

Synthesis and Characterization of Unsymmetrical Tetradentate Schiff Base Complexes of the  
Vanadyl Ion ( $\text{VO}^{2+}$ )

A Summer Research Project

By

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The purpose of chemistry is to give us control over the world around us. A chemist has the ability to do this by shaping the elements the world has given us to form something new. Changing the shape of a molecule may in turn change its function. This pushes chemists to discover and synthesize novel compounds and give them more control over their world.

The Schiff base ligand is popular amongst chemists because of their versatility as well as their biological relevance<sup>1</sup>. Due to their structure of adjacent nitrogen carbon double bonds acting as electron donors, Schiff base ligands possess the ability to easily bind with many transition metals in various forms<sup>1-3</sup>. This can be seen in Figure 1 below as the metal acts as an electron receptor.

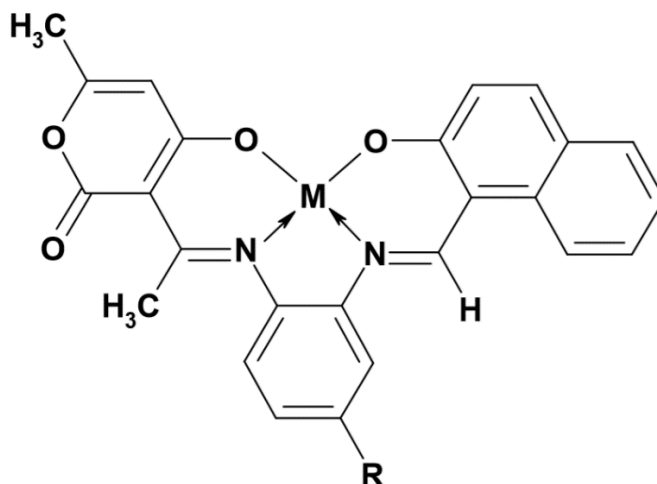


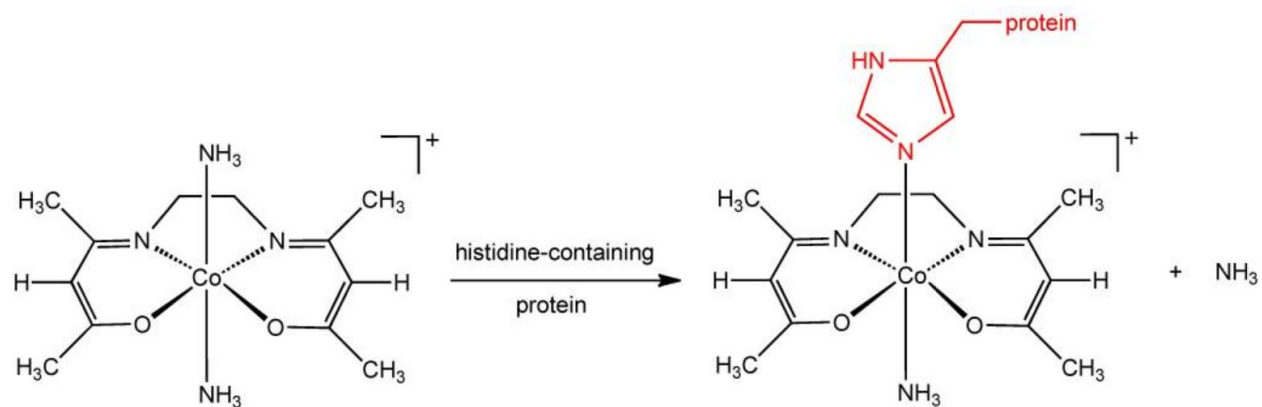
Figure 1: Metal ion (M) is bonded by four atoms to two unsymmetrical Schiff base ligand. M will be seen as Co<sup>3+</sup> and VO<sup>2+</sup>. Reproduced from Chondhekar et al.<sup>3</sup>

With each different structure, which may be changed by replacing a metal or removing a functional group, there is potential for a change in the molecule's property. There lies great importance in the synthetic processes of Schiff base chemistry as the compounds created with the most desirable properties, highest stability, and least toxicity will likely be utilized in the future as medicine for fighting off bacteria with increased immunity, or a catalyst crucial to increasing an industry's efficiency, or even as a substitute for insulin in some diabetics.

Schiff bases are currently being studied extensively around the world. From this literature search, it has been found that it is rather difficult to synthesize unsymmetric Schiff base ligands; however, the unsymmetric structure typically has stronger properties and better models the irregular binding patterns of peptide bonds in the active sites of some<sup>1,3</sup>. In many cases, the more complicated the structure of a Schiff base complex, the stronger its properties. Due to this information obtained through preliminary literature searches, the goal of this research is to find an efficient way to synthesize novel unsymmetric tetradentate Schiff base transition metal complexes. If successful, this research will aid the scientific community by presenting a new Schiff base complex, with a detailed synthetic approach that can be experimented on using methods unavailable at Hampden-Sydney. The process of synthesizing a new compound is contingent upon the investigation of the possible means of synthesis, ensuring the validity of the product through spectroscopy, and confirming its application.

The property a Schiff Base metal complex exhibits is mostly determined by the bound metal<sup>2-4</sup>. Without a bound metal, the properties of Schiff bases are typically insignificant. The interest in these ligands come from their ability to bind to nearly any transition metal. This property is attributed to the N<sub>2</sub>O<sub>2</sub> binding sites acting as Lewis bases for any metal acting as a Lewis acid. The structures that are being investigated often display biological properties due to similarities to metalloenzymes in the body<sup>1,4</sup>. Therefore, changing the metal bound to a Schiff base ligand will change its property entirely. For example, the Co<sup>3+</sup> ion, which is unstable in water, can be stabilized in an aqueous solution of an N, O donor ligand, most promising of those being the Schiff base ligand. When this Schiff base Co<sup>3+</sup> complex has been tested against viruses like Herpes Simplex Virus Type 1 (HSV-1) it's seen to have antiviral properties as the ligand binds strongly to the histidine molecule which is necessary for the virus's maturation<sup>4</sup>. This Schiff base metal complex

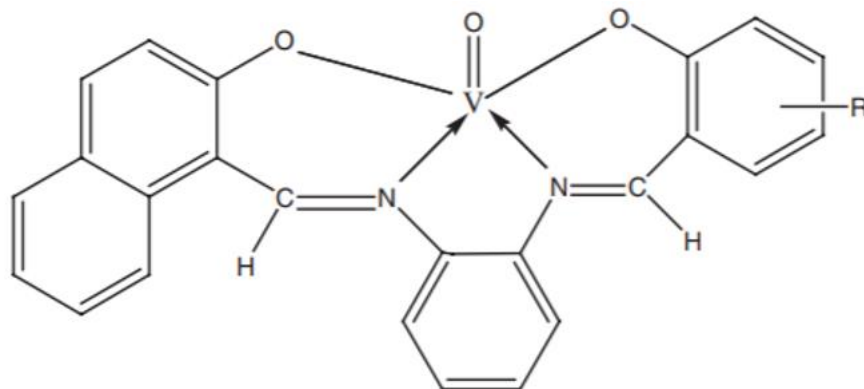
has been so successful in prior testing that researchers are investigating potential uses for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1)<sup>4</sup>.



**Figure 2:** The  $\text{Co}^{3+}$  Schiff base metal complex exhibiting antiviral activity by binding to histidine. Reproduced from Chang et al.<sup>4</sup>

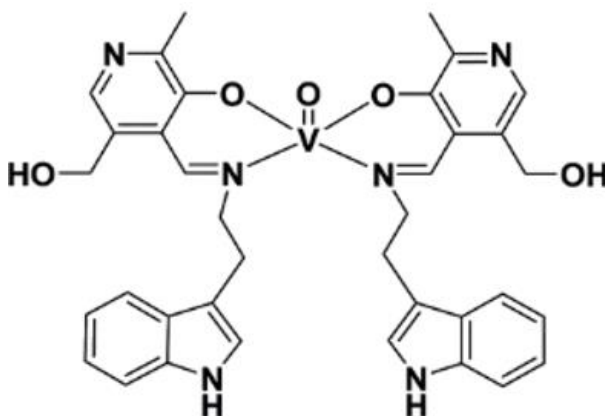
Cobalt is only one of the many metals that can be bound with Schiff base ligands.

Another metal that has great potential when bound to Schiff base ligands is vanadium. Studies have shown that vanadium, although toxic in isolation, can be used to mimic the properties of insulin<sup>1,5-6</sup>. If this metal can be stabilized to have a lower toxicity level then it could be integral in fighting insulin resistance in patients with Type 2 Diabetes. It is believed that this property is due to vanadium being a trace metal in many enzymes in the body, specifically in the vanadyl state ( $\text{VO}^{2+}$ )<sup>5</sup>. Coordination bonds using Lewis bases have been found to increase the stability of the Vanadyl ion, making the Schiff base an excellent electron donor for the ion<sup>5</sup>. When testing the insulin-mimetic effects of unsymmetric Schiff base vanadyl complexes on mice muscle cells it was found that cell glucose utilization was significantly stimulated with negligible toxicity<sup>1</sup>. The unsymmetric ligand in this case too is vital to improving the properties presented as the compound models the irregular binding found in metalloenzymes.



**Figure 3:** Vanadyl Schiff base complex used in testing for insulin mimicry. R may be interpreted as Cl, NO<sub>2</sub>, OCH<sub>2</sub>CH<sub>3</sub>, or H. Reproduced from Nejo et al.<sup>1</sup>

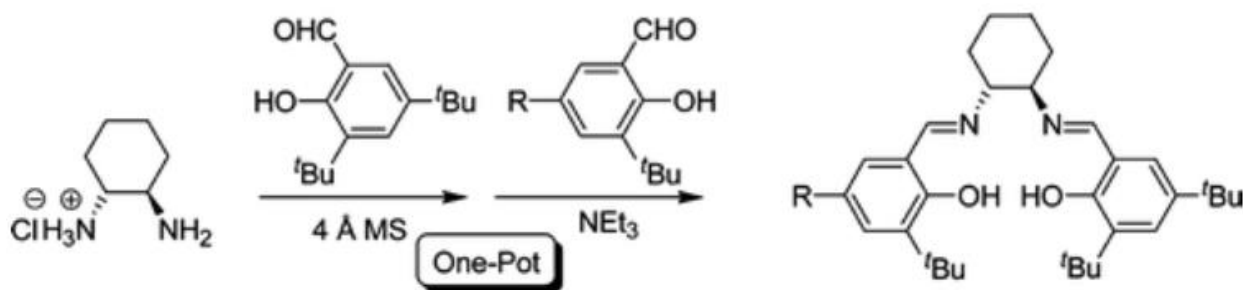
The metal present is not the only way that Schiff base ligands can positively impact medicine. Chemists have the ability to control the structure of the side chains present on the synthesized ligands as well. These can be as complex or as basic as one may desire. It was found that inflammation is another cause of continued insulin resistance in diabetic patients. Due to this finding, researchers paired vanadyl Schiff base complexes with tryptamine side chains. The tryptamine having anti-inflammatory properties led to further enhance the compound, increasing glucose uptake<sup>6</sup>. The active side chains are shown in Figure 4 below.



**Figure 4:** Bis(pyridoxylidenetryptamine) Vanadium (IV) Complex has tryptamine side chains attached to the Schiff base ligand to promote anti-inflammatory activity. Reproduced from Song et al.<sup>6</sup>

The capability of enhancing a Schiff base ligand does not stop at adding active side chains. It is also possible to implement chirality, which enhances the catalytic properties of the ligand<sup>7</sup>. The Vanadyl and Cobalt Schiff base complexes has already been found to have catalytic activity in the oxidation of benzoin and hydrogen peroxide<sup>8-9</sup>. Both processes show great potential in the future of industrial and pharmaceutical fields. These processes have been extensively studied in the production of fine chemicals<sup>8</sup>. Utilizing vanadyl and cobalt Schiff base complexes as catalysts may lead to limiting chemical waste in the industrial field. The Schiff base ligand is versatile and continued study on its formation and synthesis will lead us to efficiently grow in the fields of both medicine and industry.

Unsymmetric Schiff base ligands are condensation products of two differing aromatic aldehydes reacting with an aromatic diamine in hot ethanol using a 1:1:1 molar ratio. The first method of synthesis explored was the Holbach or “One Pot” method<sup>7</sup>. This method involved reacting one aromatic diamine with two differing aromatic aldehydes at the same time in one pot using triethylamine as a solvent<sup>7</sup>. The solution would be an unsymmetric Schiff base very similar to the famous “Jacobsen’s catalyst” which was used in the creation of the Taxol cancer drug. This method results in “bridged” or chiral geometry allowing for more flexibility of the molecule in turn granting the Schiff base the ability to be used in catalytic processes more efficiently<sup>7</sup>.



**Figure 5:** One pot synthesis in which One aromatic diamine and two differing aldehydes react to form an unsymmetric tetradentate Schiff base ligand. Reproduced from Holbach et al.<sup>7</sup>

The downside to this synthetic approach however is that multiple symmetrical Schiff base ligands are guaranteed to be formed. This is because the “condensation of the two amino groups often proceed with comparable rates” causing the average yield to be 60-85% desired unsymmetric Schiff base ligand and 15-40% undesired symmetric Schiff base ligand<sup>7</sup>. Due to this lack of consistency, continued research focused on other methods of synthesis.

Another synthetic approach explored was the Nejo, “dropwise,” or “stepwise” method. This method mostly differs in the time it takes for reactants to mix as only one drop of each solution is added over time. Both aldehydes and diamine were prepared in absolute ethanol and chilled. A cold solution of one aldehyde is stirred while over a 2-minute period the other reactants are added dropwise to the solution. After stirring the mixture at room temperature for 4 days, it was heated to 70°C. The product was filtered then purified in hot ethanol and dried in a desiccator<sup>1</sup>.

Another similar “dropwise” method is the Al-Salami approach. The synthesis of the Schiff base ligand in this scenario differed in the time it took for the reaction to go to completion. As opposed to stirring for 4 days at room temperature, the solution of aldehydes and diamines were refluxed. When a solution is refluxed the reactants are heated so a product will be made faster. The solution being in a liquid state evaporates transferring to a gas state and is condensed with the cooling jacket regressing the solution back to a liquid state. After enough of the product is formed the product can be seen and is cooled, filtered, then recrystallized. This process has a yield of about 88% and is the fastest as well<sup>8</sup>. Being the most reliable and time efficient synthetic approach this would be the suggested method for the synthesis of unsymmetric Schiff base ligands.

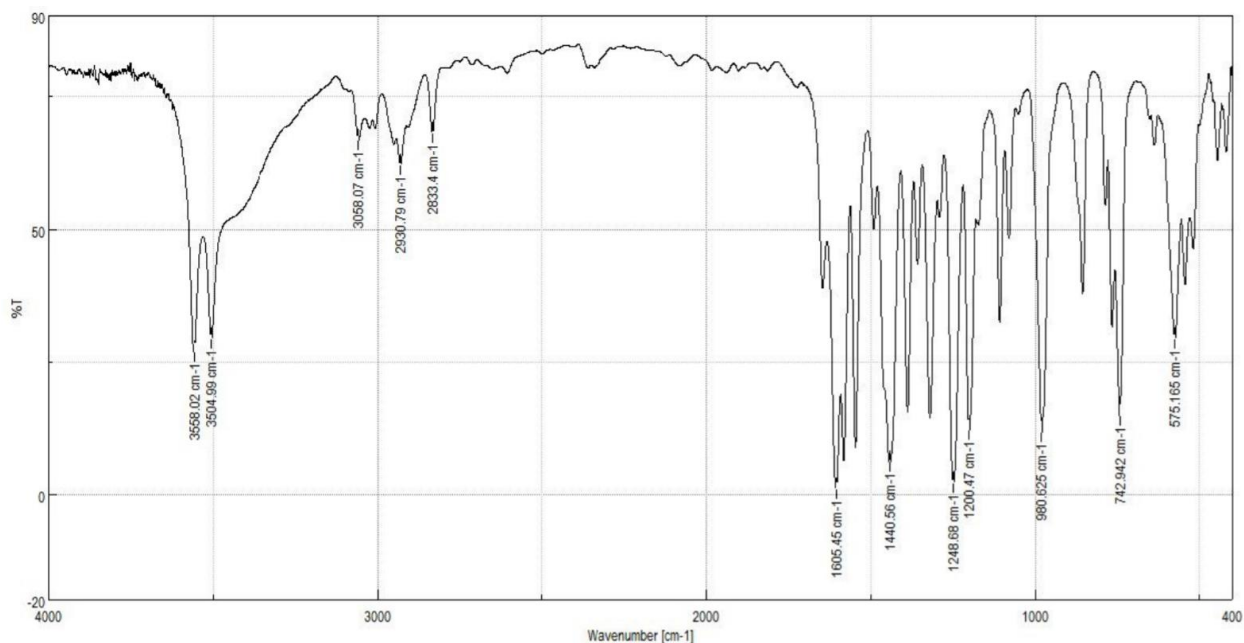
Following the synthesis of the Schiff base ligand, the next step would be to bind the metal ion to the ligand. This process is very similar to the synthesis of the Schiff base. The aqueous metal salt and Schiff base ligand are first dissolved (solvent varies dependent on metal salt and ligand).

Then the solution of the metal salt is added drop wise to the solution of the Schiff base ligand. The solution is then refluxed and cooled when a precipitate is formed. The product is filtered and washed resulting in the unsymmetric Schiff base ligand.

When synthesizing any novel compound, it is necessary to perform tests in order to validate one's findings. These tests include many forms of spectroscopy which analyze radio, infrared, and even ultraviolet waves to detect the presence, or in some cases, the absence of atoms and functional groups in a compound. This summer, extensive hours have been used to achieve mastery of several of the most common spectroscopic methods used to identify organic compounds. By successfully identifying over 100 unknown compounds and analyzing over 400 different spectra, determining the structure of a Schiff base ligand synthesized in a lab will be fairly simple.

The most practical test to conduct immediately following synthesis is infrared (IR) spectroscopy. IR spectroscopy is used to determine the presence and absence of functional groups, such as aldehydes or even Schiff bases, found in analyzed compounds. This is done by the instrument sending infrared radiation at a sample and measuring exactly how much is absorbed. Different bonds have different strengths, meaning that a carbon-hydrogen bond will be relatively weak in comparison to an oxygen-hydrogen bond, so it will absorb more infrared waves. Over time, chemists have determined the exact absorption for every common bond. This information is now readily available for anyone to view. Using known absorption values, one can determine to presence or absence of every bond in a compound. After synthesizing a Schiff base metal complex, this data would be necessary for verifying that a Schiff base was present in the ligand and to determine if the metal ion is bound to the target atoms. Upon completion of the IR spectroscopy test of a supposed Schiff base, it would become apparent that the Schiff base functional group would appear on the spectrum at around 1600 wavenumbers, verifying the validity of the synthesis.





**Figure 6:** IR spectrum of a Vanadyl Complex with peaks at 1605 wavenumbers and 980 wavenumbers confirming the presence of a Vanadium-Oxygen double bond and a Schiff base respectively. Reproduced from Al-Salami et al.<sup>8</sup>

Although the presence of each functional group is important, chemists have other spectroscopic methods in which they may find the location of each atom bound to carbon and hydrogen. These are known as Carbon-13 Nuclear Magnetic Resonance (C-13 NMR) and Proton Nuclear Magnetic Resonance (H-1 NMR) respectively. This instrument works by taking advantage of the magnetic moment present in some atoms. Only 1% of Carbon atoms have a magnetic moment because they have an odd number of nucleons. Having 6 protons and 7 neutrons means that not all of the nucleons are capable of pairing their spins against each other. This will cause the atom to have a “nuclear spin” or magnetic moment. Because of this nuclear magnetic moment, the atoms will shift in position in response to a strong external magnetic field. The NMR instrument then sends out a strong magnetic field to shift the carbon atoms. When the magnet is turned off, the carbon return to their original positions; this measurable value is called a chemical shift. This chemical shift can be measured by sending radio waves and measuring how much is absorbed. The

amount absorbed is how much energy the carbon atom needed to change its nuclear magnetic moment back to normal. This complicated process has also been tested for years and all chemical shift values are common knowledge for most chemists. This form of spectroscopy allows one to determine exactly what atom is bound to carbon or hydrogen atom. Since carbons and hydrogens are so common in organic chemistry using this information can allow chemists to easily determine the structure of entire compounds. Without these spectroscopic techniques, chemists would be forced to use very rudimentary tests to determine the validity of their synthesized compounds and complicated structures like unsymmetric Schiff base ligands would be nearly impossible to reproduce with efficiency.

The ability to efficiently reproduce a complicated compound is necessary for the continued development of chemistry, industry, and medicine. The purpose of this research into unsymmetrical Schiff base ligands was to determine the best method of synthesis. It was concluded that by using the Al-Salami method of synthesis, otherwise known as the drop wise method with reflux, the production of this metal complex will be facilitated and efficient. By determining the best method of synthesis through this project, further investigation of the applications of Schiff base ligands will become very accessible and highly encouraged. Many patients, consumers, and organizations alike will benefit from the continued study of Schiff base coordination chemistry.

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