

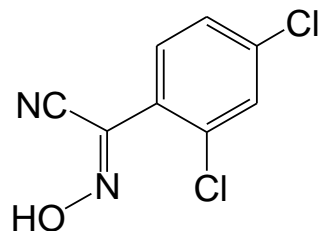


Michael Hilton: MS 2013

Thesis

“Synthesis and Characterization of Oximes-based Platinum Complexes”

Michael Hilton spent in my research group four years, one of the longest and the most successful graduate students in the group! He had two tasks to work on, with the second one crystallized as his very large and substantial MS Thesis. The first task was to repeat the synthesis of the 2,4-dichlorophenyl-cyanoxime shown below:



This compound was found to be the next strongest *Carbonic Reductase* inhibitor. This enzyme is responsible for the resistance of tumor against anticancer treatment, and deactivation of it makes chemotherapy much more effective. Michael obtained this compound in multi-gram quantities and applied several techniques to grow suitable for the X-ray analysis single crystals. After

successful trial crystal and molecular structures of protonated H(2,4-diCl-PhCO) was determined and shown in Figure 1 below:

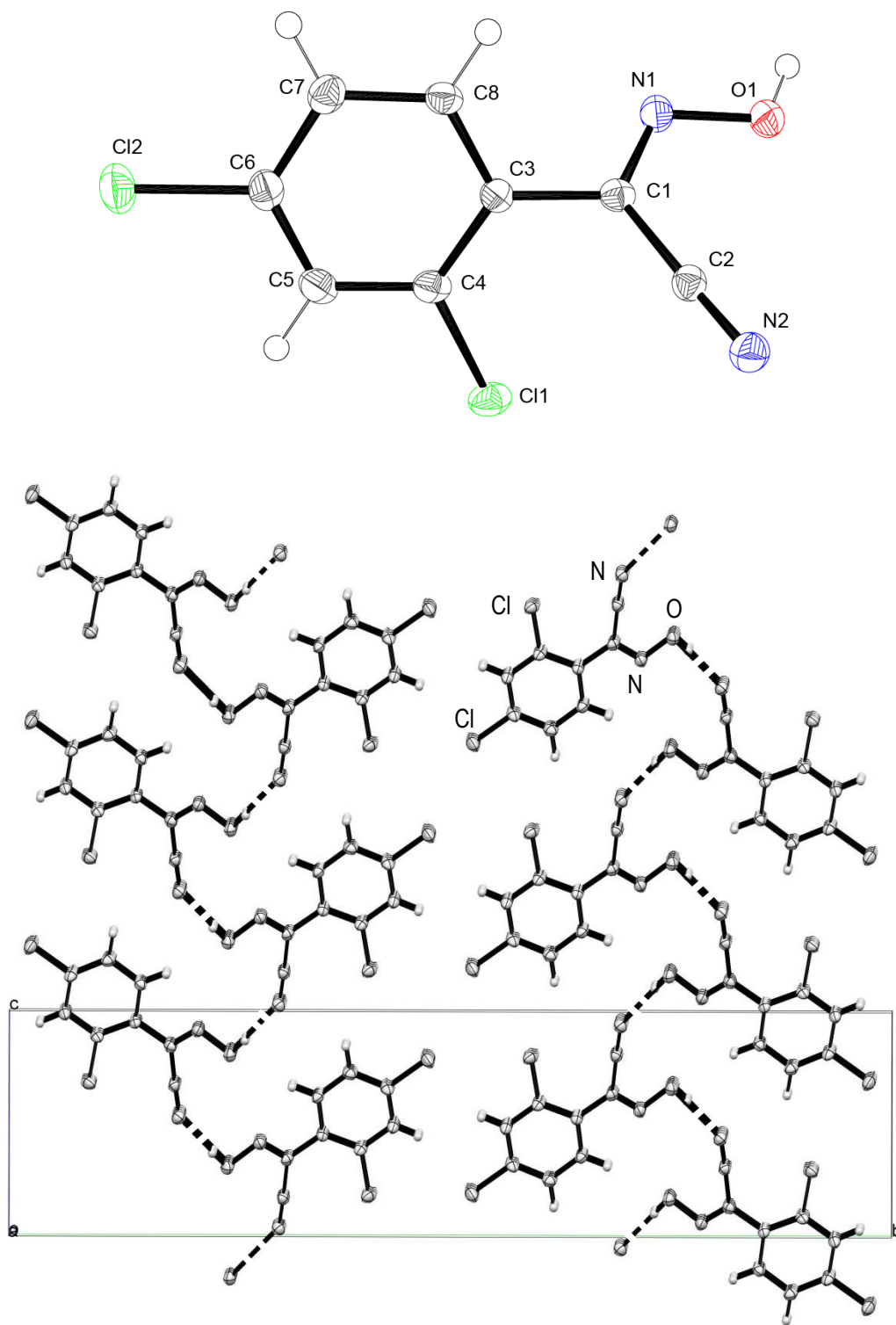


Figure 1. Molecular structure and numbering scheme for the structure of cyanoxime (A), and its packing diagram showing 3 unit cells viewed along *a*-direction (B).

The second part of Michael's work in my research laboratory was dedicated to systematic investigations of a series of Pt(II) complexes with oxime-bearing ligands displayed in Figure 2. There were 8 cyanoximes and 2 classic isomeric nitrosonaphtoles. The choice for these ligands was pretty clear: out of 38 known at that time cyanoximes only those selected (Figure 2) are able to form metallochetales. Two "old-&-famous" nitrosonaphtoles were chosen for comparison purposes since their coordination chemistry was well known.

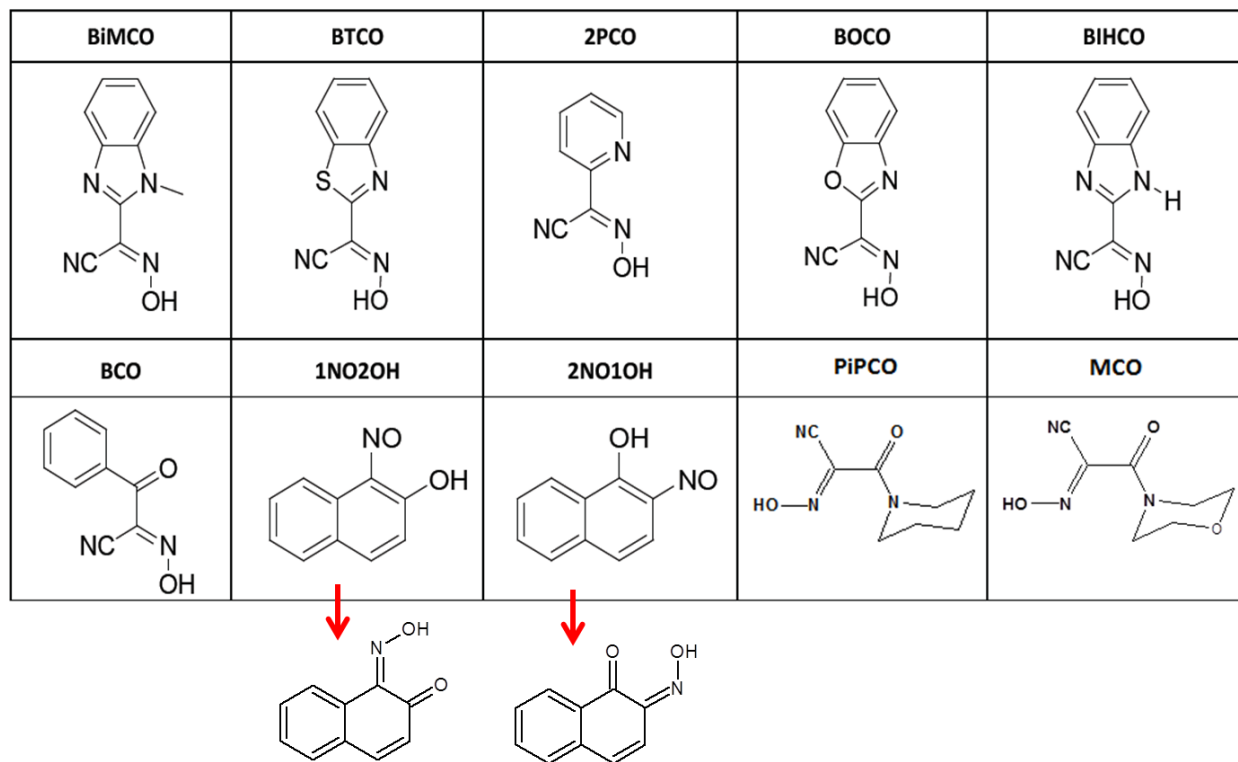


Figure 2. Chemical structures of chelating cyanoximes and nitrosonaphtols (shown with their oxime tautomers) that were used for the preparation of Pt(II) complexes.

The second project was entirely dedicated to thorough investigation of both ligands used, and their Pt(II) complexes. It turned out that prior to Michael's work there was no complete studies performed on spectroscopic properties, such as IR- and NMR-spectra, of isomeric nitrosonaphtoles! Numerous publications in the past stated erroneously that these ligands exist in the *nitroso* form and that was even carved in their trivial names: nitrosonaphtoles. Well, Michael Hilton's work proved it all wrong. Detailed NMR spectroscopic studies and isotopic labeling with ^{15}N (at 50% level) allowed unambiguous assignment of all signals and vibrations in these old organic ligands. The NMR work was carried out with a tremendous help of Dr. Sergiy Tyukhtenko from Northeastern University in Boston, MA.

Synthesis of isomeric nitrosonaphtols was performed using long ago published procedures, but this time NaNO_2 was labeled at 50% with ^{15}N to help to assign the vibrational spectra and ^{13}C NMR spectra. Using initial readily available 1-naphtol and 2-naphtol this one-steps procedure is shown in Figure 3.

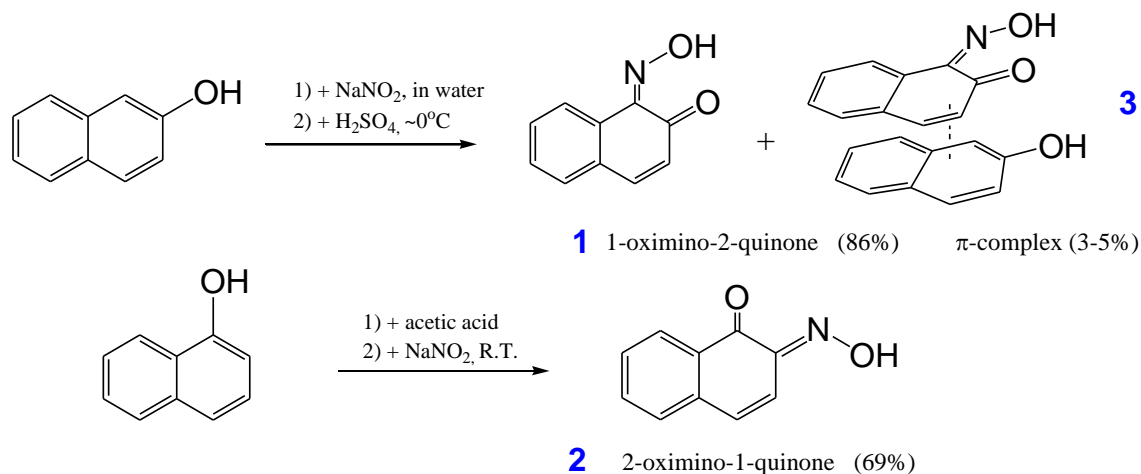


Figure 3. Preparation of isomeric nitrosonaphtols.

The red-pink compound **3** was the first time ever observed impurity, which turned out to be stable π -complex between the initial 2-naphtol and final product the oxime! After careful isolation of bright red-pink needles (Figure 4) their crystal structure was determined (Figure 5).

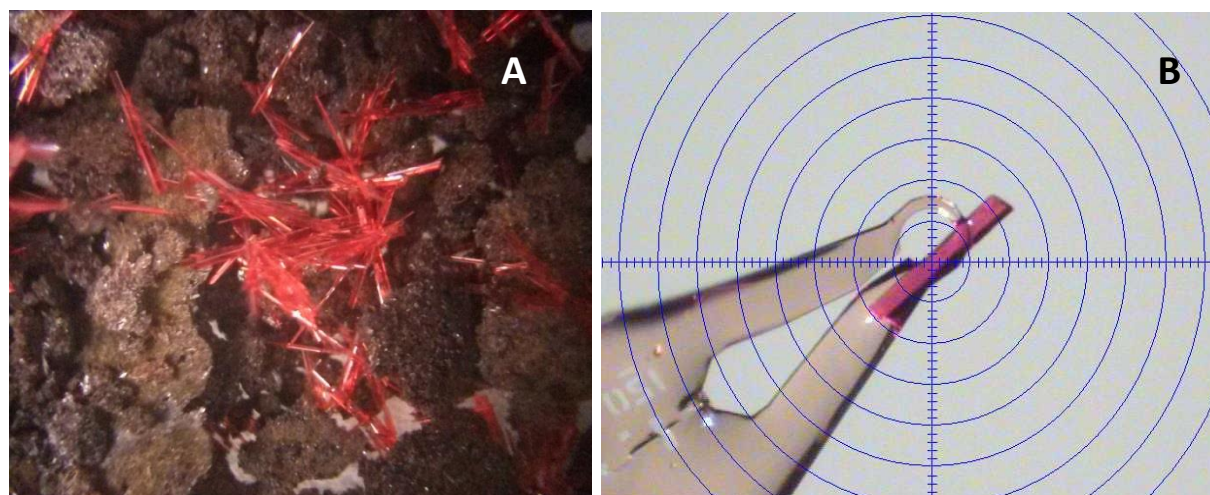


Figure 4. **A** – Actual microscope photograph of a solid 1NO-2OH containing the “red impurity,” π -complex **3**. **B** – Single crystal of compound (on the goniometer head, in the MiTeGen loop) used in determination of the crystal structure.

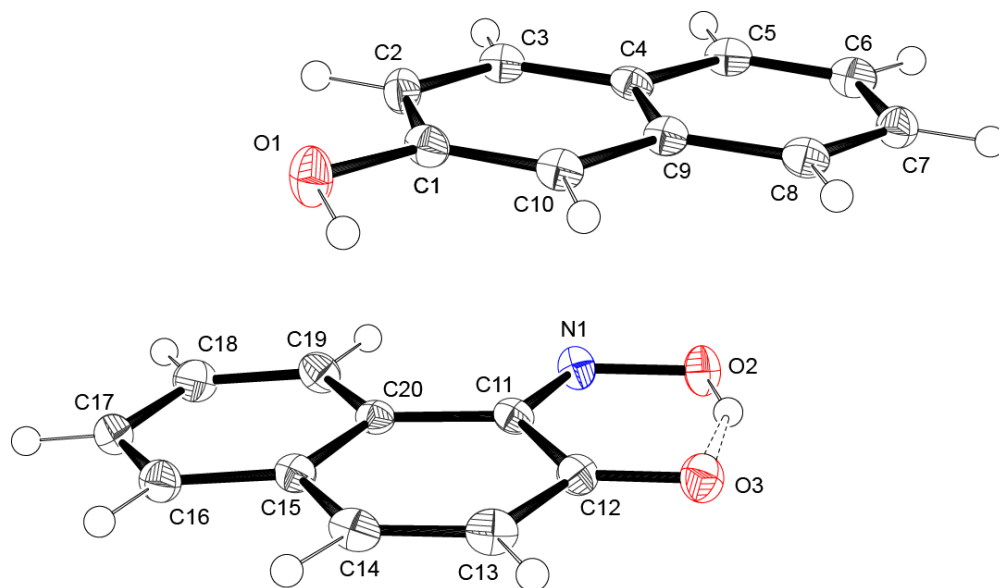


Figure 5. Molecular structure and numbering in the π - π stacked pair of the 1-nitroso-2-naphthol and 2-naphthol, which was isolated as a “red impurity”. Thermal ellipsoids are drawn at 50% probability level.

The bottom molecule of the nitrosonaphthol has strong and short intramolecular H-bond (indicated as a dashed line) and acts as electron acceptor, while the top molecule of the naphthol acts as a donor. Being combined as a “pair”, two molecules demonstrate red charge transfer band in electronic spectra in solid state.

Crystal and molecular structures of isomeric nitrosonaphthols were determined as well and presented in Figure 6. It turned out that both old-&-famous classic organic chelators used for analytical chemistry for over 100 years are actually *oximes*. This was evident from the location of H-atoms on oxygen atoms of the CNO fragment as well as from the analysis of bonds and valence angles in both structures. The 1NO-2OH compound forms very strong intramolecular H-bond that is well described as closed form (Figure 6A). Its isomer 2NO-1OH forms extensive intermolecular H-bonding with participation of the keto-group C1-O2 from neighboring molecules (Figure 6B).

As was stated above, vibrational spectra of these compounds needed to be re-examined because of numerous errors associated with wrongful assumption of the nitroso character of these classic ligands. Therefore, isotopically ^{15}N -labeled compounds were studied with respect of finding certain shifts in position of CN and NO bands depending on their either *nitroso*- or *oxime*-character with existing trends and well documented criteria shown in Figure 7 below. Actual IR-spectra of solid samples of the ligand (A) and its Pt-complex (B) are presented in Figure 8.

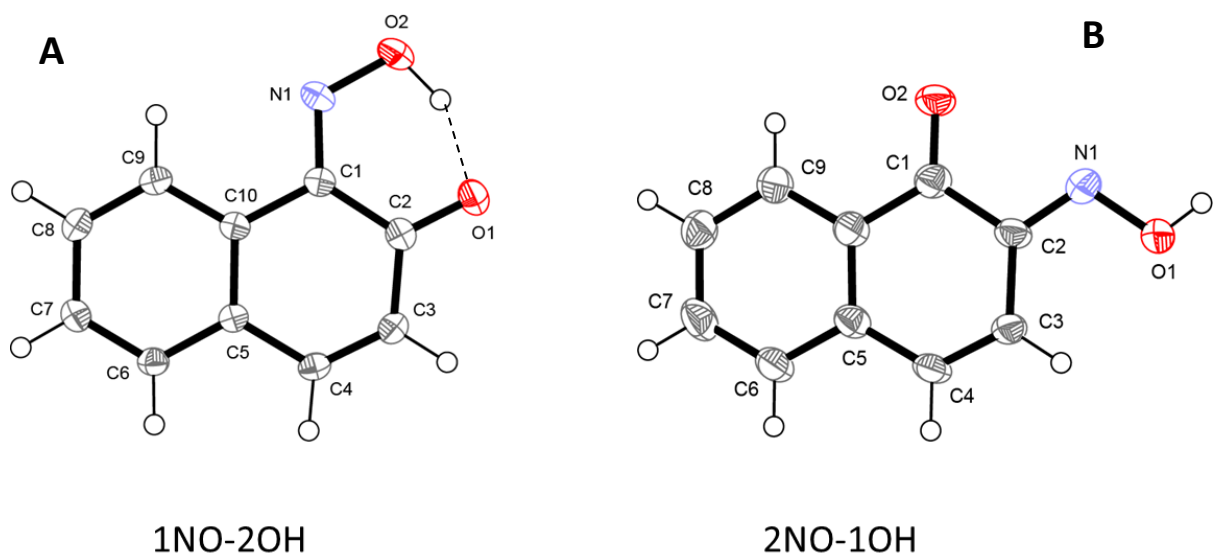


Figure 6. Molecular structures and numbering schemes for structures of isomeric oximes.

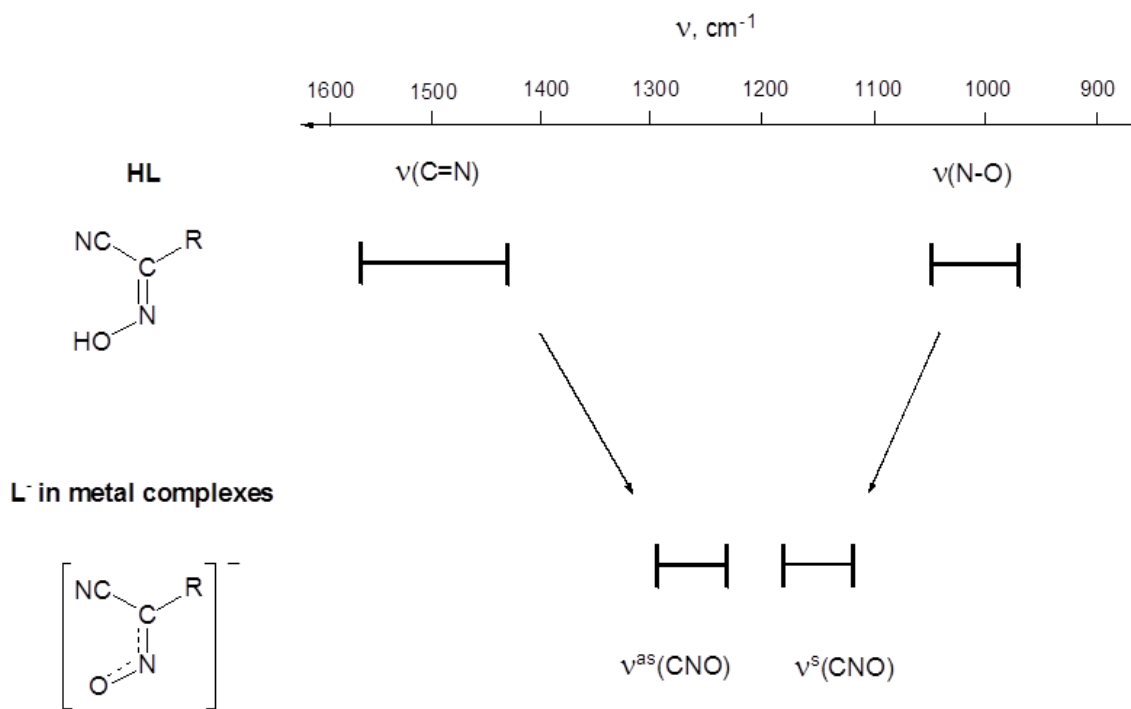


Figure 7. Observed IR-spectroscopic manifestation of changes in vibration modes and frequencies upon conversion between oxime and nitroso groups in free ligands, and their metal complexes.

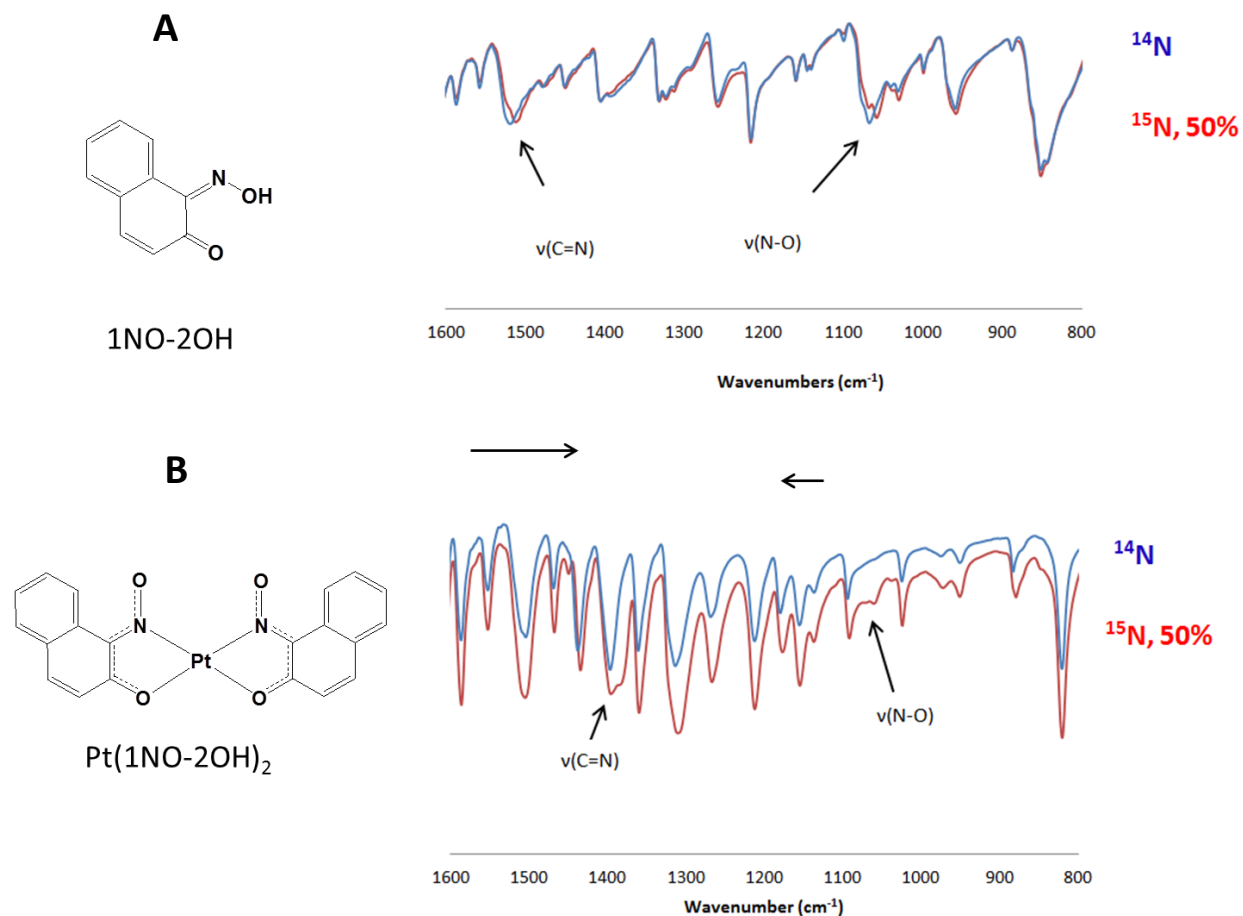
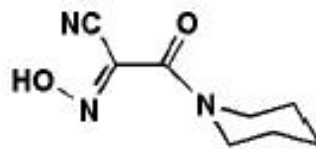


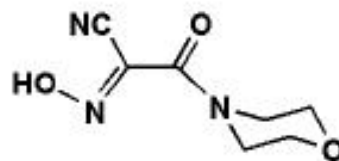
Figure 8. IR-spectra of labeled ligand (A), and its Pt(II) complex (B) in overlaid mode showing vibrations involving the C-N-O fragment.

After detailed investigation of spectra and structures of oxime-bearing ligands Michael focused on the preparation and characterization of their Pt(II) complexes. There are several reasons in this particular metal chosen for studies: 1) previous work in my research group indicated strong cytotoxicity of Pt-cyanoximates, which we would like to use for development of new anticancer agents; 2) several Pt-cyanoximates have demonstrated bright emission in the NIR region of electromagnetic spectrum beyond 1000 nm. At these wavelengths the biological tissue is transparent and there is a good possibility for the use these cytotoxic Pt-based compounds for biomedical applications as theranostic compounds: they can be imaged in the tissue and upon metabolic transformation they are able to kill cancer cells. Those NIR-emissive Pt-based complexes were found to be 1D coordination polymers held together by metallophilic interactions forming the “poker chips” stacks. Moreover, those with such structures possess dark-green colors highly unusual for common Pt-based complexes, but is the case a “stacked” complexes such Magnus’ Green Salt [Pt(NH₃)₄][PtCl₄]. Therefore, among series of synthesized Pt compounds it was easy to select ones that adopt 1D structure and form “Pt-wires” (Figure 9). All non-green complexes were excluded from Michael’s studies (Figure 10).

Pt(MCO)₂



Pt(PiPCO)₂



Pt(2PCO)₂

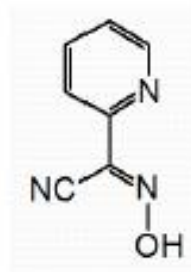
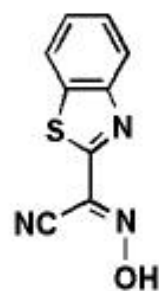
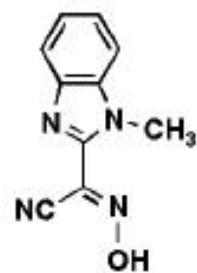


Figure 9. Actual microscope photographs of Michael's "Pr-greens" under 40x magnification.

Pt(BTCO)₂



Pt(BIMCO)₂



Pt(BIHCO)₂

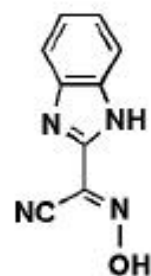


Figure 10. Actual microscope photographs of Michael's "non-green" complexes under 40x magnification.

Isolated dark-green complexes of PtL_2 composition ($L =$ monoanions of PiPCO, MCO, BCO, 2PCO cyanoximes; Figure 2) turned out to exist as three distinctive polymorphic modifications: green 1D-polymer, red dimers and yellow (monomers) (Figure 11).

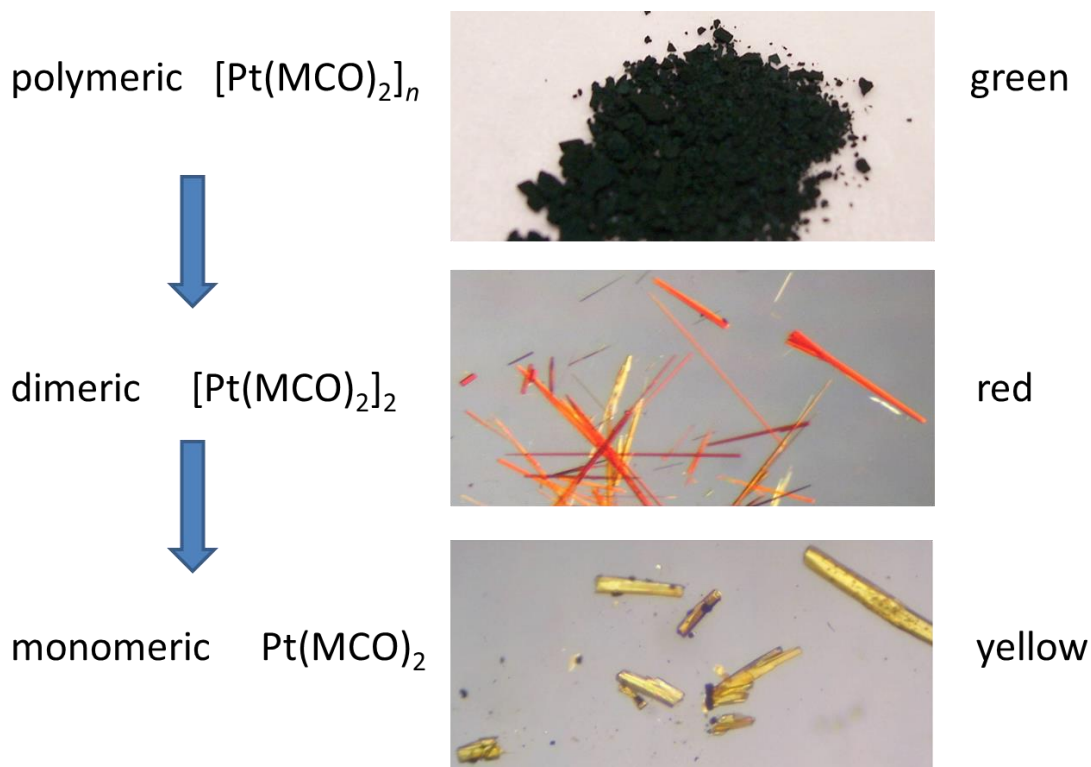


Figure 11. Actual appearance of three polymorphs of $Pt(MCO)_2$ composition.

Only two out of three polymorphs was possible to crystallize and determine their molecular and crystal structures. Unfortunately, the most interesting dark-green polymorphs were impossible to crystallize using conventional methods. It is assumed that the matter is in non-repetitive 3D ordered structure of samples Michael obtained, which resulted in the absence of necessary for the X-ray diffraction conditions. Crystal structures of those that crystallized are presented below in Figures 12 and 13. In both yellow monomeric and red dimeric complexes the coordination environment of PtN_2O_2 is cis-, and similar to that for cisplatin $[Pt(NH_3)_2Cl_2]$. Also, cis-units of $Pt(MCO)_2$ form head-to-tail dimer that requires solvent molecule DMSO to be included in the structure for its stabilization (Figure 13). Both yellow monomeric and red dimeric polymorphs are not NIR emissive.

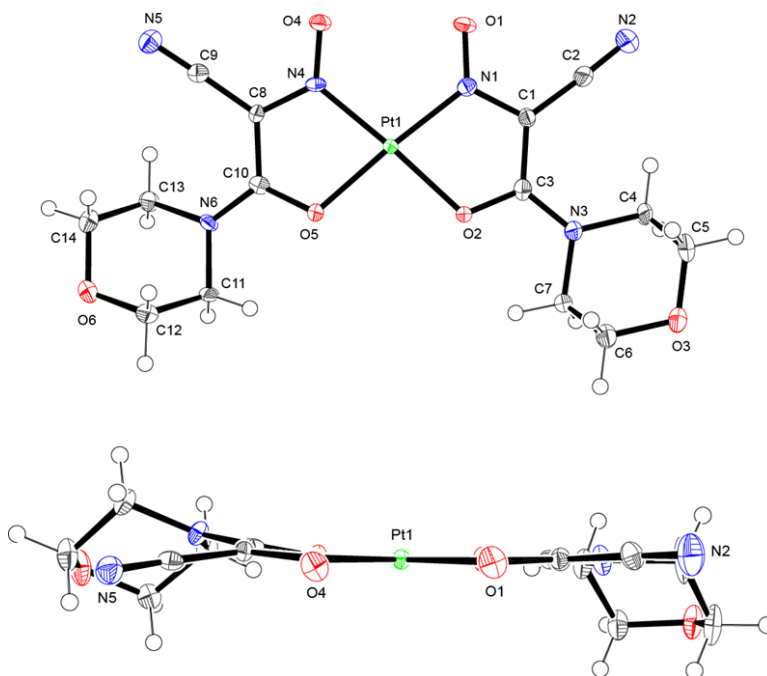
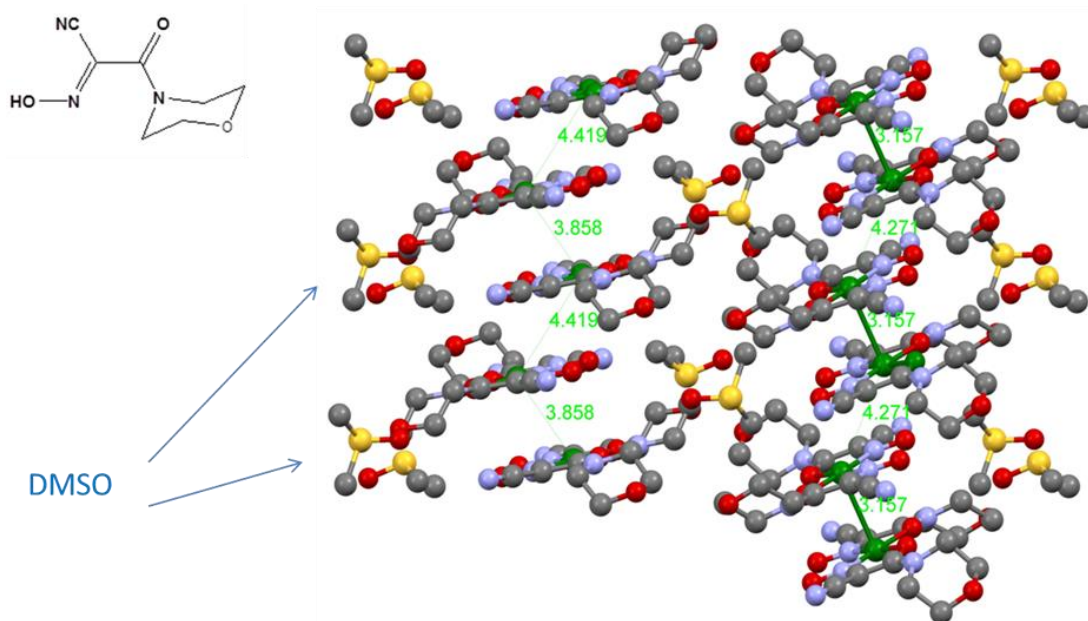


Figure 12. Crystal structure of yellow monomeric polymorph of $\text{Pt}(\text{MCO})_2$: **A** – top, and **B** – side views.



Two distinct zig-zag chains present in the red form of $\text{Pt}(\text{MCO})_2 \cdot \text{DMSO}$ viewed along b

Figure 13. Fragment of crystal structure of red dimeric polymorph showing solvent molecules stabilizing the structure and short intermetallic separations.

The overall evolution of intermetallic separations in all three polymorphs of $\text{Pt}(\text{MCO})_2$ is shown in Figure 14. Only 1D coordination polymer in dark-green form of the complex shows emission in the NIR region, which could be explained in terms of better alignment of monomeric units and formation of a “metal wire”. Also, we found that polymeric complex does conduct electricity at the level of high semiconductors (Figure 15). This unexpected finding has a long lasting effect and immediately evidenced the formation of mixed valence species in the 1D polymer. In other words, the system now behaves similar to previously observed mixed valence POCP (partially oxidized cyanoplatinates) solids with Pt(II)/Pt(IV) species. Observed dark-green intense color of several polymeric complexes indicates strong intervalence charge transfer between metal centers in Pt-cyanoximates.

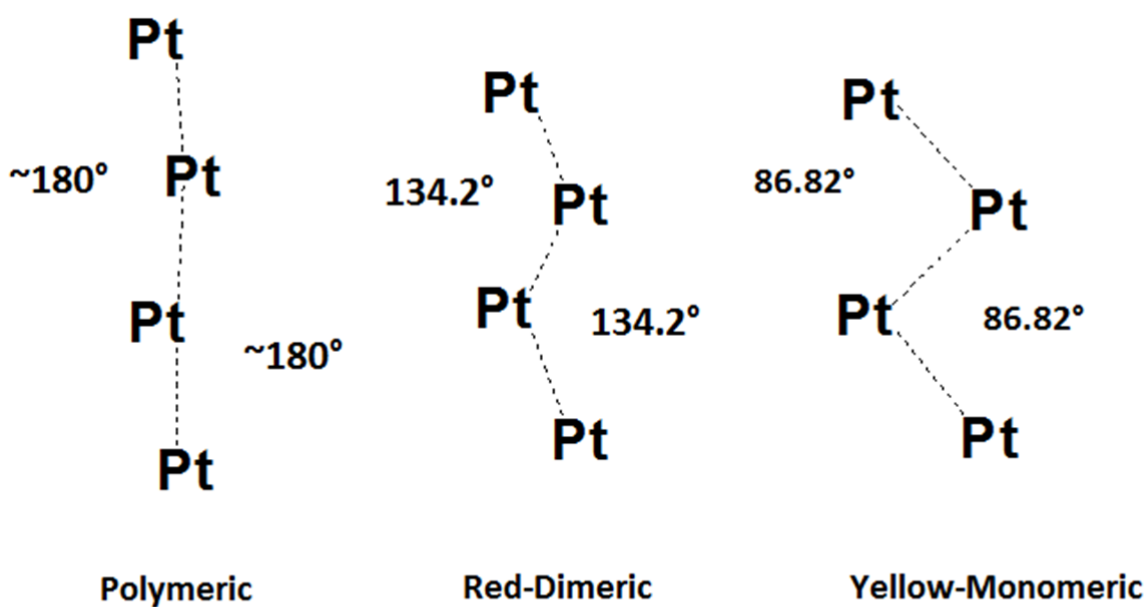
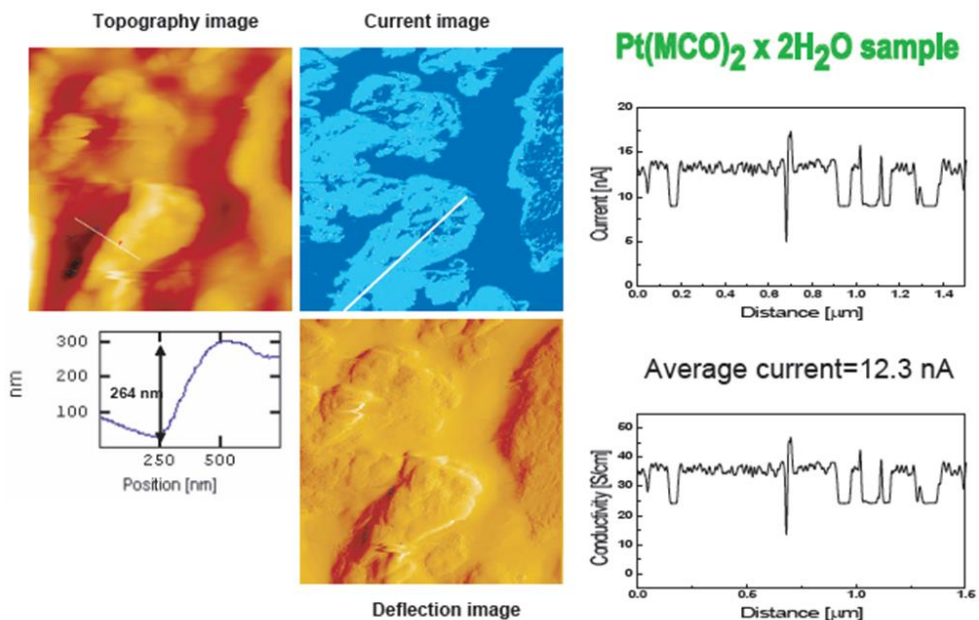


Figure 14. Angular geometry of Pt centers in three polymorphs of $\text{Pt}(\text{MCO})_2$ composition. Slippage of monomeric units leads to rather drastic color lightening from dark-green in aligned 1D polymer to red in dimer and light-yellow in the monomer.

Lastly, fluorescence in the NIR region beyond 1000 nm was detected for some of the complexes as shown in Figure 16. The temperature dependent bathochromic shift of the wavelengths of emission with simultaneous decrease in intensity of fluorescence is typical of some types of quantum dots and wells.



Pt(MCO)₂*2H₂O : $\sigma_{ave} = 33.3$ [S/cm] Pt(PiPCO)₂ : $\sigma_{ave} = 22.2$ [S/cm]

Figure 15. Results of the AFM examination of fine dark-green powders of polymeric Pt-cyanoximates.

- Excitation at 800 nm
- Emission in the Near IR
 - Very little in the human Body interferes with this region
- MGS and PO-KCP do not emit in this region

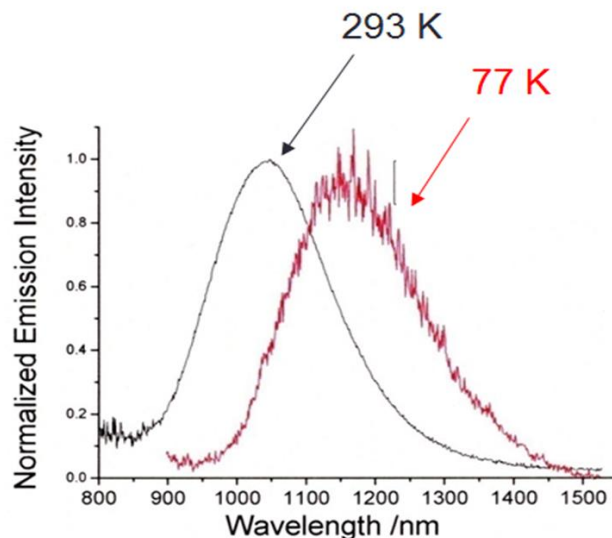


Figure 16. The photoluminescence spectra of dark-green polymeric [Pt(PiPCO)₂]_n at two different temperatures.

Finally, from Michael Hilton's work in my research group on Pt-project the following conclusions can be drawn:

1. Eight new platinum complexes were synthesized using bidentate mixed-donor chelating oximes: cyanoximes and isomeric nitroso-naphtols. All compounds were obtained via interaction between deprotonated oximes (as K or Na salts) and K_2PtCl_4 to give compounds of the composition PtL_2 . Two previously reported complexes, $Pt(MCO)_2$ and $Pt(PiPCO)_2$ were prepared for comparative studies of their properties with other complexes. The cyanoxime HBCO and isomeric 1NO-2OH and 2NO-1OH were prepared with a nitrogen-15 (~50 %) on the oxime group. In addition, Magnus Green Salt and Oxidized Tetracyanoplatinate were synthesized as standards for the photo-electrical emission and conductivity studies.
2. Eight new platinum complexes were characterized by means of IR, UV-visible spectroscopy, and elemental analysis on C, H, N content. Several ligands that included ^{15}N -label were examined using ^{13}C and ^{15}N NMR spectroscopy. The $Pt(2PCO)_2$ complex showed the most promising UV-visible spectra with a band around 675nm which is attributed to Pt...Pt interactions. The exact assignment of bands in the IR-spectra was carried out using ^{15}N -labeled ligands and their Pt-complexes. Thermal stability of metal complexes was evaluated.
3. Samples of $Pt(2PCO)_2$, $Pt(MCO)_2$, $Pt(2NO-1OH)_2$, $Pt(1NO-2OH)_2$, $Pt(BCO)_2$ and $Pt(PiPCO)_2$ were examined using dynamic light scattering. The results show that these complexes, to various degrees, form self-assembled large aggregates in solution over time.
4. Crystals structures were obtained for 6 compounds; $Pt(MCO)_2$ red form, $Pt(MCO)_2$ yellow form, $Pt(PiPCO)_2$ yellow form, 1NO-2OH, 2NO-1OH, and a charge transfer π complex consisting of 1NO-2OH and 1-naphtol. All the platinum complexes have a zig-zag 1D arrangement of the platinum centers. Only the red dimer of $Pt(MCO)_2$ had a Pt-Pt distance which is considered as direct intermetallic interaction. The red color of the crystal could be attributed to transitions between metal centers in the dimer.
5. The solid $Pt(MCO)_2$ complex does strongly emit at >1100 nm being excited at 800 nm. To the contrary, classic Magnus' Green Salt and oxidized Tetracyanoplatinates, which exhibit a direct Pt...Pt interactions, are not emissive at all. Finding of highly emissive properties of Pt(II) cyanoximates is very important for the purpose of creation of solid state NIR lasers and cell imaging.

Two major peer-reviewed publications with Michael Hilton:

- 1). Tyukhtenko, S.I.; Hilton, M.; Gerasimchuk, N. "Classic Isomeric 1,2- and 2,1-nitrosonaphthols are Oximes in Solid State and Solutions". *Current Inorganic Chemistry*, **2015**, 5 (2), 120-136.
- 2). Hilton, M.; Gerasimchuk, N.; Silchenko, S.; Charlier, H. , "Synthesis, Properties and Crystal Structure of the 2,4-dichlorophenyl-cyanoxime - a powerful carbonyl reductase inhibitor." *J. Chem. Crystallography*. **2013**, 43 (3), p.157-164.

Conference presentations with Michael Hilton:

46th Midwest Regional ACS Meeting (October 27-30, 2011; St. Louis, MO)

1. Hilton, M.*; Gerasimchuk, N.; Charlier, H. "Preparation, characterization and *Human Carbonyl Reductase* (HCBR) inhibition studies of 2,4-dichlorophenyl-cyanoxime, H(2,4-diCl-PhCO)." Poster presentation at the 46th Regional Meeting of the ACS joint Midwest and Great Lakes sections. October 27-30, St. Louis.

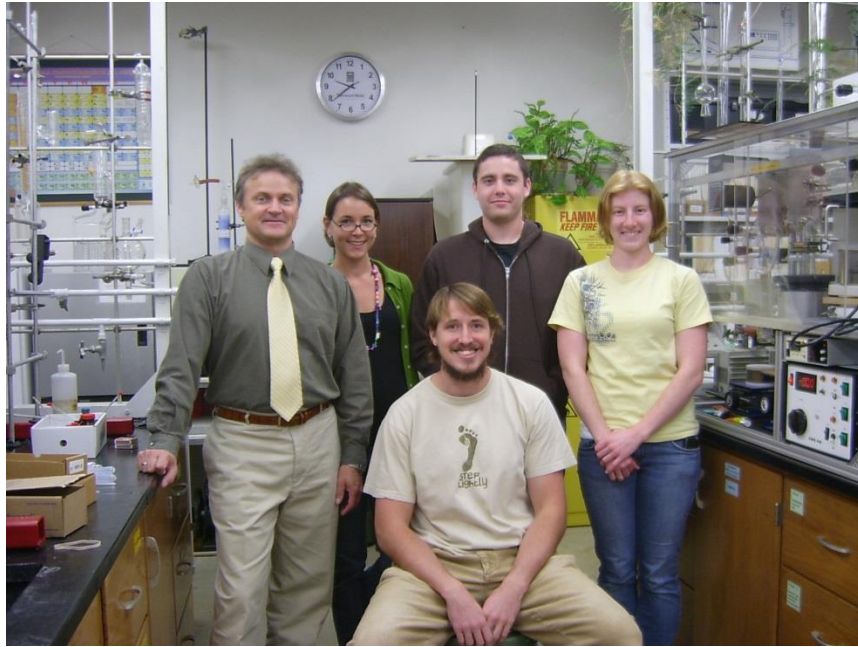
47th Midwest Regional ACS Meeting (October 24-27, 2012; Omaha, NE)

2. Hilton, M.*; Gerasimchuk, N. "Synthesis and characterization of 1D cyanoxime and nitrosonaphthol coordination complexes with semiconducting properties." Abstracts, 47th Midwest Regional Meeting of the American Chemical Society, Omaha, NE, United States, October 24-27 (2012), MWRM-434.

48th Midwest Regional ACS Meeting (October 16-19, 2013; Springfield, MO)

3. Hilton, M.*; Gerasimchuk, N. "Synthesis and characterization of 1D platinum cyanoximes and nitroso-naphthols coordination complexes with conducting properties". Abstracts, 48th Midwest Regional ACS Meeting, Springfield, MO. United States, October 16-19; MWRM-64.

2010: group picture in research laboratory.

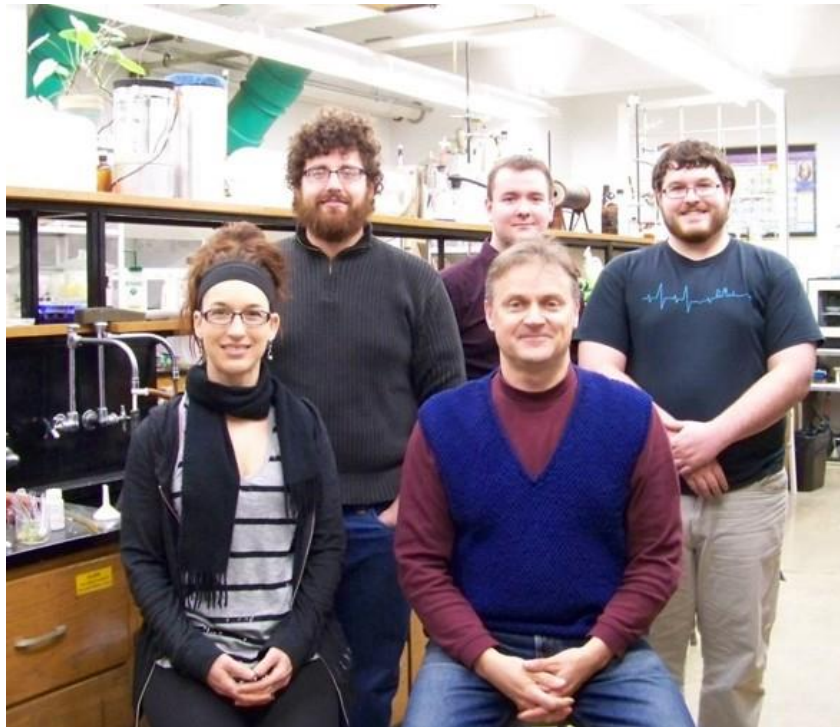


2011: travel to Bruker Users Meeting in Madison, Wisconsin.





2012: group picture in Temple 431 – research laboratory.



2014: group picture in Temple Hall break room.

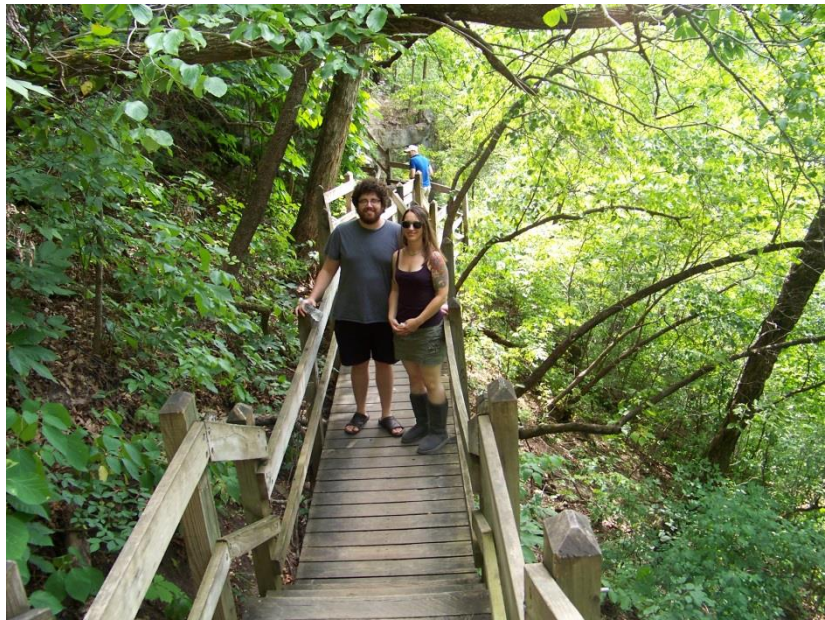


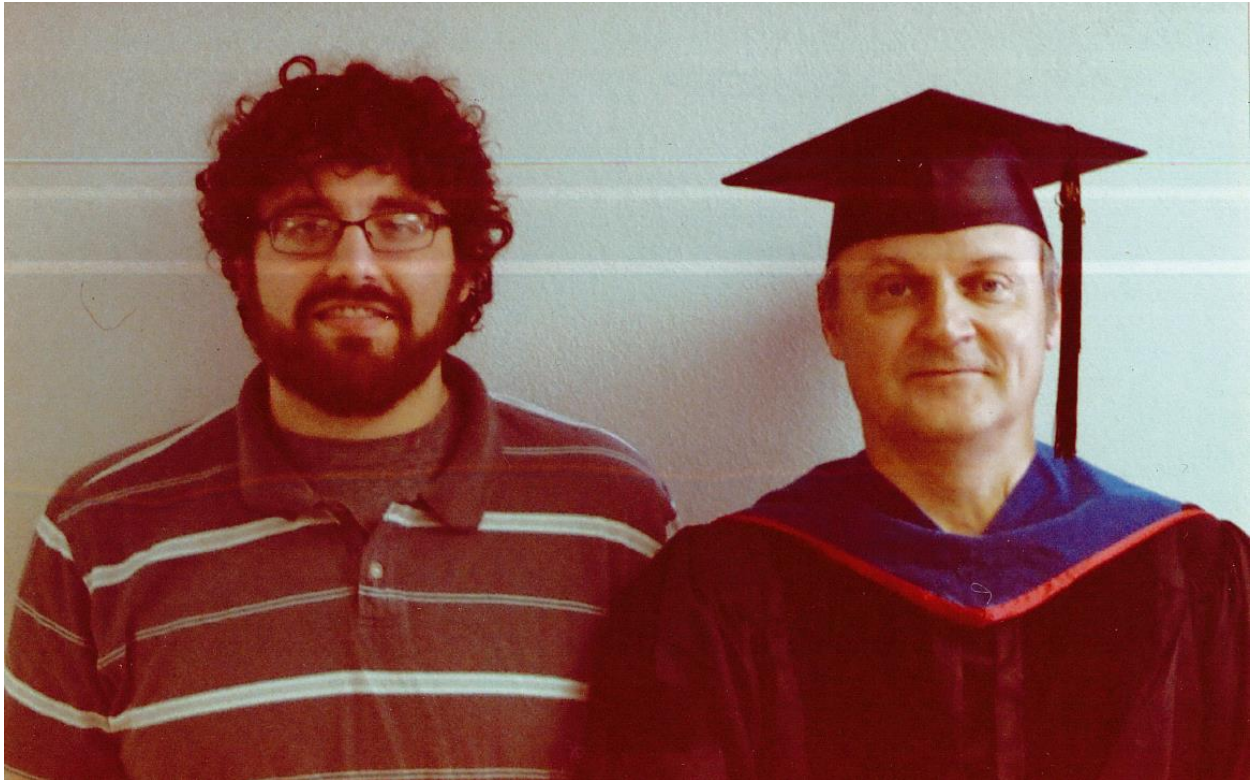
2014: research group summer trip to middle of Missouri – to Bridal Cave and Ha Ha Tonka State Park.





2014: Michael with his girlfriend Daniel Klaus!





Graduation!