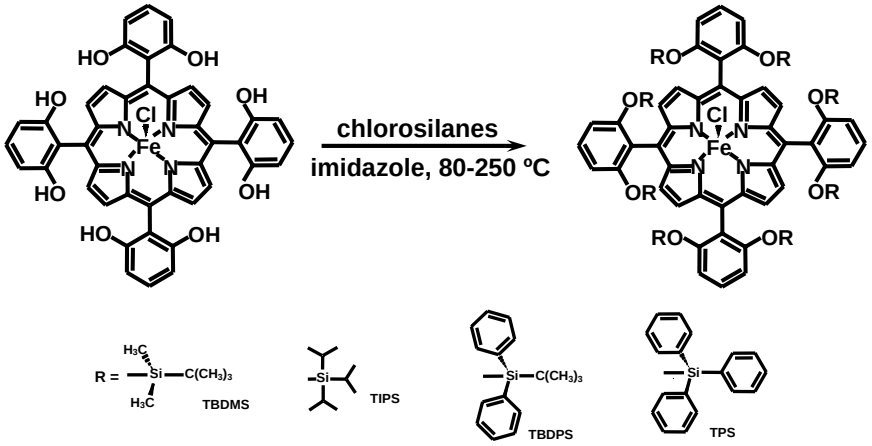
Synthesis and Coordination Complexes of Bis-Pocket Siloxyporphyrins

Ming Fang Final Seminar June 26, 2008

Iron porphyrins have been extensively studied by chemists for many years, in part because Heme (iron protoporphyrin IX) is widely found in many essential enzymes including hemoglobin, myoglobin, cytochrome P450, cytochrome c oxidase, catalase, peroxidase, nitric oxide synthase, and photosynthetic systems.[1] It is important to study the properties of iron porphyrins in order to better understand the biological functions of heme enzymes.

Many different types of iron porphyrin superstructures have been synthesized over the years. They can be roughly put into two categories, mono-face and bis-face protected porphyrins. The most notable mono-face protected porphyrin is the picket-fence porphyrin developed in Collman's group.[2] Picket-fence porphyrins have played an important role in biomimetic studies of myoglobin and hemoglobin.[3, 4] Bis-face protected porphyrins are symmetric, so their synthesis, purification, and characterization is relatively easy. Many bis-face protected porphyrins with large protection groups have been synthesized, including tetrakis(trisphenyl)phenylporphyrin, twin-coronet porphyrin, strapped porphyrin, and dendrimer porphyrins.[5-8] They have contributed enormously to the development of biomimetic regio- or enantio-selective catalytic reactions, as well as to the understanding of the mechanism of heme-containing enzyme catalyzed reactions.[9]

Scheme 1. Synthesis of bis-pocket siloxyporphyrins.



Bis-pocket siloxyporphyrins, developed in our group, have several advantages compared to the porphyrin superstructures mentioned above.[10, 11] In particular, they are the most sterically hindered porphyrin superstructures that have been reported. The pocket openings of our bis-pocket siloxyporphyrins ranges from 4 Å to 0 Å (fully closed), while the most sterically hindered porphyrin reported previously (tetrakis(trisphenyl)phenylporphyrin) has an opening of 4 Å. Moreover, the yield of the siloxyporphyrin synthesis is high, and the final product is easily purified. Gram scale syntheses of siolxyporphyrins are routinely being prepared in this lab. (Scheme 1)

Although many five- and six-coordinate iron(III) porphyrins have been synthesized, a truly four-coordinate Fe(III) porphyrin cation has never before been reported.[12] The exceptional electrophilicity of the four-coordinate $[Fe^{III}(Porph)]^+$ cation will even coordinate arene solvent upon crystallization if the counter anion is extremely non-coordinating, as in the work of Reed

with silver dihexabromocarborane, and in solution, a Br atom of the hexabromocarborane anion binds to the Fe.[13, 14]

Scheme 2. Synthesis of the four-coordinate iron(III) porphyrin.

$$Fe(2',6'\text{-}TIP)_8(P)(Cl) + AgCB_{11}H_6Br_6 \xrightarrow[RT]{CH_2Cl_2} [Fe(2',6'\text{-}TIPS)_8]^+[CB_{11}H_6Br_6]^- + AgCl_{(S)}$$

The highly sterically hindered bis-pocket siloxy porphyrin was used to isolate this very reactive four-coordinate species for the first time. (Scheme 2) NMR studies of this Fe(III) porphyrin cation with different weakly coordinating anions all give the same porphyrin proton chemical shifts in CD_2Cl_2, suggesting that no anion coordination to the iron occurs in solution. In the solid state, the four-coordinate Fe(III) bis-pocket porphyrin can be isolated with the bulky and weakly coordinating hexabromocarborane as the counter ion; the single crystal x-ray structure confirms the absence of axial ligation to the iron. (Figure 1) In contrast, with smaller anions (e.g., triflate), the Fe(III) bis-pocket porphyrin complexes are five-coordinate in the solid state, probably due to the smaller size and loss of stabilization from anion solvation in the solid state. Full characterization shows that the four-coordinate Fe(III) bis-pocket porphyrin cation has a 3/2 spin state, in agreement with theoretical predictions.

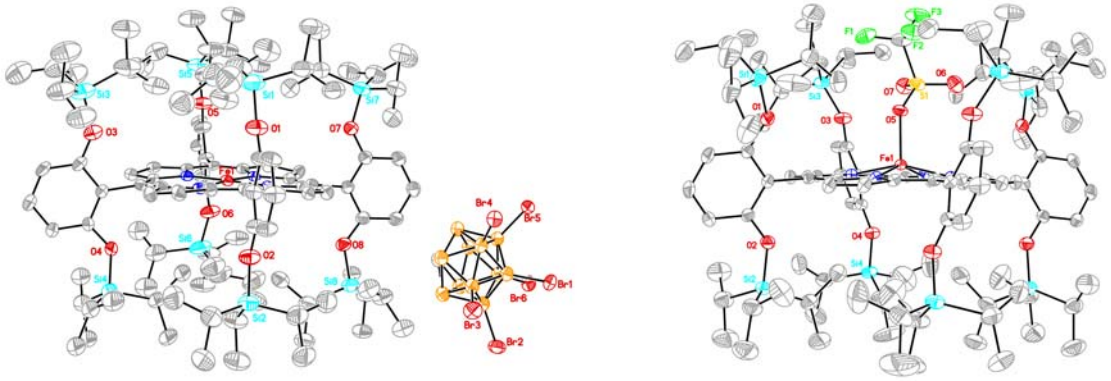


Figure 1. Single crystal x-ray structures of $[Fe(2',6'\text{-}TIPS)_8(P)]^+[CB_{11}H_6Br_6]^-$ (left) and $Fe(2',6'\text{-}TIPS)_8(P)(CF_3SO_3)$ (right).

Cytochrome P450 is a family of monooxygenase enzymes that catalyze the reaction where one oxygen atom from dioxygen is incorporated into organic substrates.[15, 16] P450 is best known for its ability to efficiently and regioselectively hydroxylate inert alkanes at room temperature under one atmosphere of oxygen. Selective C-H activation of unactivated alkanes is viewed as the Holy Grail in organic synthesis among chemists.[17] It is remarkable that nature has developed such an effective enzyme to complete such a difficult task.

Biomimetic P450 models have played an important role in understanding the structure and reaction mechanism of P450 enzymes. In the 1980s, a delicate model compound of P450 was developed in Collman's group by covalently attaching a thiol-tail to the porphyrin. The covalent modification method made the presence of an excess amount of thiol reagent unnecessary.[18] However, since the tail side of the porphyrin was not protected, the model compound was extremely sensitive to air and subject to dimerization through disulfide formation. Several subsequent covalently modified thiolate-tailed iron porphyrin models were synthesized, but all of these compounds used less basic thiolate ligands, presumably because the more basic alkyl thiolate ligands are more reducing and unstable. Although using less basic thiolate ligands

can reproduce the typical ferrous P450-CO hyperporphyrin spectrum, none of them can reproduce the characteristic high spin rhombic EPR patterns in ferric cytochrome P450, indicating that EPR is more sensitive to the electronic environment of the thiolate ligated iron than UV-Visible spectroscopy.[19, 20]

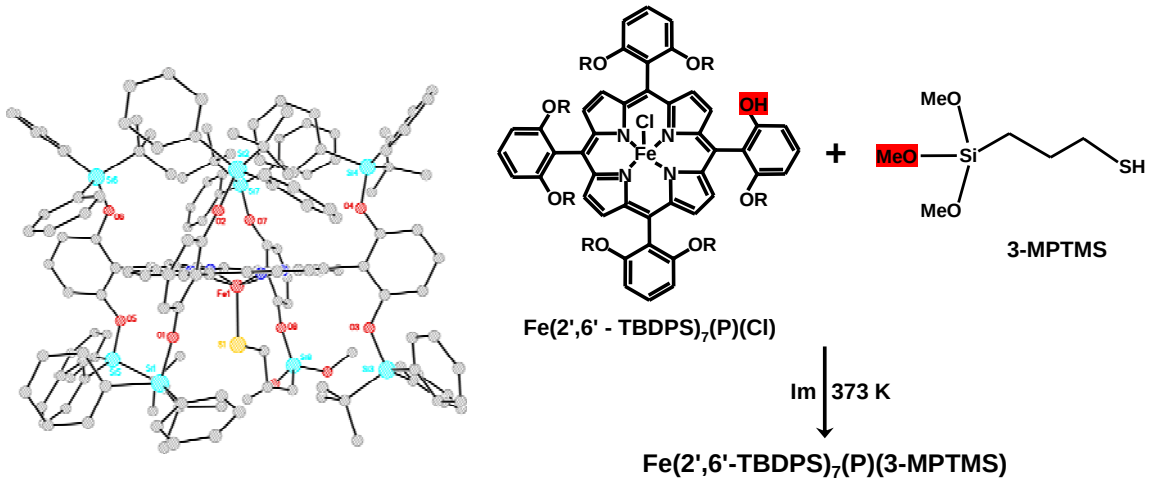


Figure 2. Single crystal x-ray structure of the thiolate-tailed porphyrin (left) and its synthesis (right).

A high yield synthetic route for an alkylthiolate-tailed bis-face protected iron porphyrin was developed. The high stability of this compound is likely due to the protection from the siloxy pocket around the thiolate tail. Very similar rhombic, high spin EPR spectra for this model compound and the P450 enzyme showed that the choice of a more basic thiolate tail is essential for model compounds to reproduce the electronic structure of the heme in P450.[21] The single crystal x-ray structure showed that the sulfur atom is bound to the iron. The Fe-S bond distance is 2.237(7) Å, and the iron is pulled out of the porphyrin plane by 0.50 Å, indicating that the iron is in the high spin state. (Figure 2) This Fe-S bond distance is very similar to the value reported for the P450 enzyme at its resting state.[22, 23] This is the first single crystal x-ray structure of a high spin alkylthiolate-tailed ferric porphyrin. UV-Vis and EPR spectroscopy also showed that methanol binding at low temperatures can induce the high spin to low spin transition for the thiolate-ligated iron porphyrin.

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