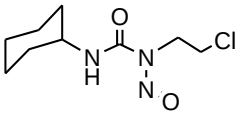
# Leon Goeden: MS 2005

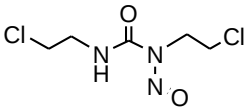
Thesis "The Synthesis, Characterization and Bilogical Activity Studies of Pt(II) and Pd(II) Disubstituted Arylcyanoximates."

Leon's research project was dedicated to the preparation of dihalogen-substituted arylcyanoximes, their Pd(II) and Pt(II) complexes and subsequent *in vitro* studies of complexes cytotoxicity against human solid tumor WiDR colon carcinoma cell line. His work is a continuation of our efforts to investigate a large group of previously unknown bivalent Pd and Pt complexes with oxime-based ligands that possess useful biological activity. In this context it is interesting to investigate possible synergistic effect or absence of thereof between the metal and the ligand. Figure 1 exhibits the most interesting examples of highly biologically active nitroso- and oxime- compounds. The cyanoximes are new class of low-molecular weight compounds that are capable of binding different metal ions (Figure 2), and currently 39 of these molecules are known and studied. The scope of Leon's work was to develop method of synthesis, prepare and characterize new dihalogen-substituted arylcyanoximes and some of their metal derivatives.

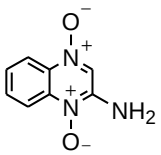
A



lomustine



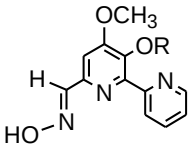
carmustine



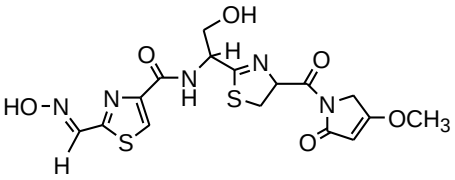
tirapazamine

B

***antibiotics:***

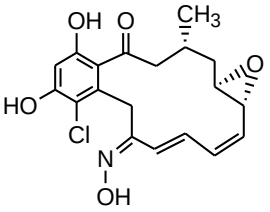


Caerulomycin *B* (R=H) and
Caerulomycin *C* (R=$CH_3$)



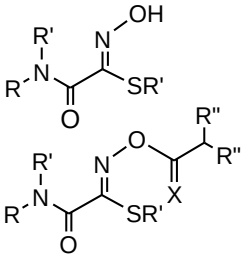
Althiomycin

***new anticancer drug:***



KF 25706

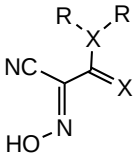
***incecticides:***



R, R' R'' = alkyl;
X = O, S

thioximes and their esters

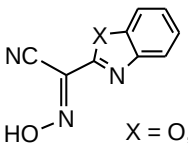
***growth regulating and antimicrobial agents:***



R = H, $CH_3$
X = O, S

amide-cyanoximes

***herbicide antidots:***



X = O, S, NH, N-$CH_3$

2-hetarylcyanoximes

**Figure 1.** **The N-nitroso compounds (A) and oximes (B) that show medico-biological importance.**

Thus, a series of new disubstituted halogenated arylcyanoximes was synthesized using nitrosation reaction of the respective phenylacetonitriles by $CH_3$-ONO at room temperature in isopropanol (Figure 3). Six synthesized colorless arylcyanoximes containing two F and/or Cl atoms at 2-, 4-, 5- and 6- positions were characterized by means of NMR, IR, UV-visible spectroscopy and $pK_a$ studies. Crystal structures were determined for four cyanoximes and revealed the presence of only the *syn*-isomers for fluorinated compounds in a solid state, while the chlorinated arylcyanoxime exists as *anti*-isomer in the crystal (Figure 4). However, five out of the six protonated arylcyanoximes HL exist as a mixture of *syn*- and *anti*- isomers in solutions (Figure 5A) that do not undergo interconversion contrary to other known non-aryl cyanoximes. Deprotonation of HL with $NaOC_2H_5$ in ether solutions leads to yellow NaL (Figure 5B, Figure 6) which were used as precursors for the synthesis of a series of monovalent Ag, Tl and bivalent Pd, Pt complexes. Seven palladium and platinum arylcyanoximates of $[M(HL)_2Cl_2]$ composition were synthesized and characterized. Obtained colored compounds are non-electrolytes in solution. However, in EtOH and DMSO solutions Pt(II) cyanoximates undergo two consecutive solvolysis reactions. First order rate constants were measured at 294 K for complexes in both solvents. Binding modes of the cyanoxime ligands and the possible solid state structures of the obtained coordination compounds are suggested on a basis of their IR spectra and MM-2 calculations (Figure 7). Because of their structural resemblance to the cisplatin family of anticancer drugs, synthesized Pd/Pt arylcyanoximates were tested *in vitro* against human colon carcinoma WiDr cell line using *cis*-$[Pt(NH_3)_2Cl_2]$ as positive control. Results showed that two Pd(II) and Pt(II) containing oximino(2,4-dichlorophenyl)acetonitrile exhibit cytotoxicity at 0.25 mM concentrations, which is ~15% of that for cisplatin at similar conditions.

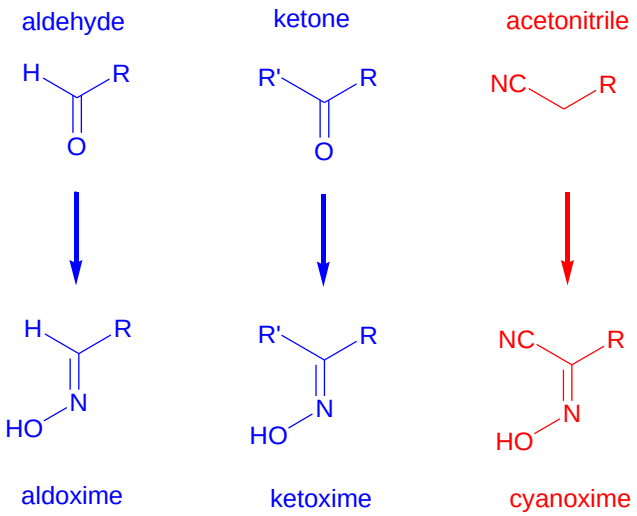



**Figure 2.** **Relationship between three known classes of oximes.**

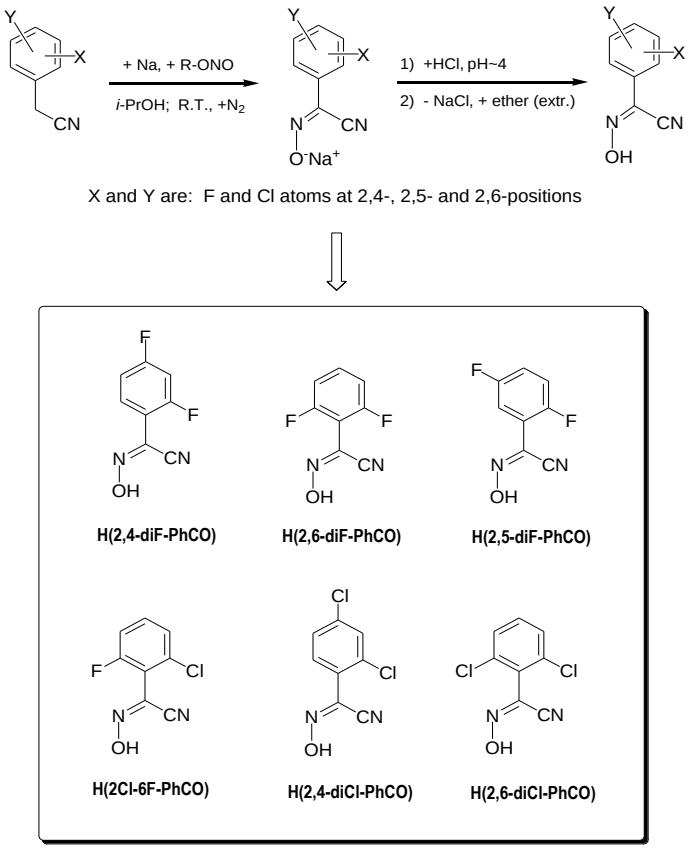



**Figure 3.** **Preparation of disubstituted arylcyanoximes and the list of cyanoxime ligands that were synthesized and studied by Leon Goeden during his research in the group.**

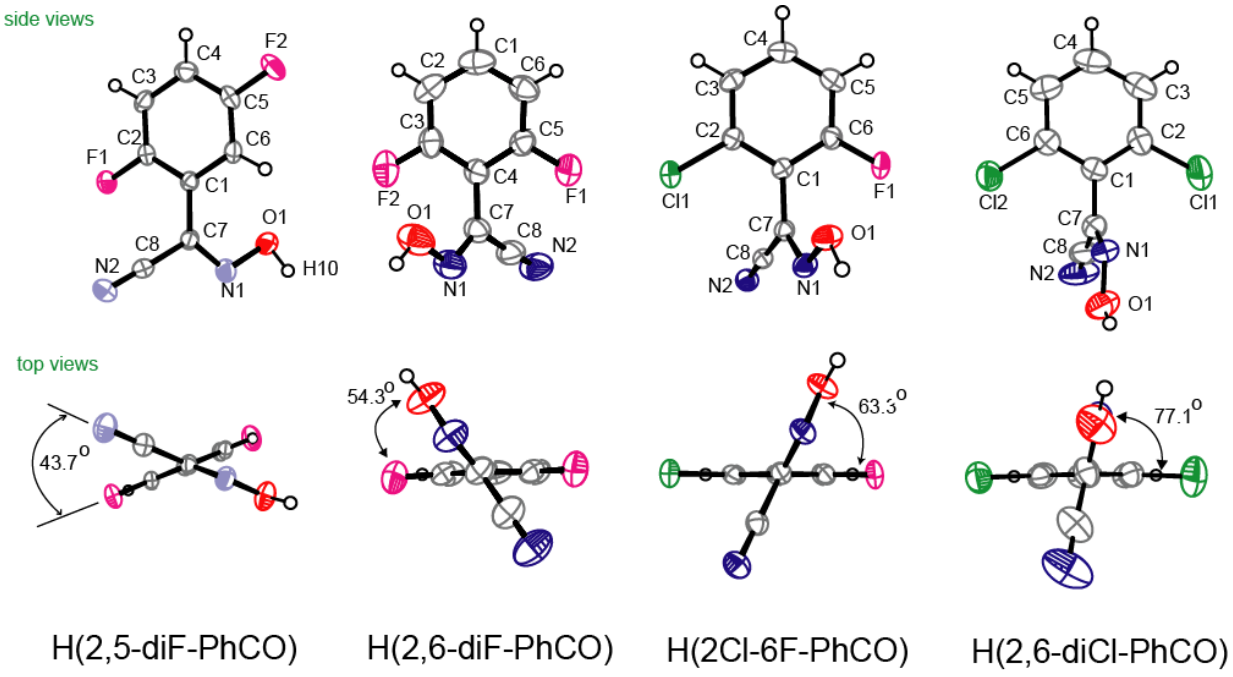



**Figure 4.** **Molecular structures of four out of six new dihalogen-substituted arylcyanoximes.**

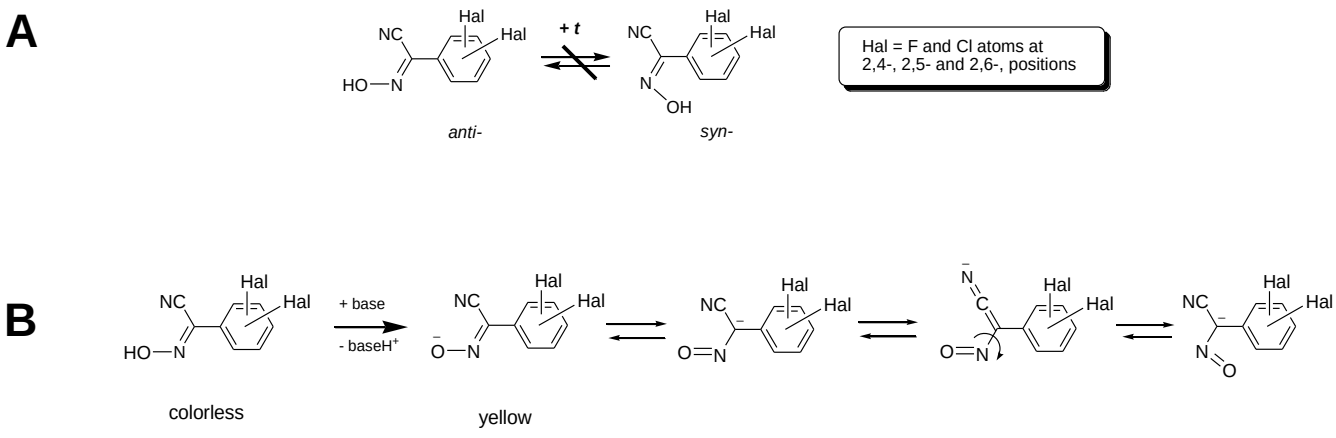
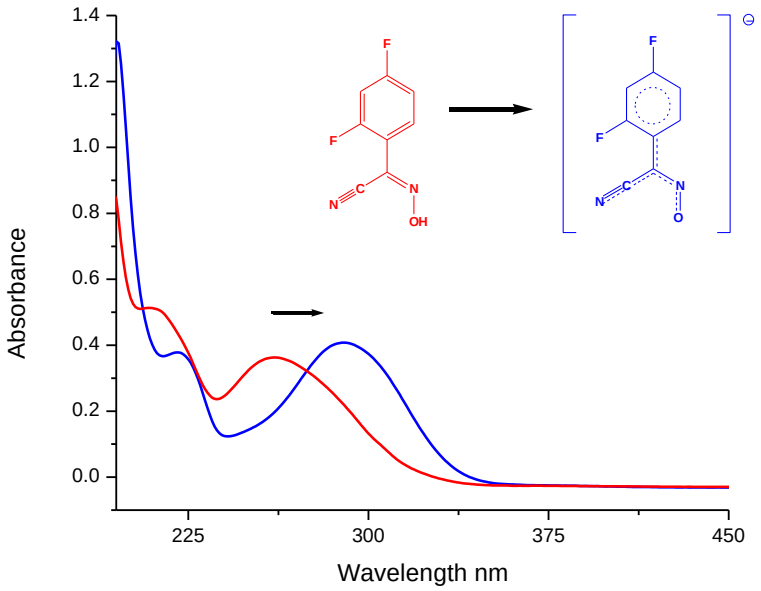



**Figure 5.** **Two geometrical isomers of disubstituted arylcyanoximes (A), and conformational flexibility + delocalization of negative charge throughout the anion (B).**

A




B

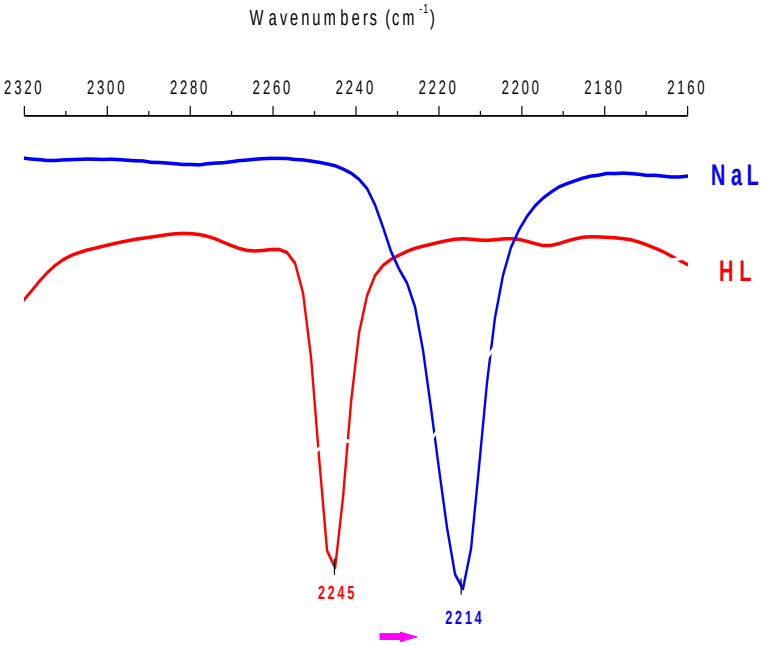
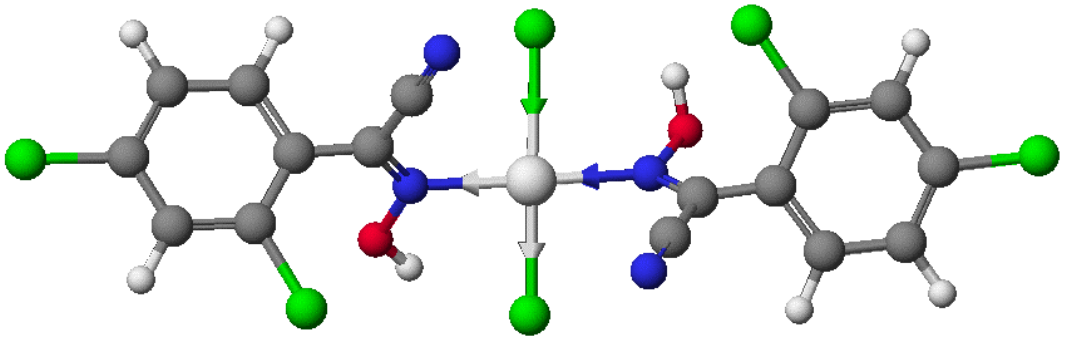



**Figure 6.** **A batochromic shift of bands in the UV-visible spectrum of $N(C_4H_9)_4^+L^-$ solution compared to that for HL (A), and low energy shift of and a low energy shift of the $\nu$(C≡N) in the IR spectra of solid samples of ionic sodium salts (B) compared to protonated HL. Both results evidenced charge delocalization in cyanoxime anions.**

A



B

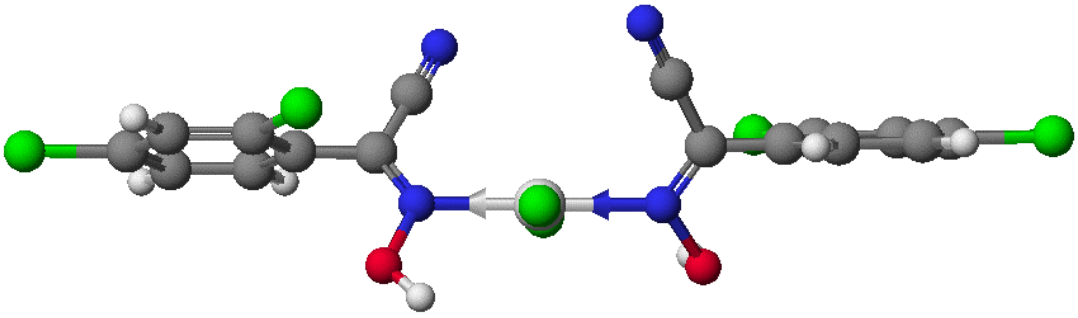


**Figure 7.** **MM-2 optimized geometry of [Pt{H(2,4-diCl-PhCO)}2Cl2]: A – top view, B – side view.**

Work of Leon Goeden in my research group has resulted in one major publication:

1) Gerasimchuk, N.; Goeden, L.; Durham, P.; Barnes, C.; Cannon, J.F. "Synthesis and Characterization of the First Disubstituted Arylcyanoximes and their Several Metal Complexes." *Inorganica Chimica Acta*, **2008**, *361*, p.1983-2001.

and in 4 presentations at the regional and national meetings of the American Chemical Society:

1. Goeden, L., Barnes, C., Gerasimchuk, N.N. "Preparation and studies of disubstituted arylcyanoximes and their Tl(I) and Ag(I) coordination compounds." Proceedings of 38th Midwest Regional Meeting of the ACS; p. 188; Columbia, MO, 2003.

2. Goeden, L., Gerasimchuk, N., Barnes, C., Cannon, J. F. "Preparation and studies of disubstituted arylcyanoximes and their bivalent platinum and palladium complexes." Proceedings of 39th Midwest Regional Meeting of the ACS; p. 292; Manhattan, KS, 2004.

3. Gerasimchuk, N.; Durham, P.; Goeden, L.; Abbey, M.; Bowen, E.; Eddings, D. "Synthesis, characterization and anticancer activity studies of several Pd(II) and Pt(II) cyanoximates." Proceedings of 40th Midwest Regional Meeting of the ACS; p.52. Joplin, MO, 2005.

4. Goeden, L., Cannon, J., Barnes, C., Gerasimchuk, N. "Synthesis of new disubstituted arylcyanoximes and their transition metal complexes". Inorganic chemistry section, poster presentation. Fall 228 ACS Meeting, August, 22-26th 2004, Philadelphia, PA.

***Graduation DAY!***


Presentation at the National ACS Meeting in Philadelphia, PA (2004)


Presentation at the Regional ACS Meeting Columbia, MO (2003)


Working on MS thesis presentation.

A photo at the bench where he spent 4 years doing undergraduate and graduate research.