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14. ABSTRACT
This project sought to employ heme-containing metal-organic framework (MOF) materials to carry out the oxidative degradation of small molecules that serve as models of chemical warfare agents. Both gas- and solution-phase experiments were be pursued, using oxidants such as molecular O-atom transfer agents and gaseous dioxygen. These initial studies included characterization of the first porphyrin iron(IV) oxo species within a MOF and the first example of a iron(I) porphyrin within a MOF. Future work is geared toward using these reactive species to catalyze the oxidative degradation of chemical warfare agents and simulants.

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a. REPORT	b. ABSTRACT	c. THIS PAGE			Thomas Harris
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Report Title

Final Report: Heme-Containing Metal-Organic Frameworks for the Oxidative Degradation of Chemical Warfare Agents

ABSTRACT

This project sought to employ heme-containing metal-organic framework (MOF) materials to carry out the oxidative degradation of small molecules that serve as models of chemical warfare agents. Both gas- and solution-phase experiments were be pursued, using oxidants such as molecular O-atom transfer agents and gaseous dioxygen. These initial studies included characterization of the first porphyrin iron(IV) oxo species within a MOF and the first example of a iron(I) porphyrin within a MOF. Future work is geared toward using these reactive species to catalyze the oxidative degradation of chemical warfare agents and simulants.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Received		Paper
04/14/2016	1.00	Audrey T. Gallagher, Margaret L. Kelty, Jesse G. Park, John S. Anderson, Jarad A. Mason, James P. S. Walsh, Shenell L. Collins, T. David Harris. Dioxygen binding at a four-coordinate cobaltous porphyrin site in a metal–organic framework: structural, EPR, and O, Inorg. Chem. Front., (04 2016): 536. doi: 10.1039/C5QI00275C
TOTAL:	**1**	

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

Received		Paper
TOTAL:		

Number of Papers published in non peer-reviewed journals:

(c) Presentations

Number of Presentations: 0.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received Paper

TOTAL:

Number of Manuscripts:

Books

Received Book

TOTAL:

Received	Book Chapter

TOTAL:

Patents Submitted

Patents Awarded

Awards

Alfred P. Sloan Research Fellowship

Graduate Students

NAME	PERCENT_SUPPORTED	Discipline
Audrey T. Gallagher	0.05	
FTE Equivalent:	**0.05**	
Total Number:	**1**	

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
Ie-Rang Jeon	0.40
Jung Yoon Lee	0.40
FTE Equivalent:	**0.80**
Total Number:	**2**

Names of Faculty Supported

NAME	PERCENT_SUPPORTED	National Academy Member
T. David Harris	0.00	
FTE Equivalent:	**0.00**	
Total Number:	**1**	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED	Discipline
Magaret Kelty	0.05	
FTE Equivalent:	**0.05**	
Total Number:	**1**	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period:	1.00
The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:.....	1.00
The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:.....	1.00
Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):.....	1.00
Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:.....	0.00
The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense	0.00
The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:	1.00

Names of Personnel receiving masters degrees

NAME

Total Number:

Names of personnel receiving PHDs

NAME

Total Number:

Names of other research staff

NAME PERCENT_SUPPORTED

FTE Equivalent:
Total Number:

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

See Attachment

Technology Transfer

Heme-Containing Metal-Organic Frameworks for the Oxidative Degradation of Chemical Warfare Agents

Statement of the problem studied

As an alternative method for the degradation of harmful chemical species, we have sought to oxidatively decompose chemical warfare agents through the generation of powerful oxidizing species in metal-organic frameworks. In designing a synthetic system with the ability to oxidatively decompose chemical warfare agents such as mustard gas and VX nerve gas, inspiration has been derived from a family of oxidase enzymes known as cytochrome P450. This class of enzymes can catalyze a wide range of reactions through the generation of a highly reactive high-valent terminal iron oxo intermediate. Many oxidase enzymes employ a catalytic cycle similar to the one shown in Figure 1, in which an O_2 molecule rapidly reacts with a ferrous heme center followed by a one electron reduction to form an Fe^{III}-peroxo species. The Fe^{III}-peroxo intermediate will then react with two protons from the surrounding solvent environment, breaking the O-O bond to form an Fe^{IV}-oxo π-radical cation species with the concurrent loss of water. The reactive Fe^{IV}-oxo π-radical cation species then activates C-H bonds, transferring an O-atom and forming a hydroxylated product. While there have been a large number of advancements in the development of synthetic systems that mimic the function of these oxidase enzymes, molecular systems suffer from deleterious bimolecular condensation reactions that result in the formation of catalytically inert oxo-bridged Fe_2 complexes.[1] In order to overcome the challenges associated with generating these reactive species in molecular form, we have utilized a porphyrinic based metal-organic frameworks to rigidly isolate reactive centers, precluding bimolecular reactivity and enabling the isolation and study of intermediates with an oxidative potential necessary for the decomposition of chemical warfare agents.

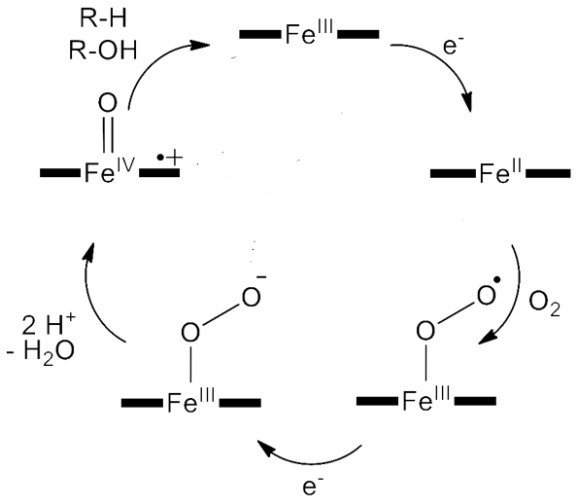

Figure 1. The oxidase cycle of many cytochrome P450 enzymes indicating the activation of C-H bonds via a

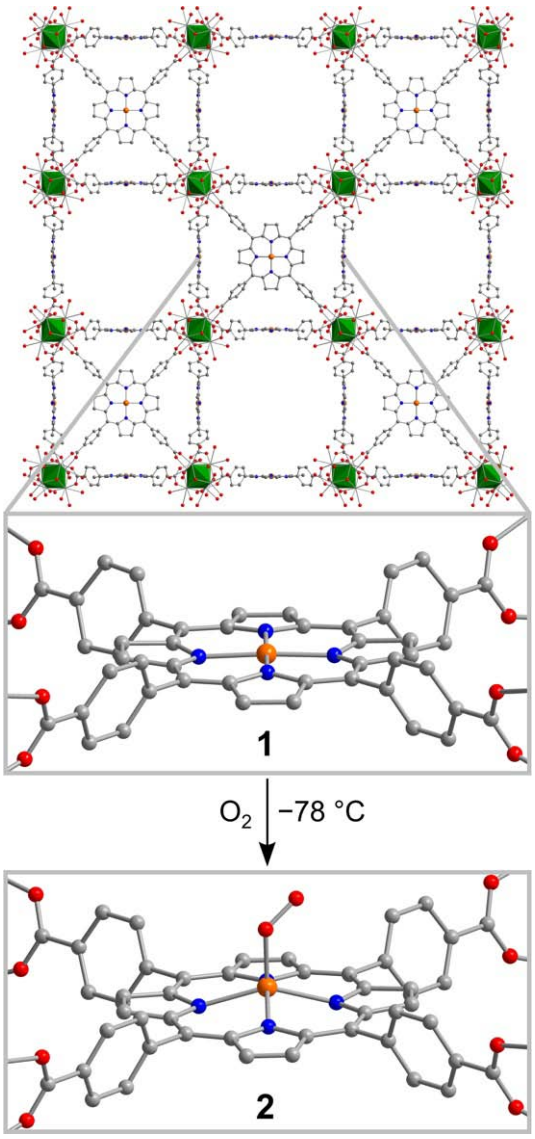

Figure 2. Reaction of PCN-224Fe with O_2 at −78 °C to form PCN-224FeO_2. Green octahedra represent Zr atoms; orange, blue, red, and gray spheres represent Fe, N, O, and C atoms, respectively; hydrogen atoms are omitted for clarity.

Summary of the most important results

Initial efforts have focused on generating reactive intermediates in the metalated form of the porphyrinic framework, **PCN-224**.[2] **PCN-224** is a robust framework featuring tetracarboxyphenylporphyrin organic linkers connected through Zr_6O_8 based clusters (Fig. 2). Several characteristics make **PCN-224** an ideal candidate for these studies; firstly, **PCN-224** is stable under a wide pH and temperature range, has large tetragonal channels of 19 Å for the facile diffusion of substrates, and lastly, a large crystallite size enables characterization via single crystal X-ray diffraction. Indeed, we have utilized this framework to isolate a rare 5-coordinate heme-dioxygen adduct at low temperature, which had previously eluded structural and spectroscopic characterization in the molecular form.[3] **PCN-224** can be metalated with Fe^{II} to yield a 4-coordinate ferrous heme-containing compound, **PCN-224Fe^{II}**, which then binds O_2 at −78 °C to give a 5-coordinate heme-O_2 complex. Variable-temperature O_2 adsorption data of **PCN-224Fe^{II}** enabled quantification of the Fe-O_2 interaction, providing a binding enthalpy of −34(4) kJ/ mol. This value is nearly half of that observed for comparable ferrous heme model complexes and in myoglobin, demonstrating the importance of an axial ligand in biological O_2 binding.[4] These results demonstrate that that rigid solid-state structure MOF, enables the isolation and thorough characterization of species that have only been observed transiently in molecular form.

Having isolated the heme-O_2 adduct in **PCN-224Fe^{II}**, current work is now geared towards generating the reactive Fe^{IV}-oxo intermediate and exploring its subsequent reactivity. Towards this aim, we have sought to generate the Fe^{IV}-oxo through a number of synthetic routes. The first strategy, and the one most relevant to the catalytic cycle of cytochrome P450, is to target low valent iron species in order to form the Fe^{III}-peroxo intermediate followed by the eventual protonation of the O_2^{2-} fragment with the simultaneous loss of water. Due to the thermal liability of the O_2 adduct, attempts to reduce the **PCN-224FeO_2** complex were performed at low temperature by soaking **PCN-224FeO_2** in a solution of THF and excess $CoCp_2$ (Cp = $\eta_5C_5H_5$) at −78 °C. However, as judged by Mössbauer spectroscopy, the low temperature reaction requirements prevented full diffusion of the reductant into the framework, resulting in a mixture of species. The next route involves reducing the parent **PCN-224Fe^{II}** and then exploring its subsequent reactivity with O_2. Following molecular precedent, soaking **PCN-224Fe^{II}** in a THF solution with an excess $CoCp^*_2$ (Cp* = (Cp = $\eta_5C_5(CH_3)_5$)

results in the formation of new species with a distinct UV/Visible spectrum, consistent with the formation of the reduced **PCN-224Fe^{I}** complex (Fig. 4). In addition, there is a significant change in the Mössbauer spectrum upon going from the ferrous state to the one-electron reduced product of **PCN-224Fe^{I}** with parameters similar to what has previously been reported for molecular iron(I) heme complexes.[5] Additionally, soaking **PCN-224Fe^{II}** in a solution of THF and an excess of the strong reducing agent, $NaC_{10}H_8$ results in a UV/Visible spectrum distinct from both the ferrous state and the one electron reduced **PCN-224Fe^{I}**, and is suggestive of the formation of the two-electron reduced state **PCN-224Fe^{0}** by comparison to molecular analogues. Current work is now geared towards adding O_2 to the reduced analogues, PCN-224Fe^{I} and PCN-224Fe^{0} to form the oxo following a similar catalytic cycle as cytochrome P450.

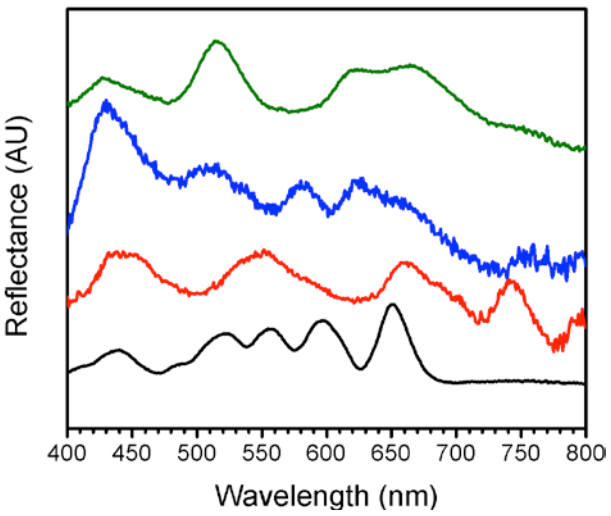

Figure 3. UV/Visible spectrum of PCN-224 (black), PCN-224Fe^{II} (red), PCN-224Fe^{I} (blue) and PCN-224Fe^{0} indicating the formation of four distinct species.

In addition to generating the oxo in **PCN-224Fe^{II}** through O_2 activation, we have also used various oxygen atom transfer agents to include peroxides such a *m*-CPBA (*m*-chloroperoxybenzoic acid), iodosylbenzene as well as O_3 (ozone). In this route, we have metalated **PCN-224** with $FeCl_3$ to form **PCN-224FeCl**. Following molecular precedent, we have soaked **PCN-224FeCl** in solutions of MeCN and excess *m*-CPBA or iodosylbenzene at various temperatures (–78 °C, –35 °C, and 25 °C) however, these reactions have consistently resulted in the formation of a high spin Fe^{III} species, likely the Fe^{III}–OH as suggested by Mössbauer spectroscopy. Similar results are observed when gaseous O_3 is added to **PCN-224FeCl**. We believe that Fe^{IV}-oxo species is transiently formed during the reaction, but due to its inherent reactivity, quickly decomposes to the thermodynamically stable Fe^{III}–OH. In order to improve the stability of the oxo without sacrificing its inherent reactivity, we have synthesized a new framework featuring fluorinated groups in the ortho positions of the phenyl rings. Molecular studies concerning the stability of the porphyrin Fe^{IV}-oxo have indicated that electronegatively substituted Fe^{III} porphyrin compounds such as F_{20}TPPFe^{III}Cl are not only oxidatively robust, but also, provide steric protection for the Fe^{IV}-oxo intermediate, making them good model compounds for cytochrome P450 relative to their unsubstituted porphyrin analogues.[6] **PCNF$_2$-224** was synthesized using tetracarboxy-2,6-difluorophenylporphyrin as the organic linker and post synthetically metalated with $FeCl_3$ to yield **PCNF$_2$-224FeCl** (Fig. 4). Initial attempts to generate the Fe^{IV}-oxo were monitored by in situ diffuse reflectance UV/visble spectroscopy of **PCNF$_2$-224FeCl** with the slow addition of O_3. Treating **PCNF$_2$-224FeCl** with O_3 at –40 °C resulted in the appearance two distinct bands at 640 nm and 686 nm, these features can be attributed to the formation of a π-radical cation on the porphyrin ligand, suggesting the formation of Fe^{IV}-oxo porphyrin π-radical cation (Fig. 4). Notably, the stability of the Fe^{IV}-oxo at –40 °C implies that this species in more stable in the MOF than the molecular congener, which has only be observed at –80 °C. Current work is now geared towards thoroughly characterizing the highly reactive Fe^{IV}-oxo as well as exploring its potential for O-atom transfer chemistry.

While efforts to isolate the oxo are ongoing, we have also attempted to observe C-H bond activation and O-atom transfer by the in situ generation of the Fe^{IV}-oxo intermediate. Due to the oxidative potential of Fe^{IV}-oxo, we have targeted a series organoposphorous containing nerve agents that can be particularly challenging to degrade.[7] When examining the structure of VX nerve type agents, it is clear that there are a number functional groups that maybe susceptible to oxidative degradation by a highly reactive Fe^{IV}-oxo intermediate. As such, current work is now geared towards the hydroxylation of C-H bonds and O-atom transfer to thioether and amine functionalities. Preliminary work has involved using model compound, diethylmethylphsphonate to monitor the potential for C-H bond activation of the methyl substituent by a transiently formed Fe^{IV}-oxo porphyrin π-radical cation. While the most common methods for the degradation of diethylmethylphsphonate have focused on the hydrolysis of the ethoxy functional groups, the generation of the high-valent iron-oxo would provide an accessible route for the hydroxylation of the methyl group via the radical rebound mechanism observed in many oxidase enzymes (see Fig. 6).[7]

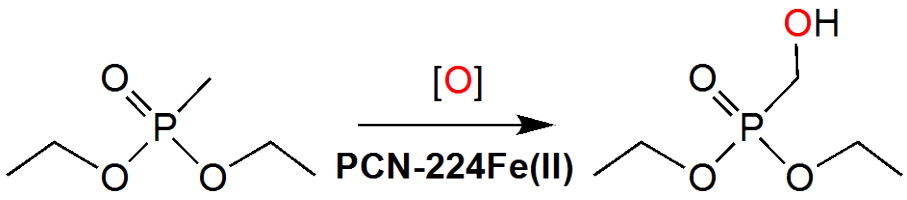

Figure 6. Proposed reaction scheme for the C-H bond activation of the methyl substituent on diethylmethylphsphonate by an Fe^{IV}-oxo poprhyrin π-radical cation.

Towards this aim, **PCN224-Fe^{II}** was soaked in a solution of diethylmethylphsphonate in benzene at 25 °C, the reaction was then purged with O_2 to generate the **PCN-224FeO_2** complex. ^{31}P NMR of the reaction mixture suggested the formation of ethoxy hydrolyzed product rather than the expected transformation of the methyl group. The hydrolysis of the ethoxy groups could have arisen from either their reaction with the hydroxyl groups on the zirconium clusters of **PCN-224** or from the generation of the Fe^{III}–OH upon the reaction of O_2 at room temperature in the presence of exogenous solvent. While initial efforts have focused on using the activation of O_2 in order to from the Fe^{IV}-oxo species, we have also used various O-atom transfer agents to include *m*-CPBA and iodosylbenzene to transiently form the Fe^{IV}-oxo intermediate. However, soaking **PCN-224FeCl** or **PCN-224Fe^{II}** in MeCN solutions of *m*-CPBA or iodosylbenzene at

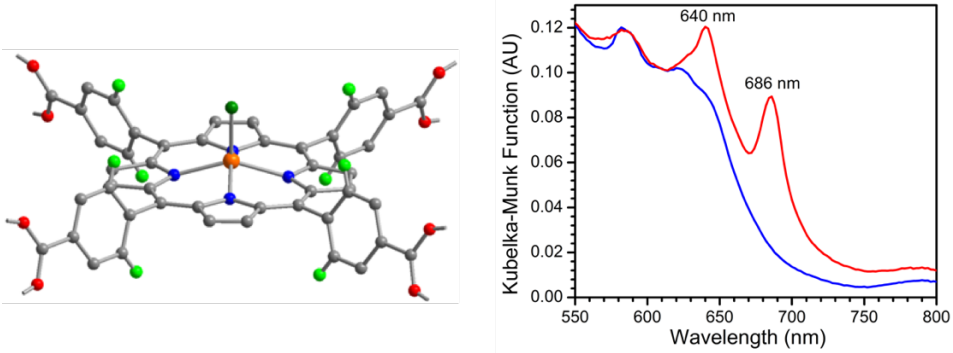

Figure 4. Left: crystal structure of $PCNF_2$-224FeCl highlighting the addition of electron withdrawing groups in the ortho positions of the phenyl rings. Orange, blue, red, gray, bright green, and dark green represent Fe, N, O, C, F, and Cl respectively; hydrogen atoms omitted from clarity. Right: Diffuse reflectance UV/visible spectroscopy illustrating the reaction of $PCNF_2$-224 (blue trace) with O_3 at –40 °C to from $PCNF_2$-224Fe^{IV}O (red trace).

various temperatures (−78 °C, −35 °C, and 25 °C) in the presence of diethylmethylphsphonate results in the formation of the same hydrolyzed ethoxy product.

We hypothesize that the challenges associated with observing the Fe^{IV}-oxo in the MOF are related to our attempts to generate this highly reactive species in the solution, where exogenous solvent can readily react with a transiently formed Fe^{IV}-oxo, resulting in what we believe to be the Fe^{III}−OH. To prevent the formation of the Fe^{III}−OH, future work will involve utilizing the recently synthesized framework **PCNF_2-224** to generate the high valent iron-oxo through the use of O_3. This route is particularly attractive because it offers (1) a method to generate a more stable Fe^{IV}-oxo by the introduction of electron withdrawing groups into the porphyrin scaffold and (2) a route to generate the Fe^{IV}-oxo from gaseous O_3, opening the doors for the degradation nerve agents in the gas phase. In addition, having isolated the reduced iron complexes, **PCN-224Fe^{I}** and **PCN-224Fe^{0}**, we will now have the opportunity to explore their reactivity with dioxygen to form the nucleophilic peroxo complexes. The nucleophility of the Fe-peroxo, makes these species especially suitable for the degradation of electrophilic phosphorous center, leading to the cleavage of P-S or P-O bond present in VX nerve agents.

Bibliography

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