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Modeling the activity of hydrogenase enzymes via transition metal catalysts

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MODELING THE ACTIVITY OF HYDROGENASE ENZYMES
VIA TRANSITION METAL CATALYSTS

A Thesis

Presented to

The faculty of the Department of Chemistry
San Jose State University

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

By

Mitra Alsadat Hosseini

August 2004

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ABSTRACT

MODELING THE ACTIVITY OF HYDROGENASE ENZYMES VIA TRANSITION METAL CATALYSTS

by Mitra A. Hosseini

Catalytic processes, such as hydrogenation, are useful to the economical production of pharmaceuticals. This thesis presents the synthesis of several water-soluble rhodium-centered catalysts, which are mimics of hydrogenase enzymes. The results of screening the activity of them by measuring the rate at which they mediate $\text{H}_2\text{-D}_2\text{O}$ exchange are presented. Gas chromatography was used to monitor the progress of the exchange by fitting the relative concentration of hydrogen isotopomers (H_2 , HD, D_2) to effective kinetic mechanisms to extract rate constants. The catalyst that mediates the exchange at an appreciable rate is a promising candidate to study the nicotinamide adenine dinucleotide, NAD^+ , reduction. Experimental results were fitted to proposed effective single and double exchange mechanisms. Among seven rhodium-centered catalysts, $\text{Rh}(\text{TPPMS})_3\text{Cl}$ was the only catalyst for which a double exchange step was necessary to fit the data.

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Dedication of this thesis is given with deepest appreciation to my mother for her continued moral support. Without her love and dedication, this endeavor would have been extremely difficult. I am very fortunate to have such a loving and caring family here and back home in Iran; I love you all.

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CHAPTER 1. INTRODUCTION

Having highly selective catalysts can be important in the synthesis or reactions of compounds, and the understanding of catalysis processes. Catalysis is crucial in the pharmaceutical industry because catalytic processes are used in the economical production of drugs. Economical and ecologically safe manufacturing of these drugs depends on two important characteristics of the catalyst: selectivity (chemo-selectivity, regio-selectivity, enantio-selectivity) and activity (number of product molecules produced per molecule of the catalyst per unit time).¹

Biochemical catalysts (known as enzymes) have very high selectivity and activity. The catalyst's stereo-selectivity for the development of drugs is very important because chirality of a compound can affect its biological properties. For instance, the dextrorotatory enantiomer of Dopa, D-Dopa, has no physiological effect on humans, but its levorotatory enantiomer, L-dopa, has activity that makes it useful in treating Parkinson's disease.¹ This stereo-selectivity has been seen in enzyme activities in other biological systems as well. For example, the reduction of ketones to chiral alcohols (Eq.1) by the enzyme alcohol dehydrogenase (ADH) is stereo-selective.^{2,3} This enzyme produces the desired enantiomer product with high yield.

A catalytic system that contains the same selective properties as ADH is beneficial because there is no need for separating by-products from the desired products,

and there is no need for handling extra waste that might be produced during the course of the reaction because ADH does not give rise to the unwanted side product.

To mimic high selectivity of the enzyme catalysis, a study examining hydrogenase enzymes from a synthetic and mechanistic standpoint is presented in this thesis. The focus has been on the isotopic exchange property of the enzyme between hydrogen gas and deuterium oxide in order to understand the mechanism of hydrogen cleavage, to increase proficiency in the synthesis of selective catalysts, and to closely mimic the enzyme catalysis. A catalyst that converts H_2 to D_2 at an appreciable rate will become a promising candidate for study in NAD^+ reduction.

Modeling activity of the hydrogenase is important because large-scale applications of enzyme catalysis are not practical for many reasons: First, isolation of a reasonable quantity of pure enzyme or coenzyme is difficult and very expensive. For instance, the cost of the cofactor nicotinamide adenine dinucleotide (NADH) is \$235,000/lb (the cost was obtained from Sigma Catalog); this makes the synthesis more expensive. Second, most enzymes are not chemically stable and separating the enzyme from the reaction mixture is difficult. The coenzymes are also unstable in water and in air, and thus have short lifetimes.⁴

Hydrogenase enzymes (H_2 ase), which mediate reduction of substrates through the process of hydrogenation, have been studied in efforts to lower the cost of drug production. These enzymes belong to a class of reductive and oxidative proteins and have the ability to catalyze reversible oxidation of dihydrogen via the following equations (Eqs. 2a, 2b).⁵

Splitting a hydrogen molecule into its single components is very important for biological systems especially anaerobic bacteria that depend on this reaction for energy. Anaerobic organisms mediate both production and uptake of hydrogen.⁶ For instance, the electrons that are produced in Equation 2a can be used to reduce sulfate to sulfide in sulfate-reducing bacteria. This reduction creates a trans-membrane protein gradient that helps to maintain pH of the cell at a physiologically nontoxic level even under extreme environmental conditions, such as high pH or high temperature.

Activation of a hydrogen molecule results in the formation of hydride (H^-) and hydrogen ion (H^+), Equation 2b.⁷ The hydrogenase enzyme uses the hydride to reduce cofactors, such as oxidized nicotinamide adenine dinucleotide (NAD^+) that are involved in metabolic electron chain reactions (Eqs.3a, 3b). Nicotinamide adenine dinucleotide cofactors, NADH and NAD^+ , act as electron carriers for the enzyme in the production of chiral products (Eq.3a, 3b).

The mechanism of molecular hydrogen activation by hydrogenase catalysts forms the subject of extensive current research.⁷ Until 1986, scientists believed that the

mechanism for the enzyme (E) driven dissociation of hydrogen (H₂) was shown as below (Eqs. 4a, 4b, 4c).

The enzymatic hydride, enzyme-hydride complex, E(H⁻), produced in Equation 4b reduces substrate. In 1986, Crabtree *et al.*⁸ proposed that since many natural enzymes have catalytic sites that are transition metal complexes, it is the metal in the enzyme that actually causes the dissociation of the hydrogen molecules. The enzyme catalyzes the reduction of substrates presumably through an intermediate hydrogen complex and/or metal hydride.⁹ Many transition metal (TM) centered catalysts have been studied¹⁰ as candidates for mediating this type of chemistry. This project extends these studies, focusing on the synthesis and catalytic characterization of water-soluble rhodium centered hydrogenase catalysts.^{3,28,30,31}

Rhodium (Rh) is used extensively in transition metal centered catalysts because it can take on several different coordination geometries that are needed for a wide range of catalytic modes.¹¹ Rhodium catalysts enable a large class of reactions, including hydrogenation, alkylation, hydroformation, hydroboration, and hydrosilylation. Rhodium serves as the active site in metal-centered catalysts like Wilkinson's catalyst, (RhCl(PPh₃)₃).¹² Rhodium (III) is also critical for biomedical applications because its

configuration confers both kinetic inertness and stability under *in vivo* conditions.¹³ The metal is capable of changing its coordination and oxidation state (+1 and +3), which makes it suitable to mediate a large variety of chemical pathways.

To closely mimic the activity of the enzyme, the synthesized catalysts were screened by studying their rate of isotopic exchange between hydrogen gas and heavy water because the enzyme hydrogenase mediate isotopic exchange of hydrogen with heavy water, D₂O, in different reactions of biological systems. The isotopic exchange can be used as a means of screening potential catalysts for formation of a metal hydride, as the formation of a metal-centered hydride is presumed to be similar to that in the NAD⁺ reduction mechanism.

Isotopic exchange was studied with a series of water-soluble analogues of the Wilkinson catalyst, RhCl(PPh₃)₃. Each catalyst was placed in a reaction cell along with hydrogen gas and D₂O. The rate of conversion of H₂ to HD and D₂ was then analyzed by gas chromatography (GC). Once the rate of formation of hydrogen isotopes is known, the proposed mechanism for the isotopic exchange can be validated.

This study is significant because if no conversion of hydrogen gas to its isotopomers occurs, there is little point in pursuing a given catalyst as a candidate for NAD⁺ reduction. The isotopic exchange provides mechanistic evidence for the binding of a metal to hydrogen molecule that can lead to different experiments, such as time-dependent Nuclear Magnetic Resonance (NMR) or infrared spectroscopy (IR), to learn about the stereo-selective reduction of a substrate, such information is invaluable towards discovering catalysts that can be used to solve many chemical problems.

CHABPERT 2. HISTORICAL BACKGROUND

2.1 Introduction to Catalytic Process.

The interaction between metal-centered complexes and small gaseous molecules such as oxygen or hydrogen play vital roles in biological systems and in many industrial processes.¹ The transport of oxygen by hemoglobin¹⁴ and myoglobin¹³, or hydrogenation of olefins over a metal surface^{15,16} are some examples involving metal centered complexes and gases. The coordination between molecules and the metal center has attracted the attention of inorganic chemists who want to understand how substrates such as hydrogen are activated by these species. Thus, enabling heterogeneous and homogenous catalytic processes.^{1,17}

In heterogeneous catalytic processes, the reactants are present as separate phases¹. In these processes, the reactant molecules are adsorbed onto the surface of the catalyst, which consists of a large array of ions or atoms. The large array of ions on the surface of the catalyst along with the high thermal stability ($>1000^{\circ}\text{C}$) of the catalyst makes heterogeneous catalytic reactions attractive for manufacturing many raw materials and a host of other chemical processes.

In homogenous catalytic processes, the catalytic reaction takes place in the liquid phase.¹ This means that all the reactants are completely soluble in the reaction solution. One major problem associated with homogenous catalysis is the solubility limit of gaseous reactants, which decreases as the temperature increases. The relationship between solubility and temperature for some gases is depicted in Figure 1.

Figure 1. Effects of temperature on the solubility of gases.

It seems that some homogenous catalysts are selective during synthesis of intermediates and optically active pharmaceutical products¹, examples of these compounds are shown in Table 1. So for stereo-selective synthesis of pro-chiral substrates into chiral pharmaceutical compounds/substrates, homogenous catalysts are used since they exhibit both the chemo-selective and regio-selective, and enantio-selective characteristics.

2.2 Homogenous Catalysis.

Homogenous catalysis is an interdisciplinary area of chemistry that has research applications for both academic and industrial laboratories. However, separation and recovery of the catalyst in some homogenous processes is a serious problem.¹ The use of a biphasic (water/organic) catalytic system is attractive due to the possibility of recovering the catalyst and the ease of product separation. If the product, for instance, is water soluble, it stays in the aqueous layer. The organic layer will be extracted from the aqueous layer by decantation or extraction. Transition metal complexes have been shown

to have this property, especially for reactions in which they bind to molecular Hydrogen.^{3, 18-22} This property of the transition metal makes their usage attractive for studying catalytic reactions.

Table 1. Some Pharmaceutical Products of Homogeneous Catalysis (Bhaduri *et al.*, p.6).

Structure	Name and Use	Process
Naproxen Anti inflammatory drug	Asymmetric hydroformylation or hydrogenation
Ibuprofen Analgesic	Catalytic carbonylation
L-Menthol Flavoring agent	Asymmetric isomerization
An intermediate for Prosulfuron Herbicide	C-C coupling (Heck Reaction)

The metal hydride that is formed from the heterolytic cleavage of a dihydrogen molecule has been proposed as the intermediate in the reduction of a substrate, as shown below (Eqs. 5a, 5b).⁹

In the above equations, the metal-hydrogen complex formed in the reaction between hydrogen and Ru(OEP)(THF)₂ gets deprotonated by KOH. The resulting

hydride

complex, $[\text{Ru(OEP)(THF)(H)}]^+$, is then used to reduced the oxidized form of the cofactor, NAD^+ to the reduced form, NADH. Thus, the design of selective homogenous catalysts for substrate reduction requires knowledge of the following mechanisms:

1a) Activation of a hydrogen molecule

2a) Formation of a metal-hydrogen intermediate or of a metal hydride

3a) Protonation of the intermediate(s) followed by elimination of a hydrogen isotopomer

It is also necessary to understand what factors affect stability of the intermediates and the rate of hydrogen evolution from the intermediate. Studying the first step shown in 1a forms the objective of this research. The binding of different metal complexes with hydrogen molecules has been used as a screening method for finding a candidate to study $\text{H}_2/\text{D}_2\text{O}$ conversion. Gas chromatography has been used for screening the catalysts, this method is significant because it gives the relative amount of each isotopomers as a function of the reaction time. Gas chromatography is a very convenient means of monitoring the progress of this model system, as it can be used to monitor the progress of isotopic exchange between H_2 and D_2O by mapping the relative concentration of H_2 , HD, D_2 as a function of reaction time.

Gas chromatography is a promising screening method of analysis of the isotopic

exchange. This study will provide new chemical information, extending the understanding gained in similar studies done by Kovacs *et al.*²¹ Kovacs and co-workers study the isotopic exchange by ^1H -NMR. They detected the monitor the rate of formation of each isotopomers by increase in the intensity of HDO. Their proposed mechanism, Figure 2, is explained more in details in chapter 5- section 5.2. As it has shown in the Figure 2, there are two cycles involve in the exchange. Kovacs *et al.* only were able to see the big cycle; they cannot monitor the rate of H_2 -RhXP₃ or HD-RhXP₃ because with ^1H -NMR only relative peak intensity of HDO is seen.

Figure 2. The isotopic exchange cycle proposed by Kovacs *et al.*²¹

With gas chromatography, the area under each peak is proportional to the partial pressure of each gas. The pressure then can be converted to the concentration of each isotopomers in solution, using Henry's Law, as a function of reaction time; details of the calculations are in chapter 4- section 4.2.2. The details on the relative rate of formation and the amount, concentration, of each isotopomers can give an insight on the part of the

mechanism of involving $\text{H}_2\text{-RhXP}_3$ or HD-RhXP_3 . The detailed information from the gas chromatography makes this study unique.

CHATER 3. THEORY

3.1 Overview of Transition Metal-Ligand Interactions.

Transition metal elements begin from group IIIB elements of the periodic table. They are the lowest atomic number elements to have electrons in 3d orbitals.²² These elements have open valence shells (n) and are characterized by $ns^2 (n-1)d$ electronic configurations. Since they usually have vacant d orbitals, they can be involved in various types of bonding with other elements in the periodic table. Before discussing the bonding in transition metal complexes, there are a few definitions that should be given at the outset.

The binding between a transition metal atom and a molecule often involves electron transfer. The molecules or ions that surround a central metal atom (M) or ion (M^{n+}) and bind to the metal are called ligands.²³ Ligands are considered Lewis bases when they form a coordinate-covalent bond or a dative bond with the metal by donating electrons to the metal center ($M \leftarrow :L$). There are times when a group of ligands may attach to the same metal atom through more than one coordinating atom. These ligands, such as bipyridine or oxalate, are known as chelate or multidentate ligands.^{22,27} Chelating ligands form very stable bonds with the metal center since they have more than one bonding interaction with the metal atom, as shown in Figure 3.

A hexadentate ligand

A bidentate ligand

Figure 3. Two examples of multi-dentate ligands.²²

Thus, these ligands are not as rapidly exchanged or displaced with other ligands during the course of a reaction. The metal-ligand complex that has a slow ligand exchange rate is known as a *nonlabile* or an *inert* complex. Ligands that exchange rapidly are said to be labile.²²

The number of ligands around the metal center is indicated as a coordination number. The field strength of the ligands affects the electronic structure of the metal center and crystal field splittings. Thus, the coordination number determines the geometry of the metal-ligand complex. Examples are shown in Table 2.²⁵

Table 2. Different Geometries of Metal Complexes (Douglas *et al.*, p. 69).

Coord. Number	σ orbitals	Geometry, Configuration	π orbitals
2	sp	Linear	p^2, d^2
3	sp^2	Trigonal plane	p, d^2
4	sp^3	Tetrahedral	-----
4	dsp^2	Square planar	p, d^3
5	$d_z^2 sp^3, d^3 sp$	Trigonal bi-pyramid	d^2
5	$d_{x^2-y^2} sp^3, d^2 sp^2, d^4 s, d^4 p$	Tetragonal pyramid	d
6	$d^2 sp^3$	Octahedral	d^3

The splitting pattern of d orbitals, Fig. 4, depends on the nature of surrounding ligands and the charge density (charge and size) of the central ion.²² Attractive forces increase as the charge on the metal ion increases, and more ligands can approach the large metal ion without experiencing steric hindrance. Increasing the number of ligands increases the observed splitting due to an increase in the electric field generated by the ligands.

There are other ligand properties that affect the splitting patterns. The metal-ligand distance is larger for bulky ligands, and thus the d-orbital splittings are smaller due to a smaller electric field generated by ligands separated by a greater distance. Large and more electronegative ions, such as cyanide ions cause a greater splitting of d-orbital than a small ion like chloride ion.²⁴ The splitting ability of ligands is as follows:

The symmetry of interaction between the metal and the ligand is another factor that affects the energy difference in d-orbital of the metal center. Metal atoms can interact with ligands to form molecular orbitals with local π or σ symmetry. In systems with octahedral or square planar symmetry, σ orbitals are formed by the combination of $d_{x^2-y^2}$ or d_{z^2} orbitals on the metal atom with p, sp, or sp^3 orbitals on the ligand (Fig. 5).²⁴

Figure 4. Relative d-orbital splitting patterns for a transition metal center (Day *et al.*, p. 292).

Orbitals that lie along the inter-nuclear axis (INA) form σ bonds with orbitals those are along the INA. The double-degenerate, e_g , orbitals of transition metals are the only orbitals that are directly pointed at the ligands in octahedral and square planar geometry and are often empty, depending on the electronic structure and the crystal field splitting of the central atom, so they can accept electron density from the ligand.

Figure 5. p and s covalent metal-ligand interactions (Purcell *et al.*, p.475).

The difference between a π and a σ orbitals is the number of angular nodes along the bond axis, which is zero for σ and is one for π . In the π interaction, the metal d_{xy} , d_{yz} , d_{xz} (triple-degenerate, t_{2g}) orbitals overlap with the p, d, π , and π^* of the ligand orbitals since they have the proper symmetry. This overlap leads to both bonding and anti-bonding orbitals (Fig. 6).²³

Figure 6. Molecular orbitals resulted from p-bonding orbitals of t_{2g} symmetry (Day *et al.*, p. 299).

As shown in Fig. 6, interaction of a metal-centered orbital with a ligand orbital yields a bonding and anti-bonding orbital. In addition to the π bond between the metal atom and the ligand, the metal donates back some of its electron density from its d-orbital to the

empty antibonding and/or bonding orbitals of the ligand (Figure 7).²⁵ This donation of electron density from a filled metal orbital to an unfilled or partially filled ligand orbital is called backbonding.²⁴

Figure 7. Back-bonding between the metal and the ligand (Douglas *et al.*, p.419).

Back-bonding weakens internal bonding in the ligand if the metal donates back the electron density to the anti-bonding orbitals of the ligand. Back bonding creates a greater negative charge on the ligand and a more positive charge on the metal center, which can result in a more polar bond between the two. The electrostatic attraction between M and L increases by increasing the polarity of the bond, which increases the d-orbital splitting.

As mentioned before the splitting pattern of the metal center determines the geometry of the M-L complex. The geometry can affect reactivity and rate laws, as can the surrounding ligands. Metal ions, such as Rh(I) or Ni (II) that have d^8 configuration usually form four-coordinate square planar complexes.²⁵ These complexes usually

follow an associative mechanism in ligand substitution reactions. This geometry leads to less steric hindrance between ligands since there are only a few around the metal center. The ligand substitution mechanism for the metal center (M) having L, X, Y ligands around is as follow (Eq. 6a, 6b, 6c, 6d, 6e):

As it is shown in Eq. 6a, ligand Y and solvent S (acting as a ligand as well) are replacing the ligand X. Thus, the steps for an associative mechanism can be expressed as follows:

The rate constant k_2 depends on the nucleophilicity of the entering ligand (Y), and k_1 depends on the solvent (S) only. The above mechanism holds only if the solvent effects can be ignored. From the above mechanism, the rate law for the overall reaction is (Eq. 6e):

$$\text{Rate} = (K [\text{Y}]) [\text{ML}_2\text{AX}], \text{ where } K = k_1 + k_2 \quad (6e)$$

The concentration of the entering ligand, Y, remains constant due to a large excess of the ligand.²⁵

The entering (Y) and leaving ligand (X) positions affect the rate of the reaction. The ligands that are in a *trans* position labilize a particular ligand to substitution (as shown in the below reaction), which lowers the activation energy for a substitution and in turn increase the rate of substitution reaction.

As has been proposed by Crabtree and co-workers¹⁸, the metal catalytic cycle can be summarized as shown in Figure 9.

Figure 9. The proposed metal catalysis by Crabtree.⁸

Hydrogen binds to the metal and forms the first intermediate, $[L_nM(H_2)]^{n+}$. The intermediate is acidic, so it is de-protonated by a base (:B) and the metal hydride complex (the second intermediate, $[L_nM(H)]^{n+}$) is formed. The metal hydride complex then reduces the substrate nicotinamide in the example shown in Figure 8.

The formation of the first active intermediate depends on the cleavage of the hydrogen bond in the H_2 ligand. The cleavage of H_2 can happen homolytically or heterolytically.²⁶ The homolytic cleavage process is similar to the oxidative addition reaction, as illustrated in Figure 10.²⁷

Figure 10. The oxidative addition mechanism of hydrogen ligand (Crabtree p. 21).

The heterolytic cleavage of H-H bonds depends on the acidity of the first metal-hydrogen complex intermediate and the acidity of the complex depends on the metal center. The

more electron donating ligands around the metal, the less the metal is able to engage in a sigma (σ) interaction with the hydrogen.

If hydrogen is not able to donate its σ -electrons to the available d-orbital of the metal, the probability of cleavage of the H-H bond decreases. When hydrogen is bonded to a cationic metal center, it can donate its σ -electrons more to an available d_z^2 -orbitals of the metal (Fig. 11).²²

Figure 11. The interaction between metal d-orbitals and hydrogen orbitals (Kubas *et al*).²²

In addition to this σ bonding scheme, the metal can donate back some electron density to the empty anti bonding orbital (σ^*) of hydrogen, forming a π -type back-bond. As the extent of back-bonding increases, the extent of heterolytic cleavage of σ -hydrogen and formation of metal-dihydride complex increases.²⁶ Depending on the acidity of $[\text{L}_n\text{M}(\text{H}_2)]^{n+}$ complex, a base (:B) can de-protonate the intermediate and form a second intermediate, $[\text{L}_n\text{M}(\text{H})]^{(n-1)+}$. The second intermediate may cause the reduction of substrates. After substrate reduction, the catalyst is recycled.

Via loss of the proton (H^+), many transition metal complexes may undergo this cycle, but the rate at which the metal-hydride is formed is different from complex to

complex. The rate is related to the ligands surrounding the metal center and the ligand configuration. For example, *cis* or *trans* ligands may affect the rate differently.

To understand the hydrogenase isotopic exchange, there is a need to know how the two intermediates, $[L_nM(H_2)]^{n+}$ and $[L_nM(H)]^{(n-1)+}$ are formed. According to Crabtree *et al.*¹⁸, the metal binds to hydrogen molecule first and then forms intermediates. This implies that hydrogen gas binds to the metal after it diffuses in the solution (Eqs. 7a, 7b):

The above equations, 8a and 8b, can be expressed as it is depicted in Figure 12.

Figure 12. An effective proposed single-exchange mechanism.

Where:

M = The active site/metal center

B: = The base/solvent, D_2O

H_2 (g) diffuses into the solution mixture and exchanges with deuterium oxide, D_2O , to make its first product, HD (g). The formation of D_2 occurs when the build up of HD concentration in the gas phase. In other words, H_2 (g) concentration decreases over time as HD is formed. The concentration of the intermediate, HD, increases at first and

then depletes over time as the second product of exchange, $D_2(g)$, is formed. The proposed mechanism can be used to develop a theoretical map for the concentration of isotopomers as a function of reaction time.

Equations 8a and 8b are applicable only if the ligand exchange or the rate of ligand coming off and on the metal center is faster than the rate of acid/base steps. Thus, D_2 is forming through the HD after its concentration has built up for some time. By given an arbitrary value to rate constant on an excel spread sheet to the 8a step and writing time-expressions for both step 8a and 8b, the theoretical curve is constructed as shown in Figure13. Details of the design and construction of the theoretical curves are described in Appendix 1.

Figure 13. Theoretical curves for single exchange.

The Figure 13 is constructed based on the following assumptions: It was assumed that there is not an isotopic effect on exchanges; the exchange of a hydrogen atom or a deuterium atom is equally likely. So the following expressions (Eqs. 8a, 8b, 8c) give the time-dependence of concentration based on the above mechanism.

$$d[H_2]/dt = -k_1 [H_2] \quad (8a)$$

$$d[HD]/dt = +k_1 [H_2] - \frac{1}{2}k_1 [HD] \quad (8b)$$

$$d[D_2]/dt = +\frac{1}{2}k_1 [HD] \quad (8c)$$

The above expressions assume a constant concentration of solvent, D_2O , can be assumed that stays constant.

The above expressions are similar to the associative mechanism:

The associative mechanism holds only if the solvent effects can be ignored. Since $[D_2O]$ is present at a high amount, it is not included in the expression of rate law.

If the experimental values follow the same pattern as the theoretical value, then the mechanism is consistent with the observations. The assumption in the above expression is rate constant for 7b, which is assumed to be half of the rate constant for 7a. For HD/D_2O exchange, it is assumed that H and D are equally likely to undergo exchange. When D-atom exchanges, there is no net reaction. So the rate constant for 8b based on the statistics is one-half of 8a.

If the acid/base exchange are extremely rapid relative to the H_2 -Rh or HD -Rh exchange steps, the net effective mechanism will be as indicated in Equation 9a. If this happens, then the isotopic reaction and the mechanism can be written as follow:

Figure 14. The effective proposed for extreme double-exchange mechanism.

The same procedures as it were done for the effective single exchange mechanism was applied to the double exchange mechanism (Eqs. 10a, 10b).

$$d[\text{H}_2]/dt = -k_2 [\text{H}_2] \quad (10a)$$

$$d[\text{D}_2]/dt = +k_2 [\text{H}_2] \quad (10b)$$

Here $[\text{D}_2\text{O}]$ is also assumed constant as explained before. Both 10a and 10b steps indicate that the rate of consumption of H_2 is two times faster than its consumption rate in the net single exchange mechanism. This mechanism means that the interaction between the metal center and the hydrogen ligand is strong and the acid-base step proceeds at a higher rate than the ligand exchange step. The mechanism is depicted as follow:

Figure 15. The effective proposed double exchange mechanism.

Both of the limiting cases will contribute to the formation of D_2 . So D_2 is formed by the following proposed effective mechanism, with the contribution of both limiting cases:

The theoretical curve is constructed the same as the other two proposed mechanism, which is based on the time-dependence expression (Eqs. 11a, 11b, 11c):

Figure 16. Proposed theoretical curves for double exchange mechanism.

The main difference between Fig. 13 and Fig. 16 is in the effective rate law depends on k_2 . If reaction 11c proceeds in a faster rate than 11a, then the concentration of D_2 builds up faster than HD concentration. Integrated rate laws can be determined to perform kinetic analysis, time dependence expressions for both mechanisms. Again, it was assumed that there is not an isotopic effect on exchanges; otherwise, the rate constant for the formation of D_2 will not be half of the rate for the formation of HD. This means that the exchange of a hydrogen atom or a deuterium atom is equally likely. The

following expressions (Eqs. 12a, 12b, 12c) give the time-dependence of concentration based on the above mechanism.

$$d[H_2]/dt = -k_1 [H_2] - k_2 [H_2] \quad (12a)$$

$$d[HD]/dt = + k_1 [H_2] - \frac{1}{2} k_1 [H_2] \quad (12b)$$

$$d[D_2]/dt = + \frac{1}{2} k_1 [HD] + k_2 [H_2] \quad (12c)$$

It is possible in some cases that data may be fit to the proposed effective mechanism while fixing the value of K_2 to zero. Only in the case that the value of a non-zero value of K_2 is necessary, the reaction step 11c is included in the mechanism. The above assumptions were used to construct the theoretical values that to analysis the data obtained from each synthesized catalyst, and to determine the appropriate mechanism for the isotopic exchange between hydrogen gas and the transition metal catalyst.

3.3 Research Objectives.

Enzymes function almost to perfection in living systems. As a result, there is a great interest in mimicking enzymatic catalysis outside living systems. The interest is due to many applications that enzymes have in organic synthesis,^{2,3} pharmaceutical, and industrial settings.¹ To design a system similar to an enzyme's kinetics, it is necessary to understand the chemical mechanisms in which the enzyme is involved. One such process, hydrogenation, is catalyzed by biological catalysts like hydrogenase enzymes. It has been shown that the active sites of hydrogenase enzymes contain transition metal atoms, such as iron.⁸ This research focuses on hydrogenase enzyme mimics, which may have their transition metal centers as their active sites.

The focus of this research is on complexes with coordination numbers 6 and 4 that have octahedral and square planar geometries respectively. As such, all of the catalysts synthesized in this study have rhodium as their active site and have either square planar or octahedral geometry. Square-planar geometry occurs in all of the compounds used in this study, except two that have octahedral symmetry. The rate of the reaction between hydrogen and water-soluble rhodium catalysts was determined by studying the kinetics of isotopic exchange between the molecular hydrogen and deuterium oxide, D_2O . The hydrogen isotopomers, deuterium hydride (HD) and deuterium (D_2), were produced over time depending on the metal electronic structure.

The application of this research is to create a recycling system that is a mimic of enzymatic catalysis in biological systems, specifically hydrogenase enzymes. To date, the study focused only on the rate of formation of hydrogen isotopomers as a means of screening the synthesized catalysts. To probe the catalytic properties of the active site, other conditions such as concentration of the catalyst and pH of the reaction in a 6.5-8.2 range, pressure effects and reaction temperature from 25-65°C for each condition were investigated. Relative concentrations of H_2 , HD, and D_2 in the reaction mixture were determined by monitoring vessel headspace and gas chromatography at liquid nitrogen temperature.

CHATEPR 4. EXPERIMENTAL METHODS

This chapter is divided into two sections. The first section of this chapter describes the experiments used to probe the catalytic activity of the compounds, especially their activity with regards to catalyzing H₂/D₂O isotopic exchange reactions, and instrumental techniques that were used to screen each catalyst. Details of instrumentation and preparations of samples are discussed in Section 4.1. The second discussion is on the syntheses of several compounds that are intended to be used for the isotopic exchange reactions and general techniques used in these syntheses. The details of each synthesis are explained in Section 4.2.

4.1 Analytical Techniques.

The catalysts synthesized as described in part 4.2 were tested as candidates to catalyze the following reactions (Eqs. 13a, 13b):

The description of these experiments is broken into two parts. The first part describes the preparation of the column for the quantification of H₂, HD, D₂. The details of the preparation of the column are in the section 4.2.1. The second part of this section is about preparation of the sample for the kinetic study. The sample preparation and the results obtained are in section 4.2.2.

4.1.1. Quantification of Hydrogen Isotope Exchange Reactions.³³

To separate and to detect isotopomers of hydrogen (H₂, HD, and D₂) an Agilent Technologies 6890N Gas Chromatograph with a thermal conductivity detector (TCD,

temp=250°C) was used. A 7-foot length of 1/8 inch outside diameter (O.D.) copper tubing was rinsed with methylene chloride and acetone. After oven drying, the column was fitted with Swagelok® fitting and was packed with activated alumina (40-60 mesh) that was impregnated with 10% MnCl₂ to equilibrate ortho and para hydrogen spin. Another stainless 1/8" O.D. steel tube (7 inch) was packed with 45-60 mesh CuO and was wrapped with heating tape.

The two columns were connected with a union. Under operating conditions, the alumina column was submerged in liquid nitrogen and the CuO catalyst column was heated to 350°C using heat tape. The column separates the isotopomers based on their average kinetic energy at the fixed column temperature. The heavier isotopomer moves slower than the lighter isotopomer, and thus the lighter molecule gets detected first. The hydrogen isotopomers were converted to their oxides (Eqs. 14a, 14b, 14c), as is shown below, in the CuO column (heated at 350°C) that was connected to the TCD.

Using a flow rate of 30 ml/min He, typical retention times for H₂, HD, and D₂ respectively were on the order of 9.1, 11.1, and 14.8 minutes with baseline separation.

A typical chromatogram is shown in Figure 18. The gas mixture of isotopomers was injected into the GC, using helium as a carrier gas (mobile phase) through the aluminum oxide column (stationary phase). When the sample reached the liquid nitrogen cooled column, the average molecular speed decreases. The separation of gases in the

column is based on their molecular weight; thus, the lighter gas is eluted first and detected by the thermal conductivity detector (TCD). The experimental set-up is depicted schematically in Figure 17.

Figure 17. The GC apparatus used for the kinetic studies.

4.1.2. Gas Chromatography Analysis.

Gas chromatograms were gathered on an Agilent Technologies 6890N Gas chromatograph. First, each catalyst was dissolved in 1 mL-degassed D_2O . Then, the solution was degassed again and the conical vial was back filled with the argon gas. The initial time for the reaction was considered to be the time hydrogen gas was added in the degassed solution mixture. Hydrogen was added by bubbling through the solution inside a 5-mL conical vial for 2 minutes for all catalysts except for $(\text{RhCp}^*\text{BipyMeOH})\text{Cl}_2$, which was five minutes. To analyze the amount of each isotopomer formed as a function of time, a 30 μL sample gas headspace was injected into the GC.

The kinetic experimental results are shown here; however, the interpretation of

the results is discussed in detail in Chapter 5. The concentration of each isotopomer in the solution was calculated based on Henry's law.

$$C_g = k \times P_g$$

Where: C_g = Molar concentration of the gas in the solution

P_g = Partial pressure of the gas

k = Solubility constant

The area under each peak on the chromatogram, as has shown in Figure 18, is proportional to partial the pressure of the gas; the total pressure of was taken as 1 atmosphere. After normalizing the area under the curve for each gas, the partial pressure of the gas was converted to the molar concentration of each isotopomers using the solubility values from *HandBook of Chemistry and Physics* (CRC). The calculations were done as follow:

$$P_{H_2} = \text{Area } H_2 / \Sigma \text{ Area } (H_2 + HD + D_2)$$

Figure 18. The typical chromatogram of the sample headspace.

Each chromatogram provides a snapshot of the concentrations of H_2 , HD , D_2 at the time the headspace was sampled. These data were plotted versus time for each catalytic system. Rate constants were chosen for each data set such that the kinetic model

gave the best fit to the data. Solid lines in all figures are related to the theoretical values of each isotopomer and the rate constant indicates the rate of conversion of hydrogen gas to HD.

Each catalyst has its own rate constant value that is indicated on its plot. The reasons for having different values are explained in details in Chapter 5. The Figure 19 is the plot of concentration of each isotopomers produced as the result of isotopic exchange catalyzed by Rh(TPPTS)₃Cl synthesized by method D synthesis. Recall the time-dependence expressions used to write the excel spreadsheet to obtain the value of rate constant.

$$d[H_2]/dt = -k_1 [H_2] - k_2 [H_2] \quad (12a)$$

$$d[HD]/dt = +k_1 [H_2] - \frac{1}{2} k_1 [H_2] \quad (12b)$$

$$d[D_2]/dt = +\frac{1}{2} k_1 [HD] + k_2 [H_2] \quad (12c)$$

Figure 19. Rate of isotopic exchange catalyzed by Rh(TPPTS)₃Cl, method D. The isotopic exchange catalyzed by Rh(TPPTS)₃Cl, method A, is shown in Figure 20. The value of the rate constant for method A synthesis is very close to value of rate constant for method D synthesis.

Figure 20. Rate of isotopic exchange catalyzed by Rh(TPPTS)₃Cl, method A.

The value of the rate constant for the Rh(TPPTS)₃Cl, method C synthesis is not very far away from the value obtained for the same catalyst with method D and A. This implies that the amount of impurity, oxidized phosphine ligand, does not have a profound effect on the rate of the reaction, Figure 21.

Figure 21. Rate of isotopic exchange catalyzed by Rh(TPPTS)₃Cl, method C.

The isotopic exchange catalyzed by RhCp*Bipy (OTf)₂ is shown in Figure 22. As it indicated by value of the rate constant, the rate of isotopic exchange catalyzed by RhCp*Bipy (OTf)₂ is much slower than Rh(TPPTS)₃Cl.

Figure 22. Rate of isotopic exchange catalyzed by RhCp*Bipy (OTf)₂.

The isotopic exchange catalyzed by the (RhCp*BipyMeOH)Cl₂ is even slower than the one with RhCp*Bipy (OTf)₂ catalyst. The rate of formation of D₂ is so slow that there are only a few points for the isotopomer, Figure 23.

Figure 23. Rate of isotopic exchange catalyzed by (RhCp*BipyMeOH)Cl₂.

The rate of isotopic exchange catalyzed by (RhCpCl₂)₂ is also slow like the other two catalysts, (RhCp*BipyMeOH)Cl₂ and RhCp*Bipy (OTf)₂. The results for the catalyst, RhCpCl₂)₂, are depicted in Figure 24.

Figure 24. Rate of isotopic exchange catalyzed by $(\text{RhCpCl}_2)_2$.

The results obtained from $\text{Rh}(\text{TPPMS})_3\text{Cl}$ catalyst did not fall into the effective single exchange mechanism, Figure 25. The plot then was fitted to the effective double exchange theoretical map, Figure 26. As it is shown in Figure 26 plot, the $\text{Rh}(\text{TPPMS})_3\text{Cl}$ follows the double exchange mechanism.

Figure 25. Rate of isotopic exchange catalyzed by $\text{Rh}(\text{TPPMS})_3\text{Cl}$.

After adding one more path to the effective single exchange mechanism steps, the results for $\text{Rh}(\text{TPPMS})_3\text{Cl}$ were fitted into the theoretical curve (solid lines) of the effective double exchange mechanism (Figure 26).

Figure 26. Rate of double exchange catalyzed by $\text{Rh}(\text{TPPMS})_3\text{Cl}$.

4.2 Synthetic Techniques.

All manipulations of chemicals were performed under a nitrogen or an argon atmosphere using standard Schlenk techniques due to the air-sensitive nature of reactants and products; air- and moist sensitive syntheses were performed in a dry box. All glassware, such as reflux condensers, round bottom flasks, and funnels were oven dried before usage.

Solvents including deionized water and NMR samples were degassed and the flask containing the solvents were backfilled with the argon gas. Reagents were used as provided by suppliers without further purification. Gel filtration with Sephadex G-15 was used for separation of rhodium impurities in some cases. The column preparation was done under an argon atmosphere, and the sample was introduced onto the column in a glove bag.

Nuclear Magnetic Resonance (NMR) measurements were done on a Varian-

INOVA 400 MHZ instrument. NMR data are described using the following keys: δ , chemical shift in part per million (ppm); s, singlet; d, doublet; t, triplet; quart, quartet; quint, quintet; m, multiplet; br, broad; dd, doublet of doublets; dt, doublet of triplets.

The syntheses were performed in round bottom flasks. In some cases, the reaction mixture was refluxed to drive the reaction to completion, which the temperature differed for each synthesis. The amount of each reagent and reaction conditions are summarized in Table 3.

Table 3. Reagents, Amounts, and Conditions Used for Each Synthesis.

Product	Reactants	FW(g/mol)	Amount	mmol	Reaction Time
RhCl (pph₃)₃ (section 4.1.1)	RhCl ₃ .3H ₂ O	209.26	101mg	0.390	20 min reflux
	P (C ₆ H ₅) ₃	262.29	603 mg	2.33	
	C ₂ H ₅ OH	46.07	20 mL		
	RhCl ₃ .3H ₂ O	209.26	200 mg	7.60	
[RhCl (1,5-C₈H₁₂)₂] (section 4.1.2)	C ₈ H ₁₂	108	3 mL		21 hrs stirring
	C ₂ H ₅ OH:H ₂ O	20 mL(5:1) ¹			
[RhCl(TPPTS)₃],A (section 4.1.3a)	RhCl ₃ .3H ₂ O	209.26	40 mg	0.152	3 hrs stirring
	TPPTS	568.43	854 mg	1.50	
	H ₂ O	18	3 mL		
[RhCl(TPPTS)₃],B (section 4.1.3b)	Rh[P(C ₆ H ₅) ₃] ₃	925.235	50 mg	0.055	over night stirring
	TPPTS	568.43	941 mg	1.65	
	OC ₄ H ₈	72.11	5 mL		
	H ₂ O	18	10 mL		
	Toluene	92.14	10 mL		
[RhCl(TPPTS)₃],C (section 4.1.3b)	[RhCl(cod) ₂] ₂	492.66	103 mg	0.21	40 min stirring
	TPPTS	568.43	700 mg	1.23	
	CH ₂ Cl ₂	84	10 mL		
	H ₂ O	18	10 mL		
[RhCl(TPPTS)₃],D (section 4.1.3d)					

¹ 95% ethanol was used for the synthesis.

[RhCl(C ₂ H ₄) ₂] ₂	388.93	101 mg	2.60	
TPPTS	568.43	858 mg	1.51	
CH ₂ Cl ₂	84	10 mL		
H ₂ O	18	10 mL		45 min stirring
[(RhCp*(H₂O)₃](OTf)₂ (section 4.1.4)				
(RhCl ₂ Cp*) ₂ ²	618.08	50 mg	0.08	
AgOTf	256.94	83 mg	0.32	
CH ₂ Cl ₂	84	4 mL		3 hrs stirring
[(RhCp*Bipy(H₂O)](OTf)₂ (section 4.1.5)				
[RhCp*(H ₂ O) ₃](OTf) ₂	590.31	100 mg	0.169	
C ₁₀ N ₂ H ₈	156.19	26.5 mg	0.169	
H ₂ O	18	2 mL		4 hrs stirring
[(RhCp*Bipy(MeOH)](OTf)₂ (section 4.1.5)				
(RhCl ₂ Cp*) ₂	618.08	313 mg	0.506	
C ₁₀ N ₂ H ₈	156.19	205 mg	1.31	
CH ₃ OH	32	10 mL		10 min stirring

Details of each synthesis are described in the sections indicated in Table 3.

To obtain a pure catalyst for kinetic analysis, different methods of Rh(TPPTS)₃Cl synthesis was performed since the reaction would not go to complete formation of the pure product. The Rh(TPPTS)₃Cl catalysts obtained by the procedures described in sections 4.1.3a, 4.1.3b, and 4.1.3c were purified using gel filtration³². In the gel filtration process, Sephadex G-15 was used as a stationary phase to separate rhodium impurities from tris (3, 3, 3''-phosphinetriylbenzenesulfonato) chloro rhodium (I), RhCl (TPPTS)₃. This method was used because the molecular weight of the main impurity, RhCl₂ (COD)₂, is smaller than the molecular weight of the desired compound, RhCl (TPPTS)₃. This means that the impurity will be eluted first from the column. The amount of packing material for the column was calculated as described in the literature, according to Darcy's Law²⁹.

The amount of Sephadex G-15 needed to pack the column was calculated using

² Synthesis of (RhCl₂Cp*)₂ was done by P.S. Wagenknecht at San Jose State University.

Darcy's Law.

$$U = K \Delta P / L$$

Where: U = Linear flow rate in units of $\text{ml}/\text{cm}^2 \text{ hr}$

K = A constant value, which is 18 for Sephadex G-15

ΔP = Change in pressure drop over gel bed in cm water

L = Bed height in cm

To determine the amount of resin required to pack the column, it is necessary to know the volume of the column. For a 53 centimeters (cm) Econo-column with inner diameter equal to 1.2 cm, the volume of water was calculated as follow: $\text{Volume (V)} = 53 \text{ cm} * \pi (0.6 \text{ cm})^2 = 59.94 \text{ cm}^3$. To have a 3-mL flow rate of water per each gram of Sephadex, the amount of resin is obtained as follows: $59.94 \text{ cm}^3 = 3 \text{ mL /g}$ (gram of resin needed). Based on these calculations, it was concluded that twenty grams of Sephadex is needed to pack the column.

According to the literature³², one liter of water is required for every 100 g gel. Thus, for twenty grams of gel, 200-mL water is needed to wash the column overnight without drying out the gel. After soaking twenty grams of Sephadex in deionized water overnight, the floating fine particulate matter was decanted off, the slurry was degassed and the glass container was backfilled with argon gas. The slurry was poured into the column under the argon atmosphere and the degassed deionized water was run through the column overnight to achieve consistent packing.

4.2.1 Synthesis of Triphenylphosphine Rhodium (I) chloride, $[\text{RhCl}(\text{PPh}_3)_3]$ ¹¹

Triphenyl phosphine, $\text{P}(\text{PPh}_3)_3$, (603 mg, 2.33 mmol)³ was added to a 25-ml two-neck round bottom flask containing 20-ml absolute ethanol that was pre-heated for 20 minutes at 30°C under reflux conditions. This was followed by treating the solution with rhodium trichloride trihydrate, RhCl_3 , (101 mg, 0.390mmol). The mixture was stirred and refluxed for 30 minutes under an argon atmosphere. The hot red reaction mixture was filtered out on a Hirsh funnel and washed with three 1-mL portions of ethyl ether. The yield of brick red crystals was 308 mg, which corresponds to an 85% yield. The purity of the product was determined by ^1H and ^{31}P spectroscopy. The ^1H and ^{31}P NMR spectra of the product are shown in Fig 27 and 28, respectively.

³ $(\text{C}_6\text{H}_5)_3$ is sometimes written as PPh_3 .

Figure 27. ¹H-NMR spectrum of RhCl[P(C₆H₅)₃]₃ in (CDCl₃).

Compound	δ(ppm)	mult.(atom)	Spectrum
RhCl [P (C ₆ H ₅) ₃] ₃	7.5	m(45H)	Figure 27
Cl-P (C ₆ H ₅) ₂ Rh-PPh ₃	48.5	dt (1P)	Figure 28
Cl-P (C ₆ H ₅) ₂ Rh-PPh ₃	31.4	dd (2 P)	Figure 28

Figure 28. ³¹P-NMR spectrum of RhCl[P(C₆H₅)₃]₃ in (CDCl₃).

4.2.2 Synthesis of Di- μ -chloro-bis (η^4 -1,5-cyclooctadiene)-dirhodium (I), $[\text{RhCl}(\eta^4\text{-C}_8\text{H}_{12})]_2$ ²⁸.

To a 100-ml three-neck round bottom flask containing 20-mL of degassed mixture of ethanol-water (5:1), RhCl_3 (200 mg, 7.60 mmol) was added. To the resulting red mixture, 3-ml degassed solution of 1,5-cyclooctadiene⁴ was added. The mixture was heated at reflux and stirred for 21 hours under an argon atmosphere. The product was isolated by vacuum filtration and washed with pentane and methanol: water (1:5). Washing stopped when no silver chloride was observed in the washings upon addition of silver (I) nitrate, indicating all the excess chloride was eliminated from the product. The yellow-green powder product was dried under a vacuum. The yield of crystals was 1.33g, which corresponds to a 57% yield. Purity of the product was determined by ^1H spectroscopy. The spectrum of the product is shown in Figure 29.

⁴ Preparation of Di- μ -chloro-bis(η^4 -1,5-cyclooctadiene)-dirhodium(I), $[\text{RhCl}(\eta^4\text{-C}_8\text{H}_{12})]_2$, was done in the absence of sodium carbonate. (1,5- C_8H_{12}) is called COD or cycloocta-1,5-diene.

Figure 29. ^1H -NMR spectra of $[\text{RhCl}(\text{C}_8\text{H}_{12})_{12}]_2$ in CDCl_3 .

Compound	$\delta(\text{ppm})$	mult.(J, Hz)	Spectrum
$(\text{RhCl}-(\text{C}_8\text{H}_{12}))_2$	4.25	s (29.50)	Figure 29
C_8H_{12}	2.46	s (32.82)	Figure 29
C_8H_{12}	1.79	d (32.43)	Figure 29

4.2.3. Synthesis of sulfonated-rhodium-centered catalysts.

Different methods of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ synthesis were tried because it was necessary to have a pure catalyst since catalytic activity of the pure catalyst was desired. The catalyst that was synthesized by method A was purified by gel filtration to remove any un-reacted TPPTS ligand. However, the purification led to more oxidized form of TPPTS compound. The same problem with oxidation of TPPTS, as method A, was encountered with method B purification. For method C, $\text{Rh}(\text{COD})\text{Cl}_2$ impurity was removed after purification by gel filtration. However, the oxidized TPPTS was formed during purification. This was probably due to detachment of TPPTS from the ligand as the result of exposure to the air. Finally, method D synthesis gave results comparable with that found in the literature. The chemical shifts ^1H , ^{31}P , and ^{13}C spectra of the synthesized catalysts were the same as ones reported in the literature.²⁹

4.2.3.1 Synthesis of Tris(3,3',3''-phosphinetriylbenzenesulfonato) rhodium(I) chloride, $[\text{RhCl}(\text{TPPTS})_3]^{29}$, method A.

To a 25 mL round bottom flask containing a degassed solution of RhCl_3 (40 mg, 0.152 mmol) dissolved in 3 mL H_2O , a degassed solution of 3,3',3'' phosphinidyne (benzene sulfonic acid) trisodium salt, TPPTS, (854 mg, 1.50 mmol) in 1.5 mL deionized water was added. After 3 hours of stirring under an argon atmosphere at room temperature, water was removed. The yield of rust red crystals was 769 mg, which corresponds to a 274% yield. The purity of the products was determined by ^1H and ^{31}P NMR spectroscopy. The oxidation state of Rh^{+3} ion was verified by UV-Vis spectroscopy. The ^1H and ^{31}P spectra of the product are shown in Figures 30, 31, 32.

Figure 30. ^1H -NMR spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ in D_2O .

Compound	$\delta(\text{ppm})$	mult.(atom)	Spectrum
HDO	4.82	s (H)	Figure 30
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_3$	7.5-8.2	m (36H)	Figure 30
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_3$	52.8	dt (1P)	Figure 31
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_2$	34.8	dd (2P)	Figure 31
$\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3$	-3.82	s (1P)	Figure 31

Figure 31. ^{31}P -NMR spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ in D_2O , before gel filtration.

Figure 32. UV-Vis spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ in water, $\lambda_{\text{max}}=436.0\text{nm}$.

4.2.3.2 Gel filtration on $[\text{RhCl}(\text{TPPTS})_3]^{29}$, method A.

The high percentage yield of the $\text{RhCl}(\text{TPPTS})_3$ catalyst and ^1H NMR spectrum indicated that there are impurities that needed to be removed. Thus, gel filtration was used as a purification method. $\text{RhCl}(\text{TPPTS})_3$ (250 mg, 0.136 mmol) was dissolved in 500 μL deionized water. To remove any un-reacted $\text{Rh}(\text{TPPTS})_3\text{Cl}$, the degassed mixture was added to the column under an argon atmosphere. The rust red band was collected and stored under an argon atmosphere for further analysis by NMR. The same procedure of

purification was performed for method B and C synthesis. The purity of the products was determined by ^{31}P spectroscopy. The spectrum of the product is shown in Figure 33.

Figure 33. ^{31}P -NMR spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ in D_2O , after gel filtration.

Compound	$\delta(\text{ppm})$	mult.(atom)	Spectrum
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)$	58.6	d (1P)	Figure 33
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_2$	52.8	dt (1P)	Figure 33
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_3$	35.8	dd (2P)	Figure 33

4.2.3.3 Synthesis of Tris(3,3',3''-phosphinetriylbenzenesulfonato)chlororhodium(I),

$[\text{RhCl}(\text{TPPTS})_3]^{29}$, method B.

A degassed solution of TPPTS (941 mg, 1.65 mmol) in 10 mL deionized water was added to a 50 mL two-neck Schlenk tube containing a degassed solution of triphenyl phosphine rhodium (I) chloride, $\text{RhCl}[\text{P}(\text{C}_6\text{H}_5)_3]_3$, (50 mg, 0.055 mmol) dissolved in 10 mL toluene and 5 mL tetrahydrofuran (THF). The organic layer was decanted from aqueous layer and discarded after overnight stirring under an argon atmosphere. The aqueous layer was extracted with degassed methylene chloride, CH_2Cl_2 , (2x2.5mL). Water was removed in a vacuum. The orange/white crystals were purified on the Sephadex G-15. The purity of the product was determined by ^{31}P NMR spectroscopy. The ^1H NMR spectrum of the dark orange product is shown in Figure 34.

Figure 34. ^1H -NMR spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ in D_2O , before gel filtration.

Compound	$\delta(\text{ppm})$	mult.(atom)	Spectrum
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_3$	7.5-8.2	m (36H)	Figure 34
HDO	4.81	s (H)	Figure 34

4.2.3.4 Gel filtration on $[\text{RhCl}(\text{TPPTS})_3]^{29}$, method B.

The purity of the products after purification was determined by ^{31}P NMR spectroscopy. The spectrum of the product is shown in Figure 35. Since ^{31}P NMR spectrum showed no improvement in reducing the amount of $\text{O}=\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3$ impurity, method C synthesis was performed.

Figure 35. ^{31}P -NMR spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ in D_2O , after gel filtration.

Compound	$\delta(\text{ppm})$	mult.(atom)	Spectrum
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)$	58.6	d (1P)	Figure 35
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_2$	52.8	dt (1P)	Figure 35
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_2$	35.8	dd (2P)	Figure 35

4.2.3.5 Synthesis of Tris(3,3',3''-phosphinetriylbenzenesulfonato)chlororhodium(I),

$[\text{RhCl}(\text{TPPTS})_3]^{29}$, method C.

To a 25 mL round bottom flask containing a degassed solution of $[\text{RhCl}(\text{cod})]_2$ (103 mg, 0.21 mmol) dissolved in 10 mL CH_2Cl_2 , a degassed solution of TPPTS (700 mg, 1.23 mmol) in 10 mL deionized water was added. After 40 minutes of stirring, the organic layer was decanted from the aqueous layer and discarded. The aqueous layer was extracted with degassed CH_2Cl_2 (3x5 mL), water was removed using warm water bath in a vacuum with stirring. The yield of brick red crystals was 711 mg, which corresponds to a 92% yield. Purity of the product was determined by ^1H and ^{31}P NMR spectroscopy. The ^1H and ^{31}P NMR spectra of the product are shown in Figures 36 and 37, respectively.

Figure 36. ^1H -NMR spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ in D_2O , before gel filtration.

Compound	$\delta(\text{ppm})$	mult.(atom)	Spectrum
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_3$	7.5-8.2	m (36H)	Figure 36
$\text{RhCl}_2-(\text{C}_8\text{H}_{12})$	2.45	d (12H)	Figure 36
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_3$	30.21	d (1P)	Figure 37
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_3$	52.8	dt (1P)	Figure 37
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_2$	34.8	dd (2P)	Figure 37

Figure 37. ^{31}P -NMR spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ in D_2O , before gel filtration.

4.2.3.6 Gel filtration on $[\text{RhCl}(\text{TPPTS})_3]^{29}$, method C.

Purity of the products was determined by comparing the chemical shifts in the ^{31}P NMR spectrum with literature²⁹, and Rh^{+3} oxidation state was verified by UV-Vis spectroscopy after comparing with results in the literature. The spectrum of the product is shown in Figures 38, and 39. The 1,5-cyclooctadiene was removed by gel filtration; however, the intensity of the impurity, $\text{O}=\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3$, was intensified after purification probably due to exposure to air.

Figure 38. ^{31}P -NMR spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ in D_2O , after gel filtration.

Compound	$\delta(\text{ppm})$	mult.(atom)	Spectrum
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)$	58.6	d (1P)	Figure 38
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)$	52.8	dt (1P)	Figure 38
$\text{RhCl}-(\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3)_2$	35.8	dd (2P)	Figure 38

Figure 39. UV-Vis Spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ in water , $\lambda_{\text{max}} = 436.0$.

4.2.3.7 Synthesis of Tris(3,3',3''-phosphinetriylbenzenesulfonato)chlororhodium(I),

$[\text{RhCl}(\text{TPPTS})_3]^{29}$ using bisethylene⁵, method D

A degassed solution of TPPTS (858mg, 1.51 mmol) in 10 mL of deionized water was added to a 25 mL round bottom flask containing a degassed solution of μ -dichlorotetraethylene dirhodium (I), $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$, (101 mg, 2.60 mmol) dissolved in 10mL CH_2Cl_2 . After 45 minutes of stirring under an argon atmosphere at room temperature, the organic layer was decanted from the aqueous layer and discarded. The aqueous layer was extracted with degassed CH_2Cl_2 (2x5mL), then water was removed using warm water bath under a vacuum with stirring. The yield of black-red crystals was 821 mg, which corresponds to an 86% yield. Purity of the product was determined by ^1H and ^{31}P spectroscopies, and oxidation state of rhodium was verified by UV-Vis spectroscopy. The ^1H and ^{31}P and UV-vis spectra of the product are shown in Figures 40, 41, 42.

⁵ R. Hembere at Eastman Chemical Company suggested the modification to this synthesis.

Figure 40. ¹H-NMR spectrum of Rh(TPPTS)₃Cl in D₂O.

Compound	δ(ppm)	mult.(J, Hz)	Spectrum
HDO	4.81	s (H)	Figure 40
RhCl-(P(C ₆ H ₄ SO ₃ Na) ₃) ₃	7.5-8.2	m (59.70)	Figure 40
RhCl- (P(C ₆ H ₄ SO ₃ Na) ₃) ₃	52.8	dt (1P)	Figure 41
RhCl-(P(C ₆ H ₄ SO ₃ Na) ₃) ₂	34.8	dd (2P)	Figure 41

Figure 41. ³¹P-NMR spectrum of Rh(TPPTS)₃Cl in D₂O.

Figure 42. UV-Vis spectrum of Rh(TPPTS)₃Cl in water, λ_{max} = 436.0 .

4.2.4 Synthesis of η^5 - pentamethylcyclopentadiene triaquo Rhodium (I) triflate,

In a dry box, silver triflate, AgOTf, (83.0 mg, 0.32 mmol) along with pentamethylcyclopentadiene rhodium (I) chloride, (RhCl₂Cp*)₂, (50.0 mg, 0.08 mmol) and 4-mL anhydrous CH₂Cl₂ were placed in a 15 mL round bottom flask. After three hours of stirring, the resulting dark orange solution was gravity filtered and removed from the box. Deionized water was added (8.7 μ L, 0.48 mmol) to the filtrate on the bench top. The filtrate was kept in a vial overnight during which orange crystals formed. The resulting orange crystals were washed several times with ethyl ether after vacuum

⁶ η^5 - pentamethylcyclopentadiene, η^5 -C₅Me₅, is abbreviated as Cp* and triflate, CF₃SO₃⁻, is abbreviated as OTf.

filtration. The yield of orange crystal was 47.8 mg, which corresponds to a 93% yield.

The purity of the products was determined by ^1H NMR spectroscopy. The spectrum of the product is shown in Figure 43.

Figure 43. ^1H -NMR spectrum of $[\text{RhCp}^* (\text{H}_2\text{O})_3](\text{OTf})_2$ in DMSO.

Compound	$\delta(\text{ppm})$	mult.(J, Hz)	Spectrum
$3\text{H}_2\text{O}$	3.38	s (6H)	Figure 43
C_5Me_5	1.53	s (15H)	Figure 43

4.2.5 Synthesis of η^5 -pentamethylcyclopentadienyl bipyridyl rhodium (I) triflate.

To a 25 mL two-neck round bottom flask ($[\text{RhCp}^*(\text{H}_2\text{O})_3](\text{OTf})_2$ (100 mg, 0.169 mmol) and bipyridine, $\text{C}_{10}\text{N}_2\text{H}_8$ (26.5 mg, 0.169 mmol) along with 2 mL of deionized water were added and the resulting mixture was degassed and the flask backfilled with the argon gas. After stirring for four hours under the argon atmosphere, the mixture was filtered with a canula equipped with the glass fiber to remove any un-reacted bipyridine. The filtrate was dried under vacuum. The yield of yellow-orange crystals was 124 mg, which corresponds to a 55% yield. Purity of the product was determined by ^1H . UV-Vis spectrum was obtained both in water and $\text{H}_2\text{O}:\text{THF}$, 1:1 ratio.

Figure 44. UV-Vis Spectrum of $\text{RhBipyCp}^*(\text{OTf})_2$ in water, $\lambda_{\text{max}} = 350.1\text{ nm}$.

Figure 45. ^1H -NMR spectrum of $[\text{RhCp}^*\text{Bipy}(\text{H}_2\text{O})](\text{OTf})_2$ in D_2O .

Compound	δ (ppm)	mult.(J, Hz)	Spectrum
$C_{10}N_2H_8$	7.85	m (8H)	Figure 45
C_5Me_5	1.65	s (15H)	Figure 45

Figure 46. UV-Vis Spectrum of $RhBipyCp^*(OTf)_2$ in $H_2O:THF(1:1)$, $\lambda_{max} = 350.9nm$.

4.2.6 Synthesis of η^5 -pentamethylcyclopentadienyl bipyridyl methanol rhodium (I) chloride $[(RhCp^*BipyMeOH)Cl_2]$ ³¹

To a 25 mL two-neck round bottom flask, $(RhCl_2Cp^*)_2$ (313 mg, 0.506 mmol), 10 mL of anhydrous CH_3OH and $C_{10}N_2H_8$ (205 mg, 1.31 mmol) were added and stirred for 10 minutes. The yellow-orange solution was gravity filtered to remove dark solid particles. The volume of the light-clear orange filtrate was reduced to 2-mL using a roto-evaporator. To the reduced filtrate, ether was added and light orange solids were collected on a glass-fritted funnel. The light orange crystals were dried in a desiccator.

^1H and ^{13}C NMR as well as UV-Vis spectroscopy determined purity of the product. The ^1H and ^{13}C and UV-Vis spectra of the products are shown in Figures 47, 48, and 49.

Figure 47. ^1H NMR spectrum of $(\text{RhCp}^*\text{BipyMeOH})\text{Cl}_2$ in D_2O .

Compound	$\delta(\text{ppm})$	mult.(J, Hz)	Spectrum
$\text{C}_{10}\text{N}_2\text{H}_8$	7.88	m (8H)	Figure 47
CH_3OH	3.19	s (3H)	Figure 47
C_5Me_5	1.68	s (15H)	Figure 47
$\text{C}_{10}\text{N}_2\text{H}_8$	120.4	m (10C)	Figure 48
CH_3OH	98.1	s (1C)	Figure 48
C_5Me_5	9.6	s (10C)	Figure 48

Figure 48. ^{13}C -NMR spectrum of $(\text{RhCp}^*\text{BipyMeOH})\text{Cl}_2$ in D_2O .

Figure 49. UV-Vis Spectrum of $(\text{RhBipyCp}^*\text{MeOH})\text{Cl}_2$ in water, $\lambda_{\text{max}} = 358.0\text{ nm}$.

4.2.7 Discussion of Spectroscopic techniques.

Two different spectroscopic techniques were used to verify the purity of the synthesized products, and then results were compared with literatures.^{29,3,31}

The ultraviolet-visible (UV-Vis) spectrum of each catalyst in water at room temperature was obtained compared to spectra in the literature to determine whether Rh(I) complexes are present as impurities. All of the UV-vis spectra indicate that only Rh^{+3} complexes are present. As reported by Joo *et al.*, the UV-Vis spectrum²⁹ of $\text{Rh}(\text{TPPMS})_3\text{Cl}$ in 0.1M HCl gave λ_{max} of 356 nm. The λ_{max} for the spectrum³ of $[\text{Cp}^*\text{Rh}(\text{bipy})(\text{H}_2\text{O})](\text{OTf})_2$ in 1:1 $\text{H}_2\text{O}/\text{THF}$ is 354 nm, and $[\text{Rh}(\text{Cp}^*\text{bipyMeOH})]\text{Cl}_2$ in MeOH at pH 10 gave λ_{max} of 347 nm.³¹ The λ_{max} results obtained from the literature^{29,3,31} are all consistent with the λ_{max} obtained for the synthesized rhodium (III) complexes as reported in this thesis. The spectrum of $\text{RhBipyCp}^*(\text{OTf})_2$ in 1:1 $\text{H}_2\text{O}/\text{THF}$ gave λ_{max} of 350.9 nm, which is comparable with the literature result.³ The experimental results showed that Rh(I) is not present in any detectable amount in any of the synthesized samples used in this study.

CHAPTER 5. EXPERIMENTAL ANALYSIS

Isotopic exchange reactions involving $\text{H}_2/\text{D}_2\text{O}$ exchange were performed in order to establish the rate of formation of hydrogen isotopomers mediated by rhodium-centered catalysts. For all five catalysts, the experiment was repeated until values for the rate constant that were used to fit the data were reproducible within a 5% difference. With one exception, all catalysts have shown results that could be modeled by an effective single exchange mechanism. The mono-sulfonated triphenyl phosphine rhodium (I) chloride, $\text{Rh}(\text{TPPMS})_3\text{Cl}$, was the only catalyst for which results required the addition of an effective double exchange step to fit the experimental data. The interpretation of the experimental results is discussed in detail in the following sections.

5.1 Discussion of Rate Constant.

The isotopic exchange reaction was used to screen the catalytic activity of each catalyst. Numerous runs were performed for each catalyst to ensure reproducibility of results; details of each experiment are shown in Table 6. As indicated in Table 5, different amount of each catalyst was used to carry the isotopic exchange. Since the concentration of 2.3 mM rhodium solution was desired to carry the isotopic exchange as shown below, the amount of each catalyst is different depending on the number of rhodium centers of the catalyst (dimer or monomer) and its formula weight.

In some cases, such as $\text{Rh}(\text{TPPTS})_3\text{Cl}$, different amount of sample were used to account for the amount of impurities contained in the sample. The mole ratio of impurities to the pure catalyst, $\text{Rh}(\text{TPPTS})_3\text{Cl}$, has been calculated based on ^1H NMR

data. A sample spectrum is shown below. In order to have a 2.3mM solution of rhodium for each sample, 42mg of sample was used doing the following calculations:

Figure 50. ^1H NMR spectrum of $\text{Rh}(\text{TPPTS})_3\text{Cl}$ synthesized by method D.

Hydrogen atoms/ Peak intensity from Figure 50:

$$87.18 / 36 = 2.24 \text{ for one H of } \text{Rh}(\text{TPPTS})_3\text{Cl}$$

$$12.82 / 12 = 1.07 \text{ for one H of } \text{Rh}(\text{COD})\text{Cl}_2$$

%Signal(ratio):

$$\text{Rh}(\text{TPPTS})_3\text{Cl} / \text{Rh}(\text{COD})\text{Cl}_2 = \% 69/31 (0.44/1)$$

Formula weight(FW):

$$\text{Rh}(\text{COD})\text{Cl}_2 = 814.78 \text{ g/mole}$$

$$\text{Rh}(\text{TPPTS})_3\text{Cl} = 1843.64 \text{ g/ mole}$$

Average (AFW) = (FW / % intensity):

$$\text{Rh(COD)Cl}_2 = 814.78 * 0.31 = 252.58 \text{ g/mol}$$

$$\text{Rh(TPPTS)}_3\text{Cl} = 1843.64 * 0.69 = 1272.11 \text{ g/mol}$$

Total formula weight of the catalyst (TFW):

$$\text{Rh(COD)Cl}_2 + \text{Rh(TPPTS)}_3\text{Cl} = (252.58 + 1272.11) \text{ g/mol} = 1524.69 \text{ g/mol}$$

Weighted AFW (AFW / TFW):

$$\text{Rh(COD)Cl}_2 = 252.58 \text{ g/mol} / 1524.69 \text{ g/mol} = 0.8343$$

$$\text{Rh(TPPTS)}_3\text{Cl} = 1272.11 \text{ g/mol} / 1524.69 \text{ g/mol} = 0.1657$$

Grams needed for a 2.3 mM solution:

$$\text{TFW} / (\text{AFW}/\text{TFW}) = 1524.69 \text{ g/mole} / 0.8343 = 1827.51 \text{ g/mol}$$

$$(2.3 \times 10^{-6} \text{ mole}) * (1827.51 \text{ g /mole}) = 0.0042 \text{ g of Rh(TPPTS)}_3\text{Cl mixture}$$

The same calculations were completed to determine the weighted average formula weight based on the spectra data obtained for the sample recovered from the method C synthesis.

Summary of results are given in Table 4.

Table 4. Summary of calculations to obtain the weight of pure catalyst.

Compound	FW,g/mole	AFW,g/mole	Wt. AFW	Peak,int.	H-tom	%signal
Rh(TPPTS) ₃ Cl	1843.64	1272.11	0.1657	12.82	36	69
Rh(COD)Cl ₂	814.78	252.58	0.8343	87.18	12	31

After filling the kinetic data, as it was explained in chapter 3-section 3.2, for the reaction as mediated by each catalyst, the activation energy for the isotopic exchange

reaction with only Rh(Cp*BipyMeOH)Cl₂ catalyst (Table 6) was obtained. This catalyst gave the lowest value of rate constant and that is why it was decided to obtain its activation energy. The same procedures were used to prepare the sample for the isotopic exchange experiment was used to obtain the rate constant for temperature. Temperature was the only parameter that was controlled and was varied for obtaining the rate constant, for calculating the activation energy. All other conditions were held constant; a summary of the results is shown in Table 5. Recall the time-dependence expressions used to calculate the value of rate constant.

$$d[H_2]/dt = -k_1 [H_2] - k_2 [H_2] \quad (12a)$$

$$d[HD]/dt = +k_1 [H_2] - \frac{1}{2} k_1 [H_2] \quad (12b)$$

$$d[D_2]/dt = +\frac{1}{2} k_1 [HD] + k_1 [H_2] \quad (12c)$$

In Table 5, the value of K₂ is set to zero for all six catalysts except Rh(TPPMS)₃Cl because an adequate fit was obtained using the effective single exchange mechanism.

Table 5. Summary of Isotopic Exchange Results.

Compound Structure	Formula weight(g/mole)	Amount (mg)	Rate Constant , 1/min	
			K ₁	K ₂
Rh(TPPTS) ₃ Cl ₂ method A	1827.51	10.5	0.0158	
Rh(TPPTS) ₃ Cl ₂ method C	1827.51	45	0.0120	
Rh(TPPTS) ₃ Cl, Using bisethylene	1827.51	50	0.0155	
Rh(TPPMS) ₃ Cl	1271.99	31	0.00380	0.00500
RhCp*BipyH ₂ O(2OTf)	728.56	17	0.000255	
(RhCp*Cl ₂) ₂	617.84	14	0.000720	
(RhCp*BipyMeOH)Cl ₂	497.31	11	0.000103	

After obtaining the rate constant for the catalyst at various temperatures, an Arrhenius plot of the natural log of the rate constant versus reciprocal of temperature was constructed for (RhCp*BipyMeOH)Cl₂.

Table 6. Summary of Results for Obtaining Activation Energy.

Compound Structure	Molecular weight(g/mole)	Amount (mg)	Temperature(°C)	Rate Constant(min ⁻¹)
(RhCp*BipyMeOH)Cl ₂	497.30	11	26	0.00010
		12	33	0.000045
		12	40	0.00012
		12	45	0.0004
		12	50	0.0008

Plotting the data obtained from the experiment gave a value for the slope of the line. The slope of the line equals to the activation energy according to the Arrhenius formula:

$$\ln k = -E_a / RT + \text{constant}$$

$$m = -E_a / R$$

Where: m = slope of the line in °k / min

E_a = Activation energy in KJ/mole

R = gas law constant equals to 8.314 J/mole

The calculated activation energy for the reaction is 79.91 kJ/mole. The error bars on the graph indicate that uncertainties of ± 5 percent. Fitting the line to data collected at different temperatures indicated that there is not a linear dependence between the

temperature and the rate constant. This means that Arrhenius relationship mechanism is not applicable for this catalyst. There is complex-multi-step mechanisms are involved.

Figure 51. Determining activation energy for $(\text{RhCp}^*\text{BipyMeOH})\text{Cl}_2$.

As shown in Table 7, there are different values for the rate constant with each catalyst despite keeping all physical conditions like catalyst concentration and stirring rate (900 rpm) constant for all runs.

Table 7. Isotopic Exchange for Each Catalyst.

$\text{Rh}(\text{TPPTS})_3\text{Cl}_2$, method A	Temperature ($^{\circ}\text{C}$)	Rate-Constant ($k_1 = 1/\text{min}$)
10.5 mg	25	0.0152
10.4 mg	26	0.0078
10.5 mg	26	0.0120
10.5 mg	26	0.0158
$\text{Rh}(\text{TPPTS})_3\text{Cl}_2$, method C	Temperature ($^{\circ}\text{C}$)	Rate-Constant ($k_1 = 1/\text{min}$)
45 mg	26	0.0120
44 mg	27	0.0120
$\text{Rh}(\text{TPPTS})_3\text{Cl}_2$, method D	Temperature ($^{\circ}\text{C}$)	Rate-Constant ($k_1 = 1/\text{min}$)
49 mg	26	0.0049
49 mg	26	0.0110
50 mg	26	0.0155
50 mg	26	0.0155
$^7\text{Rh}(\text{TPPMS})_3\text{Cl}$	Temperature ($^{\circ}\text{C}$)	Rate-Constant ($k_1 = 1/\text{min}$)
30 mg	25	0.00750
31 mg	26	0.0099

⁷ K_2 is needed to fit the results into the effective double exchange mechanism.

31 mg	26	0.0120
31 mg	25	0.0096
31 mg	25	0.0054
31 mg	26	0.0095
(RhCp*BipyMeOH)OTf ₂	Temperature (°C)	Rate-Constant (k ₁ = 1/ min)
17 mg	26	0.00026
17 mg	26	0.00025
(RhCp*Cl ₂) ₂	Temperature (°C)	Rate-Constant (k ₁ = 1/ min)
14 mg	22	0.00014
14 mg	26	0.00072
14 mg	26	0.00072
(RhCp*BipyMeOH)Cl ₂	Temperature (°C)	Rate-Constant (k ₁ = 1/ min)
12 mg	26	0.00010
12 mg	27	0.00011
11 mg	26	0.00010

The following data was used to determine the Arrhenius Activation Energy for the reaction using RhCp*BipyMeOHCl₂ catalyst:

13 mg	32	0.00030
12 mg	33	0.00010
12 mg	33	0.000044
12 mg	33	0.000046
12 mg	40	0.00012
13 mg	40	0.00012
12 mg	45	0.00040
12 mg	45	0.00040
12 mg	50	0.00080
12 mg	50	0.00080

The difference can be due to a couple of parameters: A metal center with coordination number of four can be either tetrahedral or square planar (Section 3.1) the geometry affects the electronic structure of the metal center and crystal field splittings. Since all of the synthesized catalysts have square planar geometry, the splitting pattern for d-orbitals (displayed in Figure 52¹³) is as follows:

Figure 52. Splitting pattern for Rh^{+3} square planar geometry (Huheey *et al.*, p. 410).

The coordination number for rhodium catalyst is four. This indicates that the rhodium ion in a +3 oxidation state has six electrons in its d-orbitals. The electrons can occupy all the available d orbitals and form a high spin complex. This will happen if weak field ligands surround the metal center, causing small splittings of d orbitals, leading to a lower energy gap between orbitals. All catalysts used in this study have high-spin configurations.

The cleavage of the hydrogen bond depends on the amount of electron density being donated from the σ bond of hydrogen to the d_z^2 orbital of the metal center and back-donation of electron density by the metal to anti-bonding orbitals of hydrogen ligand. If the donation of electron density happens fast, then the cleavage of the hydrogen molecule occurs fast as well and in turn the ligand exchange reaction proceeds at a faster rate. The degree of electron density exchange varies between catalysts and is affected by the nature of the ligands surrounding the rhodium center. This affects the rate constant for each reaction.

There are other reasons, such as size of surrounding ligands, which can affect the

rate constant of the reaction. The metal-ligand distance is larger for bulky ligands. A hydrogen molecule may have difficulty approaching the metal center due to steric hindrance from large ligands. In this case, the metal center is more involved in bonding with other ligands and a weaker interaction occurs between the metal and hydrogen ligand. This means the d-orbitals of the metal center are being used by other ligands and are less available for accepting electrons from hydrogen. When less electron density is donated by hydrogen to d-orbitals on the metal atom, the σ bond of hydrogen is not weakened enough and is not susceptible to cleavage as much. Therefore, the rate of isotopic exchange and the rate constant are decreased.

Experimental conditions are another reason for having different values in the rate constant. One condition is the hydrogen concentration in the reaction vial. Although the initial concentration of hydrogen is the same for all catalysts, a leak in the reaction vial can change hydrogen concentration. To keep the rate of the reaction constant, the rate constant has to be changed proportionally to the hydrogen concentration, which this has led to different values for the rate constant. Chemical degradation of the catalyst over time also leads to a smaller rate constant value.

The solvent can cause degradation of the catalyst. For instance, the concentration of O_2 in the solvent increases over time due to exposure to the air and this leads to the oxidation of the catalyst. In addition, degradation of the catalyst may be caused by multiple collections of gas mixture from the headspace since multiple collections creates a leak in the vial, which allows the interaction of air. Finally, the decreased value in the rate constant may result from incomplete degassing of D_2O before addition of the catalyst

and after the catalyst has been added to the vial.

5.2. Discussion of effective mechanisms.

The isotopic exchange between hydrogen and rhodium-phosphine complexes was studied to screen the catalytic activity of the synthesized catalysts and to learn about the underlying mechanism. The study done by Kovacs *et al.*²¹ has shown that the rhodium complexes are effective in catalysis of $\text{H}_2/\text{D}_2\text{O}$ reactions at 20°C to 27°C . The catalytic cycle that they proposed is summarized in Figure 53.

Figure 53. Suggested mechanism by Kovacs *et al.*²¹

According to Kovacs and co-workers, the deuterium (D^+) from the solvent gets attached to the hydrogen of the H-Rh-H complex. After protonation of the rhodium-hydrogen hydride complex, HDO (H^+) gets release. The cycle continues and eventually HD is produced after several exchanges between the hydride and the solvent. The relative intensity of HDO peak in the $^1\text{H-NMR}$ is an indication of formation of HD .

The $^1\text{HNMR}$ data of Kovacs *et al.* do and allow for a detailed determination of the exchange. By focusing on the formation of HDO , the data only allow for a determination

of the acid-base portion of the catalytic cycle. The focus of this research was on the formation of HD and D₂ in the gas phase. These data allow some insight into the H₂-Rh bond formation and breaking rate, as it is shown in Eqs. 15a and 15b.

If the H₂-Rh ligand exchange, labeled as α - β - γ in Fig. 20, is rapid compared to the acid-base steps, then the overall mechanism can be modeled as:

The effective mechanism for the above model is summarized in Figure 80.

Figure 54. The effective proposed mechanism for isotopic exchange.

With one exception, the experimental data of all catalysts fit the effective single exchange mechanism, shown in Table 5.1. One example is shown in Figure 55, all other catalysts product data with a similar pattern has been shown in chapter 4.

Figure 55. The effective single exchange mechanism Rh(TPPTS)₃Cl.

The only catalyst that did not follow the effective single exchange mechanism was Rh(TPPTM)₃Cl. This indicates that there must be another route for the isotopic exchange mechanism. If the H₂-Rh ligand exchange, α - β - γ , is slow compared to the acid-base steps, there will be the possibility of both H-atoms being exchanged before the ligand is released. The step 17c below is introduced to allow for a double exchange of H atoms. The overall mechanism is modeled as, Eqs. 17a, 17b, 17c:

For the Rh(TPPMS)₃Cl catalyst, more D₂ than HD is obtained early in the reaction. This implies that individual H-atom attach more strongly to the metal, and they will not fall off of the metal as rapidly as with other catalysts. This makes the acid-base steps faster than the ligand exchange steps. An example of experimental data fit to the mechanism with a double exchange step included shown in Figure 56.

Figure 56. The effective double exchange mechanism $\text{Rh}(\text{TPPMS})_3\text{Cl}$ catalyst.

5.3 Discussion of Electronic structure of catalysts.

The values reported in Table 5.1 for the rate constant for each catalyst are the average of two reproducible results, which were obtained at 26°C . According to the results, the $\text{Rh}(\text{TPPTS})_3\text{Cl}$ catalyst has the highest value for the rate constant. This is probably due to the electronic structure of the catalyst. To explain the electronic impact on the isotopic exchange, only the phosphine ligand is shown, not the structure of the whole catalyst.

Figure 57. The charges on phosphine ligand caused by sulfate groups.

Three electron donating sulfonate groups on the benzene rings make the benzene ring more electron rich, which in turn places more partial negative charge on phosphorous atom, Figure 57. In this case, phosphorous donates more electron density to the d_z^2 orbital of rhodium. As it was explained before, more electron density on the central atom makes the ligand exchange faster due to a weaker interaction between H_2 ligand and the rhodium center. Rapid H-H cleavage leads to faster acid-base chemistry.

In case of the $Rh(TPPMS)_3Cl$ catalyst, less electron density from the ligand is donated to rhodium. The metal center with available d-orbital gets more involved in interaction with hydrogen molecule. This means that the individual hydrogen atoms stay longer on the metal center, and therefore the system is more susceptible to the double exchange mechanism.

The same arguments can be applied for other catalysts. The rate of isotopic exchange varies depending on the amount of electron density on the metal orbitals. The electronic structure of the metal center, which is determined by the surrounding ligands, determines the rate of isotopic exchange. The extent of electron density donation by the surrounding ligands has profound effects on HD exchange. If many electron-donating groups are around the metal center, then the metal center gets less involved in binding interactions with hydrogen molecule. This has been seen with $RhCp^*BipyMeOH(2Cl)$ catalyst. All ligands attached by oxygen and nitrogen are donating electron density to the d-orbitals of rhodium. The methyl groups on 1,5-cyclopentadiene make the ligand more electron rich, which leads to even greater electron density in the d-orbitals of rhodium. This is the reason for having such a low rate constant for the catalyst.

Figure 58. Structures of RhCp*BipyMeOH(2OTf) and RhCp*BipyMeOH(2Cl).

The RhCp*BipyMeOH(2OTf) has a smaller value of the rate constant mostly due to steric effects. The catalyst has octahedral symmetry, so the sites for H₂ attachment are occupied due to large OTf groups and other surrounding ligands. The other catalysts with the square planar geometry do not have this problem since there are available sites for the hydrogen attachment.

CHAPTER 6. SUMMARY OF RESEARCH AND PROPOSED FUTURE STUDIES

Different water-soluble catalysts were synthesized to screen their catalytic activity via isotopic exchange of hydrogen. Learning about the ability of the catalyst in conversion of molecular hydrogen to its isotopomers is very important because if the catalyst does not have the ability to mediate an isotopic exchange reaction, then there is no point in pursuing the given catalyst as a candidate for substrate reduction reactions. The study of the isotopic exchange is important since it provides information about the mechanism of the reaction; other studies were done to learn about this mechanism. The study done by Kovacs *et al.*, followed the isotopic reaction by ^1H NMR spectroscopy. The rate of acid-base exchange of the mechanism was the only step measured by Kovacs and co-workers.²¹ They were not able to learn anything about the rate of the ligand exchange step since the only indication for the occurrence of the isotopic exchange was the relative intensity of HDO.

With gas chromatography, it is possible to measure the relative amount of each isotopomer as a function of time. The relative concentration of each isotopomer is indicative of its rate of formation. The results can be modeled either by the effective single or double exchange mechanism. With one exception, the results for catalysts were modeled by the effective single exchange mechanism. The $\text{Rh}(\text{TPPMS})_3\text{Cl}$ was the only catalyst shown to require the double exchange step within the effective mechanism.

At this point of the time, it is known that all five catalysts have the ability to mediate hydrogen isotopic exchange. To learn about steps that are involved from the

time of formation of metal hydride to the time of reduction of a given substrate, other time dependent spectroscopy experiments, such as NMR or IR need to be done. These studies could lead to the regio-selective reduction of a substrate. Discovering a catalyst that is compatible with the enzymatic reduction in the biological system is invaluable towards solving chemical problems. Such information could lead to whole new spectra of manufacturing pharmaceutical compounds with reasonable cost and no or little waste to the environment.

The difference in isotopic activity and reaction mechanisms of catalysts is related to the electronic structure of each catalyst. To fully explore the underlying reasons for differences in the activity of each catalyst, especially $\text{Rh}(\text{TPPMS})_3\text{Cl}$, it may be useful to do computational investigations. With the help of computational methods, it is possible to study the electronic structure of each catalyst, which is believed to be the main factor affecting its catalytic activity. This is another experimental area of research that needs to be further explored.

The long-term goal of this research is to learn about enzymatic catalysis in an effort to mimic the selectivity characteristics of hydrogenase enzymes for developing the simplest and the most economical methods for the regeneration of the nicotinamide cofactor (NADH). Water-soluble transition metal complexes were synthesized to screen them as potential candidates, which may catalyze the enzymatic reactions. Further studies might test the use of hydrogen gas as the reducing agent for the reduction of the oxidized cofactor, NAD^+ , to the reduced form of the cofactor, NADH. As it was mentioned before, before any further studies, the electronic structure of each catalyst

needs to fully be understood in order to have productive research studies.

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APPENDIX 1. CONSTRUCTION OF THEORATICAL CURVES FOR PROPOSED MECHANISMS

The sample calculations that were done to construct a theoretical curve, Table A, for the effective double exchange mechanism is shown in Figure A, recall:

Table A. Values used to construct the double exchange mechanism.

$k_1 =$	0.1			
$\frac{1}{2}k_1 =$	0.05			
$[\text{H}]_0 =$	1			
$[\text{HD}] =$	0			
$[\text{D}_2] =$	0			
$k_2 =$	0.2			
	$[\text{H}_2]$	$[\text{HD}]$	$[\text{D}_2]$	total
0	1.000	0.00	0.000	1.000
1	0.700	0.100	0.200	1.000
2	0.490	0.165	0.345	1.000
3	0.343	0.206	0.451	1.000
4	0.240	0.230	0.530	1.000
5	0.168	0.242	0.590	1.000
6	0.118	0.247	0.635	1.000
7	0.082	0.246	0.671	1.000
8	0.058	0.242	0.700	1.000
9	0.040	0.236	0.724	1.000

Figure A. The proposed effective double exchange mechanism.

Table A'. The time-dependence formulas used for the double exchange mechanism.

0	=B\$3	=B\$4	=B\$5	=SUM(B9:D9)
1	=B9-B\$1*B9-B\$6*B9	=C9+B\$1*B9-B\$2*C9	=D9+B\$2*C9+B\$6*B9	=SUM(B10:D10)
2	=B10-B\$1*B10-B\$6*B10	=C10+B\$1*B10-B\$2*C10	=D10+B\$2*C10+B\$6*B10	=SUM(B11:D11)
3	=B11-B\$1*B11-B\$6*B11	=C11+B\$1*B11-B\$2*C11	=D11+B\$2*C11+B\$6*B11	=SUM(B12:D12)
4	=B12-B\$1*B12-B\$6*B12	=C12+B\$1*B12-B\$2*C12	=D12+B\$2*C12+B\$6*B12	=SUM(B13:D13)
5	=B13-B\$1*B13-B\$6*B13	=C13+B\$1*B13-B\$2*C13	=D13+B\$2*C13+B\$6*B13	=SUM(B14:D14)
6	=B14-B\$1*B14-B\$6*B14	=C14+B\$1*B14-B\$2*C14	=D14+B\$2*C14+B\$6*B14	=SUM(B15:D15)
7	=B15-B\$1*B15-B\$6*B15	=C15+B\$1*B15-B\$2*C15	=D15+B\$2*C15+B\$6*B15	=SUM(B16:D16)
8	=B16-B\$1*B16-B\$6*B16	=C16+B\$1*B16-B\$2*C16	=D16+B\$2*C16+B\$6*B16	=SUM(B17:D17)
9	=B17-B\$1*B17-B\$6*B17	=C17+B\$1*B17-B\$2*C17	=D17+B\$2*C17+B\$6*B17	=SUM(B18:D18)

For the single exchange mechanism (Figure B), the ligand exchange reaction is faster. Recall time dependence expressions for the single exchange mechanism:

Table B shows the concentration values of each isotopomer. Table B' shows the formulas that were used to write the spreadsheet.

Table B. Values of each isotopomer as a function of time.

$k_1 =$	0.1			
$\frac{1}{2} k_1 =$	0.05			
$[H]_0 =$	1			
$[HD] =$	0			
$[D_2] =$	0			
	$[H_2]$	$[HD]$	$[D_2]$	tot
0	1.000	0.00	0.000	1.000
1	0.900	0.100	0.000	1.000
2	0.810	0.185	0.005	1.000
3	0.729	0.257	0.014	1.000
4	0.656	0.317	0.027	1.000
5	0.590	0.367	0.043	1.000
6	0.531	0.407	0.061	1.000
7	0.478	0.440	0.082	1.000
8	0.430	0.466	0.104	1.000
9	0.387	0.486	0.127	1.000

Figure B. The effective proposed single exchange mechanism.

The effective single exchange was constructed after writing the spreadsheet as shown in Table B'.

Table B'. Effective proposed single exchange mechanism formulas.

cell	[H ₂]	[HD]	[D ₂]	tot
0	=\$B\$3	=\$B\$4	=\$B\$5	=SUM(B9:D9)
1	=B9-\$B\$1*B9	=C9+\$B\$1*B9-\$B\$2*C9	=D9+\$B\$2*C9	=SUM(B10:D10)
2	=B10-\$B\$1*B10	=C10+\$B\$1*B10-\$B\$2*C10	=D10+\$B\$2*C10	=SUM(B11:D11)
3	=B11-\$B\$1*B11	=C11+\$B\$1*B11-\$B\$2*C11	=D11+\$B\$2*C11	=SUM(B12:D12)
4	=B12-\$B\$1*B12	=C12+\$B\$1*B12-\$B\$2*C12	=D12+\$B\$2*C12	=SUM(B13:D13)
5	=B13-\$B\$1*B13	=C13+\$B\$1*B13-\$B\$2*C13	=D13+\$B\$2*C13	=SUM(B14:D14)
6	=B14-\$B\$1*B14	=C14+\$B\$1*B14-\$B\$2*C14	=D14+\$B\$2*C14	=SUM(B15:D15)
7	=B15-\$B\$1*B15	=C15+\$B\$1*B15-\$B\$2*C15	=D15+\$B\$2*C15	=SUM(B16:D16)
8	=B16-\$B\$1*B16	=C16+\$B\$1*B16-\$B\$2*C16	=D16+\$B\$2*C16	=SUM(B17:D17)
9	=B17-\$B\$1*B17	=C17+\$B\$1*B17-\$B\$2*C17	=D17+\$B\$2*C17	=SUM(B18:D18)