Proposal for EPSCoR Student Internships

**Project title: Analysis of X-ray Data for Modeling the Chemical Bonding between Iron and Oxygen in Hemoproteins. Investigator: Charles J. Simmons (Chemistry)**

In 1964 Weiss argued in a letter to *Nature* that the bonding of iron and oxygen in hemoproteins (hemoglobin and myoglobin) is such that the iron is oxidized from Fe(II) to Fe(III), the O$_2$ becoming essentially a superoxide ion, O$_2^{-}$; Pauling, however, rebutted Weiss’s argument by positing that Fe remains Fe(II), i.e., it is not oxidized, and O$_2$ is formally neutral.

This fifty-year old plus controversy between these two extremely different models has never been resolved satisfactorily and still rages on in the chemistry and biochemistry communities today. Although the X-ray crystal structures of both oxymyoglobin and oxyhemoglobin have been determined, the resolution of the data is insufficient to distinguish between the two models because the molecules are simply too large. Although chemists have synthesized a few smaller, model compounds that mimic the active sites of these macromolecules, the accuracy of the data is mediocre due to poor crystal quality. Nonetheless, three years ago chemists at the University of Notre Dame reported (*J. Am. Chem. Soc.* 2013, 135, 15627) the crystal structure of an iron model compound that has a O-O bond length of 1.281 (12) Å and a Fe-O-O bond angle of 118.2(9)$^\circ$. Their result was a major step forward; however, they reported accurate structural data for only one such compound, which, because of its four ‘picket fence’ groups sticking up and out of the porphyrin ring, has only a limited resemblance to the active sites in hemoproteins; furthermore, they made only a passing comment concerning the nature of the bonding between Fe and O$_2$, probably because they realized that they did not have enough accurate structural data.

For the past 35 years, beginning with my post-doc at Cal. Tech in 1980, I have been involved in synthesizing and determining the structures of oxygenated cobalt compounds that mimic the active sites in these macromolecules. I obtained a $750,000 MBRS-NIH grant in 2000, my first year at UHH, to study these compounds using X-ray diffraction. My X-ray diffraction lab, obtained largely with those funds, is functioning and is the only such facility in the State (below).

During the four year grant period (2000-2004), my students and I determined the structures of about 40 such compounds, obtaining a virtual ‘gold mine’ of data. However, for various reasons I did not do much with the data until I saw the results from Notre Dame last year and realized that by combining their results with mine I would be able to resolve this long-standing and very important controversy (*vide infra*). During my recent sabbatical leave (Fall 2015 semester), I
went back and looked very carefully at my original data, obtaining a better understanding of these molecules. Obtaining a UHH seed grant (2015-2016) and some funds from Dean Brown (April 2016) allowed me to collect more data; in addition, a ‘gift’ of $500 from Dr. Platz this month will allow one final ‘push’ to obtain even more data. (Synthesizing these compounds was facilitated because I kept many of the original reactants in storage.)

As a compass to the progress of my current research, consider the following plot of O-O bond lengths (Å) vs. charge (q) for the isolated species O$_2^+$, O$_2$, O$_2^-$, O$_2^{2-}$ using the most accurate structural data available in the literature (NIST); the data can be fit nearly perfectly ($R^2 = 0.999$) with a simple quadratic polynomial. (Note: the bond length for the peroxide dianion, O$_2^{2-}$, was obtained from the Cumming’s group at MIT only last week; it represents the closest approximation yet to the actual value for a truly isolated O$_2^{2-}$ species.) Putting the average O-O bond length obtained for my oxygenated cobalt models, 1.300(1) Å, and 1.281(12) Å from Notre Dame, into the equation gives q values of -0.70 e$^-$ for Co(O-O) and -0.55 e$^-$ for Fe(O-O), indicating that the actual chemical bonding between Fe and O$_2$ is nearly exactly between the Weiss and Pauling models, resulting in a polite diplomatic ‘toss up.’ THESE ARE VERY IMPORTANT RESULTS AND ESSENTIALLY RESOLVE THE CONTROVERSY.

Alas, a comprehensive understanding of the bonding between Fe/Co and O$_2$, however, is still lacking, as the interactions between O$_2$ and its surroundings must be further understood before I can write-up the results for publication. And it is this part of the puzzle that will involve a lot of number crunching and data analysis that are the main reasons (in addition to concerns for my health) to solicit EPSCoR funding for student help. I am requesting funds to support two students, preferably chemistry majors, to perform data analysis, number crunching and create various plots using Surfer 7 in the X-ray lab under my direct supervision. Specifically, the students will use existing crystallographic software programs and a program that I wrote to do these relatively simple but time consuming computations. They can be taught how to do this work within about two hours and I had two UHH students do similar computations this past year. With their help, this project can be completed and the results write-up for publication in the immediate future.