mL of distilled water was added to the

flask via syringe. The solution was stirred magnetically and heated to reflux. After 22 hours at reflux the reaction was allowed to cool and the solvent was removed in vacuo. The white solid residue was treated with distilled methylene chloride (3 x 10 mLs) to extract the product from the excess amino acid. The solution was filtered from the solid using cannula techniques. The methylene chloride was removed in vacuo and the solids were dried under reduced pressure to yield 321 mg (0.5288 mmol), 85.4% of [Ir(D-phenylgly)(H)(PMe_3)$_3$]Cl. The hydride region of the ^1H NMR spectrum indicated a mixture of 75% meridional isomer and 25% facial isomer.
mer-[Ir(D-phenylgly)(H)(PMe_3)$_3$]Cl identified on the basis of the following data:

C, H analysis: Calculated for $C_{17}H_{36}NO_2PIrCl$ C, 33.63% H, 5.98% Found: C, 33.5% H, 6.08% ^1H NMR (D_2O): δ 7.3 - 7.6 (m, 5 H, aromatic), δ 6.5 (t, 1H, -CH-), δ 4.4 (m, 2 H, N-H), δ 1.62-1.85 (m, 27 H, PMe_3), δ -19.75 (q, J_{H-P} = 20 Hz, Ir-H) ^{31}P NMR (D_2O): δ -33.89 (d, J_{P-P} = 20.9 Hz, 2P, trans PMe_3), δ -46.45 (t, J_{P-P} = 20.9 Hz, 1P, cis PMe_3) ^{13}C NMR (D_2O): δ 179.92 (s, -COO), δ 134.28 (s, ipso phenyl), δ 124.60 (s, aromatic carbon), δ 124.08 (s, aromatic carbon), δ 123.33 (s, aromatic carbon), δ 123.11 (s, aromatic carbon), δ 55.23 (s, -CH-), δ 14.51 (d, J_{C-P} = 42.7 Hz cis PMe_3), δ 11.4 (dd, J_{C-P} = 25 Hz, J_{P-P} = 12 Hz, trans PMe_3), δ 10.58 (dd, J_{C-P} = 25 Hz, J_{P-P} = 12 Hz, trans PMe_3) IR: 2158 cm^{-1}(mer hydride), 2035 cm^{-1} (fac hydride), 1636 cm^{-1} (-COO), 952 cm^{-1} (PMe_3)

Synthesis of [Ir(L-phenylgly)(H)(PMe_3)$_3$]Cl (LAH I 31)

A 100 mL flask equipped with a stir bar and septum was charged with 190.9 mg (1.26 mmol) of L-phenylglycine. The flask was then charged 350 mg (0.620 mmol) of [Ir(COD)(PMe_3)$_3$]Cl under N_2 in the drybox. The flask was then connected to a double manifold (vacuum/nitrogen) Schlenk line and 25 mL of distilled water was added to the

flask via syringe. The solution was stirred magnetically and heated to reflux. After 23 hours at reflux the reaction was allowed to cool and the solvent was removed in vacuo. The white solid residue was treated with distilled methylene chloride (3 x 10 mLs) to extract the product from the excess amino acid. The solution was filtered from the solid using cannula techniques. The methylene chloride was removed in vacuo and the solids were dried under reduced pressure to yield 327 mg (2.16 mmol), 86.93% of [Ir(L-phenylgly)(H)(PMe_3)$_3$]Cl. The hydride region of the ^{1}H NMR spectrum indicated a mixture of 75% meridional isomer and 25% facial isomer. The product was recrystallized from methanol using diethyl ether to afford an exclusively meridional product. The solvent was removed via cannula and the colorless crystals were dried in vacuo. mer-[Ir(L-phenylgly)(H)(PMe_3)$_3$]Cl identified on the basis of the following data:

C,H analysis: Calculated for $C_{17}H_{36}NO_2PIrCl$ C, 33.63 H, 5.98 Found: C, 33.61 H, 6.28 ^{1}H NMR(D_2O): δ 7.3 - 7.6 (m, 5 H, aromatic), δ 6.0 (t, 1 H, -CH-), δ 4.4 (m, 2 H, N-H), δ 1.5 - 2.0 (m, 27 H, PMe_3), δ -19.75 (q, J_{H-P} = 20.0 Hz, Ir-H)
^{31}P NMR (D2O): δ 33.9 (d, 2P, trans PMe_3), δ -46.4 (t, J_{P-P} = 20.3 Hz, 1P, cis PMe_3)
^{13}C NMR (D_2O): δ 184.73 (s, -COO), δ 139.12 (s, ipso phenyl), δ 129.42 (s, aromatic carbon), δ 128.91 (s, aromatic carbon), δ 128.17 (s, aromatic carbon),
δ 60.10 (d, $J_{C-COO-Ir-P}$ = 9.2 Hz, -CH-), δ 19.35 (d, J_{C-P} = 43.4 Hz, cis PMe_3),
δ 16.28 (dd, J_{C-P} = 25 Hz, J_{P-P} = 14 Hz, trans PMe_3), δ 15.42 (dd, J_{C-P} = 25 Hz, J_{P-P} = 14 Hz, trans PMe_3)

Synthesis of [Ir(DL-homophenylala)(H)(PMe_3)$_3$]Cl (LAH I 89)

A 100 mL flask equipped with a stir bar and septum was charged with 267 mg (1.49 mmol) of DL-homophenylalanine. The flask was then charged 420 mg (0.745 mmol) of [Ir(COD)(PMe_3)$_3$]Cl under N_2 in the drybox. The flask was then connected to a

double manifold (vacuum/nitrogen) Schlenk line and 25 mL of distilled water was added to the flask via syringe. The solution was stirred magnetically and heated to reflux. After 18 hours at reflux the reaction was allowed to cool and the solvent was removed in vacuo. The white solid residue was treated with distilled methylene chloride (3 x 10 mLs) to extract the product from the excess amino acid. The solution was filtered from the solid using cannula techniques. The methylene chloride was removed in vacuo and the solids were dried under reduced pressure to yield 340.4 mg (0.430 mmol), 73.6% of [Ir(DL-homophenylala)(H)(PMe_3)$_3$]Cl. [Ir(DL-homophenylala)(H)(PMe_3)$_3$]Cl identified on the basis of the following data:

C,H analysis: Calculated for $C_{19}H_{40}NO_2PIrCl$ C, 35.93 H, 6.35 Found: C, 35.20 H, 6.52 ^{1}H NMR(D_2O): δ 7.36 (m, 5 H, aromatic), δ 5.45 (m, 1H, N-H), δ 4.15 (m, 1H, N-H), δ 3.2 (m, 1H, C-H), δ 2.9 (m, 2H, benzyl-CH_2-), δ 2.3 (m, 1H, -CH_2-), δ 1.9 (m, 1H, -CH_2-), δ 1.54 (t, 9H, cis PMe_3), δ 1.75 (d, J_{H-P} = 10.7Hz, 18H, trans PMe_3), d -19.9 (q, J_{H-P} = 20.0Hz, Ir-H) ^{31}P NMR(D_2O): δ -34.19 (t, J_{P-P} = 15.7Hz, 2P, trans PMe_3), δ -47.20 (t, J_{P-P} = 25.3Hz, 1P, cis PMe_3) ^{13}C NMR(D_2O): δ 185.83 (s, -COO), δ 140.82 (s, ipso phenyl), δ 128.84 (s, 2C, aromatic), δ 128.47 (s, 2C, aromatic), δ 126.50 (s, 1C, aromatic), δ 55.08 (s, -CH-), δ 36.00 (s, benzyl-CH2-), δ 31.23 (s, -CH_2-), δ 19.43 (d, J_{C-P} = 43.6 Hz, cis PMe_3), δ 16.09 (dd, J_{C-P} = 26.7, J_{P-P} = 12.3 Hz, trans PMe_3) IR: 2149 cm^{-1} (mer hydride), 1635 cm^{-1} (-COO), 950 cm^{-1} (PMe_3)

Synthesis of [Ir(DL-methylphenylala)(H)(PMe_3)$_3$]Cl (LAH I 61)

A 100 mL flask equipped with a stir bar and septum was charged with 238 mg (1.327 mmol) of DL-methylphenylalalanine. The flask was then charged 350 mg (0.621 mmol) of [Ir(COD)(PMe_3)$_3$]Cl under N_2 in the drybox. The flask was then connected to a double manifold (vacuum/nitrogen) Schlenk line and 25 mL of distilled water was added to

the flask via syringe. The solution was stirred magnetically and heated to reflux. After 18 hours at reflux the reaction was allowed to cool and the solvent was removed in vacuo. The white solid residue was treated with distilled methylene chloride (3 x 10 mls) to extract the product from the excess amino acid. The solution was filtered from the solid using cannula techniques. The methylene chloride was removed in vacuo and a yellow oily product resulted. Trituration with ether yielded a white product which was then dried under reduced pressure to yield 312 mg (0.491 mmol), 79.1% of fac-[Ir(DL-methylphenylala)(H)(PMe_3)$_3$]Cl. fac-[Ir(DL-methylphenylala)(H)(PMe_3)$_3$]Cl identified on the basis of the following data:

C,H analysis: Calculated for $C_{19}H_{40}NO_2P_3IrCl$ C, 35.93% H, 6.35% Found: C, 36.00 H, 6.45 ^{1}H NMR(D_2O): d 7.2 - 7.6 (m, 5H, aromatic), δ 4.35 (br s, N-H), δ 3.8 (br s, N-H), δ 3.55 (d, C-H), δ 3.2 (accidental overlap of d C-H), δ 2.8 (d, C-H), δ 1.4 - 1.8 (PMe_3), δ 0.93 (s, CH_3), δ 0.88 (s, CH_3), δ -9.6 (dt, $J_{H-P(trans)}$ = 160 Hz, $J_{H-P(cis)}$ = 20 Hz, Ir-H), δ -10.8 (dt, $J_{H-P(trans)}$ = 170 Hz, $J_{H-P(cis)}$ = 20 Hz, Ir-H) ^{31}PNMR(D_2O): -38.86 ppm (dd, PMe_3), -41.14ppm (dd, PMe_3), -44.84 (dd, PMe_3) ^{13}CNMR(D_2O): δ 186.52 (d, $J_{COO-Ir-P}$ = 5 Hz, -COO), δ 185.48 (d, $J_{COO-Ir-P}$ = 2.5 Hz, -COO), δ 135.05 (s, ipso phenyl), δ 134.89 (s, ipso phenyl), δ 130.50 (s, aromatic carbon), δ 130.002 (s, aromatic carbon), δ 129.76 (s, aromatic carbon), δ 129.05 (s, aromatic carbon), δ 128.58 (s, aromatic carbon), δ 127.93 (s, aromatic carbon), δ 45.09 (s, -CH_2-), δ 43.85 (s, -CH_2-), δ 64.75 (s, quarternary carbon), δ 62.67 (s, quarternary carbon), δ 26.66 (s, -CH_3), δ 23.059 (s, -CH_3), δ 19.02 (dd, J_{C-P} = 44 Hz, J_{P-P} = 4 Hz, PMe_3 cis to hydride), δ 18.79 (dd, J_{C-P} = 44 Hz, J_{P-P} = 4 Hz, PMe_3 cis to hydride), δ 17.87 (dd, J_{C-P} = 43 Hz, accidental overlap of PMe_3 cis to hydride of both isomers), δ 13.19 (d, J_{C-P} = 28 Hz, PMe_3 trans to hydride), δ 12.02 (d, J_{C-P} = 28 Hz, PMe_3 trans to hydride)

Addition of trimethylphosphine to [Ir(diphenylglycine)(PMe_3)$_3$]Cl (LAH II 53):

20 mg (29 mmol) of [Ir(diphenylglycine)(PMe_3)$_3$]Cl was weighed into a NMR tube in the drybox. The NMR tube was removed from the drybox and 0.6 mL D_2O was added via syringe followed by 19 μL (.18 mmol) of PMe_3. The ^1H NMR spectrum was taken immediately after the addition and the spectral data matched that of the original [Ir(diphenylglycine)(PMe_3)$_3$]Cl complex except that the hydride resonance at -24 ppm was not present.

Heating aqueous solutions of the amino acid complexes (LAH II 47):

Complexes of valine, homophenylalanine, and phenylglycine were weighed into a pressure tube in the drybox. The pressure tubes were removed from the drybox and 7 mL of H_2O was added and the tubes were heated in a 100°C oil bath. The complexes were heated for 74 hours and the solution was transfered to a small round bottom flask and the solvent was removed under reduced pressure. The ^1H NMR spectrum was obtained for each complex in D_2O. The D_2O solution was then returned to the round bottom flask and the deuterated solvent was removed under reduced pressure. The solid was dissolved in 7 mLs of H_2O and was returned to the pressure tube and the oil bath. The spectra were then obtained for each complex in the same manner after an additional 100 hours of heating. After obtaining the spectrum, the phenyl glycine complex was heated again for an additional 124 hours. Results are given in table 2.2.4.

Addition of t-Butylacetylene to [Ir(diphenylglycine)(PMe_3)$_3$]Cl (LAH I 145):

30 mg (0.044 mmol) of [Ir(diphenylglycine)(PMe_3)$_3$]Cl was weighed into a NMR tube in the drybox. The NMR tube was removed from the drybox and 0.6 mL H_2O was added via syringe followed by 11 μL (.088 mmol) of t-butylacetylene. The reaction was heated for 18 hrs in a 75°C oil bath. The solution was then transfered to a side arm round bottom flask and the solvent was removed under vacuum. The ^1H NMR spectrum was then taken in D_2O and the spectral data matched that reported for [Ir(diphenylglycine)(PMe_3)$_3$]Cl except that the hydride resonance at -24 ppm was not present.

Addition of t-Butylacetylene to [Ir(phenylala)(PMe_3)$_3$]Cl (LAH I 101):

25 mg (0.040 mmol) of [Ir(phenylala)(PMe_3)$_3$]Cl was weighed into a NMR tube in the drybox. The NMR tube was removed from the drybox and 0.6 mL H_2O was added via syringe followed by 10 μL (0.08 mmol) of t-butylacetylene. The solution was heated at 86°C for 41.5 hours in an oil bath. The solution was the transfered to a 10 mL side arm flask and the H_2O was removed *in vacuo*. The NMR tube was coated with a small amount of oily subsatance. The resonances corresponding to both the facial and meridional isomers were still prominant in the hydride region of the ^1H NMR spectra. No evidence of an insertion product was observed.

Addition of t-Butylacetylene to [Ir(homophenylala)(PMe_3)$_3$]Cl (LAH I 103):

27 mg (0.043 mmol) of [Ir(homophenylala)(PMe_3)$_3$]Cl was weighed into a NMR tube in the drybox. The NMR tube was removed from the drybox and 0.6 mL H_2O was

added via syringe followed by 10 μL (0.08 mmol) of t-butylacetylene. The solution was heated at 86°C for 41.5 hours in an oil bath. The solution was the transfered to a 10 ml side arm flask and the H_2O was removed in vacuo. The NMR tube was coated with a small amount of oily subsatance. The resonances corresponding to both the facial and meridional isomers were still prominant in the hydride region of the ^1H NMR spectra. No evidence of an insertion product was observed.

Addition of t-Butylacetylene to [Ir(D-phenylgly)(PMe_3)$_3$]Cl (LAH I 87):

30 mg (0.05 mmol) of [Ir(D-phenylgly)(PMe_3)$_3$]Cl was weighed into a NMR tube in the drybox. The NMR tube was removed from the drybox and 0.6 mL H_2O was added via syringe followed by 12 μL (0.10 mmol) of t-butylacetylene. The solution was heated at 86°C for 41.5 hours in an oil bath. The solution was then transfered to a 10 mL side arm flask and the H_2O was removed in vacuo. The resonances corresponding to both the facial and meridional isomers were still present in the hydride region of the ^1H NMR spectra. No evidence of an insertion product was observed.

Addition of Methylpropiolate to [Ir(diphenylglycine)(PMe_3)$_3$]Cl (LAH II 55):

15 mg (0.022 mmol) of [Ir(diphenylglycine)(PMe_3)$_3$]Cl was weighed into a NMR tube in the drybox. The NMR tube was removed from the drybox and 0.6 mL D_2O was added via syringe followed by 13 μL (0.13 mmol) of methylpropiolate. The spectral data matched that of the original [Ir(diphenylglycine)(PMe_3)$_3$]Cl complex.

Addition of Acrylamide to [Ir(diphenylglycine)(PMe_3)$_3$]Cl (LAH I 75)

18 mg (0.026 mmol) of [Ir(diphenylglycine)(PMe_3)$_3$]Cl was weighed into a 10 mL round bottom side arm flask in the drybox. The flask was removed from the drybox and

connected to the Schlenk line. 180μL (0.053 mmol) of a 0.295 M aqueous (H_2O) solution of acrylamide was added to the flask via syringe. A reflux condenser was attached and the solution was refluxed overnight. The hydride resonances corresponding to the facial isomer were still present. No evidence of an insertion product was observed.

References for Chapter 2:

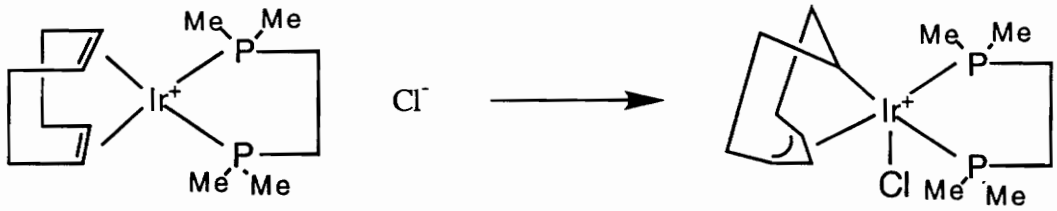
1. a) Merola, J.S. *Organometallics* **(1989)**, 8, 2975. b) Selnau, H.E.; Merola, J. S. *J. Am. Chem. Soc.* **(1991)**, 113, 4008. c) Selnau, J.S. *Organometallics*, **(1993)**, 12, 1583.
2. Knorr, J. R.; Merola, J. S. *Organometallics* **(1990)** 9, 3008.
3. a) Ladipo, F.T.; Kooti, M.; Merola, J.S. *Inorg. Chem.* **(1989)** 8, 2975. b) Ladipo, F.T.; Merola, J. S.; *Inorg. Chem.* **(1990)** 29, 4172. c) Selnau, .E.; Merola, J. S. *Organometallics* **(1993)** 12, 1583.
4. a) Ladipo, F. T.; Merola, J. S. *Inorg. Chem.* **(1990)** 29, 4172. b) Ladipo, F.T.; Merola, J. S.; *Inorg. Chem.* **(1993)** 32, 1681-1688.
5. Le, Trang; Ph. D. dissertation, **1992**, VPI&SU
6. Ladipo, F.; T. Ph.D. dissertation, July **1991**, VPI&SU.
7. Clark, R. D. Ph. D. dissertation, August **1995**, VPI&SU.
8. Roy, C.P.; Frazier, J.F.; Merola, J.S.
9. Beck, W.; Severin, K.; Sunkel, K. *Chem. Ber.*, **(1994)**, 127, 615-620.
10. Roy, C.P.; Ph. D. thesis, **1993**, VPI&SU.
11. Matthews, Kelly; Ph. D. thesis; **1994**, VPI&SU
12. Herde, J.L.; Lambert, J.C.; Senoff, C.V. *Inorg. Synth.* **(1974)** 15, p.18.
13. Frazier, J.F.; Merola, J. S. *Polyhedron* **(1992)** 11, pp. 2917-27.

Chapter 3. The Oxidative Addition of Amino Acids to [Ir(COD)(DEPE)]Cl

Section 3.1 Introduction

The lack of reactivity of [HIr(aa)(PMe_3)$_3$]Cl towards unsaturates prompted the synthesis of an alternative bisphosphine complex, Ir(DEPE)(Gly)Cl (DEPE = bis(diethylphosphinoethane). Greater reactivity with unsaturates is expected for Ir(DEPE)(Gly)Cl since the chloride ligand is more labile than the trimethylphosphine of [HIr(aa)(PMe_3)$_3$]Cl. Furthermore, dissociation of the chloride ligand should be favorable in aqueous solution since charged species are better stabilized in water than neutral ones. The hard water ligand is a poor match for the soft iridium center and may easily be displaced by unsaturates. The aqueous solution therefore promotes the reaction with unsaturates by creating the reactive aquo complex.

A similar synthesis of HIr(aa)(DMPE)Cl (DMPE = bis(dimethylphosphino)ethane) was previously attempted by Roy[1]. The expected addition product was not observed and instead a rearrangement of the COD ring (Equation 3.1.1) was established based on crystal structure analysis.



Equation 3.1.1 Rearrangement of the COD ring of [Ir(COD)(DMPE)]Cl

The metal center is first protonated by the amino acid, then the olefin of the COD ring inserts into the M-H bond and finally successive β-hydride eliminations and insertions take

place to yield the product shown above. This type of rearrangement has been observed with [Ir(COD)(DPPM)]Cl by Werner (Figure 3.1.1).[2]

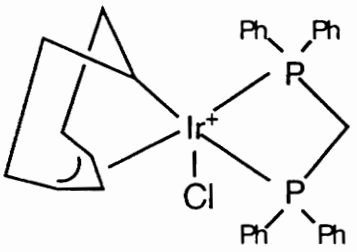
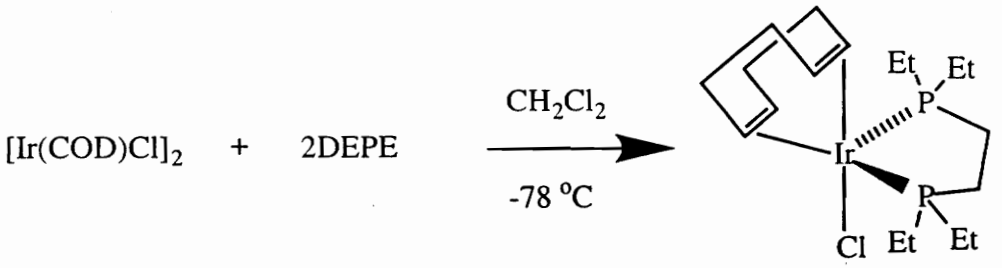


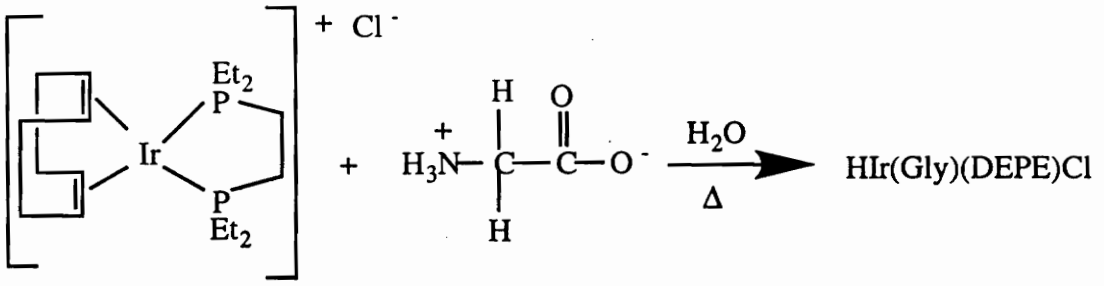
Figure 3.1.1 Rearrangement of [Ir(COD)(DPPM)]Cl observed by Werner

Section 3.2 Results and Discussion

Ir(COD)(DEPE)Cl was previously synthesized (Equation 3.2.1) by Robert Pafford and was used as a hydrogenation catalyst. The amino acid, glycine, was refluxed with Ir(COD)(DEPE)Cl in water to give the oxidative addition product, HIr(Gly)(DEPE)Cl (Equation 3.2.2).



Equation 3.2.1 Synthesis of Ir(COD)(DEPE)Cl



Equation 3.2.2 Synthesis of HIr(Gly)(DEPE)Cl

There are three possible isomers of HIr(Gly)(DEPE)Cl present in methylene chloride solution (Figure 3.2.1).

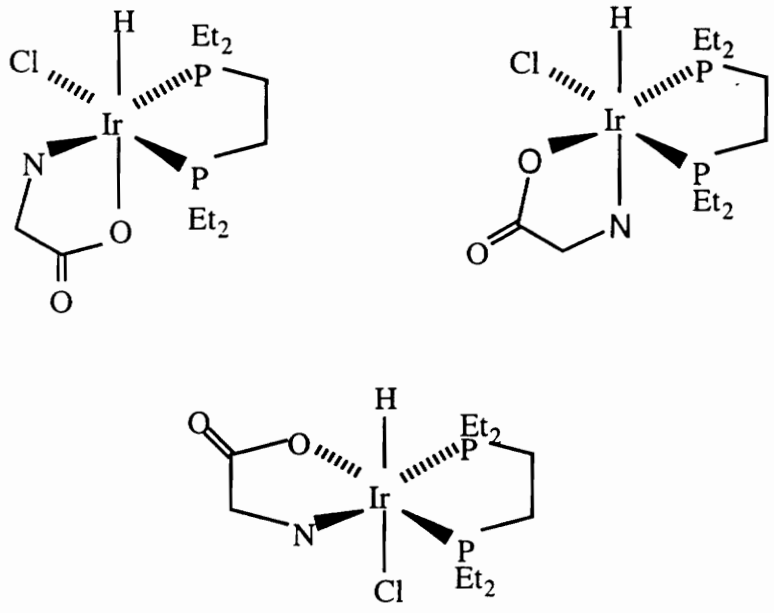


Figure 3.2.1 The three possible isomers of HIr(Gly)(DEPE)Cl in methylene chloride

The hydride region of the proton NMR spectrum could reveal up to three resonances corresponding to each of these three isomers. The spectrum in Figure 3.2.2 shows that all three isomers are present in CD_2Cl_2. When the NMR spectrum is taken in D_2O, six hydride resonances are observed (Figure 3.2.3) . The additional hydride resonances indicate that D_2O exchange for chloride is occuring in aqueous solution. The spectrum of the D_2O solution taken after the addition of excess NaCl contains only three resonances in the hydride region of the ^1H NMR spectrum (Figure 3.2.4). These resonances at -20.2, -23.75, and -26.1 ppm therefore correspond to complexes which contain chloride. Chloride ion may also be removed from solution by the addition of $AgPF_6$. The white solid, AgCl, precipitates immediately from an aqueous solution of HIr(Gly)(DEPE)Cl

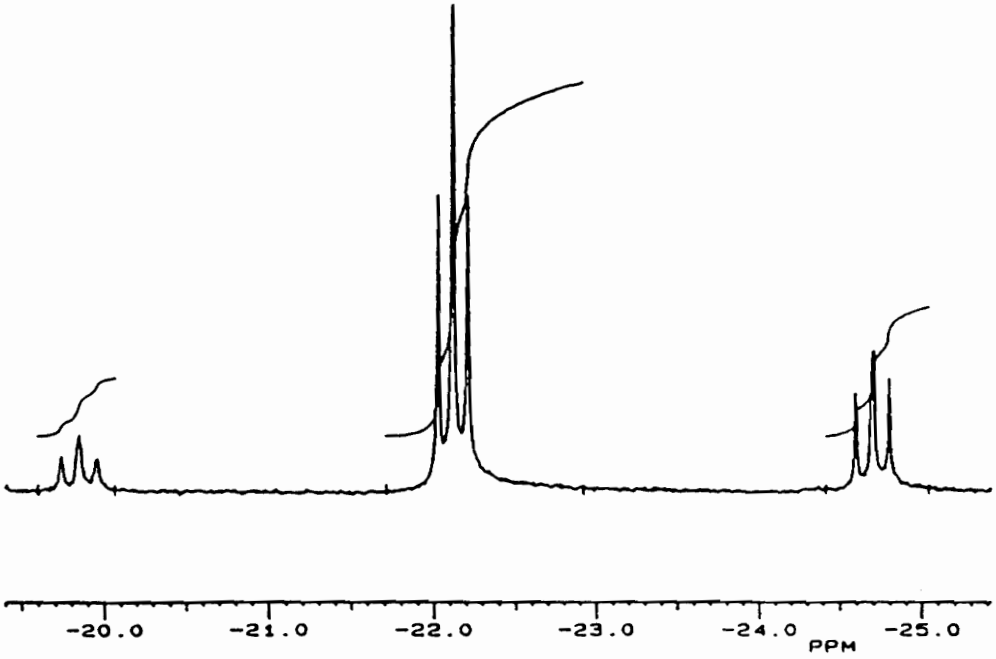


Figure 3.2.2 Hydride region of ^1H NMR spectrum in CD_2Cl_2

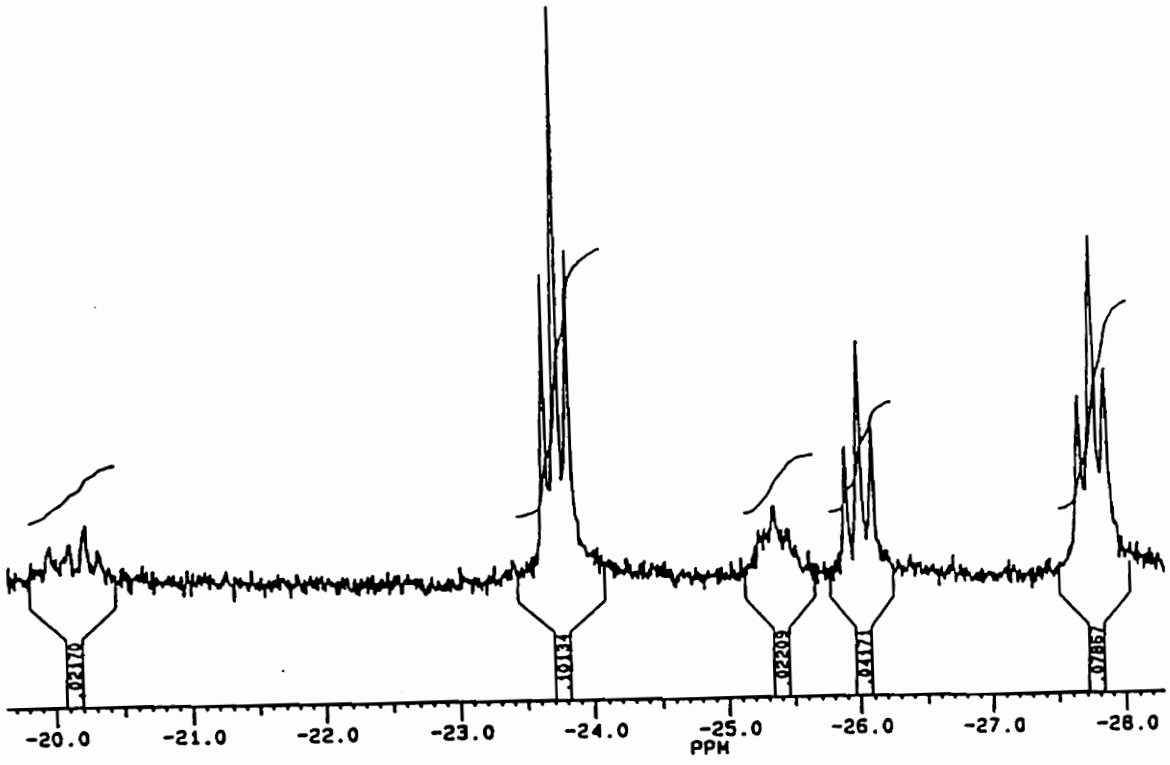


Figure 3.2.3 Hydride region of ^1H NMR spectrum in D_2O

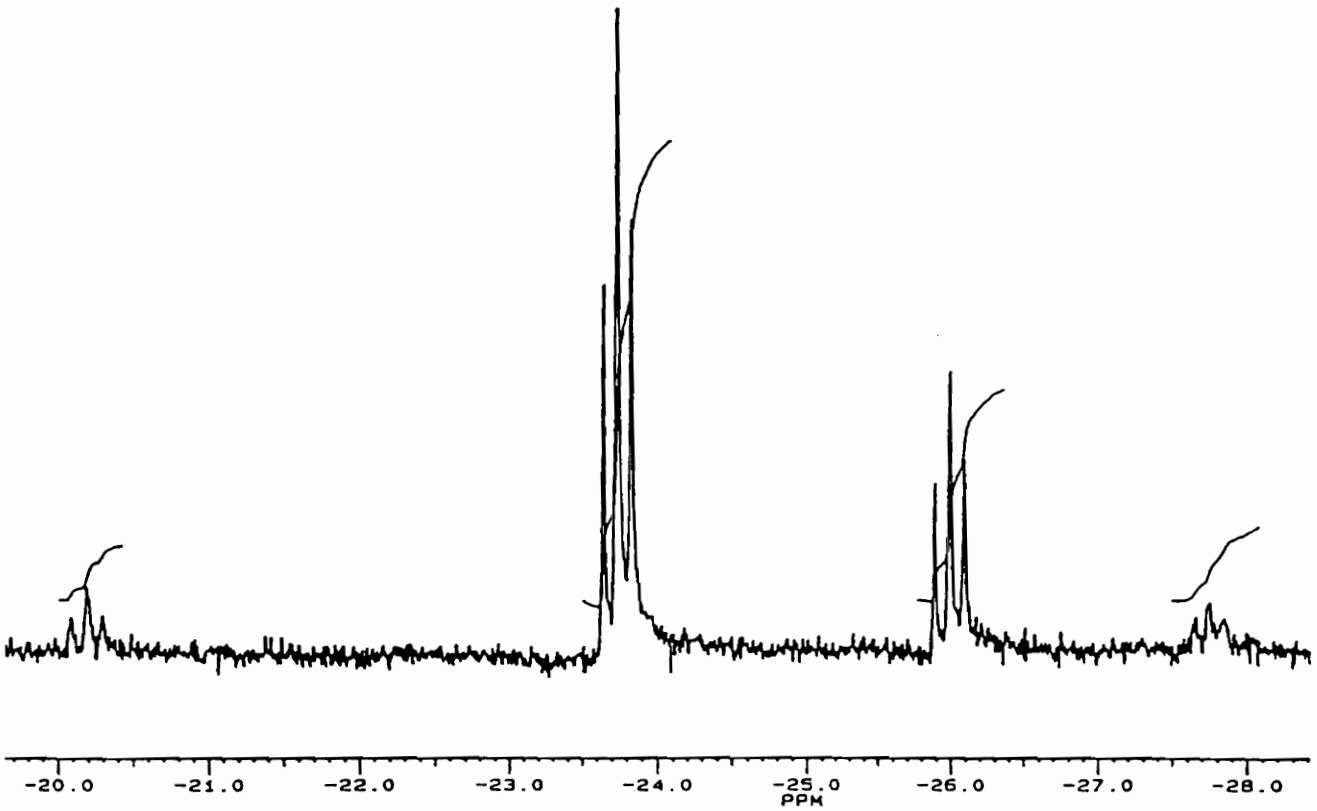


Figure 3.2.4 Hydride region of ^1H NMR spectrum after NaCl addition

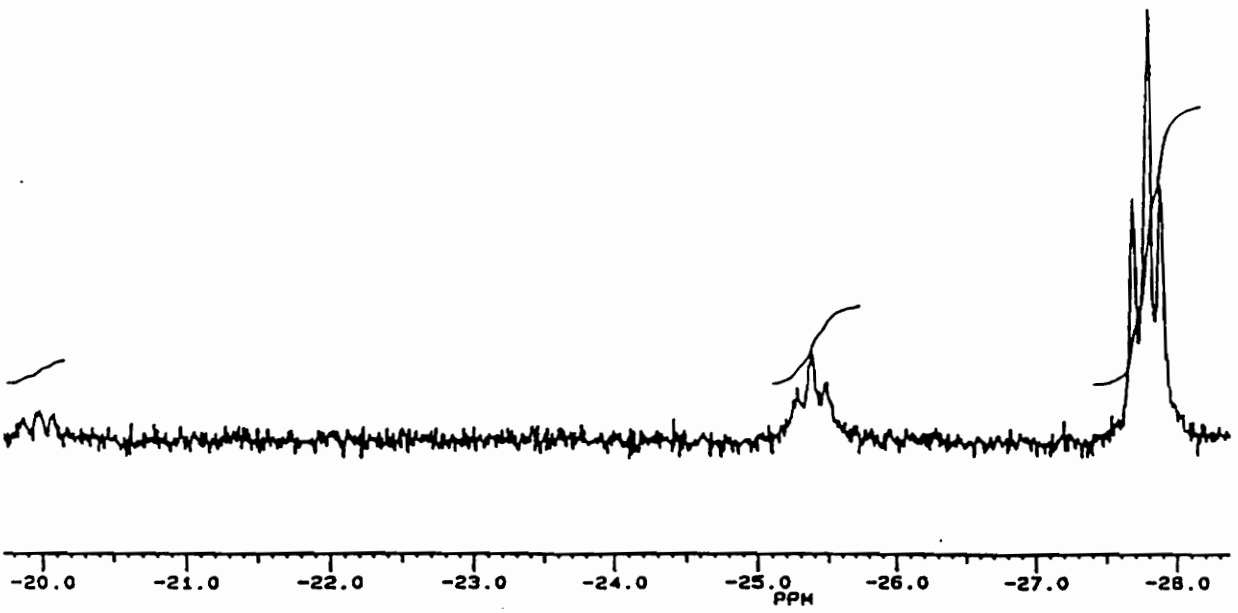


Figure 3.2.5 Hydride region of ^1H NMR spectrum after $AgPF_6$ addition

upon the addition of $AgPF_6$. Silver hexafluorophosphate was chosen because of the inability of KPF_6 to precipitate [HIr(DEPE)(Gly)(H_2O)]Cl from aqueous solution. Therefore, silver chloride precipitates out of solution leaving behind the soluble hexafluorophosphate salt of the isomers that contain water as a ligand (Figure 3.2.5). The three peaks at -19.95, -25.4, and -27.8 ppm that disappeared upon chloride addition are now the only three peaks remaining. The complementary experiments of chloride addition and chloride removal prove that an equilibrium mixture of chloride bound species and water bound species exists in solution. Furthermore, the resonances corresponding to complexes containing chloride and complexes containing water have been identified.

Previous studies of chemical shifts of hydride resonances by Kelly Matthews[3] allow for the correlation of each isomer with the appropriate hydride resonance. Matthews studied the correlation of the chemical shift of a hydride resonance as a function of the electronegativity of the trans and cis substituents. He prepared several cis dihydride complexes of the type shown in Figure 3.2.6 and plotted the chemical shifts of the different hydride and phosphine ligands as a function of the electronegativity (ε) of the X substituent (Figure 3.2.7).

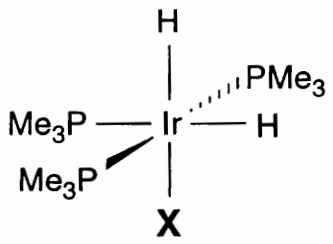


Figure 3.2.6

Table 3.2.1 Ligand Chemical Shifts of $IrH_2(PMe_3)_3X$ in CD_2Cl_2

X	∈	H_{cis}	H_{trans}	$P_{downfield}$	$P_{upfield}$
$\underline{O_2}CPh$	3.4	-10.6	-26.4	-40.4	-44.7
Cl	3.2	-11.4	-24.0	-43.6	-49.3
Br	3.0	-11.3	-23.0	-45.8	-52.8
$\underline{N}C_5H_5$	3.0	-10.7	-23.6	-	-
I	2.7	-12.1	-20.8	-51.6	-60.9

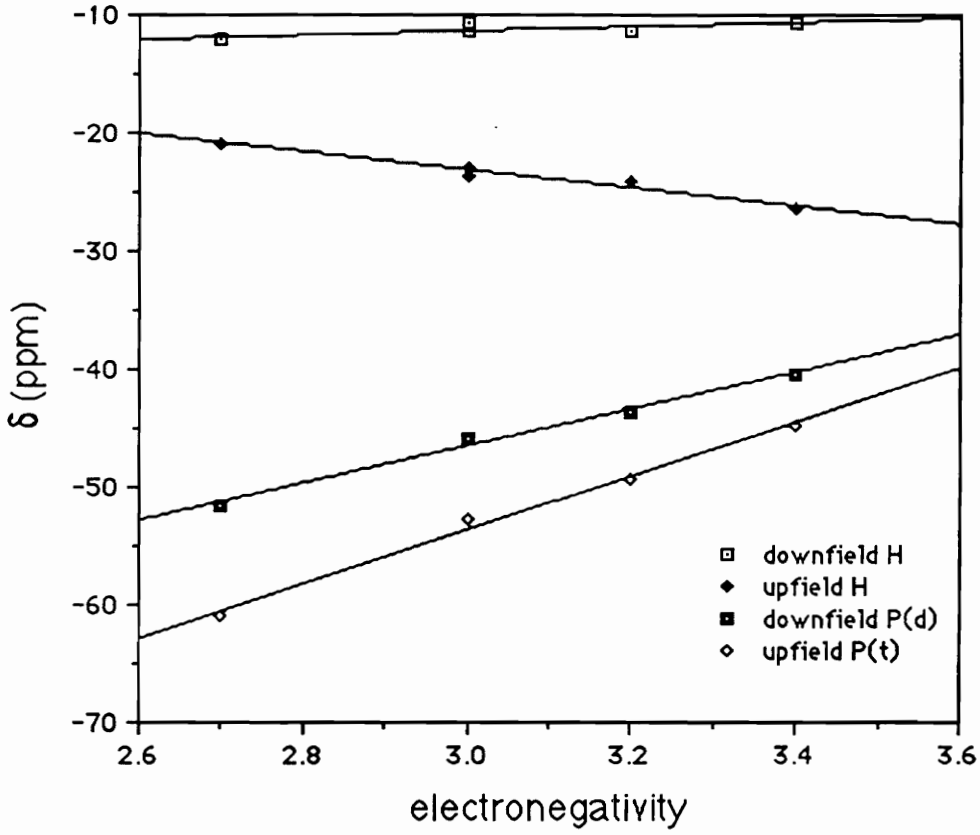


Figure 3.2.7 Plot of Chemical Shifts vs Electronegativity of $IrH_2(PMe_3)_3X$ in CD_2Cl_2

In order to fully understand Matthew's results, it is important to define the symbiotic effect and the antisymbiotic effect. Jorgenson[4] explained the symbiotic effect as the observation that soft ligands increase the polarizability of the metal and encourage

binding with other soft ligands. The antisymbiotic effect states that two soft ligands trans to one another impart an overall destabilizing effect on the complex due to the competition between the ligands for the p orbital. Therefore, binding of a hard ligand trans to a soft ligand is encouraged. The antisymbiotic effect developed by Chatt and Heaton[5] therefore appears to contradict the symbiotic effect.

In octahedral complexes, the cis ligands experience the symbiotic effect and the trans ligands experience the antisymbiotic effect. A downfield shift of the NMR resonances arising from the cis ligands with increasing electronegativity of X is expected since the X ligand is less able to donate electron density and therefore the Ir-H and Ir-P bonds experience less covalency. The plot of the chemical shifts of the cis hydride and the cis phosphine resonances produces the expected positive slope. It should be noted that pyridine which is bonded to the iridium through an aromatic ring was the only ligand that showed poor correlation of its chemical shift verses electronegativity. The lone pair on the nitrogen is tied up in the aromaticity of the ring and therefore reduces the σ-donating ability of the nitrogen. The chemical shifts of the resonances arising from the trans hydride produces a negative slope with increasing electronegativity of X due to the decreased covalency of the Ir-X bond and the increased covalency of the Ir-H bond.

The magnitude of the slope gives an idea of the relative importance of the trans effect verses the cis effect. For the hydrides, the slope of the line representing the trans effect is much larger than the slope of the line representing the cis effect. Therefore, the ligand trans to the hydride dictates the chemical shift of the hydride resonance in the proton NMR spectrum. The hydride resonances of the six isomers of HIr(Gly)(DEPE)Cl present in aqueous solution appear at -20.0, -20.2, -23.75, -25.4, -26.1, and -27.8 ppm (Figure 3.2.3). The hydride may be trans to either water, chloride, the carboxylate, or the amine. The covalency of the Ir-X bond decreases in the order of increasing electronegativity (N < Cl < O). The chemical shifts of the hydrides trans to these atoms should respectively

become more negative (more shielded) as the covalency of Ir-X decreases and the covalency of Ir-H increases. In methylene chloride, the resonances at -19.9, -22.1, and -24.75 ppm therefore correspond to the hydride trans to the amine, the chloride ligand, and the carboxylate respectively. In aqueous solution, the two resonances near -20 ppm correspond to the hydride trans to the amine; the resonance at -23.75 to the hydride trans to Cl; and the three resonances furthest upfield to the hydrides trans to the carboxylate and the water ligand. The softer carboxylate ligand should provide a larger covalency with the iridium center than the water ligand. Therefore, the chemical shifts of the resonances corresponding to the hydride trans to the carboxylate should be further downfield from the chemical shifts of the resonances corresponding to the hydride trans to the water ligand. The hydride trans to the carboxylate corresponds to the peaks at -25.4 and -26.1 ppm and the hydride trans to water corresponds to the peak at -27.8 ppm.

The cis effect may be taken in to effect to identify the resonances corresponding to each of the isomers. The chemical shifts of the hydride resonances become less negative as the electronegativity of the cis substituent increases. Therefore, the two resonances corresponding to a hydride trans to nitrogen, -20.2 and -20.0 ppm, correspond to complexes with a cis chloride and water ligand respectively. Likewise, the two resonances corresponding to a hydride trans to the carboxylate, -26.1 and -25.4 ppm, correspond to complexes containing a cis chloride and water ligand respectively. The two resonances at -23.75 and -27.8 ppm have already been assigned to the isomer with the hydride trans to chloride and the hydride trans to water respectively. The six isomers are shown in Figure 3.2.8 along with the corresponding chemical shifts.

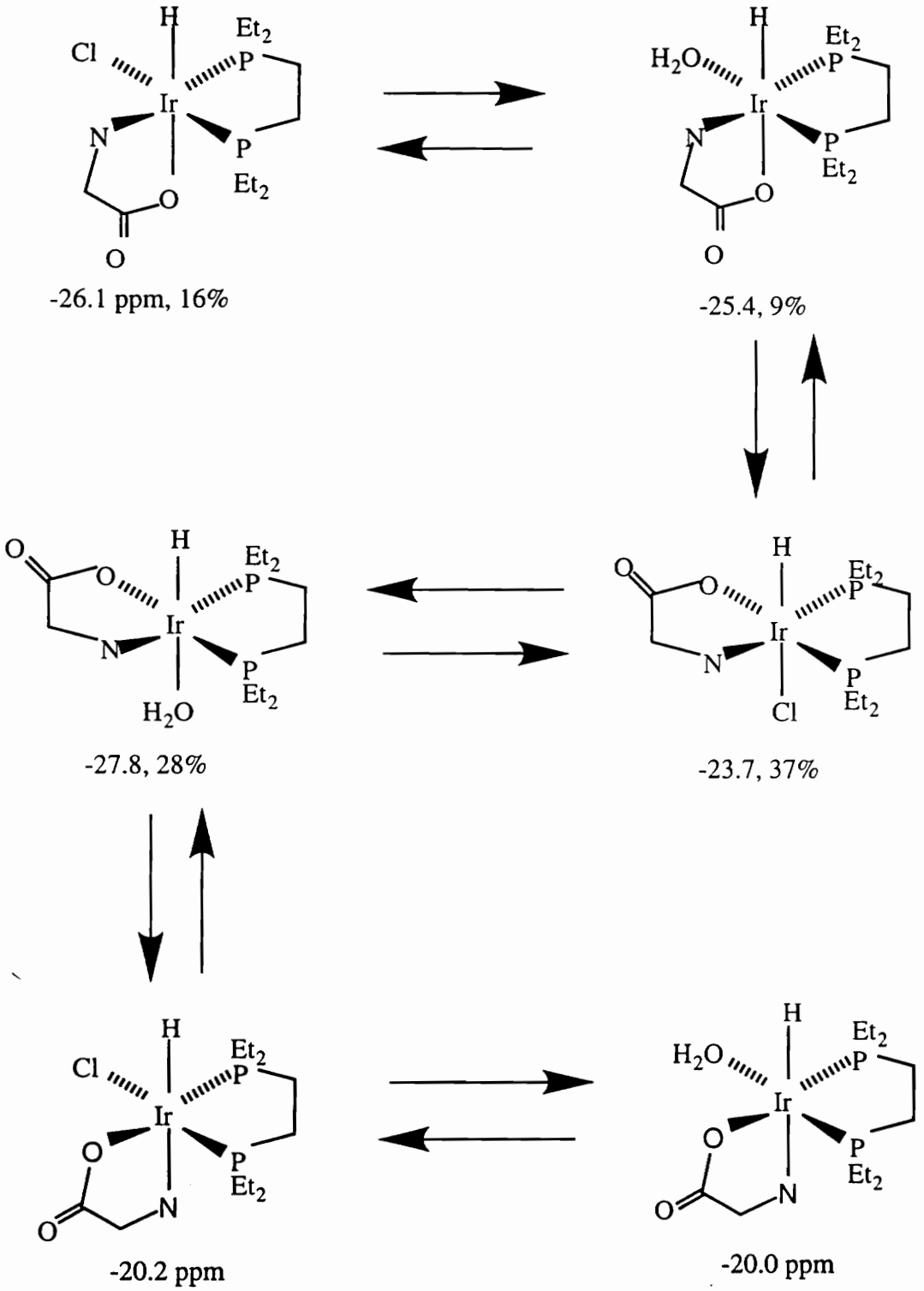
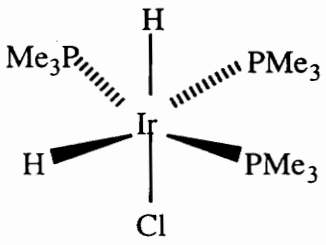
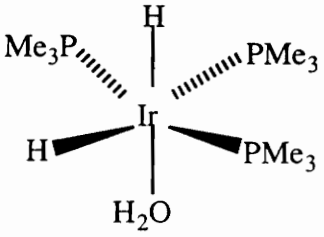


Figure 3.2.8 Equilibrium Mixture of Six Isomers In Aqueous Solution

Additional evidence for the chemical shift assignments made in Figure 3.2.8 is provided by examining the hydride region of the ^1H NMR spectra of the two complexes in Figure 3.2.9 that have been prepared by the Merola group.[6] The complexes are identical except that in one the hydride is trans to chloride and in the other the hydride is trans to water. The chemical shifts of these two complexes are seperated by 4.1 ppm which represents the effect of exchanging the chloride ligand trans to the hydride with water. Similarly, the resonances at -23.7 and -27.8 ppm corresponding to the HIr(DEPE)(aa)Cl and [HIr(DEPE)(aa)(H_2O)]Cl complexes with the hydride trans to chloride and water respectively are separated by 4.1 ppm.



H-Ir-Cl -25.4 ppm



H-Ir-OH_2 -29.5 ppm

Figure 3.2.9 Comparison of the above complexes gives the chemical shift difference, 4.1 ppm, of the hydride resonances associated with exchanging the chloride trans to a hydride with water.

Three singlets are observed in the ^{31}P NMR spectrum of HIr(gly)(DEPE)Cl in methylene chloride (Figure 3.2.10) while six singlets are observed in aqueous solution (Figure 3.2.11). The percent areas of the singlets in the ^{31}P NMR spectrum, 13.1%, 49.9%, and 37.0%, in methylene chloride correspond to the three different types of phosphines present in the three possible isomers (Figure 3.2.1).

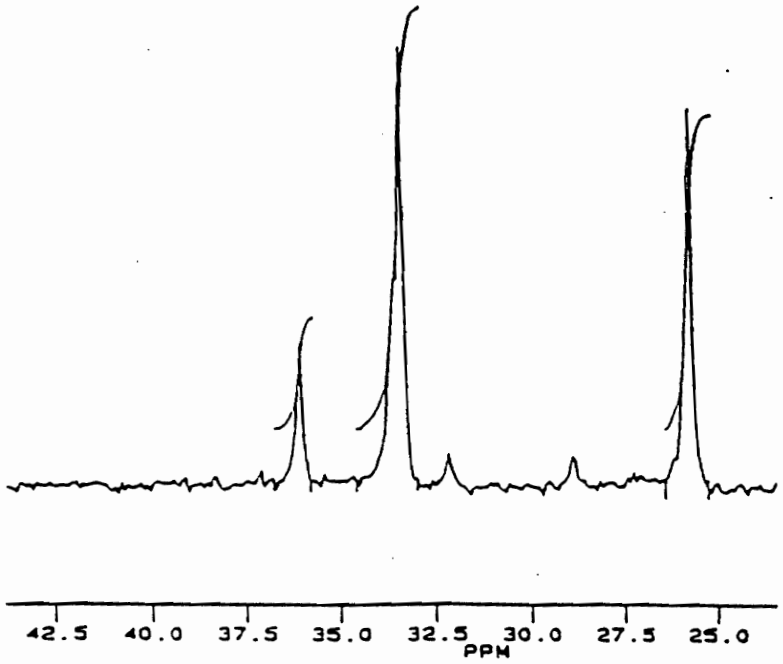


Figure 3.2.10 ^{31}P NMR of HIr(gly)(DEPE)Cl in CD_2Cl_2

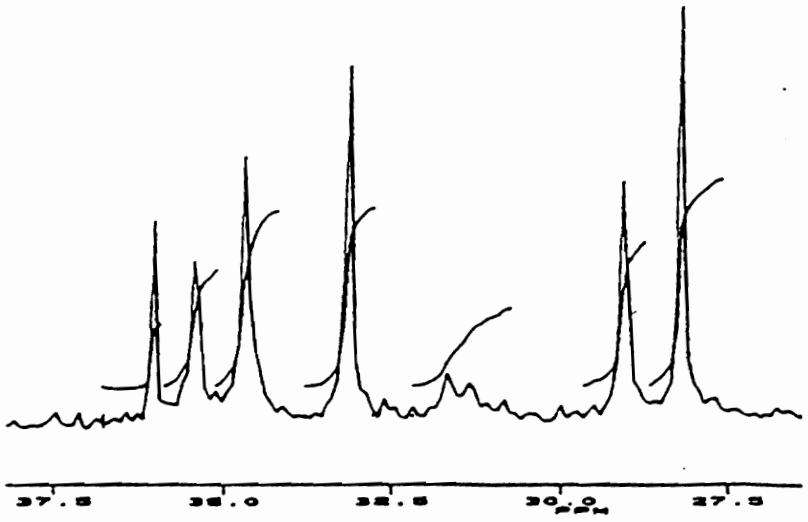


Figure 3.2.11 ^{31}P NMR of HIr(gly)(DEPE)Cl in D_2O

The phosphine may be trans to oxygen and cis to chloride and nitrogen, trans to chloride and cis to oxygen and nitrogen, or trans to nitrogen and cis to oxygen and chloride. The percent areas of the three hydride resonances in methylene chloride, which have already been identified, may be used to identify the three phosphine resonances. The percent area of a hydride resonance represents the percent area of two phosphines. Dividing the three hydride resonance percent areas, 4.7, 71.4, and 23.9, by two gives 2.35, 35.7, and 11.95 respectively. Table 3.2.2 gives the percent areas of all six phosphines calculated from the percent areas of the three hydride resonances. The percent areas of the phosphines in Table 3.2.2 that contain the same trans and cis ligands can be added together to give three percent areas of 37.0%, 49.9%, and 13.1% which respectively represent the three types of phosphines, P-Ir-O, P-Ir-Cl, and P-Ir-N. Therefore the resonances in the ^{31}P NMR spectrum appearing at 25.76 ppm (38.1%), 33.48 ppm (47.65%), and 36.25 ppm (14.3%) correspond to a phosphorous atom trans to oxygen, chloride, and nitrogen respectively.

Table 3.2.2 Percent areas of the six phosphines present in the three isomers of HIr(aa)(DEPE)Cl (Figure 3.2.1) in mehylene chloride calculated from the hydride region of the ^{1}H NMR spectrum.

Type of Phosphine	Percent Area
P-Ir-O (cis to N and Cl)	2.35
P-Ir-Cl (P cis to O and N)	2.35
P-Ir-O (P cis to N and Cl)	35.7
P-Ir-N (P cis to O and Cl)	35.7
P-Ir-Cl (P cis to O and N)	11.95
P-Ir-N (P cis to O and Cl)	11.95

Likewise, the six singlets in the ^{31}P NMR spectrum in D_2O correspond to the six possible types of phosphines, P-Ir-O (cis to N and Cl), P-Ir-N (cis to O and Cl), P-Ir-O (cis to N and OH_2), P-Ir-N (cis to O and OH_2), P-Ir-OH_2 (cis to O and N), and P-Ir-Cl (cis to O and N), present in the six different types of isomers. Conclusive identification of the peaks could not be made because of the error associated with integrating the ^{31}P NMR spectrum. Table 3.2.3 gives the six percent areas calculated for each different phosphine using the hydride region of the ^{1}H NMR spectrum and Table 3.2.4 gives the percent areas of the six peaks calculated from the ^{31}P NMR spectrum. The largest two areas may be concluded to be due to the P-Ir-O (cis to N and Cl) at 33.1 ppm and P-Ir-N (cis to O and Cl) at 28.1 ppm but the distinction between the remaining four peaks is difficult.

Table 3.2.3 Percent areas of the six different phosphines present in the six different isomers of HIr(aa)(DEPE)Cl (Figure 3.2.8) in D_2O calculated from the hydride region of the ^{1}H NMR spectrum.

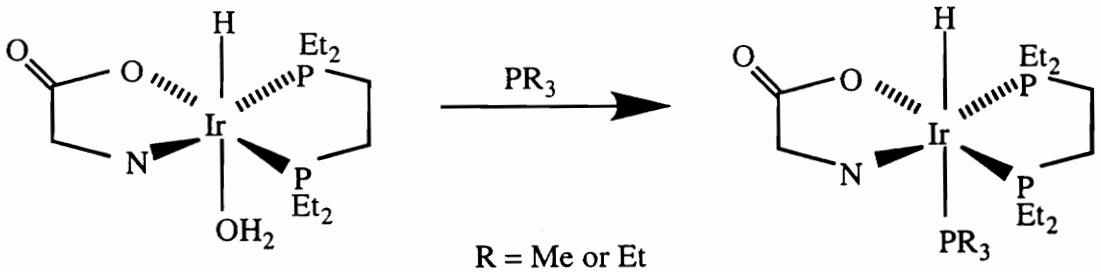
Type of Phosphine	Percent Area
P-Ir-O (cis to N and Cl)	21.8
P-Ir-N (cis to O and Cl)	26.95
P-Ir-O (cis to N and OH_2)	16.44
P-Ir-N (cis to O and OH_2)	18.95
P-Ir-OH_2 (cis to O and N)	5.79
P-Ir-Cl (cis to O and N)	10.6

Table 3.2.4 Percent areas of the six peaks in ^{31}P NMR spectrum

Chemical Shift (ppm)	Percent Area
36.0	9.13
35.5	12.0
34.75	15.8
33.08	22.9
29.17	13.8
28.13	26.3

Section 3.2 Addition of Phosphines to [(DEPE)(Gly)Ir]Cl

The addition of phosphines to [(DEPE)(Gly)Ir]Cl was attempted in both methylene chloride and in aqueous solution. It was neccessary to heat the sample in order for the substitution reaction to occur in methylene chloride solution , but the sample still did not completely convert to the substitution product even after being left in an oil bath at 56°C for four days. In aqueous solution, the chloride was immediately displaced at room temperature by an excess of either PMe_3 and PEt_3 (Equation 3.2.3).



Equation 3.2.3

The facial isomer is pictured in equation 3.2.3, but in both methylene chloride and in aqueous solution a mixture of both meridional and facial isomers were formed. The addition of phosphines was expected to yield a mixture of three isomers. The complex may have a facial arrangement of phosphines with the hydride positioned trans to the phosphine or two posible meridional arrangements of phosphines in which the hydride is either trans to N or O of the amino acid. The hydride region of the ^1H NMR spectrum after phosphine addition contained only two resonances at -10.3 ppm and -25.85 ppm (Figure 3.2.12). The doublet of triplets at -10.3 ppm corresponds to the hydride being split into a doublet by the trans phosphine and then further split into a triplet by the two cis phosphines. The resonance at -25.85 ppm corresponds to the hydride being split into a triplet by the equivalent trans phosphines and then further split into a doublet by the third phosphine. The trans splitting in the facial isomer is much larger than the cis splitting in the meridional isomer since the hydride and phosphine ligands both share the same p orbital in the facial isomer. The resonance at -25.85 ppm was identified as the isomer in which the hydride is trans to oxygen based on chemical shift arguements. The peak at -25.85 ppm converts to a peak at -19.9 ppm when heated at 60^oC for about 2 hours (Figure 3.2.13). The peak at -19.9 ppm appears in an identical region of the ^1H NMR spectra as the hydrides of [HIr(aa)(PMe_3)$_3$]Cl discussed to in chapter 2. The meridional isomer in which the hydride is trans to the oxygen is formed as the kinetic product from phosphine addition and the meridional isomer in which the hydride is trans to the nitrogen is the thermodynamic product from the addition. This corresponds with the observation that mer-[HIr(aa)(PMe_3)$_3$]Cl, formed by refluxing in aqueous solution, excusively yields the isomer in which the hydride is trans to nitrogen.

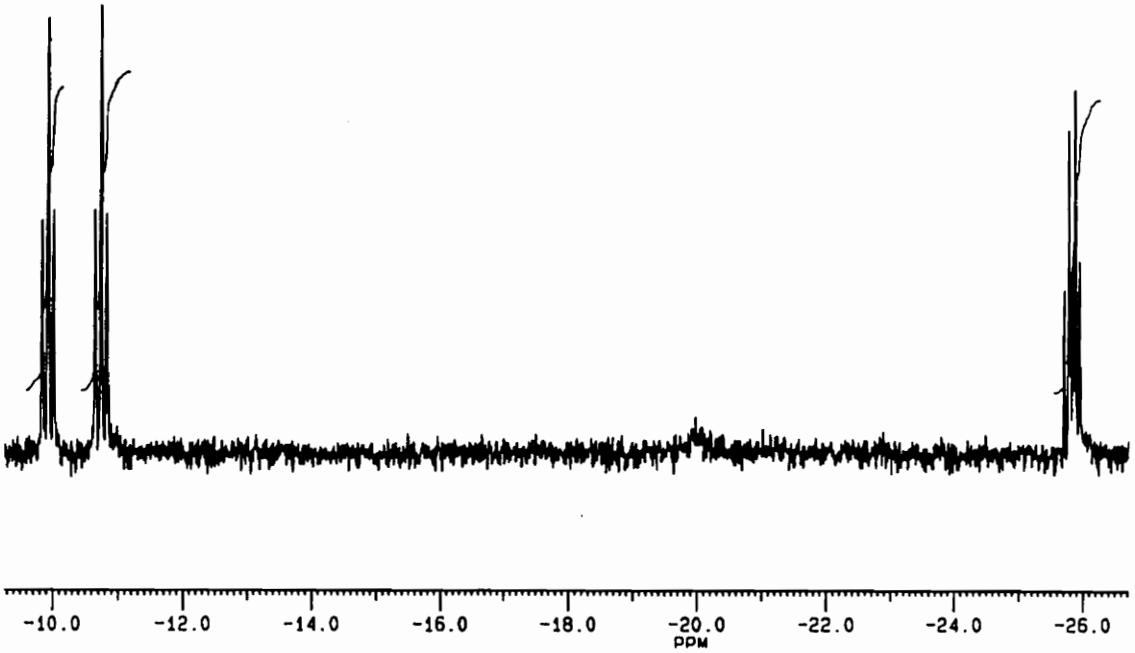


Figure 3.2.12 Hydride region of the ^1H NMR spectrum of [HIr(Gly)(DEPE)(PEt_3)]Cl in D_2O

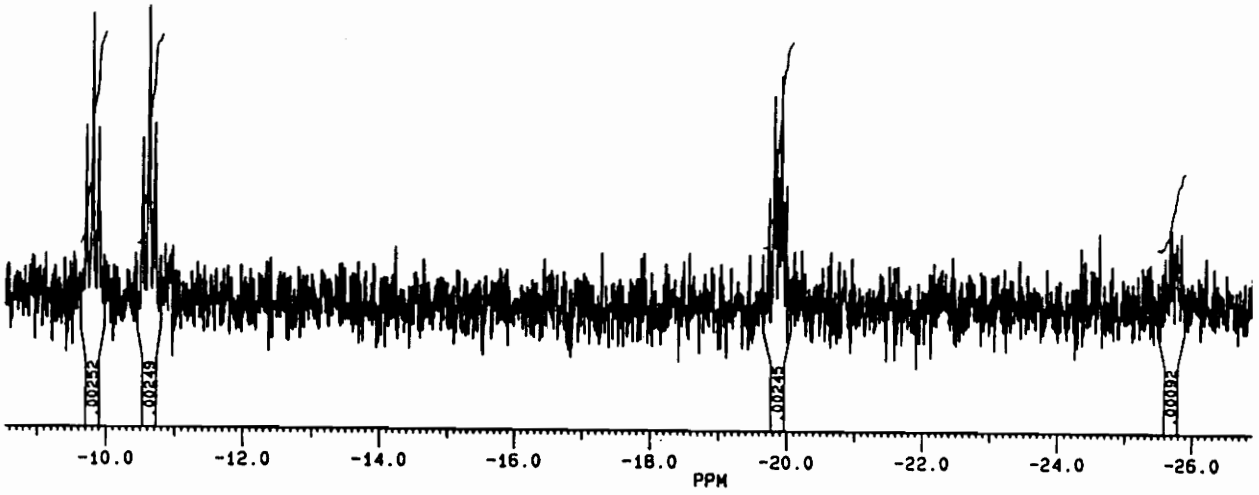


Figure 3.2.13 [HIr(Gly)(DEPE)(PEt_3)]Cl heated at 60°C for 2 hours

3.3 Addition of Unsaturates to [HIr(DEPE)(Gly)]Cl

The relatively hard aquo ligand may easily be displaced by the softer unsaturate to provide a better match for the soft iridium center. Since an equilibrium mixture of chloride bound complexes and water bound complexes exists in solution (Figure 3.2.8), replacement of the water ligand with an unsaturate continues to shift the equilibrium in the direction of the water bound complex until the reaction is complete. Aqueous solution therefore promotes the substitution reaction by producing an intermediate aquo species. Substitution reactions in methylene chloride would be expected to be much slower since the chloride ligand is much more tightly bound to the iridium than the aquo ligand.

The reaction of t-butyl acetylene and HIr(DEPE)(Gly)Cl in methylene chloride did not occur even after heating at 56°C for four days. The reaction of the water soluble unsaturate, methyl propiolate, and HIr(DEPE)(Gly)Cl occurred immediately in aqueous solution (Figure 3.2.14). Insertion into the Ir-H bond was identified based on the disappearance of the hydride resonances and the appearance of the alkene proton resonances in the ^{1}H NMR spectrum. The number of isomers of this complex has not been identified since the ^{13}C and ^{31}P NMR spectra of this compound were both complex. This coordination of the unsaturate and insertion into the Ir-H bond is the first step in what is hoped to be a catalytic cycle for the addition of the amino acids to unsaturates.

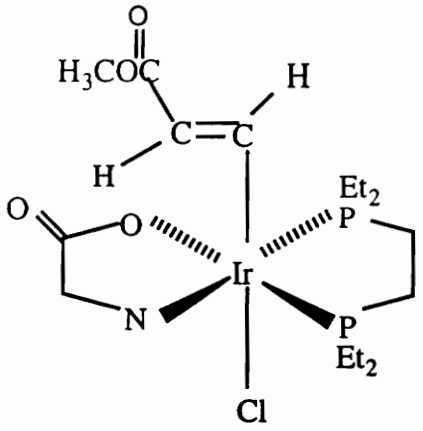


Figure 3.2.14 Insertion product of HIr(Gly)(DEPE)Cl

Section 3.3: Experimental

General Considerations

Unless otherwise specified, the following procedures were conducted under an inert atmosphere of argon or nitrogen using Schlenk techniques and a glove box purchased from M. Braun, Germany. Bis-diethylphosphinoethane, glycine, and cyclooctadiene were purchased from Strem Chemicals, Fischer Scientific, and Aldrich respectively and were used as received. Ether and pentane were purchased from Fisher Scientific and distilled from Na/K alloy/benzophenone under nitrogen. Methylene chloride was purified by passing through a column of activated grade I basic alumina under argon. Deionized water was used when water was required as a solvent. Deuterated water and deuterated methylene chloride were purchased from Cambridge Isotope Laboratories and stored under argon. Iridium trichloride was puchased from Johnson Matthey and hexachloroiridic acid, H_2IrCl_6, was purchased from PGM chemicals, Inc. Both were used as received. $[Ir(COD)Cl]_2$ was prepared according to previously reported literature procedures.

^1H and ^{31}P NMR spectra were obtained using a Bruker WP-200 NMR spectrometer. ^{13}C NMR were obtained using a Varian UN-400 MHz NMR spectrometer. Chemical shifts are reported in δ(ppm) and are referenced to the solvent peak. Elemental Analyses were performed by Atlantic Microlabs, Norcross, Georgia.

Synthesis of [(DEPE)(COD)Ir]Cl: LAH I 259

$[Ir(COD)Cl]_2$ (0.842 g, 1.25 mmol) was placed in a 200 mL side arm flask with a magnetic stir bar. Methylene chloride was charged via syringe into the flask forming an orange solution. The flask was placed into a dry ice/acetone bath and was cooled -78°C. A pressure equalizing addition funnel and gas adapter were attached to the flask. Methylene chloride was then added to the funnel. DEPE (0.570 mL, 2.44 mmol) was charged into the funnel. Additional methylene chloride (30 mL) was then added to the

funnel to facilitate mixing. The DEPE solution was then added dropwise into the flask over a period of about 30 minutes. The mixture slowly turned a yellow-brown color upon addition of the DEPE solution. The mixture was stirred and warmed to room temperature over a period of 8 hours. Solvent was removed under reduced pressure and the yellow-brown oil was triturated with pentane. The yellow-brown solid was dried under vacuum overnight. The dried solid was weighed (887 mg) and the percent yield (71.6 %) was determined.*

*Spectroscopic data agreed with that reported in the Master's thesis of Robert J. Pafford, IV; VPI&SU; Blacksburg, VA; 1995

Synthesis of HIr(DEPE)(Gly)Cl: LAH I 201

[(COD)(DEPE)Ir]Cl (212 mg, 0.391 mmol) was weighed into a 50 mL side arm flask equipped with a septum in the drybox. The flask was then removed from the drybox and the side arm was attached to a double manifold Schlenk line. The septum was removed briefly while the flask was under argon to add glycine (54.6 mg, 0.728 mmol) and to insert a stir bar into the flask. About 15 mL of deionized water was added to the flask and a small reflux condenser was attached. The initial solution was a deep red / greenish color. The solution was refluxed for 20.5 hours on a heating mantle. After refluxing, the solution was a clear yellow color. A small amount of brown material was observed at the bottom of the flask and adhering to the stirbar. The brown material was filtered from the solution via cannula and the product was dried overnight. CH_2Cl_2 (3 x 5 mLs) was used to extract the product from the excess glycine via cannula into another side arm flask. The product was dried in vacuo for about six hours. The product was then triturated with ether (5 x 1 ml) and filtered via cannula and dried in vacuo overnight. The yellow powder (57.8 % yield) was characterized as follows.

C, H analysis: Calculated for $C_{12}H_{31}P_2O_2NIrCl$ C, 28.31% H, 5.74% Found: C, 28.85% H, 5.81% ^1H NMR (D_2O): δ 1.04 (m, 24 H, DEPE methyls), δ 1.94 (m, 24 H, DEPE methlene protons), δ 3.63 (m, 2 H, CH_2 of glycine), δ -19.95 (hydride, t), -20.2 (hydride, t), -23.75 (hydride, t), -25.4 (hydride, br t), -26.1 (hydride, t), -27.8 (hydride, t) ^{31}P NMR (D_2O): 36.0 ppm (s), 35.5 ppm (s), 34.75 ppm (s), 33.08 ppm (s), 29.17 ppm (s), 28.13 ppm (s) ^{13}C NMR (D_2O): 187.32, 187.17 ppm (COO), 44.84, 44.53 ppm (CH_2 of amino acid), 23.66 ppm (m, DEPE), 21.90 ppm (d, DEPE), 19.05 ppm (m, DEPE), 16.75 ppm (m, DEPE), 7.26 ppm (DEPE), 6.44 ppm (DEPE)

Addition of PMe_3 to HIr(DEPE)(Gly)Cl in methylene chloride: LAH I 275

HIr(DEPE)(Gly)Cl (20 mg, 0.04 mmol) was weighed into a NMR tube in the drybox. The NMR tube was then removed from the drybox and 0.5 mLs of CD_2Cl_2 was added via syringe followed by 5μL (0.04 mmol) of trimethylphosphine. An initial ^1H NMR spectrum was taken and the NMR tube was placed in a 56°C oil bath and the ^1H NMR spectrum was obtained every day for four days. After heating for 24 hours, hydride resonances corresponding to the substitution product were observed at -10.6 ppm (dt) corresponding to the facial isomer and at -24.4 ppm (dt) corresponding to the meridional isomer with the hydride trans to O of the amino acid. This peak at -24.0 overlapped the resonance arising from the original complex. After four days, a resonance at -22.2 ppm (dt) was observed corresponding to the meridional isomer with the hydride trans to the nitrogen. This peak also overlapped the hydride resonance arising from the original complex. After four days, almost complete conversion to the substitution product appeared to take place.

Addition of PMe_3 to HIr(DEPE)(Gly)Cl in water: LAH II 33

HIr(DEPE)(Gly)Cl (15 mg, 0.03 mmol) was weighed a NMR tube in the drybox. The NMR tube was then removed from the drybox and 0.5 mLs of D_2O was added via syringe followed by 18μL (0.18 mmol) of trimethylphosphine. The product HIr(DEPE)(Gly)PMe_3 was identified based on the hydride region of the ^1H NMR spectra: -10.3 (dt) and -25.8 (dt). The solution was then heated for 2.5 hours and the resonance at -25.8 was observed to convert to a resonance at -19.9 ppm (dt).

Addition of methyl propiolate to HIr(DEPE)(Gly)Cl: LAH 293

HIr(DEPE)(Gly)Cl (123 mg, 0.242 mmol) was weighed into a 10 ml round bottom side arm flask in the drybox. H_2O (5 mLs) was then added to the flask via syringe followed by 45 μL (0.483 mmol) of methylpropiolate. The yellow solution was left to stir magnetically for four hours. A small amount of brown material was observed clinging to the side of the flak and the stir bar. The product was then dried in vacuo for about 5 hours. The oily yellow-brown product was recrystallized from CH_2Cl_2 (2mLs) by the addition of excess pentane (5 mLs).

References for Chapter 3:

1. Roy, C.P. Ph.D. Thesis, Virginia Polytechnic and State University, **1993**.

2. Werner et al, *Organometallics* **(1992)** 11, 1126.

3. Matthews, K. Ph.D. Thesis, Virginia Polytechgnic and State University, **1993**.

4. Jorgenson, C. K. *Inorg. Chem.* **(1964)** 3, 1201.

5. Heaton, I.; Chatt, J. *J. Chem. Soc.* **(1955)** 2937.

6. Le, Trang Ph.D. Thesis, Virginia Polytechnic and State University, **1992**.

Chapter 4. Conclusions and Future Work:

The reaction of $[Ir(COD)(PMe)_3]Cl$ with the disubstituted amino acids, diphenylglycine and methylphenylalanine, led to an almost exclusively facial product. Monosubstituted amino acids were observed to be mixtures of the meridional and facial isomers with the meridional isomer largely predominating. The facial isomer was overlooked by Roy and its presence may have to do with reaction time and temperature. The predominantly meridional mixture was observed to convert to a predominantly facial mixture when heated at 100°C for several days. The facial isomer therefore appears to be the thermodynamic product for complexes containing both monosubstituted and disubstituted amino acids. It may be that the facial arrangement of the phosphines is more thermodynamically favorable due to positive Van Der Waals interactions.

The presence of two R groups in the disubstituted amino acids was thought to produce a more sterically strained complex capable of a more rapid conversion to the facial isomer than the monosubstituited amino acid complexes. It was predicted that the facial diastereomer in which the R group is oriented away from the phosphine would predominate over the other, but both the phenylalanine complex and the methylphenylanine complex produced a nearly 50:50 distribution of these two isomers. This observation indicates that the steric interactions of the R groups with the phosphines do not destabilize the complex to a large extent and that the R groups may not be responsible for the faster conversion rate of disubstituted amino acid complexes to the facial isomer compared with monosubstituted amino acid complexes. Alternatively, the relatively acidic proton of the α-amino acid may lead to deprotonation reactions that slow the conversion of the monosubstituted amino acid complex to the facial isomer. Support for this theory would require further studies to determine if racemization at the α-carbon is occuring.

Some evidence for an insertion product was observed for the reaction of

t-butylacetylene with the diphenylglycine complex. The hydride peak at -24 ppm was found to dissappear after heating the complex in aqueous solution, but it is also possible that the dissapearance of this peak may result from the conversion of this complex to another isomer. A reaction with the water soluble unsaturates, methylpropiolate and acrylamide, was not observed.

An equilibrium mixture of 3 isomers of HIr(DEPE)(aa)Cl and 3 isomers of [HIr(DEPE)(aa)(H_2O)]Cl exist in aqueous solution. The addition and removal of chloride ion from solution allowed for the determination of resonances in the hydride region corresponding to the isomers that contain choride as a ligand and the isomers that contain water as a ligand. Further assignment of the peaks was made using chemical shift arguments. Phosphine substitution was found to occur readily in water, but in methylene chloride solution substitution was only observed after heating. The water soluble unsaturate, methylpropiolate, was found to easily insert into the Ir-H bond at room temperature in aqueous solution. However, the insertion product was not observed for the reaction of t-butylacetylene with the amino acid complexes in methylene chloride solution. The aqueous solution therefore promotes the reaction of these complexes with phosphines and unsaturates by creating a reactive intermediate aquo complex.

In the future, other Ir(aa)(DEPE)Cl complexes should be synthesized and these complexes should be tested for their biological activity. In addition, the facial and meridional isomers of the [HIr(aa)(PMe_3)]Cl complexes should be separated and the biological activity of the two should be compared. It may be possible to acheive separation through the formation of the PF_6 salt of these complexes. The facile insertion of methylpropiolate into the Ir-H bond indicates that the HIr(aa)(DEPE)Cl complexes have potential as catalysts for the amination or esterification of amino acids or for oligomer formation. This catalytic potential should be investigated. Crystal structure analysis of fac-[HIr(aa)(PMe_3)]Cl and Ir(aa)(DEPE)Cl should also be conducted.

Vita

The author was born in Akron, Ohio on July 1, 1972. She graduated from Goose Creek High school in Goose Creek, South Carolina in May 1990. She began her studies in Chemistry at Clemson University in August 1990. She was the recipient of the Westinghouse Environmental Scholarship Award while at Clemson and she graduated with a B.S. in Chemistry in May 1994. She began graduate studies at Virginia Tech in August of 1994 and joined the research group of Dr. Joseph Merola in December of 1994.