# O-H Activation in Phosphates: Oxidative Addition to an Iridium(I) Center and Reactivity of the Resulting Iridium(III) Species

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APPROVED

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(ABSTRACT)

The oxidative addition of E-H bonds to [Ir(1,5-COD)($PMe_3$)$_3$]Cl (1,5-COD = 1,5-cyclooctadiene) has been previously studied (E = B, C, N, O, S). Some of the resulting species have shown activity as catalysts for hydrogenation and the addition of other molecules to unsaturated species. More recently, the addition of amino acids to [Ir(1,5-COD)($PMe_3$)$_3$]Cl was studied in an attempt to create molecules with biological activity as well as species which might be active in asymmetric catalysis. Although inactive as catalysts, one of the these amino acid complexes was shown to be an anti-HIV agent. This finding prompted research into the additions of other molecules of biological importance to [Ir(1,5-COD)($PMe_3$)$_3$]Cl.

Since phosphates are an important functional group in biochemistry, the purpose of this research was to study the possible binding modes of the phosphate group to the iridium center and then to react biologically occurring phosphates with [Ir(1,5-COD)($PMe_3$)$_3$]Cl. The reaction of dibenzyl phosphate (DBP) with [Ir(1,5-COD)($PMe_3$)$_3$]Cl has been studied in detail. The resulting complex, Ir($PMe_3$)$_3$(H)(DBP)Cl, is soluble in most common laboratory solvents with the exception of ether and was characterized by infrared, $^1$H, $^{31}$P, and $^{13}$C NMR spectroscopy and elemental analysis. The dibenzyl phosphate ligand is labile and is easily displaced by nucleophiles. The complex does not undergo reaction with molecular hydrogen at ambient temperatures.

Dialkyl phosphate complexes were easily made using the same synthesis as the dibenzyl phosphate. This reaction was unsuccessful for the preparation monoalkyl and diaryl phosphate complexes.

The reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl with the nucleotides 2'-deoxyadenosine-5'-monophosphate (d-AMP) and (-)-adenosine-3'-5'-cyclic monophosphate (cyclic-AMP) did not result in the formation of a single product perhaps because the phosphate groups in these compounds are diacids. The reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl with 1,2-dihexadecanoyl-rac-glycero-3-phosphoethanolamine (PEA), a dialkyl phosphate, produced only the N-H addition product.

*This thesis is dedicated to*
*Mom and Dad*
*who will never know how much*
*their support and love mean to me*

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## Schemes

# Chapter 1: Literature Review

## Section 1.1: Introduction

Since the discovery of the anti-tumor activity of cis-platin (*cis*-diamminedichloro-platinum(II)),[1] the interaction of transition metal complexes with DNA and other biologically interesting molecules has become an important are of study. Similarly these complexes have been studied in an attempt to understand the mechanisms by which these compounds facilitate the destruction of unhealthy cell tissue. Biologically important molecules include DNA, nucleotides and nucleosides, amino acids, peptides, etc.[2] There are many common functional groups found among these compounds including amines, carboxylic acids, hydroxyl groups, and phosphates. The interaction of metal centers with amines and carboxylic acids has been carefully studied,[12] but complexation of the phosphate moiety in such compounds has not been as closely examined.

Although it has been argued that phosphorus is the fifth most important element in biological systems (following carbon, hydrogen, oxygen and nitrogen), the biochemistry of phosphorus is limited mainly to derivatives of the orthophosphate ion, which places phosphorus in a position bound only to oxygen.[3] Phosphates play two key roles in the chemistry of living things. Their first role is structural. Phosphate groups are included in the backbone of DNA molecules, which consist of a series of cyclic sugar molecules bound to a purine or pyrimidine base and a phosphate. Other structural roles of phosphates include calcium phosphate deposits found in bones and teeth. The second biological role of phosphates is energy transfer. Through the transfer of phosphoryl groups ($PO_3$) from high energy species to low energy acceptors, energy is released in living organisms allowing for such endergonic processes to occur as the contraction of muscles as well as the transfer of ions across membranes against a concentration gradient.[3]

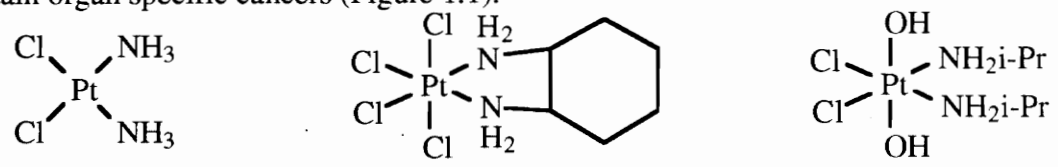
In recent years, transition metal phosphate complexes have also become important in catalytic organic transformations. The similarity of the two groups has permitted substitution of the phosphate group in previously studied systems containing a carboxylate.[4] The utilization of chiral phosphates in such systems has allowed for asymmetric induction in catalyzed cyclopropanation and C-H insertion reactions and sigmatropic rearrangements.[5]

Although complexes of biologically important phosphates with zinc, manganese, cadmium, and cobalt have been explored,[3] this literature review concentrates mainly on the interaction of phosphates with platinum group metals, particularly platinum, rhodium and iridium since this is the chemistry which is most relevant to this document. In addition to platinum metal complexes, there has also been a great deal of interesting research on the types of chemistry listed above using cobalt complexes which will also be discussed. Finally, the review includes a discussion of non-biologically active and catalytically active transition metal phosphate complexes.

## Section 1.2: *cis*-Platin and Related Compounds

The discovery in 1969 of anti-cancer activity in the platinum(II) complex commonly known as *cis*-platin (*cis*-diamminedichloroplatinum(II), Figure 1.1) has spawned much interest in the quest for more highly active transition metal complexes containing both platinum(II) and platinum(IV).[1] In general, platinum(II) complexes have been more widely studied as anti-tumor agents than their platinum(IV) counterparts. It is believed that most active platinum(IV) complexes are reduced *in vivo* to platinum(II) species.[6,7] The most commonly studied systems have simply replaced the ammine ligands with alkylated or chelating amines giving compounds of the general formula cis-$Pt(Am)_2(X)_2$ (where Am=amine and X=usually an anionic ligand). For example, chelating ethylenediamine compounds[6] and the alkylamine compounds such as tetraplatin (tetrachloro-

(diaminocyclohexane)platinum(IV)) and iproplatin (*cis*-dichloro-*trans*-dihydroxo-*cis*-bis(isopropylamine)platinum(IV)) have shown superior activity to *cis*-platin in combating certain organ specific cancers (Figure 1.1).[6a]




***cis*-platin** **tetraplatin** **iproplatin**

**Figure 1.1: *Cis*-platin and Some of Its Anti-Tumor Active Analogues**

After careful review of the several *cis*-platin analogues which have been identified as anti-tumor active, three common characteristics seem to be necessary in order to achieve this activity.[7] First, although it has not been clearly established in the case of hexacoordinate platinum(IV) compounds, for square planar platinum(II) complexes the amine ligands should be in a cis arrangement. Second, the ligands X should be only weakly to moderately bound to the metal center. Some examples of X ligands in active compounds are $Cl^-$, $SO_4^{2-}$ and $C_2O_4^{2-}$. Finally, the amine ligands should possess at least one N-H group perhaps to allow for hydrogen bonding with the phosphate groups present in DNA.[7] From numerous studies, it is now commonly accepted that the antitumor activity exhibited by platinum(II) compounds is a result of the reaction of the metal center with the nucleobases of cellular DNA thus disrupting the helical nature of the DNA strand.[8,9a] Since they lack DNA repair capability, tumorous cells are believed to be more sensitive than normal cells to this interaction with the metal.[9a] In healthy cells, disruptions in the DNA structure are therefore more likely to be identified by the cell and corrected while the unhealthy cells do not have this capability.

In theory, nucleophilic attack at the metal center should be possible through any site in DNA which has a lone pair of electrons, i.e. the oxygen of phosphate groups or hydroxyl groups, or the nitrogen atom of amines. In reality, however, there are very few

sites on the nucleotides and nucleic acids studied that bind to the platinum center and most of these sites are amine residues in the purine and pyrimidine bases. Also the bases which are found in DNA do not bind with the same frequency to the metal center. After several studies of binding sites, it has been established that preferred binding to the metal center occurs in the following order: guanine>adenine>cytosine>thymine.[9]

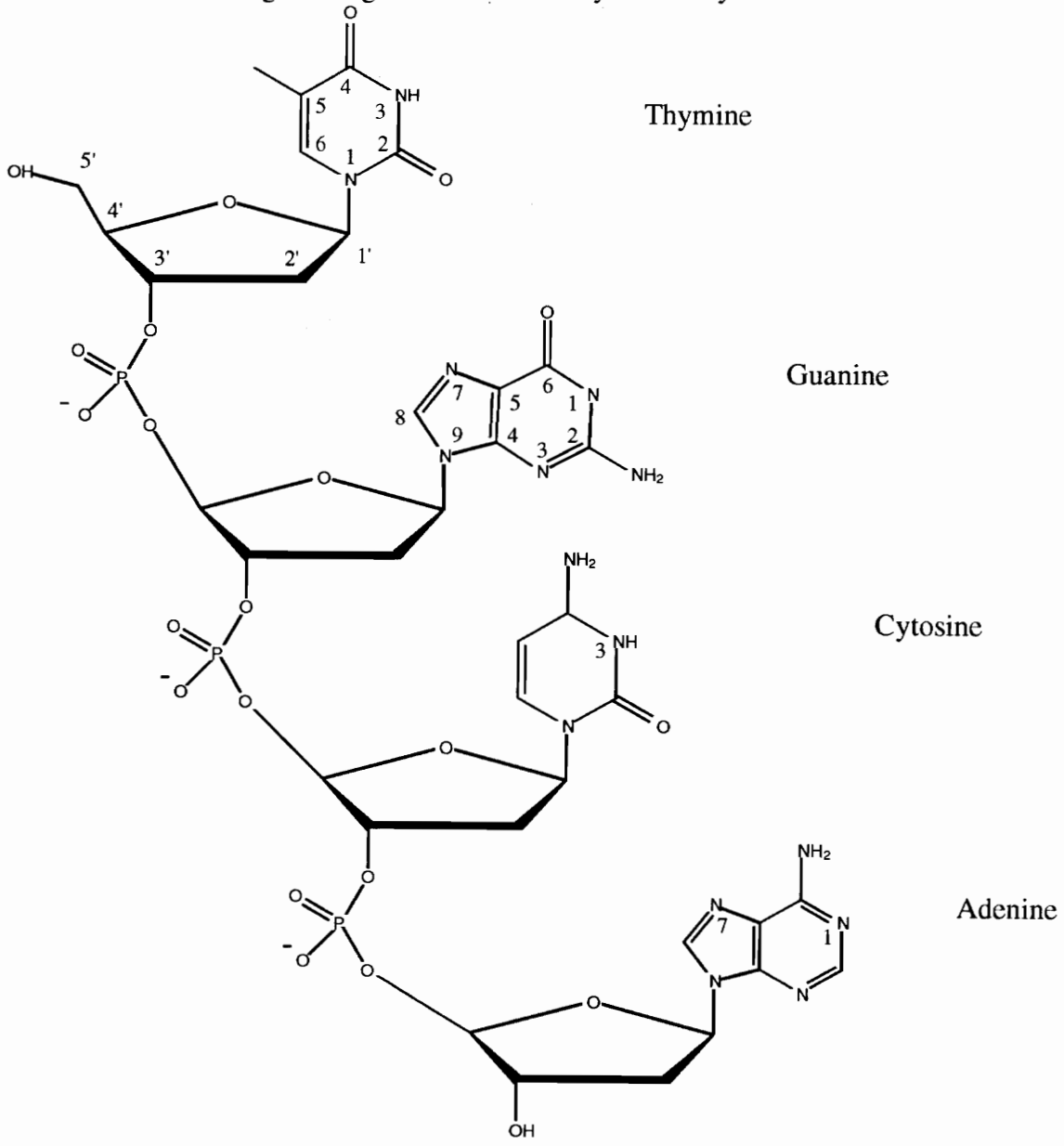
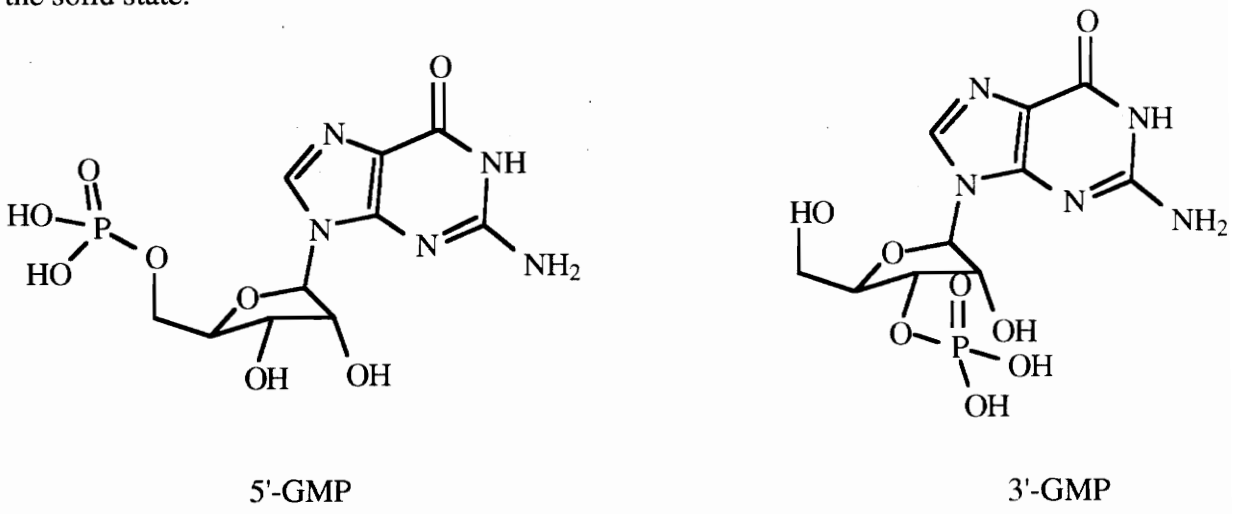



**Figure 1.2: Numbering System for Nucleotides**

Specifically, binding with the platinum center has been shown to occur mostly through guanosine-N7,[10] but has also been identified through adenosine-N1, adenosine-N7, and cytosine-N3 (Figure 1.2).[11] Although binding of the platinum to the phosphate groups of nucleotides has not been observed, the binding of phosphates to main group metals is quite common (for example, Mg(II) and Ca(II)).[9a,12] Even though the metal center does not have direct interaction with the phosphate group in such *cis*-bis(amine)Pt-nucleotide complexes, the role of the phosphate is a very important one.

In a study comparing the competitive platination by *cis*-platin of two nucleotides which differred only in the placement of the phosphate group, there was a distinct preference for platination at the guanosine-N7 of the 5'-GMP (guanosine-5'-monophosphate) over 3'-GMP (guanosine-3'-monophosphate).[6b] The placement of the phosphate group is believed to be important from both a thermodynamic and a kinetic standpoint. Prior to coordination of the N7 amine to the metal center, the negatively charged phosphate is thought to stabilize the platinum(II) center through an electrostatic interaction as it approaches the amine. Since the 5'-phosphate group is in close proximity to the base, the platinum center is poised for interaction with guanosine-N7 thus exhibiting a kinetic directing effect. There is no possibility for this interaction to occur in the 3'-GMP since the phosphate group faces away from the guanosine residue in the nucleotide structure (Figure 1.3).[6b] Since this directing effect in 5'-GMP is presumed to be electronic, but does not occur in 3'-GMP, the ratio of bound 5'-GMP to bound 3'-GMP should increase as the pH of the solution increases (i.e. as the phosphate becomes deprotonated and therefore more negatively charged). This is indeed the observation and, in fact, the ratio of $[Pt(Am)_2(5'\text{-GMP-N7})]$:$[Pt(Am)_2(3'\text{-GMP-N7})]$ increases dramatically as the pH corresponding to the pKa of the phosphate is approached.[6b] Once the platinum is bound to the nucleotide, the phosphate is able to thermodynamically stabilize the product through a hydrogen bonding interaction with the platinum bound amines (this is probably

why active *cis*-platin analogues require the incorporation of amines containing an N-H group). This hydrogen bonding phenomenon has been observed both in solution[13] and in the solid state.[14]



5'-GMP 3'-GMP

**Figure 1.3: Positioning of the Phosphate Group in 5'-GMP Versus 3'-GMP**

There is one reported case of direct binding of the platinum center in *cis*-platin with a phosphate group of a nucleotide. Bose *et al.*[32] saw chelation of the phosphate in uridine-5'-di- and triphosphates (UDP and UTP). Binding of the phosphate to the metal center was shown to increase the rate of phosphate hydrolysis. The uridine moiety showed little tendency to bind to the platinum center in DNA studies when in competition with other bases.[9] In this case, the phosphate was a better ligand to this platinum(II) center than any of the nucleophilic sites available in UDP or UTP.

Even though there is very little evidence of formal bonding between the phosphate groups found in DNA or simple nucleotides and the platinum center in *cis*-platin, it has become clear that the interactions of the phosphate group with both the metal center and the platinum bound amine are important factors contributing to the anti-tumor activity of the *cis*-platin analogues. Since the phosphate oxygens appeared to be unreactive towards the platinum center, some groups have studied the reactivity of *cis*-platin in biological systems

using phosphate buffers to control pH.[33] Studies of the aqueous chemistry of *cis*-platin in the presence of ortho-, pyro-, or triphosphate anions has indicated that the phosphate can bind to the metal center in a mono- or bidentate fashion depending upon experimental conditions.[34] These researchers therefore warned that the results of the aforementioned studies using both phosphate and acetate buffer systems be interpreted with caution.

## Section 1.3: Phosphoryl Transfer and Phosphate Hydrolysis

Another important role of phosphates in biological systems involves the transfer of a phosphoryl group ($PO_3$) from a higher energy species to a low energy acceptor molecule. Organic phosphates in living systems therefore act as storage sites for energy. The phosphate bond is cleaved upon the addition of a water molecule to form the protonated phosphate and the corresponding organic residue (equation 1.1).

$$ROPO_3^{2-} + H_2O \rightleftharpoons ROH + HOPO_3^{2-} \qquad \textbf{(1.1)}$$

The free energy released upon hydrolysis of a phosphate bond can be as high as 13 kcal/mol (Table 1.1).

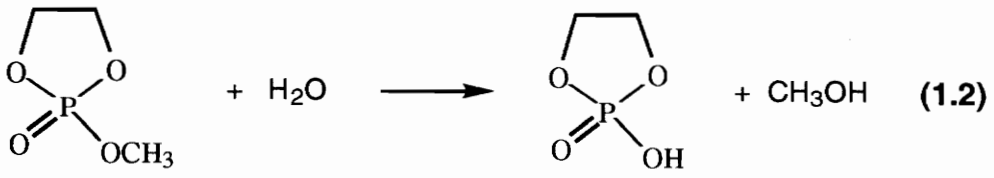
**Table 1.1: Standard Free Energy of Hydrolysis of Selected Phosphate Derivatives[3]**

| Compound | -ΔG (kcal/mol) |
|---|---|
| Enolpyruvate-P | 12.8 |
| Creatine-P | 10.5 |
| Acetyl-P | 10.1 |
| ATP | 8.0 |
| ADP | 6.4 |

Phosphate hydrolysis and the related phosphorolysis reaction, which involves the cleavage of bonds by phosphate instead of water, normally occur *in vivo* by enzymatic pathways.[15] There are many different enzymes which carry out phosphoryl transfer and those which catalyze these processes usually require the presence of some type of metal ion in order to carry out their function. Most of the phosphate transfer enzymes that have been

studied require divalent metal cations for activation. Under physiological conditions, it is believed that only $Mg^{2+}$ and $Ca^{2+}$ are present in large enough quantities to assist the phosphatases in their function.[3] The activity of the enzymes may change when the concentration of the cation is varied. Additionally, each metal cation interacts differently with a given enzyme. For instance, $Mg^{2+}$ usually gives the highest activity, but in some cases $Ca^{2+}$ activates the enzyme while $Mg^{2+}$ acts as an inhibitor. *In vitro* it has been found that many divalent cations of first row transition metals, in particular manganese, nickel, cobalt, zinc, and copper, are also capable of activating certain enzymes.[15]

Although most of the research concerning the activity associated with metal cation activated enzymes has been carried out with the metals mentioned above,[3,15] the cleavage of P-O bonds by certain second and third row transition metal complexes has been studied in an attempt to futher elucidate the mechanism by which metal activated enzymes may operate. Studies performed in the 1960s by Westheimer[16] and others[17] showed that the non-metal catalyzed hydrolysis of organic phosphates in which the phosphorus is included in a five-membered ring (Equation 1.2) occurs up to $10^7$ times faster than the hydrolysis of their acyclic analogues which often require a metal ion to be present in order for hydrolysis to occur. It is believed that the ring strain associated with this system which is somewhat relieved as the phosphorane intermediate is formed is responsible for the increased reactivity of the cyclic phosphate.[16]



**(1.2)**

Further studies have also suggested that a rate enhancement occurs in the enzymic hydrolysis of phosphate monoesters perhaps due to chelation of the phosphate by a metal

ion.[15] The formation of a strained four-membered ring is thought to be responsible for the increased susceptibility of the phosphate ester to nucleophilic attack in such systems. This phenomenon has been studied in both cobalt(III)[18] and iridium(III)[19] phosphato complexes.

Although syntheses of phosphato metal complexes were claimed prior to the 1960s, reproducibilty of these experiments remained elusive. Among the first to successfully explore such compounds were Lincoln and Stranks[18a] who in 1967 published a series of papers examining the structure and reactivity of $Co(NH_3)_4PO_4$ and $Co(en)_2PO_4$ at various pH values. Detailed kinetic analyses of the hydrolysis of these complexes and their protonated analogues was given. The compounds were characterized by $^{31}P$ NMR, IR, and UV-visible spectroscopy. Their observations suggested that an equilibrium existed in solution between the mono- and bidentate phosphato complexes. Although analogous species had been identified for sulphato complexes[20] and for carbonato complexes,[21] this was the first evidence for such phosphate species in solution. Lincoln and Stranks were able to synthesize $Co(NH_3)_4PO_4$ and $Co(en)_2PO_4$ in the anhydrous state and believed the phosphates to be coordinated to the metal center in a bidentate fashion. The complexes $[Co(NH_3)_4OH_2.HPO_4]^+NO_3^-$ and $[Co(en)_2OH_2.HPO_4]^+ClO_4^-$ could only be isolated in the solid state containing one mole of water suggesting that the phosphates were monodentate (Figure 1.4).

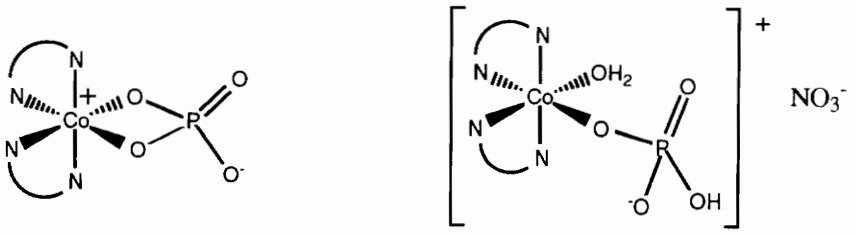
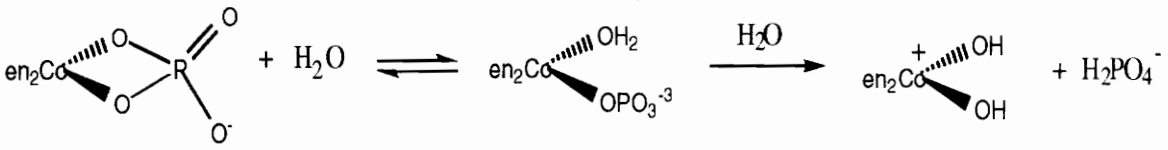



**Figure 1.4: Structure of Chelating and Non-chelating Cobalt(III) Phosphate Complexes**

Between pH 5.5-7.5, 85% of the phosphate was coordinated to the cobalt(III) center mostly in the bidentate form. Outside of this pH range, a reversible ring opening to the monodentate species took place rapidly resulting ultimately in complete hydrolysis (Scheme 1.1).




**Scheme 1.1: Hydrolysis of Chelated Phosphate**

In comparing the above metal catalyzed reaction with the non-metal catalyzed hydrolysis of the cyclic phosphate mentioned previously, some significant differences should be noted.[18a] First, whereas there is an equilibrium established in the metal complex between the mono- and bidentate forms of the phosphate, the ring opening reaction of the organic phosphate is irreversible. In fact, at certain pH values, the bidentate phosphate complex is the thermodynamically preferred form. The stability of this four-membered ring is explained in kinetic terms. The ring opening reaction is opposed by a much faster chelation reaction which is especially rapid when the monodentate phosphate is set up for hydrogen bonding with the coordinated water or hydroxyl ligand. The proposed transition state is shown in Figure 1.5.

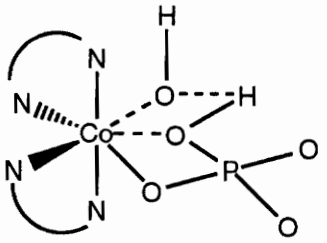
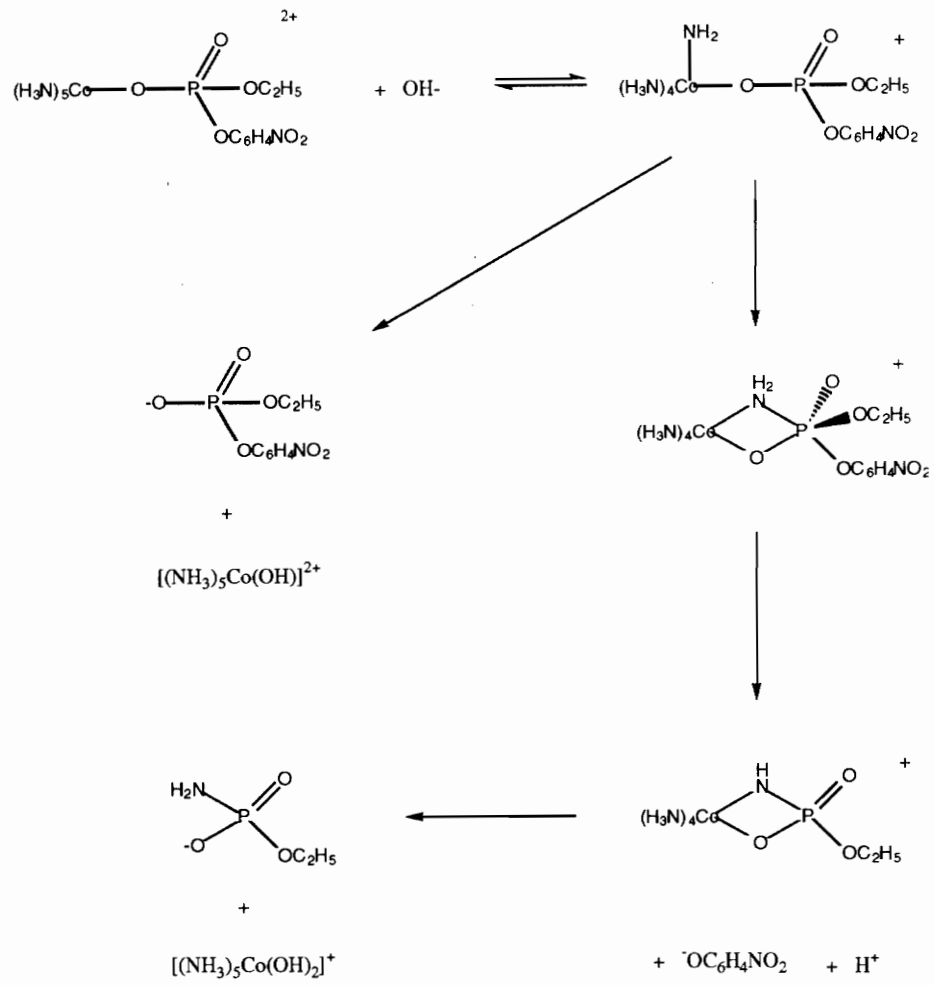



**Figure 1.5: Proposed Transition State for Chelation of Monodentate Phosphate**

It is postulated that the unavailability of hydrogen bonding to the organic phosphate prevents this type of equilibrium between mono- and bidentate phosphates to occur in that

system. A second difference in the metal catalyzed vs. non-catalyzed systems is the mechanism of ring opening. Whereas the ring opening reaction usually occurs in the organic phosphate by cleavage of the P-O bond except in the case of the methyl ester which can undergo C-O cleavage upon nucleophilic attack at the methyl carbon[22], the mechanism in the catalyzed system mostly involves cleavage of the Co-O bond although the mechanism varies at different pH values. It is interesting to note that the authors of this study believe there is some significance to the fact that the maximum stability of the bidentate form of the phosphate is achieved at pH around 5-7. This observation in such an important pH range could perhaps be related to the effects of phosphate catalysis in living systems.

The difficulty associated with isolation of these complexes suggests that they may be highly reactive and therefore worthy of further investigation. Several groups have tried to synthesize chelating Co(III) phosphate compounds in order to probe the reactivity of the phosphate bonds in these species, but isolation of these complexes in the solid state has remained elusive. In related studies, Sargeson et al.[23] showed that the phosphate esters (4-nitrophenyl phosphato)pentaamminecobalt(1+), (fluorophosphato)pentaamminecobalt(1+), and (2,4-dinitrophenylphosphato)pentaamminecobalt(1+) yielded under basic conditions 4-nitrophenolate, flouride, and 2,4-dinitrophenolate, respectively (see Scheme 1.2). This reaction was thought to proceed via attack of a *cis*-deprotonated ammine ligand at the phosphorus center to produce a four-membered phosphorane chelate intermediate. Under basic conditions this chelate complex eliminated 4-nitrophenolate to yield the bidentate phosphoramidate complex and still further reaction gave the free phosphoramidate presumably by cleavage of the Co-N bond (Scheme 1.2).[23a] None of these chelating intermediates were isolable and their identity was inferred from spectroscopic data.




**Scheme 1.2: Ring Opening of Phosphoramidate Chelate**

In another attempt to isolate the chelated phosphate complex, Ir(III) was substituted for Co(III) since ligand exchange reactions of Ir(III) complexes are typically slower than those involving similar Co(III) compounds. From previous studies it was believed that the phosphorus center was activated toward nucleophilic attack in such strained four-membered ring systems. It was anticipated that the formation of a more stable Ir(III) chelate species may allow for subsequent reactions at the phosphorus center to be studied before ring open could occur. The formation of these chelate complexes was achieved under basic conditions by intramolecular attack of a cis-coordinated hydroxyl group or amide group.[24] Again the chelated species could not be isolated. Loss of the ester group from the

pentacoordinate phosphorus center is followed by attack of HO- and a rapid ring opening reaction. Even though the Ir-O bonds were thought to be less labile than Co-O, the ring opening reaction was more favorable due to the increased size of the iridium which destabilized the four-membered chelate ring.

Although isolation in the solid state of the chelated phosphate species has thus far remained elusive, it has been useful for investigators to study the hydrolysis reactions of coordinated phosphate esters. The mechanism of hydrolysis in most transition metal coordinated phosphates seems to be one of attack at the phosphorus atom resulting in cleavage of the P-O bond in most systems. The relevance of these findings to biological systems is still under investigation.

## Section 1.4 Transition Metal Phosphate Complexes in Catalysis

Several characteristics of the phosphate group have made it ideally suited as a ligand for transition metal catalyst complexes. Phosphate complexes have been found to be more labile than their carboxylate counterparts and are more likely to form polymeric transition metal complexes.[25] Depending upon the degree of protonation, phosphates contain several nucleophilic oxygens which are capable of binding to the metal center. The labile nature of the phosphate group can allow for a phosphate which is bound bi- or tridentate to partially dissociate from the metal center thus creating an open coordination site for catalysis. This phenomenon has been explored by Klemperer, et al., in an Ir(I) system containing the tridentate phosphate $P_3O_9^{3-}$.[26] The complex $[(COD)Ir(P_3O_9)](TBA)_2$ (COD=1,5-cyclooctadiene, TBA=tetra-n-butylammonium) is prepared by allowing $[(COD)Ir(CH_3CN)_2]PF_6$ and $(P_3O_9)(TBA)_3$ to react in methylene chloride. The resulting complex has been characterized by x-ray crystallography which shows a five-coordinate, square-pyramidal configuration about the 18 electron iridium(I) center. The base of the pyramid is occupied by the two olefinic C=C bonds of the COD and two of the oxygens of

the tridentate $P_3O_9^{3-}$ (Figure 1.6). At the apex of the square pyramid is the third oxygen of the $P_3O_9^{3-}$ ligand.

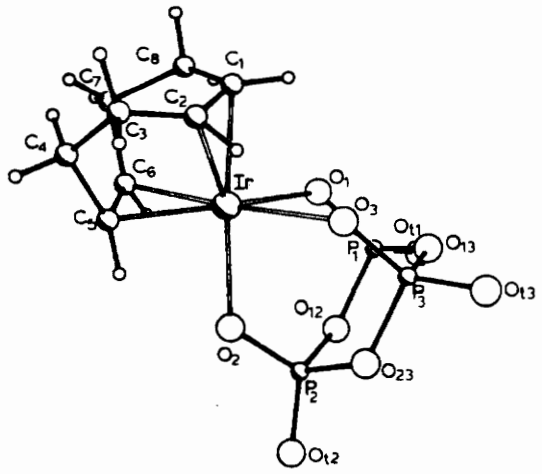
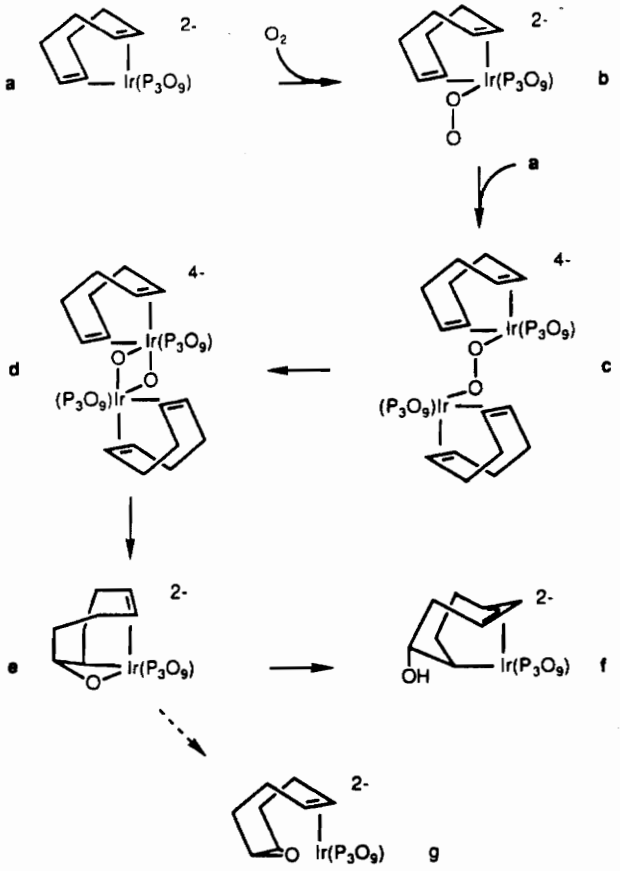



**Figure 1.6: Structure of $[(COD)Ir(P_3O_9)](TBA)_2$ Determined by X-ray Crystallography**

Epoxidation of olefins is a very important transformation for synthetic organic chemists. The addition of an oxygen atom across a C=C bond results in the formation of two new chiral centers and the resulting epoxide is still quite reactive thus lending itself to further reaction chemistry. In the hope that $[(COD)Ir(P_3O_9)](TBA)_2$ might be used as a catalyst for selective epoxidation, Klemperer studied the reactions of this complex with oxygen.[26] Upon reacting $[(COD)Ir(P_3O_9)](TBA)_2$ with 1/2 equivalent of $O_2$ at ambient temperature, the iridium is oxidized resulting in the formation of a six coordinate, 18 electron iridium(III) species that has been characterized by x-ray crystallography (compound f in Scheme 1.4). The $P_3O_9^{3-}$ ligand occupies three facial sites around the pseudooctahedral metal center. The other three octahedral positions are occupied by the COD moiety which is attached to the iridium center via a $\pi$-bonded allyl group and a $\sigma$-bonded carbon. The proposed mechanism for this transformation which is supported by $^{31}P$ NMR spectroscopy is given in Scheme 1.3.[26] Oxygen initially reacts with one equivalent of $[(COD)Ir(P_3O_9)]^{2-}$ to form the $\eta^1$-$O_2$ complex **b** which reacts with a second

equivalent of $[(COD)Ir(P_3O_9)]^{2-}$ to produce the $\mu-\eta^2-O_2\ \kappa^3-P_3O_9$ complex **c**. At this point, an internal redox reaction occurs which oxidizes both metal centers to iridium(III) while dissociating one of the $P_3O_9$ oxygens to produce $\kappa^2-P_3O_9$ thus preserving the six coordinate, 18 electron iridium.

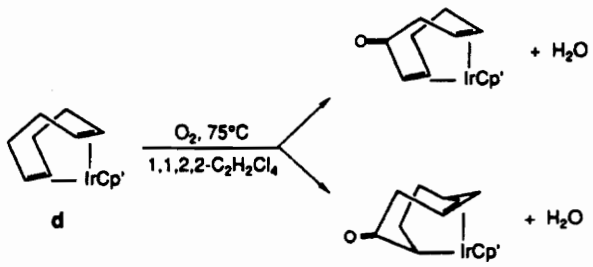



**Scheme 1.3: Mechanism of Oxygen Addition to $[(COD)Ir(P_3O_9)]^{2-}$**

The coordinated oxygen atoms are inserted into the Ir-C bonds to form the $\kappa^2-P_3O_9$ complex **e**. This type of insertion is supported in the literature.[27] Complex **e** reacts further to create complex **f** where one of the acidic allylic protons from the COD has been transferred to the oxygen thus forming the alcohol. It is because of the presence of the acidic allylic protons that Klemperer suggests none of the desired epoxide product **g** was

formed. His group continues to pursue complexes of this type as epoxidation catalysts using non-acidic substrates.

Klemperer has also prepared the complex [(COD)Ir(Cp')] (where Cp'=1,3-$C_5H_3(SiMe_3)_2$), which is analogous to $[(COD)Ir(P_3O_9)]^{2-}$, in order to study the role of the phosphate $P_3O_9^{3-}$ in the oxidation chemistry described previously.[28] In order to react [(COD)Ir(Cp')] with oxygen, forcing conditions are required which ultimately result in the oxidative dehydrogenation of the COD ring forming two different ketonated products (Scheme 1.4).




**Scheme 1.4: Reaction of [(COD)Ir(Cp')] with Oxygen**

This process is believed to proceed via a free-radical chain reaction where the oxygen attacks the COD ring directly and is never attached to the metal center as seen for the phosphate complex.[28] The ease with which the $P_3O_9$ complex reacts with oxygen as compared to the Cp' complex can be explained by the flexidentate nature of the phosphate anion. From the crystal structure of the $P_3O_9$ complex (Figure 1.6) it is evident that the Ir-O bond (2.70 Å) of the apical oxygen in the phosphate ligand is lengthened as compared to the other two Ir-O bonds (2.18 Å). This weakening of the apical Ir-O bond favors facile dissociation of this phosphate linkage allowing oxygen to react easily with the coordinatively unsaturated metal center. This behavior is not possible for the Cp' complex in which all five Ir-C bonds for Cp' are equal in length (by x-ray crystallographic determination). This unique flexidentate nature of the phosphate as well as the weak nature

of the metal phosphate bond[25] thus makes the complex $[(COD)Ir(P_3O_9)]^{2-}$ more susceptible to nucleophilic attack and therefore a better potential catalyst.

In the past few decades, asymmetric catalysis has become very important to synthetic organic chemists. The ability to create enantiomerically enriched compounds is critical for the synthesis of pharmaceuticals and natural products. With the advent of FDA regulations that identify inert enantiomers of a drug as impurity, the chemical industry faces two options: 1) the separation of racemic product mixtures or 2) the development of new syntheses capable of producing the desired enantiomer in great excess. The former option is both labor and cost intensive because the properties of enantiomers do not allow their separation on large scale by common analytical techniques. It is of primary importance to chemical manufacturers to explore inexpensive and effective ways of introducing reactions which produce asymmetry. The most efficient way to effect asymmetric synthesis is to use a small amount of a chiral material (catalyst) to impart chirality onto a large amount of substrate. The use of transition metals as catalysts has been a logical course to pursue for asymmetric organic transformations such as hydrogenation, hydrosilation, oligomerization (polymerization), and epoxidation.[12] Because the phosphate group is so versatile, the production of chiral phosphate catalysts such as BINAP phosphate ((S)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate) has spurred much research into the use of these phosphates as ligands for transition metal catalyzed asymmetric synthesis.

The similarity of the phosphate anion to the carboxylate anion has lent itself to the replacement of carboxylates by phosphates in established catalytic processes. For instance, bimetallic Rh(II) complexes containing bridging chiral carboxylates or carboxamides are known to catalyze asymmetric carbon-carbon bond forming reactions of α-diazoketones such as cyclopropanation, sigmatropic rearrangement, or aromatic cycloaddition with enantiomeric excesses as high as 94%.[29] The general structure of these catalysts is $Rh_2L_4$ where L is the bridging carboxylate or carboxamide (for example, see Figure 1.7).

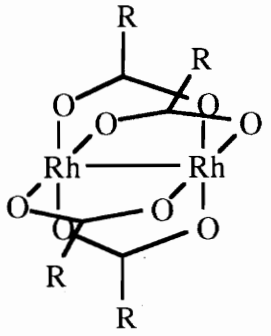
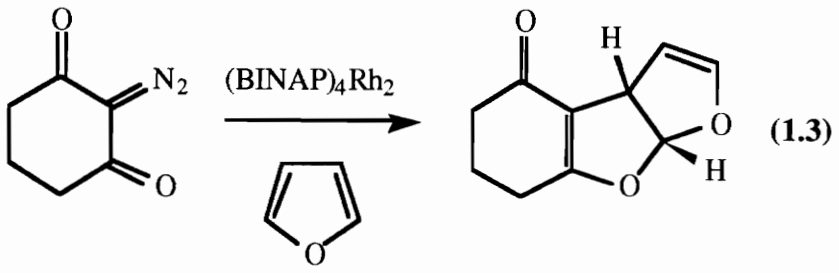



**Figure 1.7: Structure of $Rh_2L_4$**

The complex also contains a Rh-Rh bond which is usually approximately 0.1Å longer for analogous phosphate complexes.[5] This notable feature prompted studies into what effect this structural difference would have on the catalytic properties of the such complexes.

The decompositon of α-diazoketones results in the formation of a very reactive carbene. This decomposition reaction has been catalyzed traditionally by copper salts[30] and more recently by rhodium(II) catalysts.[29] Tetrakis(binaphthol)phosphate dirhodium, $(BINAP)_4Rh_2$, was used in its homochiral form to catalyze the intermolecular addition of diazocyclohexane-1,3-dione to furan (Equation 1.3),[4] a reaction known to be catalyzed by other binuclear rhodium catalysts such as $Rh_2(OAc)_4$. The reaction with the $(BINAP)_4Rh_2$ proceeds with 44% yield and 50% enantiomeric excess of the cycloadduct shown.

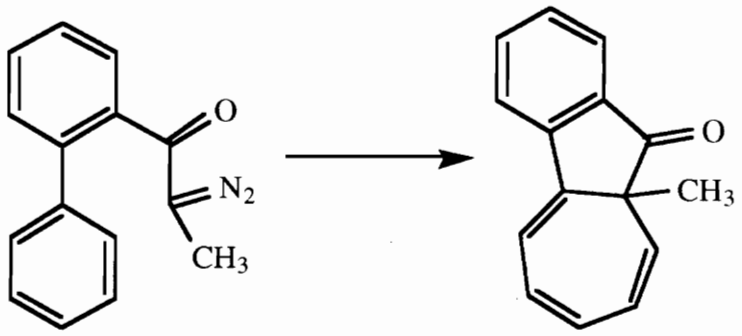



**(1.3)**

A second chiral phosphate catalyst which has been utilized for α-diazoketone decomposition is $Rh_2(HCO_3)_2(BINAP)_2 \cdot 5H_2O$. Although absent from the literature, the structure is probably similar to the $Rh_2L_4$ compounds in Figure 1.7. This complex was

studied for its efficiency in the decomposition of several diazocarbonyl compounds and its ability to effect asymmetric syntheses. Aromatic cycloaddition, C-H insertion, and 2,3-sigmatropic rearrangement reactions were investigated (Equations 1.4-1.6). Overall yields for these reactions were >80% and enantiomeric excesses ranged from 9-60%. From the reactions listed above, the synthetic utility of the chiral phosphate rhodium(II) complexes as catalysts for the asymmetric decomposition of α-diazoketones has become clear. The two complexes described are the first chiral phosphate containing catalysts to be studied thus far and the moderate values of enantiomeric excesses obtained have prompted researchers to continue in their efforts towards making asymmetric catalyst precursors using chiral phosphates.

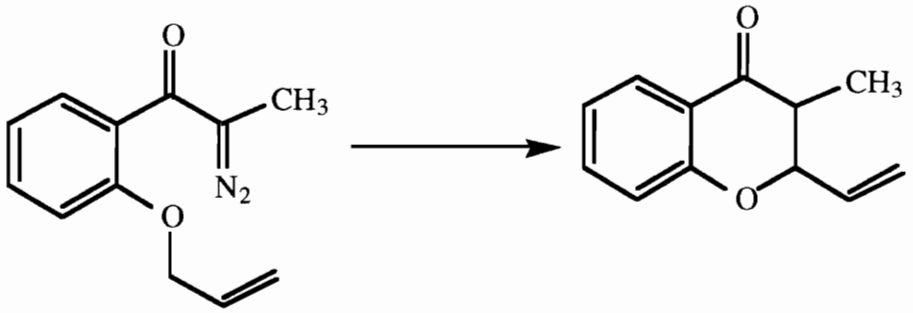
Aromatic cycloaddition




80% yield
60% e.e.

**(1.4)**

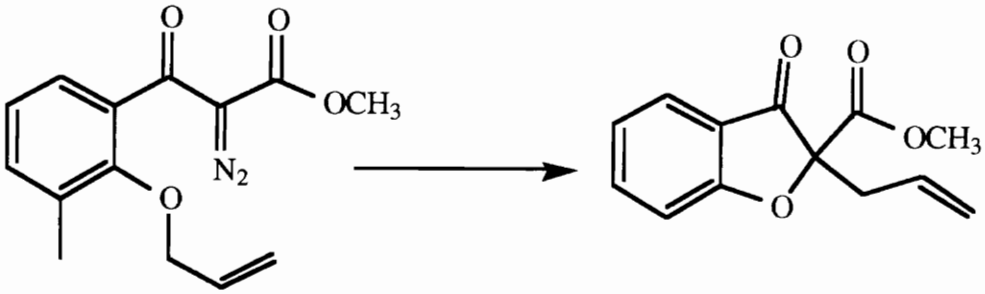
C-H insertion




93% yield
33% e.e.

**(1.5)**

2,3-sigmatropic rearrangement




92% yield
30% e.e.

**(1.6)**

## Section 1.5 References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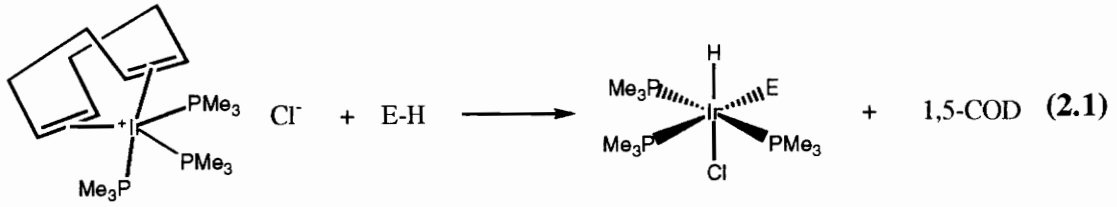
# Chapter 2: Synthesis of Iridium Phosphate Complexes

## Section 2.1: Introduction

The iridium(I) species [Ir(1,5-COD)($PMe_3$)$_3$]Cl is fluxional in solution and roughly square pyramidal in the solid state.[1] The water solubility of [Ir(1,5-COD)($PMe_3$)$_3$]Cl is derived from solvation of the cationic complex by water molecules and is not the result of a molecule of water replacing one of the existing ligands.[1] Facile loss of the 1,5-cyclooctadiene makes this a good source for "Ir($PMe_3$)$_3^+$" and thus a very reactive species carrying with it the ability to possibly impart water solubility to the products of subsequent reactions. Oxidative addition to [Ir(1,5-COD)($PMe_3$)$_3$]Cl of E-H bonds (where E=B,[2] C,[3] N,[4] O,[5] S[6]) has been previously studied (Equation 2.1).




**(2.1)**

The importance of the resulting iridium(III) complexes has been twofold. The species formed in the oxidative addition of E-H now possesses an iridium hydride. Metal hydrido complexes have proven to be key intermediates in a number of catalytic processes including hydrogenation, hydrosilation, hydrocyanation, polymerization, alkene isomerization, and hydroformylation.[7] On an industrial scale, many of these processes are performed in solvents that are environmentally hazardous. Depending upon the compound which has been added to [Ir(1,5-COD)($PMe_3$)$_3$]Cl, the resulting hydride product of the oxidative addition is often water soluble. With water soluble transition metal complexes, the possibility exists for converting such catalytic processes into a more environmentally benign solvent.

[Ir(1,5-COD)($PMe_3$)$_3$]Cl has been shown to oxidatively add amino acids in water under refluxing conditions.[8] The resulting hydrido amino acid complexes showed chelation through the amine nitrogen and carboxylate oxygen resulting in a five-membered metallacycle. Although the facial arrangement could sometimes be detected in solution, most of the complexes observed showed a meridional arrangement of the phosphines since this isomer is believed to be thermodynamically more favorable.[9] It was believed that these chiral complexes might accomplish asymmetric catalytic transformations resulting in enantiomerically enriched products, but these stable, 18 electron octahedral species were found not to be susceptible to further reaction. This result is consistent with many other studies which show iridium(III) complexes to be kinetically inert.[10] Even though they proved to be inert with respect to the addition of alkenes and acetylenes, one of the complexes the L-phenylalanine derivative was identified as an anti-HIV agent[8] (Figure 2.1).

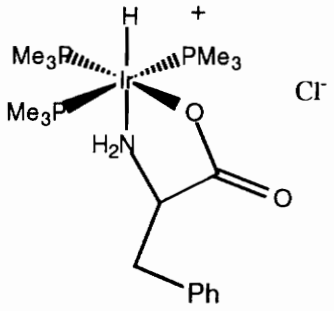
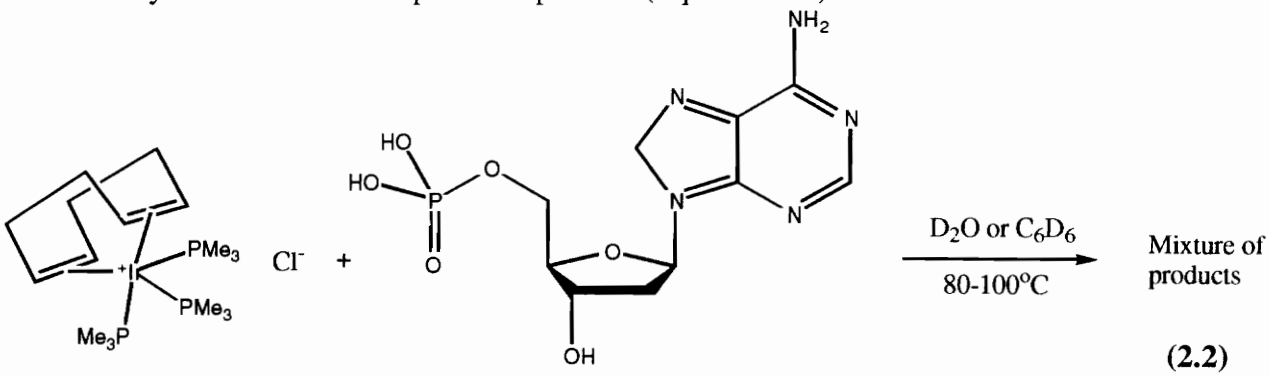



**Figure 2.1: [Ir($PMe_3$)$_3$(H)(L-phenylalanine)]Cl**

Since the amino acid derivatives showed limited activity, oxidative addition of nucleotides to [Ir(1,5-COD)($PMe_3$)$_3$]Cl was studied in hopes of generating improved catalytic reactivity or biological activity. In an attempt to understand the antitumor reactivity of *cis*-platin and related compounds, many groups have studied nucleotide coordination to transition metal complexes using platinum compounds to simulate the binding of the metal center to DNA. Although assisted by hydrogen bonding from the phosphate, most of the

platinum compounds studied do not interact directly through the phosphate group of nucleotides or DNA, but show coordination through an amine in one of the bases (usually N7 of guanosine, see Section 1.2).[11] Though not much information was available on reactions of nucleotides with iridium, it was believed that the iridium center could oxidatively add across either an N-H bond in the base or one of the phosphate O-H bonds in the nucleotide. Oxidative addition of the phosphate O-H would be analogous to the oxidative addition of carboxylic acids to $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$.[12] This reaction has been fully characterized by Ladipo and is discussed in detail in Section 3.1.

In the preparation of the phosphate and nucleotide iridium complexes, a synthetic strategy identical to that of the amino acid complexes was first employed.[8] Initial reactions of $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ and the nucleotide d-AMP (2'-deoxyadenosine-5'-monophosphate) in $D_2O$ at elevated temperature gave unidentifiable mixtures of products as evidenced by $^1H$ and $^{31}P$ NMR spectroscopic data (Equation 2.2).



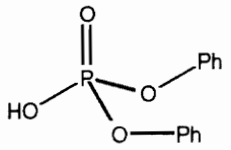

**(2.2)**

d-AMP

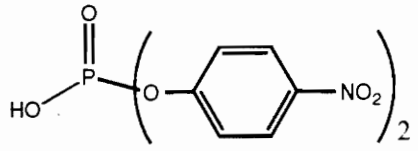
Since there were several sites in the nucleotide available for bonding with the metal center (i.e. lone pairs on oxygen and nitrogen), it was necessary to revert to reactions of $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ with simple alkyl phosphates in an attempt to identify possible binding

modes of the phosphate to the iridium center. Reactions of both mono- and dialkyl phosphates were examined.

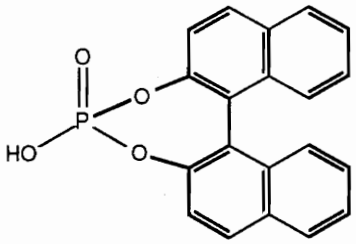
The phosphates which were studied included the disubstituted diphenyl phosphate (DPP), bis(4-nitrophenyl) phosphate (BNPP), (±)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BINAP phosphate), dibenzyl phosphate (DBP), diisooctyl phosphoric acid (DIOPA), bis(2,6-dimethyl-4-heptyl) phosphoric acid (BDHPA), diethylhexyl phosphoric acid (DEHPA), and dihexadecyl phosphate (DHDP) (Figure 2.2), and the monosubstituted isodecyl acid phosphate (IDAP), hexyl acid phosphate (HAP), and mono(2-ethylhexyl) phosphoric acid (MEHPA) (Figure 2.3).



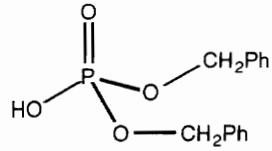

DPP



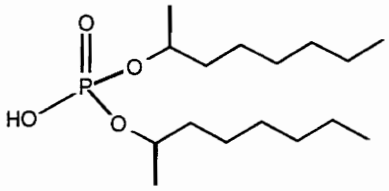

DNPP



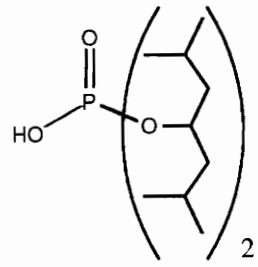

BINAP
phosphate



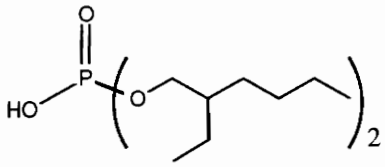

DBP



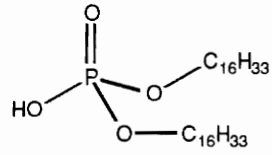

DIOPA




BDHPA

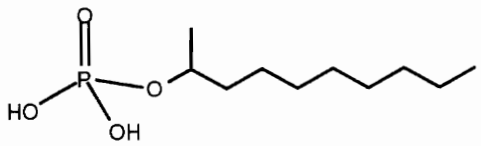



DEHPA

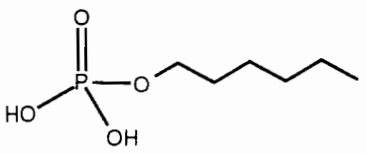



DHDP

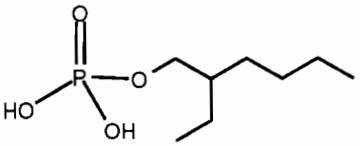
**Figure 2.2: Disubstituted Phosphate Compounds Studied**




IDAP




HAP




MEHPA

**Figure 2.3: Monosubstituted Phosphate Compounds Studied**

## Section 2.2: Synthesis of a Dibenzyl Phosphate Iridium(III) Complex

Preliminary studies on an NMR tube scale revealed that a 1.1:1 mixture of dibenzyl phosphate (DBP) and $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ in $D_2O$ at room temperature probably resulted in protonation of the metal center by the acidic phosphate. No hydride was evident by $^1H$ NMR spectroscopy suggesting that H/D exchange had occurred. In the $^1H$ NMR spectrum, the methyl groups of the phosphines were split into two doublets suggesting a facial arrangement of phosphines. $^{31}P$ NMR spectroscopy confirmed the presence of the protonated species (Figure 2.4). Two singlets were present at 3.7 and -51.6 ppm which corresponded to free dibenzyl phosphate and $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ starting material, respectively. There was a doublet present in the spectrum at -42.9 ppm which corresponded to the two equivalent phosphines trans to the COD ring in the protonated complex $[Ir(D)(1,5\text{-}COD)(PMe_3)_3](Cl)(O_2P(OCH_2Ph)_2)$. A multiplet at -59.1 ppm corresponding to the phosphine trans to a deuterium was further evidence that H/D exchange had occurred.

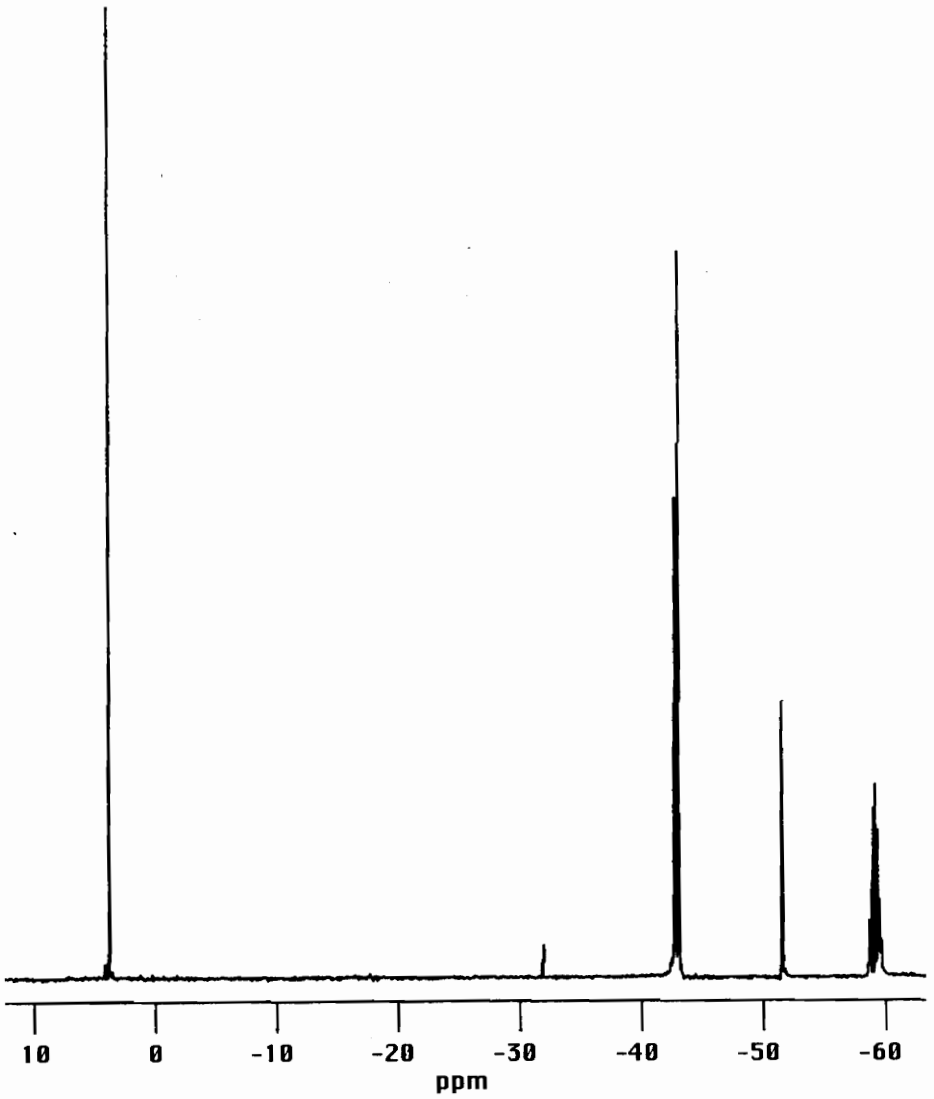



**Figure 2.4: 200 MHz $^{31}P$ NMR Spectrum of [Ir(D)(1,5-COD)($PMe_3$)$_3$](Cl)($O_2P(OCH_2Ph)_2$)**

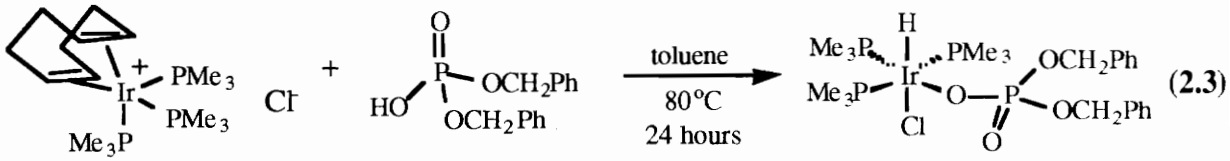
When the tube containing dibenzyl phosphate and [Ir(1,5-COD)($PMe_3$)$_3$]Cl in $D_2O$ was heated to 55°C and higher, several peaks appeared in the hydride region, the most predominant being a broad multiplet at -22.5 ppm, but no single species could be identified from either $^1H$ or $^{31}P$ NMR spectroscopy.

No reaction was evident between a 1.1:1 mixture of dibenzyl phosphate (DBP) and [Ir(1,5-COD)($PMe_3$)$_3$]Cl in $C_6D_6$ at ambient temperature, but when heated to 75-80°C for

several hours, a triplet and doublet appeared in the $^{1}H$ NMR spectrum for the methyl protons of $PMe_3$ indicating that a meridional isomer had been formed. The predominant peak in the hydride region appeared to be a five line resonance at -20.5 ppm. Studies using a 400 MHz NMR spectrometer revealed that this hydride was actually a ten line resonance whose splitting will be discussed later. Peaks were also present for the attached methylene and phenyl protons of the coordinated phosphate. $^{31}P$ NMR spectroscopy revealed three major peaks which were assigned to the attached phosphate, the two equivalent trans $PMe_3$ ligands, and the third $PMe_3$ ligand. It was not evident from these preliminary spectra in which position the phosphate was coordinated to iridium although it did appear that the phosphines were arranged in a meridional fashion.

In an attempt to isolate and purify the product from the oxidative addition described above, a large scale reaction between dibenzyl phosphate (DBP) and [Ir(1,5-COD)$(PMe_3)_3$]Cl in a 1:1 mole ratio was carried out at 80°C initially using mesitylene as a solvent. Mesitylene was utilized to ensure the absence of C-H activation which had been observed in reactions of benzene and [Ir(1,5-COD)$(PMe_3)_3$]Cl.[1] Further studies indicated that C-H activation was not seen in this system so that subsequent large scale reactions were performed in toluene which is easier to remove from the product mixture than the higher boiling mesitylene. Dibenzyl phosphate (DBP) and [Ir(1,5-COD)$(PMe_3)_3$]Cl were allowed to react in a 1:1 mole ratio in toluene at 80°C for 18-24 hrs. Toluene was removed *in vacuo* from the resulting yellow solution leaving a yellow oily solid. Recrystallization was attempted by dissolving the oily solid in $CH_2Cl_2$, but the addition of pentane or ether did not result in an appreciable amount of precipitation. None of the yellow oil seemed to dissolve upon the addition of hexanes. Finally, trituration of the oil using several portions of ether resulted in removal of the yellow impurity into the ether layer leaving a fluffy white solid. The white solid was dried *in vacuo* and was characterized by $^{1}H$, $^{13}C$, and $^{31}P$ NMR spectroscopy, elemental analysis, and infrared spectroscopy. The complex is

believed to have the phosphines arranged meridionally around the iridium center with the phosphate attached in the same plane as the phosphines (Equation 2.3).




**(2.3)**

NMR spectroscopic data support the structural assignment made above. In $C_6D_6$, the phosphate is attached to the metal center and the $^1H$ NMR spectrum is given in Figures 2.5 and 2.6. The spectrum displays a complex multiplet at 7.3 ppm corresponding to the phenyl protons of the phosphate, a doublet at 5.2 ppm corresponding to the methylene protons of the attached phosphate, a virtual triplet at 1.54 ppm corresponding to the methyl groups of the trans $PMe_3$, a doublet at 1.02 ppm corresponding to the methyl protons of the $PMe_3$ which is trans to the phosphate, and a ten line resonance at -20.4 ppm corresponding to the hydride. The hydride is split by all four of the phosphorus nuclei in the complex and is formally a doublet of doublets of triplets. The coupling of the hydride to the two equivalent phosphorus of the trans $PMe_3$ groups splits the peak into a triplet. The magnitude of the coupling constant to the other cis $PMe_3$ phosphorus is coincidentally exactly twice that of the other $PMe_3$ resulting in five lines. Finally, a very small three bond coupling to the phosphorus nucleus in the phosphate results in the splitting of the five line resonance into a ten line resonance (Figure 2.6).

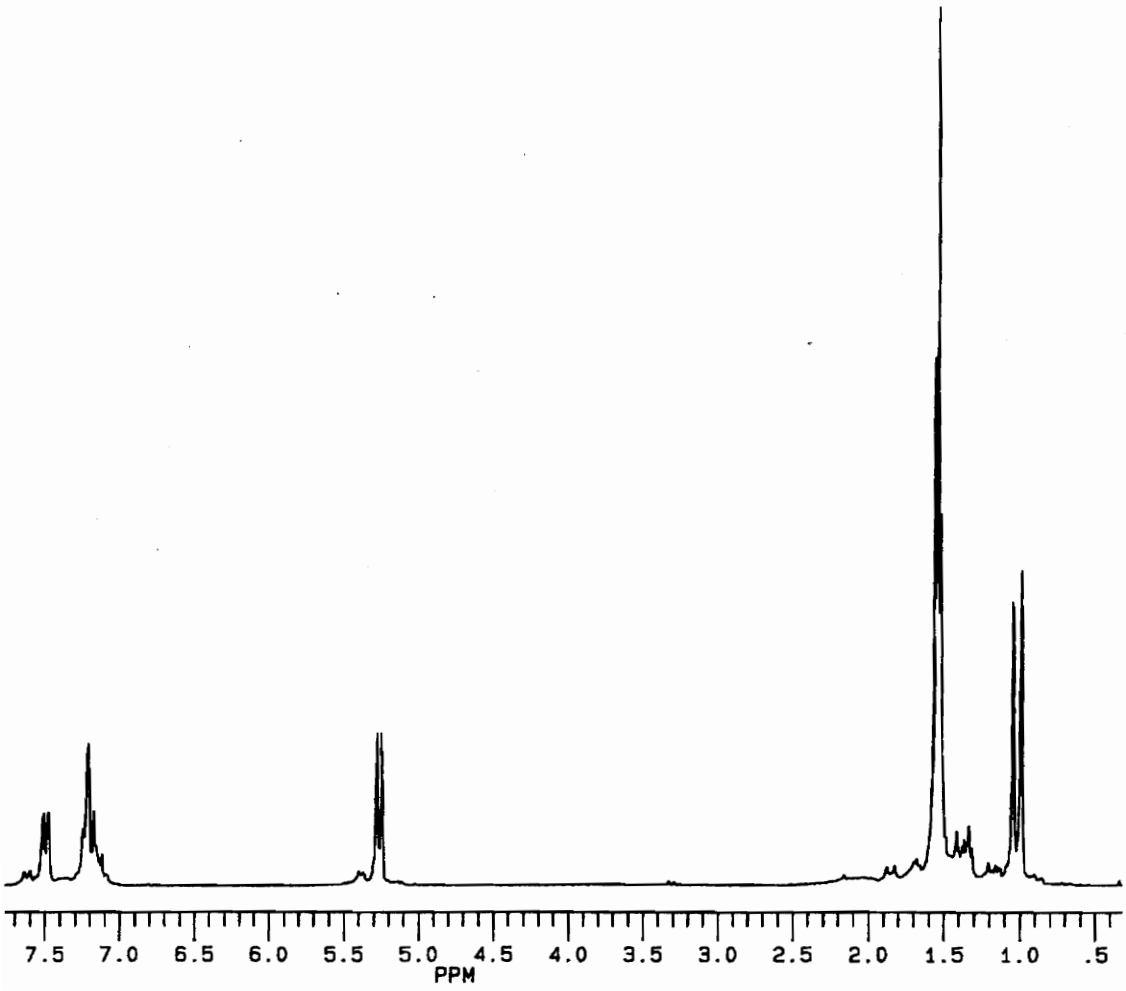



**Figure 2.5: 200 MHz $^1$H NMR Spectrum of *mer*-[Ir(PMe$_3$)$_3$(H)(DBP)Cl] in $C_6D_6$**

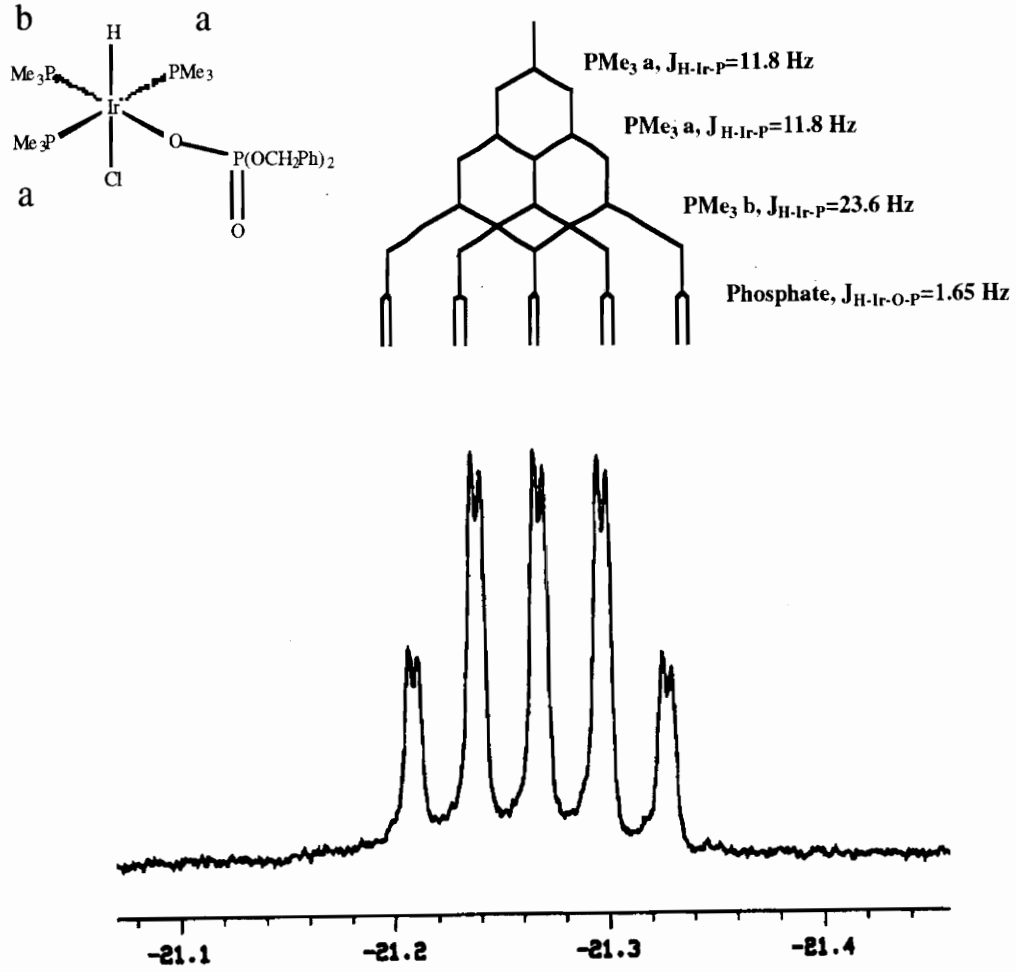



**Figure 2.6: 400 MHz $^{1}H$ NMR Splitting Pattern of the Hydride Resonance in *mer*-[Ir(PMe$_3$)$_3$(H)(DBP)Cl]**

In order to obtain a suitable $^{31}P$ NMR spectrum revealing all of the phosphorus-phosphorus splitting which occurs in [Ir(PMe$_3$)$_3$(H)(DBP)Cl], a high field NMR spectrometer (400 MHz) must be employed taking care to properly position the pulse which decouples proton resonance to eliminate any coupling to the hydride. The $^{31}P$ NMR spectrum in $CDCl_3$ revealed three phosphorus resonances, a doublet at 5.92 ppm corresponding to the coordinated phosphate which is split into a doublet by the phosphine to which it is trans (additional splitting by the two cis phosphines to give a doublet of triplets would be expected, but is small and not seen due to line broadening), a doublet of

doublets at -29.86 ppm corresponding to the two trans phosphines which are split both by the phosphate and the third phosphine, and a doublet of triplets at -47.60 ppm corresponding to the phosphine trans to the phosphate which is split by the pair of cis phosphines and the trans phosphate (Figure 2.7). The resolution of the spectrum is poor presumably due to incomplete decoupling of the hydride resonance.

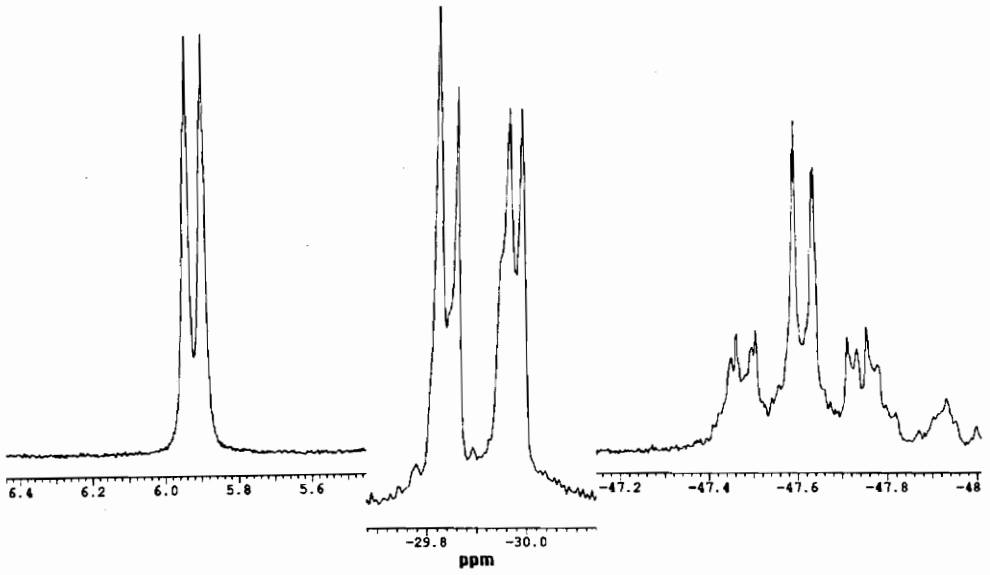



**Figure 2.7: 400 MHz $^{31}P$ NMR Spectrum of *mer*-[Ir(PMe$_3$)$_3$(H)(DBP)Cl]**

A $^{13}C$ APT (attached proton test) spectrum was obtained for [Ir(PMe$_3$)$_3$(H)(DBP)Cl] in $C_6D_6$. The APT spectrum results in normal resonances for methyl and methine carbons and inverted peaks for methylene and quaternary carbons. A doublet of triplets was observed at 19.94 ppm corresponding to the methyl carbon of the PMe$_3$ trans to the phosphate, a triplet at 14.95 ppm corresponding to the methyl groups of the trans PMe$_3$, an inverted doublet at 67.90 ppm corresponding to the methylene carbon of the phosphate, three singlets at 127.49, 128.34, and 128.36 ppm corresponding to the methine protons in the phenyl rings, and an inverted doublet at 139.64 ppm corresponding to the quaternary carbon of the phenyl rings (Figure 2.8).

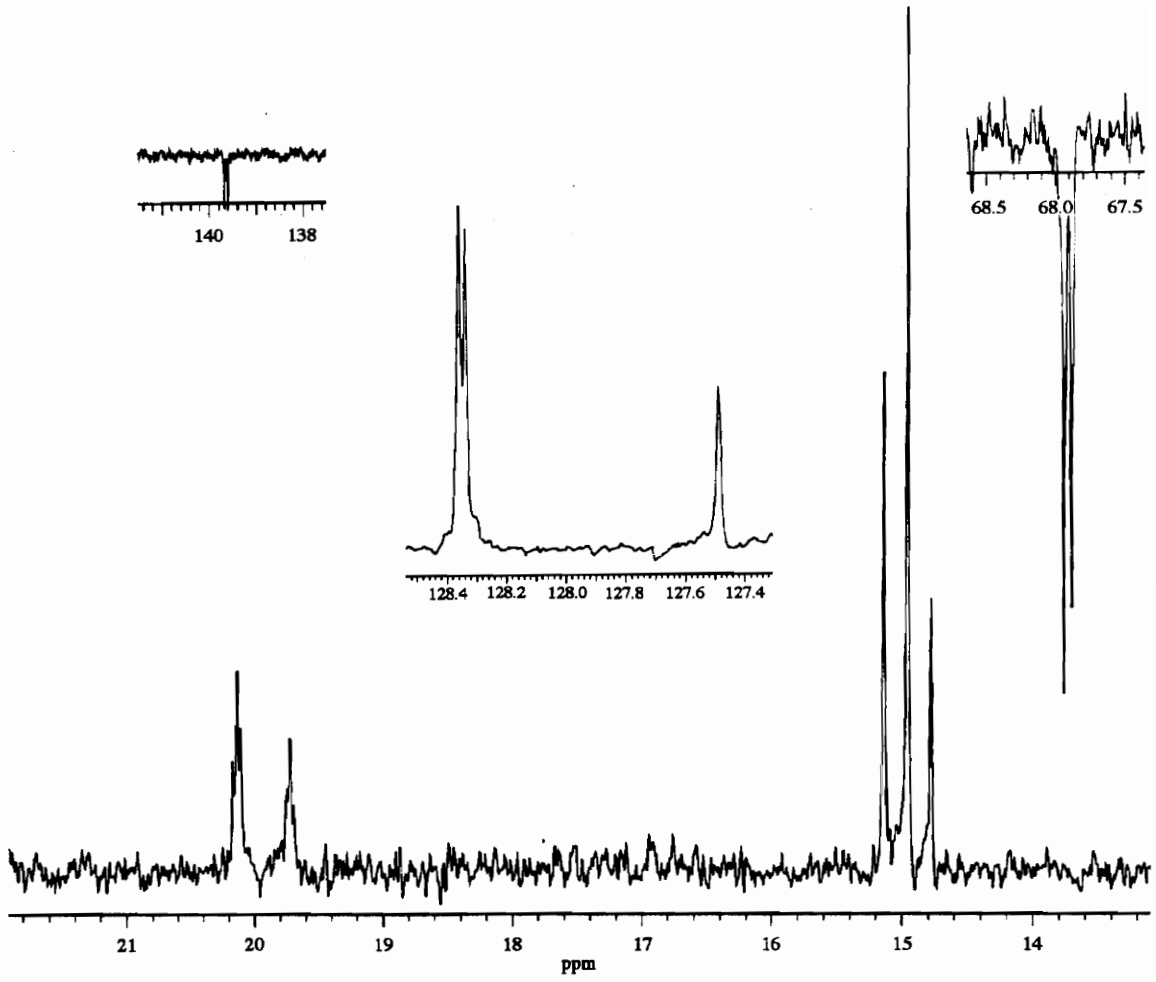



**Figure 2.8: 400 MHz $^{13}C$ APT Spectrum of *mer*-[Ir($PMe_3$)$_3$(H)(DBP)Cl] in $C_6D_6$**

## Section 2.3: Synthesis of Dialkyl Phosphate Iridium(III) Complexes

The general synthesis described in Section 2.2 for the dibenzyl phosphate complex was applied to the remaining phosphate compounds. The other phosphates can be placed in one of three categories: dialkyl phosphates which are monophosphoric acids (DEHPA, DIOPA, BDHPA and DHDP), monoalkyl phosphates which are diphosphoric acids (IDAP, HAP and MEHPA), and diaryl substituted phosphates (DPP, DNPP and BINAP

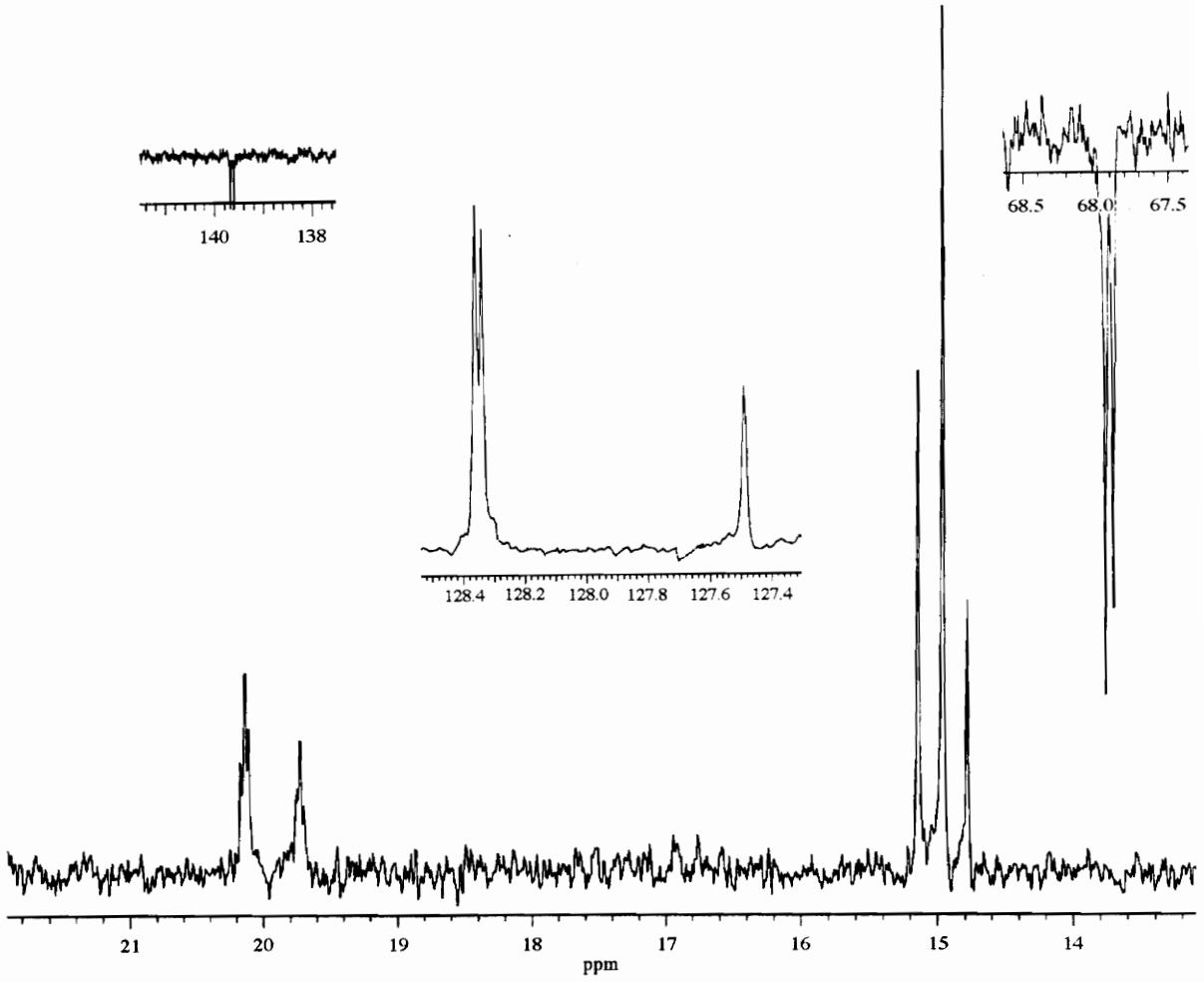



**Figure 2.8: 400 MHz $^{13}C$ APT Spectrum of *mer*-[Ir(PMe$_3$)$_3$(H)(DBP)Cl] in $C_6D_6$**

## Section 2.3: Synthesis of Dialkyl Phosphate Iridium(III) Complexes

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(IDAP, HAP and MEHPA), and diaryl substituted phosphates (DPP, DNPP and BINAP phosphate). Each of these types of phosphates displayed different reactivity with [Ir(1,5-COD)($PMe_3$)$_3$]Cl.

The dialkyl phosphates were the only species to yield pure products under the same reaction conditions as the dibenzyl phosphate. The dihexadecyl phosphate (DHDP) complex was only partially soluble in ether and trituration yielded a white powder as described for the dibenzyl phosphate complex in Section 2.2. The complexes formed from the dialkyl phosphates diethylhexyl phosphoric acid (DEHPA), diisooctyl phosphoric acid (DIOPA) and bis(2,6-dimethyl)-4-heptyl phosphoric acid (BDHPA) were soluble in solvents such as ether and pentane and could not be recrystallized or triturated for purification. In fact, no technique was identified for the purification of these complexes. In the cases of BDHPA and DEHPA, the crude product mixtures which remained after removal of the toluene solvent were light brown oily solids which produced acceptable elemental analyses and NMR and IR spectra so that further purification was unnecessary. For the DIOPA complex, a dark brown oil was consistently obtained which was impure both by elemental analysis and NMR spectroscopy and could not be purified.

The dialkyl phosphate complexes were characterized by elemental analysis and $^1$H NMR, $^{31}$P NMR, $^{13}$C NMR, and IR spectroscopy. $^{31}$P NMR spectra were very similar to the spectrum described for the dibenzyl phosphate complex in section 2.2. $^1$H NMR spectra were not easily understood in the aliphatic region for two reasons. Unlike the dibenzyl phosphate, all of the dialkyl phosphates contain aliphatic protons whose chemical shifts coincide with the chemical shift of the methyl protons of the phosphines. Also, a small amount of unidentified impurity remained in the final products due to the lack of an acceptable means of purification. The peaks for some of these impurities also appeared in the aliphatic region of the $^1$H NMR spectrum.

## Section 2.4: Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl with Diaryl Phosphates

As described previously for the dibenzyl phosphate complex, reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl with the diaryl phosphates shown in Figure 2.2, diphenyl phosphate (DPP), bis(4-nitrophenyl) phosphate (BNPP), and (±)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BINAP phosphate), was followed by $^1H$ and $^{31}P$ NMR spectroscopy. BINAP phosphate and [Ir(1,5-COD)($PMe_3$)$_3$]Cl were first reacted in $D_2O$. Immediately upon mixing the two reactants, it appeared by $^{31}P$ NMR spectroscopy that the iridium center had been protonated and the hydride exchanged for a deuterium. This is difficult to explain since the BINAP phosphate is never seen by $^1H$ or $^{31}P$ NMR due to a lack of solubility in $D_2O$. When heated to 55°C or 100°C, some reaction had occurred but no aryl or hydrido protons were evident by $^1H$ NMR. $^{31}P$ NMR spectra were also quite complex. It is notable that BINAP phosphate peaks are never detected in these NMR spectra even at increased reaction temperatures.

Although a single product is not obtained, the initial reaction which occurs upon mixing the phosphate with [Ir(1,5-COD)($PMe_3$)$_3$]Cl in water may give some insight as to the mechanism by which the phosphates oxidatively add to the metal center. As seen with the initial diaryl phosphate and dibenzyl phosphate (Section 2.2, p. 26) reactions in water, the metal center is protonated at room temperature. If protonation of iridium is the first step in the oxidative addition, it is feasible that nucleophilic attack by the phosphate anion could follow thus displacing the cyclooctadiene ring at elevated temperatures. This might explain the lack of such reactivity in the diaryl phosphates. Since resonance can occur throughout the pi system of the aromatic ring thus delocalizing the negative charge on the oxygen, the nucleophilicity of the diaryl phosphate anions is decreased as compared to the anions of the dialkyl or dibenzyl phosphates. This decreased nucleophilicity could slow the desired reaction and allow for side reactions to occur.

The reaction between BINAP phosphate and [Ir(1,5-COD)($PMe_3$)$_3$]Cl was next attempted using $C_6D_6$ as solvent. At 75°C although the aliphatic region of the $^1H$ NMR spectrum was complex, peaks were present in both $^1H$ and $^{31}P$ NMR which seemed to correspond to the desired BINAP phosphate complex. The main hydride resonance appeared at -20 ppm as the familiar 5-line resonance seen in 200 MHz $^1H$ NMR spectroscopy and the predominant peaks in the $^{31}P$ NMR spectrum were a singlet at 11 ppm and two complex multiplets at -29 and -46 ppm all of which were unresolved by the 200 MHz spectrometer.

In order to isolate some of the product for further study, the reaction between BINAP phosphate and [Ir(1,5-COD)($PMe_3$)$_3$]Cl was carried out on a larger scale using toluene as solvent. $^1H$ NMR spectroscopy of the crude product mixture in $C_6D_6$ revealed that purification was necessary. Trituration using diethyl ether left a tan colored solid while a small amount of a yellow substance was soluble in ether. Both solids were dried and NMR spectra of the tan solid in $CDCl_3$ revealed that it was not one pure product as speculated, but an unidentifiable mixture. $^1H$ and $^{31}P$ NMR spectra in $CDCl_3$ of the ether soluble yellow oil showed a fairly pure compound. $^{31}P$ NMR spectroscopy showed a doublet at -38 ppm and a triplet at -42 ppm indicative of a meridional arrangement of three phosphines around the metal center, but no peak was evident for the BINAP phosphate. In the $^1H$ NMR spectrum there were no peaks in the aryl region also showing the absence of the phosphate. A triplet and doublet overlapped in the aliphatic region confirming meridional phosphines. The only hydride peak was present as a doublet of triplets at -22.4 ppm which had been the minor product in the crude reaction mixture. Further attempts to purify the product were not made.

Small scale reaction of bis(4-nitrophenyl) phosphate (BNPP) with [Ir(1,5-COD)($PMe_3$)$_3$]Cl in $C_6D_6$ gave a complex mixture by $^1H$ and $^{31}P$ NMR spectroscopy and was therefore not pursued on a larger scale.

Preliminary reactions of diphenyl phosphate (DPP) and [Ir(1,5-COD)($PMe_3$)$_3$]Cl in $C_6D_6$ at 80°C yielded promising results. After 22 hours, although a mixture of hydrides was present, the aliphatic region of the $^1H$ NMR spectrum showed a clear doublet and triplet due to the meridional arrangement of phosphines. The $^{31}P$ NMR spectrum was more complicated, but the main peaks were similar to those identified as the dibenzyl phosphate complex. Because of these preliminary findings, a large scale reaction was attempted, but attempts to generate any of the pure diphenyl phosphate complex were unsuccessful. Although no peaks were clearly identified from the NMR spectra, it was believed that activation of the aryl C-H bonds may be occurring after coordination of the phosphate. Similar aryl C-H activation has been seen in the phenyl groups of certain Ir(I)-phosphine complexes.[13] This reaction was not pursued further.

## Section 2.5: Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl with Monoalkyl Phosphates

Reactions of the monoalkylated phosphate species were also modeled after the dibenzyl phosphate system. Each of the three monoalkyl phosphates, isodecyl acid phosphate (IDAP), hexyl acid phosphate (HAP), and mono(2-ethylhexyl) phosphoric acid (MEHPA), were allowed to react with [Ir(1,5-COD)($PMe_3$)$_3$]Cl at 80°C in $C_6D_6$ while the reaction was monitored by $^1H$ and $^{31}P$ NMR spectroscopy. The many methyl and methylene groups of the phosphates made identification of peaks in the aliphatic region of the $^1H$ NMR spectrum difficult, but the presence of several peaks in the hydride region along with a complex $^{31}P$ NMR spectrum suggested that a mixture of products existed. It should be noted that a hydride peak which was similar in splitting and chemical shift to the hydride of the dibenzyl phosphate complex was present in the spectra of each of the monoalkyl phosphate species studied. The presence of the second acid functionality does not therefore impede the desired reaction, but seems to cause other side reactions to take

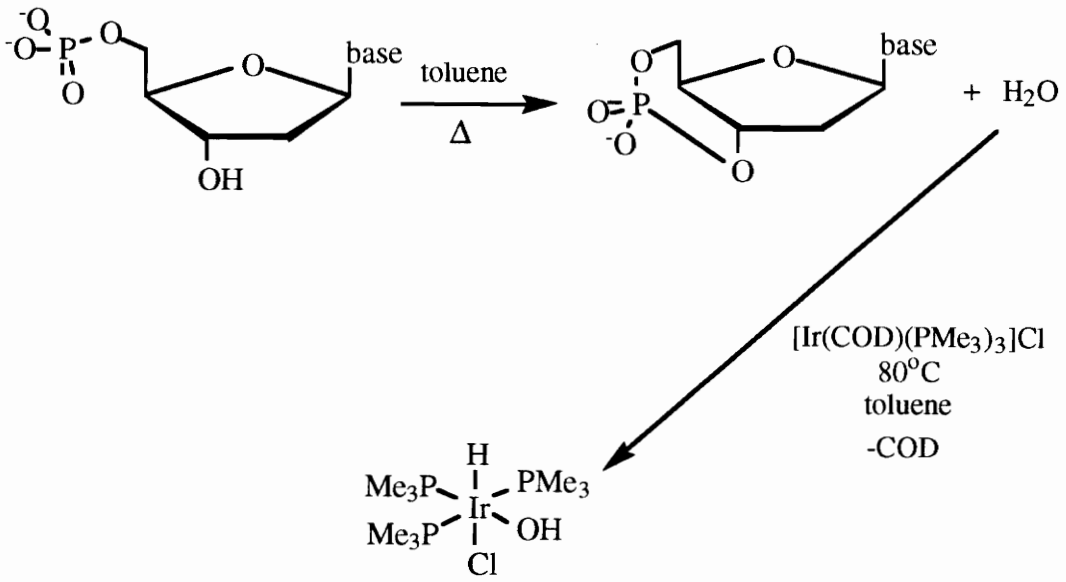
place. A peak in the $^1H$ NMR spectrum which typically occurs anywhere between 9.3 and 13.0 ppm is present throughout the entire time allotted for the reactions and corresponds to the second acid proton of the phosphate. It is presumed since this peak does not disappear that the second acid functionality does not undergo a second oxidative addition either with the same iridium center resulting in an unlikely iridium(V) species or with a second molecule of [Ir(1,5-COD)($PMe_3$)$_3$]Cl resulting in a bridging phosphate complex, although experiments were not performed using more than one equivalent of iridium.

Even though the findings of the preliminary NMR study were unfavorable, the reaction of hexyl acid phosphate was repeated on a larger scale. HAP was allowed to react with [Ir(1,5-COD)($PMe_3$)$_3$]Cl at 75°C in toluene. After 20 hours, solvent was removed *in vacuo* and a green oily solid remained. Trituration with ether left a grayish-green solid. $^1H$ and $^{31}P$ NMR in $C_6D_6$ revealed the presence of the desired product however several impurities remained. Synthesis of the monoalkyl phosphate complexes was not pursued further.

## Section 2.6: Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl with Some Biologically Interesting Phosphates

The reaction of d-AMP (2'-deoxyadenosine-5'-monophosphate) with [Ir(1,5-COD)($PMe_3$)$_3$]Cl was discussed briefly in Section 2.1. When reacted in $D_2O$, a mixture of products is obtained. When the reaction is carried out in $C_6D_6$, the product seems to be the result of the oxidative addition of water to [Ir(1,5-COD)($PMe_3$)$_3$]Cl. Since no water was originally present in the reaction mixture, it has been postulated that the d-AMP undergoes dehydration to lose one mole of water forming the cyclic-d-AMP. The water then reacts with [Ir(1,5-COD)($PMe_3$)$_3$]Cl to form the hydrido hydroxo iridium(III) complex, Ir($PMe_3$)$_3$(H)(OH)Cl (Scheme 2.1). The complex was previously synthesized and characterized by Ladipo by allowing two equivalents of water to react with [Ir(1,5-

COD)($PMe_3$)$_3$]Cl in mesitylene at 90°C.[12] Although Ladipo performed spectroscopic measurements using $CD_2Cl_2$ as solvent, the $^1H$ and $^{31}P$ NMR spectra for the complex made in the d-AMP reaction in $C_6D_6$ solvent are similar. Though extraneous peaks were present, the main resonances in the $^1H$ NMR spectrum in $C_6D_6$ were a triplet at δ 1.5 ppm corresponding to the methyl protons of the two trans $PMe_3$ ligands, a doublet at δ 1.1 ppm corresponding to the methyl protons of the third $PMe_3$ ligand, and a doublet of triplets at δ -21.5 ppm corresponding to the hydride. The hydroxyl proton could not be identified, but may have been buried beneath peaks present in the aliphatic region of the NMR. The $^{31}P$ NMR spectrum consisted of a doublet at δ -38.6 ppm corresponding to the mutually trans $PMe_3$ and a triplet at δ -42.3 ppm corresponding to the central $PMe_3$ ligand.



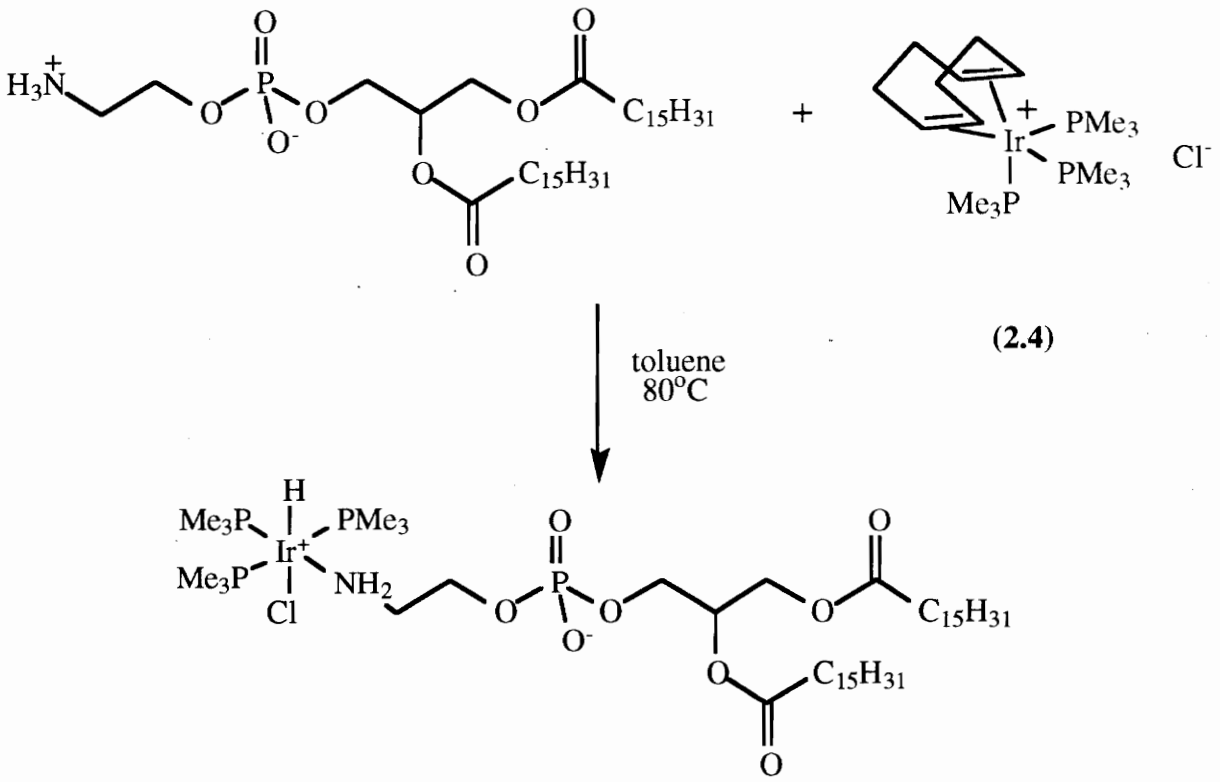

**Scheme 2.1: Reaction of d-AMP with [Ir(1,5-COD)($PMe_3$)$_3$]Cl**

Next, the reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl with (-)-adenosine-3',5'-cyclic monophosphate (cyclic-AMP) in $C_6D_6$ was studied. Cyclic-AMP is a nucleotide which has already been dehydrated. This compound was used in an attempt to keep all sources of water out of the system. However, upon reaction at 80°C spectroscopy seemed to again

indicate the presence of the hydroxo hydrido iridium(III) complex, $Ir(PMe_3)_3(H)(OH)Cl$. The source of water in the system has not been identified.

The lack of reactivity of both of these nucleotides with $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ may be explained by their insolubility in $C_6D_6$. No resonances for the nucleotides could be found in the $^1H$ or $^{31}P$ NMR spectra even upon extensive heating indicating that the compounds were insoluble in $C_6D_6$. Perhaps a different solvent could be used in future studies.

Phospholipids are another type of biologically important phosphate containing molecule. Phospholipids are a major component of biological membranes and can be derived from either glycerol, a three carbon alcohol, or sphingosine, a more complex alcohol. Phospholipids derived from glycerol are known as phosphoglycerides and consist of a glycerol backbone, two fatty acid chains, and a phosphorylated alcohol.[14] In this study, the phosphoglyceride 1,2-dihexadecanoyl-rac-glycero-3-phosphoethanolamine (PEA) was initially allowed to react with $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ in $C_6D_6$ at 70°C. Scale-up of the reaction in toluene resulted in the formation of the N-H addition product $Ir(PMe_3)_3(H)(PEA)Cl$ (Equation 2.4) which was characterized by elemental analysis and $^1H$, $^{31}P$, and $^{13}C$ NMR spectroscopy.




**(2.4)**

The region from δ 1-2 ppm in the $^{1}H$ NMR spectrum was complex, due to the large number of inequivalent aliphatic protons in PEA. A quartet appears at δ -20.85 ppm corresponding to the hydride. From studying the $^{31}P$ NMR spectrum, it becomes obvious from the lack of phosphate-phosphine coupling that the phosphate oxygen is not directly attached to the iridium center. The $^{31}P$ NMR spectrum consists of a singlet at δ 3.2 ppm corresponding to the phosphate, a doublet at δ -41.3 ppm corresponding to the trans $PMe_3$, and a triplet at δ -43.3 ppm corresponding to the third $PMe_3$ ligand. Although PEA is not attached to the iridium center through the phosphate oxygen as proposed, this complex awaits testing for biological activity.

## Section 2.7: Experimental

### General Considerations

Unless otherwise specified, all manipulations were carried out using a double manifold Schlenk line under an atmosphere of dinitrogen or argon. Especially air sensitive manipulations were carried out under an atmosphere of dinitrogen in a MB-150-M glovebox purchased from M. Braun. Toluene, pentane, ether and methylene chloride were purchased from Fisher Scientific. Pentane and ether were distilled from sodium/potassium alloy and benzophenone under nitrogen. Methylene chloride was distilled from $P_2O_5$ under nitrogen and toluene was distilled from either $P_2O_5$ or potassium/benzophenone under nitrogen. Where water was used as a solvent, deionized water, not distilled, was utilized unless otherwise noted. Deuterated solvents were obtained from Cambridge Isotopes and were used without further purification. Iridium trichloride trihydrate, $IrCl_3 \cdot 3H_2O$, was purchased from Johnson Matthey and hexachloroiridic acid, $H_2IrCl_6$, was purchased from PGM Chemicals, Inc. Both were used as received. Dibenzyl phosphate (DBP), diphenyl phosphate (DPP), bis(4-nitrophenyl)phosphate (BNPP), dihexadecyl phosphate (DHDP) and (±)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BINAP phosphate) were purchased from Aldrich Chemical Company. 2'-Deoxyadenosine-5'-monophosphate (d-AMP), (-)-adenosine-3',5'-cyclic monophosphate (cyclic-AMP), and (PEA) were purchased from Sigma Chemical Company. Diisooctyl phosphoric acid (DIOPA), bis(2,6-dimethyl-4-heptyl) phosphoric acid (BDHPA), diethylhexyl phosphoric acid (DEHPA), isodecyl acid phosphate (IDAP), hexyl acid phosphate (HAP), and monoethylhexyl phosphoric acid (MEHPA) were obtained from Albright & Wilson, Americas. All phosphates were used as received.

$^{1}H$ and $^{31}P$ NMR spectra were obtained using a Bruker WP-200 MHz (at 200.132 or 81.015 MHz, respectively) or a Varian UN-400 MHz NMR (at 399.944 or 161.903 MHz) spectrometer. $^{13}C$ NMR spectra were obtained on the Varian UN-400 MHz

instrument at 100.578 MHz. Chemical shifts are reported in δ units and are referenced to residual solvent peaks. Infrared spectra were obtained by KBr pellet using a Perkin Elmer 283B infrared spectrometer unless otherwise specified. Elemental analyses were obtained from either Atlantic Microlab in Norcross, Georgia or Galbraith Laboratories in Knoxville, Tennessee.

**Synthesis of $[Ir(1,5\text{-}COD)Cl]_2$: SRCI023**

To a 250 mL side arm flask equipped with a magnetic stirbar was charged $IrCl_3.3H_2O$ (10.00 grams, 28.36 mmol). To the flask was charged 100 mL deionized water and 36 mL isopropanol. 1,5-Cyclooctadiene (5.0 mL, 0.040 mmol) was added via syringe. The flask was fitted with a reflux condenser and the solution was stirred and heated to reflux. The mixture has held at reflux for 21 hours during which a red precipitate formed. The mixture was cooled to ambient temperature and the red crystalline solid was collected on a fritted glass funnel. The solid was washed using two 75 mL portions of methanol followed by two 75 mL portions of pentane. The solid was transferred to a 250 mL side arm flask and was dried *in vacuo*. Mass of $[Ir(1,5\text{-}COD)Cl]_2$ = 7.74 grams (81.3% yield based on $IrCl_3.3H_2O$).

**Synthesis of $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$: SRCI027**

Into a 250 mL side arm flask equipped with septum and stirbar was charged $[Ir(1,5\text{-}COD)Cl]_2$ (7.74 grams, 11.5 mmol). Toluene (200 mL) was added and the solid was allowed to dissolve. Trimethylphosphine (7.27 mL, 70.3 mmol) was added slowly via syringe. Immediately a beige colored solid precipitated from the orange-red solution. The off-white slurry was stirred for 24 hours. The solid was collected in a fritted tube under nitrogen atmosphere and was washed with two 75 mL portions of toluene followed

by two 75 mL portions of pentane. The off-white solid was dried *in vacuo*. Mass of $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ = 8.21 grams (63.1% yield based on $[Ir(1,5\text{-}COD)Cl]_2$).

**Reaction of $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ and Dibenzyl Phosphate in $D_2O$: SRCI061, SRCI067**

A screw cap NMR tube was charged with $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ (38 mg, 0.067 mmol) and dibenzyl phosphate (21 mg, 0.074 mmol). $D_2O$ (0.75 mL) was added via syringe. Upon mixing most of the solids dissolved immediately. $^1H$ and $^{31}P$ NMR spectra were obtained after 30 minutes at ambient temperature. NMR spectra were also recorded after 24 and 72 hours at ambient temperature. The tube was heated 55°C and NMR spectra were obtained after heating for several hours. In a second experiment (SRCI067), a mixture of the two reactants in the same mole ratio as above was heated to 100°C immediately after mixing. $^1H$ and $^{31}P$ NMR spectra were obtained after 24 hours. Upon mixing at room temperature, NMR spectra revealed that the protonated species $[Ir(1,5\text{-}COD)(PMe_3)_3(D)]^{2+}$ had been formed where the counterions were $Cl^-$ and $(PhCH_2O)_2PO_2^-$ and the hydride had begun to exchange with deuterium from the $D_2O$ solvent. Upon heating, a mixture of products which were not identifiable by NMR spectroscopy was formed.

**Reaction of $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ and Dibenzyl Phosphate in $C_6D_6$: SRCI071**

To a screw cap NMR tube was charged $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ (38 mg, 0.067 mmol) and dibenzyl phosphate (21 mg, 0.074 mmol). $C_6D_6$ (0.7 mL) was added via syringe. Upon mixing most of the solids dissolved leaving a cloudy light yellow solution. Upon heating slightly, all solids dissolved. The tube was heated 75-80°C. After 18 hours, $^1H$ and $^{31}P$ NMR spectra were obtained of the dark yellow solution. The main compound in the crude product was identified as $[Ir(PMe_3)_3(H)(DBP)Cl]$ based on the following data (integration was omitted due to impurities in the crude product mixture): $^1H$ NMR (200

MHz, $C_6D_6$): δ 7.34 ppm (cm, PhH); δ 5.19 ppm (m, $PhCH_2$); δ 1.49 ppm (t, trans $PMe_3$); δ 1.02 ppm (d, $PMe_3$); δ -20.50 ppm (dt, Ir-H). $^{31}P$ NMR (200 MHz, $C_6D_6$): δ 6.0 ppm (s, phosphate); δ -29.4 ppm (d, trans $PMe_3$); δ -47.2 ppm (dt, $PMe_3$).

**Synthesis of $[Ir(PMe_3)_3(H)(DBP)Cl]$: SRCI231**

To a 100 mL side arm flask equipped with stirbar and septum was charged [Ir(1,5-COD)$(PMe_3)_3$]Cl (411 mg, 0.728 mmol) and dibenzyl phosphate (203 mg, 0.729 mmol). Toluene (25 mL) was added via syringe. Upon mixing the solids did not completely dissolve immediately. The flask was heated to 75-80°C. After a few hours the solids dissolved leaving a clear yellow solution. Heating was continued for 20 hours total after which the flask was cooled to ambient temperature. Toluene was removed under vacuum and the product was dried under vacuum for approximately 18 hours. Ether (10 mL) was added to the remaining oily yellow solid. The solid was crushed thoroughly using a spatula and allowed to stir in the ether for one hour. The yellow ether solution was removed via cannula technique. This procedure was repeated using 10 mL portions of ether until the solution being removed from the solid was no longer yellow (approximately 6 times). The white solid was dried in vacuo. Mass of product: 499 mg (93.3% yield based on [Ir(1,5-COD)$(PMe_3)_3$]Cl). Identified as $[Ir(PMe_3)_3(H)(DBP)Cl]$ based on the following data: $^1H$ NMR (200 MHz, $C_6D_6$): δ 7.34 ppm (cm, 10H, PhH); δ 5.25 ppm (d, 4H, $PhCH_2$); δ 1.54 ppm (t, 18H, trans $PMe_3$); δ 1.02 ppm (d, 9H, $PMe_3$); δ -20.39 ppm (ddt, 1H, Ir-H). $^{31}P$ NMR (400 MHz, $C_6D_6$): δ 5.92 ppm (d, $J_{P\text{-}O\text{-}Ir\text{-}P\ trans}$=7.4 Hz,, 1P, Ir-O-P); δ -29.86 ppm (dd, $J_{P\text{-}Ir\text{-}P}$=21.7 Hz, $J_{P\text{-}Ir\text{-}OP}$=4.9 Hz, 2P, trans $PMe_3$); δ -47.60 ppm (dt, $J_{P\text{-}Ir\text{-}P}$=20.2 Hz, $J_{P\text{-}Ir\text{-}O\text{-}P}$=6.9 Hz, 1P, $PMe_3$). $^{13}C$ NMR (400 MHz,$C_6D_6$): δ 139.63 ppm (d, quaternary phenyl C); δ 128.36 ppm (s, phenyl); δ 128.34 ppm (s, phenyl); δ 127.49 ppm (s, phenyl); δ 67.90 ppm (d, $Ph\underline{C}H_2$); δ 19.93 ppm (dt, $P(\underline{C}H_3)_3$); δ 14.95 ppm (t, trans $P(\underline{C}H_3)_3$). IR (KBr): $\nu_{Ir\text{-}H}$, 2155.3 $cm^{-1}$ (m); $\nu_{P=O}$, 1231.5 $cm^{-1}$

(m); $\nu_{P\text{-}O\text{-}C}$, 949.5 $cm^{-1}$ (s). Elemental analysis: Calc'd for $Ir_1C_{23}H_{42}P_4O_4Cl$: C: 37.63%; H: 5.77%. Found: C: 37.54%; H: 5.88%.

### Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and Dialkyl Phosphates in $C_6D_6$: SRCI131, SRCI135, SRCI137, and SRCI177

To screw cap NMR tubes was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl and each of the dialkyl phosphates in approximately a 1:1 mole ratio (usually with a slight excess of phosphate): BDHPA, SRCI131; DIOPA, SRCI135; DEHPA, SRCI137; and DHDP, SRCI177. $C_6D_6$ (0.7-0.8 mL) was added via syringe. Upon mixing most of the solids dissolved leaving cloudy light yellow solutions. In each case any remaining solids dissolved upon heating slightly. The tubes were heated to 75-80°C. After 18-20 hours, $^1H$ and $^{31}P$ NMR spectra were obtained of the dark yellow solutions. Although impurities existed, it was evident from the NMR spectra that the main product was similar to that obtained when using dibenzyl phosphate. As a consequence, each of these reactions was carried out on a larger scale.

### Synthesis of [Ir($PMe_3$)$_3$(H)(DEHPA)Cl]: SRCI145

A 50 mL side arm flask equipped with septum and stirbar was charged with [Ir(1,5-COD)($PMe_3$)$_3$]Cl (427 mg, 0.757 mol). Toluene (20 mL) was added via syringe. Diethylhexyl phosphoric acid (DEHPA, 259 mg, 0.803 mmol) was added via syringe. Upon mixing, a light yellow slurry resulted. The flask was heated to 80°C. After a few hours, the solids had dissolved completely leaving a clear yellow solution. The solution was heated for a total of 20 hours and cooled to ambient temperature. Toluene was removed *in vacuo*. The yellow oily solid was dissolved in 1 mL methylene chloride and was tranferred a 1 dram vial. Methylene chloride was removed *in vacuo*. The light brown product appeared to be a glassy solid. Mass of solid: 526 mg (89.2% yield based on [Ir(1,5-COD)($PMe_3$)$_3$]Cl). Identified as [Ir($PMe_3$)$_3$(H)(DEHPA)Cl] based on the

following data: $^1$H NMR (400 MHz, $C_6D_6$): δ 4.13 ppm (m, 2H, DEHPA methine); δ 1.63 ppm (t, $J_{P\text{-}C\text{-}H}$=3.98 Hz, 18H, trans $PMe_3$); δ 1.10 ppm (d, $J_{P\text{-}C\text{-}H}$=10.16 Hz, 9H, $PMe_3$); δ -20.47 ppm (ddt, $J_{P\text{-}O\text{-}Ir\text{-}H}$=1.7 Hz, $J_{P\text{-}Ir\text{-}H}$(trans $PMe_3$)=11.6 Hz, $J_{P\text{-}Ir\text{-}H}$($PMe_3$)=23.2 Hz, 1H, Ir-H); all other aliphatic protons could not be assigned due to overlap. $^{31}$P NMR (400 MHz, $C_6D_6$): δ 6.22 ppm (dt, $J_{P\text{-}O\text{-}Ir\text{-}P\ trans}$=6.9 Hz, $J_{P\text{-}O\text{-}Ir\text{-}P\ cis}$=3.0 Hz, 1P, Ir-O-P); δ -29.67 ppm (d, $J_{P\text{-}Ir\text{-}P}$=21.2 Hz, 2P, trans $PMe_3$); δ -47.78 ppm (dt, $J_{P\text{-}Ir\text{-}P}$=21.2 Hz, $J_{P\text{-}Ir\text{-}O\text{-}P}$=6.9 Hz, 1P, $PMe_3$). $^{13}$C NMR (400 MHz,$C_6D_6$): δ 67.94 ppm (d, $J_{P\text{-}O\text{-}C}$=6.13 Hz, P-O-$CH_2$); 41.08 ppm (d, $J_{P\text{-}O\text{-}C\text{-}C}$=7.64 Hz, P-O-C-CH); 30.88, 30.75, 29.46 ppm (s, P-O-C-C-$CH_2$); 24.06, 23.99, 23.58 ppm (s, DEHPA $CH_2$); δ 20.05 ppm (dt, $J_{P\text{-}C}$=41.94 Hz, central P($\underline{C}H_3)_3$); δ 15.06 ppm (t, $J_{P\text{-}C}$=18.30 Hz, trans P($\underline{C}H_3)_3$); δ 11.37, 14.38 ppm (d, DEHPA $CH_3$). IR (KBr): $\nu_{Ir\text{-}H}$, 2169.6 cm$^{-1}$ (m); $\nu_{P=O}$, 1226.0 cm$^{-1}$ (m); $\nu_{P\text{-}O\text{-}C}$, 954.5 cm$^{-1}$ (s). Elemental analysis: Calc'd for $Ir_1C_{25}H_{62}P_4O_4Cl$: C: 38.58%; H: 8.02%. Found: C: 38.52%; H: 8.08%.

**Synthesis of [Ir($PMe_3$)$_3$(H)(BDHPA)Cl]: SRCI215**

To a 100 mL side arm flask equipped with septum and stirbar was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (259 mg, 0.459 mol). Toluene (20 mL) was added via syringe. Bis(2.6-dimethyl-4-heptyl) phosphoric acid (BDHPA, 173 mg, 0.494 mmol) was added via syringe. Upon mixing, a light yellow slurry resulted. The flask was heated to 80°C. After a few hours, the solids had dissolved completely leaving a clear yellow solution. The solution was heated for a total of 18 hours and cooled to ambient temperature. Toluene was removed *in vacuo* resulting in a light brown oily solid. Mass of solid: 175 mg (47.4% yield based on [Ir(1,5-COD)($PMe_3$)$_3$]Cl). Identified as [Ir($PMe_3$)$_3$(H)(BDHPA)Cl] based on the following data: $^1$H NMR (400 MHz, $C_6D_6$): δ 4.63 ppm (dp, $J_{H\text{-}C\text{-}C\text{-}H}$=$J_{P\text{-}O\text{-}C\text{-}H}$=6.81 Hz, P-O-CH); δ 1.52 ppm (t, $J_{P\text{-}C\text{-}H}$=3.85 Hz, trans $PMe_3$); δ 0.98 ppm (d, $J_{P\text{-}C\text{-}H}$=10.16 Hz, $PMe_3$); δ -20.64 ppm (ddt, $J_{P\text{-}O\text{-}Ir\text{-}H}$=2.20 Hz, $J_{P\text{-}Ir\text{-}H}$(trans $PMe_3$)=11.74 Hz,

$J_{P\text{-}Ir\text{-}H}(PMe_3)$=23.48 Hz, Ir-H); all other aliphatic protons could not be assigned due to overlap. $^{31}P$ NMR (400 MHz, $C_6D_6$): δ 5.71 ppm (d, $J_{P\text{-}O\text{-}Ir\text{-}P\ trans}$=6.96 Hz, 1P, Ir-O-P); δ -29.68 ppm (d, $J_{P\text{-}Ir\text{-}P}$=21.37 Hz, 2P, trans $PMe_3$); δ -48.19 ppm (dt, $J_{P\text{-}O\text{-}Ir\text{-}P}$=6.53 Hz, $J_{P\text{-}Ir\text{-}P}$=21.16 Hz, 1P, $PMe_3$). $^{13}C$ NMR (400 MHz,$C_6D_6$): δ 72.30 ppm (d, $J_{P\text{-}O\text{-}C}$=5.33 Hz, P-O-CH); δ 46.29 ppm (t, P-O-C-$\underline{C}H_2$); δ 24.84, 24.66 ppm (s, P-O-C-C-$\underline{C}H$); δ 23.55, 23.33, 23.27, 23.24 ppm (s, BDHPA $CH_3$); δ 20.17 ppm (dt, $J_{P\text{-}C}$=41.94 Hz, central P($\underline{C}H_3)_3$); δ 15.10 ppm (t, $J_{P\text{-}C}$=18.30 Hz, trans P($\underline{C}H_3)_3$). IR (KBr): $\nu_{Ir\text{-}H}$, 2154.3 $cm^{-1}$ (m); $\nu_{P=O}$, 1197.5 $cm^{-1}$ (m); $\nu_{P\text{-}O\text{-}C}$, 953.2 $cm^{-1}$ (s). Elemental analysis: Calc'd for $Ir_1C_{27}H_{63}P_4O_4Cl$: C: 40.22%; H: 8.25%. Found: C: 40.04%; H: 8.07%.

**Synthesis of [Ir(PMe$_3$)$_3$(H)(DIOPA)Cl]: SRCI197**

To a 100 mL side arm flask equipped with septum and stirbar was charged [Ir(1,5-COD)(PMe$_3$)$_3$]Cl (410 mg, 0.727 mol). Toluene (20 mL) was added via syringe. Diisooctyl phosphoric acid (DIOPA, 255 mg, 0.791 mmol) was added via syringe. Upon mixing, a light yellow slurry resulted. The flask was heated to 80°C. After a few hours, the solids had dissolved completely leaving a clear yellow solution. The solution was heated for a total of 18 hours and cooled to ambient temperature. Toluene was removed *in vacuo* resulting in a light brown oily solid. Identified as [Ir(PMe$_3$)$_3$(H)(BDHPA)Cl] based on the following data: $^1H$ NMR (400 MHz, $C_6D_6$): δ 1.54 ppm (t, trans $PMe_3$); δ 1.04 ppm (d, $J_{P\text{-}C\text{-}H}$=10.03 Hz, $PMe_3$); δ -20.64 ppm (dt, $J_{P\text{-}Ir\text{-}H}$(trans $PMe_3$)=11.79 Hz, $J_{P\text{-}Ir\text{-}H}(PMe_3)$=23.59 Hz, Ir-H); all other aliphatic protons could not be assigned due to overlap. $^{31}P$ NMR (400 MHz, $C_6D_6$): δ 6.15 ppm (m, 1P, Ir-O-P); δ -29.65 ppm (d, $J_{P\text{-}Ir\text{-}P}$=18.99 Hz, 2P, trans $PMe_3$); δ -48.19 ppm (m, 1P, $PMe_3$).

**Synthesis of [Ir(PMe$_3$)$_3$(H)(DHDP)Cl]: SRCI213**

To a 100 mL side arm flask equipped with septum and stirbar was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (336 mg, 0.596 mol) and dihexadecyl phosphate (DHDP, 326 mg, 0.596 mmol). Toluene (20 mL) was added via syringe. Upon mixing, a light yelow slurry resulted. The flask was heated to 80°C. After a few hours, the solids had dissolved completely leaving a clear yellow solution. The solution was heated for a total of 16 hours and cooled to ambient temperature. Toluene was removed *in vacuo* resulting in a brownish-green oily solid. Mass of solid: 380 mg (63.6% yield based on [Ir(1,5-COD)($PMe_3$)$_3$]Cl). Identified as [Ir($PMe_3$)$_3$(H)(DHDP)Cl] based on the following data: $^1$H NMR (400 MHz, $C_6D_6$): δ 4.22 ppm (m, P-O-$CH_2$); δ 1.59 ppm (t, $J_{P\text{-}C\text{-}H}$=3.89 Hz, trans $PMe_3$); δ 1.00 ppm (d, $J_{P\text{-}C\text{-}H}$=10.25 Hz, $PMe_3$); δ -20.41 ppm (ddt, $J_{P\text{-}O\text{-}Ir\text{-}H}$=1.86 Hz, $J_{P\text{-}Ir\text{-}H}$(trans $PMe_3$)=9.40 Hz, $J_{P\text{-}Ir\text{-}H}$($PMe_3$)=18.80 Hz, Ir-H); all other aliphatic protons could not be assigned due to overlap. $^{31}$P NMR (400 MHz, $C_6D_6$): δ 6.81 ppm (d, $J_{P\text{-}O\text{-}Ir\text{-}P\ trans}$=6.15 Hz, 1P, Ir-O-P); δ -29.15 ppm (dd, $J_{P\text{-}Ir\text{-}P}$=21.77 Hz, $J_{P\text{-}O\text{-}Ir\text{-}P}$=8.01 Hz, 2P, trans $PMe_3$); δ -47.31 ppm (m, 1P, $PMe_3$). $^{13}$C NMR (400 MHz,$C_6D_6$): δ 65.70 ppm (d, $J_{P\text{-}O\text{-}C}$=6.13 Hz, P-O-$CH_2$); δ 20.08 ppm (dt, $J_{P\text{-}C}$=41.47 Hz, $J_{P\text{-}Ir\text{-}P\text{-}C}$=3.05 Hz, central P($\underline{C}H_3$)$_3$); δ 15.04 ppm (t, $J_{P\text{-}C}$=17.95 Hz, trans P($\underline{C}H_3$)$_3$); δ 14.35 ppm (s, hexadecyl $CH_3$); other peaks could not be assigned due to the complexity of the spectrum. IR (KBr): $\nu_{Ir\text{-}H}$, 2167.3 cm$^{-1}$ (m); $\nu_{P=O}$, 1242.0 cm$^{-1}$ (m); $\nu_{P\text{-}O\text{-}C}$, 952.1 cm$^{-1}$ (s). Elemental analysis: Calc'd for $Ir_1C_{41}H_{94}P_4O_4Cl$: C: 49.11%; H: 9.45%. Found: C: 44.20%; H: 8.81%.

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and BINAP Phosphate in $D_2O$: SRCI065, SRCI069**

To a screw cap NMR tube was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (47 mg, 0.083 mmol) and BINAP phosphate (33 mg, 0.095 mmol). $D_2O$ (1 mL) was added via syringe. BINAP phosphate appeared to be very insoluble in $D_2O$. The tube was heated to 55°C and $^1$H and $^{31}$P NMR spectra were obtained after heating for 5 hours. At this point the BINAP

phosphate remained undissolved as a yellow oil at the bottom of the tube. $^{1}H$ and $^{31}P$ NMR spectra were repeated after 24 hours at 55°C. In a second experiment (SRCI069), the two reactants were mixed in the same mole ratio as above and $^{1}H$ and $^{31}P$ NMR spectra were obtained immediately after mixing. The tube was heated to 100°C and $^{1}H$ and $^{31}P$ NMR spectra were obtained after 24 hours. Upon mixing at room temperature, NMR spectra revealed that the protonated species $[Ir(1,5\text{-}COD)(PMe_3)_3(D)]^{2+}$ had been formed where the counterions were $Cl^-$ and $(PhCH_2O)_2PO_2^-$ and the hydride had begun to exchange with deuterium from the $D_2O$ solvent. Upon heating at 55°C or 100°C for 24 hours, a mixture of products was detected by NMR spectroscopy. No peaks corresponding to the BINAP phosphate seemed to be present in the $^{31}P$ NMR spectrum although a doublet and triplet at -27.5 and -43.0 ppm, respectively, indicated that one of the products may have the phosphine ligands arranged in a meridional fashion. This could not be confirmed by $^{1}H$ NMR spectroscopy since the region from 1.5-2.0 ppm was very complex. No hydride was detected by $^{1}H$ NMR spectroscopy.

**Reaction of $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ and BINAP Phosphate in $C_6D_6$: SRCI075**

To a screw cap NMR tube was charged $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ (26 mg, 0.046 mmol) and BINAP phosphate (16 mg, 0.028 mmol). $C_6D_6$ (0.8 mL) was added via syringe. Upon mixing and heating slightly, all solids did not dissolve. The tube was heated to 75°C for 20 hours after which $^{1}H$ and $^{31}P$ NMR spectra were obtained. NMR spectra revealed a mixture of products. Two hydride resonances were present in the $^{1}H$ NMR spectrum; a doublet of triplets at -20.1 ppm and a weaker doublet of triplets at -21.5 ppm. Unexpectedly there were several peaks present in the region from 1-2 ppm and no distinct triplet could be found. $^{31}P$ NMR showed three main peaks; a singlet at 11.2 ppm, doublet at -29.9 ppm , and a doublet of doublets at -46.4 ppm.

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and BINAP Phosphate in Toluene: SRCI111**

To a 100 mL side arm flask equipped with stirbar and septum was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (249 mg, 0.441 mmol) and BINAP phosphate (154 mg, 0.442 mmol). Toluene (20 mL) was added via syringe. Upon mixing the solids did not completely dissolve immediately. The flask was heated to 80°C. After a few hours solution began to turn yellow but all solids did not dissolve. Heating was continued for 24 hours total after which the flask was cooled to ambient temperature and toluene was removed *in vacuo* for approximately 18 hours. Ether (15 mL) was added to the remaining oily, bright yellow solid. A $^1H$ NMR spectrum was obtained of the crude product in $C_6D_6$. The solid was crushed thoroughly using a spatula and allowed to stir in the ether for one hour. The yellow ether solution was removed via cannula technique. This procedure was repeated using 15 mL portions of ether until the solution being removed from the solid was no longer yellow (approximately 6 times). At the end of the trituration, a powdery tan solid remained which was dried overnight *in vacuo*. The solid was insoluble in $C_6D_6$ so $^1H$ and $^{31}P$ NMR spectra were obtained of the triturated product in $CDCl_3$. Although not very soluble in $C_6D_6$, $^1H$ NMR of the crude product showed a doublet and triplet in the phosphine region, a weak hydride at approximately -21.5 ppm and aromatic resonances underneath the residual solvent peak. Spectra of the triturated product in $CDCl_3$ were very complex and any products were thought to have reacted with the solvent.

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and Bis(4-nitrophenyl)phosphate in $C_6D_6$: SRCI115**

To a screw cap NMR tube was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (41 mg, 0.072 mmol) and bis(4-nitrophenyl)phosphate (25 mg, 0.073 mmol). $C_6D_6$ (0.7 mL) was added via syringe. Upon mixing and heating slightly, all solids did not dissolve. The tube was heated to 80°C for 18 hours after which $^1H$ and $^{31}P$ NMR spectra were obtained. $^1H$ and

$^{31}P$ NMR spectra were again obtained after a total of 3 days at 80°C. NMR spectra revealed an unidentifiable mixture of products.

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and Diphenyl Phosphate in $C_6D_6$: SRCI077**

To a screw cap NMR tube was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (33 mg, 0.058 mmol) and diphenyl phosphate (15 mg, 0.059 mmol). $C_6D_6$ (0.8 mL) was added via syringe. Upon mixing and heating slightly, the sample separated into two phases, a clear solution above a small amount of a light yellow oil. The tube was heated to 80°C for 22 hours after which $^1H$ and $^{31}P$ NMR spectra were obtained. The main product in the mixture was identified as [Ir($PMe_3$)$_3$(H)(DPP)Cl] based on the following data: $^1H$ NMR (200 MHz, $C_6D_6$): δ 7.0-8.0 ppm (m, Ph-H); δ 1.55 ppm (t, $J_{P\text{-}C\text{-}H}$=4.37 Hz, trans $PMe_3$); δ 1.06 ppm (d, $J_{P\text{-}C\text{-}H}$=10.86 Hz, $PMe_3$); δ -20.3 ppm (dt, Ir-H). $^{31}P$ NMR (200 MHz, $C_6D_6$): δ -5.1 ppm (d, $J_{P\text{-}O\text{-}Ir\text{-}P\ trans}$=10.9 Hz, Ir-O-P); δ -29.3 ppm (d, $J_{P\text{-}Ir\text{-}P}$=19.9 Hz, trans $PMe_3$); δ -46.7 ppm (m, $PMe_3$).

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and Diphenyl Phosphate in $C_6D_6$: SRCI109**

To a 100 mL side arm flask equipped with septum and stirbar was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (271 mg, 0.480 mmol) and diphenyl phosphate (120 mg, 0.480 mmol). Toluene (20 mL) was added via syringe. The flask was heated to 80°C. Within a few hours, the solids had dissolved leaving a bright yellow solution. After heating for 26 hours, the flask was cooled to room temperature and toluene was removed *in vacuo*. Trituration with ether did not yield a pure product.

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and Monoalkyl Phosphates in $C_6D_6$: SRCI123, SRCI139, and SRCI141**

To screw cap NMR tubes was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl and each of the monoalkyl phosphates in approximately a 1:1 mole ratio (usually with a slight excess of

phosphate): MEHPA, SRCI123; IDAP, SRCI139; and HAP, SRCI141. $C_6D_6$ (0.7-0.8 mL) was added via syringe. Upon mixing most of the solids dissolved leaving cloudy light yellow solutions. In each case any remaining solids dissolved upon heating slightly. The tubes were heated to 75-80°C. After several hours, $^1H$ and $^{31}P$ NMR spectra were obtained of the light yellow solutions. $^1H$ and $^{31}P$ NMR spectra indicated that complex mixtures had resulted from the reactions with [Ir(1,5-COD)($PMe_3$)$_3$]Cl.

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and Hexyl Acid Phosphate in Toluene: SRCI259**

To a 50 mL side arm flask equipped with septum and stirbar was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (325 mg, 0.576 mmol). Toluene (20 mL) was added via syringe. Hexyl acid phosphate (111 mg, 0.609 mmol) was added via syringe. The flask was heated to 75°C. After heating for 20 hours, the flask was cooled to room temperature and toluene was removed *in vacuo*. The green oily solid was triturated with 10 mL portions of ether resulting in the formation of a grayish-green solid. $^1H$ and $^{31}P$ NMR spectra revealed that a complex mixture of products had formed.

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and d-AMP in $D_2O$: SRCI057**

To a screw cap NMR tube was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (24 mg, 0.043 mmol) and 2'-deoxy-5'-monophosphate (d-AMP, 30 mg, 0.091 mmol). $D_2O$ (0.7 mL) was added via syringe. Upon mixing d-AMP did not dissolve. The tube was heated to 100°C. Almost immediately, all solids dissolved leaving a clear solution. After 24 hours and again after 48 hours, $^1H$ NMR spectra were obtained which revealed the formation of a complex and unidentifiable mixture of products.

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and d-AMP in $C_6D_6$: SRCI083**

To a screw cap NMR tube was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (29 mg, 0.051 mmol) and 2'-deoxy-5'-monophosphate (d-AMP, 17 mg, 0.051 mmol). $C_6D_6$ (0.7 mL)

was added via syringe. The tube was heated to 80°C. Even after heating, not all solids dissolved. After 24 hours, $^{1}H$ and $^{31}P$ NMR spectra were obtained of the $C_6D_6$ solution. The main product was identified as $Ir(PMe_3)_3(H)(OH)Cl$ based on the following data: $^{1}H$ NMR (200 MHz, $C_6D_6$): $\delta$ 1.49 ppm (t, $J_{P\text{-}C\text{-}H}$=4.10 Hz, trans $PMe_3$); $\delta$ 1.18 ppm (d, $J_{P\text{-}C\text{-}H}$=8.86 Hz, $PMe_3$); $\delta$ -20.3 ppm (dt, Ir-H). $^{31}P$ NMR (200 MHz, $C_6D_6$): $\delta$ -38.6 ppm (d, trans $PMe_3$); $\delta$ -42.3 ppm (t, $PMe_3$).

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and cyclic-AMP in $C_6D_6$: SRCI089**

To a screw cap NMR tube was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (26 mg, 0.046 mmol) and (-)-adenosine-3',5'-cyclic monophosphate (cyclic-AMP, 15 mg, 0.045 mmol). $C_6D_6$ (0.7 mL) was added via syringe. The tube was heated to 80°C. Even after heating, not all solids dissolved. After 24 hours, $^{1}H$ and $^{31}P$ NMR spectra were obtained of the $C_6D_6$ solution. The main product was identified as $Ir(PMe_3)_3(H)(OH)Cl$ based on the following data: $^{1}H$ NMR (200 MHz, $C_6D_6$): $\delta$ 1.50 ppm (t, $J_{P\text{-}C\text{-}H}$=3.54 Hz, trans $PMe_3$); $\delta$ 1.18 ppm (d, $J_{P\text{-}C\text{-}H}$=10.16 Hz, $PMe_3$); $\delta$ -20.3 ppm (dt, $J_{P\text{-}Ir\text{-}H}$(trans $PMe_3$)=13.80 Hz, $J_{P\text{-}Ir\text{-}H}$(central $PMe_3$)=19.90 Hz, Ir-H). $^{31}P$ NMR (200 MHz, $C_6D_6$): $\delta$ -38.6 ppm (d, trans $PMe_3$); $\delta$ -42.3 ppm (t, $PMe_3$).

**Reaction of [Ir(1,5-COD)($PMe_3$)$_3$]Cl and PEA in $C_6D_6$: SRCI221**

To a screw cap NMR tube was charged [Ir(1,5-COD)($PMe_3$)$_3$]Cl (17 mg, 0.030 mmol) and 1,2-dihexadecanoyl-rac-glycero-3-phosphoethanolamine (PEA, 21 mg, 0.030 mmol). $C_6D_6$ (0.7 mL) was added via syringe. The tube was heated to 70°C. After heating 4 hours, all solids dissolved leaving a yellow solution. After 18 hours, $^{1}H$ and $^{31}P$ NMR spectra were obtained of the orange solution. The main product was identified as

$Ir(PMe_3)_3(H)(PEA)Cl$ based on the following data: $^1H$ NMR (200 MHz, $C_6D_6$): δ -20.3 ppm (q, $J_{P\text{-}Ir\text{-}H}$=17.31 Hz, Ir-H). The region from δ 1-2 ppm in the $^1H$ NMR spectrum was complex and could not be assigned. $^{31}P$ NMR (200 MHz, $C_6D_6$): δ 0.33 ppm (s, 1P, phosphate); δ -44.0 ppm (d, 2P, $J_{P\text{-}Ir\text{-}P}$=20.15 Hz, trans $PMe_3$); δ -42.3 ppm (t, 1P, JP-Ir-P=17.09 Hz, $PMe_3$).

**Synthesis of $[Ir(PMe_3)_3(H)(PEA)Cl$ in Toluene: SRCI229**

To a 25 mL side arm flask equipped with septum and stirbar was charged [Ir(1,5-COD)$(PMe_3)_3$]Cl (82 mg, 0.145 mol) and 1,2-dihexadecanoyl-rac-glycero-3-phosphoethanolamine (PEA, 101 mg, 0.146 mmol). Toluene (10 mL) was added via syringe. Upon mixing, a light yellow slurry resulted. The flask was heated to 80°C. After a few hours, the solids had dissolved completely leaving a clear yellow solution. The solution was heated for a total of 24 hours and cooled to ambient temperature. Toluene was removed *in vacuo*. Diethyl ether was added to the brownish-yellow oily solid in an attempt to purify by trituration, but the solid instead dissolved. After removal of ether in vacuo, a brown powder remained. Mass of solid: 91 mg (54.5% yield based on [Ir(1,5-COD)$(PMe_3)_3$]Cl). Identified as $Ir(PMe_3)_3(H)(PEA)Cl$ based on the following data: $^1H$ NMR (400 MHz, $C_6D_6$): δ 1.63 ppm (m, trans $PMe_3$); δ 1.56 ppm (d, $J_{P\text{-}C\text{-}H}$=10.39 Hz, $PMe_3$); δ -20.85 ppm (q, $J_{P\text{-}Ir\text{-}H}$=17.01 Hz, Ir-H); all other aliphatic protons could not be assigned due to overlap. $^{31}P$ NMR (400 MHz, $C_6D_6$): δ 2.96 ppm (s, 1P, Ir-O-P); δ -41.31 ppm (d, $J_{P\text{-}Ir\text{-}P}$=19.7 Hz, 1P, trans $PMe_3$); δ -43.37 ppm (t, $J_{P\text{-}Ir\text{-}P}$=19.8 Hz, 1P, $PMe_3$). $^{13}C$ NMR (400 MHz,$C_6D_6$): δ 173.10 ppm (s, C=O); δ 21.64 ppm (dt, $J_{P\text{-}C}$=40.03 Hz, central $P(\underline{C}H_3)_3$); δ 17.85 ppm (t, $J_{P\text{-}C}$=18.71 Hz, trans $P(\underline{C}H_3)_3$); δ 14.35 ppm (s, hexadecyl $CH_3$); other peaks could not be assigned due to the complexity of the spectrum. IR (KBr): $\nu_{Ir\text{-}H}$, 2162.2 $cm^{-1}$ (m); $\nu_{P=O}$, 1243.9 $cm^{-1}$ (s); $\nu_{P\text{-}O\text{-}C}$, 952.6 $cm^{-1}$

(s). Elemental analysis: Calc'd for $Ir_1C_{46}H_{101}P_4O_8Cl_1N_1$: C: 48.13%; H: 8.87%; N: 1.22%. Found: C: 46.84%; H: 8.60%; N: 1.14%.

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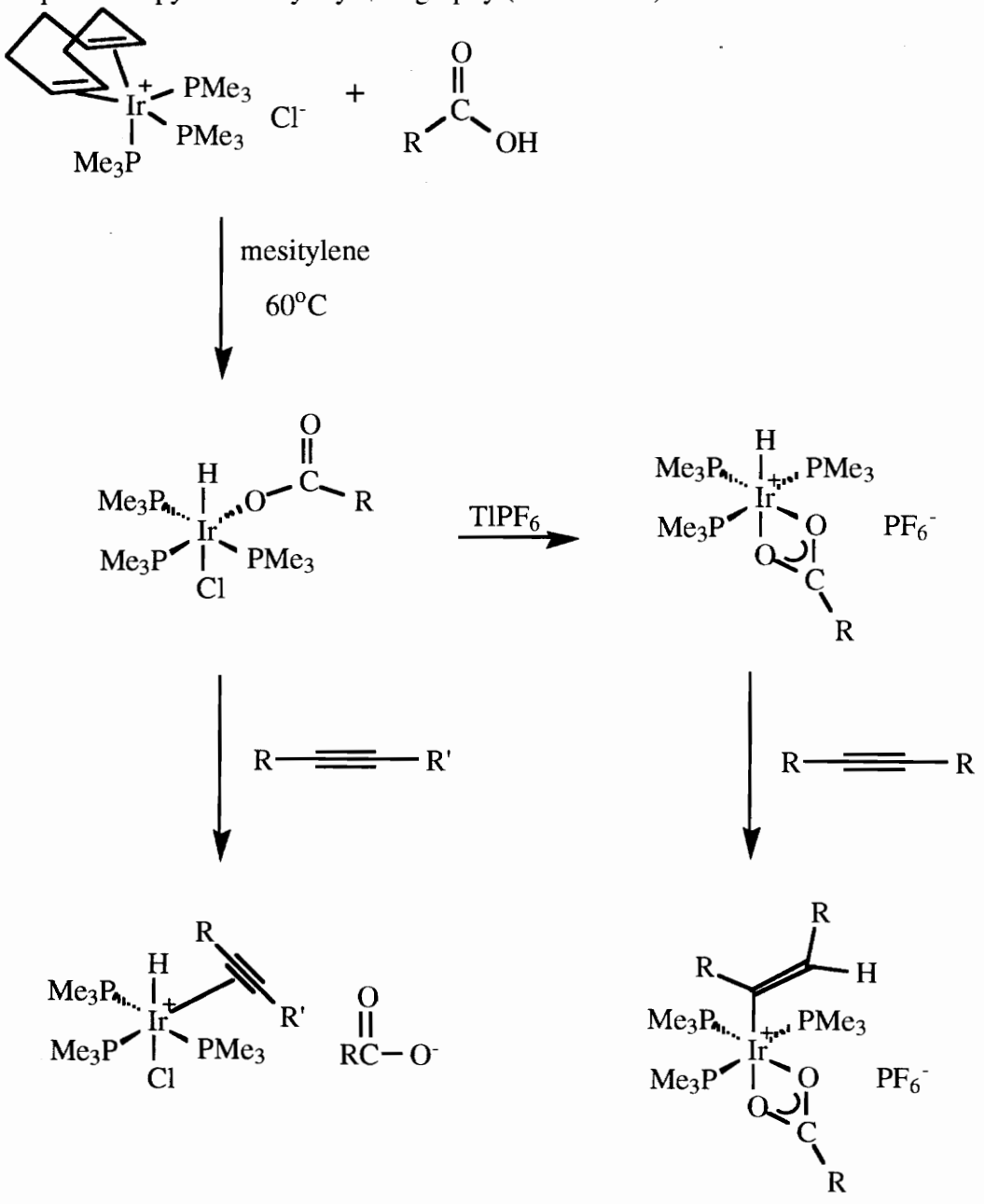
# Chapter 3: Reactivity and Solution Behavior of the Dibenzyl Phosphate Iridium(III) Complex

## Section 3.1: Introduction

In an attempt to probe its utility as a catalyst, the reactivity of the dibenzyl phosphate complex, $[Ir(PMe_3)_3(H)(DBP)Cl]$ (Figure 3.1), with several reagents was examined. The oxidative addition of many compounds to the iridium(I) precursor, $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$, has resulted in the formation of complexes that have demonstrated activity as catalysts for hydrogenation as well as the addition of other compounds to unsaturated species.[1] However, the products which resulted from the oxidation of amino acids to the iridium center lacked catalytic activity (Figure 2.1).[2] Since most catalytic cycles rely on the ability of the active species to become coordinately unsaturated allowing for the association of a substrate molecule,[3] this apparent lack of activity was thought to be the consequence of the stability of the 18 electron octahedral iridium(III) complex. This chelating amino acid complex contained no weakly bound ligands which could dissociate in solution to form a coordinatively unsaturated species. On the other hand, the dibenzyl phosphate complex exists in $C_6D_6$ solution with the chloride bound to the iridium center as an inner sphere ligand, rather than a counterion. In water it was believed that the chloride ligand could be displaced thus opening a coordination site and perhaps allowing the phosphate anion to form a chelate with the metal center. The flexidentate nature of phosphate anions has been previously studied.[4] It was thought that this could also open a coordination site thereby creating the possibility for entrance into a catalytic cycle.

The phosphate complexes were believed to be analogous to the carboxylate complexes studied by Ladipo.[1b] The carboxylate anion is capable of several modes of binding to a metal center: unidentate, chelating, or bridging, as well as acting as a counterion not directly bound to the metal. As a result there is a great deal in the literature

concerning carboxylate transition metal chemistry.[5] In his studies of the reactivity of carboxylates with [Ir(1,5-COD)($PMe_3$)$_3$]Cl, Ladipo found that oxidative addition of either benzoic acid or acetic acid in mesitylene at elevated temperatures gave the hydrido $\eta^1$-carboxylato iridium(III) complexes which were characterized by IR and $^1H$, $^{13}C$, and $^{31}P$ NMR spectroscopy and x-ray crystallography (Scheme 3.1).




**Scheme 3.1: Reactivity of Carboxylate Complexes**

Removal of the chloride ion by refluxing with thallium hexafluorophosphate ($TlPF_6$) in methylene chloride resulted in isolation of the hydrido $\eta^2$-carboxylato complex. At room temperature, reaction of the hydrido $\eta^1$-carboxylato iridium(III) complex with (trimethylsilyl)acetylene resulted in the displacement of the monodentate carboxylate to form the $\pi$-bonded acetylene complex. Heating the $\pi$-bonded acetylene complex resulted in the formation of a mixture of products. When the hydrido $\eta^2$-carboxylato complex was allowed to react with an acetylene, dimethyl acetylene dicarboxylate (DMAD), the product was a vinyl $\eta^2$-carboxylato complex (Scheme 3.1). Initial $\pi$-coordination of the acetylene occurred by displacing one of the carboxylate oxygen atoms due to the flexidentate nature of the carboxylate ligand. After hydride migration to the acetylene to form the vinyl complex, the displaced oxygen atom can recoordinate to the metal center. Further studies showed the vinyl $\eta^2$-carboxylato complex to be a catalytic intermediate for the addition of benzoic acid to unsaturates.[1b]

The ability of the carboxylate ligand to act either as a two or four electron donor makes it an ideal ligand for transition metal catalysis which often involves the two electron oxidation and reduction of the metal center. Because of the similarity of the phosphate and carboxylate anions, it was believed that the phosphate complex, $[Ir(PMe_3)_3(H)(DBP)Cl]$, might experience reactivity analogous to the carboxylate complexes.

## Section 3.2: Solution Behavior of $[Ir(PMe_3)_3(H)(DBP)Cl]$

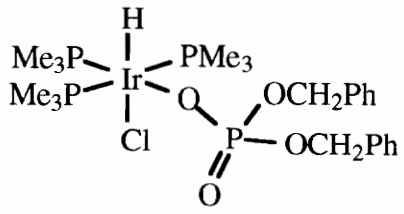



**Figure 3.1: $[Ir(PMe_3)_3(H)(DBP)Cl]$**

$[Ir(PMe_3)_3(H)(DBP)Cl]$ (Figure 3.1) is soluble in most polar, organic solvents. The chemical shifts of some of the nuclei vary greatly in the $^1H$ NMR spectra as the solvent is changed. $^1H$ NMR spectra were recorded for the complex in several solvents and the chemical shifts and multiplicities of the protons are given in Table 2.1. The chemical shifts and multiplicities of the protons when using $D_2O$ and $CD_3OD$ as solvent are significantly different from the shifts recorded in less polar solvents which do not coordinate easily. This is a result of replacement of the phosphate ligand by a molecule of solvent so that the chemical shifts in $D_2O$ and $CD_3OD$ (Table 3.1) represent the solvato compound (Figure 3.2). This phenomenon will be explained in detail later.

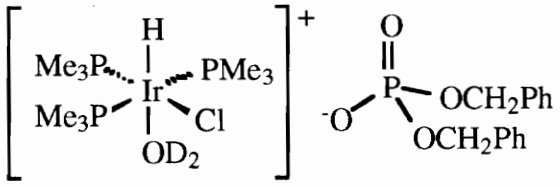
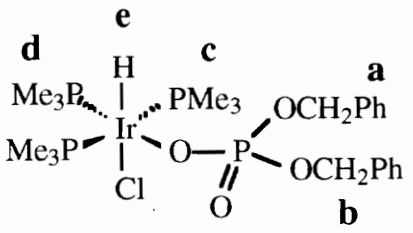



**Figure 3.2: Chloride Solvato Complex**

The $[Ir(PMe_3)_3(H)(DBP)Cl]$ complex decomposed to a mixture of unidentified products before NMR spectra could be obtained in $d_6$-dimethyl sulfoxide or $d_3$-acetonitrile. Decompositon occurred more slowly in both $d_6$-acetone and $d_2$-methylene chloride although the product seemed to be unusually stable over a long period in d-chloroform which is commonly more reactive than methylene chloride.[6] The largest proton chemical shift differences were recorded for the solvents $D_2O$ and $C_6D_6$ which would be expected since the phosphate is coordinated to the metal center in $C_6D_6$, but is no longer attached to iridium in $D_2O$. The differences between chemical shifts in $C_6D_6$ and the polar, non-coordinating solvents, $CDCl_3$ and $CD_2Cl_2$, are less pronounced for the phenyl, methylene, and trans $PMe_3$ protons, but the hydride proton and the methyl protons of the odd $PMe_3$ are noticeably shifted.

**Table 3.1: 200 MHz $^1$H NMR Shifts for [Ir(PMe$_3$)$_3$(H)(DBP)Cl] in Various Solvents**



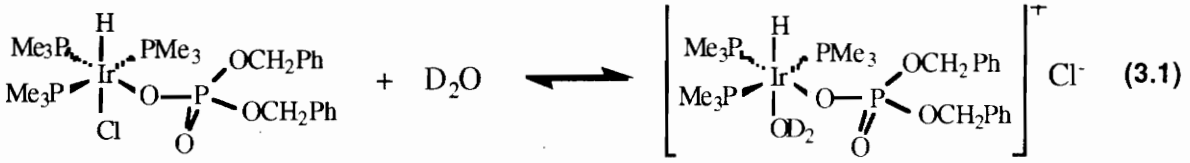

| Solvent | a Ph-H | b $PhCH_2$ | c trans $PMe_3$ | d $PMe_3$ | e Ir-H |
|---|---|---|---|---|---|
| $D_2O$ | 7.39 (s) | 4.85 (d) | 1.60 (t) | 1.69 (d) | -22.75 (bm) |
| $C_6D_6$ | 7.34 (m) | 5.25 | 1.54 | 1.02 | -20.40 (ddt) |
| $d_6$-acetone | 7.30 (m) | 4.83 | 1.58 | 1.63 | -21.90 (ddt) |
| $CDCl_3$ | 7.26 (m) | 4.90 | 1.6?* | 1.6?* | -21.2 (ddt) |
| $CD_3OD$ | 7.30 (m) | 4.86 | 1.67 | 1.70 | -21.5 (bm) |
| $CD_2Cl_2$ | 7.30 (m) | 4.86 | 1.58 | 1.6?* | -21.3 (ddt) |
| $d_6$-DMSO | decomposes | | | | |
| $CD_3CN$ | decomposes | | | | |

* the ? indicates that the doublet and triplet could not be resolved due to overlap and therefore the chemical shifts are reported as approximations.

Whereas the phenyl protons of the phosphate do not shift greatly with changing solvent, it is quite interesting to note that they are accidentally equivalent appearing as a singlet in $D_2O$, but are split into complex multiplets in all of the other solvents used in this study including methanol, in which the phosphate is also believed to be dissociated. The methylene protons of the phosphate appear as a "doublet" in all solvents when the spectra are obtained using a 200 MHz instrument, but when the spectra are obtained using a 400 MHz spectrometer it becomes evident that the splitting is much more complex. The

methylene protons are shifted most upfield when polar solvents such as $CDCl_3$ (4.90 ppm) are used. In comparison, the peaks are shifted 0.4 ppm downfield when the solvent is benzene (5.25 ppm). The most intriguing shift discrepancy lies with the methyl protons of the phosphine ligands. The methyl groups of the two trans phosphines appear as a virtual triplet due to splitting by the attached phosphorus and the trans phosphorus via communication through shared metal orbitals. The peak for these protons comes at approximately 1.7 ppm in all the solvents tested. The peak for the methyl protons of the other phosphine is a doublet which shifts as much as 0.7 ppm depending on the solvent. This peak is shifted upfield in nonpolar $C_6D_6$ (1.02 ppm), while in polar solvents such as $CDCl_3$ the peak shifts so far as to overlap the triplet for the other methyl phosphines (1.6 ppm). Finally, the hydride peak appears at approximately -20 ppm which is indicative of an iridium(III) hydride trans to an electronegative atom like chlorine.[1b] Not only does the peak for the hydride shift as much as 2.35 ppm by changing solvent, but the ten line resonance in $C_6D_6$ becomes a broad multiplet in polar, coordinating solvents such as $D_2O$ and $d_4$-methanol as a result of the replacement of the phosphate ligand by a solvent molecule.

Dissolving the $[Ir(PMe_3)_3(H)(DBP)Cl]$ complex in $D_2O$, removing $D_2O$ *in vacuo*, and replacing the solvent with $C_6D_6$ results in the expected doublet of doublets of triplets for the hydride indicating that the solvato complex quickly reverts back to the coordinated phosphate complex as $D_2O$ is removed and that the hydride does not undergo H/D exchange rapidly. It was originally believed that an equilibrium was established upon dissolution of the complex in $D_2O$ where chloride ligand was being displaced by a molecule of water thus explaining the shape of the hydride peak (broad multiplet).




(3.1)

Although this equilibrium seemed feasible, there were two pieces of evidence to prove that the phosphate solvato complex in Equation 3.1 was not being formed. First, the $^{1}H$ and $^{31}P$ NMR spectra for the phosphate complex in solvents such as $C_6D_6$ or $CDCl_3$ clearly show splitting of other magnetic nuclei by the phosphate, whereas in $D_2O$ the phosphate splitting disappears and the phosphate resonance in the $^{31}P$ NMR spectrum is a singlet. This suggests that the phosphate is not attached to the metal center in $D_2O$ solution.

The equilibrium (Equation 3.1) was further disproven by adding a large excess of chloride ion to the $D_2O$ solution of $[Ir(PMe_3)_3(H)(DBP)Cl]$. Instead of pushing the proposed equilibrium to the left which would have been evidenced by the appearance of the typical ten line hydride resonance at approximately -21 ppm, a new hydride resonance appeared as a quartet at -24.0 ppm with the addition of NaCl (Figure 3.3). This pattern of hydrides is characteristic of the dichloro complex, $[Ir(PMe_3)_3(H)(Cl)_2]$, in $D_2O$ which has been previously characterized in the Merola group.[7] When dissolved in $D_2O$, the phosphate ion dissociates from $[Ir(PMe_3)_3(H)(DBP)Cl]$ to form the complex, $[Ir(PMe_3)_3(H)(OD_2)Cl]^+$, with the phosphate acting as counterion (Figure 3.2). The hydride resonance for $[Ir(PMe_3)_3(H)(OD_2)Cl]^+$ is seen in Figure 3.3a.

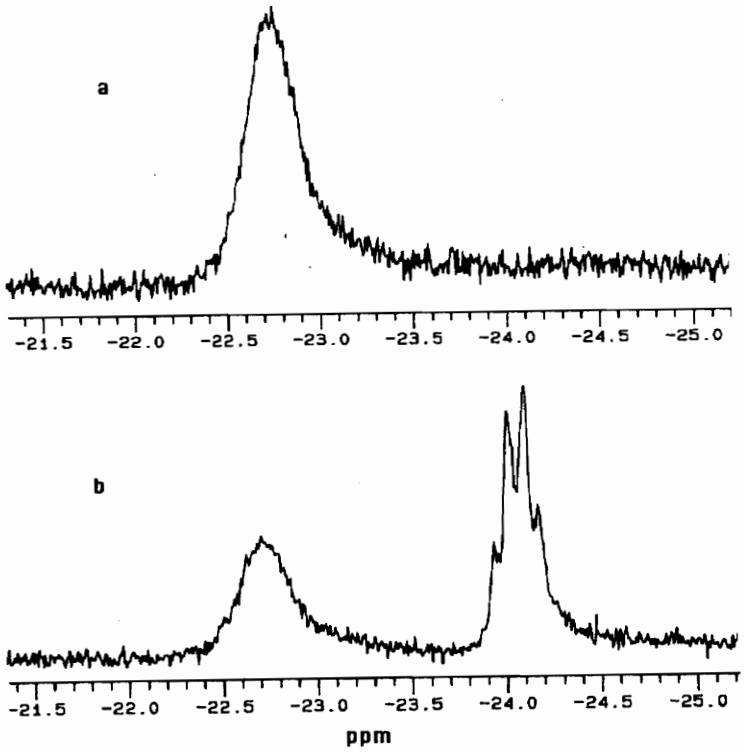
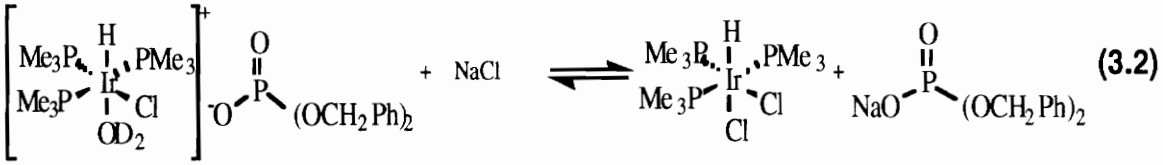



**Figure 3.3: a) 200 MHz $^1$H NMR Spectrum of the Hydride of [Ir(PMe$_3$)$_3$(H)(DBP)Cl] in D$_2$O b) With Excess Chloride Ion Added**

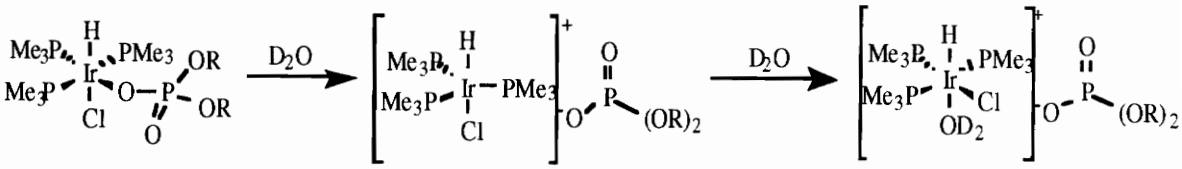
When NaCl is added to the $D_2O$ solution, an equilibrium is established between the $[Ir(PMe_3)_3(H)(OD_2)Cl]^+$ and $[Ir(PMe_3)_3(H)(Cl)_2]$ complexes (Equation 3.2). A large excess of NaCl (>5 eq) is required to push the equilibrium completely toward the dichloro complex.




**(3.2)**

It is interesting to note that spectra of the solvato complex which is formed upon the dissolution of $[Ir(PMe_3)_3(H)(DBP)Cl]$ in $D_2O$ suggest that the water molecule occupies the

position trans to the hydride. In other meridional tris(trimethylphosphine) complexes where the hydride proton is cis to a coordinated $D_2O$ molecule, it has been shown that the hydride undergoes rapid H/D exchange.[1a] For the complex $[Ir(PMe_3)_3(H)(OD_2)Cl]^+$ dissolved in $D_2O$, the hydride peak does not exchange even over a period os several days. In solvents like $C_6D_6$ or $CDCl_3$, in which the phosphate does not dissociate from the metal center, the position trans to the hydride is occupied by the chloride ligand. When the complex is dissolved in water, a rearrangement takes place leaving the chloride cis to the hydride in the position originally occupied by the phosphate. When $[Ir(PMe_3)_3(H)(DBP)Cl]$ is dissolved in $D_2O$, perhaps the phosphate dissociates leaving a 5-coordinate, 16 electron, fluxional species. Upon attack by a molecule of $D_2O$, the solvato complex is formed (Scheme 3.2).



**Scheme 3.2: Reactivity of $[Ir(PMe_3)_3(H)(DBP)Cl]$ in $D_2O$**

## Section 3.3: Chelated Phosphate Complex, $[Ir(PMe_3)_3(H)(\eta^2\text{-DBP})]Cl$

Upon dissolution of $[Ir(PMe_3)_3(H)(DBP)Cl]$ in $D_2O$, there is always a second hydride resonance shifted upfield in the $^1H$ NMR spectrum which is not seen in other solvents. This doublet of triplets at -27.6 ppm is very similar in chemical shift and splitting to the hydride resonance of the chelating carboxylate shown in Scheme 3.1. This hydride is attributed to the chelating phosphato complex, $[Ir(PMe_3)_3(H)(\eta^2\text{-DBP})]Cl$, (Figure 3.4), and is present in small quantities (<10%). This peak disappears upon the addition of nucleophile ($Cl^-$). Attempts were made to synthesize larger quantities of this chelate species.

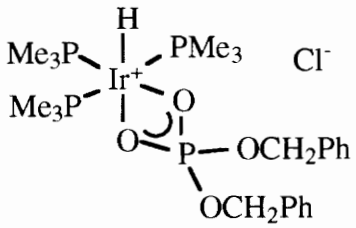


**Figure 3.4: [Ir(PMe3)3(H)(η2-DBP)]Cl**

The monodentate phosphate species was allowed to react with potassium hexafluorophosphate, $KPF_6$, in water in an attempt to precipitate the chelating species from solution as its $PF_6$ salt. Since the phosphate is never bound to the iridium center in water in the first place, this reaction was unsuccessful. $[Ir(PMe_3)_3(H)(DBP)Cl]$ was then allowed to react with thallium hexafluorophosphate, $TlPF_6$, in $CDCl_3$, in which the phosphate is bound to the iridium center. After 24 hours, a mixture of products was present evidenced by five separate hydride resonances in the $^1H$ NMR spectrum. The same reaction was carried out in $C_6D_6$. Preliminary studies on an NMR tube scale revealed that the $PF_6^-$ salt may be precipitating from solution. The reaction was repeated on a larger scale in toluene. A white precipitate formed which was washed several times with water to remove thallium chloride. $^1H$ and $^{31}P$ NMR spectra in $CDCl_3$ revealed an unidentifiable mixture of products. None of the chelating phosphate complex seemed to be present in the mixture.

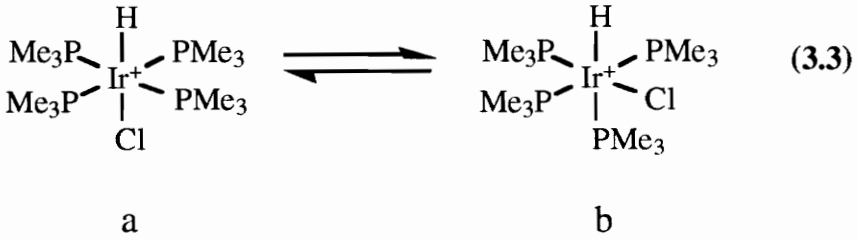
Unlike the carboxylato complexes, isolation of the phosphato chelate species is difficult. This is in agreement with observations that phosphate complexes are usually more labile than their carboxylate counterparts and tend to form bridging rather than chelating species.[8]

## Section 3.4: Reactivity of $[Ir(PMe_3)_3(H)(DBP)Cl]$ with Nucleophiles

As described in Section 3.1, water and chloride ion are both nucleophilic enough to displace the monodentate phosphate ligand of $[Ir(PMe_3)_3(H)(DBP)Cl]$ when the complex is

dissolved in water. The addition of a large excess of dibenzyl phosphate anion to a $D_2O$ solution of $[Ir(PMe_3)_3(H)(DBP)Cl]$ does not cause the phosphate to become coordinated to the metal center. NMR spectra for the complex dissolved in $D_2O$ with and without phosphate anion are identical.

Addition of one equivalent of trimethylphosphine to a $D_2O$ solution of $[Ir(PMe_3)_3(H)(DBP)Cl]$ results in the formatio of both isomers, a and b, of the tetrakis(trimethylphosphine) complex, $[Ir(PMe_3)_4(H)(Cl)]^+$, where the counterion is the dibenzyl phosphate anion (Equation 3.3).




**(3.3)**

a b

These two isomers are clearly identified by their $^1H$ and $^{31}P$ NMR spectra. In the $^1H$ NMR spectrum (Figures 3.5 and 3.6), the methyl protons of the four phosphines in complex a appear as a virtual triplet at 1.71 ppm and the hydride resonance appears at -23.19 ppm as a pentet split equally by the four equivalent phosphorus nuclei. For complex b, the methyl protons of the two trans phosphines, which are chemically,but not magnetically equivalent, should appear as a virtual triplet and are presumably buried beneath the triplet for complex a. The methyl protons of the phosphines trans to the chloride and hydride appear as doublets at 1.78 and 1.55 ppm, respectively and the hydride appears as a doublet of quartets at -11.67 ppm.

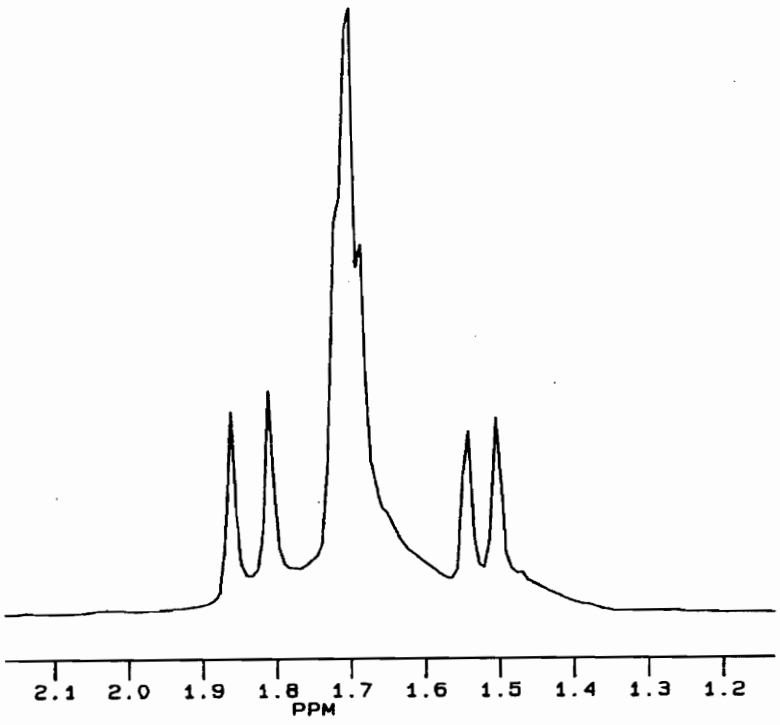



**Figure 3.5: $^{1}H$ NMR Spectrum of Complexes a and b**

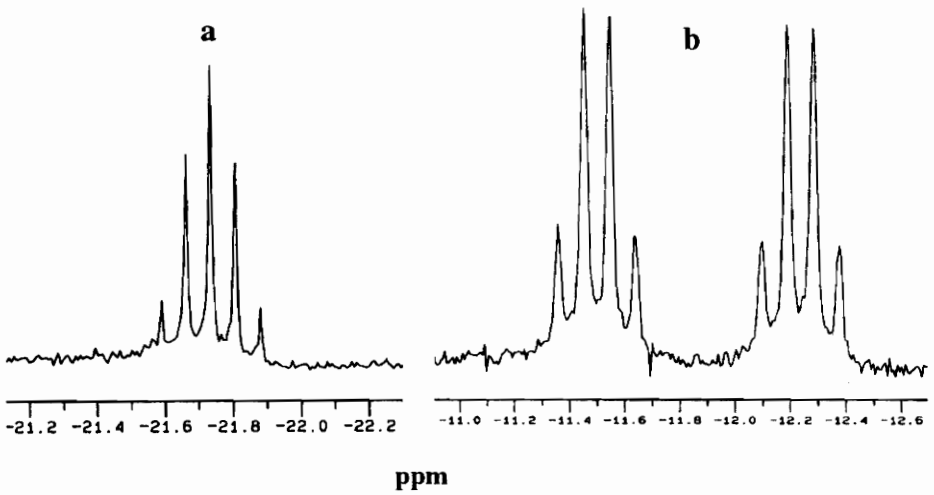



**Figure 3.6: Hydride Resonances of the $^{1}H$ NMR Spectrum of Complexes a and b**

In the $^{31}P$ NMR spectrum, complex a appears as a singlet at -46.45 ppm. For complex b, an unresolved doublet of triplets corresponding to the phosphine trans to the hydride

appears at -45.48 ppm, a triplet corresponding to the two trans phosphines appears at -48.70 ppm, and a quartet corresponding to the phosphine trans to the chloride appears at -54.55 ppm.

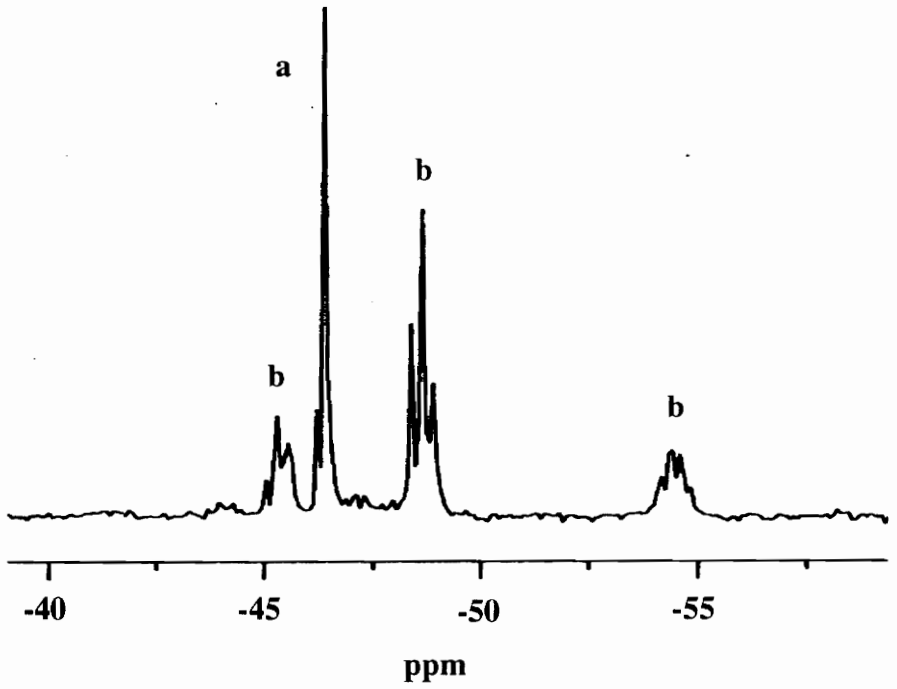



**Figure 3.7: $^{31}P$ NMR Spectrum of Complexes a and b**

There is a small amount (<10%) of the tetrakis(trimethylphosphine) complex present in $D_2O$ solution whose structure is analogous to complex b with $D_2O$ replacing the chloride ligand. The hydride resonance for this species appears at approximately -10.7 ppm as a doublet of quartets. Upon heating to 65°C for several hours, complexes a and b are present in a 1:2.63 ratio from examination of the intergration of their respective hydride peaks.

Because of the facile dissociation of the phosphate ligand in $D_2O$ solution, the nucleophilic addition of phosphate in $D_2O$ was not surprising. The same study was performed using $CDCl_3$ as solvent since the phosphate ligand was known to be coordinated to the metal center when dissolved in $CDCl_3$. One equivalent of trimethylphosphine was added to the $CDCl_3$ solution of $[Ir(PMe_3)_3(H)(DBP)Cl]$. After four days at ambient

temperature, peaks for $[Ir(PMe_3)_3(H)(DBP)Cl]$ were completely absent from $^1H$ and $^{31}P$ NMR spectra while peaks for complexes a and b had appeared. Complexes a and b were present in a 1:2.65 ratio.

From these findings, it is clear that the dibenzyl phosphate ligand is labile in both polar coordinating and non-coordinating solvents and may therefore be useful as a catalyst precursor in any number of solvents.

## Section 3.5: Reactivity of $[Ir(PMe_3)_3(H)(DBP)Cl]$ with Hydrogen

In order to probe its potential reactivity as a hydrogenation catalyst, the reaction of the dibenzyl phosphate with hydrogen was studied. $[Ir(PMe_3)_3(H)(DBP)Cl]$ was dissolved in $D_2O$ and hydrogen gas was bubbled through at ambient temperature for 30 minutes. $^1H$ and $^{31}P$ NMR spectra revealed that no reaction had occurred.

## Section 3.6: Experimental

### Reaction between $[Ir(PMe_3)_3(H)(DBP)Cl]$ and NaCl in $D_2O$: SRCI247

To a screw capped NMR tube was charged $[Ir(PMe_3)_3(H)(DBP)Cl]$ (49 mg, 0.066 mmol). $D_2O$ (0.7 mL) was added via syringe. Sodium chloride was added in small increments and $^1H$ and $^{31}P$ NMR spectra were recorded after each addition.

| Total NaCl added (mg) | # equivalents NaCl |
|---|---|
| 1.5 | 0.4 |
| 2.7 | 0.7 |
| 4.2 | 1.1 |
| 7.2 | 1.8 |
| 11.2 | 2.9 |
| 20.2 | 5.2 |
| 58.0 | 15.1 |

Upon the addition of a large excess of NaCl, the main component in solution was identified as $Ir(PMe_3)_3(H)(Cl)_2$ based on the following data: $^1H$ NMR (200 MHz, $D_2O$): $\delta$ 7.51 ppm (s, free dibenzyl phosphate Ph-H), $\delta$ 4.95 ppm (d, free dibenzyl phosphate $CH_2$), $\delta$

1.83 ppm (d, central $PMe_3$), δ 1.74 ppm (t, trans $PMe_3$), δ 24.02 ppm (q, Ir-H). $^{31}P$ NMR ($D_2O$): δ 0.76 ppm (s, free dibenzyl phosphate), δ -38.28 ppm (d, trans $PMe_3$), δ -41.25 ppm (t, central $PMe_3$).

**Reaction of $[Ir(PMe_3)_3(H)(DBP)Cl]$ and potassium hexafluorophosphate in $D_2O$**

$[Ir(PMe_3)_3(H)(DBP)Cl]$ (20 mg, 0.027 mmol) was charged to a screw capped NMR tube. $D_2O$ (0.7 mL) was added via syringe. An excess of $KPF_6$ was dissolved in 0.5 mL $D_2O$ and the solution was transferred to the NMR tube via syringe. No solids precipitated after several days at ambient temperature.

**Reaction of $[Ir(PMe_3)_3(H)(DBP)Cl]$ and thallium hexafluorophosphate in $CDCl_3$: SRCI209**

$[Ir(PMe_3)_3(H)(DBP)Cl]$ (43 mg, 0.058 mmol) and $TlPF_6$ (21 mg, 0.060 mmol) were charged to a screw capped NMR tube. $CDCl_3$ (0.7 mL) was added via syringe. Upon mixing, $TlPF_6$ did not dissolve completely and the resulting solution was pale yellow. After 24 hours at room temperature, $^1H$ and $^{31}P$ NMR spectra were recorded. A mixture of products was observed by the presence of several resonances in the hydride region of the $^1H$ NMR spectrum.

**Reaction of $[Ir(PMe_3)_3(H)(DBP)Cl]$ and thallium hexafluorophosphate in $C_6D_6$: SRCI225**

$[Ir(PMe_3)_3(H)(DBP)Cl]$ (59 mg, 0.080 mmol) and $TlPF_6$ (28 mg, 0.080 mmol) were charged to a screw capped NMR tube. $C_6D_6$ (0.7 mL) was added via syringe. Upon mixing, $TlPF_6$ did not dissolve completely and the resulting solution was pale yellow. After 5 hours at room temperature, a white solid had precipitated from solution. The yellow $C_6D_6$ solution was filtered away from the solid. $^1H$ and $^{31}P$ NMR spectra of the solution revealed that unreacted $[Ir(PMe_3)_3(H)(DBP)Cl]$ remained in solution. The solid was dried *in vacuo* and dissolved in $CDCl_3$. $^1H$ and $^{31}P$ NMR spectra of the solid revealed

the presence of a $PF_6^-$ salt. The hydride resonance was identical to that for $[Ir(PMe_3)_3(H)(DBP)Cl]$, but the other peaks in the $^1H$ NMR spectrum took on slighly different shape.

**Reaction of $[Ir(PMe_3)_3(H)(DBP)Cl]$ and thallium hexafluorophosphate in toluene: SRCI227**

$[Ir(PMe_3)_3(H)(DBP)Cl]$ (98 mg, 0.12 mmol) and $TlPF_6$ (44 mg, 0.13 mmol) were charged to a 10 mL side arm flask equipped with septum and stirbar. Upon the addition of toluene (5 mL) via syringe, most solids dissolved. The solution was stirred overnight at ambient temperature during which a solid precipitated. The toluene solution was removed via cannula technique and the beige solid was washed with several 5 mL portions of water to remove TlCl. The beige solid was dried *in vacuo*. $^1H$ and $^{31}P$ NMR spectra in $CDCl_3$ revealed the presence of a complex mixture of products.

**Reaction of $[Ir(PMe_3)_3(H)(DBP)Cl]$ and trimethylphosphine in $D_2O$: SRCI267**

$[Ir(PMe_3)_3(H)(DBP)Cl]$ (25 mg, 0.034 mmol) was charged to a screw capped NMR tube. $D_2O$ (0.65 mL) was added via syringe. $PMe_3$ (3.5 mL, 0.033 mmol) was added via microsyringe. Upon mixing vigorously, $^1H$ and $^{31}P$ NMR spectra were obtained immediately. The tube was allowed to sit at ambient temperature for 8 hours after which $^1H$ and $^{31}P$ NMR spectra were obtained again. The tube was heated to 65°C for 12 hours after which $^1H$ and $^{31}P$ NMR spectra were obtained again. Equilibrium between the cis and trans isomers of $[Ir(PMe_3)_4(H)(Cl)]^+$ was established based on the following data: $^1H$ NMR ( 200 MHz, $D_2O$): δ 7.38 ppm (s, free dibenzyl phosphate Ph-H), δ 4.86 ppm (d, free dibenzyl phosphate $CH_2$), δ 1.78 ppm (d, $PMe_3$ trans to chloride in cis complex), δ 1.71 ppm (t, $PMe_3$ in trans complex), δ 1.71 ppm (t, trans $PMe_3$ in cis complex), δ 1.55 ppm (d, $PMe_3$ trans to hydride in cis complex), δ -11.67 ppm (dq, Ir-H of cis complex), δ -23.19 ppm (p, Ir-H of trans complex). $^{31}P$ NMR (200 MHz, $D_2O$): δ 0.61 ppm (s, free

dibenzyl phosphate), δ -45.61 ppm (t, $PMe_3$ trans to hydride in cis complex), δ -46.45 ppm (s, $PMe_3$ of trans complex), δ -48.70 ppm (t, trans $PMe_3$ in cis complex), δ -54.55 ppm (q, $PMe_3$ trans to chloride in cis complex).

**Reaction of $[Ir(PMe_3)_3(H)(DBP)Cl]$ and trimethylphosphine in $CDCl_3$: SRCI267**

$[Ir(PMe_3)_3(H)(DBP)Cl]$ (27 mg, 0.036 mmol) was charged to a screw capped NMR tube. $D_2O$ (0.7 mL) was added via syringe. $PMe_3$ (3.7 mL, 0.035 mmol) was added via microsyringe. Upon mixing vigorously, $^1H$ and $^{31}P$ NMR spectra were obtained immediately. The tube was allowed to sit at ambient temperature for 4 days after which $^1H$ and $^{31}P$ NMR spectra were obtained again. Equilibrium between the cis and trans isomers of $[Ir(PMe_3)_4(H)(Cl)]^+$ was established based on $^1H$ and $^{31}P$ NMR spectra that were identical to the $D_2O$ solutions above.

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# Chapter 4: Conclusion and Future Work

## Section 4.1: Conclusion

The studies in this thesis were aimed at the synthesis and characterization of the products of oxidative addition of the O-H bond of phosphates to [Ir(1,5-COD)($PMe_3$)$_3$]Cl. This was done in an atempt to gain insight into the possible interaction of this iridium(I) species with molecules of biological interest which contain phosphate groups. A second goal was to study the solution reactivity of these compounds and to compare the reactivity of the phosphate complexes with the similar carboxylate complexes which have been previously characterized.

In this thesis, the synthesis and characeterization of several dialkyl phosphate iridium(III) complexes has been described. Complexes of the form, *mer*-Ir($PMe_3$)$_3$(H)(phosphate)Cl were easily made with dialkyl phosphates (phosphate=DBP, DEHPA, DIOPA, DHDP, BDHPA) while diaryl and monoalkyl phosphate complexes could not be synthesized. The dialkyl phosphate complexes are soluble in a variety of solvents including water, benzene, chloroform, and ether (with the exception of the dibenzyl phosphate). These 18-electron iridium(III) complexes are stable with respect to phosphate dissociation in non-coordinating solvents like benzene and chloroform. In polar, coordinating solvents like methanol and water, the phosphate is displaced by a molecule of solvent.

The solution reactivity of the dibenzyl phosphate complex, Ir($PMe_3$)$_3$(H)(DBP)Cl, was investigated more thoroughly than the remaining dialkyl phosphates. Preliminary studies have shown that the dibenzyl phosphate ligand is very labile in solution. In chloroform or water, the phosphate is displaced by an equivalent of a nucleophile, trimethylphosphine. This suggests that this phosphate complex may be a possible source

of coordinatively unsaturated iridium(III) and therefore useful as a catalyst precursor. The addition of molecular hydrogen to $Ir(PMe_3)_3(H)(DBP)Cl$ in water at room temperature produced no reaction.

An effort was made to synthesize the chelated dibenzyl phosphate complex. All attempts at making making the $\eta^2$ phosphate complex analogous to the $\eta^2$ carboxylates studied by Ladipo were unsuccessful. This suggests that the phosphate complexes coordinate more weakly with the iridium(III) center than their carboxylate counterparts. This behavior is supported in the literature.

The reactivity of $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ with phosphate containing molecules of biological importance was briefly explored. Complex mixtures of products were obtained from reactions of $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ with nucleotides (d-AMP and cyclic-AMP) in water, while synthesis of the hydrido hydroxo species, $Ir(PMe_3)_3(H)(OH)Cl$ was attained in benzene solution presumably due to a lack of nucleotide solubility. Reactions of the phospholipid PEA with $[Ir(1,5\text{-}COD)(PMe_3)_3]Cl$ resulted in the formation of the N-H addition product.

## Section 4.2: Future Work

The lability of the dibenzyl phosphate ligand has suggested that the aforementioned phosphate complexes may be useful as precursors in catalysis. Although the complex $Ir(PMe_3)_3(H)(DBP)Cl$ was unreactive at ambient temperature with an atmosphere of molecular hydrogen, it would be beneficial to study the catalytic hydrogenation of unsaturates at increased temperatures and pressures using these phosphate complexes. It may be that these species are active catalysts in both water and in less polar solvents.

These complexes $Ir(PMe_3)_3(H)(phosphate)Cl$ may also be utilized for other types of organic catalytic transformations. Klemperer's work has shown that certain iridium(III) complexes are capable of oxidizing carbon-carbon double bonds upon the addition of

oxygen. The addition of molecular oxygen to a solution of the labile phosphate complexes may create a series of compounds capable of selectively epoxidizing unsaturated species.

The discovery of the antitumor activity of cis-platin and the anti-HIV activity of a recently synthesized iridium-amino acid complex has spurred interest into the oxidative addition of other biologically useful compounds to late transition metal centers. Further studies into the addition of biologically important phosphate compounds may be useful in the quest for new antitumor and anti-HIV drugs, although it seems that the presence of other nucleophilic atoms may prevent coordination of the phosphate group.

## Vita

Shannon Carol Rice was born in Richmond, Virginia on November 5, 1969 to James and Carolyn Rice. She graduated from Patrick Henry High School in Ashland, Virginia in 1987 and entered Westhampton College at the University of Richmond later in that year. After receiving a B.S. in Chemistry in December of 1990, she accepted a position as Chemist at Albright & Wilson, Americas. In the fall of 1993, she began her pursuit of a graduate degree at Virginia Tech under the direction of Dr. Joseph Merola. Shannon will continue her pursuit towards a Ph.D. in Chemistry at the University of Southern California.