

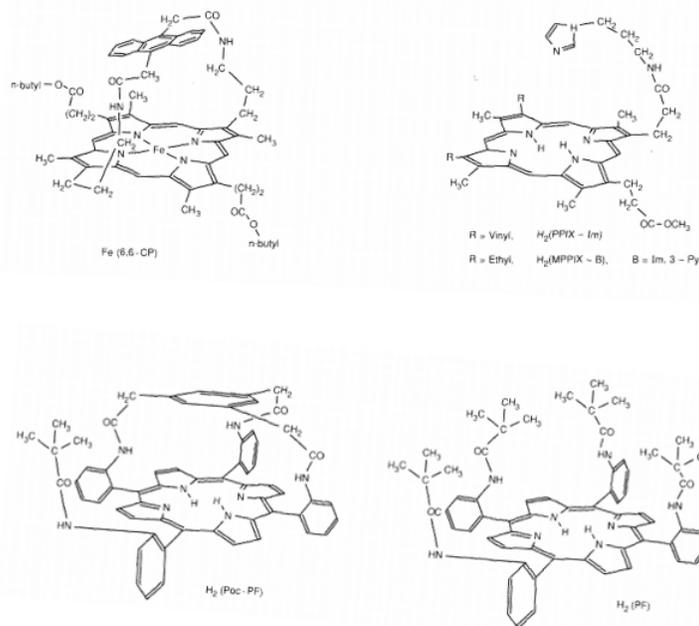
4.13: Requirements for a Model System for Hemoglobin

For hemoglobin, the majority of ligands around the iron center are provided by a fairly rigid macrocycle, the protoporphyrin IX dianion (Figure 4.1), that by itself enforces a square-planar stereochemistry. Thus, the task of assembling synthetic analogues of the active site in hemoglobin is simplified. Essentially, any square-planar, tetradentate ligand containing at least a couple of nitrogen atoms will suffice: to this end a variety of other porphyrins have been used, as well as Schiff-base and non-porphyrinato nitrogen-containing macrocycles that serve to delineate the role of the porphyrin in dioxygen binding. Tetraphenylporphyrin, in place of the naturally occurring porphyrins, has served as the basis of numerous model systems. It is easily synthesized and derivatized (see below). Its fourfold symmetry precludes formation of chemical isomers that may arise if substitution on the asymmetric, naturally occurring porphyrins is attempted. Moreover, its derivatives can be crystallized. Finally, with the porphyrin *meso* positions occupied by phenyl groups, the molecule is less susceptible to photoinduced oxidation.

In order to obtain five-coordinate species, putative models for a deoxy hemoglobin, access to one side of the porphyrin must be blocked to the coordination of a second axial base (Reaction 4.33), but still must be accessible for the binding of small molecules (O_2 , NO, CO, etc). Or second, an axial base may be attached covalently to the porphyrin, to give so-called "tail-under" or "chelated" porphyrins. Here the chelate effect ensures an effectively 100 percent five-coordinate complex with only a 1:1 stoichiometric ratio of axial base to porphyrin. These two approaches are illustrated in Figure 4.14. A third means is to incorporate a sterically bulky substituent in the 2-position of the base, such as a methyl group, to give 2-methylimidazole (4.34). The formation of the hemochrome $Fe(porph)(2-MeIm)_2$, where the iron atom is in the center of the porphyrin ring, is strongly disfavored relative to the 1-methylimidazole analogue, because the 2-methyl substituents clash with the porphyrin ring. The axial base needs to be a strong σ donor, such as imidazole or pyridine, in order to increase affinity at the iron (or cobalt) center for dioxygen (Figure 4.18).

Steric hindrance on one side, or on both, provides a pocket for small molecules to bind and, for O_2 , prevents the bimolecular contact of two iron(II)-porphyrinato species that would lead to irreversible oxidation (Reaction 4.29). A picturesque collection of substituted porphyrins has been synthesized. Some of these are illustrated in Figure 4.23.^{31,72,160-164} The only system that has led to crystalline dioxygen complexes stable at room temperature is the "picket-fence" porphyrin.^{72*} A derivative of this, the "pocket" porphyrin,¹⁶⁵ and various "capped" porphyrins,¹⁶⁶ provide binding sites with steric hindrance even to small diatomic molecules.

In the next section the structures of various derivatives of hemoglobin and its models are presented, and the relationship of structure to ligand-binding properties is examined. Although there is now a wealth of thermodynamic data available from model systems, attention is focused primarily on those for which structural data are also available.



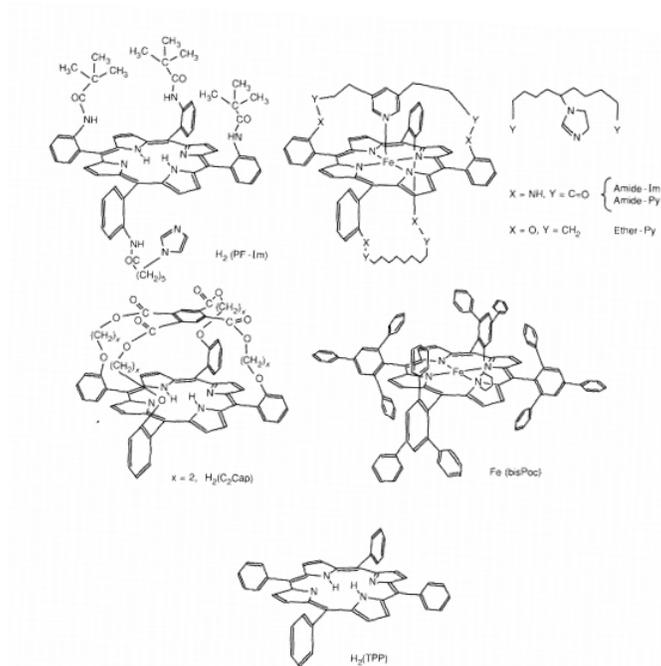


Figure 4.23 - A selection of synthetic porphyrins used to probe the dioxygen-binding process.

* The pivalamido pickets ($-NH-CO-C(CH_3)_3$) of the picket-fence porphyrin are sufficiently bulky that their free rotation is sterically hindered. Thus the various *atropisomers*— $\alpha\alpha\alpha\alpha$, $\alpha\alpha\alpha\beta$, $\alpha\beta\alpha\alpha$, $\alpha\alpha\beta\beta$, where α denotes picket "up" and β denotes picket "down"—can be separated chromatographically on the basis of their different polarities. The tail-under picket-fence porphyrin is derived from the $\alpha\alpha\alpha\beta$ atropisomer.⁷²

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