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Transmetallation of a Lithium Porphyrin with Iron(II)

Kidus Debesai

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Faculty Sponsor

Abstract:

Synthesis and characterization of the iron(III) derivative of the 2,3,7,8,12,13,17,18-octabromo-meso-tetrakis(N-methylpyridium-4-yl)porphyrin was accomplished via metal metathesis of the lithium porphyrin and iron(II) ion. Preliminary molecular orbital analysis of the iron(II) and iron(III) derivatives demonstrate that the iron(III) porphyrin exists at a lower energy state.

INTRODUCTION

Porphyrins have been considered among the most important molecules and have been studied extensively because of their major role in oxygen transport (heme), photosynthesis in plants (chlorophyll), and their oxidation and reduction capabilities in biological systems.¹ Figure 1 below represents the simplest structure of a porphyrin, porphine. Porphyrins are cyclic organic compounds with four pyrrole rings. The structure and function of porphyrins can be changed by replacing the beta and gamma carbons with various substituents and replacing the core protons with metal ions.

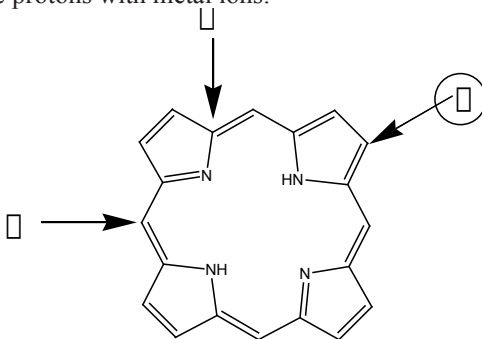
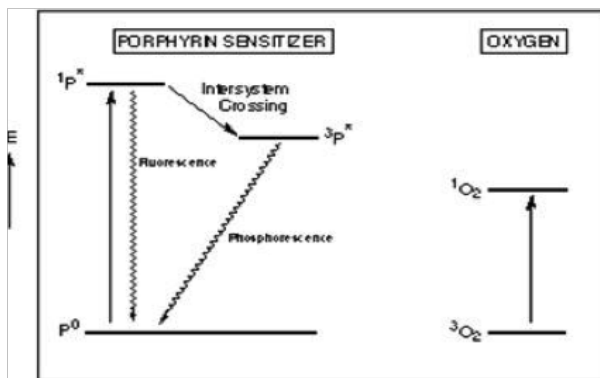


Figure 1. Structure of the simplest porphyrin, porphine

Since iron porphyrin plays a central role in biological systems, the study of iron porphyrin has been a major component of porphyrin investigations.² Aside from their function as heme, iron porphyrins have been implicated in several medicinal applications such as the photodynamic therapy (PDT) of cancers.³ Scheme 1 shows the first process of photosensitization.

Transmetallation of a Lithium Porphyrin with Iron(II)



Scheme 1: PDT sensitization (vibrational levels omitted)

In the presence of light, some porphyrins excite ground state triplet state (3O_2) oxygen to the excited state, singlet state (1O_2). Singlet state oxygen is highly toxic and has the potential to destroy the cancer cells or tumors by reacting irreversibly with cellular bodies. This approach shows much promise in the non-invasive treatment of cancer. However, for PDT to be effective, photosensitizers must absorb light at wavelengths that can penetrate target tissue (> 630 nm) and efficiently transfer energy to the dioxygen agent.³

MOTIVATION

We recently reported on the synthesis of a novel gadolinium(III) porphyrin for application as a contrast agent for magnetic resonance imaging (MRI) and as a PDT agent.⁴ We have extended our studies to the iron(III) porphyrin derivative since iron porphyrin complexes could provide the optimal conditions required as a photosensitizer including (a) low cytotoxicity; (b) selectivity for tumor cells; (c) light absorption at long wavelengths; (d) ability to photosensitize triplet oxygen to the singlet species; (e) robustness in the presence of the reactive singlet oxygen species; (f) oxygen aqueous solubility in injectable fluids; and (g) ease of synthesis.⁵

MATERIALS AND METHODS

meso-tetrakis(N-methylpyridium-4-yl)porphyrin 4-toluenesulphonate ($H_{21}MPyPTos$) was purchased from Frontier Scientific, Inc. Bromine (Br_2), dimethylformamide [$(CH_3)_2NCHO$], copper(II) acetate ($Cu(OAc)_2 \cdot 2H_2O$), iron(II) chloride ($FeCl_2$), 2-propanol, methanol, ammonium hexafluorophosphate (NH_4PF_6), diethyl ether, lithium hexafluorophosphate ($LiPF_6$), sodium hydroxide

(NaOH), n-butylammonium chloride ($n\text{Bu}_4\text{Cl}$), and acetone [$(\text{CH}_3)_2\text{CO}$]. All other reagents were purchased from Sigma Aldrich and used without further purification. Absorption spectroscopy was performed on a Shimadzu UV-2401PC. Molecular orbital diagram modeling was conducted using the Amsterdam Density Functional Software program (ADF 2010) by Scientific Computing and Modeling.

EXPERIMENTAL

Synthesis of $\text{H}_2\text{TMPyPBr}_8(\text{PF}_6)_4$: The starting material, $\text{H}_2\text{TMPyP}^{4+}$, was characterized by absorbance spectroscopy and showed an absorbance spectrum that was diagnostic of porphyrin (Figure 1). The octabrominated freebase porphyrin, $\text{H}_2\text{TMPyPBr}_8^{4+}$, was prepared as the PF_6^- salt via bromination of the copper derivative using a procedure reported by Richards *et al.*⁶

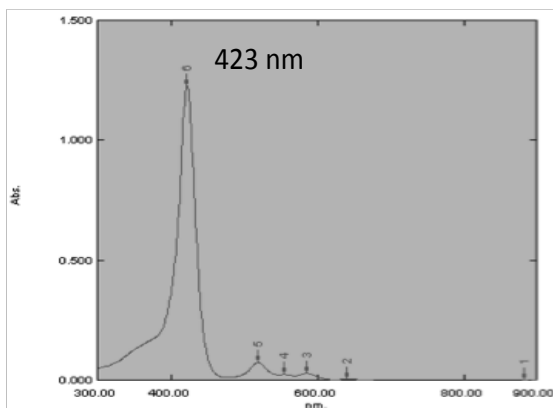
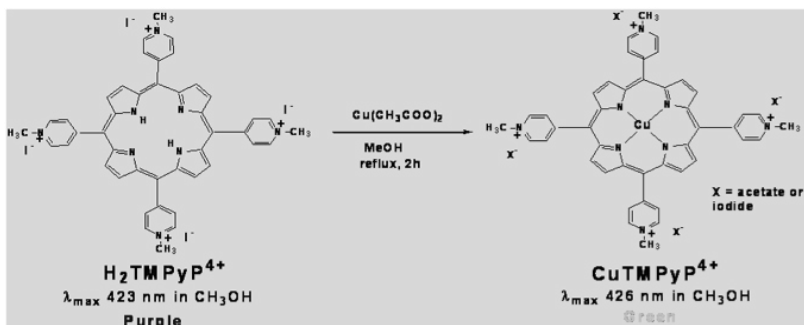


Figure 1. Absorption spectrum of $\text{H}_2\text{TMPyP}^{4+}$ at pH 7

First, CuTMPyP^{4+} was synthesized by mixing 0.252 g $\text{H}_2\text{TMPyP}^{4+}$ and 0.251 g $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ in a 27 mL methanol:water solution (25:2.5 v/v). The rust-brown mixture was heated to $\sim 50^\circ\text{C}$ for 1 hr and the crude copper(II) porphyrin derivative was isolated by removing the solvent via simple distillation (Scheme 2). Then, the solid was washed with small aliquots of 2-propanol (total 7.5 mL) and the brown solid was collected.

Transmetallation of a Lithium Porphyrin with Iron(II)



Scheme 2: Insertion of Cu²⁺ ions

The absorption spectrum was consistent with formation of the Cu(II) complex (Figure 2).

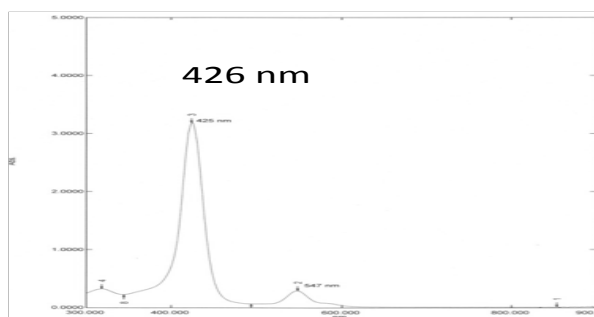
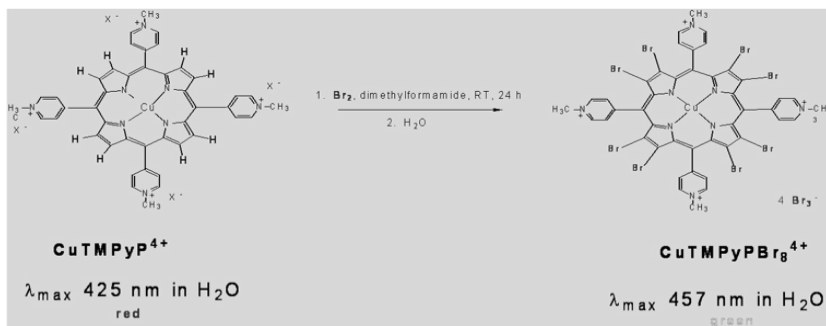


Figure 2. UV-Vis spectrum of CuTMPyP⁴⁺ in H₂O

A bromine solution (0.5 mL in a 10 ml DMF) was added drop-wise for 30 minutes at room temperature to 10 mL DMF containing 0.159 g of the copper porphyrin. The solution turned green upon addition of bromine and was stirred for 12 h to ensure completion of reaction. The reaction was quenched by addition of 30 mL water. A green precipitate was collected by suction filtration, washed with water (3 aliquots of 5 mL each) and air-dried (Scheme 3).



Scheme 3: Bromination of β -pyrrole carbons

The absorbance spectrum shifted from 425 nm to 456 nm, indicating that octabromination had occurred (*Figure 3*).

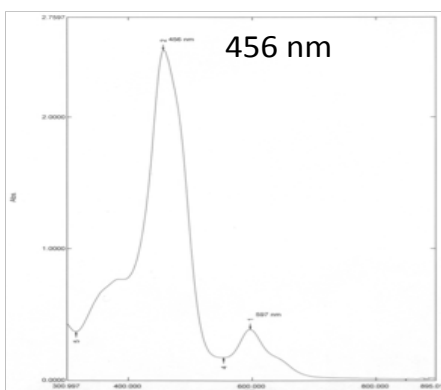
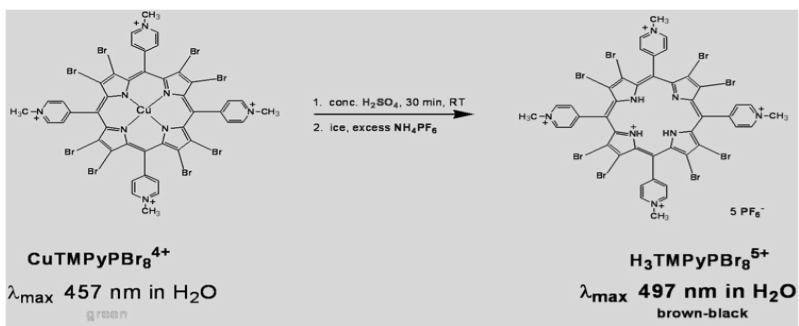


Figure 3. Absorption spectrum of CuTMPyPBr_8^{4+} at pH 7

The free-base octabrominated porphyrin, $\text{H}_2\text{TMPyPBr}_8^{4+}$, was synthesized by demetallating the Cu(II) complex. Exactly 0.221 g CuTMPyPBr_8^{4+} was added slowly to 7.5 mL of concentrated sulfuric acid cooled to 10°C. The solution turned orangish-gold immediately. The solution was stirred for 2 hr and poured over ~100 g of ice. After all the ice had melted, excess NH_4PF_6 (~3.5 g) was added and green tinsel-like crystals precipitated. The solid was washed with 20 mL of diethylether/propanol (1:1 v/v) solution and dried overnight (*Scheme 4*).

Transmetallation of a Lithium Porphyrin with Iron(II)



Scheme 4: Demetallation of Cu²⁺ ions

The Soret band shifted from 456 nm to 497 nm (Figure 5).

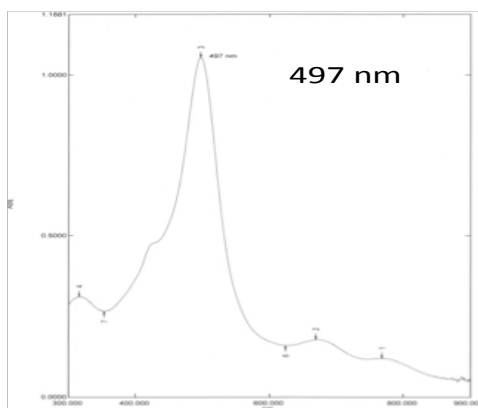
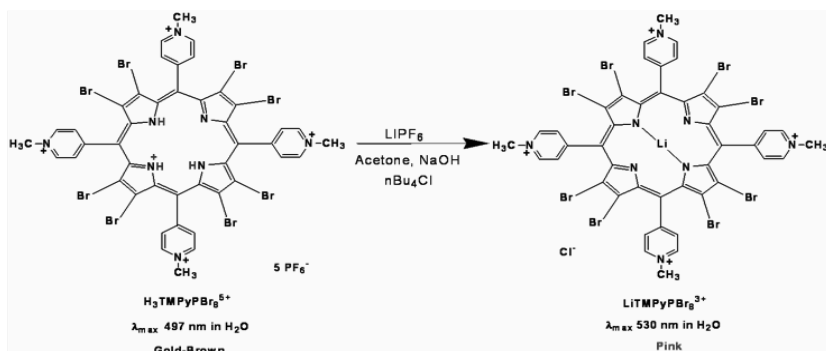


Figure 4. Absorption spectrum of H₃TMPyPBr₈⁵⁺ at pH 7

Synthesis of LiTMPyPBr₈³⁺: To prepare the lithium porphyrin derivative, the free-base H₃TMPyPBr₈⁵⁺ was deprotonated in 0.1M NaOH and excess LiPF₆ was added. The solution turned pink and eventually dark brown precipitate appeared. The precipitate was collected by suction filtration. To increase the water-solubility of the lithium complex, the solid was dissolved in acetone (5 mL) and excess nBu₄Cl was added to the solution. A red precipitate formed immediately and was collected by suction filtration (Scheme 5).



Scheme 5: Synthesis of LiTMPyPBr_8^{3+}

Absorption spectroscopy revealed a Soret band at 532 nm, consistent with previous findings.

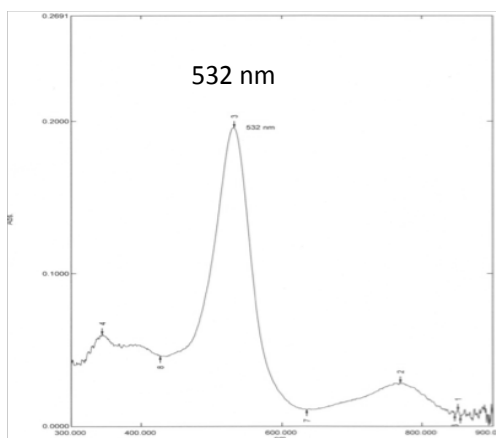


Figure 5. Absorption spectrum of LiTMPyPBr_8^{3+} in 0.1M NaOH

Approximately 1 mg of the chloride salt of LiTMPyPBr_8^{3+} was dissolved in water at pH 7 solution and excess FeCl_2 was added. The solution changed color from pink to rust-red. The absorption spectrum showed two distinct peaks in the Soret region (Figure 6).

Transmetallation of a Lithium Porphyrin with Iron(II)

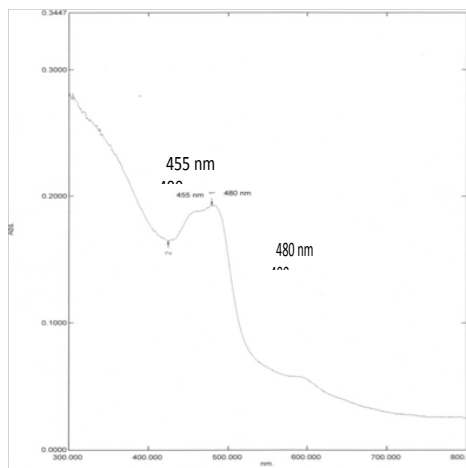


Figure 6. Absorption spectrum of reaction between LiTMPyPBr_8^{3+} and Fe(III) ion (pH 7)

RESULTS AND DISCUSSION

The following table shows the porphyrin derivatives synthesized and their spectral data.

Table 1. Absorbance Data for Porphyrin Derivatives

Porphyrin Derivative	λ_{max} (nm)	Solvent
$\text{H}_2\text{TMPyP}^{4+}$	423	pH 7
CuTMPyP^{4+}	426, 597	pH 7
CuTMPyPBr_8^{4+}	456, 597	pH 7
H3TMPyPBr_8^{5+}	497, 640, 730	pH 7
LiTMPyPBr_8^{3+}	537, 730	1 M NaOH
FeTMPyPBr_8^{5+}	455, 470	pH 7

Absorbance data confirmed were consistent with literature for the synthesis of the freebase porphyrin and revealed bathochromic shifts of the Soret band upon bromination by about 9 nm per bromine atom.^{6,ibid} Synthesis of the lithium porphyrin complex was accomplished via the deprotonated porphyrin species, TMPyPBr_8^{2+} , in aqueous base.

Subsequent addition of the iron(II) ion in aqueous solution resulted in two Soret peaks at 455 nm and 480 nm. While the peak at 455 nm is likely due to

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the axially-ligated bis-aquo Fe(III) porphyrin derivative, the absorbance at 480 nm could be explained by the formation of the mono-hydroxo/aquo Fe(III) porphyrin complex in an equilibrium mixture at pH 7. This is supported by other experiments in our labs.⁷ When the $\text{H}_3\text{TMPyPBr}_8^{5+}$ is mixed with Fe(II) acetate under nitrogen, a black solid formed. Dry acetone solutions of the product revealed a single Soret band at 470 nm. On exposure of the solution to air, the color immediately changed from black to green with a single Soret band at 455 nm, suggesting that oxidation of the metal ion had occurred. In addition, analysis of pH-dependent cyclic voltammetry of the iron(III) complex, FeTMPyPBr_8^{5+} , gave a pKa of 6.5 for the axially-ligated aquo-species (Equation 1).



Therefore, at pH 7, mono-hydroxo/aquo Fe(III) porphyrin complex would be the predominant solution species. Cyclic voltammetry was confounded above pH 8, presumably due to formation of demetallation of the iron ion from FeTMPyPBr_8^{5+} and formation of $\text{Fe}(\text{OH})_4$ species.

Density Function Analysis: ADF 2010 was used to construct molecular orbital diagrams for both Fe(II) and Fe(III) porphyrins as illustrated in Figure 7. Preliminary results of energetic studies of Fe(II) and Fe(III) porphyrin via ADF 2010 predicted that Fe(III) porphyrin complex is more stable than the Fe(II) derivative.

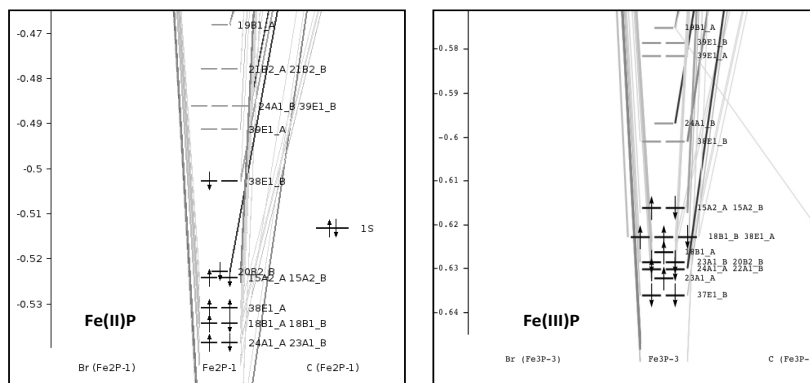


Figure 7. Molecular orbital diagrams for Fe(II) and Fe(III) derivatives of $\text{H}_3\text{TMPyPBr}_8^{5+}$

Table 2 shows that the triplet state of the Fe(II)P and the quadruplet state of the Fe(III)P are the most stable forms of the metalloporphyrin complexes. These

Transmetallation of a Lithium Porphyrin with Iron(II)

results are preliminary and further studies are currently underway.

Table 2. Energetics of Fe(II) and Fe(III) porphyrins

Porphyrin Moiety	Electronic State	Energy (kcal/mol)
Fe(II)P	singlet	do not converge
	triplet	-12415.4953
	quintuplet	-12406.1834
Fe(III)P	doublet	do not converge
	quadruplet	-12052.5869
	Sextuplet	-12074.3291

CONCLUSIONS AND OUTLOOK

The metal metathesis reaction between the lithium porphyrin and iron(II) allowed for the synthesis of the Fe(III) species. Further characterization is required via NMR, elemental analysis, and Mossbauer. Scale up of the LiTMPyPBr₈³⁺ provides opportunities to prepare not only the Fe(III) porphyrin complex but other transition metal ions under ambient conditions. Preliminary findings in this work provides the foundation for synthesizing a library of transition metal and lanthanide porphyrin derivatives.

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