Tiffany Maher: MS 2004

Thesis "Synthesis, characterization and Anti-cancer properties of Organotin(IV) Cyanoximates"

Tiffany's research project was dedicated to preparation of series of cyanoxime ligands that possess a variety of interesting features that allow investigations of "structure-activity" relationship in a group of similar molecules. For example, 9 molecules that she made and studied represent a spectrum of hydrophilic/lyophilic compounds that also exhibit a range of steric factors, ability to form intermolecular H-bonds or π-stacking interactions (Figure 2). Organotin part of Tiffany's complexes was chosen to be dibutyltin, leaving sufficient space around the metal center to accommodate cyanoxime anions. Predominantly dibutyltin(IV) compounds have shown a very significant cytotoxicity against numerous human cancer cell lines and yet very small general toxicity as compared to the cisplatin – [Pt(NH₃)₂Cl₂] - leading metal based anticancer drug. Established places of interaction of inorganics with the DNA are shown in Figure 1.
In recent years, numerous organotin(IV) derivatives have exhibited remarkable cytotoxicity against several types of cancer. However, the properties of the cyanoxime-containing organotin(IV) complexes are unknown. Previously it has been shown that cyanoximes displayed an interesting spectrum of biological activity ranging from growth-regulation to antimicrobial and pesticide detoxification actions. The work presented here attempts to combine the useful properties of both groups of compounds and investigate the likely antiproliferating activity of the new substances. A series of 19 organotin(IV) complexes, with nine different cyanoxime ligands, were anaerobically prepared by means of the heterogeneous metathesis reaction between the respective organotin(IV) halides (Cl, Br) and ML (M=Ag, Tl; L=cyanoximate anion), using an ultrasound in the CH$_3$CN at room temperature. The compounds were characterized using spectroscopic methods (UV-visible, IR, $^1$H, $^{13}$C NMR, $^{119}$Sn Mössbauer) and X-ray analysis. The crystal structures of the complexes revealed the formation of two types of tin(IV) cyanoximates: mononuclear five-coordinated compounds of R$_{4-x}$SnL$_x$ composition (R=Me, Et, n-Bu, Ph; x = 1, 2; L= cyanoximate anion), and the tetranuclear R$_8$Sn$_4$(OH)$_2$O$_2$L$_2$ species (R=n-Bu, Ph). The latter complex contains a planar [Sn$_4$(OH)$_2$O]$_2^{2-}$ core, consisting of three adjacent rhombs with bridging oxo- and hydroxo- groups. The tin(IV) atoms are five-coordinated and have distorted trigonal-pyramidal surrounding. This is the first instance when the organic anions were found to act as monodentate O-bound planar oxime ligands. All compounds were studied in vitro for antiproliferating activity, using human cervical cancer HeLa and WiDR colon cancer cell lines; cisplatin was used as a positive control substance. The two dibutyltin(IV) cyanoximates showed cytotoxicity similar and greater to that of cisplatin.
Figure 1. Schematic drawing of the DNA showing places of action of inorganic or physical cytotoxic agents such as metal complexes and radiation.
Figure 2. The list of cyanoxime ligands that were synthesized and studied by Tiffany Maher in her research.
Figure 3. Developed in our research laboratory high-yield Mayer reaction for the synthesis of cyanoximes from substituted acetonitriles.

Figure 4. Synthetic route used for the preparation of organotin(IV) cyanoximates.
Figure 5. UV-visible spectra anionic cyanoximates as NBu₄⁺ salts. A – methanol solutions in the region of $\pi \rightarrow \pi^*$ transition; 0.5 mM solutions, 1 mm cell pathlength. B – DMF solutions in visible region showing $n \rightarrow \pi^*$ solvent dependent transitions; 5 mM solutions, 1 cm cuvette pathlength.
Figure 6. Fragment of molecular structure of highly cytotoxic Sn₄Bu₈(OH)₂O₂(ACO)₂. The butyl groups are thermally disordered, and only first carbon atoms attached to the metal are shown.

Figure 7. Molecular structure of Sn₄Ph₈(OH)₂O₂(ACO)₂, ether solvate: A – side view showing practically planar Sn₄(OH)₂O₂ core, B – top view.
Work of Tiffany Maher in my research group has resulted in one major publication:


and 3 presentations at the regional and national meetings of the American Chemical Society:


Graduation DAY!

[Image of two graduates smiling]

Graduation DAY!
A family picture from the laboratory.

With supportive family.