How Pure is *Pure*? Metal Complexation Studies Directed Towards Pharmaceutical Drug Purification

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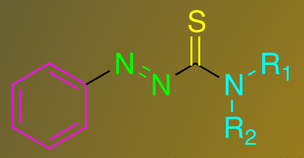
Motivation:

Catalytic processes play critical roles in the modern-day industrial syntheses of many commonplace materials such as plastics, fuel production, electronics, and pharmaceuticals. Transition metal catalysts may become homogenously embedded within solid nanomaterials during their synthetic scheme, which may result in many deleterious effects on both the construction and durability of the material and its intended functionality. Traditional purification methods of these materials rely upon harsh reaction conditions that may either affect or allow for specific functionalities.

Generic construction of the (ATF) ligand

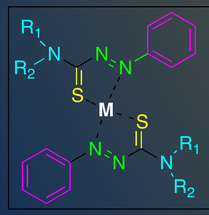


Arylazothioformamide (ATF) ligands have proven to be a mild alternative for their ability to chelate these solid transition metal catalysts. This work will describe the synthetic steps towards developing a versatile library of ATF ligands, the characterization of those synthesized, and initial chelation studies directed towards the purification of pharmaceutical drugs which employ catalytic processes in their production.

Background:

Originally, Jensen[1] synthesized the (ATF) ligands and metal complexation studies were reported by Krebs, and Bechegaard[2] citing complexes of Palladium (Pd), Platinum (Pt), Copper (Cu), and Nickel (Ni) metals. Intense absorption changes were noted and X-ray crystallography revealed a 2:1 ligand-to-metal (bis) complexation ratio. Few variations of the original ligands (again by Krebs) were developed with slight further advancement or applications.[3]

This project has been directed towards developing new variations of the original (ATF) ligand synthesized by Jensen, as well as studying chelation of the original ligand with transition metal catalysts utilized during pharmaceutical synthesis.



Krebs Initial Study
M = Cu, Pd, Pt, Ni
R_1=R_2 = Et
R_1=R_2 = PEOM

This Study
Various Metals
M = Cu, Cu(I), Cu(II), Pd, Pd(II)

Pharmaceuticals derived from Metal Catalysis
i.e Naproxen, Ibuprofen

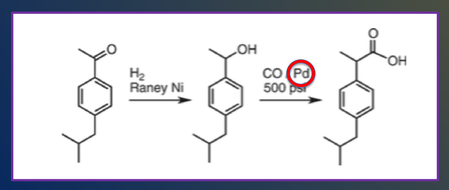
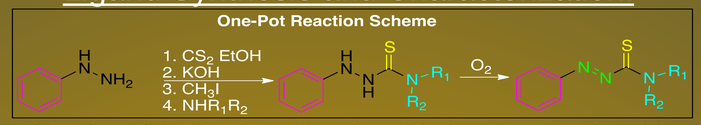


Figure 1: An Industrial Scale Synthesis of Ibuprofen Developed by BHC[4]

Ligand Synthesis and Characterization:

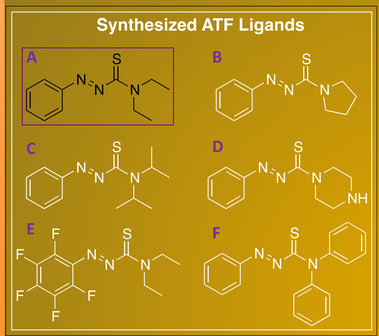
One-Pot Reaction Scheme



Beginning with phenyl hydrazine, CS_2 is added to create the thiocarbamic acid , addition of KOH followed by methyl iodide converts the compound to the thioester. Upon solvent removal, the secondary amine is added and refluxed to prepare the azothiocarbazide, which is then finally exposed to air and undergoes oxidization to the various arylazothioformamide (ATF) ligands.

Synthesis:

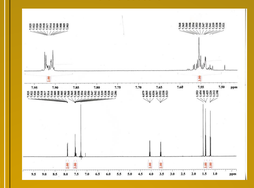
Synthesized ATF Ligands



A ⇒ Jensen's Original Ligand (*This Study*)
B-F ⇒ future coordination complex studies

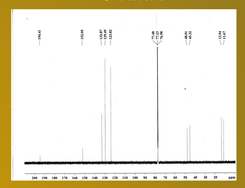
Characterization:

^{1}H NMR

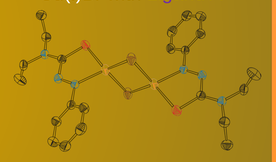


Single X-Ray Crystal Structure of Ligand A

^{13}C NMR

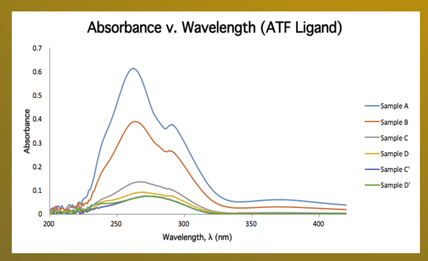


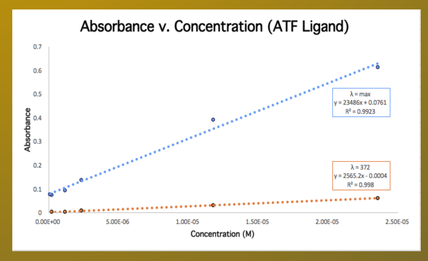
X-Ray Crystal Structure of Cu(I)Br with Ligand A



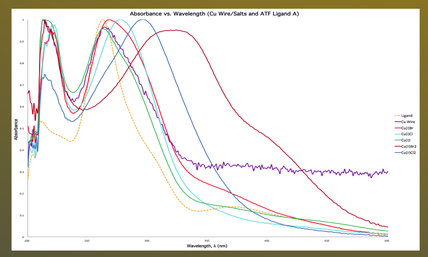
UV-Visible Absorbance Spectra and Analyses:

(ATF) Ligand Extinction Coefficient Determination:

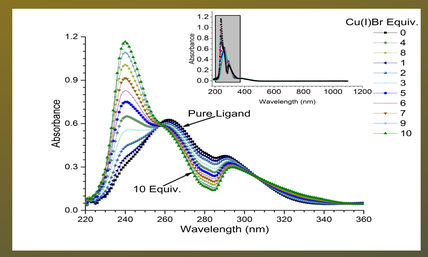




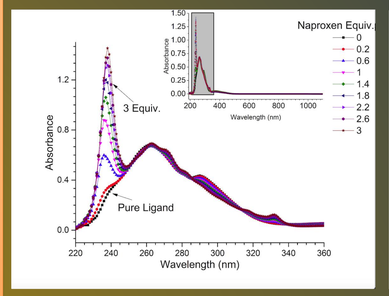
Copper Wire and various Copper Salts Treated with (ATF) Ligand:



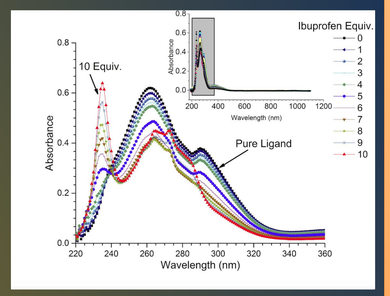
Cu(I)Br Treated with (ATF) Ligand:



Naproxen Treated with (ATF) Ligand:



Ibuprofen Treated with (ATF) Ligand:



Results and Significance of Data:

The Absorbance Spectra Graphs are interesting for a number of reasons:

Cu(I)Br and Copper Wire and Copper Salts:

- Three distinct isosbestic points can be see on the graph.
- After ten equivalents of Copper(I)Bromide are added to the pure ligand, a dramatic shift in the absorbance signature can be seen.
- This data suggests, but does not entirely confirm that the (ATF) ligand is chelating the Copper metal, forming a coordination complex, as see in the crystal structure above.
- This also suggests that these ATF ligands are capable of chelating these metals (Copper or Palladium) in various oxidative states.

Naproxen and Ibuprofen:

- Both Naproxen and Ibuprofen exhibit substantial changes in their absorbance signatures when treated with the ATF ligand. Naproxen shows the most dramatic shift, which may suggest more trace metal impurities are within the drug
- Future studies of this project will involve treating these pharmaceutical drugs with the ATF ligand and analyzing the treated drug with Inductively-Coupled Plasma-Mass Spectrometry to check for residual trace metal impurities

Future Studies:

Additional metal complexation studies will be carried out with various transition metals with the modified ligands already synthesized. Synthetic modifications to the original ligand will be carried out in the future, with an interest in developing a new class of semi-perfluorinated and hydrophilic ATF ligands. This will potentially enable enhanced metal extraction from a multitude of immiscible phases (aqueous, organic, and a distinct fluorous phase). Further chelation studies will be carried out on atom-transfer radical polymerization (ATRP) initiated polymers, carbon nanotubes, and metal impurities in solution. Eventually, studies will be directed towards providing an improved method of recycling catalytic materials and various metals.

Acknowledgements:

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References:

[1] Jensen, K.A; Bechgaard, K.; Pedersen, C.T. *Acta Chem. Scand.* **1972**, *26*, *2913-2922.*
[2] Nielsen, K.T.; Bechgaard, K.; Krebs, F.C. *Macromolecules*, **2005**, *38*, 658-9.
[3] Nielsen, K.T.; Bechgaard, K.; Krebs, F.C. *Synthesis*, **2006**, *10*, 1639-44.
[4] (a) Elango, V. et al. . U.S. Patent 4,981,995, 1991. (b) Lindley, D. D. et al. . U.S. Patent 5,068,448, 1991.