Design and Synthesis of a Novel Tetraphenylporphyrin-based Metal-Organic Framework for Photodynamic Therapy and Drug Delivery

Landon Carter[1,2], Seth Barrett[3], Joseph Falkowski[2,3], Sophie Liu[2,3], Wenbin Lin[3,4]
[1]North Carolina School of Science and Mathematics; [2]Massachusetts Institute of Technology
[3]University of North Carolina – Chapel Hill; [4]University of Chicago

Abstract

In recent years, cancer has become the third leading cause of death in the world, and its prevalence and severity cannot be overstated. Photodynamic therapy (PDT) has been shown to be an elegant, precisely controllable, and non-invasive treatment for cancer. Fluorescence imaging has also recently arisen as an effective imaging technique to identify tumors more accurately and completely than white light, leading to earlier detection and an overall decrease in cancer recurrence in patients. In this study, I have designed and synthesized two novel and tunable 5,15-bis(4-methoxycarbonylphenyl)-10,20-diphenylporphyrin based metal-organic frameworks, and have demonstrated them to be highly crystalline and porous. I have designed tests to evaluate their potential applications in PDT, drug delivery, and fluorescence imaging, and have shown them to exhibit favorable properties for use in all of these cancer treatments and diagnoses. I have shown that one of the ligand precursors has an activation wavelength closer to the near-IR window of tissue transparency than all existing photosensitizers approved for use in the US according to a 2009 review article[1]. This indicates that this photosensitizer could be used to extend the range of cancers PDT is capable of treating by allowing light to penetrate deeper into the body.

(1) O'Connor, A. E.; Gallagher, W. M.; Byrne, A. T. *Photochemistry and Photobiology* **2009**, *85*, 1053-74.

Introduction

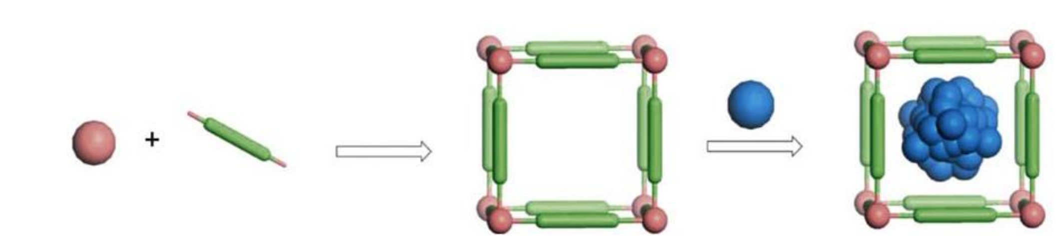


Figure 1: General MOF formation and drug molecule integration. Only one repeating unit is shown for clarity.[4]

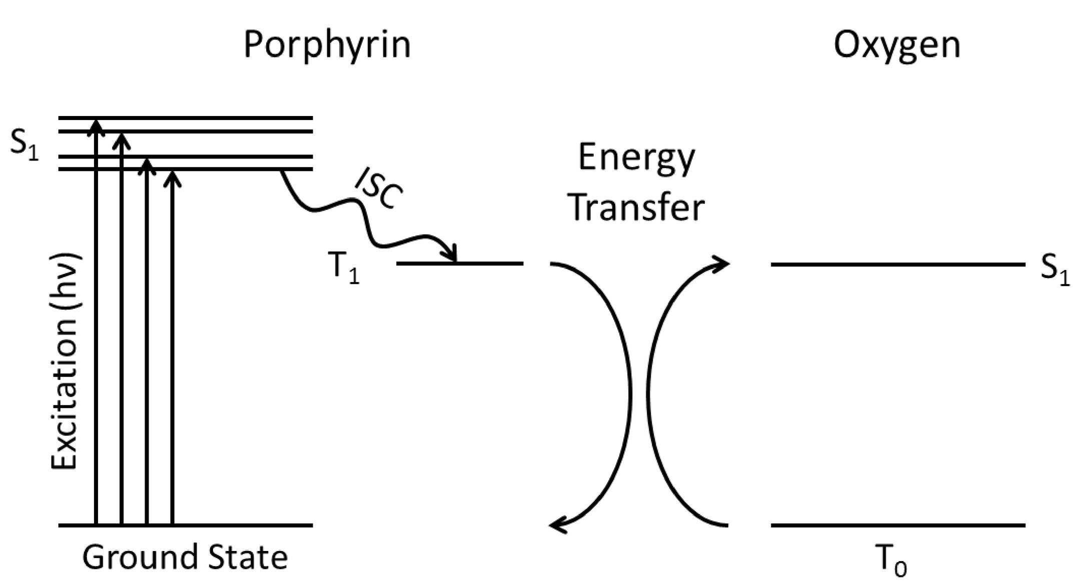


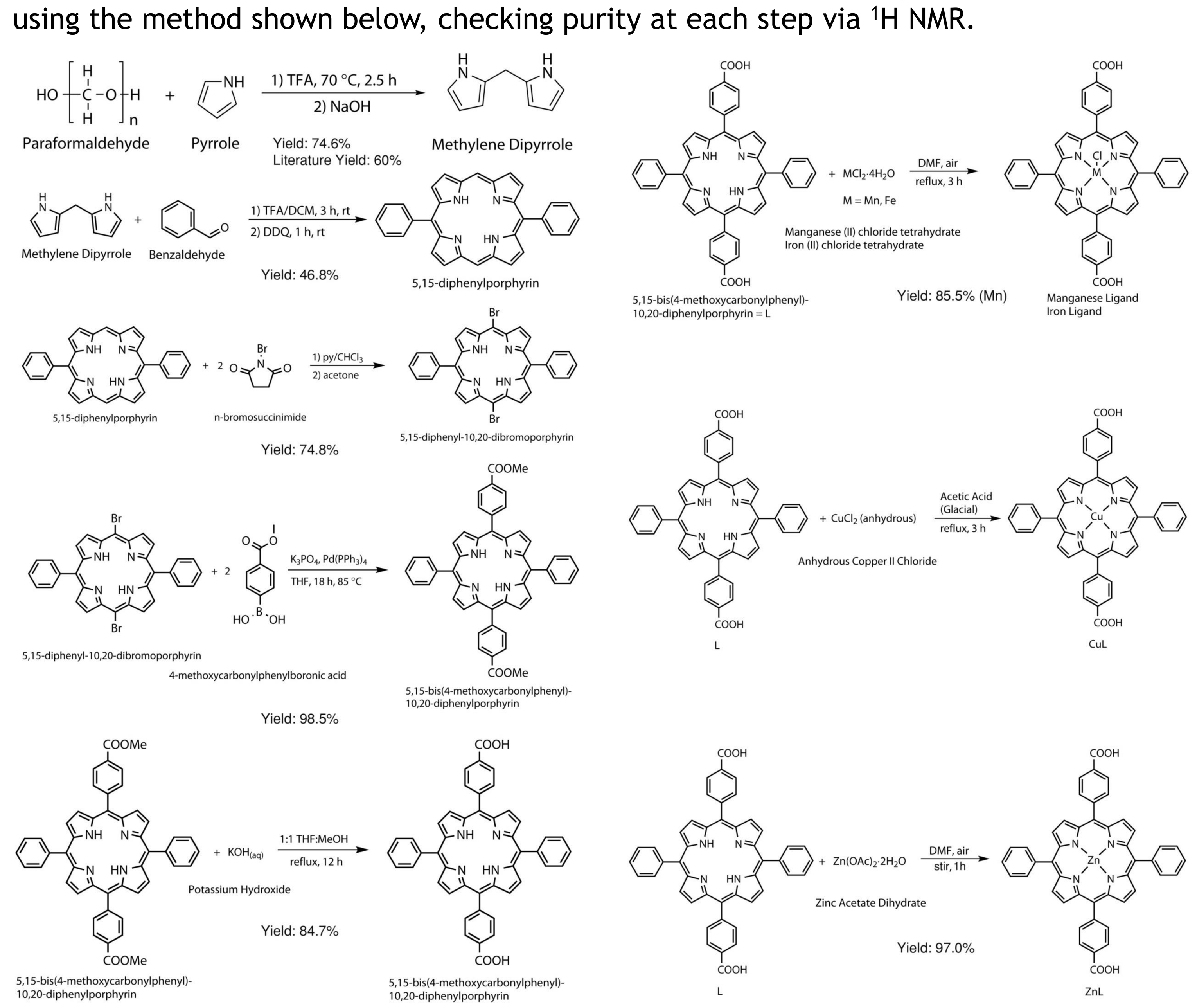
Figure 2: Graphical depiction of the photophysical mechanism behind singlet oxygen production in PDT.

Motivation

Porphyrins are currently used as photosensitizers in photodynamic therapy, and recent research has shown metal-organic frameworks to have good promise for use in drug delivery. By combining the two, we aimed to create an engineered structure for use in both photodynamic therapy and drug delivery. Reaction scheme was selected for high yields and simple reactions. A new procedure for testing singlet oxygen production for photodynamic therapy was implemented that is cheaper, requires less specialized equipment, and requires less training and specialized lab space.

Synthesis

Synthesis of 5,15-bis(4-methoxycarbonylphenyl)-10,20-diphenylporphyrin was completed using the method shown below, checking purity at each step via ^{1}H NMR.



Once the various ligands were synthesized, MOFs were grown by combining $ZrCl_4$ with the ligand in DMF and TFA, then heating to 100 °C for ~120 h.

$$L_x + ZrCl_4 \xrightarrow[100\ °C]{DMF,\ TFA} MOF \qquad L_x = L,\ MnLCl,\ FeLCl,\ CuL,\ ZnL$$

Analysis

Structure Determination

- PXRD taken for both phases of Mn MOF, Zn MOF, and a control MOF growth with unmetallated ligand.
- Single crystal XRD taken for one phase of Mn MOF and matching phase of Zn MOF.

Photophysical Analysis

- UV-Vis of metallated and unmetallated ligands taken in DMSO.
- Provides valuable insight into potential use in PDT (maximum absorption wavelength).
- Fluorescence emission spectra taken in DMSO.
- Provides valuable insight into potential use as a fluorescent dye.

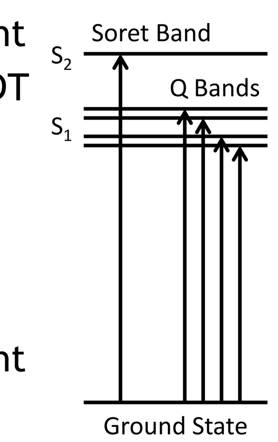


Figure 2: Graphical depiction of the electronic transitions responsible for the UV-Vis spectra of porphyrins.

Methyl Violet Oxidation

- Tests for potential applications in PDT.
- Replace cells with representative organic molecule – methyl violet.
- Mix methyl violet with ligands in water.
- Monitor concentration of methyl violet via UV-Vis.
- Illuminate samples with wavelength of most redshifted absorption peak.

Results

Photophysical Analysis

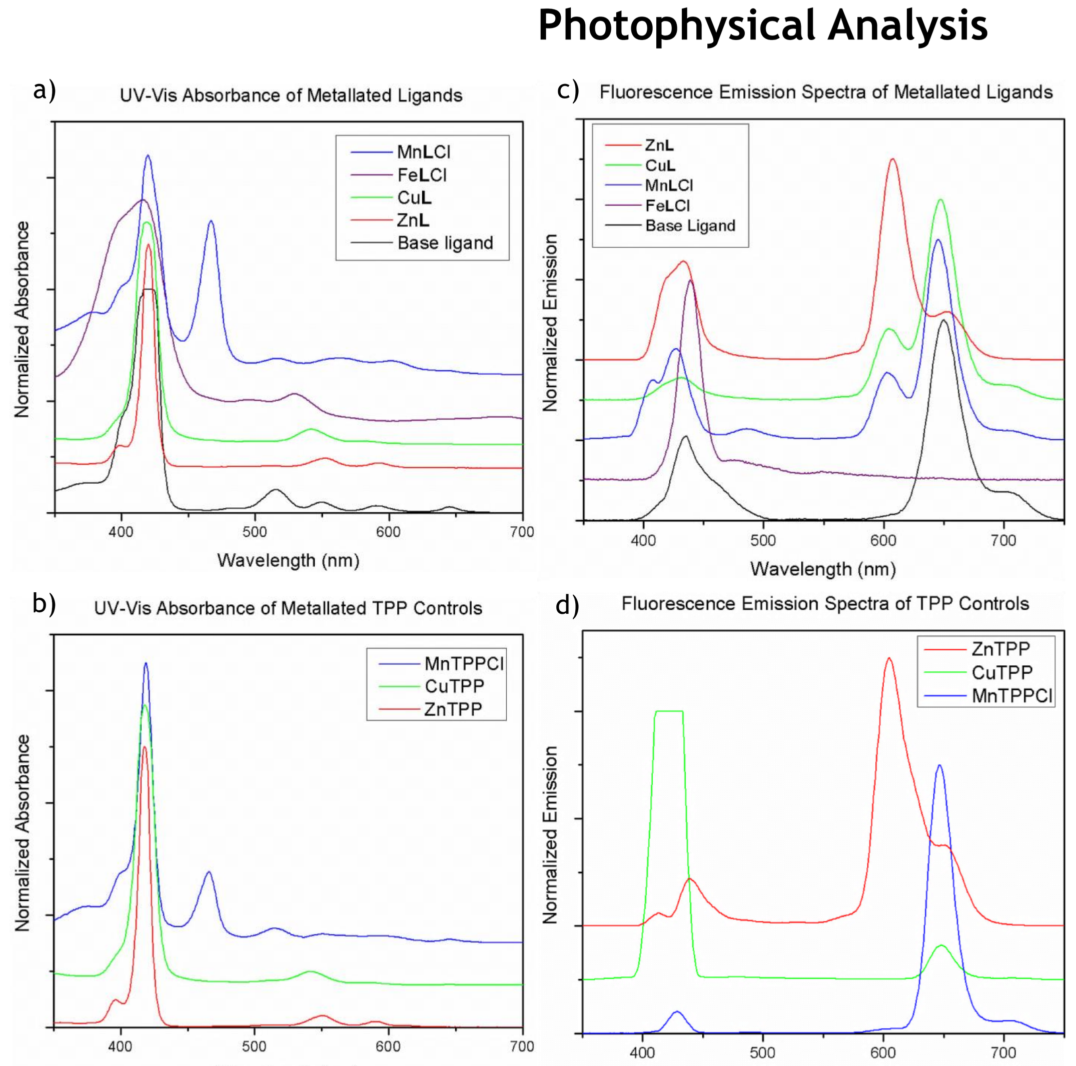


Figure 3: Results of photophysical analysis on ligands and controls (tetraphenylporphyrin – TPP). UV-Vis (a-b) shows how the Q bands (500-700 nm) collapse due to restored symmetry in the metallated porphyrins, as well as the shifting of the absorption wavelength closer to the optimal range, especially in FeLCl.
In (c-b), the fluorescence measurements show the possibility of using these ligands as fluorescent dyes, for all ligands except FeLCl. This is as expected due to the low energy first excited singlet state of FeLCl, leading to optimal absorption for PDT but an energy level too low in energy for decay in the form of fluorescence – instead, it decays non-radiatively.

Methyl Violet Oxidation

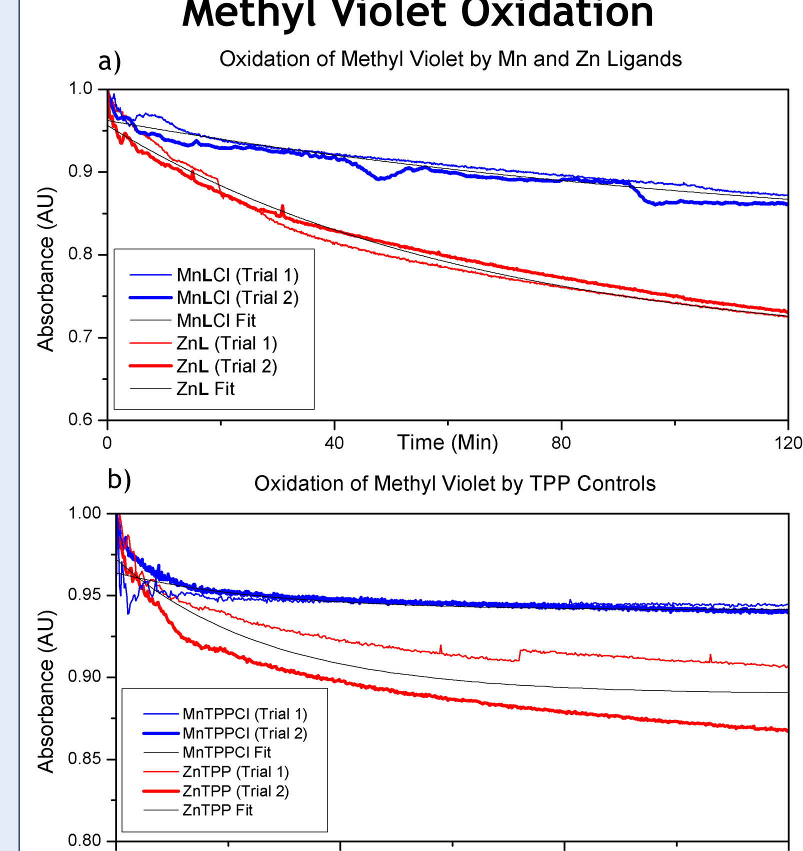


Figure 4: Results of PDT representative studies in methyl violet oxidation, showing that ZnL was most effective. This was predicted due to Zn's higher T_1 state lifetime and the carboxylic acid groups of the ligand increasing quantum efficiency.

Results (continued)

Structure Determination

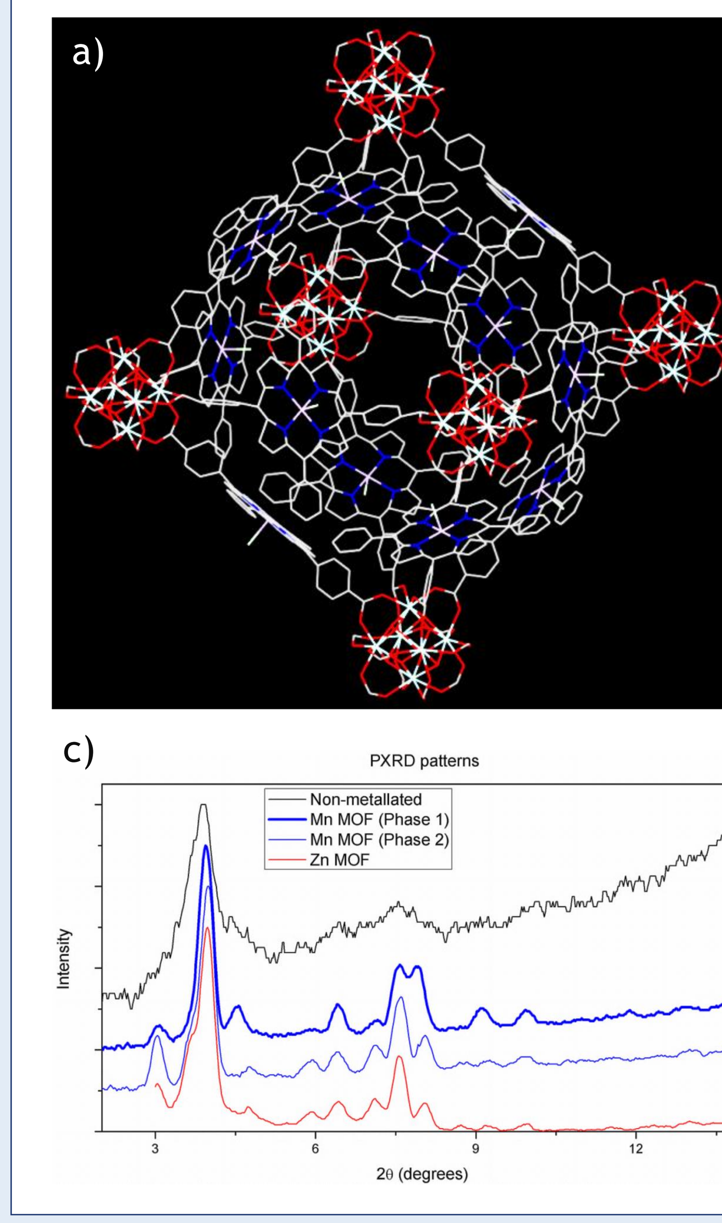


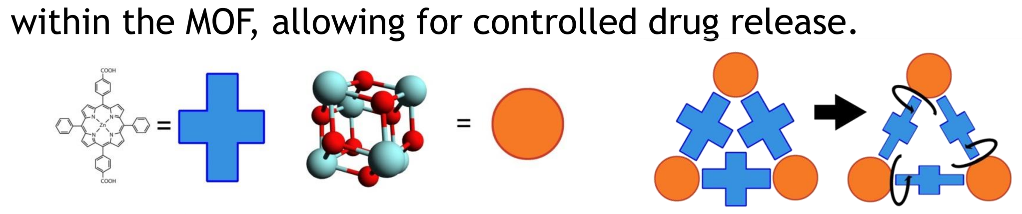
Figure 5: Results of structure determination studies on MOFs. In (a), from single-crystal X-ray diffraction patterns, we see that the MOF takes on an octahedral repeat unit, and based on PLATON calculations (b), we have calculated 70% pore-accessible volume. In (c), PXRD patterns for MOFs, show that Mn MOF has at least two phases, and Zn MOF is isostructural to one of the phases of the Mn MOF. Moreover, the non-metallated MOF is not very crystalline. The common phase is shown in (a).

Discussion & Future Work

Fluorescence Imaging
- All ligands except FeLCl are highly fluorescent.

Photodynamic Therapy
- Methyl violet studies suggest efficient production of ROS.
- UV-Vis spectra show good activation wavelengths (near NIR range).

Drug Delivery
- PLATON calculations suggest possibility for high loading efficiencies.
- Currently some solubility issues, possibly addressed in future work.
- From single crystal structure determination, a porphyrin ring rotation mechanism is proposed to allow creation of channels within the MOF, allowing for controlled drug release.



Future Work
- Photophysical MOF studies
- Silica coating or Zn growths
- Drug uptake and release study
- Ligand modification

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