cyclophane.[1,2] The lengths of dipoles were considered to be standard C-X bond distances when X was a single atom. When X was a group of atoms, the dipole length was considered to be the maximum extension of the group as projected on the C-X bond axis. The dipole lengths used were C-H (1.09 Å), C-CN (2.62 Å), C-Br (1.94 Å), and CO_2R (2.99 Å). The position of the ionizable hydrogen was fixed at 1.45 Å beyond the carboxyl carbon on the extension of the C-C bond in accordance with the suggestion of Kirkwood and Westheimer.[7]

Bond or group moments were assessed from data tabulated by Smyth[29] for the dipole moments of substituted methanes in benzene solution. It is suggested that these values be used as they present a better interpretation than those based on gas-phase measurements.[29] It has been assumed that the bond moment of the C-H bond is 0.4 with hydrogen as the negative terminus.[7] Symth[29] devotes considerable discussion to this point and concludes that popular opinion supports 0.4 as the magnitude, but the controversy continues over the direction.

The effective dielectric (D_E) was calculated by the spherical cavity model of Kirkwood and Westheimer,[6] assuming an external dielectric of 32 and an internal dielectric of 2. The center of the dipole was placed 1.5 Å below the surface of the cavity, according to the suggestion of Tanford.[7e] This procedure fixes the cavity dimensions so that the effective dielectric may be calculated from the tabulations of Westheimer, Jones, and Lad.[7d]

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"Mercaptan-Tail" Porphyrins: Synthetic Analogues for the Active Site of Cytochrome P-450[1]

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Abstract: The synthesis and characterization of a series of tetraarylporphyrins which bear covalently attached alkyl and aryl mercaptans designed to serve as axial ligands are described. The coordination chemistry of the iron(II) complexes of these "mercaptan-tail" porphyrins has been investigated by ^1H NMR, IR, and electronic absorption spectroscopy, magnetic circular dichroism, and magnetic susceptibility measurements. Ferrous complexes of the alkyl mercaptan-tail porphyrins appear to remain four-coordinate, intermediate spin ($S = 1$) in solution. The situation is less clear in the case of appended aryl mercaptans and a "tail-on/tail-off" equilibrium is implicated. In the presence of carbon monoxide, however, binding of thiol trans to CO is observed in both the alkyl and aryl cases. By the addition of an appropriate base, six-coordinate mercaptide-Fe(II)-CO complexes can be generated; these reproduce quite well the characteristic absorption and MCD spectra of cytochrome P-450, suggesting that such compounds are indeed viable models for the active site of cytochrome P-450.

Introduction

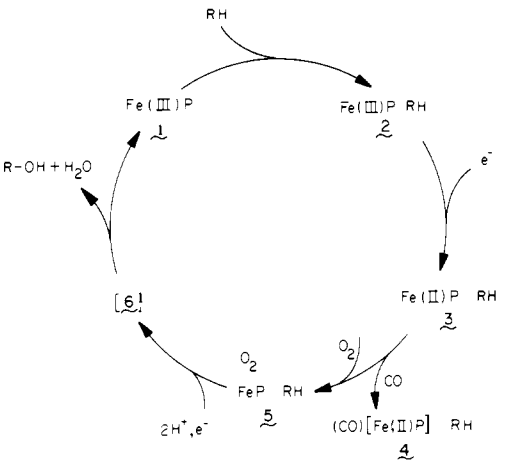
The activation of molecular oxygen has been a topic of considerable interest in recent years.[2-5] Despite the simplicity of the O_2 molecule, the chemist's ability to direct one or both atoms of dioxygen into an organic substrate in a highly specific manner remains severely limited. Biological systems, however, carry out reactions of this type readily and efficiently;[2,6-8] an understanding of the molecular dynamics of such systems thus might prove invaluable in designing simpler, synthetically useful oxidation catalysts.

We have been particularly interested in a class of enzymes known collectively as "cytochrome P-450".[9,10] These heme proteins are monooxygenases—i.e., they catalyze the hydroxylation of a substrate RH at the expense of molecular oxygen, through the reductive cleavage of the O-O bond:

$$R\text{-}H + O_2 \xrightarrow{2e^-,\ 2H^+} R\text{-}OH + H_2O \qquad (1)$$

Cytochrome P-450, found in plants, animals, and bacteria, participates in numerous metabolic pathways. Of particular importance in mammalian systems are the roles played by P-450

Scheme 1



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in steroid biosynthesis[11] and in the hydroxylation of such foreign lipophilic substances[12,13] as drugs, insecticides, and hydrocarbons. The latter process has the beneficial aspect of rendering these xenobiotic materials water soluble and thus excretable; on the other hand, this action of P-450 on certain substrates results in the production of highly reactive intermediates, which can then disrupt other cellular components.[14,15] (The carcinogenicity of polycyclic aromatics, for example, has been attributed to their conversion in vivo to arene oxides by P-450.[16])

The ability of cytochrome P-450 to generate an extremely potent oxidizing agent from dioxygen stands in sharp contrast to the more familiar oxygen- or electron-transport functions of many other heme proteins. Similarly, P-450 exhibits a number of spectroscopic characteristics which differ from those of other heme systems; the most striking of these, perhaps, is the unusual "hyper"-Soret absorption spectrum (λ_{max} ~380, 450 nm) seen in the carbon monoxide adduct of the enzyme. Such observations have led to the hypothesis[9,10] that an "uncommon" axial ligand is present at the iron protoporphyrin IX active site and is in large part responsible for many of the enzyme's atypical properties. Consequently, much work has been directed at the identification of the axial ligand(s) in P-450.

In general, most P-450 enzymes appear to follow the catalytic cycle illustrated in Scheme I,[10] where P represents protoporphyrin IX; R, the substrate; and R–OH, hydroxylated product. Mercaptide ligation from a cysteinate residue has been implicated in the ferric (**1**, **2**)[17-26] and ferrous + CO (**4**)[27-33] reaction stages, as a result of studies of both proteins and model systems. The data, however, are fewer and less convincing with respect to the conservation of mercaptide as a ligand in stages **3**, **5**, and **6**.[31-35] It has been suggested,[25] for example, that mercapt*an* (RSH) rather than mercapt*ide* (RS^-) may be bound in the ferrous deoxy form **3**, based on the absence of a "hyper"-type spectrum for **3** (predicted if RS^- were ligated). The idea of a mercaptan/mercaptide proton "shuttle" operating during catalysis is an intriguing one, which might in part account for the presence of thiolate as an axial ligand.

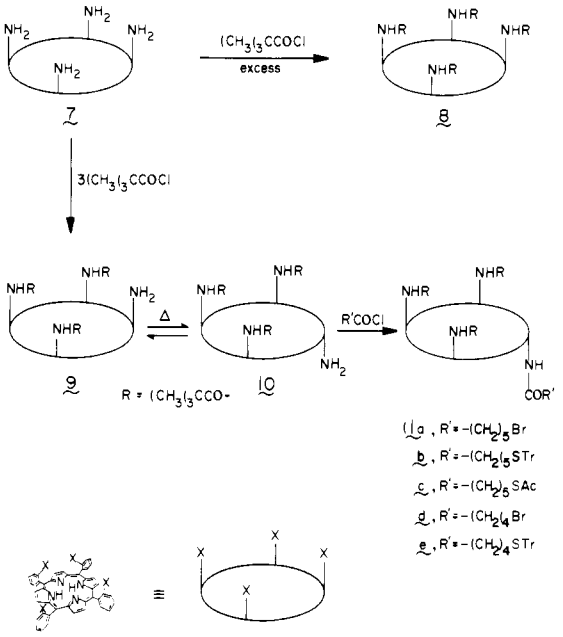

Figure 1. Synthesis of precursors to tripivalamide alkyl "mercaptan-tail" porphyrins.

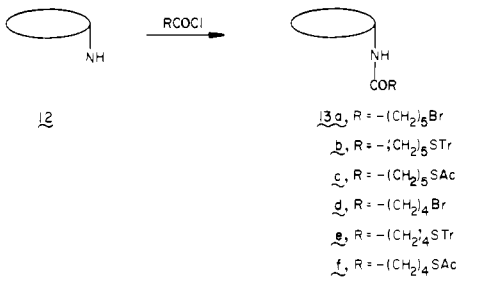

Figure 2. Synthesis of precursors to "picketless" alkyl "mercaptan-tail" porphyrins.

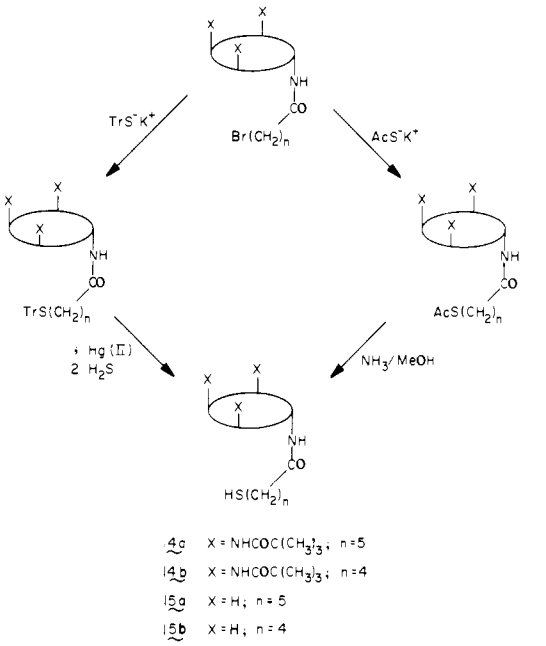

Figure 3. Synthesis of alkyl "mercaptan-tail" porphyrins.

We thus were interested in extending our earlier model studies of cytochrome P-450, in the hope both of assessing the role of axially ligated sulfur in determining the properties of the active site and of devising a simple system which might eventually be useful in mimicking the oxygen-activating abilities of the enzyme.

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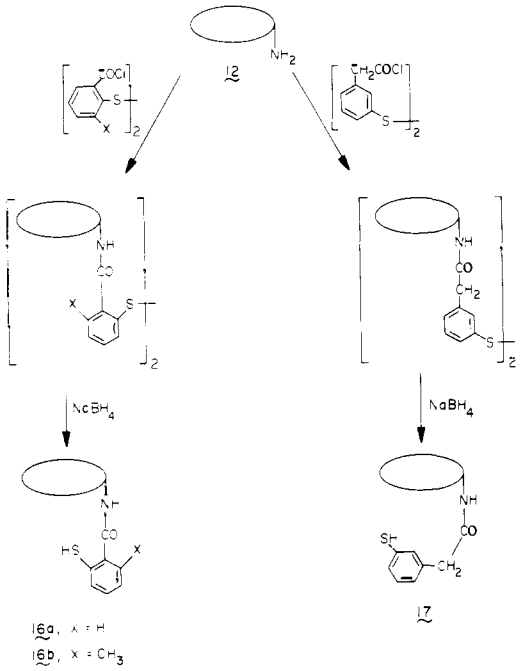

Figure 4. Synthesis of aryl "mercaptan-tail" porphyrins.

We report here the synthesis and characterization of the resulting novel class of tetraaryl "mercaptan-tail" porphyrins and present, in addition, selected aspects of their coordination chemistry.

Results

Ligand Design. Our ultimate goal of investigating the oxygen chemistry of sulfur-ligated iron porphyrins called for a model system which would be capable of interacting with O_2 in a nondestructive manner. The autoxidation of ferrous porphyrins in the presence of dioxygen is a well-known phenomenon;[36,37] previous work, however, has shown that this process, which requires the interaction of two iron sites, can be blocked by the incorporation of steric bulk on one face of the porphyrin macrocycle.[38,39] A second problem concerns the reactivity of thiol and thiolate groups with respect to oxygen; these species are readily oxidized to disulfides in the presence of O_2.[40] Earlier model studies involving the interaction of mercaptides with Fe(II) porphyrins implied that a gross excess of ligand (10^2–10^4-fold) was necessary in order to promote binding.[28,31] This requirement for such a large quantity of a noninnocent ligand (RS^- is also a reducing agent) was foreseen as leading to potentially serious complications in a study of oxygen binding and activation.

We have sought to circumvent these problems through the covalent attachment of a mercaptan to a sterically shielded porphyrin macrocycle. Appending the axial ligand in this way provides for a high local concentration of ligand at the metal binding site, while at the same time retaining a 1:1 metal:ligand stoichiometry. The presence of three pivalamide groups on the opposite side of the porphyrin provides sufficient steric bulk to inhibit autoxidation. "Tripivalamide-tail" porphyrins incorporating imidazoles[41] and thioethers[42] as appended ligands have been prepared previously in our laboratories; we now extent this series to include alkyl and aryl mercaptans and mercaptides.

Table I. Tailed Tripivalamide and "Picketless" Porphyrins Prepared (Including "Trivial" Name)

series	tripivalamide	picketless
alkyl	11a, tC_5Br	13a, mC_5Br
	11b, tC_5STr	13b, mC_5STr
	11c, tC_5SAc	13c, mC_5SAc
	11d, tC_4Br	13d, mC_4Br
	11e, tC_4STr	13e, mC_4STr
	14a, tC_5SH	13f, mC_4SAc
	14b, tC_4SH	15a, mC_5SH
		15b, mC_4SH
aryl	16a, mPhSH	
	16b, m3MSH	
	17, mPASH	

Synthesis. The general route to synthesis of "mercaptan-tail" porphyrins involves formation of an amide linkage between a "parent" (*o*-aminophenyl)triphenylporphyrin and an acid chloride "tail" bearing the protected mercaptan; following attachment of the tail to the macrocycle, the thiol may be freed from its protecting group (Figures 1–4). The parent tripivalamide compound, *meso*-β-(*o*-aminophenyl)-α,α,α-tris[*o*-(pivalamido)phenyl]-porphyrin (**10**), was prepared through a modification of the original "picket-fence" porphyrin (**8**, H_2T pivPP) synthesis.[38] The readily available tetrakis(*o*-aminophenyl)porphyrin (**7**) was treated with 3 equiv of pivaloyl chloride to afford a mixture from which the desired α-NH_2 tripivalamide species **9** could be isolated by column chromatography in 35% yield. Heating **9** in refluxing benzene for 2 h resulted in rotation of the free *o*-amino group to give a 1:1 mixture of **9** and the desired β-amino isomer **10**; **9** could then be reequilibrated to obtain more of the β isomer (Figure 1). For many investigations, the three "picket" groups were not required; consequently, a parallel series of "picketless" tailed porphyrins was also prepared, based on the parent compound *meso*-(*o*-aminophenyl)triphenylporphyrin (**12**). The condensation of pyrrole with a 2:1 mixture of benzaldehyde and *o*-nitrobenzaldehyde gave a statistical mixture of (*o*-nitrophenyl)porphyrins. Through column chromatography, the desired (*o*-nitrophenyl)-triphenylporphyrin was obtained; reduction of the nitro group with $SnCl_2$ and HCl produced compound **12** in good yield (Figure 2).

Protection of the thiol group during tail attachment was necessary in order to avoid competing thioester formation. In the alkyl mercaptan-tail series, this was accomplished through use of *S*-trityl and *S*-acetyl groups. Thus, treatment of the salt of 6-bromohexanoic acid with either $(C_6H_5)_3CS^-K^+$ (i.e., TrS^-K^+) or $CH_3COS^-K^+$ (AcS^-K^+) gave in good yield the ω-substituted *S*-trityl or *S*-acetyl carboxylic acids. The corresponding S-protected pentanoic acid tails could not be prepared in this fashion, due to competing lactonization. The shorter-tailed porphyrins were thus obtained by first adding 5-bromopentanoyl chloride to the parent aminoporphyrin; treatment of this "bromo-tail" species with either TrS^-K^+ or AcS^-K^+ then afforded the protected sulfur-tail porphyrin.

A variety of methods for removing acetyl and trityl protecting groups from sulfur have been explored; we have found that in our systems, deacetylation is best accomplished by treatment with an ammonia-saturated solution of methanol over several hours at room temperature. (In general, reaction conditions requiring temperatures in excess of ~70 °C were avoided, in order to minimize any chances for picket or tail rotation.) Even under these conditions, however, yields of only 50–60% were realized, together with incomplete conversion of starting material. Use of the trityl protecting group was found to be much more efficient. Detritylation was initiated by the addition of Hg(II) to an *S*-trityl-tail porphyrin in 1:1 CH_2Cl_2–C_2H_5OH; treatment of the resulting Hg–SR complex with H_2S gave the desired mercaptan-tail porphyrin in nearly quantitative yield (Figure 3).

The porphyrins synthesized by these various procedures are listed in Table I. [In the abbreviated nomenclature used, t indicates a tripivalamide porphyrin (**11**, **14**); m, a derivative of the aminoporphyrin **12** (**13**, **15**); and C_n, the number of CH_2 units

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in the tail.] All of the tail porphyrins prepared have been thoroughly characterized by elemental analysis, electronic and ^1H NMR spectroscopy, and mass spectrometry (the latter for compounds of molecular weight <1200) (see Experimental Section). The presence of free SH groups has been verified further by chemical derivatization, using the thiol-specific fluorescent tag 4-(*N*-(iodoacetoxyethyl)-*N*-methylamino]-7-nitrobenz-2-oxa-1,3-diazole (IANBD).[43] In addition, a sample of mC_5SAc, prepared by the acetylation of detritylated mC_5STr, was shown by TLC R_f and ^1H NMR to be identical with a sample of mC_5SAc prepared by the addition of $AcS(CH_2)_5COCl$ to **12**.

The alkyl mercaptan-tail porphyrins (and, to a lesser extent, the S-protected derivatives) were found to be quite sensitive to the combination of light and air. This phenomenon was noticed earlier with the imidazole-appended porphyrins[41] and has been attributed to destructive side reactions resulting from the porphyrin-catalyzed production of singlet oxygen.[44] This light-induced decomposition could be avoided by carrying out all manipulations involving sulfur-containing porphyrins under an inert atmosphere, with a 25-W red light as the only source of illumination.

During the course of our investigation, it became apparent (vide infra) that the 4- and 5-methylene-carbon alkyl tails, while quite capable of delivering a thiol to the metal binding site, were nevertheless too flexible actually to hold the ligand at the metal—a feature which was necessary in order to compensate for the relatively low affinity of Fe(II) for RSH.[45] The need for a more rigid tail, plus the idea that a less electron-donating mercaptan might be a better ligand, led to the design of a series of *aryl* thiol-tail porphyrins (Figure 4). In these compounds, the tails are derived from either *o*-mercaptobenzoic acid or (*m*-mercaptophenyl)acetic acid and are attached to the parent aminoporphyrin via an amide bond.

In this series, the potential thiol moiety was introduced as the disulfide; thus, treatment of **12** with an excess of the diacid chloride of 2,2′-dithiobis[benzoic acid], followed by reduction of the disulfide bond with $NaBH_4$ in ethanol, gave the free mercaptan-tail species **16a** in good yield. The (*m*-mercaptophenyl)acetic acid derivative **17** was prepared in an analogous fashion, as was the methyl-substituted compound **16b**. (The latter feature was introduced to facilitate assignment of resonances in the NMR spectrum.) The aryl mercaptan-tail porphyrins proved to be even more sensitive to light and air than the alkyl series, decomposing to the extent of 50% after 10-min exposure. Consequently, these species were best handled under an argon blanket, especially during chromatography.

The aryl tail porphyrins (Table I) were also thoroughly characterized (see Experimental Section). Here, in particular, the ^1H NMR data for the free-base porphyrins are especially informative (Experimental Section). The spectra reveal that the resonance positions for the tail phenyl protons have been shifted well upfield from the normal aromatic region of 7–8 ppm (from Me_4Si). These shifts are due to the shielding effect of the porphyrin ring current and indicate clearly that the aryl tails are constrained to lie under the plane of the macrocycle. The effect is particularly striking in compound **17**, mPASH; here, tail phenyl and thiol proton resonances as far upfield as 2.9 and 1.4 ppm, respectively, are observed. Thus, as implied by an examination of molecular models, the tail configuration in mPASH appears especially well suited for delivery of an axial mercaptan to the metal binding site.

Metal Complexes. Complexes of Fe(II) with both alkyl and aryl mercaptan-tail porphyrins have been prepared and characterized (vide infra) (Figure 5). Iron was inserted into the macrocycle by the so-called "direct method",[41] in which the free-base porphyrin is heated briefly in 1:1 C_6H_6–THF containing a trace of the proton scavenger 2,6-lutidine. Treatment of this solution with solid anhydrous $FeBr_2$ gives complete metalation within 10–20 min. The ferrous alkyl tail complexes were separated from residual iron salts via passage through a small column of silica gel or neutral alumina. The metal-free aryl mercaptan-tail porphyrins had been found to react with alumina; consequently, these ferrous complexes were purified on silica. The coordination chemistry of iron(II) in these complexes has been investigated by a variety of physical methods, including UV/visible, IR, and NMR spectroscopy, magnetic circular dichroism, and magnetic susceptibility measurements. The results of these studies will be discussed on the basis of technique (below).

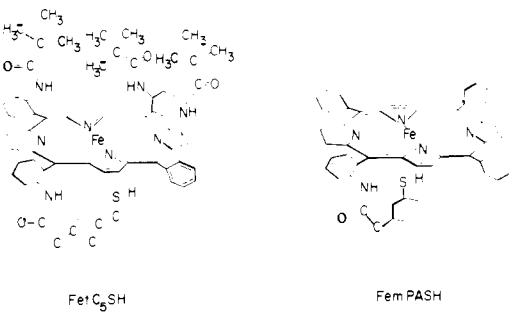

Figure 5. Representative Fe(II) mercaptan-tail porphyrins.

Table II. Electronic Absorption Data for Various Iron(II) Porphyrins[a]

complex	λ, nm (ε, 10^{-3} M^{-1} cm^{-1})
	Alkyl SH Tails
$FemC_4SH$	400,[b] 418 (86), 442 (63), 537 (8.7)
$FemC_5SH$	400,[b] 418, 441, 537
$FetC_5SH$	400,[b] 415 (37.6), 441 (37.5), 536 (5.8)
$Fe(mC_4SH)(CO)$	422 (196), 542 (8.7), 516[c]
$Fe(mC_5SH)(CO)$	422, 541, 516[c]
$Fe(tC_5SH)(CO)$	423 (100), 540 (3.9)
	Aryl SH Tails
FemPhSH	400,[b] 419 (140.5), 442 (102.6), 538 (15.6)
Fem3MSH	400,[b] 418, 441, 537
FemPASH	400,[b] 421 (79.0), 440,[c] 528 (3.7), 548 (3.3)
Fe(mPhSH)(CO)	412 (207.4), 422,[c] 517 (13.0), 548 (12.6), 590,[c] 620[c]
Fe(m3MSH)(CO)	413, 422,[b] 518, 548, 590,[c] 620[c]
Fe(mPASH)(CO)	422 (159.9), 512 (10.2), 543 (11.1)
	Miscellaneous
FeTPP[d,e]	400,[b] 419 (107), 442 (79.5), 537 (9.5)
FeTpivPP[d]	400,[b] 415 (96.6), 440 (93.0), 536 (2.8)
Fe(TPP)(2-MeIm)[d,e]	368 (21.8), 436 (260), 537 (7.7), 565 (8.1), 610 (3.3)
Fe(TPP)(*N*-MeIm)[d,e]	427 (252), 535 (20.5), 565 (4.8)
Fe(TPP)(MeOH)	424, 545

[a] In toluene, 25 °C. [b] Inflection point. [c] Shoulder. [d] Reference 41. [e] 2-MeIm = 2-methylimidazole; *N*-MeIm = *N*-methylimidazole; TPP = *meso*-tetraphenylporphyrinate.

Discussion

UV/Visible Spectroscopy. Electronic absorption data for various Fe(II) alkyl and aryl mercaptan-tail porphyrins and their carbon monoxide adducts are presented in Table II. In the absence of CO, both the tripivalamide and picketless alkyl mercaptan tails exhibit essentially identical spectra, characterized by a split Soret band with maxima at 415–418 nm > 441–442 nm and a single visible band at 536–537 nm. These spectra are quite similar to those of the square-planar complexes FeTPP and FeTpivPP and are in marked contrast to features observed for five-coordinate, $S = 2$ complexes with either nitrogen or oxygen ligands. This was unexpected since it had been presumed that thiols, like alcohols,[46] would behave as weak-field ligands and lead

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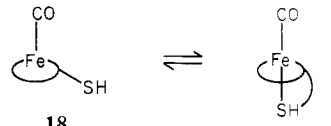
to high-spin, five-coordinate complexes. Instead, the electronic absorption data suggest that RSH has little, if any, tendency to coordinate to Fe(II) in solvents such as toluene or dichloromethane. (Parallel experiments with FeTPP and *n*-propyl mercaptan support this point; no change from the spectrum of FeTPP was observed, even in the presence of a 300-fold excess of mercaptan.) Attempts to enforce coordination of the appended mercaptan by lowering the temperature were unsuccessful; at −45 °C, the spectrum of Fe(mC$_4$SH), for example, was essentially identical with that recorded at room temperature. Apparently, the entropic advantage gained by delivering an axial mercaptan in this way is insufficient to overcome the low affinity of Fe(II) for RSH. This result led to the development of the aryl mercaptan-tail series (vide supra). [It should be noted that thiol ligation has been assumed to lead to an $S = 2$ system; we have not, however, been able to rule out the intriguing possibility of an intermediate-spin ($S = 1$), five-coordinate Fe(II)-RSH complex.]

The ability of these appended alkyl mercaptans to serve as axial ligands under suitable conditions is, nevertheless, without question. The addition of carbon monoxide to a solution of a ferrous alkyl mercaptan-tail porphyrin leads to immediate and distinctive changes in the visible spectrum. The CO adducts are marked by a single sharp Soret absorption maximum at 422 nm, together with a band near 542 nm and a shoulder around 517 nm. (The latter feature is lacking in the tripivalamide derivatives.) These spectral changes correlate well with those observed for other six-coordinate, low-spin Fe(II)–CO complexes;[41,42] in addition, an identical spectrum could be obtained by treating a solution of FeTPP with CO in the presence of excess *n*-C$_3$H$_7$SH. Thus, the presence of a π acid such as CO as a fifth ligand apparently induces binding of mercaptan at the sixth site—presumably by causing a decrease in the effective electron density at iron through π-back-bonding.

Although quantitative studies have not yet been conducted, we have observed that CO is not bound as tightly in the alkyl mercaptan-tail complexes as in comparable imidazole-tail systems.[47] Removal of solvent in vacuo from a solution of Fe(tC$_5$SH)(CO), for example, led to formation of the square-planar complex Fe(tC$_5$SH); subsequent exposure to CO regenerated the six-coordinate CO–Fe(II)–RSH adduct. Similarly, dilution of a solid sample of Fe(tC$_5$SH)(CO) into toluene in the absence of additional CO resulted in a mixture of the four- and six-coordinate species. This relatively low affinity for CO is of interest, in light of similar behavior in cytochrome P-450[48] and suggests further the feasibility of solid–gas equilibration methods[49] in eventual O_2 binding studies.

Comparison of the electronic absorption characteristics of the ferrous aryl mercaptan-tail complexes with those of the alkyl series reveals some interesting differences. The spectrum of the *o*-mercaptobenzamide-tail porphyrin, Fe(mPhSH) (Table II), is much like those of the ferrous alkyl tail species, implying that Fe(mPhSH) is also an $S = 1$, square-planar complex. The (*m*-mercaptophenyl)acetamide tail compound, Fe(mPASH), however, exhibits, in place of the split Soret band of other $S = 1$ systems, a rather broad absorption centered at 421 nm, together with an asymmetric feature comprising overlapping α and β bands at 528 and 548 nm. This perturbation, we believe, may reflect the presence, to some extent, of a five-coordinate, $S = 2$, Fe(II)–thiol complex (vide infra).

Under carbon monoxide, the two types of aryl tails again behave in distinctive manners. Exposure of Fe(mPASH) to CO gave cleanly a spectrum of the type expected for a six-coordinate Fe(II)–RSH–CO complex, with λ_{max} at 422 nm. The same treatment in the case of Fe(mPhSH) and Fe(m3MSH), however, led to Soret maxima near 412, rather than 422 nm. The similarity between these spectra and that obtained upon treatment of FeTPP itself with CO[50] suggests that the presence of carbon monoxide is *not* sufficient to induce trans ligation of thiol in the *o*-mercaptobenzamide-tail compounds. Such ligation could be promoted, though, by lowering the temperature to 0–15 °C; under these conditions, a sharp Soret band at 422 nm was observed, together with a shift in the α- and β-band intensities (such that 548 > 517 nm), as expected for a CO–Fe(II)–RSH complex. These results suggest that in Fe(mPhSH) and Fe(m3MSH) there exists a "tail-off/tail-on" type of equilibrium in the presence of CO:



(2)

18 λ_{max} = 412 nm 19 λ_{max} = 422 nm

At 25 °C the equilibrium lies in favor of the "tail-off" species, and λ_{max} is 412 nm. A decrease in temperature, however, causes the "tail-on" species to predominate, as signaled by the shift in λ_{max} to 422 nm. This hypothesis also gains support from ^{1}H NMR data: the chemical shifts relative to one another of the tail phenyl protons in Fe(mPhSH)(CO) are different in spectra recorded at 25 and 0 °C (while the resonant positions for other protons remain unchanged). This suggests that an alteration in tail conformation does in fact accompany the observed change in the visible spectrum, as expected for such an equilibrium.

^{1}H NMR Spectroscopy. The proton NMR spectra of simple iron porphyrin complexes have been extensively investigated by La Mar and others.[51-55] Several factors can influence the resonant position of a proton in such a complex: these include the porphyrin ring current and, for paramagnetic species, an isotropic shift comprising contact and dipolar contributions. La Mar and Walker[53] have shown that the meso-phenyl groups in tetraarylporphyrin complexes are effectively insulated against spin

Table III. ^{1}H NMR Shifts Observed for β-Pyrrole Protons in Various FeTPP Complexes

compound	spin state	(vs. Me$_4$Si)	ref
[FeTPP(1m)$_2$]Cl[a]	$^1/_2$	+16.7	53
FeTPP	1	−4.7	52
FeTPP(2-Melm)	2	−52.2	51
FeTPPCl	$^5/_2$	−79	56

[a] 1m = imidazole

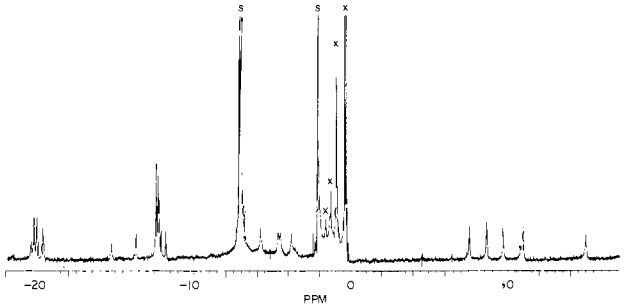


Figure 6. 360-MHz ^{1}H NMR spectrum of Fe(mC$_5$SH) in toluene-d_8. S = solvent, X = impurity. (Shifts here and in other spectra are relative to Me$_4$Si.)

(46) Brault, D.; Rougee, M. *Biochemistry* **1974**, *13*, 4591–4597, 4598–4602.
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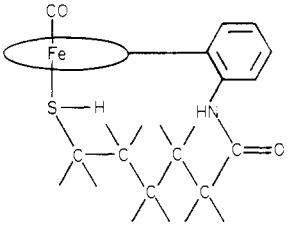
(49) Collman, J. P.; Brauman, J. I.; Rose, E.; Suslick, K. S. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 1052–1055.
(50) Wayland, B. B.; Mehne, L. F.; Swartz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2379–2383.
(51) Goff, H.; La Mar, G. N. *J. Am. Chem. Soc.* **1977**, *99*, 6599–6606.
(52) Goff, H.; La Mar, G. N.; Reed, C. A. *J. Am. Chem. Soc.* **1977**, *99*, 3641–3646.
(53) La Mar, G. N.; Walker, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 1782–1790.
(54) Mispelter, J.; Momenteau, M.; Lhoste, J. M. *Mol. Phys.* **1977**, *33*, 1715–1728.
(55) Mispelter, J.; Momenteau, M.; Lhoste, J. M. *J. Chem. Phys.* **1980**, *72*, 1003–1012.

transmission by virtue of their orientation perpendicular to the macrocyclic π system; thus, the isotropic shifts observed for such protons are essentially dipolar in origin. The β-pyrrole protons, on the other hand, experience significant contact interactions;[51-55] the chemical shifts of these protons are, in fact, quite sensitive indicators of the spin and oxidation state of the metal (Table III).

Proton NMR spectra of the Fe(II) alkyl and aryl mercaptan-tail porphyrins and their CO adducts have been obtained at 100 and 360 MHz by pulsed Fourier transform techniques. The spectrum of Fe(mC_5SH) in toluene-d_8 (Figure 6) is representative of the ferrous alkyl tail complexes. Peak assignments are based on integrated values and on data previously reported for FeTPP[52] and FeTpivPP;[54] the asymmetry induced by appending a tail has precluded, however, the exact assignment of individual resonances. Despite this asymmetry, Fe(mC_5SH) clearly exhibits the key features of an $S = 1$ system:[52] β-pyrrole resonances at -4.5 ppm, o-phenyl signals at -20 ppm, and m- and p-phenyl signals at -12 ppm vs. Me_4Si. (By convention, shifts downfield from Me_4Si in paramagnetic species are defined as negative.[52]) The tail CH_2 protons appear as singlets in the region +7-16 ppm; this upfield shift results from dipolar shielding and is similar to the shifts observed for the "pickets" in FeTpivPP (~+14 ppm).[54] The SH resonance could not be determined unequivocally; integration and D_2O-exchange experiments, however, suggest that it may lie buried in the methylene signal at +11 ppm.

The NMR data thus support the assignment of an $S = 1$ spin state for Fe(II) in the alkyl tail complexes. Variable-temperature investigations were conducted, with the idea of enforcing mercaptan ligation and an $S = 2$ spin state. At -50 °C, however, Fe(tC_5SH), for example, exhibited only signals appropriate for an intermediate-spin system (based on shifts predicted assuming Curie law behavior[57] and using the data for FeTPP[52])—in agreement with the electronic absorption spectra.

The addition of CO results in dramatic changes, as seen in the NMR spectrum of Fe(mC_5SH)(CO) (Figure 7). The position of the β-pyrrole and phenyl resonances in the "normal" region of 7-9 ppm indicates a low-spin, diamagnetic species. This spectrum differs strikingly, however, from that of the metal-free compound mC_5SH (which is also diamagnetic) (see Experimental Section) by the presence in the former of several well-resolved triplets upfield from Me_4Si. By their multiplicity and integrated values, these signals undoubtedly arise from the tail CH_2 units. Their positions so far upfield in an $S = 0$ complex reflect a sizeable shielding effect from the porphyrin ring current and strongly imply coordination of the appended thiol (**20**). Thus, as observed previously, the presence of CO as a ligand does induce *trans* binding of thiol in the alkyl tail complexes.



20

The NMR spectra of the aryl thiol-tail metalloporphyrins differ from those of the alkyl tails in several respects, providing an interesting insight into the behavior of these species in solution. The spectrum of the o-mercaptobenzamide-tail porphyrin Fe(mPhSH) (Figure 8) shows resonances characteristic of an $S = 1$ system in the regions of -19 and -15 to -12 ppm. Here, however, the relative intensities of these peaks have changed (with the -19-ppm signal integrating to less than half of the -12-ppm peak); in addition, the meso-phenyl proton resonances (particularly the ortho signals) are broader and the tail phenyl resonances (upfield from Me_4Si) less well-resolved in comparison to FeTPP or Fe(mC_5SH). Most striking, though, is the absence of any signals attributable to the β-pyrrole protons—either in the -6- to -3-ppm range (expected for $S = 1$) or near -52 ppm (for an $S = 2$ case[51]).

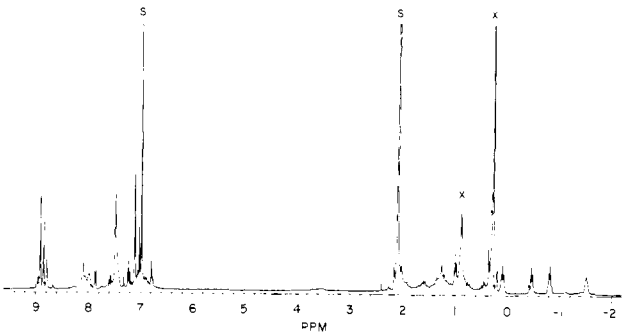


Figure 7. 360-MHz ^1H NMR spectrum of Fe(mC_5SH)(CO) in toluene-d_8. S = solvent, X = impurity.

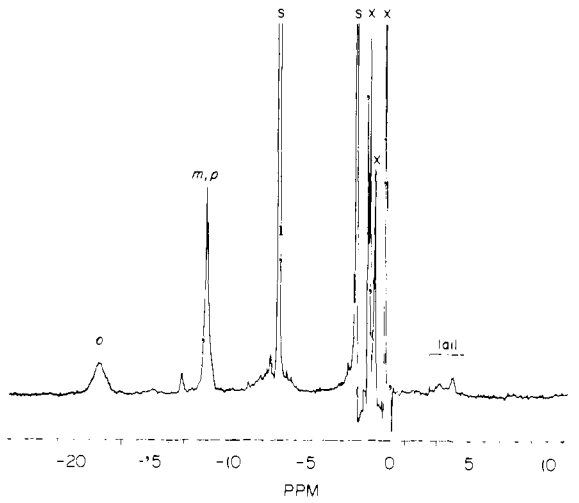
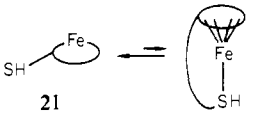


Figure 8. 100-MHz ^1H NMR spectrum of Fe(mPhSH) in toluene-d_8. S = solvent, X = impurity.

These features, interestingly, could be reproduced by titrating a solution of FeTPP with p-methylthiophenol. The addition of 1 equiv of mercaptan resulted in a partial collapse of the β-pyrrole protons; after 250 equiv had been added, the β-pyrrole signals were totally eradicated, affording a spectrum quite like that of Fe(mPhSH). (Significantly, *no* loss of the β-pyrrole resonance of FeTPP was observed after the addition of 500 equiv of n-dodecyl mercaptan.)

Such behavior points to the existence of a mechanism whereby the magnetic environments of the porphyrin protons—particularly at the β-pyrrole positions—are "averaged".[58] A mixture of $S = 1$ and $S = 2$ spin states, resulting from slow ligand exchange at iron, could account for this magnetic averaging and the consequent changes in the NMR spectrum, as has been demonstrated by the titration of FeTPP with 2-methylimidazole (a sterically hindered ligand which binds only once to FeTPP to give a high-spin complex).[51] On the basis of this, we propose that aryl mercaptan-tail porphyrins participate in a similar type of exchange process—i.e., there exists an equilibrium in solution between the four-coordinate, $S = 1$, "tail-off" species and the five-coordinate, $S = 2$, "tail-on" complex:



(3)

21
$S = 1$

22
$S = 2$

(56) La Mar, G. N.; Eaton, G. R.; Holm, R. H.; Walker, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 63-75.

(57) Jesson, J. P. In "NMR of Paramagnetic Molecules"; La Mar, G. N., Horrocks, W. D., Holm, R. H., Eds.; Academic Press: New York, 1973; Chapter 1.

(58) Swift, T. J. In ref 57, Chapter 2.

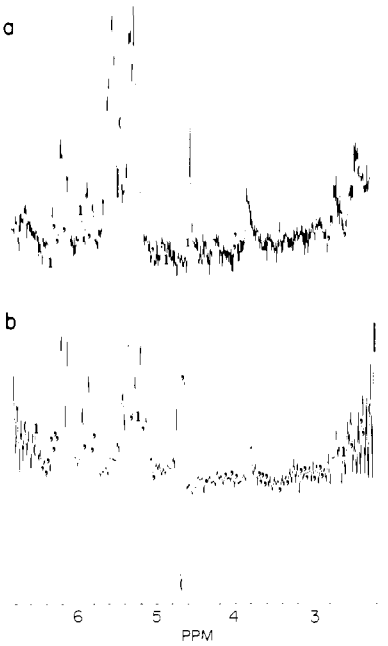


Figure 9. Expansions of 100-MHz ^{1}H NMR spectra of Fe(mPhSH)(CO) in toluene-d_8 at (a) 25 and (b) 0 °C.

In the case of the *o*-mercaptobenzamide-tail porphyrin Fe(mPhSH), this equilibrium apparently lies largely to the left, as indicated both by visible absorption data and by the fact that the NMR spectrum retains most of the features of an $S = 1$ species; nevertheless, some extent of mercaptan ligation to iron is indicated.

In the (*m*-mercaptophenyl)acetamide-tail porphyrin, Fe(mPASH), this equilibrium appears to lie more in favor of the five-coordinate side. Although the data (not shown) are of lesser quality [due to the limited solubility of Fe(mPASH)], one again observes the absence of the β-pyrrole signals; in addition, the meso-phenyl resonances have shifted slightly upfield, lying within −14 to −10 ppm. Signals, presumably due to the tail phenyl protons, can be resolved from 10 to 40 ppm upfield from Me_4Si. Such behavior is analogous again to that observed in the titration of FeTPP with 2-methylimidazole and suggests an enhanced interaction between the thiol and Fe(II) in this porphyrin, perhaps due to a more favorable tail configuration (a result anticipated from the ^{1}H NMR spectrum of the metal-free porphyrin mPASH—vide supra).

The addition of carbon monoxide to either Fe(mPhSH) or Fe(mPASH) afforded "normal" diamagnetic spectra. Here, as expected, the aryl tail proton resonances are found in the same region as in the free-base porphyrins since the tails lie under the porphyrin ring in both instances and thus experience similar ring-shielding effects. The electronic absorption data for Fe(mPhSH)(CO), however, had indicated an equilibrium between "tail-off" and "tail-on" CO complexes, with the latter being favored at lower temperatures. The spectrum of Fe(mPhSH)(CO) was therefore recorded at both 25 and 0 °C. Expansions of the pertinent spectral regions (Figure 9) clearly show the resultant changes in tail conformation, further supporting the postulate of mercaptan ligation at lower temperature.

Magnetic Circular Dichroism. Magnetic circular dichroism (MCD) has been found to be a sensitive probe of the coordination number, spin, and oxidation states of iron porphyrins and heme proteins.[59,60] Here, MCD spectra have been used primarily as "fingerprints" for the various spin states of Fe(II) complexes; consequently, theoretical interpretations will not be advanced. Recent work from this laboratory[29,41,61] has led to a "catalog" of MCD spectra comprising a wide range of ligand type, spin state,

(59) Sutherland, J. C. In "The Porphyrins"; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. IIIA, Chapter 4.
(60) Holmquist, B. In ref 59, Chapter 5.
(61) Marrocco, M. L. Ph.D. Dissertation, Stanford University, 1980.

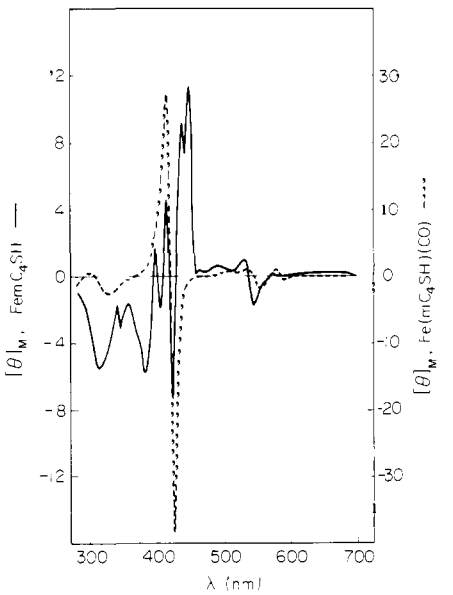


Figure 10. MCD spectra of Fe(mC$_4$SH) and Fe(mC$_4$SH)(CO) in benzene.

Table IV. Infrared Carbonyl Stretching Frequencies for Various Iron(II) Porphyrin–CO Adducts

complex	ν(CO), cm^{-1}	solvent
Fe(mC$_4$SH)(CO)	1970	benzene
Fe(mC$_5$SH)(CO)	1980	toluene
Fe(tC$_5$SH)(CO)	1977	toluene
Fe(mPhSH)(CO)	2030, 1960	benzene
Fe(mPASH)(CO)	1981	benzene
Fe(TPP) + CO	2045, 1970	Nujol mull[a]

[a] Reference 50

and coordination number; these data can be used in empirical determinations of such characteristics in new species. In particular, $S = 0$, $S = 1$, and $S = 2$ spin states are readily distinguished from one another on the basis of band shape and intensity.

MCD spectra of Fe(mC$_4$SH) are shown as an example in Figure 10. The spectral features observed (with and without CO) are shared by all the alkyl mercaptan-tail complexes and by the aryl tail Fe(mPhSH). The fine structure appearing in the Soret region in the absence of CO is typical of an intermediate-spin system and supports our earlier assignments. Similarly, the clean, "first-derivative" bands seen in the presence of CO are characteristics of six-coordinate, low-spin, carbonyl complexes. Interestingly, the (*m*-mercaptophenyl)acetamide tail porphyrin, Fe(mPASH), while exhibiting the same general type of spectra, does show some small differences in the fine structure within the Soret band envelope. The reasons for this difference are not well understood but presumably are related to the changes observed in the visible spectrum of Fe(mPASH) with respect to the other systems.

Low-temperature (0 °C) MCD spectra were also obtained for Fe(tC$_5$SH), Fe(mPhSH), and Fe(mPASH), with and without CO; with the exception of Fe(mPhSH)(CO), none of these spectra differed from those obtained at room temperature. In Fe(mPhSH)(CO), the decrease in temperature resulted in the loss of a shoulder near 420 nm, as well as a red shift and decrease in intensity of the strong positive band in the same region—behavior in keeping with changes observed in the visible spectrum.

IR Spectroscopy. The carbonyl stretching frequencies for a number of ferrous porphyrin CO adducts are given in Table IV. In solution, the alkyl mercaptan-tail complexes all exhibit a single band within the range 1970–1981 cm^{-1}, as does the aryl tail Fe(mPASH)(CO). Such a value for ν(CO) appears indicative of mercaptan ligation trans to CO, since each of these adducts is also characterized by λ_{max} of 422 nm in the visible spectrum. [Identical ν(CO) and λ_{max} values are also shown by the model

compound Fe(TpivPP)(*n*-PrSH)(CO).[28]]

On the other hand, the CO adduct of Fe(mPhSH) exhibits two values for ν(CO)—neither of which lies in the above range. These stretches, however, are quite similar to those attributed to the species Fe(TPP)(CO) and Fe(TPP)$(CO)_2$.[50] Thus, these data further support the contention that mercaptan is *not* a sixth ligand in Fe(mPhSH)(CO) at 25 °C. (Cooling the solution to 0 °C, however, is predicted to result in a stretching frequency for CO of 1975 ± 5 cm^{-1}, in accord with formation of the six-coordinate, thiol-ligated species.)

Magnetic Susceptibility. The spin-only value of the magnetic moment for Fe(II) in the $S = 1$ state is 2.8 μ_B; the four-coordinate complex FeTPP, however, has been shown to have $\mu_{eff} = 4.4\ \mu_B$.[62] The difference between these values has been attributed to a large orbital contribution to the magnetic moment, although the origins of such an interaction have been elusive. Recently, Mitra et al.[63] have addressed this question through single-crystal measurements of the average magnetic susceptibility and magnetic anisotropy of FeTPP from 4 to 300 K. Their calculations suggest that whereas the triplet ground state of FeTPP is mainly $^3A_2$ in character, the low-lying, excited states $^3B_1$ and ^3E are sufficiently close in energy that terms from each of these states are extensively mixed in the presence of spin-orbit coupling. Furthermore, they show that a magnetic moment as high as 4.9 μ_B is theoretically feasible at 300 K for an $S = 1$ state; this is of interest since moments of 4.8–5.1 μ_B have commonly been considered diagnostic for high-spin, $S = 2$ Fe(II).[41,63] Similarly, a detailed study of the Mössbauer spectrum of FeTPP has been interpreted by Lang et al. in terms of a $^3A_{2g}$ orbital ground state which interacts, via spin-orbit coupling, with a low-lying, excited ^3E_g orbital.[64]

Magnetic susceptibility measurements of alkyl and aryl mercaptan-tail porphyrins were carried out in toluene, using a modification of the Evans method.[65] (This technique has been used successfully by others in similar studies of iron porphyrins.[41,46]) The alkyl tail complex Fe(tC_5SH) exhibited (after correction for the diamagnetic susceptibility of the compound[66]) a μ_{eff} of 4.7 μ_B; this is in good agreement with the value of 4.52 ± 0.28 μ_B determined for FeTPP by Rougee and Brault, using the same method.[46] Interestingly, the magnetic moment of the aryl tail complex Fe(mPhSH) was found to be somewhat higher: $\mu_{eff} = 4.93\ \mu_B$. To our knowledge, this value is higher than any yet observed experimentally for an $S = 1$ porphyrin and may simply reflect the same type of perturbation seen in the ^1H NMR—i.e., a contribution from a small but finite population of an $S = 2$ spin complex. Alternatively, the relative contributions of the triplet states $^3A_2$, $^3B_1$, and ^3E to the ground state may be seen as different in Fe(mPhSH) as compared to Fe(tC_5SH) or FeTPP [from an interaction between Fe(II) and ArSH], leading to an increase in the magnetic moment while remaining within a triplet ground state manifold.[63]

In this regard, knowledge of the magnetic moment of the *m*-mercaptoaryl thiol-tail porphyrin Fe(mPASH) would be most interesting since this complex seems to deviate the most in other respects from a classical $S = 1$ system. Unfortunately, solubility limitations have again interfered; use of the more soluble tripivalamide species Fe(tPASH) should allow such a study, however.

Mercaptide-Tail Complexes. In light of our interest in cytochrome P-450, of particular concern has been the preparation of the corresponding mercapt*ide*-tail Fe(II) porphyrins. An important criterion which must be met by a potential model for the P-450 active site is the ability to mimic the unique "hyper"-absorption spectrum which characterizes the CO adduct of the enzyme. We have found that the appropriate complexes can be generated in both the alkyl and aryl series of tailed porphyrins. Determination of the optimal conditions for this procedure has been difficult, and a thorough characterization of all these species has not yet been completed. Nevertheless, our findings to date verify that this class of sulfur-ligated porphyrin is indeed quite appropriate for modeling the active site of cytochrome P-450.

In the presence of carbon monoxide, the addition of a suitable base to an Fe(II) alkyl or aryl mercaptan-tail porphyrin results in the formation of a six-coordinate Fe(II)–mercaptide–CO adduct, as signaled by the appearance of a split Soret absorption at 450 and 380 nm. Figure 11 illustrates the consequence of treating the *m*-mercaptoaryl tail complex Fe(mPASH)(CO) with the anion of acetanilide, $(C_6H_5NCOCH_3)^-K^+$.[68] In this case,

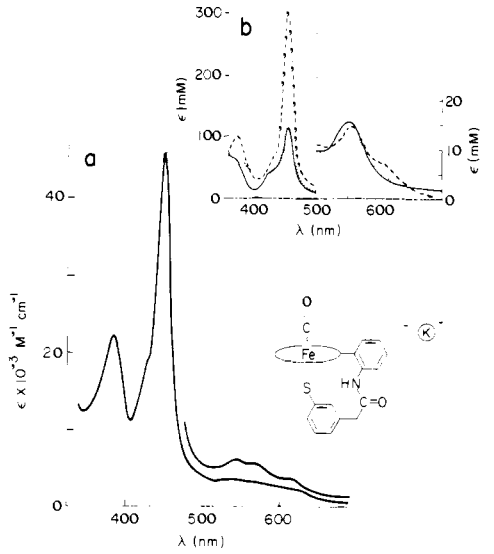


Figure 11. (a) Electronic absorption spectrum of Fe(mPAS$^-K^+$)(CO) in toluene, obtained by treatment of Fe(mPASH) with $PhNCOCH_3K^+$. (b) Absorption spectra for (—) highly purified P-450 (reduced + CO), (– – –) FeTpivPP and $NaSCH_3$ + CO in benzene, and (···) FePPIXDEE and $NaSCH_3$ + CO in benzene (taken from ref 29).

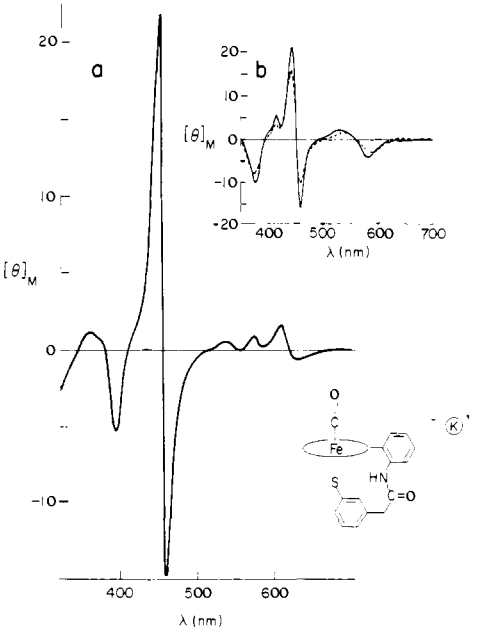


Figure 12. (a) MCD spectrum of Fe(mPAS$^-K^+$)(CO) in toluene. (b) MCD spectra for (—) highly purified P-450 (reduced + CO) and (– – –) FePPIXDEE + $NaSCH_3$ + CO in benzene (taken from ref 29).

(62) Collman, J. P.; Reed, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 2048–2049.
(63) Boyd, P. D. W.; Buckingham, D. A.; McMeeking, R. F.; Mitra, S. *Inorg. Chem.* **1979**, *18*, 3585–3591.
(64) Lang, G.; Spartalian, K.; Reed, C. A.; Collman, J. P. *J. Chem. Phys.* **1978**, *69*, 5424–5427.
(65) Evans, D. F. *J. Chem. Soc.* **1959**, *2003*–2005.
(66) Values of $\chi_g = -5.66 \times 10^{-7}$ and -7.4×10^{-7} cgsu · g^{-1} were used as corrections for the diamagnetic susceptibilities of Fe(tC_5SH) and Fe(mPhSH), respectively. These values were obtained through the use of Pascal's constants and χ_g values determined experimentally for TpivPP and TPP.[67]
(67) Gagné, R. R. Ph.D. Dissertation, Stanford University, 1974.
(68) Prepared by treatment (under inert atmosphere) of a crown ether complex of potassium triphenylmethide in toluene with acetanilide, the end point being signaled by discharge of the characteristic red color of the trityl anion.

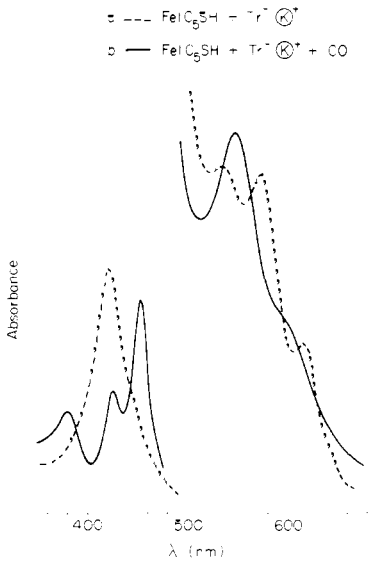


Figure 13. Electronic absorption spectrum of Fe(tC_5SH) in toluene after (a) treatment with Tr^-K^+ and (b) subsequent addition of carbon monoxide.

conversion to the mercaptide complex is essentially complete. Further evidence for thiolate ligation trans to CO can be found in the MCD spectrum (Figure 12); the large negative feature near 380 nm, in particular, has been seen only in complexes involving mercaptide as a ligand.[29]

The extent of conversion from mercaptan to mercaptide appears to depend critically both on the nature of the base[69] used and on the mercaptan in question. A difficulty intrinsic to the appended ligand approach is the necessity of preparing the mercaptide ion in situ after metalation of the porphyrin. Consequently, the potential role of the deprotonating reagent as a ligand must be taken into account. Furthermore, generation of an anionic species in a solvent required to be noncoordinating introduces the problem of charge separation in a fairly nonpolar medium.

Thus, a wide variety of agents was tested for their ability to produce mercaptide-tail complexes, including alkoxides, hydroxides, hydrides (with and without complexing agents), amines, and ylides. Many of these were found, in control experiments, to coordinate to either FeTPP or FeTpivPP; in no case, however, in which a P-450-like hyper spectrum was obtained was it possible to obtain the same type of spectrum in the absence of the mercaptan tail. The reagents found to be most effective in generating such spectra were tetramethylammonium hydroxide, the triphenylmethyl anion,[70] and the anion of acetanilide. (In the latter two cases, the potassium counterion was complexed by a crown ether.)

The facility of mercaptide deprotonation and/or coordination also depends on the nature of the tail complex. The aryl tail porphyrin Fe(mPASH), as seen above, is especially well suited in this regard, giving clean conversion to the mercaptide. Other tails, however, yield less satisfying results. In the alkyl series, the triphenylmethyl anion (Tr^-K^+) is the most effective base—yet even with an excess of this reagent, quantitative production of the thiolate–Fe(II)–CO complex was not achieved (Figure 13). Similar behavior was observed with the *o*-mercaptoaryl tail porphyrin Fe(mPhSH). These results suggest that an exact balance of factors such as geometric disposition and electronic character of the appended mercaptan is critically important in promoting mercaptide ligation. Such a balance seems to have been met in the (*m*-mercaptophenyl)acetamide-tail system, and future modeling of the properties of cytochrome P-450 using compounds like Fe(mPASH) and Fe(tPASH) promises to be most rewarding.

(69) Similar behavior has been observed in related systems: ref 31.
(70) Prepared by treatment of triphenylmethane with KH in the presence of a crown ether.

Experimental Section

General Procedures. Melting points were obtained on a Mel-Temp Laboratory Devices capillary apparatus and are uncorrected. Electronic spectra were obtained on either a Beckman DB-G or Cary 219 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 457, Beckman Acculab 3, or Nicolet 7199 FT IR spectrometer, using septum-sealed CaF_2 solution cells (path length of 0.1 or 1.0 mm). NMR spectra were obtained from Varian T-60 or XL-100 instruments or from a Bruker HXS-360 instrument (Stanford Magnetic Resonance Laboratory), using sealed 5-mm tubes. Pulsed Fourier transform spectra from the XL-100 and HXS-360 instruments were collected and processed with a Nicolet Model 1180 FT disk data system, as were FT infrared spectra from the Nicolet 7199 system. Mass spectra were obtained on a Ribermag R-10-10B quadrupole mass spectrometer, using the D/Cl mode. Elemental analyses were done by the Stanford Microanalytical Laboratory. Magnetic circular dichroism (MCD) spectra were recorded on a Jasco Model J-40 instrument. The data were stored and processed on a Data-General Nova model 840 computer.

All manipulations involving Fe(II) were carried out under an inert atmosphere. Metal insertions and subsequent purifications of ferrous porphyrins were performed in a Vacuum Atmospheres drybox with an MO-40 Dri-Train capable of maintaining an atmosphere of N_2 with <1 ppm of O_2 or H_2O. The oxygen content was monitored with a Vacuum Atmospheres Model AO 316-C O_2 analyzer, a 25-W light bulb with a small hole in the glass, and a solution of diethylzinc in heptane or a solution of Cp_2TiCl_2 over Zn in THF.[71]

Solution magnetic susceptibilities were determined with a Varian XL-100 NMR spectrometer. The metalloporphyrin was dissolved in toluene-h_8, the solution was loaded into a 1.7-mm capillary tube, and the latter was sealed with silicone grease. The capillary was centered, using a Teflon insert, in a standard 5-mm NMR tube containing a 5:1 mixture of toluene-h_8 and -d_8 and sealed with a septum.

Materials. All reagents and solvents were of reagent grade quality, purchased commercially, and used without further purification, except as noted below or elsewhere. Toluene and benzene were distilled from Na under N_2. THF was distilled from CaH_2 under nitrogen. Heptane was purified by stirring with concentrated H_2SO_4 for 12–24 h and then with 0.1 M $KMnO_4$ in 1 M H_2SO_4 for 12 h, washed with H_2O, dried over $MgSO_4$, and distilled from CaH_2 under N_2. Methylene chloride, when used in the inert-atmosphere box, was distilled from P_2O_5 under nitrogen. Methanol was distilled under nitrogen from $Mg(OMe)_2$. 2,6-Lutidine was purified by passage through an alumina column, followed by distillation from $BF_3{\cdot}Et_2O$. Anhydrous Et_2O was purchased from Mallinckrodt. Thionyl chloride was distilled from triphenyl phosphite. Acetanilide was recrystallized from hot toluene and dried in vacuo at ambient temperature. *p*-Methylthiophenol (Aldrich) was purified by sublimation at ambient temperature (1.5 mm). *n*-Dodecanethiol (Matheson Coleman and Bell) was purified by fractional distillation (2×) [bp 94 °C (1.5 mm)]. Triphenylmethyl mercaptan (Aldrich) was recrystallized from hot absolute EtOH. Carbon monoxide (99.5%, Liquid Carbonic) was purified by passage through a 60-cm brass tube containing BASF R3-11 catalyst (Chemical Dynamics Corp.) and 3-Å Linde molecular sieves. All liquids used in the inert-atmosphere box were thoroughly degassed, either by several freeze–pump–thaw cycles or by bubbling with N_2 or Ar (outside of the box) for ≥1 h, followed by a further bubbling with the box atmosphere for ≥15 min.

Two types of silica gel were used in column chromatography: type 62 (60–200 mesh), purchased from W. R. Grace, and PF-254, TLC grade, from EM Reagents (Merck). These were activated by storage in a 55 °C oven for at least 12 h prior to use. Alumina for column chromatography was Woelm neutral, generally of either activity I or III. (Alumina of activity other than I was prepared according to the procedure furnished by Woelm.) For TLC, commercially prepared silica and alumina plates of various thicknesses were purchased from Analtech.

6-Bromohexanoic Acid. ϵ-Caprolactone (50 g, 0.44 mol), concentrated HBr (48%, 400 mL), and concentrated H_2SO_4 (2 mL) were combined in a 1000-mL round-bottomed flask and heated at reflux for 10 h. The dark orange-brown solution was cooled, the organic phase removed, and the aqueous phase extracted with 4 × 50 mL of benzene. The combined organic portions were treated with decolorizing charcoal and filtered. Removal of the solvent by rotary evaporation afforded an orange oil; fractional distillation at reduced pressure yielded 61 g of white crystalline product: mp 31–32 °C; bp 105 °C (2 mm); yield 70%; IR (neat) ν(CO) 1700 cm^{-1}; NMR ($CDCl_3$) δ 11.25 (s, 1 H, CO_2H), 3.4 (t, 2 H, CH_2Br), 2.4 (t, 2 H, CH_2CO_2H), 2.0–1.4 (m, 6 H, CH_2). Anal. ($C_6H_{11}O_2Br$): C, H, Br.

6-Bromohexanoyl Chloride. 6-Bromohexanoic acid (80 g, 0.41 mol) and thionyl chloride (80 mL, 1.1 mol) were combined and stirred at

(71) Sekutowski, D. G.; Stucky, G. D. *J. Chem. Educ.* **1976**, *53*, 110.

ambient temperature for 1 h and then heated to reflux to ensure complete reaction. The product, a colorless liquid, was obtained by distillation at reduced pressure: bp 90 °C (3.5 mm); yield 86 g (98%); IR (neat) ν(CO) 1780 cm^{-1}; NMR ($CDCl_3$) δ 3.35 (t, 2 H, CH_2Br), 2.9 (t, 2 H, CH_2COCl), 2.1–1.3 (m, 6 H, CH_2).

6-(Tritylthio)hexanoic Acid. Trityl mercaptan (27 g, 0.10 mol), H_2O (250 mL), and 95% EtOH (250 mL) were combined in a 2-L, three-necked flask fitted with stir bar, dropping funnel, and gas inlet. After the system had been flushed with N_2, 13.8 g (0.10 mol) of K_2CO_3 was added, and the mixture was stirred until gas evolution had ceased. A solution of 6-bromohexanoic acid (15 g, 7.7×10^{-2} mol) and K_2CO_3 (10.6 g, 7.7×10^{-2} mol) was then added, and the resulting mixture was heated at reflux for 12 h. The pale gold solution was cooled to room temperature and decanted from a small amount of white precipitate. The pH of the solution was adjusted with concentrated HCl to pH 6, resulting in the precipitation of a large quantity of a white, flocculent solid. The mixture was transferred to a separatory funnel and extracted several times with CH_2Cl_2. The organic fraction was washed with H_2O (2 × 200 mL) and brine (1 × 200 mL), dried over Na_2SO_4, and concentrated to a yellow oil. This material was taken up in CH_2Cl_2 (75 mL) and heated to boiling. Heptane (25 mL) was added to the hot solution with swirling; the one-phase system was set aside to cool. Eventually, a white crystalline precipitate was collected: mp 90–91 °C; yield 19.9 g (66%); NMR ($CDCl_3$) δ 9.5 (s, 1 H, CO_2H), 7.25 (m, 15 H, CPh_3), 2.3 (m, 4 H, CH_2), 1.5 (m, 6 H, CH_2). Anal. ($C_{25}H_{26}O_2S$): C, H, S.

6-(Tritylthio)hexanoyl Chloride. 6-(Tritylthio)hexanoic acid (250 mg, 6.4×10^{-4} mol) was dissolved in CH_2Cl_2 (30 mL) in a 100-mL flask under a stream of N_2. One equivalent of Et_3N (0.09 mL) was added, and the mixture was cooled to 0 °C in an ice bath. Excess oxalyl chloride (0.1 mL, 1.2×10^{-3} mol) was added dropwise; the resulting pale yellow solution was stirred at 0 °C for 30 min. The ice bath was then replaced by a heating mantle, and the solvent was boiled off under a stream of N_2. The volume of solvent was kept relatively constant during this time by replenishment with benzene. This process was continued until approximately 150 mL of benzene had been used. The solution—pale brown in color and clouded with precipitated $Et_3NH^+Cl^-$—was filtered and used immediately in subsequent reactions; IR (C_6H_6) ν(CO) 1800 cm^{-1}.

6-(Acetylthio)hexanoic Acid. Freshly distilled thioacetic acid (4.4 mL, 0.06 mol) and K_2CO_3 (9 g, 0.065 mol) were dissolved in 30 mL of H_2O in a 250-mL flask flushed with N_2. A solution of 6-bromohexanoic acid (10 g, 0.05 mol) and K_2CO_3 (6.9 g, 0.05 mol) was added dropwise, and the resulting mixture was stirred at room temperature for 12 h. Benzene (30 mL) was added, and the mixture was transferred to a separatory funnel. After the pH had been adjusted to pH 6 with concentrated HCl, the aqueous phase was extracted several times with C_6H_6. The combined organic fractions were washed with brine and concentrated to a yellow oil. This was distilled under reduced pressure in a Kugelrohr apparatus to yield a pale yellow, viscous liquid: bp 140–150 °C (~2 mm); IR ($CHCl_3$) ν(CO) 1710, 1690 cm^{-1}; NMR ($CDCl_3$) δ 11.2 (s, 1 H, CO_2H), 2.9 (t, 2 H, CH_2SAc), 2.3 (s, 3 H, CH_3COS; m, CH_2CO_2H; 5 H), 1.5 (m, 6 H, CH_2). Anal. ($C_8H_{14}O_3S$): C, H, S.

6-(Acetylthio)hexanoyl Chloride. Ninety-five milligrams of 6-(acetylthio)hexanoic acid (5.0×10^{-4} mol) was dissolved in CH_2Cl_2 (15 mL), together with 1 equiv of Et_3N (0.07 mL). The solution was cooled to 0 °C in an ice bath under a stream of N_2; an excess of oxalyl chloride (0.1 mL) was then added dropwise. After 0.5 h, the solution was removed from the ice bath and heated to reflux, in the same fashion as described above for the *S*-trityl derivative. After filtration to remove precipitated $Et_3NH^+Cl^-$, the acid chloride solution was used directly in subsequent syntheses; IR (C_6H_6) ν(CO) 1790 cm^{-1}.

5-Bromopentanoyl Chloride. 5-Bromopentanoic acid (10 g, Aldrich) was heated to reflux in neat thionyl chloride under N_2 for 1 h. The solution was then distilled under reduced pressure to afford the product, a colorless liquid: bp 55–57 °C (~0.5 mm); IR (neat) ν(CO) 1780 cm^{-1}.

2,2′-Dithiobis[benzoyl chloride]. Ten grams (0.033 mol) of 2,2′-dithiobis[benzoic acid] (Aldrich) was added to a 250-mL flask, along with thionyl chloride (75 mL) and a catalytic amount of DMF (5 drops). The opaque, tan suspension was heated to reflux under N_2 and stirred at that temperature for 0.5 h, until the solution was a clear, light brown color. At this point, 50 mL of C_6H_6 was added, and the solvent was boiled off under a stream of N_2. Benzene was added to maintain a constant solvent volume, until approximately 150 mL had been used. All residual liquid was then removed in vacuo. The pale gold solid which remained was taken up in hot benzene, filtered, and set in the refrigerator. Large, well-formed, brown-gold crystals were obtained by this procedure; the crystals were collected, washed well with heptane, and dried: mp 157–158 °C (lit.[72] mp 153 °C); yield (first crop) 4.7 g (47%); IR (Nujol mull) ν(CO) 1750, 1715 cm^{-1}; NMR ($CDCl_3$) δ 8.82 (d of d, 2 H), 8.1–7.2 (m, 6 H). Anal. ($C_{14}H_8Cl_2O_2S_2$): C, H, S, Cl.

2,2′-Dithiobis[3-methylbenzoic acid]. Into a 500-mL Erlenmeyer flask fitted with a stir bar were placed 10 g of 2-amino-3-methylbenzoic acid (0.066 mol, Aldrich), 16 mL of concentrated HCl (3 equiv), and 144 mL of H_2O. The flask was immersed in a salt–ice water bath, and the temperature of the bright orange solution was brought to 0–5 °C. Sodium nitrite (4.56 g, 0.066 mol), dissolved in 10 mL of cold H_2O, was added slowly by pipet to the amine hydrochloride solution until a pale, almost colorless solution was obtained. (Complete formation of the diazonium salt was verified by a positive KI–starch paper test.)

The cold diazonium solution was added *carefully*, by pipet, to a stirred 60 °C solution of potassium ethyl xanthate (33.8 g, 0.26 mol, in 150 mL of H_2O) in a 500-mL flask. [**Caution:** It is important that the cold diazonium solution be delivered in *small* portions below the surface of the hot xanthate solution in order to minimize the danger of explosion.[73]] This process was accompanied by vigorous gas evolution; by the time all of the diazonium salt had been added, the bright yellow xanthate solution had darkened and become somewhat cloudy, containing a foamy orange scum.

The mixture was heated to 90 °C for 0.5 h to ensure complete formation of the aryl xanthate intermediate. Hydrolysis of the xanthate in situ was then initiated by the careful addition of NaOH (31 g, 0.78 mol) [**Caution:** Exothermic!]. The resulting clear orange solution was heated at reflux for 5 h. After cooling, the solution was transferred to a separatory funnel, where it was acidified carefully to pH 1 with 50% (v/v) H_2SO_4. [**Caution**: Exothermic! Stench!] Diethyl ether was added to the *cool* aqueous solution to dissolve the milky white precipitate formed and was used to extract the aqueous solution several times. The yellow organic layer was washed with brine, dried briefly over Na_2SO_4, filtered, and taken to dryness via rotary evaporation in the fume hood.

The crude, pale yellow mercaptan thus obtained was dissolved in Me_2SO (150 mL) and heated at 80 °C for 8–10 h. The resulting red-orange solution was cooled, poured into a 10-fold excess of ice and water, and allowed to settle for at least 3 h. A fine, pale yellow-white precipitate was collected by gravity filtration and air-dried. The crude material was recrystallized from hot methanol/petroleum ether: yield 6.5 g (65%); mp 254–255 °C (lit.[74] mp 251–253 °C); IR (KBr pellet) 1690 cm^{-1}; NMR (Me_2SO-d_6) δ 12.9 (s, 2 H, CO_2H), 7.4 (s, 6 H, Ph), 2.2 (s, 6 H, CH_3). Anal. ($C_{16}H_{14}O_4S_2$): C, H, S.

2,2′-Dithiobis[3-methylbenzoyl chloride]. 2,2′-Dithiobis[3-methylbenzoic acid] (500 mg, 1.5×10^{-3} mol) was placed in a 50-mL flask fitted with a stir bar, condenser, and vacuum adapter. Thionyl chloride (5 mL, double distilled from triphenyl phosphite) and a catalytic amount of DMF (2 drops) were added, and the mixture was refluxed under N_2 until all the diacid had dissolved (~0.5 h). The yellow solution was then taken to dryness in vacuo. A fluffy yellow solid was obtained in quantitative yield; mp 125 °C; IR (KBr pellet) ν(CO) 1760 cm^{-1}; NMR ($CDCl_3$) δ 7.5 (m, 3 H, Ph), 2.5 (s, 3 H, CH_3).

(3-Aminophenyl)acetic Acid. A solution of $FeSO_4 \cdot 7H_2O$ (107.4 g, 0.39 mol) in 500 mL of H_2O was prepared in a 1-L Erlenmeyer flask and brought just to reflux. To this gold-brown solution was added 10 g of *m*-nitrophenyl)acetic acid (0.066 mol, Aldrich) in 100 mL of warm 10% (v/v) NH_4OH. The mixture was adjusted to pH 10 by the addition of 200 mL of concentrated NH_4OH; the resulting black solution was heated at reflux for 10 min. The mixture was then filtered hot through a Büchner funnel lined with filter paper.

The beige filtrate was concentrated on a hot plate to 200 mL and set aside in the refrigerator. Tiny, pale beige crystals were collected, rinsed with small amounts of cold H_2O, and dried in vacuo at 70 °C for several hours: yield 7 g (70%); mp 154–155 °C (lit.[75] mp 151 °C); NMR (Me_2SO-d_6) δ 6.9 (m, 1 H, Ph), 6.4 (m, 3 H, Ph), 3.3 (s, 2 H, CH_2).

3,3′-Dithiobis[phenylacetic acid]. The preparation of this compound parallels that of 2,2′-dithiobis[3-methylbenzoic acid]. A fine white precipitate was obtained from the Me_2SO oxidation of the crude mercaptan. This material was recrystallized from hot ethanol, yielding a white powder, mp 182–185 °C. NMR analysis in D_2O/NaOD revealed the presence of Me_2SO in this powder, even after copious washings with H_2O. Consequently, a good elemental analysis could not be obtained, although the incorporation of 0.25 mol of Me_2SO as solvate gives a reasonable fit: IR (KBr pellet) ν(CO) 1705 cm^{-1}; NMR (Me_2SO-d_6): δ 7.4 (m, 4 H, Ph), 3.6 (s, 2 H, CH_2). Anal. ($C_{16}H_{14}O_4S_2$): C; H; S: calcd 19.23, found 20.5.

3,3-Dithiobis[phenylacetyl chloride]. 3,3′-Dithiobis[phenylacetic acid] (150 mg, 4.5×10^{-4} mol) was dissolved in 5 mL of $SOCl_2$ (doubly

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(73) Hilgetag, G.; Martini, A. "Preparative Organic Chemistry", 4th ed.; Wiley: New York, 1972; p 654.

(74) Ponci, R.; Baruffine, A.; Borgna, P. *Farmaco, Ed. Sci.* **1966**, *21*, 249; *Chem. Abstr.* **1967**, *66*, 37816.

(75) Jacobs, W. A.; Heidelberger, M. *J. Am. Chem. Soc.* **1917**, *39*, 1435.

distilled from triphenyl phosphite) in a 50-mL flask fitted with a stir bar, condenser, and N_2 inlet. The mixture was heated at reflux for 0.5 h and then stripped in vacuo, leaving an orange-yellow, semicrystalline oil, which was used immediately in subsequent syntheses; IR (CH_2Cl_2) ν-(CO) 1790 cm^{-1}.

***meso*-(*o*-Nitrophenyl)triphenylporphyrin, mNO$_2$.** This compound was prepared essentially as described in ref 41. The purification procedure used, however, was slightly different, in that 3 g of the crude condensation mixture was dissolved in 60 mL of CH_2Cl_2, filtered, and eluted from a 4 in. × 24 in. column of grade 62 silica gel with 1:1 (v/v) CH_2Cl_2–cyclohexane as the eluting mixture; yield 0.8 g of mNO_2 per column.

***meso*-(*o*-Aminophenyl)triphenylporphyrin, mNH$_2$ (12).** The procedure of ref 41 was used to prepare compound **12**. Once obtained, the crude reduced porphyrin was purified on a 3 in. × 18 in. grade 62 silica gel column, using 3:2 (v/v) CH_2Cl_2–cyclohexane as the eluting solvent. Residual TPP and mNO_2 came off first, followed by a large major band of the desired aminoporphyrin **12**; this was removed with pure CH_2Cl_2; yield 2.5 g (78%).

***meso*-α-(*o*-Aminophenyl)-α,α,α-tris[(*o*-pivalamido)phenyl]porphyrin, α-tNH$_2$ (9).** This compound was synthesized as described in ref 41.

***meso*-β-(*o*-Aminophenyl)-α,α,α-tris[(*o*-pivalamido)phenyl]porphyrin, β-tNH$_2$ (10).** This compound was prepared by the procedure of ref 41.

***meso*-[*o*-(6-Bromohexanamido)phenyl]triphenylporphyrin, mC$_5$Br (13a).** The aminoporphyrin **12** (1.0 g, 1.6 mmol) was treated with 6-bromohexanoyl chloride (1.2 g, 5.6 mmol) in 700 mL of CH_2Cl_2 containing 4.5 mL of pyridine. The mixture was stirred for 12 h and then quenched with 10% NH_4OH. The organic layer was washed with brine and stripped to an oil; toluene (5 mL) was added, and the residue was taken to dryness in vacuo.

The desired product was obtained by chromatographic separation from mNH_2 (and any residual mNO_2), using grade 62 silica gel (900 mL, 3-in.-diameter column). The first two bands (mNH_2 and mNO_2) were removed with C_6H_6; switching solvents to $CHCl_3$ allowed collection of the major product band. This material was stripped and recrystallized from ether/heptane; NMR ($CDCl_3$) δ 8.8 (m, 8 H, β-pyrrole H), 8.2 (m, 7 H, *o*-Ph), 7.7 (m, 12 H, *m*- and *p*-Ph), 6.7 (s, 1 H, amide), 2.7 (t, 2 H, CH_2Br), 1.4–0.5 (m, tail protons), −2.7 (s, 2 H, internal pyrrole H). Anal. ($C_{50}H_{40}N_5OBr$) Calcd: Calcd: C, 74.43; H, 5.00; N, 8.68; Br, 9.90. Found: C, 74.17; H, 5.57; N, 7.93; Br, 9.39.

***meso*-[[6-(Tritylthio)hexanamido]phenyl]triphenylporphyrin, mC$_5$STr (13b). Method 1.** Trityl mercaptan (68.5 mg, 2.48 × 10^{-4} mol) was dissolved in 500 mL of DMF; 10% (w/w) NaOH was added (under a stream of N_2) until pH 8 was reached. To this mixture a solution of mC_5Br (200 mg, 2.48 × 10^{-4} mol) in DMF was added dropwise. The dark green reaction mixture was stirred at room temperature for 12 h and then transferred to a separatory funnel containing 100 mL of C_6H_6. Water (300 mL) was added, the red-brown organic layer removed, and the aqueous phase extracted several times with C_6H_6. The combined organic fractions were washed with H_2O (1 × 50 mL). The solution was stripped to dryness, and the crude residue was purified on a PF-254 silica gel column (150 mg) by elution with $CHCl_3$. One major band was collected; yield 230 mg (93%).

Method 2. The aminoporphyrin mNH_2 (1.0 g, 1.7 mmol) was dissolved in 500 mL of CH_2Cl_2 containing 0.5 mL of pyridine. To this was added a solution of 6-(tritylthio)hexanoyl chloride (1.4 g, 3.6 mmol) in benzene. The mixture was stirred at room temperature for 8 h and quenched with an equal volume of 10% NH_4OH. The organic layer was removed, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic fractions were washed with brine (2 × 50 mL), dried briefly over Na_2SO_4, filtered, and evaporated to an oil. Toluene (5 mL) was added, and the material was taken to dryness in vacuo.

The residue was eluted from PF-254 silica gel (200 g, 2-in.-diameter column) with $CHCl_3$. A minor band of mNO_2 was removed first, followed by an intense major band, which was collected and stripped. The product was recrystallized from $CHCl_3$/MeOH, yielding 1.06 g of a fine purple powder (66%): NMR ($CDCl_3$) δ 8.8 (m, 8 H, β-pyrrole H), 8.2 (m, 7 H, *o*-Ph), 7.8 (m, 12 H, *m*- and *p*-Ph), 7.1 (m, 15 H, CPh_3), 6.7 (s, 1 H, amide), 0.4–1.7 (series of multiplets, tail protons), −2.7 (s, 2 H, internal pyrrole H); mass spectrum principal peaks in parentheses, *m/e* 1001–1002 (M^+), 771–774 (−$(Ph)_3$), 758–761 (−CPh_3), 725 (−$SCPh_3$). Anal. ($C_{69}H_{55}N_5OS$): C, H, N, S.

***meso*-[*o*-[6-(Acetylthio)hexanamido]phenyl]triphenylporphyrin, mC$_5$SAc (13c).** Aminoporphyrin **12** (1.0 g, 1.6 mmol) was treated with 647 mg (3.4 mmol) of 6-(acetylthio)hexanoyl chloride, in the same manner as described in method 2 for mC_5STr. The crude porphyrin obtained was purified by elution with $CHCl_3$ from a grade 62 silica gel column (15 in. × 3 in.); one major band was collected and recrystallized from $CHCl_3$/EtOH/heptane; yield 1.2 g (93%); NMR ($CDCl_3$) δ 8.8, 8.2, 7.7, 6.8, 2.1–1.4, and −2.7 as in **13a**; δ 1.95 (s, 3 H, $COCH_3$). Anal. ($C_{52}H_{43}N_5O_2S$): N; H; S; C: calcd 77.87, found 75.09.

***meso*-[*o*-(5-Bromopentanamido)phenyl]triphenylporphyrin, mC$_4$Br (13d).** Aminoporphyrin **12** (400 mg, 6.35 × 10^{-4} mol) was dissolved in 200 mL of CH_2Cl_2. A solution containing 200 mg (1 mmol) of 5-bromopentanoyl chloride and pyridine (0.5 mL) was added in one portion, and the resulting mixture was stirred at room temperature for 10 h. The reaction was quenched with 10% NH_4OH (150 mL), and the organic phase was separated, washed with brine, and taken to dryness.

The product was separated from residual starting material by column chromatography, using grade 62 silica gel (700 mL) and $CHCl_3$. Recrystallization from Et_2O/heptane gave 325 mg of **13d** (65%); NMR ($CDCl_3$) δ 8.8 (m, 8 H, β-pyrrole), 8.2 (m, 7 H, *o*-Ph), 7.7 (m, 12 H, *m*- and *p*-Ph), 6.8 (s, 1 H, amide), 2.7 (t, 2 H, CH_2Br), 1.0–1.7 (m, tail protons), −2.7 (s, 2 H, internal pyrrole H). Anal. ($C_{49}H_{38}N_5OBr$): C, H, N, Br.

***meso*-[*o*-[5-(Tritylthio)pentanamido]phenyl]triphenylporphyrin, mC$_4$STr (13e). Method 1.** This method was analogous to method 1 for mC_5STr; yield 63%.

Method 2. The bromo-tail porphyrin **13d** (250 mg, 3.15 × 10^{-4} mol), trityl mercaptan (874 mg, 3.16 mmol), and K_2CO_3 (464 mg, 3.36 mmol) were combined in a 250-mL flask under N_2. Acetonitrile (125 mL) was added, and the mixture was stirred at room temperature for 12 h. The solution was then transferred to a separatory funnel, and H_2O (80 mL) and CH_2Cl_2 (80 mL) were added. The organic phase was separated, washed with water (2 × 100 mL) and brine (1 × 100 mL), dried over $MgSO_4$, and stripped to an oil. The residue was purified on a PF-254 silica gel column (800 mL) with $CHCl_3$. A small amount of starting material was recovered; the major product band was collected and taken to dryness: yield 200 mg (64%); NMR ($CDCl_3$), analogous to mC_5STr; mass spectrum, *m/e* 987–990 (parent cluster).

***meso*-[*o*-[5-(Acetylthio)pentanamido]phenyl]triphenylporphyrin, mC$_4$SAc (13f).** Potassium carbonate (280 mg, 2.02 mmol) was dissolved in 40 mL of acetone in a 250-mL flask; under N_2, freshly distilled thioacetic acid (0.3 mL, 4.03 mmol) [Stench!] was added, and the mixture was stirred as a solution of mC_5Br (300 mg, 3.78 × 10^{-4} mol) in acetone was added dropwise. After 12 h, benzene (100 mL) was added, and the organic phase was separated and washed with H_2O (4 × 200 mL), 10% $NaHCO_3$ (2 × 100 mL), and brine (100 mL). The solvent was then stripped in vacuo and the residue recrystallized from $CHCl_3$/heptane: NMR ($CDCl_3$) δ 8.8, 8.1, 7.8, 6.7, and 2.4–0.7 as in **13d**; δ 1.7 (s, 3 H, $COCH_3$).

***meso*-β-[*o*-(6-Bromohexanamido)phenyl]-α,α,α-tris[*o*-(pivalamido)-phenyl]porphyrin, tC$_5$Br (11a).** This compound was prepared from β-amino tripivalamide **10** in the same fashion as described for the "picketless" derivative, mC_5Br. Purification from residual starting material was accomplished by chromatography on PF-254 silica gel (100 g), using 6:1 $CHCl_3$–Et_2O as the eluting mixture. The product was recrystallized from $CHCl_3$/Et_2O: yield 70%; NMR ($CDCl_3$) δ 8.8–7.3 [three multiplets: β-pyrrole H (8), phenyl H (16), and C(O)N*H*Bu^t (3); 30 H], 6.6 (s, 1 H, tail amide), 2.7 (t, 2 H, CH_2Br), 1.4–0.5 (m, tail protons), 0.19 (s, 18 H, Bu^t), 0.09 (s, 9 H, Bu^t), −2.6 (s, 2 H, internal pyrrole H). Anal. ($C_{65}H_{67}N_8O_4Br$): C, H, N, Br.

***meso*-β-[*o*-[6-(Tritylthio)hexanamido]phenyl]-α,α,α-tris[*o*-(pivalamido)phenyl]porphyrin, tC$_5$STr (11b).** This compound was prepared from β-amino tripivalamide **10** by routes analogous to methods 1 and 2 described for preparation of mC_5STr. Purifications involved the same chromatography systems described above for tC_5Br: yield ~100% (method 1), ~80% (method 2); NMR ($CDCl_3$) δ 8.8–7.4,, 6.5, 2.5–0.5, 0.18, 0.08, and −2.7 as in tC_5Br; δ 7.1 (m, CPh_3).

***meso*-β-[*o*-[6-(Acetylthio)hexanamido]phenyl]-α,α,α-tris[*o*-(pivalamido)phenyl]porphyrin, tC$_5$SAc (11c).** The preparation of this porphyrin parallels that of mC_4SAc. The crude product was purified by elution from PF-254 silica gel (100 g) with 6:1 $CHCl_3$–Et_2O and recrystallized from ether/heptane: yield 67%; NMR ($CDCl_3$) δ 8.8–7.4, 6.5, 1.7–0.5, 0.18, 0.08,, and −2.7 as in tC_5Br; δ 1.85 (s, t superimposed, 5 H, CH_2SCOCH_3). Anal. ($C_{66}H_{70}N_8O_4S$): C, H, N, S.

***meso*-β-[*o*-(5-Bromopentanamido)phenyl]-α,α,α-tris[*o*-(pivalamido)-phenyl]porphyrin, tC$_4$Br (11d).** Preparation of **11d** follows the procedure employed for tC_5Br: yield 54%; NMR ($CDCl_3$), as in tC_5Br. Anal. ($C_{64}H_{65}N_8O_4Br$) Calcd: C, 70.51; H, 6.01; N, 10.28; Br, 7.33. Found: C, 69.34; H, 6.39; N, 9.56; Br, 8.58.

***meso*-β-[*o*-[5-(Tritylthio)pentanamido]phenyl]-α,α,α-[*o*-(pivalamido)-phenyl]porphyrin, tC$_4$STr (11e).** This compound was prepared from tC_4Br by the same route used in preparing mC_4STr (method 1) in essentially quantitative yield.

***meso*-[*o*-(6-Mercaptohexanamido)phenyl]triphenylporphyrin, mC$_5$SH (15a). Method 1.** Mercuric acetate (230 mg, 7.24 × 10^{-4} mol) and the trityl-protected porphyrin mC_5STr (220 mg, 2.2 × 10^{-4} mol) were placed in a 250-mL side-arm, round-bottomed flask. Under a stream of argon, CH_2Cl_2 (50 mL) and absolute EtOH (50 mL) were added, and the

mixture was stirred at ambient temperature for 6 h. Hydrogen sulfide [Stench!] was then bubbled through the dark green mixture at a moderate rate for 2 h. After having been stirred for another 0.5–1 h, the murky brown suspension was filtered through a Celite pad (rinsing with CH_2Cl_2) to remove precipitated HgS. The solution was then transferred to a separatory funnel, washed several times with brine, dried briefly over Na_2SO_4, filtered, and stripped in vacuo. TLC indicated ~95% conversion to the mercaptan. (Due to their air sensitivity, mercaptan-tail porphyrins were manipulated as little as possible outside of the drybox; thus, yields are based on TLC data.) The product was purified on a column of PF-254 silica gel (600 mL, 2-in. diameter), using CH_2Cl_2; removal of solvent in vacuo afforded a red-purple powder.

Method 2. The S-acetylated compound mC_5SAc (540 mg, 6.7×10^{-4} mol) was added to a flask containing 150 mL of NH_3-saturated methanol and $CHCl_3$ (75 mL) under N_2. The mixture was stirred at room temperature for 12 h and then transferred to a separatory funnel. Water (100 mL) and $CHCl_3$ (50 mL) were added and the pH was adjusted to 6 with concentrated HCl. The organic phase was collected, washed with brine, and taken to dryness. The product was isolated by preparative TLC (2-mm plates, using toluene–1% MeOH as the eluting solvent) from residual starting material; conversion was estimated at 50–60%: NMR (toluene-d_8) δ 9.3 (d, 1 H) and 8.8 (s, 7 H; β-pyrrole H), 8.2–7.1 (two m, 19 H, *o*-, *m*-, and *p*-Ph), 6.7 (s, 1 H, amide), 1.4–0.5 (m, tail protons—TLC impurities from silica also present), –2.3 (s, 2 H, internal pyrrole H); mass spectrum, *m/e* 758–762 (M^+), 726–727 ($-H_2S$), 711–712 ($-CH_2SH$), 698–699 [$-(CH_2)_2SH$], 684–685 [$-(CH_2)_3SH$], 671–672 [$-(CH_2)_4SH$], 656 [$-(CH_2)_5SH$], 628 [$-C(O)(CH_2)_5SH$]. Anal. ($C_{50}H_{41}N_5OS$): C; S; N: calcd 9.21, found 8.56.

***meso*-[*o*-(5-Mercaptopentanamido)phenyl]triphenylporphyrin, mC_4SH (15b).** This compound was prepared in a fashion analogous to method 1 described for mC_5SH: yield ~90%; NMR (C_6D_6), analogous to that of mC_5SH; mass spectrum, *m/e* 745–746 (M^+), 712 ($-H_2S$), 685 ($-CH_2CH_2SH$), 656 [$-(CH_2)_4SH$], 628 [$-C(O)(CH_2)_4SH$].

***meso*-β-[*o*-(6-Mercaptohexanamido)phenyl]-α,α,α-tris[*o*-(pivalamido)phenyl]porphyrin, tC_5SH (14a).** Preparation of this compound parallels that of mC_5SH (both methods). The crude porphyrin was separated from minor trailing bands on a grade 62 silica gel column (800 mL), using 6:1 $CHCl_3$–Et_2O as the eluting solvent: estimated yield 90% (method 1), 70% (method 2); NMR (toluene-d_8) δ 9.3 (t), 8.5 (d), 7.7 (m), and 7.2 (m) (26 H, β-pyrrole H, Ph, and C(O)N*H*Bu^t), 6.5 (s, 1 H, tail amide), 1.9–0.5 (m, tail protons), 0.27 (s, 9 H, Bu^t), 0.08 (s, 18 H, Bu^t), –2.1 (s, 2 H, internal pyrrole H). Anal. ($C_{65}H_{68}N_8O_4S \cdot 0.35CHCl_3$): C; S; Cl; H: calcd 6.27, found 6.70; N: calcd 10.20, found 9.79.

***meso*-β-[*o*-(5-Mercaptopentanamido)phenyl]-α,α,α-tris[*o*-(pivalamido)phenyl]porphyrin, tC_4SH (14b).** Synthesis of this compound parallels method 1 of tC_5SH; yield ~90%. Recrystallization from toluene/heptane afforded well-formed purple crystals: NMR (toluene-d_8), analogous to that for tC_5SH; mass spectrum, *m/e* 1042–1043 (M^+). Anal. ($C_{64}H_{66}N_8O_4S$): C; H; S; N: calcd 10.74, found 9.94.

***meso*-[*o*-(2-Mercaptobenzamido)phenyl]triphenylporphyrin, mPhSH (16a).** Aminoporphyrin **12** (300 mg, 4.76×10^{-4} mol) was dissolved in CH_2Cl_2 (200 mL) containing 0.50 mL of pyridine. To this a solution of 2,2′-dithiobis[benzoyl chloride] (654 mg, 1.9×10^{-3} mol) in CH_2Cl_2 (90 mL) was added dropwise over a 1–2-h period. The reaction mixture was stirred at room temperature for at least 8 h and then quenched with 10% NH_4OH. The solution was transferred to a separatory funnel, and the organic phase was washed several times with brine, dried briefly over Na_2SO_4, filtered, and evaporated to dryness.

The crude porphyrin disulfide mixture, under a stream of N_2, was suspended in 250 mL of absolute ethanol and treated with 1 g of $NaBH_4$, and the mixture was stirred at room temperature for 6–8 h. An equal volume of H_2O was then added to the green-black solution, together with ~50 mL of CH_2Cl_2. The aqueous layer was discarded and a saturated solution of NaCl was added, regenerating the normal purple color in the organic phase. The organic fraction was washed several times with brine, dried briefly over Na_2SO_4, filtered, and taken to dryness.

The residue was purified by elution from PF-254 silica gel (700 mL, 3 in. × 10 in. column) with CH_2Cl_2; one large major band was separated from several trailing bands. This band was collected,, stripped, and recrystallized in the drybox from toluene/heptane: yield ~50%; NMR (toluene-d_8) δ 9.3 (d, 1 H), 8.8 (d, 8 H, β-pyrrole H), 8.05 (m, 8 H), 7.7 (m, 4 H), and 7.5–7.3 (m, 10 H, *o*, *m*, and *p*-Ph, amide H), 6.1 (d, 1 H, tail Ph), 5.8 (d of t, 1 H, tail Ph), 5.76 (d of d, 1 H, tail Ph), 5.25 (d of t,, 1 H, tail Ph), 4.2 (s, 1 H, SH), –2.27 (s, 2 H, internal pyrrole H); mass spectrum, *m/e* 764–768 (M^+), 690–694 (–Ph), 628–633 [$-C(O)C_6H_4S$-H]. Anal. ($C_{51}H_{35}N_5OS$): H; N; S; C: calcd 79.97, found 79.43.

***meso*-[*o*-(2-Mercapto-3-methylbenzamido)phenyl]triphenylporphyrin, m3MSH (16b).** A solution of 2,2′-dithiobis[3-methylbenzoyl chloride] (1 g, 2.7 mmol) in 100 mL of $CHCl_3$ was added dropwise over 1–2 h to a 500-mL flask containing aminoporphyrin **12** (300 mg, 4.76×10^{-4} mol) and pyridine (2 mL) in $CHCl_3$ (200 mL). The mixture was refluxed for 48 h and then quenched by the addition of an equal volume of 10% NH_4OH. The organic phase was separated, washed with brine, dried briefly over Na_2SO_4, filtered, and taken to dryness. One major product was separated from residual mNH_2 on a grade 62 silica gel column (1000 mL, 3-in. diameter), using CH_2Cl_2 as the eluting solvent; yield ~180 mg.

This disulfide-tail porphyrin was then suspended in 150 mL of absolute ethanol (under argon) and treated with $NaBH_4$ (375 mg); the mixture was stirred at ambient temperature for 6 h and then worked up in the same manner described for mPhSH. The crude material was purified on a PF-254 silica gel column (400 mL, 3-in. diameter), using CH_2Cl_2. The major product band was collected, stripped, and recrystallized in the drybox from toluene/heptane; fine, well-formed, purple crystals were obtained: NMR (toluene-d_8) δ 9.5–7 as in mPHSH; δ 5.83 (s, 1 H, SH), 5.78 (d, 1 H, tail Ph), δ 5.54 (d, 1 H, tail Ph), 5.15 (t, 1 H, tail Ph), 1.5 (s, 3 H, CH_3), –2.37 (s, 2 H, internal pyrrole H); mass spectrum, *m/e* 778–780 (M^+), 690–693 (–Ph), 627–629 [$-C(O)C_6H_4(CH_3)(SH)$]. Anal. ($C_{52}H_{37}N_5OS$): H; S; C: calcd 80.08, found 79.48; N: calcd 8.98, found 8.14.

***meso*-[*o*-[(3-Mercaptophenyl)acetamido]phenyl]triphenylporphyrin, mPASH (17).** Three hundred milligrams of mNH_2 (4.76×10^{-4} mol) and 2 mL of pyridine were dissolved in 250 mL of CH_2Cl_2 in a 500-mL flask; 3,3′-dithiobis[phenylacetyl chloride] (707 mg, 1.9×10^{-3} mol) was added dropwise as a solution in 80 mL of CH_2Cl_2, and the mixture was stirred for ~15 h. The reaction was quenched with 10% NH_4OH and worked up in the manner described above for mPhSH. The disulfide porphyrins (two bands) were separated from residual mNH_2 by column chromatography (grade 62 silica gel, 3 in. × 16 in., CH_2Cl_2); yield ~250 mg.

The mixture of disulfide porphyrins thus obtained was reduced with $NaBH_4$ in the same fashion described above for mPhSH. The mercaptan-tail species was isolated by column chromatography in the inert-atmosphere box, using PF-254 silica gel (600 mL, 2-in. diameter, toluene–1% MeOH): NMR (toluene-d_8) δ 9.3 (d, 1 H), 8.88 (s, 4 H, β-pyrrole H), 8.74 (d, 2 H, β-pyrrole), 8.54 (d, 2 H, β-pyrrole), 8.4–7.5 (multiplets, 19 H, Ph), 6.55 (s, 1 H, amide), 5.06 (s, 1 H, tail Ph), 4.6 (d, 1 H, tail Ph), 3.18 (t, 1 H, tail Ph), 2.9 (d, 1 H, tail Ph), 2.41 (s, 2 H, tail CH_2), 1.36 (s, buried in impurity signal, SH), –2.55 (s, 2 H, internal pyrrole); mass spectrum, *m/e* 778–780 (M^+), 656–658 ($-CH_2C_6H_4SH$), 628–629 [$-C(O)CH_2C_6H_4SH$]. Anal. ($C_{52}H_{37}N_5OS$): S.

[*meso*-β-[*o*-(6-Mercaptohexanamido)phenyl]-α,α,α-tris[*o*-(pivalamido)phenyl]porphyrinato]iron(II), Fe(tC_5SH). In the inert-atmosphere box, the ligand tC_5SH (20 mg, 0.019 mmol) was dissolved in 6 mL of 1:1 C_6H_6–THF containing 0.1 mL of 2,6-lutidine and heated just to reflux. Anhydrous $FeBr_2$ (40 mg, 0.19 mmol) was added and the solution heated for an additional 10 min. The solvent was removed under reduced pressure and the residue chromatographed on neutral activity I alumina (1 × 8 cm column), eluting with 1% MeOH in toluene. The red-orange porphyrin solution was collected, taken to dryness, and recrystallized from toluene/heptane, affording shiny purple crystals: UV/vis (toluene) 416, 552, sh 400, 537 nm; NMR (toluene-d_8) (downfield from Me_4Si = negative δ) δ –19.4 (s), –18.6 (s), –17.8 (s), –15.6 (s), –14.8 (s), –13.8 (d), –13.5 (d), –12.5 (m), –11.6 (m) (20 H, *o*-, *m*-, and *p*-Ph, amide H), –3.5 (m, 8 H, β-pyrrole), 1.9 (s), 6.4 (s), 8.3 (s), 8.5 (s), 10.4 (s) (10 H, CH_2); 11.5 (s, 18 H, *t*-Bu), 13.0 (s, 9 H, *t*-Bu); mass spectrum (sample run as CO complex), *m/e* 1108–1113 (–CO), 1102–1107 ($-H_2S$), 1076–1081 (–CO, H_2S), 978–983 [$-C(O)(CH_2)_5SH$]; χ_m (solution, toluene) 4.70 ± 0.06 μ_B. Anal. ($C_{65}H_{66}N_8O_4SFe$): C; H; S; N: calcd 10.08, found 9.33; Fe: calcd 5.03, found 4.55.

[*meso*-[*o*-(6-Mercaptohexanamido)phenyl]triphenylporphyrinato]iron(II), Fe(mC_5SH). This compound was prepared as described above for Fe(tC_5SH): UV/vis (toluene) 418, 441, sh 400, 537 nm; NMR, see Figure 6; mass spectrum, *m/e* 812–815 (M^+), 779–782 ($-H_2S$), 681–686 [$-C(O)(CH_2)_5SH$].

[*meso*-[*o*-(5-Mercaptopentanamido)phenyl]triphenylporphyrinato]iron(II), Fe(mC_4SH). This compound was prepared as described above for Fe(tC_5SH): UV/vis (toluene) 418, 442, sh 400, 536 nm; NMR (toluene-d_8) (downfield from Me_4Si = negative δ) δ –20 (s), –19.6 (s), –19.2 (s), –18.8 (s), –14.6 (s), –13.4 (s), –12.1 (d), –11.8 (s), –11.5 (s) (20 H; *o*-, *m*-, and *p*-Ph, amide H), –5.8 (s), –4.8 (d), –3.8 (s) (8 H, β-pyrrole), 8.4 (d), 8.8 (s), 14.3 (8 H, CH_2).

[*meso*-[*o*-(2-Mercaptobenzamido)phenyl]triphenylporphyrinato]iron(II), Fe(mPhSH). This compound was prepared by the same procedure used in the synthesis of Fe(tC_5SH), except that the crude metalloporphyrin was purified by passage through grade 62 (60–200 mesh) silica gel instead of neutral alumina. The main red-orange band was collected and filtered, and the solvent was removed in vacuo, affording a red-violet powder. Despite copious washings with heptane, the compound could not be completely freed from residual silicone grease: UV/vis (toluene) 419,

441, sh 400, 539 nm; NMR, see Figure 8; mass spectrum, m/e 817-818 (M^+), 683 [$-C(O)C_6H_4SH$]; χ_m (solution, toluene) 4.93 ± 0.06 μ_B. Anal. ($C_5H_{33}N_5OSFe$): H; S; Fe; C: calcd 74.72, found 72.62; N: calcd 8.54, found 8.00.

[*meso*-[*o*-[(3-Mercaptophenyl)acetamido]phenyl]triphenylporphyrinato]iron(II), Fe(mPASH): UV/vis (toluene) 420 (broad), sh ~400, 440, 526, 548 nm; mass spectrum, m/e 831-834 (M^+), 683 [$-C(O)CH_2C_6H_4SH$].

[*meso*-[*o*-(2-Mercapto-3-methylbenzamido)phenyl]triphenylporphyrinato]iron(II), Fe(m3MSH): UV/vis (toluene) 418, sh 400, 441, 539 nm; mass spectrum, m/e 832-833 (M^+), 681-686 [$-C(O)C_6H_4(CH_3)(SH)$]; χ_m (solution, toluene) 4.94 ± 0.05 μ_B.

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Registry No. 9, 75557-89-0; **10**, 75557-90-3; **11a**, 80441-39-0; **11b**, 80441-40-3; **11c**, 80447-62-7; **11d**, 80441-41-4; **11e**, 80441-42-5; **12**, 69082-94-6; **13a**, 80441-43-6; **13b**, 80441-44-7; **13c**, 80441-45-8; **13d**, 80441-46-9; **13e**, 80441-47-0; **13f**, 80441-48-1; **14a**, 80441-49-2; **14b**, 80461-70-7; **15a**, 80441-50-5; **15b**, 80441-51-6; **16a**, 80441-52-7; **16b**, 80441-53-8; **17**, 80441-54-9; mNO_2, 62813-29-0; Fe(tC_5SH), 80441-18-5; Fe(mC_5SH), 80441-19-6; Fe(mC_4SH), 80441-20-9; Fe(mPhSH), 80441-21-0; Fe(mPASH), 80441-22-1; Fe(m3MSH), 80441-23-2; Fe(mC_4SH)(CO), 80441-24-3; Fe(mC_5SH)(CO), 80447-59-2; Fe(tC_5SH)(CO), 80448-78-8; Fe(mPhSH)(CO), 80441-17-4; Fe(m3MSH)(CO), 80461-59-2; Fe(mPASH)(CO), 80447-61-6; ε-caprolactone, 502-44-3; 6-bromohexanoic acid, 4224-70-8; 6-bromohexanoyl chloride, 22809-37-6; trityl mercaptan, 3695-77-0; 6-(tritylthio)hexanoic acid, 80441-55-0; 6-(tritylthio)hexanoyl chloride, 80441-56-1; thioacetic acid, 507-09-5; 6-(acetylthio)hexanoic acid, 80441-57-2; 6-(acetylthio)-hexanoyl chloride, 80441-58-3; 5-bromopentanoic acid, 2067-33-6; 5-bromopentanoyl chloride, 4509-90-4; 2,2′-dithiobis(benzoic acid), 119-80-2; 2,2′-dithiobis(benzoyl chloride), 19602-82-5; 2,2′-dithiobis(3-methylbenzoic acid), 13363-59-2; 2-amino-3-methylbenzoic acid, 4389-45-1; 2-diazonium-3-methylbenzoic acid chloride, 65911-34-4; 2-[(ethoxythioxomethyl)thio]-3-methylbenzoic acid, 80447-63-8; 2-mercapto-3-methylbenzoic acid, 77149-11-2; 2,2′-dithiobis(3-methylbenzoyl chloride), 13363-60-5; (3-aminophenyl)acetic acid, 14338-36-4; (*m*-nitrophenyl)acetic acid, 1877-73-2; 3,3′-dithiobis(phenylacetic acid), 80441-59-4; 3,3′-dithiobis(phenylacetyl chloride), 80441-60-7.

Biosynthesis of the Pyrrolidine Rings of Cocaine and Cuscohygrine from [5-^{14}C]Ornithine via a Symmetrical Intermediate[1]

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Contribution from the Natural Products Laboratory,[2] School of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455. *Received July 27, 1981*

Abstract: After many unsuccessful attempts, cocaine containing a significant level of radioactivity was obtained by painting the leaves of the *Erythroxylon coca* plant with an aqueous solution of DL-[5-^{14}C]ornithine hydrochloride. A systematic degradation of this cocaine indicated that essentially all the activity was located at the bridgehead carbons (C-1 and C-5) of its tropane moiety and equally divided between these positions. The activities of degradation products of the radioactive cuscohygrine obtained from the same plant were also consistent with symmetrical labeling of the pyrrolidine rings of this alkaloid. These results indicate that the [5-^{14}C]ornithine is incorporated into these alkaloids via a symmetrical intermediate such as putrescine. This biosynthetic pathway to the tropane moiety of cocaine is, thus, different from the one previously established for hyoscyamine and scopolamine in *Datura* species.

Introduction

Cocaine (**12**), the active principle of the coca plant (*Erythroxylon coca*) and other species of the *Erythroxylon* genus,[3] has had a long and interesting history which continues to the present day.[4] The degradative work carried out by Willstätter and others at the end of the 19th century led to the current structure in 1898[5] confirmed by the first total synthesis in 1923.[6] The relative and absolute configuration was not established until the 1950's.[7,8] Stereospecific syntheses of cocaine have recently been described by Tufariello and co-workers.[9]

Cocaine is a tropane alkaloid, characterized by the presence of the 8-azabicyclo[3.2.1]octane ring system. Extensive tracer work dating back to 1954[10] has established that ornithine is incorporated into the pyrrolidine ring of hyoscyamine (**14**) unsymmetrically. Thus, DL-[2-^{14}C]ornithine yielded hyoscyamine which was labeled only at the C-1 bridgehead carbon.[11,12] Scheme I

(1) A preliminary account of part of this work has appeared: Leete, E. *J. Chem. Soc., Chem. Commun.* **1980**, 1170. It was also presented at the 28th Congress of the IUPAC, Vancouver, Canada, Aug 16-22, 1981.

(2) Contribution number 178 from this laboratory. This paper is dedicated to Lorraine Margaret, my fourth daughter, who was born June 23, 1981, the same day that the degradation of the labeled cocaine (from experiment 2) was completed.

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(4) The literature on cocaine, currently indexed in *Chemical Abstracts* as 3-(benzoyloxy)-8-methyl-8-azabicylo[3.2.1]octane-2-carboxylic acid, methyl ester [1*R*-(*exo,exo*)], is vast. Several monographs describing its biological, social, and chemical aspects are available: (a) Mortimer, W. G. "Peru: History of Coca"; Vail and Co.: New York, 1901; reprinted as "History of Coca"; And/Or Press: San Franciso, 1974. (b) Peterson, R. C.; Stillman, R. C., Eds. *NIDA Res. Monogr.* **1977**, *No. 13*. (c) Mulé, S. J., Ed. "Cocaine: Chemical, Biological, Clinical, Social, and Treatment Aspects"; C.R.C. Press: Cleveland, OH, 1976.

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