THE CHEMISTRY OF FLUORINATED HIGH SPIN IRON COMPLEXES

By

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Abstract

Among the most essential processes for sustaining the world's population is nitrogen fixation, the conversion of atmospheric nitrogen (N_2) into ammonia (NH_3), the major component of fertilizer. The industrial Haber-Bosch process for N_2 fixation requires extreme temperatures and pressures, and consequentially consumes much of the world's energy. In contrast, bacteria containing the nitrogenase enzyme fix N_2 under ambient conditions despite the robust N_2 triple bond. A popular approach towards studying the complex mechanism of nitrogenase is to synthesize model complexes of its active site, the iron-molybdenum co-factor (FeMoco). Most model complexes to date are low-spin and thus poorly resemble FeMoco's high-spin environment. The first high-spin iron (I) terminal N_2 adduct was recently synthesized by the Harman Lab using an adamantyl-substituted trispyrazolylborate (Tp) ligand. However, its electron-rich nature renders it incapable of forming N-H bonds. We propose the synthesis of a more electron-deficient, fluorinated Tp ligand, Tp(3,5-$(CF_3)_2$Ph, CF_3 (hydrotris-3-(3,5-bis(trifluoromethyl) Phenyl)-5-(trifluoromethyl)borate). When bound to iron, this should facilitate the reduction at less negative potentials and the functionalization of N_2. Synthesis of (3,5-bis(trifluoromethyl) phenyl) methyl ketone has been completed. Claisen condensation with trifluoroethylacetate, followed by condensation with hydrazine to form the pyrazole ring is underway. Combing the pyrazole with sodium borohydride will generate the Na Tp(3,5-$(CF_3)_2$Ph, CF_3. Subsequent metalation with iron(II) chloride under an inert atmosphere should generate the corresponding iron compound. Compounds will be characterized by a variety of methods including ^{1}H & ^{19}F-NMR, EPR, IR, Raman, X-ray crystallography, and cyclic voltammetry.

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Introduction

Nitrogen is an essential element for all life, yet much of it is in the form of dinitrogen (N_2), an in inert gas that comprises 78% of the earth's atmosphere. In biology, atmospheric dinitrogen is transformed into ammonia by a chemical reaction that takes place within bacteria present inside the root nodules of leguminous plants. The bacteria require anoxic conditions as the enzyme required for fixation is rapidly denatured in the presence of oxygen; the root nodules provide anoxic conditions. The robust triple bond in molecular atmospheric nitrogen is broken and the nitrogen's are then combined with hydrogen atoms by the enzyme nitrogenase, which features an active site containing iron-molybdenum-sulfur cluster or FeMoco (Iron-Molybdenum-Cofactor) (Fig 1).[1, 2]

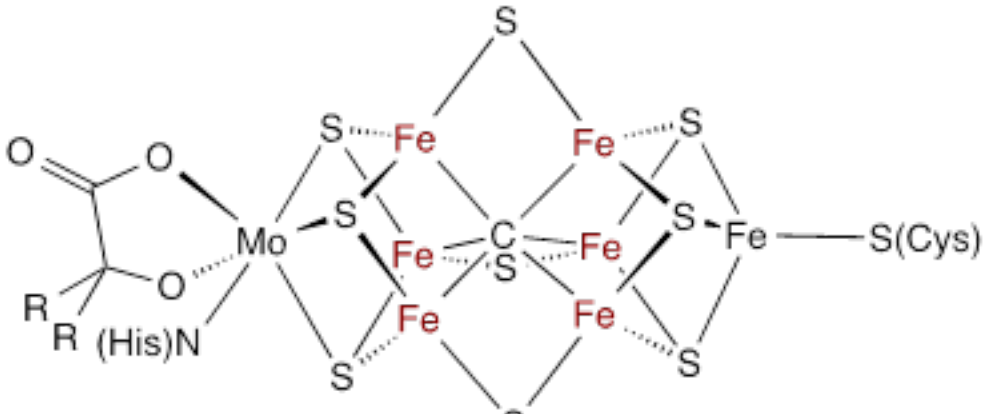

Figure 1. The iron-molybdenum cofactor of the nitrogenase enzyme.

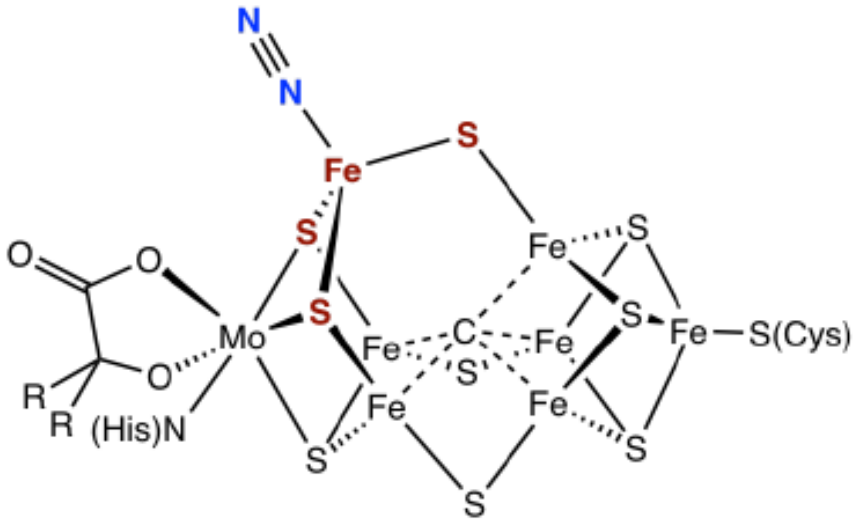

Figure 2. FeMoco of the nitrogenase enzyme bound to dinitrogen

This process occurs under mild physiological conditions and results in the formation of compounds that the plants can use to make proteins, nucleic acids and ATP units, essentially, this process of making ammonia produces natural fertilizer, enriching the soil for future plantation and supporting the plant. The industrial equivalent of nitrogen fixation is the Haber-Bosch process, a challenging and energy demanding reaction.[3]

$$N_2 + 16ATP + 8e^- + 8H^+ \longrightarrow 2NH_3 + H_2 + 16ADP + 16Pi$$

$$N_2(g) + 3H_2(g) \longleftrightarrow 2NH_3(g)$$

Figure 3. Note the similarities between biological nitrogen fixation (above) and Haber process (below).

To create ammonia from atmospheric nitrogen and hydrogen, temperatures of over 900°F and pressures of approximately 250 atm are used along with an iron catalyst to produce an ammonia yield of approximately 15%. The relatively high temperatures, high pressures and low yield are in stark contrast with biological nitrogen fixation. The industrial reaction suggests a question: How is nature—via the FeMoco active site—doing this so effortlessly and using substantially easier conditions? The field of bioinorganic chemistry explores this question via several different avenues. One includes the study of the native enzyme itself. This approach comes with obstacles as isolating the protein in solution during its catalytic phase is not easy. Also, using Ultraviolet–Visible Spectroscopy or Nuclear Magnetic Resonance, may not always reveal detailed molecular information about the target reactions when characterizing these proteins. Consequently, a complementary approach uses synthetic chemistry to design and synthesize model complexes similar in structure and properties to FeMoco.[4-6] These model complexes are then studied with various spectroscopic techniques to understand their electronic structure and also reacted with target compounds to explore their reactivity and catalytic ability. This approach allows for the exploration of hypotheses related to nitrogen fixation in systems that are much less complicated than the native enzyme itself. Ultimately, these insights can lead to advances in our understanding of biological nitrogen fixation as well as the development of new, more efficient industrial processes for nitrogen fixation.

The Harman lab is currently focused on high-spin iron complexes that bind dinitrogen. The iron centers in FeMoco are also high spin, but synthetic examples of high-spin iron compounds that bind N_2 are rare. Only the Mo and Fe containing ligands have been studied thoroughly previously and even the Fe in these ligands have only been in the low spin state. What this essentially means is that the electrons in iron have only been studied when in paired states, not like

the unpaired states in nature. Recently the Harman lab was successful in creating the first terminal N_2 complex of high spin iron (Fig 4).[7] One shortcoming of this first generation N_2 complex is how readily it loses an electron (become oxidized), resulting also in loss of the bound N_2. In order to overcome this challenge we hypothesized that the addition of electron withdrawing groups such as triflouromethyl to the periphery of this molecule would stabilize it with respect to oxidation and facilitate N_2 fixation reactivity. (Fig 5 - far left).

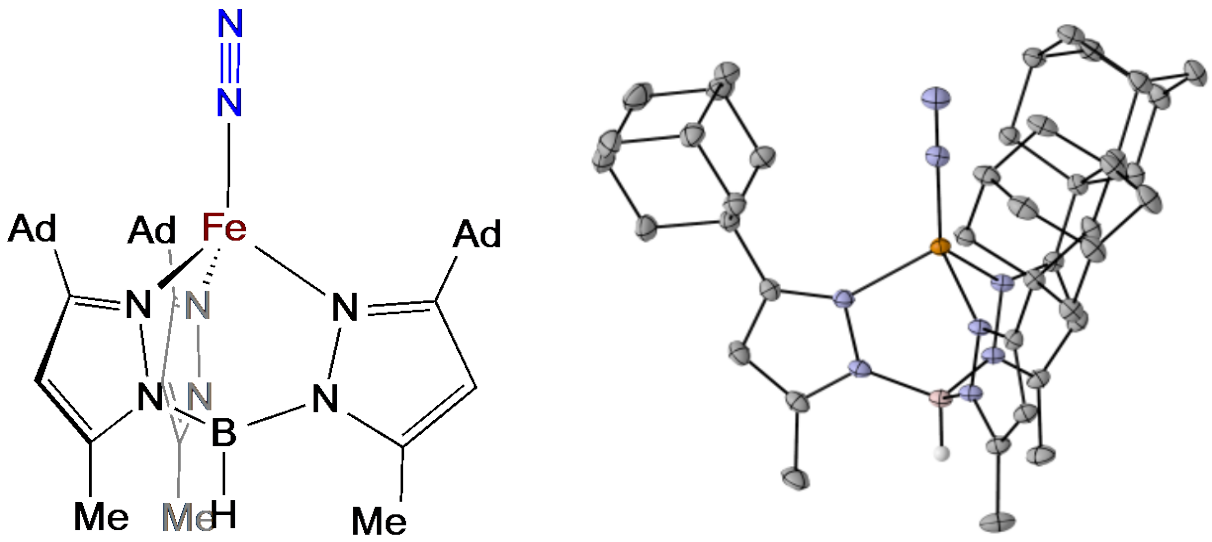

Figure 4. The first example of a high-spin iron complex with a terminal N2 ligand. Chemical line drawing (left) and solid-state structure from single-crystal X-ray diffraction (right) of $Tp^{Ad,Me}Fe(N_2)$.

Materials and Methods

To create the proposed molecule as shown in Figure 5, a retrosynthetic approach was adopted—to synthesize a material by working backwards in the direction of the preceding reactants. In order to create the Fe-Tp complex {$Tp^{(CF3)2}FeCl$ }, first a tris(pyrazolyl) borate {$NaTp^{(CF3)2}$ } framework must be made. This framework must be created by joining 3, 3,5-bis(trifouromethyl)pyrazole {3,5-$(CF_3)_2$Pz-H} units together with a boron atom. Finally, the pyrazole must be synthesized by

reacting hexafluoroacetylacetone (Hfac) with hydrazine monohydrate. Over the course of the research period these set of reactions and preparations were optimized and improved.

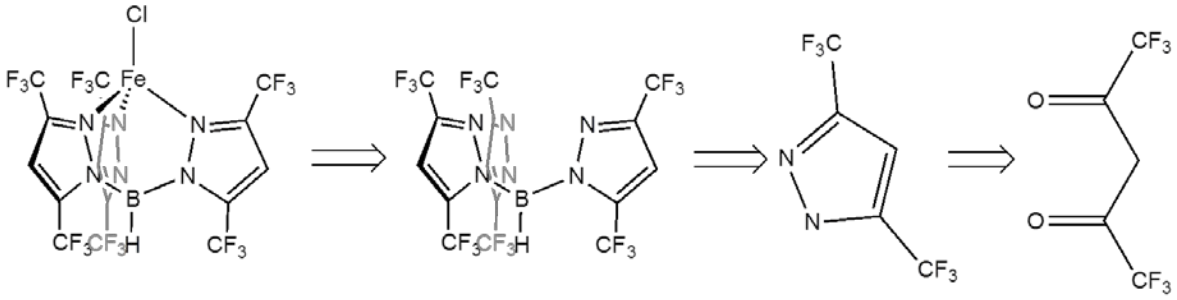

Figure 5. Retrosynthetic strategy for the construction of trifluoromethyl-substituted high-spin iron dinitrogen adduct.

General Procedures.

Air sensitive manipulations were carried out under an atmosphere of purified dinitrogen either using a glovebox or Schlenk techniques. Other operations were done inside a standard lab fumehood. Solvents were purified by distillation or passage through a JC Meyers solvent purification system. ^{1}H NMR and ^{19}F NMR tests were recorded at room temperature with a Varian Inova 300 spectrometer. Glassware was dried in a lab oven at 120°C or higher for 2 hours to remove residual water.

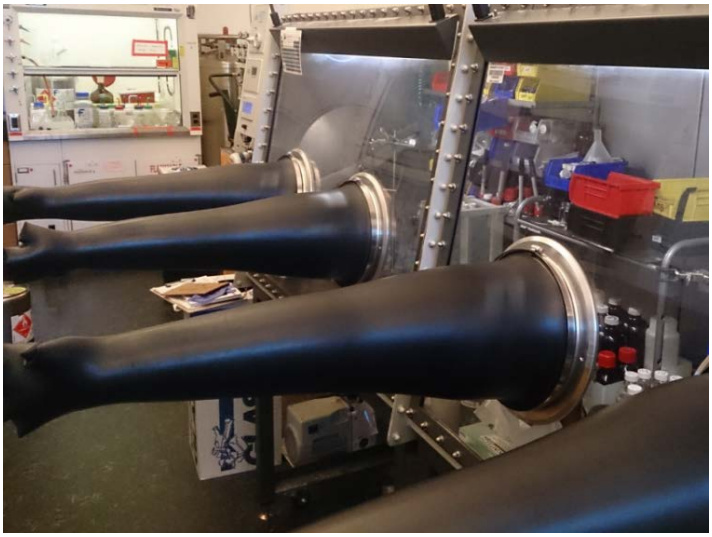

Figure 6. Glovebox: provides inert atmosphere, allowing stable handling of air sensitive metal complexes.

Synthesis of 3,5-bis(trifluoromethyl)pyrazole. This compound was synthesized by the modification of a literature procedure by Mariano et al[8]. The pyrazole was synthesized by dropwise addition of hydrazine monohydrate (928mg) to a solution of hexafluoroacetylacetonate (hfac) (1000mg) in chloroform in a round bottom flask while stirring with a magnetic stir bar. White fumes were observed upon the addition of the hydrazine. The reaction was refluxed at 65°C for 1 hour. P_2O_5 (3g), a desiccant, was added to the flask to remove any water from the reaction and prevent the formation of unwanted side products. The reaction was then left to reflux overnight, resulting in a color change from colorless to light yellow. After the overnight reflux the organic layer was extracted with water using a separatory funnel. The organic layer was concentrated and placed in the lab freezer overnight (–30°C) resulting in the formation of crystals of the product. The crystals were isolated by filtration and then sublimed using a hot plate/ice beaker.

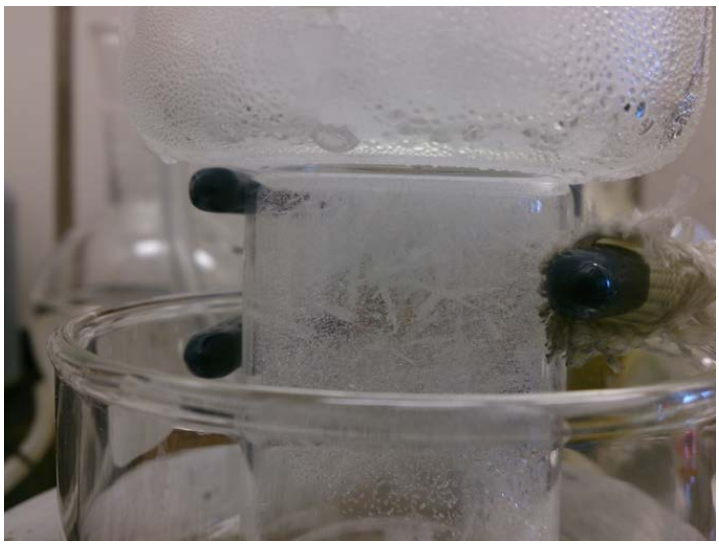

Figure 7. Formation of Pure 3,5-bis(trifluoromethyl)pyrazole crystals via sublimation.

The resulting crystals of pure 3,5-bis(trifluoromethyl)pyrazole were then collected and stored in the lab freezer due to its tendency to sublime at room temperature. The first few batches of pyrazole were made using a 1 gram scale, after becoming familiar with the techniques involved and improving the sublimation setup, eventually a 3 gram scale was used. Formation of the product was tested for purity using ^{1}H NMR and ^{19}F NMR.

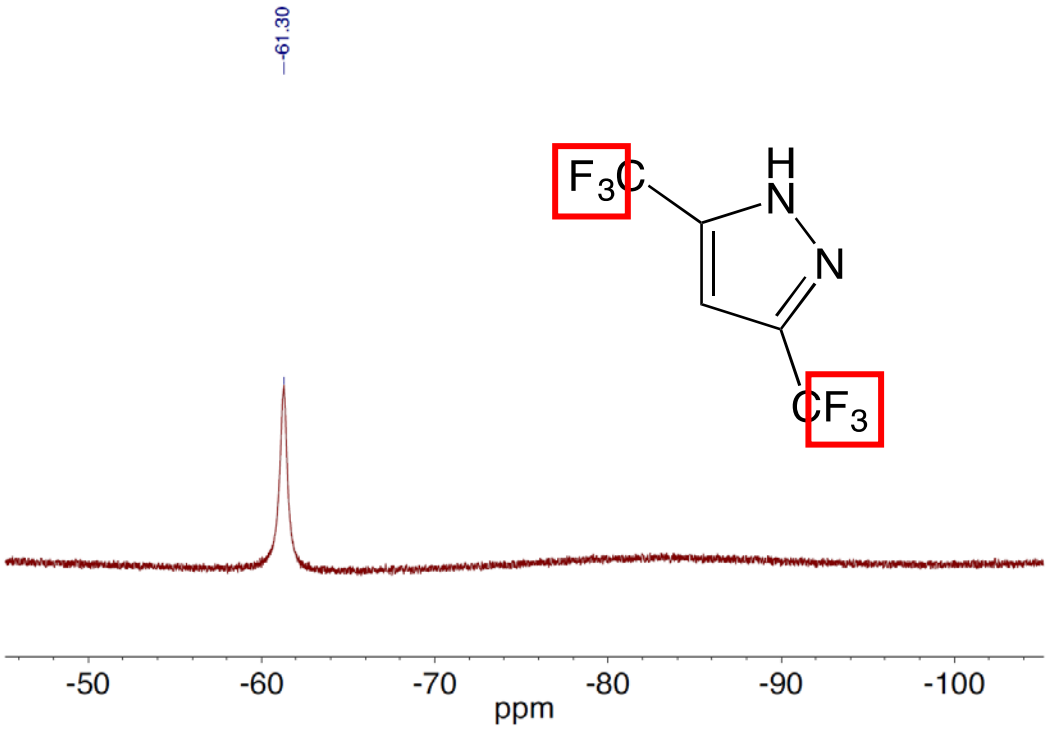

Figure 8. ^{19}F NMR of 3,5-bis(trifluoromethyl)pyrazole

Synthesis of $NaTp^{(CF3)2}$. This compound was synthesized by the modification of a literature procedure by HV Rasika Dias and Timothy KHH Goh[9]. A 50mL schlenk tube was retrieved from the oven and attached to a Schlenk line. The hot flask was evacuated and then refilled with dinitrogen. The reason an inert atmosphere was used was because one of the reactants, sodium borohydride ($NaBH_4$) is hydroscopic, i.e. it absorbs water from the surrounding air. The sodium borohydride was first weighed inside a glove box (25 mg) and then put into the Schlenk tube. 4

equivalents of the pyrazole (320mg) were then added to the $NaBH_4$. For the reaction to begin the pyrazole was melted by heating to 100°C using a heating mantle. The temperature was slowly increased over a period of 25 minutes to 170°C at an average rate of 2.8°C/min. Hydrogen gas was evolved during the reaction. This high temperature was maintained for 2 hours. During this time the pyrazole would sublime onto the cooler parts of schlenk tube, this was counteracted by using a heat gun to re-melt the pyrazole to the bottom of the tube. After the reaction was over a grimy white solid was seen at the bottom of the tube and pyrazole was seen as a thick clear band near the top. To separate the NaTp from the pyrazole, a vacuum line was used to pump on the tube for 1 hour, simultaneously a condenser with dry ice taped around it was connected to the schlenk tube to capture the excess pyrazole. After removing any excess starting material, the NaTp was dried overnight under vacuum to remove any water that may have been present. The purity was confirmed using NMR testing.

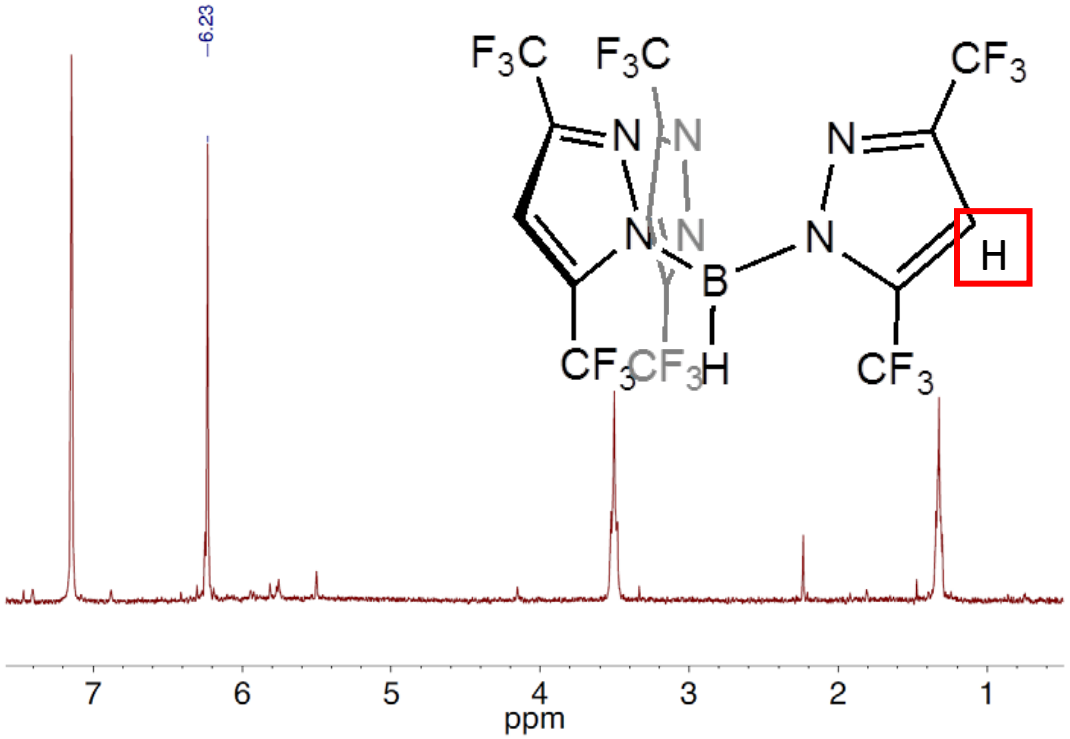

Figure 9. ^{1}H NMR of tris(3,5-bis(trifluoromethyl)pyrazolyl)borate ligand.

Synthesis of $Tp^{(CF3)2}FeCl$. NaTp was introduced into a glovebox as the TpFe complex is projected to be sensitive to air and moisture. NaTp (15mg), $AgPF_6$ (6mg), and $FeCl_2$ (6mg) were measured out and dissolved in tetrahydrofuran (THF). The solutions were combined while stirring and the reaction vial was covered with aluminum foil for 1 hour. To confirm the presence of the TpFe complex, an NMR spectrum of the product was taken and analyzed.

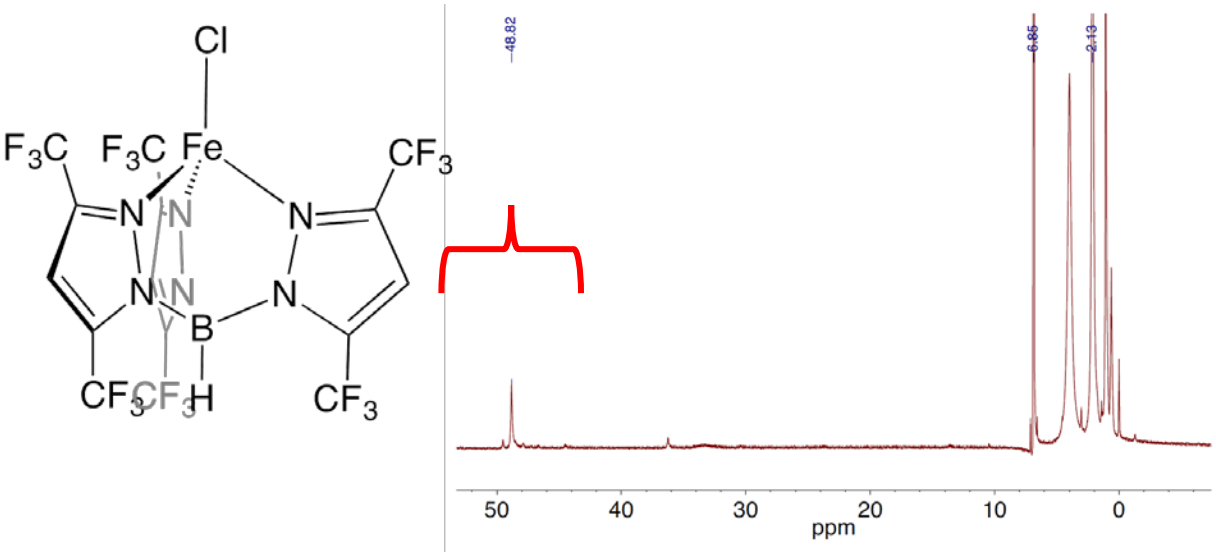

Figure 10. ^1H NMR of synthesized TpFeCl complex.

Results

During this program, fluorinated trispyrazolylborate ligand metallated with $FeCl_2$ was synthesized to give the targeted TpFeCl complex. A proton NMR of the product has been taken thus far (Fig 6). Future experiments will target structural characterization by X-ray diffraction and reduction of the complex to evaluate its reactivity with dinitrogen. Cyclic voltammetry will also be performed on the complex to determine the effect of the electron withdrawing trifluoromethyl groups on the redox chemistry of the compound. Infrared and Raman spectroscopy will be used to confirm the presence of an N_2 ligand.

Discussion

An X-ray structure will provide the three dimensional structure of the iron complex. Taking both an IR and Raman spectrum can provide details on how the complex combines with atmospheric nitrogen: whether it binds in a bridging or terminal fashion. The reaction of the TpFe with N_2 may reveal insight into the mechanism of fixation. Cyclic voltammetry will give an understanding of how strongly the complex donates or accepts an electron. Further research will depend on the results of these experiments, but future plans include new ligands with other electron withdrawing groups and reacting the complex with other small molecules such as O_2 and CO_2.

While this field of this research has a deterministic focus on uncovering the mechanism of biological nitrogen fixation, by making representative ligands and testing them in specific conditions with target compounds, important discoveries can be made along the way. Understanding the interplay of electron withdrawing groups, electron spin states, orbital structure and other chemical parameters and how they interact in real space is difficult but rewarding. The sum up of the personal capstone experiences can be likened to piecing together Lego bricks and then observing what the properties of the new creation are. Modifications and novel observations then stem from the new creation.

Future Research

Further study of high spin iron complexes that advance the research discussed above may warrant further modification of TpFe framework. In order to prevent binding of dinitrogen by multiple iron centers, a bulkier pyrazole such as 3-(3,5-bis(trifluoromethyl)phenyl)-5-trifluoromethylpyrazole may be used. The pyrazole would still be hypothesized to retain its electron withdrawing capabilities due to the presence of the trifluoro groups attached to the phenyl rings. Synthesizing this pyrazole and incorporating it into the Tp framework to create a larger ligand is shown below (Fig 11). This synthesis could be carried out through formation of a Grignard reagent using Mg^0, followed by acylation and Claisen condensation with trifluroacetic anhydride. The resulting precursor would then undergo hydrazine condensation to give the pyrazole, NaTp formation via $NaBH_4$ reduction, then metalation using $FeCl_2$.

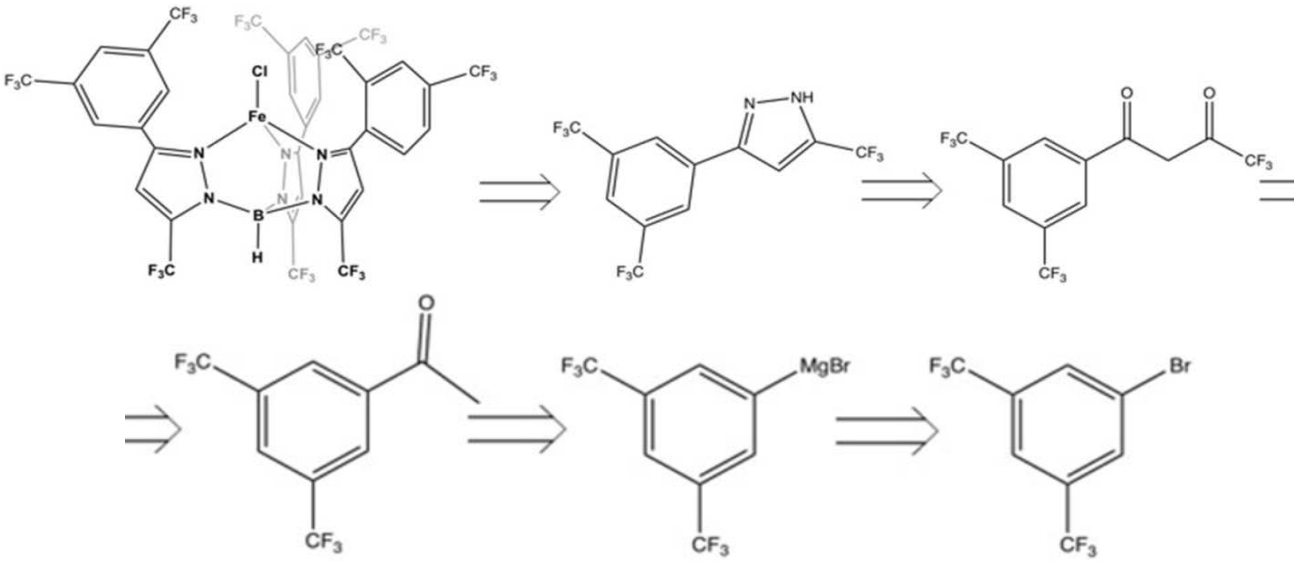

Figure 11. Retro-synthetic model of proposed ‘bulkier’ ligand.

Limitations

Limitations that also make the pathway presented above (Fig 11) attractive is the difficulty of handling the 3,5-bis(trifluoromethyl)pyrazole. This pyrazole is extremely difficult to work with as it sublimes into the air very quickly at room temperature, producing smaller yield than anticipated and also prevents recovery if excess is left over after the formation of the $NaTp^{(CF3)2}$ ligand. Even when the compound is sitting in a closed vial in the fumehood it is susceptible to compound loss via sublimation. Having low starting mass at the start of the retrosynthetic pathway as shown in Fig 4, leads to even lower subsequent yields of the following products, giving very low final $Tp^{(CF3)2}FeCl$ mass. For future considerations, the volatility of the compounds may be more strongly considered to allow greater reaction yields and ease of handling. This factor was strongly taken into consideration while also proposing a ligand that may not be able to bind dinitrogen more than once. Lastly, a mechanical failure with the glovebox unit in the lab degraded the only sample vial of the $Tp^{(CF3)2}FeCl$ complex, making process of starting from scratch even more daunting.

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