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Synthesis and Characterization of "Tailed Picket Fence" Porphyrins

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Abstract: The synthesis of "picket fence" porphyrin derivatives bearing covalently attached axial bases is described. These porphyrins have been well characterized, primarily as the iron(II) complexes, *meso*-tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-5-(*N*-imidazolyl)valeramidophenylporphyrinatoiron(II) and *meso*-tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-4-(*N*-imidazolyl)butyramidophenylporphyrinatoiron(II), by UV/visible, MCD, ^{1}H NMR, and Mössbauer spectroscopy, magnetic susceptibility, and elemental analysis. Preliminary results of carbon monoxide binding studies are reported.

Introduction

The development of simple compounds modeling the reactivity of the oxygen transport and storage proteins hemoglobin (Hb)[51] and myoglobin (Mb) is of continuing interest.[2-4] A series of models has appeared in the literature,[2-11] and the reactions of these, both in solution[2b,c,3-10] and in the solid state,[11] have been extensively investigated. Recent studies have been directed toward the elucidation of the mechanism of cooperativity in hemoglobin. According to the Hoard–Perutz theory,[12] Hb has two alternative quaternary structures: the liganded, "R" state, in which the O_2 (and CO) affinity is essentially that of the isolated subunits, and the deoxy, "T" state, in which the O_2 (and CO) affinity is greatly diminished. Cobalt-reconstituted hemoglobin (CoHb) also demonstrates cooperativity in O_2 binding,[13] and for this reason model complexes of both iron and cobalt have been examined.

Solution studies demonstrated the capability of the "picket fence" porphyrin,[14] **2** (Figure 1), in which the "pickets" prevent irreversible oxidation, to mimic the O_2 affinity of the low-affinity, "T" state of Hb,[10] as well as that of CoMb and both the "R" (high affinity) and "T" states of CoHb.[15] Direct solution measurements of the O_2 affinities of possible models for Mb and the "R" state of Hb, however, are not possible with the "picket fence" system, owing to the equilibria

$$\mathrm{PFe} + \mathrm{L} \overset{K_1}{\rightleftharpoons} \mathrm{PFeL}$$

$$\mathrm{PFeL} + \mathrm{L} \overset{K_2}{\rightleftharpoons} \mathrm{PFeL_2}$$

where P represents the porphyrin ligand and $K_2 > K_1$ for sterically unhindered axial nitrogen bases.[16] A solution measurement would thus yield not the desired equilibrium constant

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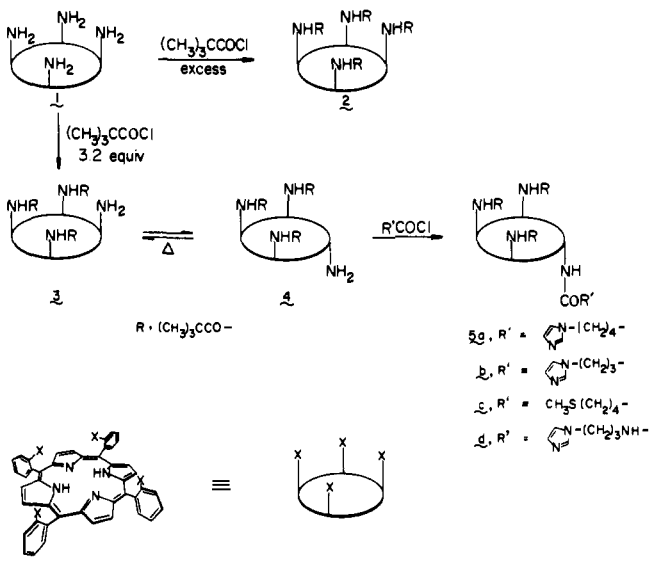


Figure 1. Synthetic strategy for the "tailed picket fence" porphyrins.

for O_2 binding to a five-coordinate iron(II) porphyrin, but instead a constant describing the replacement of one axial ligand (L) of a six-coordinate iron(II) porphyrin species by O_2. Though it has been found possible to model effectively Mb and the "R" and "T" states of Hb with the "picket fence" porphyrin, using solid–gas reactions,[11] solution studies are also desirable. What is needed is a system enforcing five coordination about iron while retaining the reversible O_2 binding capability and the resistance to irreversible oxidation of the "picket fence" porphyrin. We now wish to report the synthesis and characterization of "picket fence" porphyrins with covalently attached axial bases, which satisfy these requirements. These porphyrins have permitted the direct determination of the thermodynamic parameters describing O_2 and CO binding under conditions of equilibrium. Traylor and co-workers[2b,c] have carried out extensive studies of oxygen binding in model compounds which also contain covalently attached bases.[3] However, these simpler, unhindered models are susceptible to irreversible oxidation, so that oxygen binding must be determined through use of kinetic analyses rather than by direct equilibrium measurements.

Results

The readily available intermediate from the original "picket fence" porphyrin synthesis,[14] *meso*-tetra($\alpha,\alpha,\alpha,\alpha$-*o*-aminophenyl)porphyrin (**1**), was treated with slightly over 3 equiv of pivaloyl chloride, affording the "three picket" α-aminoporphyrin **3** in roughly 35% yield after chromatography (optimum yields were obtained using 3.2 equiv of the acid chloride). Heating in solution equilibrated this α-aminoporphyrin to a 1:1 mixture of the α-amino and β-amino isomers, from which the β-amino isomer, **4**, was separated by chromatography. (The remaining α-amino isomer may be carried through this equilibration/chromatography routine repeatedly to increase the overall conversion.) Attachment of an axial base to the porphyrin through the β-amino group completed the synthesis of the "tailed picket fence" porphyrins.

An amide linkage between porphyrin and "tail" was chosen for ease of synthesis, though more difficulty was encountered than anticipated. Several standard peptide bond forming reactions (e.g., DCC coupling and *p*-nitrophenyl ester activation of the acid) failed when these were attempted with β-aminoporphyrin **4** and 5-(*N*-imidazolyl)valeric acid, probably because the ortho amino group is too hindered. Initial attempts to generate 5-(*N*-imidazolyl)valeryl chloride, which is less subject to steric effects in peptide bond formation, led only to insoluble and uncharacterized materials. Successful coupling

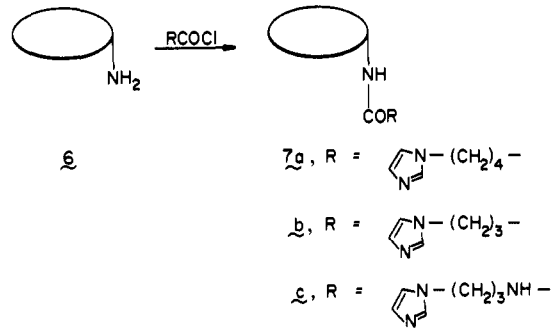


Figure 2. Synthesis of "tailed" porphyrins without "pickets".

was accomplished only when the acid chloride was generated with 1 equiv of $SOCl_2$ in DMF and used immediately, without isolation, leading to the "tailed picket fence" compound, *meso*-tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-5-(*N*-imidazolyl)valeramidophenylporphyrin, $H_2Piv_3(5CImP)Por$ (**5a**) (Figure 1). Analogous reactions led to *meso*-tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-4-(*N*-imidazolyl)butyramidophenylporphyrin, $H_2Piv_3(4CImP)Por$ (**5b**), and to a methyl thioether compound,[17a] **5c**. In fact, the "β-aminoporphyrin" derivative **4** is a versatile intermediate, and a whole series of sulfur-containing "tailed picket fence" porphyrins has recently been prepared.[17b]

In an attempt to alter the solubility of the imidazole "tail" porphyrins, a similar compound, in which a urea linkage replaces the amide, was synthesized. Attempts to produce the urea through the mediation of *N,N'*-carbonyldiimidazole[18] failed, again presumably owing to the hindered nature of the ortho amino group. Phosgene, however, reacts readily with the β-aminoporphyrin **4**, generating either the carbamoyl chloride or the isocyanate.[19] Addition of 3-(*N*-imidazolyl)propylamine[20] gave the desired *meso*-tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-3-(*N*-imidazolyl)propylureidophenylporphyrin (**5d**) in good yield. This compound has been characterized only by IR and ^1H NMR (reported in the Experimental Section) and will not be discussed further.

Because the β-aminoporphyrin is tedious to prepare, all "tail"-forming reactions were tested first and optimized using *meso*-mono(*o*-aminophenyl)triphenylporphyrin (**6**). "Mixed" condensation[21] of *o*-nitrobenzaldehyde, benzaldehyde, and pyrrole gave a mixture of nitrophenylporphyrins, from which the mononitro compound was isolated; subsequent reduction produced the monoaminophenylporphyrin, which was used to prepare *meso*-mono[*o*-5-(*N*-imidazolyl)valeramidophenyl]-triphenylporphyrin (**7a**), *meso*-mono[*o*-4-(*N*-imidazolyl)butyramidophenyl]triphenylporphyrin (**7b**), and *meso*-mono[*o*-3-(*N*-imidazolyl)propylureidophenyl]triphenylporphyrin (**7c**).

The imidazole "tail" porphyrins were found to be very sensitive to the combination of light and oxygen, so that all synthetic steps involving their preparation and purification must be carried out under a nitrogen atmosphere and/or in the dark. High-pressure liquid chromatography has been used to examine the sensitivity of $H_2Piv_3(5CImP)Por$ to light and oxygen—this porphyrin has a half-life of less than 30 min when exposed to air and room light in dilute benzene solution. It is known that metal-free porphyrins activate molecular oxygen in the pressure of light, forming singlet oxygen,[22] and furthermore singlet oxygen readily attacks and destroys imidazoles.[23] Though the decomposition products in the present cases have not been characterized, it appears plausible that singlet oxygen is formed and immediately attacks the appended imidazole.

In the original "picket fence" porphyrin synthesis,[14] the iron(II) complex was obtained by chromous acetylacetonate reduction of the iron(III) bromide; the sparingly soluble

Table I. Electronic Spectral Data for Selected Iron(II) Tetraarylporphyrins[a]

	Soret region		visible region		
		Four-Coordinate			
FeTPP	419 (10.7)[b]	442 (7.95)	537 (0.95)		
FeTpivPP	415 (9.66)	435 (9.32)	535 (1.17)	565 (0.27)	
Fe "capped porphyrin"[c]	420	447	537		
		Five-Coordinate (N Base)			
FeTPP (2-MeIm)[d]	368 (2.18)	436 (26.0)	537 (0.77)	565 (0.81)	610 (0.33)
FeTPP (1,2-Me_2Im)[d]	369 (1.3)	438 (14.3)	534 (0.71)	565 (0.63)	610 (0.30)
FeTpivPP (2-MeIm)	370	436	540	558	600 (sh)[f]
FeTpivPP (1,2-Me_2Im)	371 (3.0)	437 (20.3)	538 (0.62)	559 (0.74)	600 (sh) (0.14)
Fe "capped porphyrin" (pyridine)	*e*	435	537	565 (sh)	615 (sh)
FeM5T[g]	371	437	537	560 (sh)	609 (sh)
FeM4T[h]	370	437	537	565	610 (sh)
$FePiv_3$(5ClmP)Por (**8**, *n* = 4)	371 (3.3)	438 (19.8)	536 (0.86)	558 (sh) (0.75)	608 (sh) (0.16)
$FePiv_3$(4ClmP)Por (**8**, *n* = 3)	372 (3.3)	438 (19.7)	537 (0.86)	559 (sh) (0.77)	606 (sh) (0.24)
		Six-Coordinate (N Base)$_2$			
FeTPP(*N*-MeIm)$_2$	427 (25.2)		535 (2.05)	565 (0.48)	
FeTpivPP(*N*-MeIm)$_2$	432 (22.8)		537 (2.10)	562 (sh) (0.38)	
FeM5T + *N*-MeIm	428 (22.2)		534 (1.65)	565 (0.34)	
$FePiv_3$(5ClmP)Por (**8**, *n* = 4) + *N*-MeIm	427		533 (2.07)	561 (sh) (0.32)	
FeM5T + $MeNH_2$	425 (24.0)		531 (2.04)	561 (0.29)	
$FePiv_3$(5ClmP)Por (**8**, *n* = 4) + $MeNH_2$	424		534	558	
		O_2 Complexes			
FeTpivPP(*N*-MeIm)(O_2)		426 (15.9)		548 (1.5)	582 (sh) (0.24)
Fe "capped porphyrin" (pyridine)(O_2)		434		545	580 (sh)
$FePiv_3$(5ClmP)Por(O_2) (**9a**, *n* = 4)		425(13.4)		546 (1.4)	585 (sh) (0.26)
$FePiv_3$(4ClmP)Por(O_2) (**9a**, *n* = 3)		426 (12.9)		548 (1.2)	585 (sh) (0.40)
		CO Complexes			
FeTPP (*N*-MeIm)(CO)		427 (31.3)		542 (1.4)	
FeM5T (CO)		424 (29.0)		541 (0.9)	
$FePiv_3$(5ClmP)Por(CO) (**9b**, *n* = 4)		425 (32.7)		540 (1.3)	
$FePiv_3$(4ClmP)Por(CO) (**9b**, *n* = 3)		424 (31.0)		540 (1.2)	

[a] Benzene or toluene solution, 25 °C. [b] Wavelength in nm; extinction coefficient $\epsilon \times 10^{-4} \pm 20\%$ in parentheses where available. [c] Reference 9c. [d] 2-MeIm = 2-methylimidazole; 1,2-Me_2Im = 1,2-dimethylimidazole. [e] Not reported. [f] Shoulder. [g] Iron(II) derivative of the "nonpicketed" valeramido "tail" porphyrin. [h] Iron(II) derivative of the "nonpicketed" butyramido "tail" porphyrin.

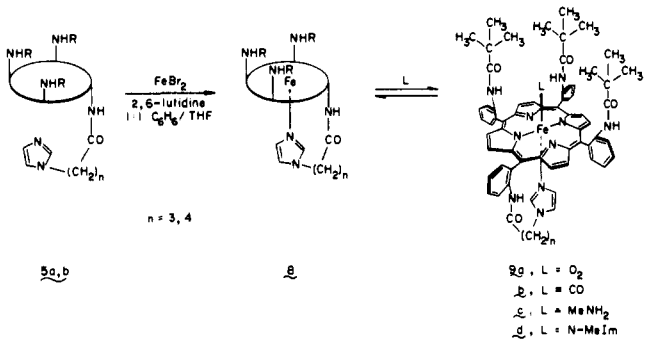


Figure 3. Synthesis of five- and six-coordinate iron(II) complexes of the "tailed picket fence" porphyrins.

FeTpivPP was easily crystallized away from any chromium byproducts. The "tail" compounds, however, are quite soluble, and thus the chromium byproducts are extremely difficult to remove. A new procedure for the direct insertion of iron(II) using anhydrous $FeBr_2$ and a noncoordinating base (2,6-lutidine) was developed to circumvent this problem (Figure 3). After removal of 2,6-lutidine hydrobromide and excess $FeBr_2$ by filtration through activity 1 neutral alumina, nearly quantitative yields of the five-coordinate iron(II) "tail" porphyrins, **8**, are obtained. These complexes and their adducts with externally provided ligands (O_2, CO, $MeNH_2$, *N*-MeIm), **9a–d**, have been characterized by a wide variety of physical techniques (UV/visible, NMR, MCD, and Mössbauer spectroscopy, magnetic susceptibility, elemental analysis). The results from each of these studies are discussed separately below.

Discussion

UV/Visible Spectroscopy. The solution electronic spectra of all new complexes were routinely recorded and compared to those of well-known and characterized iron(II) porphyrin complexes. Table I presents the pertinent electronic spectral data, organized according to coordination type.

Each of the five general types of iron(II) axial coordination examined has very distinctive characteristics. Square-planar iron(II) tetraarylporphyrins exhibit two bands of roughly equal intensity in the Soret region (350–500 nm) and a relatively broad peak at about 535 nm in the visible region (500–700 nm), with a shoulder sometimes apparent near 565 nm. Five-coordinate complexes with a single axial nitrogen base also exhibit two absorptions in the Soret region, but in this case the lower wavelength band is much weaker and considerably blue shifted. The visible region of these five-coordinate complexes is also more complex, with three distinct absorptions, near 535, 560, and 610 nm. Six-coordinate iron(II) tetraarylporphyrins, in which one axial position is occupied by a nitrogen base and the other by either O_2, CO, or a second nitrogen base, exhibit electronic spectra which can be distinguished on the basis of differences in extinction coefficients. All six-coordinate complexes examined have a single Soret band between 424 and 434 nm and one major peak in the visible region between 534 and 548 nm. However, the Soret band of a typical CO complex is significantly more intense than that of a bis nitrogen base complex, and more than twice as intense as that of an O_2 complex. In the visible region, it is the bis nitrogen base complex which exhibits sharper and more intense bands, while the

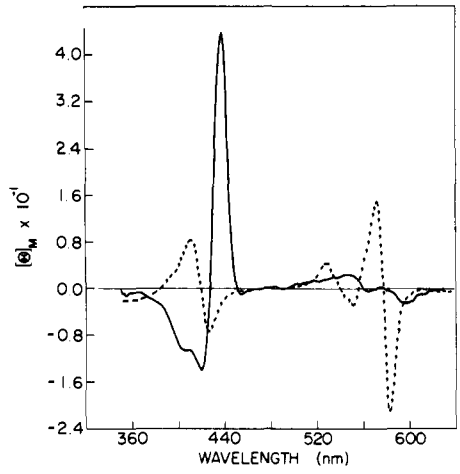


Figure 4. MCD spectra (aqueous solution): —— = deoxy Mb; --- = oxy Mb.

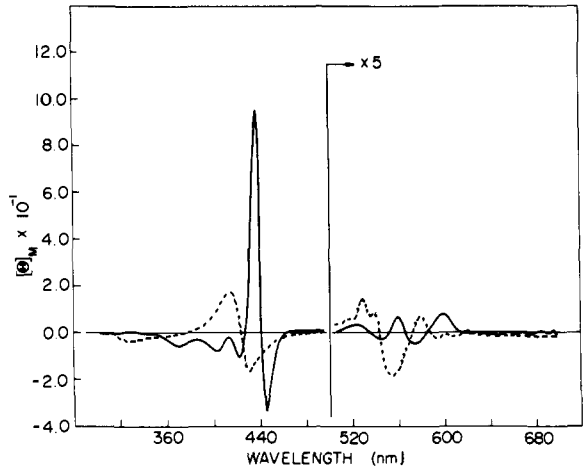


Figure 5. MCD spectra (toluene solution): —— = FeTpivPP(1,2-Me_2Im); --- = FeTpivPP (1,2-Me_2Im)(O_2).

Table II. Iron(II) Porphyrins Characterized by MCD Spectroscopy

four-coordinate	FeTPP
five-coordinate Fe(L)	FeTpivPP(2-MeIm) FeTpivPP(1,2-Me_2Im) $FePiv_3$(5ClmP)Por (**8**, n = 4) $FePiv_3$(4ClmP)Por (**8**, n = 3)
six-coordinate Fe(L)(O_2)	FeTPP(N-MeIm)$_2$ FeTpivPP(N-MeIm)(O_2) FeTpivPP(1,2-Me_2Im)(O_2) $FePiv_3$(5ClmP)Por(O_2) (**9a**, n = 4) $FePiv_3$(4ClmP)Por(O_2) (**9a**, n = 3)
six-coordinate Fe(L)$_2$	FeTPP(N-MeIm)$_2$ FeTpivPP(N-MeIm)$_2$ $FePiv_3$(4ClmP)Por(N-MeIm) (**9d**, n = 3)
six-coordinate Fe(L)(CO)	FeTPP(N-MeIm)(CO) $FePiv_3$(4ClmP)Por(CO) (**9a**, n = 3)

O_2 and CO complexes have nearly identical weaker absorptions.

These generalizations of spectra for iron(II) tetraarylporphyrins were developed from observations on well-characterized complexes in the tetraphenylporphyrin and "picket fence" porphyrin series. Spectra of the "tail" compounds uniformly matched these generalizations, supporting the assignments of coordination modes made for these new compounds.

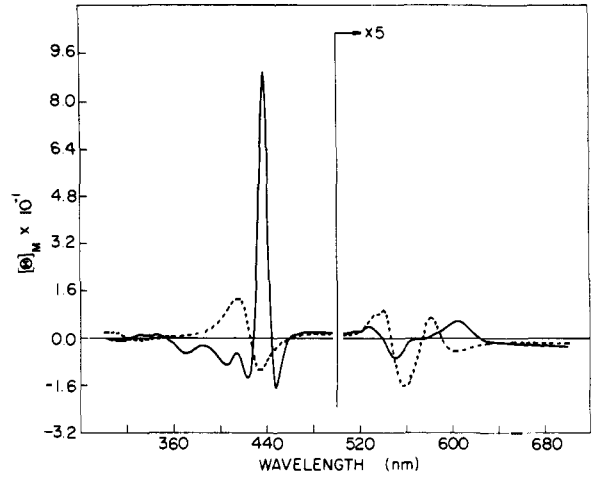


Figure 6. MCD spectra (toluene solution): —— = $FePiv_3$(4ClmP)Por; --- = $FePiv_3$(4ClmP)Por(O_2).

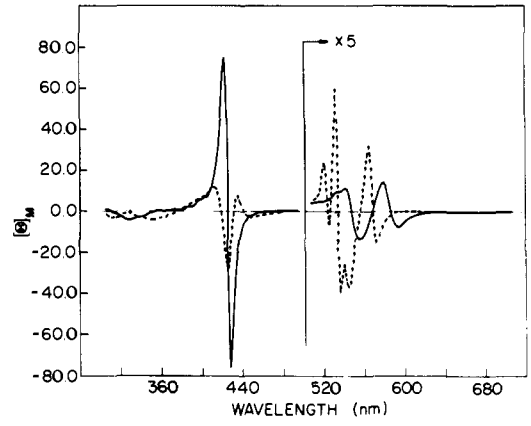


Figure 7. MCD spectra (toluene solution): —— = FeTPP(N-MeIm)(CO); --- = FeTPP(N-MeIm)$_2$.

Magnetic Circular Dichroism. Magnetic circular dichroism (MCD) has been applied to the study of porphyrins[24] and heme proteins[25] for both analytical and theoretical reasons. Whereas simple absorption spectra display bands of only one sign, the bands in an MCD spectrum may be either positive or negative. In addition, the particular type of band (A, B, or C term bands[57]) observed is intimately related to the electronic structure of the molecule. For iron porphyrins, these factors combine to make MCD a senstive probe for changes in oxidation state, spin state, and axial ligation.

We have used MCD as a "fingerprint" for the various complexes of the iron(II) "tailed picket fence" porphyrins, as well as those of simpler tetraarylporphyrins for purposes of comparison (Table II). This application is based on the observation that the MCD band shape in the Soret region of hemoglobin[58-60] and myoglobin[25c,60] is very different for the five- and six-coordinate species, as is illustrated by the MCD spectra of deoxy- and oxymyoglobin shown in Figure 4. The S-shaped Soret MCD band of oxymyoglobin is not sensitive to temperature changes[25c] and is thus identified as the A-term band expected for a low-spin iron(II) porphyrin. The Soret region of the MCD spectrum of deoxymyoglobin, however, is temperature sensitive,[25c] as is required for the C terms expected for a high-spin iron(II) porphyrin.

Similar MCD band shapes in the Soret region are observed for the iron(II) tetraarylporphyrin complexes (Figures 5–9). The Soret region MCD of the five-coordinate complex FeTpivPP(1,2-Me_2Im) (Figure 5) shows a strong positive band at about the same wavelength as the positive band observed for deoxymyoglobin. It appears that this positive MCD band at

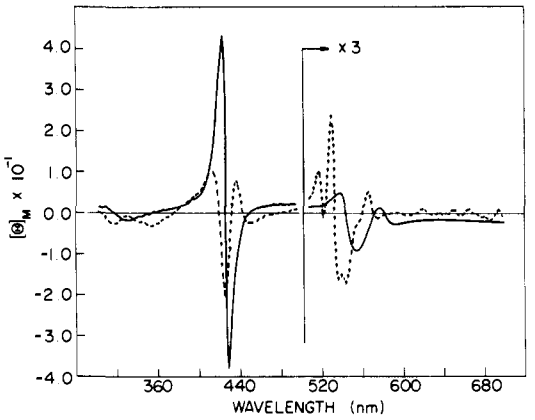


Figure 8. MCD spectra (toluene solution): — = $FePiv_3$(4ClmP)Por(CO); --- = $FePiv_3$(4ClmP)Por + *N*-MeIm.

435–440 nm is characteristic of high-spin five-coordinate iron(II) porphyrins with imidazole as the fifth ligand. The differences in the MCD spectra of deoxymyoglobin and FeTpivPP(1,2-Me_2Im) may be attributed to the differences between protoporphyrin IX and tetraarylporphyrins. Admission of O_2 to FeTpivPP(1,2-Me_2Im) yields the six-coordinate complex FeTpivPP(1,2-Me_2Im)(O_2), which displays an S-shaped A-term MCD band in the Soret region (Figure 5), as in the spectrum of oxymyoglobin. Analogous MCD spectra were recorded for the high-spin iron(II) "tailed" porphyrins $FePiv_3$(4ClmP)Por and $FePiv_3$(5ClmP)Por and their corresponding low-spin dioxygen complexes. Spectra of $FePiv_3$(4ClmP)Por and its O_2 adduct are reproduced in Figure 6. Those for $FePiv_3$(5ClmP)Por and its O_2 adduct are nearly indistinguishable and are not shown. The carbon monoxide and *N*-MeIm adducts are also low spin and are expected to display A-term MCD bands; such bands are indeed observed (Figures 7 and 8). The decrease in intensity of the Soret MCD absorption for the three sixth ligands examined, CO, O_2, and *N*-MeIm (with *N*-MeIm or an appended imidazole as the fifth ligand), parallels that in the UV/visible spectra (i.e., CO > O_2 > *N*-MeIm).

NMR and Mossbauer measurements (vide infra) indicate a significant dimerization of the iron(II) "tailed picket fence" porphyrins, $FePiv_3$(4ClmP)Por and $FePiv_3$(5ClmP)Por, at lower temperatures (−25 °C) and higher concentrations ($\sim 10^{-3}$ M) than were used for the MCD measurements (20 °C, $\sim 5 \times 10^{-5}$ M). The Soret regions of the MCD spectra of relevant models for the dimerization products, FeTPP and FeTPP(N-MeIm)$_2$, however, are relatively weak and devoid of distinguishing characteristics. For this reason, a detailed computer curve analysis was not performed. The $[\theta]_m$ values for the positive MCD bands at 440 nm of FeTpivPP(1,2-Me_2Im) (Figure 5), $FePiv_3$(4ClmP)Por (Figure 6), and $FePiv_3$(5ClmP)Por are nearly equal (96, 90, and 100 deg cm^2 dmol^{-1} G^{-1}, respectively); we attribute the small differences to experimental errors and believe that dimeric species do not contribute appreciably to the optical spectra.

Magnetic Susceptibility. Six-coordinate iron(II) porphyrins are invariably low spin in the ground state,[26] and are expected to be diamagnetic, with $\mu_{eff} = 0$. In fact, though, one of the best characterized low-spin six-coordinate complexes, FeTPP(piperidine)$_2$, is reported[27] to have $\mu_{eff} = 1.2\ \mu_B$. This is relatively slight paramagnetism, and can be accounted for with approximately 3% high-spin iron(III) impurity. Though several rigorously diamagnetic six-coordinate iron(II) complexes have been isolated in our laboratory, any value of μ less than 1.0 μ_B has been considered acceptable for such a complex.

The "spin-only" magnetic moment μ_s for the $S = 2$ state is 4.9 μ_B. Reported values for five-coordinate high-spin iron(II) porphyrins have been between 4.9 and 5.1 μ_B.[28,29] The intermediate-spin state ($S = 1$) has a "spin-only" magnetic moment of 2.8 μ_B, though orbital contributions may raise the value as high as 4.5 μ_B. The recently characterized[28,30,31] four-coordinate FeTPP is an example of intermediate-spin iron(II) and has been reported to have $\mu_{eff} = 4.4\ \mu_B$.

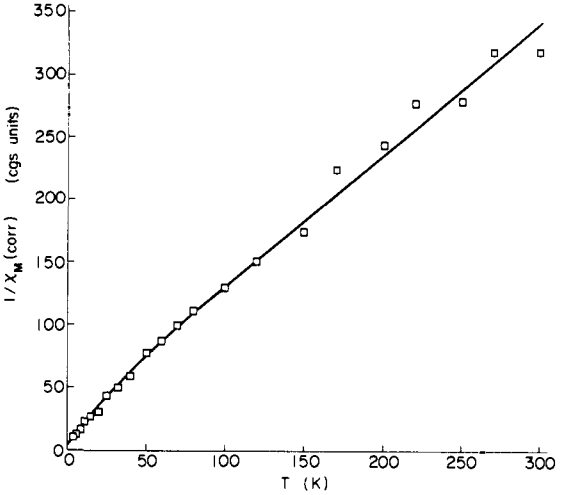


Figure 9. Variable temperature magnetic susceptibility of $FePiv_3$(5ClmP)Por(O_2).

The effective magnetic moments of all new iron(II) porphyrins isolated as solids were determined at room temperature by the Faraday method[32] and are reported in the Experimental Section. Good agreement was found with the proposed spin and coordination types with the exception of those compounds noted here.

The μ_{eff} values for solid samples of $FePiv_3$(5ClmP)Por and $FePiv_3$(4ClmP)Por are approximately 4.4 μ_B. This is too low for pure five-coordinate high-spin iron(II), and it seems likely that the coordination state of iron(II) in these compounds is complex. (Mössbauer results support this conclusion, vide infra.) Removal of $MeNH_2$ from the diamagnetic $FePiv_3$(5ClmP)Por($MeNH_2$) under vacuum (140 °C, 24 h, <1 μ) produces a solid believed to be the five-coordinate $FePiv_3$(5ClmP)Por on the basis of its characteristic high-spin iron(II) μ_{eff} of 5.1 μ_B.

All isolated solid dioxygen complexes of the "tail" porphyrins have typically had $\mu_{eff} = 2.0$–$2.8\ \mu_B$. Such values are too high to permit the conclusion that these solids are pure low-spin dioxygen complexes. Cerdonio has recently reported[33] that the susceptibility of oxy-Hb shows temperature-dependent behavior typical of a thermal equilibrium between a singlet ground state and a triplet excited state, with energy separation ($2J$) = 146 cm^{-1}. However, the variable-temperature susceptibility of $FePiv_3$(5ClmP)Por(O_2) (Figure 9) is not consistent with the concept of such a spin state equilibrium in this complex. The residual paramagnetism of these dioxygen complexes, then, has been assigned to iron(III) contaminants, and, in fact, a high-spin iron(III) signal is observed in the ESR spectra of these complexes.[4]

The magnetic susceptibility of several complexes has also been determined in toluene solution by the NMR method first outlined by Evans[34] and used successfully on iron porphyrins by Rougée and Brault.[35] While $FePiv_3$(5ClmP)Por and $FePiv_3$(4ClmP)Por exhibited μ_{eff}(20 °C) = 5.0 and 5.1 μ_B, respectively, their corresponding O_2 and CO complexes gave no observable paramagnetic shifts. From the concentrations used and the estimated minimum noticeable shift (~1.0 Hz on a 360-MHz instrument), $\mu_{eff} < 1.6\ \mu_B$ is indicated for these complexes in solution.

Proton Nuclear Magnetic Resonance. The ^{1}H NMR spectra of all new metal-free porphyrins were recorded and used for routine characterization and are reported in the Experimental

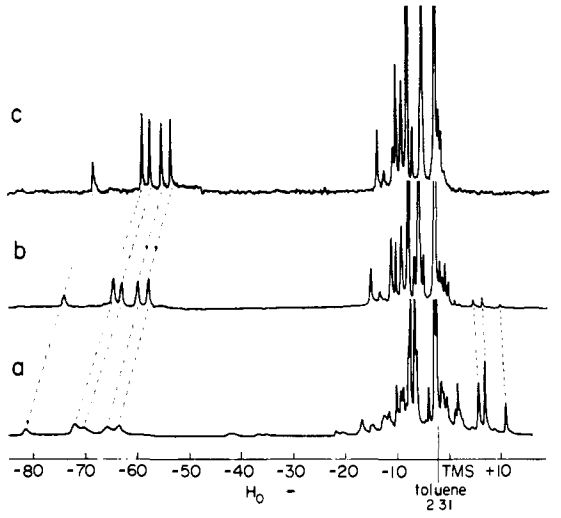


Figure 10. Variable temperature ^1H NMR spectra of $FePiv_3(4ClmP)Por$: (a) −25 °C; (b) 0 °C; (c) +25 °C.

Table III. Observed NMR Shifts of Pyrrole β Protons in Iron(II)/(III) TPP Complexes

complex	spin state	isotropic shift (vs. NiTPP)	chemical shift (vs. Me_4Si)	ref
FeTPP(Cl)	5/2	−70.2	−78.95	38a
FeTPP(2-MeIm)	2	−43.4	−52.2	40
$(FeTPP)_2O$	*a*	−4.7	−13.48	38a
FeTPP	1	+4.1	−4.65	31
$[FeTPP(Im)_2]^+Cl^-$	1/2	+25.4	+16.65	38b

[a] Antiferromagnetically coupled, $S = 5/2$.

Section. Well-resolved NMR spectra of the iron(II) complexes of the "tail" porphyrins have also been obtained.

Hemoproteins and model complexes in the high- and low-spin iron(III) forms,[36,37,38] as well as the physiologically more important iron(II) hemoproteins,[36,39] have been studied extensively by ^1H NMR during the past several years. However, work on simple iron(II) porphyrin model complexes has only recently been reported.[31,40] Invariably, the porphyrin and ligand proton signals have been found to be narrow and well resolved.

In tetraarylporphyrins, the large isotropic shifts of the pyrrole β protons are very characteristic of oxidation and spin state. Large contact shifts are also observed for coordinated axial ligands, while the shifts for the phenyl ring protons are relatively small. Table III contains chemical-shift data observed for the pyrrole β protons of a number of FeTPP complexes in different oxidation and spin states.

The ^1H NMR spectra of $FePiv_3(4ClmP)Por$ in toluene-d_8 at several temperatures are shown in Figure 10. The pyrrole β protons of this "picket fence" porphyrin give rise to four singlets (two protons each). At room temperature, these singlets are centered around −56 ppm vs. Me_4Si (convention designated downfield shifts as negative[31]), clearly indicating that the iron(II) is five coordinate and high spin. When the temperature is lowered, the Curie effect[41] causes the peaks to shift position somewhat; in addition, a new set of peaks between +5 and +10 ppm (vs. Me_4Si) appears. These peaks are assigned to the pyrrole β protons of square-planar iron(II) porphyrin (shifted to higher field[31] than in Table III as a result of the Curie effect) which apparently begins to form at this concentration (~1 mM) and temperature as the result of a dimerization process (eq 1). The peaks due to the diamagnetic, $S = 0$ complex which must be formed in this dimerization are expected to fall in the congested region between 0 and −10 ppm

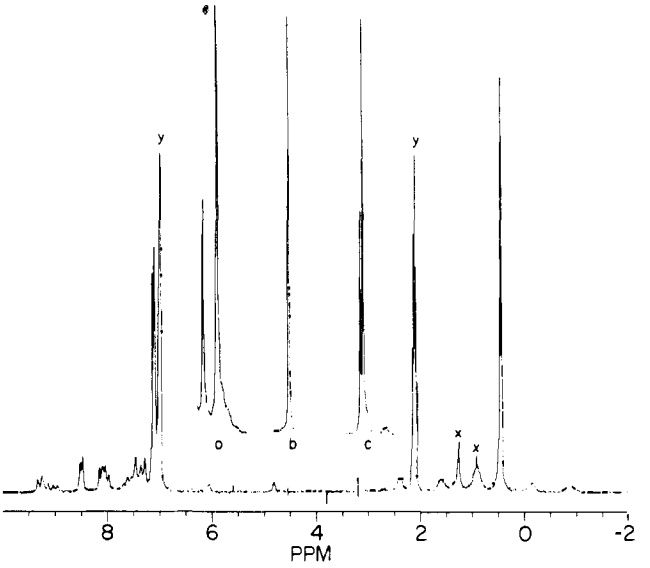
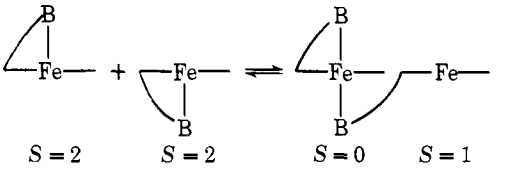


Figure 11. ^1H NMR spectrum of $FePiv_3(5ClmP)Por(O_2)$. y = toluene-d_8; x = heptane. (a) "Picket" region of $FePiv_3(4ClmP)Por(O_2)$, offset δ 5.5. (b) "Picket" region of $FePiv_3(5ClmP)Por(CO)$, offset δ 4.0. (c) "Picket" region of $FePiv_3(4ClmP)Por(CO)$, offset δ 2.5.



(1)

(vs. Me_4Si) and have not been assigned. When the temperature is lowered to −25 °C, the $S = 1$ peaks become quite pronounced; comparison with the remaining $S = 2$ peaks suggests >50% dimerization at this temperature and concentration. $FePiv_3(5ClmP)Por$ shows qualitatively the same behavior, though for this complex there is <50% dimerization at −25 °C. An analogous dimerization has been reported[3] for a different "tailed" porphyrin. It is expected that decreasing concentration will favor five coordination, although no study of the concentration dependence of this process has been carried out. Thus, at the concentrations used for UV/visible and MCD spectroscopy (~5×10^{-5} M), the dimerization process probably becomes significant only at temperatures below −25 °C.

When O_2 is admitted to samples of $FePiv_3(5ClmP)Por$ and $FePiv_3(4ClmP)Por$, all signals shift to their expected diamagnetic positions (pyrrole β protons at −8.5 ± 1 ppm vs. Me_4Si). No evidence of paramagnetic behavior in the pure O_2 complexes was found between −60 and +40 °C.

The ^1H NMR spectra of the CO complexes of the iron(II) "tail" porphyrins were also recorded, and are compared with those of the O_2 complexes in Figure 11. Of particular interest are the signals for the "picket" protons (two singlets, ratio 2:1); while these peaks are separated by ~5.5 Hz for $FePiv_3(4ClmP)Por(CO)$ and ~1.5 Hz for $FePiv_3(5ClmP)Por(CO)$, they are separated by ~25 Hz for $FePiv_3(4ClmP)Por(O_2)$ and ~7 Hz for $FePiv_3(5ClmP)Por(O_2)$. Though the actual separations of peaks are different for the two "tail" porphyrins, the increase in separation on going from the CO complex to the O_2 complex is about the same (proportionally) for both. The large effect of "tail" length is interesting, but until structures can be determined we cannot predict what porphyrin deformations are occurring. X-ray structures have shown CO to be bound linearly in model complexes[26] (Fe-C-O angle = 180°, normal to the porphyrin plane), while O_2 is bound in a bent geometry[42] (Fe-O-O angle ≃ 135°). In the structure of the original "picket fence" dioxygen complex,[42] $FeTpivPP(N\text{-}MeIm)(O_2)$, the O_2 was found to be fourfold disordered. Coupled with the reduction in symmetry of the binding pocket

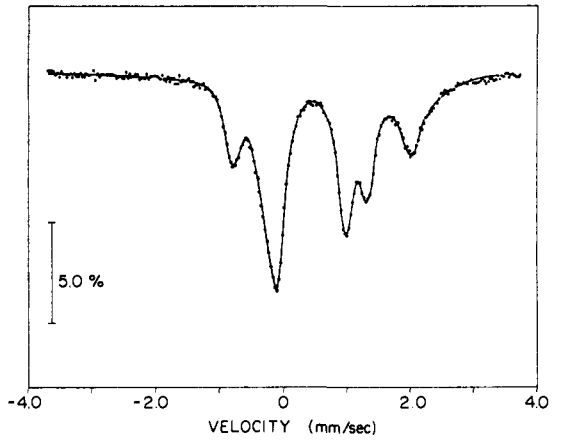


Figure 12. Mössbauer spectrum of $FePiv_3$(4ClmP)Por, 77 K, frozen benzene solution.

in the "three-picket" compounds, the NMR evidence suggests that the O_2 may be ordered in these complexes. The preferred orientation is presumably toward the open side of the "pocket", thus creating a large difference in the environments of the two types of "pickets" (whereas they are in nearly identical environments in the CO complexes). This remains a postulate, however, until the X-ray structure of the O_2 complex of one of the "tail" porphyrins can be determined.

Mössbauer Spectroscopy. Mössbauer spectroscopy yields useful information about the electronic configurations of diamagnetic as well as paramagnetic states[43a] and has been widely applied to the study of hemoproteins and simple model porphyrin complexes.[43,44] In an effort to probe further the coordination sphere of iron in the "tailed picket fence" porphyrins, zero field Mössbauer spectra of >90% ^{57}Fe enriched samples of $FePiv_3$(5ClmP)Por and $FePiv_3$(4ClmP)Por and their O_2 adducts were determined for frozen benzene solutions and powdered solid samples at 77 and 195 K. In all cases, the spectra were complex, overlapping doublets, indicating two or three major components (see, for example, Figure 12). The spectra were computer fit to pairs of Lorentzian lines, and isomer shift and quadrupole splitting parameters, as well as relative percent composition factors, were assigned to each doublet.

Table IV contains the zero-field Mössbauer parameters for several well-characterized iron(II) tetraarylporphyrins and for the frozen benzene solutions of the "tail" porphyrins. For both $FePiv_3$(5ClmP)Por and $FePiv_3$(4ClmP)Por, one major component of the spectrum can be assigned to the expected $S = 2$, five-coordinate species. The other major component in both cases is believed to be due to a mixture of six-coordinate ($S = 0$) and four-coordinate ($S = 1$) species, which arises from the previously mentioned dimerization at low temperature. (The remaining component in both spectra is probably due to partial oxygenation during sample preparation and handling.)

The major component in both oxygenated samples is clearly the dioxygen complex, with parameters nearly identical with those for FeTpivPP(*N*-MeIm)(O_2). The identity of the minor component has not been determined. It is possible for high-spin iron(III) to exhibit similar δ and ΔE values,[43a] and measurements were made in small applied magnetic fields at 4.2 K in order to investigate this possibility. No magnetic hyperfine structure was observed, indicating that this component, if iron(III), is not magnetically dilute. The possibility remains that it is iron(III), but magnetically coupled as a result of dimerization or segregation into a concentrated phase upon freezing of the solution.

Spectra of the powdered solid samples are qualitatively the same as those of the frozen benzene solutions discussed above.

Table IV. Mössbauer Spectral Parameters of Selected Iron(II) Tetraarylporphyrins[a]

complex	δ, mm/s	δE, mm/s	spin state	% of sample
FeTPP[b]	0.50	1.51	1	100
FeTPP(2-MeIm)[b]	0.92	2.26	2	100
$FeTPP(piperidine)_2$[b]	0.50	1.44	0	100
FeTpivPP(N-MeIm)(O_2)[c]	0.27	2.04	0 (oxy)	100
$FePiv_3$(5ClmP)Por (**8**, $n = 4$)	0.89	2.38	2	45
	0.44	1.05	1 and/or 0?	48
	0.26	2.12	0 (oxy)	7
$FePiv_3$(4ClmP)Por (**8**, $n = 3$)	0.98	2.13	2	29
	0.40	1.17	1 and/or 0?	46
	0.29	2.12	0 (oxy)	24
$FePiv_3$(5ClmP)Por(O_2) (**9a**, $n = 4$)	0.27	2.09	0 (oxy)	78
	0.43	1.02	1 and/or 0?	22
$FePiv_3$(4ClmP)Por(O_2) (**9a**, $n = 3$)	0.27	2.13	0 (oxy)	80
	0.44	1.02	1 and/or 0?	20

[a] 77 K, frozen benzene solution. [b] Reference 30. [c] Reference 44.

Both $FePiv_3$(5ClmP)Por and $FePiv_3$(4ClmP)Por are mixtures of five-coordinate, $S = 2$ species with $S = 0$ and $S = 1$ dimerization products. In these cases,the highly concentrated solutions from which the solids are precipitated probably contain reasonable quantities of the dimers. When the solids are exposed to oxygen, a proportion roughly equal to the amount of five-coordinate complex in the deoxy samples is converted to dioxygen complex, while the rest remains unchanged.

Elemental Analysis. Elemental analyses were obtained for key intermediates in the synthesis of the "tail" porphyrin complexes and are reported in the Experimental Section. Though highly crystalline CO adducts of the iron(II) "tail" porphyrins were obtained, only $FePiv_3$(5ClmP)Por(CO) gave a satisfactory analysis. However, an acceptable analysis has been obtained for $FePiv_3$(4ClmP)Por. Thus, at least one key complex in both the Piv_3(5ClmP)Por and Piv_3(4ClmP)Por series has been isolated in an analytically pure form. No analyses were attempted on the $MeNH_2$ adducts, as they slowly lose $MeNH_2$ upon standing, becoming paramagnetic. Solid dioxygen adducts also were not analyzed, primarily because of spectroscopic evidence, already discussed, for contamination of Fe(III) impurities.

Reactions with O_2 and CO. A large body of spectroscopic evidence has been presented to demonstrate that, near room temperature, $FePiv_3$(5ClmP)Por and $FePiv_3$(4ClmP)Por are predominantly five-coordinate, high-spin complexes in dilute toluene solution. An especially attractive feature of these complexes is that they allow the direct determination of the thermodynamic constants for the binding of dioxygen under *equilibrium* conditions, whereas recent studies[2] of simpler porphyrins have resorted to the extraction of thermodynamic constants from *kinetic* data. The apparatus and experimental details have been described elsewhere.[10] Inasmuch as these constants are a form of characterization for these compounds, the results of these studies are reproduced in Table V and compared with those for the natural proteins.

As mentioned (vide supra), carbon monoxide is bound linearly in simple iron(II) porphyrins. In Hb and Mb, however, the distal histidine (residue E7) serves to push CO off axis,[45] and it has been postulated[45a,46] that this distortion decreases the affinity of the natural proteins for CO. For this reason, it was suggested that model complexes should bind CO more strongly than the natural proteins, and qualitative evidence to this effect was reported.[11] Recent studies with $FePiv_3$(5ClmP)Por have shown this compound, in toluene solution, to bind CO approximately 100 times better than Hb and 1000

Table V. O_2 Affinities of Iron(II) Porphyrins and Hemoproteins

system	physical state	$P_{1/2}^{O_2}$ (25 °C), Torr	ref
Mb, sperm whale	pH 8.5	0.70	52
Hb, human ("R")	various	0.15-1.5[a]	13
FeTpivPP(*N*-MeIm)	solid state	0.49	11a
$FePiv_3$(5ClImP)Por	toluene solution	0.58	10
$FePiv_3$(4ClImP)Por	toluene solution	0.60	10
Hb, human ("T")	various	9-160	13
FeTpivPP(1,2-Me_2Im)[b]	toluene solution	38	10

[a] These are actually the first and fourth intrinsic $P_{1/2}$ values. [b] 1,2-Me_2Im = 1,2-dimethylimidazole.

times better than Mb (Table VI). The full details of this work will be presented elsewhere.[56]

Experimental Section

General. Proton magnetic resonance spectra were recorded on a Varian Instruments T-60 or XL-100 spectrometer. Variable-temperature studies on the five-coordinate "tail" complex were carried out on a JEOL PS-100 pulsed Fourier transform NMR spectrometer interfaced with a Digilab NMR-3 disk data system. Infrared spectra were obtained in KBr wafers or Nujol mulls on a Perkin-Elmer 457 or 621 grating spectrometer. Electronic spectra were recorded on a Beckman DB-G, Cary 17, or Cary 219 spectrometer. Analytical high-pressure liquid chromatography was carried out on a Du Pont "Zorbax Sil" silica gel column (¼ m) employing a Du Pont 830 pumping system and a Schoeffel Instruments tunable wavelength UV/visible detector.

Magnetic susceptibilities were determined on solid samples at room temperature using a Model 7600 Cahn Faraday apparatus, as previously described.[48] Variable-temperature measurements on solids were conducted on a Superconducting Technology, Inc., susceptometer, employing sampling techniques developed by Gillum and Laskowski.[49] Solution magnetic susceptibilities were measured on a Varian XL-100 NMR spectrometer, and the temperature of the probe was calibrated from observed peak separations for a MeOH sample. The concentric tube arrangement used was a standard 5-mm NMR tube with a Wilmad WGS-5 BL insert.

MCD spectra for toluene solutions were obtained on a JASCO Model J-40 spectrometer containing a 15.0 kG (1.5 T) electromagnet with field direction parallel to the direction of light propagation. All spectra were recorded, normalized, smoothed, and manipulated on a Data-General Nova Model 840 computer and stored on magnetic tape. $[\theta]_m$ is in units of deg cm^2 dmol^{-1} G^{-1}.

Mössbauer spectra were recorded on ^{57}Fe-enriched samples; details of the apparatus and techniques have appeared elsewhere.[44] Elemental analyses were performed by the Stanford Microanalytical Laboratory or by Spang Microanalytical Laboratory (Ann Arbor, Mich.).

Syntheses and purifications of the imidazole "tail" free base porphyrins were carried out in a darkroom lit by a 25-W red light bulb. Final recrystallizations were done in a Vacuum Atmospheres drybox, equipped with an MO-40 Dri-Train, under an atmosphere of N_2 with <1 ppm O_2 or H_2O. The atmosphere was monitored with a 1 N solution of diethylzinc in heptane and with a 25-W light bulb with a hole in the glass. Insertion of iron(II) was also carried out in the drybox.

Materials. All solvents and reagents were purchased commercially and used as supplied except as follows. DMF was distilled from BaO, under reduced pressure, onto activated Linde 4A molecular sieves. HMPA and NMP were distilled from CaH_2 under reduced pressure. Toluene was distilled from sodium under N_2. Benzene and THF were distilled from CaH_2 under N_2. Methanol was distilled from $Mg(OMe)_2$ under N_2. Heptane was stirred with 6 N H_2SO_4, then 0.5 M $KMnO_4$ in 6 N H_2SO_4, washed with dilute $NaHCO_3$ and H_2O, dried over $MgSO_4$, and distilled from sodium under N_2. 2,6-Lutidine was passed through alumina, then distilled from BF_3·Et_2O. *N*-MeIm was vacuum distilled from KOH. $^{57}Fe_2O_3$ (>90% enriched) was purchased from Oak Ridge National Laboratories and reduced to ^{57}Fe powder. Fe powder and ^{57}Fe powder was converted to $FeBr_2$ and $^{57}FeBr_2$ by literature procedure.[50]

Column chromatography was done on PF-254 silica gel 60 purchased from E. Merck (TLC grade) or on Type 62 (60-200 mesh) silica gel purchased from W. R. Grace. In both cases, the silica gel was dried for 24 h at 100 °C before use. Woelm activity grade I neutral alumina was also used for chromatography. TLC was done on commercially prepared silica gel or alumina plates purchased from Analtech, Inc.

Table VI. CO Affinities of Iron(II) Porphyrins and Hemoproteins

system	physical state	$P_{1/2}^{CO}$(20-25 °C), Torr	ref
Mb	pH 7-7.5	1.2×10^{-2} to 2.8×10^{-2}	53
Hb (α chains)	pH 7-7.5	2.5×10^{-3}	54
Hb (β chains)	pH 7-7.5	1.6×10^{-3}	54
Hb ("R" state)	pH 7-7.5	1×10^{-3} to 4×10^{-3}	55
$FePiv_3$(5ClImP)-Por	toluene solution	2.2×10^{-5}	56

***meso*-Mono(α-*o*-aminophenyl)tri(α,α,α-*o*-pivalamidophenyl)porphyrin (3).** *meso*-Tetra(α,α,α,α-*o*-aminophenyl)porphyrin (0.25 g, 0.37 mmol) was dissolved in 100 mL of CH_2Cl_2 and 0.25 mL of pyridine. Pivaloyl chloride (0.143 g, 1.18 mmol) in 10 mL of CH_2Cl_2 and 0.25 mL of pyridine was added in one portion and the solution allowed to stir for 8 h; 10% NH_4OH (250 mL) was added and the solution stirred for 2 h. The organic layer was separated and the aqueous layer extracted with $CHCl_3$. The combined organic portion was stripped to dryness and toluene (50 mL) added. The solution was again evaporated to dryness and the residue washed with petroleum ether. After the solvent was decanted, the material was dried in vacuo. Two such preparations were combined and chromatographed on 200 g of PF-254 silica using 6:1 $CHCl_3/Et_2O$ as the eluent. The second band was collected and stripped to dryness. Average yield was 233 mg (34%). This compound was identified by its NMR spectrum and by its conversion to the known H_2TpivPP. NMR ($CDCl_3$): δ 0.1 [s, 9 H, $(CH_3)_3C$-], 0.2 [s, 18 H, $(CH_3)_3C$-], 7-9 (m, 28 H, pyrrole β, phenyl, amide NH).

***meso*-Mono(β-*o*-aminophenyl)tri(α,α,α-*o*-pivalamidophenyl)porphyrin (4).** The α-amino compound **3** (500 mg, 0.54 mmol) was dissolved in 100 mL of benzene and the solution allowed to reflux for 2 h. The solution was then evaporated to dryness and the residue chromatographed on 175 g of PF-254 silica with 10:1 $CHCl_3/Et_2O$ as the eluent. The first band was collected and evaporated to dryness, affording 180 mg (36%) of the desired β-amino compound. The second band was removed from the column and recycled. Spectral properties of this compound were identical with those of the α-amino isomer. High-pressure liquid chromatography was used to identify desired products during chromatography and to test for purity. Best separations of the α- and β-amino isomers, as well as any other porphyrinic contaminants, were obtained using 65:35 hexane/CH_2Cl_2 containing 0.1% pyridine and 0.5% EtOH, 2000 psi, ¼ m Zorbax-Sil column, UV/vis detector at 420 nm.

***meso*-Mono(*o*-nitrophenyl)triphenylporphyrin.** Benzaldehyde (70.8 g, 0.667 mol) and *o*-nitrobenzaldehyde (50.5 g, 0.334 mol) were dissolved in 2 L of hot glacial acetic acid. The mixture was brought to reflux and 69.4 mL of pyrrole (1.0 mol) was added as rapidly as possible without causing uncontrollable exothermic reaction. The resulting black solution was heated at reflux for 20 min, then cooled in ice to 35 °C. Filtration through a course sintered glass funnel, followed by methanol washes and air drying at 100 °C, gave 11.0 g of fine, purple crystals. This mixture of porphyrins was stirred with 250 mL of benzene. The resulting solution was diluted with 250 mL of cyclohexane, filtered, and loaded onto a 4 × 24 in. column of 60-200 mesh silica, then eluted with 1:1 benzene/cyclohexane. The second band was the desired mononitrophenylporphyrin. This chromatographic procedure was repeated with the crude mixture that remained undissolved in the first run. The combined yield of mono(*o*-nitrophenyl)triphenylporphyrin was around 3.0 g, or approximately 2% based on starting pyrrole. IR (KBr): $\nu_{asym}NO_2$ 1522, $\nu_{sym}NO_2$ 1346 cm^{-1}. Anal. Calcd for $C_{44}H_{29}N_5O_2$: C, 80.10; H, 4.43; N, 10.62. Found: C, 78.62; H, 4.65; N, 10.26.

***meso*-Mono(*o*-aminophenyl)triphenylporphyrin (6).** The mononitroporphyrin (3.3 g, 5×10^{-3} mol) was dissolved in 200 mL of concentrated HCl, and 6.8 g of $SnCl_2 \cdot 2H_2O$ was added. The bright green solution was stirred at room temperature for 45 min and then heated at 65 °C for 30 min. After the solution was cooled in ice, concentrated ammonia was added to bring the pH of the suspension to 10. The

brown-violet mixture was stirred for 1 h with 500 mL of $CHCl_3$. The organic layer was separated, washed twice with H_2O, and dried over Na_2SO_4. After filtration, the solvent was removed on a rotary evaporator.

A chromatography column packed with 200 g of PF-254 silica gel in benzene was charged with 100 mL of a saturated benzene solution of the resulting mixture and eluted with benzene. The major slow-moving violet band afforded ~0.5 g of the pure aminoporphyrin. The same column was used several times; after all the mixture had been chromatographed, the final yield was 1.9 g (60%) of bright purple microcrystals. NMR ($CDCl_3$): δ −2.66 (s, 2 H, pyrrole NH), 3.36 (s, 2 H, NH_2), 6.8–8.3 (m, 19 H, phenyl), 8.6–9.1 (m, 8 H, pyrrole β). Anal. Calcd for $C_{44}H_{31}N_5$: C, 83.92; H, 4.96; N, 11.12. Found: C, 83.40; H, 5.18; N, 10.89.

5-Bromovaleryl Chloride. 5-Bromovaleric acid (50 g, 0.276 mol) was dissolved in 100 mL of dry benzene and heated at 50 °C. Oxalyl chloride (35 mL, 52 g, ~0.4 mol) was added slowly over the course of 3 h. When gas evolution ceased, the benzene was distilled off under reduced pressure and the residue vacuum distilled. Clear liquid (53 g, 97%) was obtained, bp 52–55 °C (0.3 mm), IR (film) ν_{CO} 1780 cm^{-1}.

Diphenylmethyl 5-Bromovalerate. 5-Bromovaleryl chloride (20 g, 0.1 mol) was dissolved in 50 mL of dry Et_2O and added over a period of 30 min to a solution of 18.4 g of diphenylcarbinol (0.1 mol) and 14 mL of Et_3N (0.1 mol) in 200 mL of dry Et_2O cooled to 0 °C. When the addition was complete, the resulting mixture was heated at reflux for 1 h. The precipitate of Et_3N·HCl was filtered off and washed with dry Et_2O; the organic solution was washed with 4 × 100 mL of H_2O and dried over $MgSO_4$. After removal of solvent under reduced pressure, the remaining pale yellow oil was dried at room temperature and 0.1 mm pressure for 2 h, affording 29 g (85%) of viscous liquid. IR (film): ν_{CO} 1730 cm^{-1}. NMR ($CDCl_3$): δ 1.8–2.1 (m, 4 H), 2.3–2.7 (m, 2 H), 3.2–3.6 (m, 2 H), 6.87 (s, 1 H), 7.27 (s, 10 H).

Diphenylmethyl 5-(*N*-Imidazolyl)valerate. A solution of *n*-BuLi in hexane (2.4 M, Alfa Chemicals) was added slowly by syringe to a solution of 2.72 g of imidazole (0.04 mol, recrystallized from benzene) and 0.005 g of triphenylmethane in 100 mL of THF under N_2 at 0 °C, until a faint pink color presisted on stirring. A concentrated solution of imidazole in THF was then added dropwise until the pink color just disappeared. The solution was stirred at 0 °C for 30 min (a white precipitate formed) and then warmed to room temperature. A solution of 6.88 g of diphenylmethyl 5-bromovalerate (0.02 mol) in 20 mL of THF was added, followed by 10 mL of HMPA, at which point the precipitate dissolved. The resulting pale yellow solution was stirred overnight at room temperature. The THF was then removed under reduced pressure on a rotary evaporator, and 400 mL of benzene added to the remaining liquid. The solution was washed with 2 × 250 mL of brine and 3 × 250 mL of H_2O and dried over Na_2SO_4. Solvent was removed on a rotary evaporator, and the remaining yellow oil purified by chromatography on 200 g of PF-254 silica gel with 5% MeOH in benzene eluent to give 6.25 g (93%) of pale yellow oil. IR (film): ν_{CO} 1725 cm^{-1}. NMR ($CDCl_3$): δ 1.7 (m, 4 H), 2.4 (m, 2 H), 3.8 (m, 2 H), 6.7 (s, 1 H), 6.8 (s, 1 H), 6.9 (s, 1 H), 7.1 (s, 1 H), 7.2 (s, 17 H). Product may contain some residual diphenylcarbinol or benzene (based on NMR integration).

5-(*N*-Imidazolyl)valeric Acid Hydrochloride. Diphenylmethyl 5-(*N*-imidazolyl)valerate (6 g, 0.018 mol) was dissolved in 50 mL of glacial acetic acid. Dry HCl was passed through the solution with vigorous stirring for 1 h. Acetic acid and HCl were removed under reduced pressure. The remaining oil was dissolved in 50 mL of H_2O and washed with 3 × 80 mL of Et_2O. The H_2O was removed under reduced pressure, leaving a pale yellow-green oil which was triturated with Et_2O to produce a pale yellow-white solid. Drying at <1 mm overnight (P_2O_5) afforded 3.0 g (82%) of product as a granular, pale tan solid. NMR (D_2O): δ 1.5 (m, 4 H), 2.4 (t, 2 H), 4.2 (t, 2 H), 7.4 (s, 2 H), 8.6 (s, 1 H).

Sodium Imidazolate. Imidazole (100 g, 1.47 mol) was dissolved in THF in an inert atmosphere box. Sodium hydride (34.7 g, 1.45 mol, 57% suspension washed three times with hexane to remove oil) was slowly added. The solution was allowed to stir until evolution of gas ceased (several hours). The white, crystalline product was isolated by suction filtration, washed with THF, and dried in a vacuum desiccator for 3 days, yield 123 g (93%). NMR (D_2O): δ 7.3 (s, 2 H), 7.9 (s, 1 H). NMR indicates approximately 0.6 mol of THF solvate.

4-(*N*-Imidazolyl)butyronitrile. 4-Bromobutyronitrile (16.6 g, 0.112 mol) was dissolved in 100 mL of dry THF in an inert atmosphere box. Sodium imidazolate (17.8 g, 0.199 mol) was added, and the solution was stirred for 24 h. After removal from the inert atmosphere box, the solution was filtered, the solid washed with $CHCl_3$, and solvent removed on a rotary evaporator. The crude product was vacuum distilled, and the fraction boiling at 148–150 °C (<1 mm) was collected, yield 10 g (66%). NMR (neat): δ 2.4 (m, 4 H), 4.0 (t, 2 H), 7.1 (s, 2 H), 7.6 (s, 1 H).

4-(*N*-Imidazolyl)butyric Acid Hydrobromide. Potassium hydroxide pellets (86%, 23.66 g, 0.363 mol) were dissolved in a minimum amount of H_2O (~5 mL). 4-(*N*-Imidazolyl)butyronitrile (10.9 g, 0.081 mol) was added, followed by enough ethanol to make the solution homogeneous. The solution was heated at reflux for 5 h. Hydrobromic acid (48%) was added until the pH reached ~4.0, causing KBr to precipitate as white crystals. The KBr was filtered off and solvent removed from the solution on a rotary evaporator. The solid was dried in a vacuum drying pistol at 100 °C (P_2O_5), affording 27 g of white powder containing ~50% KBr and ~50% desired product. NMR (D_2O): δ 2.4 (m, 4 H), 4.4 (t, 2 H), 7.7 (s, 2 H), 9.1 (s, 1 H).

***meso*-Tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-5-(*N*-imidazolyl)valeramidophenylporphyrin, $H_2Piv_3(5ClmP)Por$ (5a).** 5-(*N*-Imidazolyl)-valeric acid hydrochloride (110.3 mg, 0.538 mmol) was dissolved in 10 mL of freshly distilled DMF under N_2 and the solution cooled to 0 °C. A solution of 64.1 mg of $SOCl_2$ (0.538 mmol) in 2 mL of DMF was added and the solution allowed to warm to room temperature under a blanket of N_2. After 25 min, a solution of the "three picket β-amino" porphyrin **4** (250 mg, 0.29 mmol) in 5 mL of DMF was added and the resulting green solution stirred in the dark under N_2 for 12 h. The solution was then poured into 50 mL of benzene (in a darkroom with a weak red light), washed with 2 × 30 mL of 10% Na_2CO_3 and 2 × 30 mL of H_2O, and dried over Na_2SO_4. Solvent was removed on a rotary evaporator and the residue purified by chromatography on a column packed with 60 g of 60–200 mesh silica gel in CH_2Cl_2. Elution with 3% MeOH in CH_2Cl_2 removed a fast-moving minor band of unreacted starting material; 6% MeOH in CH_2Cl_2 was then used to remove the product. Removal of solvent on a rotary evaporator, followed by vapor diffusion of heptane into a concentrated benzene solution of the product, afforded 200 mg (64%) of the "picket fence" imidazole "tail" as shiny purple, crystalline clumps. Anal. Calcd for $C_{67}H_{68}N_{10}O_4$: C, 74.69; H, 6.36; N, 13.00. Found: C, 73.79; H, 6.39; N, 12.58. NMR ($CDCl_3$): δ 0.1 [s, 9 H, $-C(CH_3)_2$], 0.2 [s, 18 H, $-C(CH_3)_3$], 0.8–1.4 [m, 8 H, $-(CH_2)_3-$ + 2 H impurity], 3.2 (t, 2 H, CH_2), 6.1 (s, 1 H), 6.5 (s, 1 H), 6.65 (s, 1 H), 6.8 (s, 1 H), 7.1–8.1 (m, 16, phenyl), 8.4–8.9 (m, 11 H, pyrrole β + amide NH).

***meso*-Tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-4-(*N*-imidazolyl)butyramidophenylporphyrin, $H_2Piv_3(4ClmP)Por$ (5b).** 4-(*N*-Imidazolyl)-butyric acid hydrobromide (360 mg, 0.8 mmol, assuming 50% KBr by weight) was dissolved in 10 mL of freshly distilled DMF under N_2 and the solution cooled to 0 °C. A solution of 72 mg of $SOCl_2$ (0.6 mmol) in 2 mL of DMF was added and the solution allowed to warm to room temperature under a blanket of N_2. After 25 min, a solution of the "three picket β amino" porphyrin **4** (250 mg, 0.29 mmol) in 5 mL of DMF was added and the resulting green solution stirred in the dark under N_2 for 12 h. The remainder of the procedure was identical with that for $H_2Piv_3(5ClmP)Por$ (**5a**), as described above. Yield, after recrystallization, was 190 mg (61%) of bright clumps of dark violet crystals. NMR ($CDCl_3$): δ 0.1 [s, 9 H, $-C(CH_3)_3$], 0.2 [s, 18 H, $C(CH_3)_3$], 0.8–1.5 [m, 4 H, $-(CH_2)_2-$], 2.7 (t, 2 H, CH_2), 5.5 (s, 1 H), 5.65 (s, 1 H), 5.9 (s, 1 H), 7.0–82 (m, 16 H, phenyl), 8.3–9.0 (m, 12 H, pyrrole β + amide NH).

***meso*-Mono[*o*-5-(*N*-imidazolyl)valeramidophenyl]triphenylporphyrin (7a).** 5-(*N*-Imidazolyl)valeric acid hydrochloride (300 mg, 1.466 mmol) was dissolved in 20 mL of freshly distilled DMF under N_2 and the solution cooled to 0 °C. A solution of 174 mg of $SOCl_2$ (1.46 mmol) in 2 mL of DMF was added and the resulting solution allowed to warm to room temperature under a blanket of N_2. After 25 min, a solution of mono(*o*-aminophenyl)triphenylporphyrin (**6**, 500 mg, 0.794 mmol) in 10 mL of DMF was added and the resulting green solution stirred in the dark under N_2 for 12 h. The solution was then poured into 200 mL of benzene (in a darkroom with a weak red light), washed with 2 × 100 mL of 10% Na_2CO_3 and 2 × 100 mL of H_2O, and dried over Na_2SO_4. Solvent was removed on a rotary evaporator and the residue separated by chromatography on a column packed with 150 g of 60–200 mesh silica gel in CH_2Cl_2. The column was eluted with 1% MeOH in CH_2Cl_2 until the faster moving band of unreacted aminoporphyrin was removed and then with 5% MeOH in

CH_2Cl_2 to remove the purified product. After removal of solvent on a rotary evaporator, the product was taken into the drybox and recrystallized by vapor diffusion of heptane into a concentrated benzene solution, affording 410 mg (66%) of dark violet, crystalline product. Anal. Calcd for $(C_{52}H_{41}N_7O$: C, 80.07; H, 5.30; N, 12.57. Found: C, 79.60; H, 5.46; N, 12.30. NMR ($CDCl_3$): δ 0.8-1.4 [m, 6 H, $-(CH_2)_3-$], 3.1 (t, 2 H, CH_2), 6.27 (s, 1 H), 6.67 (s, 1 H), 6.81 (s, 1 H), 6.93 (s, 1 H), 7.4-8.4 (m, 18 H, phenyl), 8.6-9.0 (m, 9 H, pyrrole β + amide NH).

***meso*-Mono[*o*-4-(*N*-imidazolyl)butyramidophenyl]triphenylporphyrin (7b).** 4-(*N*-Imidazolyl)butyric acid hydrobromide (940 mg, 2.0 mmol, assuming 50% KBr by weight) was dissolved in 20 mL of freshly distilled DMF under N_2 and the solution cooled to 0 °C. A solution of 188 mg of $SOCl_2$ (1.6 mmol) in 2 mL of DMF was added and the resulting solution allowed to warm to room temperature under a blanket of N_2. After 25 min, a solution of mono(*o*-aminophenyl)triphenylporphyrin (**6**, 500 mg, 0.794 mmol) in 10 mL of DMF was added and the resulting green solution stirred in the dark under N_2 for 12 h. The remainder of the procedure was identical with that for the valeramido "tail" as described above. Yield, after recrystallization, was 430 mg (71%) of dark violet, crystalline clumps. NMR ($CDCl_3$): δ 0.8-1.4 [m, 4 H, $-(CH_2)_2-$], 2.9 (t, 2 H, CH_2), 5.75 (s, 1 H), 6.0 (s, 1 H), 6.4 (s, 1 H), 6.8 (s, 1 H), 7.3-8.3 (m, 19 H, phenyl), 8.4-8.9 (m, 9 H, pyrrole β + amide NH).

***meso*-Tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-3-(*N*-imidazolyl)propylureidophenylporphyrin (5d).** "Three picket β amino" porphyrin **4** (200 mg, 0.22 mmol) was dissolved in 75 mL of THF in a three-necked round-bottom flask equipped with three-way stopcock, stopper, and rubber septum. Phosgene (use extreme caution!) was blown over the stirred solution for 20 min, and the excess bubbled through aqueous base. Solvent was removed in vacuo, and 15 mL of THF was added with N_2 purge and removed in vacuo. The green residue was dissolved in 50 mL of THF and ~0.5 mL of pyridine. 3-(*N*-Imidazolyl)propylamine[20] (162 mg, 1.29 mmol) was dissolved in 3 mL of THF and a trace of pyridine and dipped into the red-brown porphyrin solution in the dark. The solution was stirred for 2 h; then solvent was removed in vacuo. The residue was taken up in toluene (in a darkroom with a weak red light), washed thrice with H_2O, and run into a 1 × 6 in. column of dry 60-200 mesh silica gel. Elution with EtOAc removed unreacted aminoporphyrin; then THF was used to elute a broad reddish-purple band of product. Solvent was removed on a rotary evaporator and the product recrystallized by vapor diffusion of heptane into a concentrated toluene solution in the drybox, yielding 170 mg (73%) of purple-red powder. IR: ν_{CO} 1690 $cm.^{-1}$

***meso*-Mono[*o*-3-(*N*-imidazolyl)propylureidophenyl]triphenylporphyrin (7c).** Mono(*o*-aminophenyl)triphenylporphyrin (**6**, 25 mg, 0.04 mmol) was dissolved in 20 mL of CH_2Cl_2. Phosgene was passed over the stirred solution for 10 min; then solvent and excess phosgene were removed in vacuo. CH_2Cl_2 (10 mL) was added, with N_2 purge, and then removed in vacuo. The residue was dissolved in 25 mL of CH_2Cl_2 and ~0.25 mL of pyridine. A solution of 28 mg of 3-(*N*-imidazolyl)-propylamine[20] (0.22 mmol) in 0.1 mL of CH_2Cl_2 and a trace of pyridine was dripped into the red-brown solution in the dark, and the solution stirred for 2 h. The rest of the procedure was identical with that for the "three picket" compound (**5d**) as described above. Yield, after recrystallization, was 18 mg (56%) of violet crystals. IR: ν_{CO} 1690 cm^{-1}. NMR (CD_2Cl_2): δ −2.89 (s, 2 H, internal pyrrole), 2.44 [m, 2 H, $-(CH_2)-$], 2.92 [t, 2 H, $-(CH_2)-$], 3.40 [t, 2 H, $-CH_2)-$], 5.6-6.3 (m, 5 H), 7.0-8.3 (m, 17 H), 8.5-8.9 (m, 8 H, pyrrole β).

***meso*-Tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-5-(*N*-imidazolyl)valeramidophenylporphyrinatoiron(II), FePiv$_3$(5ClmP)Por (8, *n* = 4).** In the inert atmosphere box, H_2Piv_3(5ClmP)Por (**5a**, 180 mg, 0.17 mmol) was dissolved in 6 mL of THF, 6 mL of benzene, and 0.1 mL of 2,6-lutidine. Anhydrous $FeBr_2$ (180 mg, 0.83 mmol) was added and the solution stirred at room temperature for 20 min. After an additional 25 min of heating at reflux, the solvent was removed under reduced pressure and the residue chromatographed on neutral activity I alumina (1 × 8 cm column), eluting with 2% MeOH in benzene. The porphyrin solution was collected and filtered. Heptane was added and the solution concentrated by removing solvent under reduced pressure. The red-violet powder which precipitated was filtered, washed with heptane, and dried, yield 177 mg (94%). Anal. Calcd for $C_{67}H_{66}N_{10}O_4Fe$: C, 71.14; H, 5.88; N, 12.38. Found: C, 70.18; H, 5.64; N, 12.24. μ_{eff}: solid (25 °C), 4.4 μ_B; solution (toluene, 30 °C), 5.0 μ_B. UV/vis: see Table I.

***meso*-Tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-4-(N-imidazolyl)butyramidophenylporphyrinatoiron(II), FePiv$_3$(4ClmP)Por (8, *n* = 3).** This compound was prepared as described above for FePiv$_3$(5ClmP)Por. Anal. Calcd. for $C_{66}H_{64}H_{10}O_4Fe$: C, 70.96; H, 5.77; N, 12.54; Fe, 5.00. Found: C, 70.47; H, 5.59; N, 12.47; Fe, 4.76. μ_{eff}: solid (25 °C), 4.3 μ_B; solution (toluene, 30 °C), 5.1 μ_B. UV/vis: see Table I.

***meso*-Mono[*o*-5-(*N*-imidazolyl)valeramidophenyl]triphenylporphyrinatoiron(II).** This compound was prepared as described above for FePiv$_3$(5ClmP)Por. Anal. Calcd for $C_{52}H_{39}N_7OFe$: C, 74.91; H, 4.71; N, 11.76. Found: C, 74.53; H, 5.11; N, 11.05. μ_{eff}: solid (25 °C), 4.3 μ_B. UV/vis: see Table I.

***meso*-Mono[*o*-4-(*N*-imidazolyl)butyramidophenyl]triphenylporphyrinatoiron(II).** This compound was prepared as described above for FePiv$_3$(ClmP)Por. μ_{eff}: solid (25 °C), 4.1 μ_B. UV/vis: see Table I.

FePiv$_3$(5ClmP)Por(O$_2$) (9a, *n* = 4). A concentrated solution of FePiv$_3$(5ClmP)Por in benzene was placed under an atmosphere of O_2. Vapor diffusion of heptane afforded an amorphous solid. NMR (toluene-d_8): δ −0.88 (m, 4 H, CH_2), −0.15 (m, 4 H, CH_2), 0.41 [s, 18 H, $C(CH_3)_3$], 0.48 [s, 9 H, $C(CH_3)_3$], 4.80 (s, 1 H), 6.05 (s, 1 H); 7.1-9.4 (m, 29 H, phenyl, pyrrole β, amide NH, imidazole). μ_{eff}: solid (25 °C), 2.2 μ_B. UV/vis: see Table I.

FePiv$_3$(4ClmP)Por(O$_2$) (9a, *n* = 3). The same vapor diffusion technique produced an amorphous solid. NMR (toluene-d_8): δ 0.36 [s, 18 H, $C(CH_3)_3$], 0.65 [s, 9 H, $C(CH_3)_3$], 1.47 (m, 2 H, CH_2), 1.80 (m, 4 H, CH_2), 4.85 (s, 1 H), 5.62 (s, 1 H), 7.1-9.4 (m, 29 H, phenyl, pyrrole β, amide NH, imidazole). μ_{eff}: solid (25 °C), 2.8 μ_B. UV/vis: see Table I.

FePiv$_3$(5ClmP)Por(CO) (9b, *n* = 4). A solution of FePiv$_3$(5ClmP)Por in benzene was evaporated under an atmosphere of CO. The solid was dissolved in toluene, and heptane was added to give a dilute solution. After several days, clumps of purple crystals formed. Anal. Calcd for $C_{68}H_{66}H_{10}O_5Fe$: C, 70.46; H, 5.74; N, 12.08; Fe, 4.82. Found: C, 70.18; H, 6.06; N, 11.73; Fe, 4.5. NMR (toluene-d_8): δ −1.17 (m, 4 H, CH_2), −0.40 (m, 4 H, CH_2), 0.31 [s, 18 H, $C(CH_3)_3$], 0.33 [s, 9 H, $C(CH_3)_3$], 4.02 (s, 1 H), 6.44 (s, 1 H), 7.1-9.4 (m, 29 H, phenyl, pyrrole β, amide NH, imidazole). μ_{eff}: solid (25 °C), 0.5 μ_B; solution (toluene, 30 °C), no observable paramagnetic shifts. UV/vis: see Table I.

FePiv$_3$(4ClmP)Por(CO) (9b, *n* = 3). The same dilution technique afforded small, dark red, single crystals. Anal. Calcd for $C_{67}H_{64}N_{10}O_5Fe$: C, 70.27; H, 5.63; N, 12.23. Found: C, 69.46; H, 5.72; N, 11.56. NMR (toluene-d_8): δ −0.10 (m, 4 H, CH_2), 0.32 [s, 18 H, $C(CH_3)_3$], 0.38 [s, 9 H, $C(CH_3)_3$], 3.35 (m, 2 H, CH_2), 3.94 (s, 1 H), 5.65 (s, 1 H), 7.2-9.4 (m, 29 H, phenyl, pyrrole β, amide NH, imidazole). μ_{eff}: solid (25 °C), 0.6 μ_B; solution (toluene, 30 °C), no observable paramagnetic shifts. UV/vis: see Table I.

FePiv$_3$(5ClmP)Por(MeNH$_2$) (9c, *n* = 4). A concentrated solution of FePiv$_3$(5ClmP)Por in benzene was placed under an atmosphere of $MeNH_2$. Vapor diffusion of heptane afforded clumps of dark purple crystals. The compound slowly loses weight in air and cannot be dried under vacuum without loss of $MeNH_2$, so no elemental analysis was obtainable. μ_{eff}: solid (25 °C), 0.7 μ_B; solid (140 °C, in vacuo, 24 h), 5.16 μ_B. UV/vis: see Table I.

FePiv$_3$(4ClmP)Por(MeNH$_2$) (9c, *n* = 3). The same procedure yielded only an amorphous film; no characterization was accomplished. UV/vis: see Table I.

FePiv$_3$(5ClmP)Por(*N*-MeIm) and FePiv$_3$(4ClmP)Por(*N*-MeIm) (9d). No attempts were made to isolate solids. Solutions were generated by the addition of 1 equiv of *N*-MeIm to solutions of the corresponding five-coordinate complexes, FePiv$_3$(5ClmP)Por and FePiv$_3$(4ClmP)Por. UV/vis: see Table I.

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References and Notes

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(51) Abbreviations: TPP = *meso*-tetraphenylporphyrinate, TpivPP = *meso*-tetra($\alpha,\alpha,\alpha,\alpha$-*o*-pivalamidophenyl)porphyrinate, Piv_3(4ClmP)Por = *meso*-tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-4-(*N*-imidazolyl)butyramidophenylporphyrinate, Piv_3(5ClmP)Por = *meso*-tri(α,α,α-*o*-pivalamidophenyl)-β-*o*-5-(*N*-imidazolyl)valeramidophenylporphrinate, *N*-MeIm = 1-methylimidazole, 1,2-Me_2Im = 1,2-dimethylimidazole, Hb = hemoglobin, Mb = myoglobin, CoHb = apohemoglobin reconstituted with cobalt protoporphyrinate IX, CoMb = apomyoglobin reconstituted with cobalt protoporphyrinate IX.
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