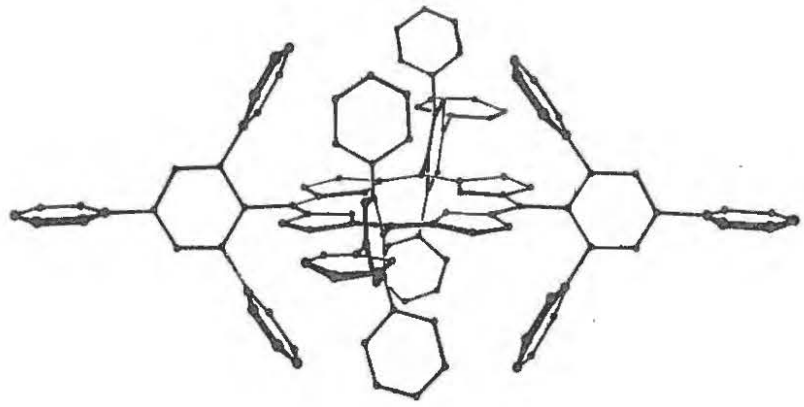
The Bis-Pocket Porphyrin: A Synthetic Analog for Heme Proteins

Mary M. Fox Final Seminar September 12, 1983

Porphyrin analog studies of heme containing proteins have had to overcome two major obstacles. These are the tendencies for iron porphyrins to oxidatively cleave at the meso-positions and to form the ferric μ-oxo dimer under oxidative conditions [1,2]. Substituents introduced at the meso positions inhibit the porphyrin ring cleavage reaction. Furthermore, if the substituents at the meso-carbons are sufficiently bulky, the bimolecular reaction of two iron porphyrin species is prevented. Two of the more successful porphyrin model systems in dealing with the second obstacle have incorporated bulky substituents; these are Collman's [3] "picket-fence" and Baldwin's [4] "Capped" porphyrins.

A similar approach was used to develop a more versatile porphyrin system. The condensation of 2,4,6-triphenylbenzaldehyde with pyrrole in refluxing propionic acid produced 5,10,15,20-tetrakis-(2,4,6-triphenylphenyl)porphyrin or H_2TTPPP. The structural representation of H_2TTPPP is presented in the figure below.



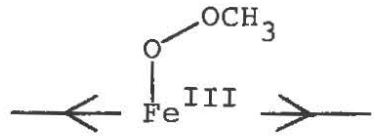
CPK models of the porphyrin suggest a "pocket-like" nature to the steric protection hence the use of the more trivial name "Bis-Pocket" porphyrin. Insertion of iron into the "bis-pocket" porphyrin is accomplished using iron pentacarbonyl and iodine in refluxing toluene [5]. The ferric complex is reduced with $(CH_3)_4NBH_4$ in THF. The 5-coordinate iron (II) complex is generated by the addition of a sterically hindered imidazole, 1,2-dimethylimidazole (1,2-Me_2Im) [6].

Fe(II)TTPPP(1,2-Me_2Im) demonstrates reversible O_2 and CO binding [7] at room temperature. Reversible O_2 binding is observed at temperatures as high as 60°C with a corresponding half-life of 2.0 hours. Surprisingly, the oxygen affinity (expressed as the $P_{\frac{1}{2}}$) of the "bis-pocket" porphyrin is 508 torr at 25° which is more than 10 times poorer than hemoglobin [8] and Collman's picket-fence complex [3]. This result cannot be accounted for in terms of steric encumberance of the O_2 ligand by the "pockets" of TTPPP. Equilibrium

binding studies with the axial bases, N-methylimidazole and 1,2-Me Im, reveal the "pockets" do not impede the ligation of bulky axial ligands. Thermodynamic data likewise show no enthalpic barrier to coordination of O_2 as compared with the "picket-fence" systems and hemoglobin and myoglobin. In contrast, Baldwin's "Capped" porphyrin shows an even lower O_2 affinity ($P_{\frac{1}{2}}$=4000 torr) under similar conditions. The explanation for the reduced affinity in the Capped system is believed to be due to distortion of the porphyrin macrocycle induced by the "cap" thus affecting the binding of all axial ligands [9].

A solvent dependent O_2 affinity study shows that polarity of the solvent can modulate the O_2 affinity by a factor of three. Using the solvents: mesitylene, toluene, benzene, chlorobenzene, dichlorobenzene (specifically chosen to minimize complicating effects due to solvent coordination or H-bonding), increased solvent polarity resulted in increased O_2 affinity. Interestingly, the opposite effect is observed with CO affinities (i.e. increased solvent polarity diminishes CO affinity by a factor of two). The results of the O_2 and CO binding studies with the "bis-pocket" porphyrin demonstrate that polarity can play an important role in modulating ligand affinities. It is believed that a similar polarity effect in the form of distal H-bonding [10] interactions may exist in biological systems as a means of discriminating O_2 over CO. This is physiologically important as a mechanism for detoxifying against endogeneously produced CO.

The versatility of the "bis-pocket" porphyrin as a model for a variety of biological heme systems is evidenced by its oxidative stability in the presence of a wide variety of oxidants: cumene and t-butyl hydroperoxides, peracetic and m-chloroperbenzoic acids, and iodosobenzene and iodoso-m-xylene. For comparison, chlorotetraphenylporphyrinatoiron (III) in the presence of methanol and iodoso-m-xylene decomposes in a matter of minutes, whereas the bis-pocket porphyrin under similar conditions, is stable for a period of days. Much of the current interest in porphyrin/oxidant systems is the hope of isolating and studying intermediates in the enzymic cycles of P-450 [11], catalase and peroxidase [12]. The reaction of Fe(III)-TTPPPCl with iodosobenzene (or any oxidant previously mentioned) and methanol generates an unusual red complex. NMR, EPR, UV-vis and titration results suggest the red species is:



The metalloalkylperoxide complex is not an active hydroxylating agent but can be reduced with sodium dithionite or phenyltrimethylammonium iodide to give quantitatively the original ferric species. Treatment of cyclohexene with Fe(III)TTPPPI in CH_2Cl_2 without methanol present does give cyclohexene epoxide as its major oxidation product. Thus, the apparent role of methanol appears to be to stabilize the active oxygen atom transfer agent by trapping it is the metalloperoxide complex (i.e. the "red" species). Groves et al. [13]

have reported observing an Fe^{IV}=0 species at low temperatures. Unusual highly oxidized iron species are believed to be the active intermediates of the catalytic cycle of P-450 and have been observed spectrally for the enzyme systems horseradish peroxidase [14] and peroxidases [15].

Of future interest is continued efforts in the oxidation chemistry of the bis-pocket porphyrin. The steric protection of the pockets allows one to mimic enzymatic substrate specificity and regio- and stereoselectivity [16], in for example shape selective alkane hydroxylation [17].

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