IRON MACROCYCLE COMPLEXES

by

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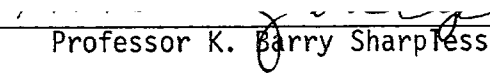
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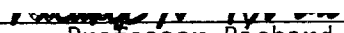Accepted by _____

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Submitted to the Department of Chemistry, January, 1975

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ABSTRACT

Chapter 1

The incorporation of Iron(II), using ferrous acetate, into a series of bis(β-imino amino) macrocycles containing 14-, 15-, and 16-membered rings yielded $Fe(II)N_4$ complexes, which possess 6565, 6566, and 6666, chelate ring size patterns. The magnetic susceptibility and polarography of these 4-coordinate complexes were examined and discussed in relation to the changes in the macrocycle ring size.

Chapter 2

The synthesis and properties of Iron(III) complexes $(Fe(III)N_4X)$ of the series of bis(β-imino amine) macrocycles containing 14-, 15-, and 16-membered rings are described. The 5-coordinate $Fe(III)N_4X$ complexes (X = halide and carboxylate) were synthesized by direct metal insertion using ferric acetate, oxidative addition of the $Fe(II)N_4$ compounds, and ligand substitution on the $Fe(III)N_4$ carboxylate complexes. The electronic ground states of the $Fe(III)N_4X$ complexes were assigned by magnetic susceptibility measurements. $Fe(6565)X$ and $Fe(6566)X$ complexes possessed intermediate-spin (S = 3/2) ground states, while $Fe(6666)X$ complexes had high-spin ground states.

Chapter 3

Stable, isolable Iron(III)thiolate complexes $(Fe(III)N_4SR$, R = Ph, $CH_2Ph)$ of the bis(β-imino amine) macrocycle series were synthesized by oxidative addition $(Fe(II)N_4$ + diphenyl disulfide) and ligand substitution reactions $(Fe(III)N_4$ carboxylate + RSH). The $Fe(III)N_4SR$ complexes provided examples of all the possible spin ground states of Fe(III),

$S = 1/2$, $S = 3/2$, and $S = 5/2$. These ground state determinations resulted from magnetic susceptibility measurements, Mössbauer and epr spectroscopy. Six-coordinate pyridine adducts $Fe(III)N_4SPh(Py)$ have been isolated and studied by epr spectroscopy.

Chapter 4

Ferric octaethylporphyrin thiolates (SPh and $SC_6H_4NO_2$) were synthesized. Their high-spin ground state was assigned from magnetic susceptibility measurements, Mössbauer, epr, and electronic spectroscopy. An X-ray crystal structure determination revealed 5-coordinate geometry with the Fe displaced out of the porphyrin plane toward the axial thiolate. Adduct formation by a variety of Lewis bases has been examined by epr spectroscopy. The chemical and physical studies of the ferric porphyrin thiolates have led to their postulation as model complexes for the ferric reaction states of cytochrome P-450.

Chapter 5

Several routes were examined in an attempt to synthesize bis-(β-imino amine) macrocycles of various ring sizes and substitution patterns.

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CHAPTER 1

Synthesis and Properties of Iron(II) Tetraaza
Macrocycles Containing 14-, 15-, and 16-Membered Rings

Introduction

Intense interest in the structural, electronic, and reactivity

properties of heme-proteins and enzymes has resulted in a substantial

amount of recent work on the Iron complexes of porphyrins[1] and macro-

cyclic ligands[2]. The particular interest in simple models for the

ferrous reaction states of the oxygen binding proteins, myoglobin and

hemoglobin, has led to the synthesis and study of Iron(II) complexes

of porphyrins and tetraaza macrocycles (Fe(II)N_4).

Low-spin 6-coordinate complexes of the type Fe(II)(porphyrin)L_2

(L = pyridine (py) or piperidine[3]) have been well characterized.

Busch[4] and Goedken[5,6] have published extensively in the past three

years on the synthesis and properties of 5- and 6-coordinate Iron(II)

complexes for a variety of tetraaza macrocycles. The number of well

characterized 4-coordinate Fe(II)(N_4) complexes is small. Previous to

the start of this work, only two compounds of this type had been

synthesized. Phthalocyanine Iron(II) has been extensively studied by

Mössbauer spectroscopy and magnetic susceptibility[7]. Truex and Holm[8]

have reported the synthesis of an Iron(II) complex of a 14-membered

bis(β-imino amine) macrocycle. During the course of this work, Collman,

et al., reported the synthesis of the 4-coordinate Iron(II) complexes

of meso-tetraphenylporphyrin (TPP)[9] and some substituted TPP derivatives[10].

Baldwin and Huff have also synthesized some Iron(II) complexes of

octaaza[14]annulene macrocycles.[11]

Recently Tang, et al.,[12] have described the synthesis of a series

of metal complexes of tetraaza macrocycles containing 14-, 15-, and

16-membered rings, whose ring size patterns are shown schematically by

I, II, and III.
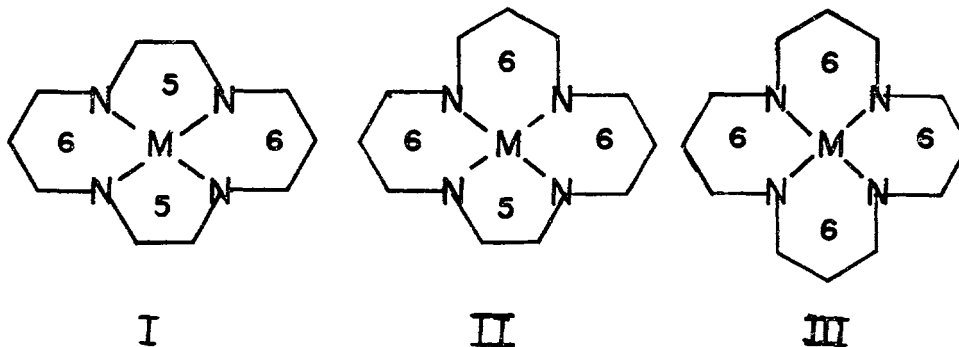
The macrocycles can be considered to be made up of fused 5- and 6-

membered chelate rings resulting in ring size patterns of I-6565,

II-6566, and III-6666. Ring patterns, II and III, are analogues to

the inner rings of corrins and porphyrins, while pattern I is the

most commonly found ring size for synthetic macrocycles but is un-

known in biological materials.

The particular macrocycles that were synthesized, 1, 2, and 3,

are of the bis(β-imino amine) type (see Chapter 5). They were

synthesized by a non-template method based on the reactions of primary

diamines with the 4-phenyl-1, 2-dithiolium cation.

1 H_2(HPhH(en)$_2$)*
or
H_2(6565)

2 H_2(HPhH(en)(tn))
or
H_2(6566)

3 H_2(HPhH(tn)$_2$)
or
H_2(6666)
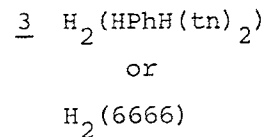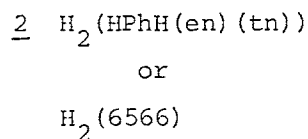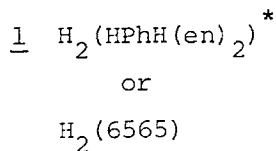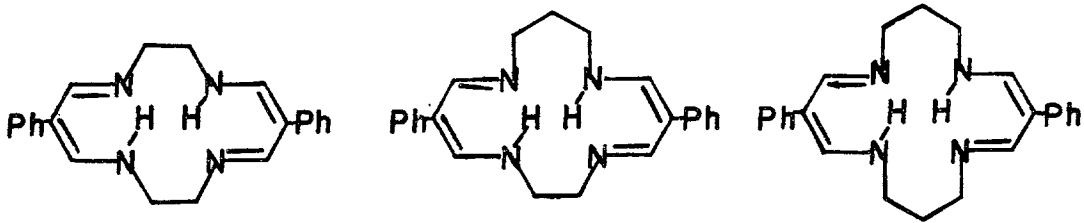
The diprotic nature of 1, 2, and 3, similar to that of porphyrin ligands, results in neutral metal complexes, when they are formed from dipositive metal ions. Tang, et al.,[12] have described the incorporation of Ni(II), Cu(II), and Co(II).

The existence of the macrocycle series 1, 2, and 3 afforded a unique opportunity to investigate the chemistry of Fe(II) and Fe(III) as a function of macrocycle ring size. The changes in ring size with the attendant changes in the tetragonal N_4 ligand field strength were expected to have significant effects on the chemical and electronic properties of the Fe(II) and Fe(III) complexes of 1, 2, and 3. In this chapter the synthesis of the 4-coordinate Iron(II) complexes, utilizing ferrous acetate insertion, is described. Their chemical, electrochemical, and magnetic properties are examined and discussed in relation to the

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*Abbreviations of the macrocycles and their complexes consist of the substituents on the β-imino amine rings followed by the diamine-derived methylene connecting rings; en = ethylenediamine, tn = tri-methylenediamine. The more compact abbreviation of the ring size patterns will be used for 1, 2, and 3 and their metal complexes.

changes in macrocycle ring size. Co(II) complexes have also been
synthesized. The synthesis and properties of the Iron(III) complexes
of 1, 2, and 3 will be the subject of Chapters 2 and 3.

Experimental Section

Preparation of compounds. All manipulations were performed using
degassed solvents under a pure nitrogen atmosphere. Uncorrected melting
points were obtained in sealed capillary tubes.

Ferrous acetate. Fe(OAc)$_2$ was synthesized by a modification of
the method of Hardt and Möller[13]. Iron powder (10g, 0.18 mol), in a
60 ml stemless course fritted funnel, was placed in an Soxhlet extractor
fitted to a 3-neck 500 ml flask. Glacial acetic acid (300 ml) and
acetic anhydride (100 ml) were added to the flask, all joints were wired
tight, and the apparatus was degassed by vacuum pumping and flushing
with nitrogen. Refluxing the stirred solution resulted in the quick
reaction of the iron powder to form the very slightly soluble ferrous
acetate. The ferrous acetate was slowly extracted over 24 to 36 hours
to give pure white crystals. The product was filtered, washed with
diethyl ether, and dried under vacuum for 12 hours. The anhydrous
ferrous acetate (28g, 93% yield) obtained was stored under nitrogen.
It can be exposed to air for short periods of time. Prolonged exposure
to air resulted in its reaction to red crystalline ferric acetate.

Iron(II) Macrocycles a) Fe(6565) (4). Ferrous acetate (2.5g, 15 mmol)
and H$_2$(6565) (5.0g, 13 mmol) were heated in 20 ml of DMF at 80° for one
hour, during which time red crystals formed in a green solution. The
product was filtered and washed with ethanol (4.7g, 80% yield). The
compound was not recrystallized due to low solubility; mp. 312-314°.
Anal. Calcd. for C$_{22}$H$_{22}$N$_4$Fe; C, 66.35; H, 5.57; N, 14.07. Found:
C, 66.29; H, 5.51; N, 14.12.

b) <u>Fe(6566)</u> (<u>5</u>). Method I. Ferrous acetate (0.65g, 3.7 mmol) and H_2(6566) (1.3g, 3.6 mmol) were reacted in 15 ml of DMF at 80° for one hour. Cooling the red solution resulted in the formation of red crystals, which were collected and washed with ethanol. Recrystallization from hot DMF ($\sim$40 ml) afforded red plates (1.3g, 84%); mp. 246–248°. <u>Anal</u>. Calcd. for $C_{23}H_{24}N_4Fe$: C, 67.00; H, 5.87; N, 13.59. Found: C, 66.96; H, 5.91; N, 13.61.

Method II. The procedure takes advantage of the more readily obtained macrocycle H_2(6666) compared to H_2(6566)[12]. Ferrous acetate (0.93g, 5.4 mmol) and H_2(6666) (2.0g, 5.4 mmol) were heated in 20 ml of DMF at 80° for 20 minutes. Ethylenediamine (0.4g) was added and heating was continued for 30 minutes, during which time the reaction mixture went from green-brown to red-brown. The addition of 100 ml of ethanol and cooling gave red plates (0.4g, 18% yield); identical to that obtained by Method I by mixed melting point.

c) <u>Fe(6666)</u> (<u>6</u>). Ferrous acetate (1.4g, 8.1 mmol), H_2(6666) (3.0g, 8.0 mmol), and pyridine (1.3g, 16.1 mmol) were stirred in 20 ml of DMF at 60° for 3 hours. Crystalline product was filtered from the cooled reaction solution and was washed with ethanol. Recrystallization from $\sim$180 ml of hot DMF (90°) gave 1.9g of pyridine-free product in 55% yield. The red crystalline product was dried under vacuum for 24 hours; mp. 204–205°. <u>Anal</u>. Calcd. for $C_{24}H_{26}N_4Fe$: C, 67.61; H, 6.15; N, 13.14. Found: C, 67.60; H, 6.37; N, 13.32.

<u>Co(II) Macrocycles</u> a) <u>Co(6565)</u>. Cobaltous acetate tetrahydrate (1.9g, 7.6 mmol) and H_2(6565) (2.6g, 7.6 mmol) were reacted in 20 ml of DMF at 80° for 45 minutes. The red reaction mixture was cooled and filtered to give red crystalline product (1.4g, 63% yield). The product was not recrystallized due to its insolubility; mp. 336–338°. <u>Anal</u>.

Calcd. for $C_{22}H_{22}N_4Co$: C, 65.83; H, 5.52; N, 13.96. Found: C, 65.41; H, 5.51; N, 14.32.

b) Co(6666). Cobaltous acetate tetrahydrate (1.4g, 5.4 mmol) and $H_2(6666)$ (2.0g, 5.4 mmol) was heated in 20 ml DMF to 80°. Trimethylene-diamine (0.5 ml) was added and the heating was continued for 12 hours. On cooling, red crystals separated and were filtered. Recrystallization from hot DMF (80°) afforded red crystals (1.0g, 45%); mp. 263-265°. Anal. Calcd. for $C_{24}H_{26}N_4Co$: C, 67.13; H, 6.10; N, 13.05. Found: C, 67.18; H, 5.78; N, 13.12.

Physical Measurements

The magnetic susceptibility of solids was measured using a Bruker Faraday balance. Susceptibility measurements were made at four field settings (10, 20, 25 and 30 amps). The susceptibility was found to be in-dependent of field strength in all cases; the average of the three high-field susceptibilities was used. Diamagnetic corrections were calculated using Pascal's constants. $HgCo(SCN)_4$[14] and $Ni(en)_3S_2O_3$[15] were used as calibration standards. The calibration constants (β) were averages of at least five measurements using different amounts of $HgCo(SCN)_4$. Compounds reactive to air were measured in a nylon cup with a screw cap. The cup, which was filled in a nitrogen atmosphere glove box, was quickly transferred into the apparatus, where it was placed immediately under vacuum or a helium atmosphere.

Variable temperature measurements were done using a commercial helium flow type cryostat (Leybold-Hereaus obtained from Bruker Scientific). The cryostat's temperature control system was calibrated[16] using a platinum resistance (300°-40°K) and a germanium-arsenic diode (40°-12°K). Tempera-ture control regulation of ±0.25° was achieved from 288° to 14°K. The susceptibilities were measured at 10 to 15 temperatures (room temperature

to 17°K); at ∿40° intervals from room temperatures to 50°K and ∿10°

intervals for 50° to 17°K. The minimum sample weight for each compound

was determined so that its field-on field-off displacements at room

temperature could be measured to 3 significant figures (∿10.00 mg dis-

placements) for the 3 largest field settings. The maximum sample weight

was determined so that the estimated displacements at the lowest tempera-

ture to be measured did not exceed the capacity of the balance (∿200.00 mg).

Sample weights of 25 to 80 mg were used depending on the two above criteria,

which were estimated from previously measured room temperature susceptibilities.

At low temperature, the fluctuations in temperature (∿±0.25°) cause paral-

lel fluctuations in the measured displacements. In these cases satisfactory

results were obtained by averaging the extreme displacements. The standardi-

zation procedure for variable temperature measurements is identical to

that for room temperature measurements. The β values used were those

determined by repeated measurements at room temperature using $HgCo(SCN)_4$

as the standard. The corrections for the empty cups were determined as

a function of temperature. The validity of this approach was confirmed

by the variable temperature measurements on $HgCo(SCN)_4$ for 295-17°K,

which was in good agreement with the reported values.[14]

Solution magnetic susceptibilities were measured in methylene chloride

containing TMS (2%) by the nmr method of Evans[17] using concentric tubes.

The shifts in the TMS resonances were measured using the frequency counter

of a R-20B or R-22B nmr spectrometer. Measurements at reduced temperature

were corrected for changes in solvent density.

Electronic spectra were recorded on a Cary Model 14 or Model 17

spectrophotometer. Epr measurements were made on a Varian E-9 spectro-

meter at ∿95°K in frozen solution glasses. The field was measured

with a Harvey-Wells Precision NMR Gaussmeter, Model G-502. A Princeton

Applied Research Model 170 Electrochemistry System was employed for electrochemical measurements. The usual polarographic measurememts were carried out using a rotating platinum electrode as the working electrode. Solutions were $\sim 10^{-3}$M in complex and 0.05M in tetra-n-propyl or tetra-n-butyl ammonium perchlorate as the supporting electrolyte. All potentials were determined at 25° vs a saturated calomel reference electrode. Infrared spectrum were obtained on a Perkin-Elmer Model 337 grating spectrophotometer, Kel-F mulls using NaCl plates in the 4000-1200 cm^{-1} range and nujol mulls using KBr plates in the 1333-400 cm^{-1} range. Elemental analyses were performed by Spang Micro-analytical Laboratories, Ann Arbor, Michigan; Galbraith Laboratories, Inc., Knoxville, Tennessee; and Alfred Bernhardt, West Germany.

Results and Discussion

Fe(II) Incorporation Using Ferrous Acetate

Ferrous acetate, generated in situ by the reaction of acetic acid on iron metal, has been used for the incorporation of Fe(II) and Fe(III) into porphyrins.[18] The use of ferrous acetate in a solvent other than acetic acid necessitates its isolation. The two reported syntheses of anhydrous ferrous acetate entail the reaction of glacial acetic acid on iron powder[13] or on $Fe(CO)_5$[14]. The product isolated from the former reaction was of a higher crystallinity and was less reactive with air. Ferrous acetate, made by a modification of the procedure of Handt and Möller,[13] is a pure white crystalline compound, which can be stored indefinitely under a nitrogen atmosphere. It can be weighed out quickly in air without detectable reaction.

4   **5**   **6**
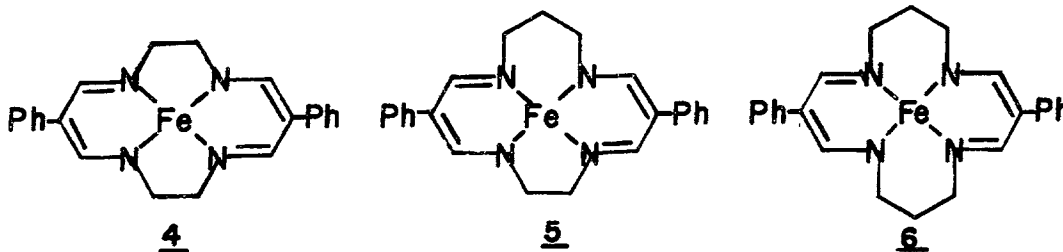
The reaction of $H_2(6565)$ (**1**) and $H_2(6566)$ (**2**) with ferrous acetate in DMF gave Fe(6565) (**4**) and Fe(6566) (**5**) in good yields. No product could be isolated from a similar reaction using $H_2(6666)$ (**3**). Similar behavior has also been observed for Ni(II), Co(II), and Co(II) insertion into the 16-membered macrocycle.[12] In these cases the addition of trimethylenediamine was necessary for metal incorporation. The addition of trimethyldiamine did not lead to the isolation of production in this case. Fe(II) insertion into **3** was achieved by the addition of two equivalents of pyridine to the reaction mixture. The product, Fe(6666) (**6**), isolated contained no bound pyridine in the axial positions. The exact function of the added pyridine is not known, as other bases such as methoxide and triethylamine could not be substituted. It is possible that the reaction of pyridine with ferrous acetate gives a new species, which is necessary for Fe(II) insertion into the large macrocycle. Fe(6565), Fe(6566), and Fe(6666), all red crystalline compounds, are very reactive in solution and in the solid state. They are stable, however, when handled and stored under a nitrogen atmosphere.

Co(6565) was synthesized by the reaction of cobalt(II) acetate with $H_2(6565)$. Co(6666) was synthesized by the reaction of cobalt(II) acetate with $H_2(6666)$ with the necessary addition of trimethylenediamine. No product was isolated on substitution of pyridine for the trimethylenediamine. The cobalt complexes, Co(6565) and Co(6666), have magnetic moments of 2.05 BM and 1.96 BM (295°K) consistent with a low-spin d^7 ground state.[20]

Magnetic Properties

Fe(6565) (**4**) showed Curie-Weiss behavior (χ_M^{corr} = 1.354/(T + 6.75),

$295-22°K)^*$ with μ = 3.26 BM at 295°K. Fe(6566) (5) gave a similar

magnetic moment, μ = 3.25 BM at 295°K. Fe(6666) (6) exhibited Curie-

Weiss behavior $(\chi_M^{corr}$ = 2.558/(T + 0.22), 295-17°K) with μ = 4.54 BM

at 295°K. There are three possible spin ground states for Fe(II) in

a tetragonal field (D_{2h}), which are shown together with their spin-

only magnetic moments.

Low Spin	Intermediate Spin	High Spin
S = 0	S = 1	S = 2
diamagnetic	μ = 2.83 BM	μ = 4.90 BM

While the magnetic moments for 4 and 5 seem to be in agreement with a

S = 1 ground state, the moments differ from the spin-only values,

especially for 6. The observed Curie-Weiss behavior rules out the

possibilities of spin equilibrium effects or antiferromagnetic coupling

effects on the magnetic moments, at least in the experimental tempera-

ture intervals.

There are a few well-characterized 4-coordinate ferrous complexes

of the Fe(II)N_4 type. Their magnetic moments vary almost continuously

from 2.8 to 5.0 BM. The dibenzo-octaaza macrocycle(II) complex (IV),

reported by Baldwin and Huff[11], has a magnetic moment of 2.87 BM.[21]

Fe(II)(MeHMe(en)$_2$) (V) has reported moment of 3.95 BM[8]; the small change

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*The Curie-Weiss plots were obtained by least-squares fit of the data
to the equation χ = C/(T + θ).
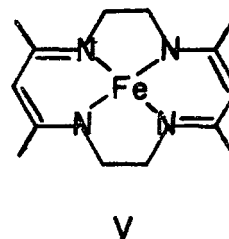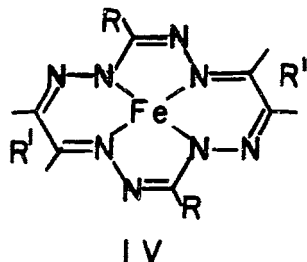
in substitution on the β-imino amine ring compared with $\underline{4}$, apparently

has a large effect oɩ the observed magnetic moment. Fe(II)phthalo-

cyanine[7] (μ = 3.89 BM) is the only compound of the Fe(II)N_4 type,

which has been subjected to detailed measurement and analysis.

Magnetic anisotropy measurements[7] have shown its electronic struc-

ture to be $(xz,yz)^4 (xy)^1 (z^2)^1$, an S = 1 ground state. Fe(II)(TPP)

has a reported moment of 4.4 BM (25°C) and has been assigned an S = 1

ground state[9]. While the picket fence substituted TPP, meso-tetra-

(α,α,α,α-ortho-pivalamidophenyl)porphyrin Iron(II), has a moment of

5.0 BM (25°C) and has been assigned a S = 2 high-spin ground state.[10]

From the variety of magnetic moments for $\underline{4}$, $\underline{5}$, and $\underline{6}$, reported here,

and the literature data, discussed above, it can be seen that more

detailed magnetic measurements and analysis are needed before all of

the reported moments can be interpreted satisfactorily.

Polarographic Results

The polarographic data for $\underline{4}$, $\underline{5}$, and $\underline{6}$ (Table I) indicate two

separate oxidations for each compound. The first (1e$^-$) oxidation waves

come at quite negative potentials and can be readily assigned to the

oxidation of Fe(II) to Fe(III). There appears to be no large effect

Table I. Polarographic Data

Complex	Solvent	Couple[a,b]	$E_{1/2}$,V	Slope[c]
Fe(6565)	DMSO	0/1+	-0.37	61
		1+/2+	+0.42	73
Fe(6566)	DMF	0/1+	-0.32	73
		1+/3+	+0.45	80
Fe(6666)	DMF	0/1+	-0.36	75
		1+/3+	+0.50	80
[Fe(6666)]$_2$O	DMF	0/1-	-1.19	65
		0/4+	+0.40	84

[a]Notation used indicates the number of electrons transferred but does not imply strict electrochemical reversibility.

[b]The number of electrons transferred was determined by a comparison of diffusion currents for

$$[Ni(tdt)_2]^{-2} \rightleftarrows [Ni(tdt)_2]^{-1}$$
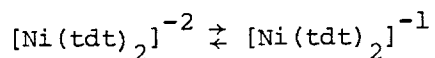
[c]Slope of the plot E versus $\log(\frac{i_d - i}{i})$

on the Fe(II)/Fe(III) couple due to the changes in macrocycle ring
size. Each complex exhibited a second more irreversible oxidation
at (+0.4 to 0.5 v). For 4 it is a one electron oxidation, while for
5 and 6 it corresponds to a two electron oxidation. Similar oxida-
tions were observed for some Fe(III) complexes of 1, 2, and 3 (to be
discussed in Chapter 3). Although electrochemical measurements of
ferric porphyrins indicate the existence of Fe(IV) species,[24] the
second oxidations for 4, 5, and 6 are more readily ascribed to ligand
oxidations. For 5 and 6 this assignment is due to the multi-electron
character of the waves and to the existence of similar oxidations in
the Ni(II) complexes of 2 and 3.[12,22] The assignment is more tenuous
for 4 due to its one electron character. Truex and Holm[8] have found
similar one electron oxidations for a series of metal complexes
(Ni(II), Cu(II), and Zn(II)) of a 14-membered ring macrocycle
[(MeHMe(en)$_2$)] differing from 1 only in the substitution on the β-
imino amine rings. They assigned their metal-independent potentials
to an oxidation of the ligand Π system rather than a metal oxidation.
However, Busch, et al.,[23] obtained epr evidence for Ni(III) in the
single electron oxidation of the Ni(II) complex of another related
bis(β-imino amine) macrocycle. More work is needed, before the mode
of the oxidation of the metal complexes of bis(β-imino amine) macro-
cycles is completely understood.

Due to the extreme air sensitivity of the Fe(II) complexes in
dilute solutions, the polarographic solutions gradually oxidized with
a resultant decrease in the Fe(II) to Fe(III) oxidation wave and the
increase in a new reduction wave. For 6 this air oxidation was almost
quantitative giving the polarogram of [Fe(III)6666]$_2$O, which was

independently synthesized (see Chapter 2). [Fe(III)6666]$_2$O showed an apparent 4e$^-$/dimer oxidation, which can be ascribed to ligand oxidation. The electrochemistry supports the formulation as a dimer; there is a quasi-reversible reduction 1e$^-$/dimer at -1.2 volts, which corresponds to Fe(III)-O-Fe(III) → Fe(II)-O-Fe(III). No further reductions were observed.

CHAPTER 2

Synthesis and Ground State Electronic Properties of Ferric

Tetraaza Macrocycles Containing 14-, 15-, and 16-Membered Rings

Introduction

The ferric oxidation state has been found to be an in vivo reaction

state in a large number of heme-proteins and enzymes, such as the

cytochromes[25], catalase, peroxidase[51], and cytochrome P-450[44]. Although

the Fe(III) oxidation state in the heme-proteins, hemoglobin and

myoglobin, does not have an active biological role, much valuable in-

formation on the structure and function of these proteins has been

obtained by investigating their Fe(III) complexes[26]. Ferric heme-

proteins and enzymes, as well as ferric macrocycle and porphyrin com-

plexes, are susceptible to study by a variety of physical techniques

including epr, nmr, Mössbauer spectroscopy, and magnetic susceptibility.[26]

The primary information derived from these physical measurement is the

identification of the spin ground state of Fe(III). The three possible

spin ground states for Fe(III) are shown together with their expected

spin-only magnetic moments.
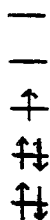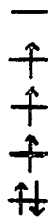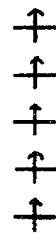
Low Spin (S=1/2)	Intermediate Spin (S=3/2)	High Spin (S=5/2)
μ = 1.73 BM	μ = 3.88 BM	μ = 5.92 BM

In an octahedral ligand field the intermediate-spin case is forbidden[27];

however, in tetragonal or lower symmetry it becomes an allowed possibility.

Ferric complexes of porphyrins have been extensively investigated. Their magnetic ground state properties can be summarized by the two following statements:[1,30]

1) All 5-coordinate ferric porphyrins are high spin with the Fe displaced out of the N_4 plane.

2) All 6-coordinate ferric porphyrins are low spin with the Fe located in the N_4 plane.

The reported work on Fe(III) macrocyclic complexes is limited. Busch, et al.,[28] have reported a series of low-spin 6-coordinate complexes with several 14-membered ring macrocycles. Busch, et al.,[29] have also reported a high-spin 7-coordinate pentagonal-bipyamidal iron(III) complex.

This chapter deals with some investigations of the chemistry of Fe(III) in the 14-, 15-, 16-membered tetraaza macrocycles discussed in the previous chapter. General synthetic methods for ferric macrocycle complexes have been developed. These include direct insertion of Fe(III) utilizing ferric acetate, substitution reactions on the Fe(III)N_4 acetates, and oxidative addition reactions of the ferrous macrocycles, Fe(II)N_4, (synthesized in Chapter 1). Fe(III)N_4X complexes have been synthesized for the 14-, 15-, and 16-membered macrocycles and for a variety of axial ligands (X = halides and carboxylates). Their ground state electronic properties have been determined by magnetic susceptibility and epr spectroscopy. The effect of the systematic changes in macrocycle ring size and in the fifth coordinated ligand is considered on the electronic and reactivity properties of these ferric tetraaza macrocycle complexes.

Experimental Section

Preparation of Compounds. All manipulations were performed with degassed solvents under a pure nitrogen atmosphere, unless otherwise indicated. Characterization data for new compounds are given in Table I. Structural formulas are set out in Scheme I. The electronic spectra for the synthesized complexes are tabulated in Table II.

Ferric acetate. Ferrous acetate (10.0g) was heated in 100 ml of glacial acetic acid at 100°, exposed to the air. A brick-red powder precipitated and was collected to give 9.8g product, which was presumed to have the "basic ferric acetate" formulation $Fe_3O(OAc)_7$.[32,87]

Fe(6565)OAc (7). H_2(6565) (5.0g, 15 mmol) and ferric acetate (3.5g, 18 mmol) were heated in 35 ml of ethanol at 70° for two hours. The color of the reaction mixture changed from brown, to green, to purple. Filtering the cooled reaction mixture and washing with isopropanol afforded 4.7g of black crystals. Two recrystallizations from hot ethanol were necessary to give an analytically pure sample in reduced yield; ν_{OAc} 1600 cm^{-1} (mull).

Fe(6566)OAc (8). H_2(6566) (0.95g, 2.7 mmol) and ferric acetate (0.61g, 3.1 mmol) were heated in 25 ml of isopropanol for 1 1/2 hours at 70°. Crystallization occurred on cooling for 24 hours. Two recrystallizations from isopropanol gave 0.80g of purple-black crystalline product. A satisfactory combustion analysis was not obtained. The product was used successfully in the synthesis of Fe(6566)Cl.

Fe(6666)OAc (9). H_2(6666) (2.0g, 5.4 mol) and ferric acetate (1.3g, 6.5 mmol) were heated in 30 ml of DMF at 80° for one hour. Prolonged

heating caused product decomposition. The deep green solution was
filtered, and the DMF was removed under vacuum. The residue was re-
crystallized from 40 ml of hot isopropanol to give dark-green crystals
(0.8g, 31% yield).

Fe(6565)Br (10). Fe(6565) (2.6g, 6.5 mmol) was suspended in 30 ml of
DMF. Bromine (0.53g, 3.3 mmol) in 5 ml DMF was added. The reaction
mixture immediately turned red-violet, crystals gradually formed over
an hour. Further crystallization was induced by the dropwise addition
of 200 ml of ethanol. The filtered product was dissolved in 200 ml of
warm DMF. The solution was filtered, 200 ml ethanol was added dropwise
to the filtrate to give purple-black crystals (2.0g, 64% yield).

Fe(6566)Br (11). Bromine (0.18g, 1.2 mmol) in 5 ml of DMF was reacted
with a suspension of Fe(6566) (0.94g, 2.3 mmol). Ethanol (180 ml) was
added slowly to the blue reaction solution. The solution was cooled
and filtered to give green-blue crystals. The product was redissolved
in a minimum amount of warm DMF (∿50 ml). Slow addition of ethanol
afforded dark green-black micro-crystalline product (0.55g, 50% yield).

Fe(6666)Br (12). Bromine (0.34g, 2.1 mmol) in 5 ml of DMF was added to
Fe(6666) suspended in 20 ml of DMF. Dark green crystals separated from
the blue-green reaction solution on the slow addition of isopropanol
(200 ml). The product was redissolved in the minimum amount of warm
DMF (50°). The dropwise addition of 200 ml of isopropanol to the
filtered solution and cooling gave dark green crystals (2.0g, 90% yield).

Fe(6666)O$_2$CPh (15). Dibenzoylperoxide (0.71g, 3.0 mmol) in 15 ml of
DMF was added slowly to a stirred suspension of Fe(6666) (2.4g, 5.9 mmol)

in 15 ml of DMF. The reaction was exothermic, becoming blue-green
immediately. Stirring for one hour resulted in crystallization of
product. Addition of 40 ml of ethanol completed product separation.
The collected product was redissolved in 50 ml of DMF ($\sim$70°). Ethanol
(200 ml) was added dropwise to the filtered solution to induce crystal-
lization. Cooling and filtering gave 1.4g of green-black crystals in
44% yield.

Fe(6565)Cl (<u>13</u>). Method I. To a suspension of Fe(6565)OAc (1.8g, 4.0
mmol) in 50 ml of ethanol, 4 ml of 4<u>N</u> HCl (16 mmol) was added. The
reaction was stirred overnight and was filtered. The product was
recrystallized twice from DMF/isopropanol to give black crystals
(1.3g, 76% yield).

Method II. Fe(6565) (1.5g, 3.8 mmol) was stirred for 12 hours
in 25 ml chloroform. Solvent was removed under vacuum. The residue
was recrystallized twice from DMF(80°)/ethanol. The product from
this method was identical in melting point and infrared spectrum with
the product obtained by Method I.

Fe(6565)I (<u>16</u>). To a suspension of Fe(6565)OAc (1.5g, 3.3 mmol) in
50 ml of ethanol was added 0.82 ml (6.2 mmol) of 57% HI. The suspension
was stirred overnight and filtered. The reaction product was recrystal-
lized twice from DMF/ethanol to give purple-black crystals (0.7g, 41%
yield).

Fe(6566)Cl (<u>14</u>). To a suspension of Fe(6566)OAc (0.80g, 1.71 mmol)
in 30 ml of isopropanol was added   0.8 ml (3.2 mmol) of 4<u>N</u> HCl.
The reaction mixture was stirred overnight. The filtered product was
recrystallized twice from DMF(60°)/ethanol to give blue-green micro-

crystals (0.20g, 26% yield).

[Fe(6666)]$_2$O (17). Fe(6666)O$_2$CPh (1.0g, 1.8 mmol) was partially dissolved in 20 ml of DMF. The addition of sodium hydroxide (0.10g, 2.5 mmol) in 10 ml of DMF resulted in an immediate reaction and the precipitation of a brown powder. The filtered product was washed with water and isopropanol, and was dissolved in hot DMF. Isopropanol was added dropwise to the filtered DMF solution, which caused the separation of black crystals (0.37g, 23% yield); ν_{FeOFe} 855 cm^{-1}.

Physical Measurements

Measurements were done as described in Chapter 1.

Results and Discussion

Scheme I: Synthesized Fe(III)N$_4$X Complexes and Their Precursors
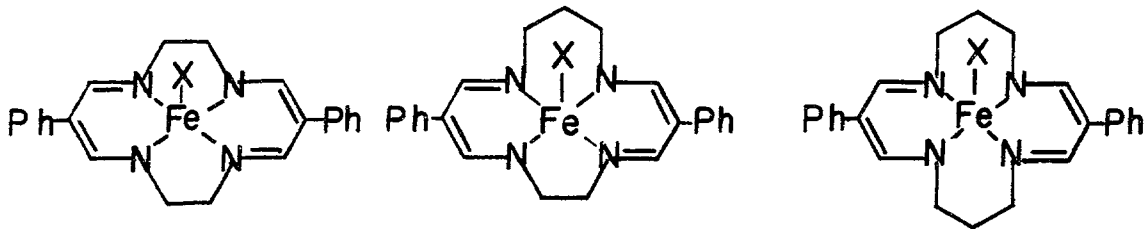
H$_2$(6565) (1)   H$_2$(6566) (2)   H$_2$(6666) (3)

Fe(6565) (4)   Fe(6566) (5)   Fe(6666) (6)

Fe(6565)X   Fe(6566)X   Fe(6666)X

X = OAc (7)   X = OAc (8)   X = OAc (9)

   = Br (10)   = Br (11)   = Br (12)

   = Cl (13)   = Cl (14)   = O$_2$CPh (15)

   = I (16)   [Fe(6666)]$_2$O (17)

Table I. Characterization Data for Fe(III)N$_4$ Complexes

Compound	Mp,[a] °C	Calcd, %			Found, %		
		C	H	N	C	H	N
Fe(6565)OAc	305-307	63.03	5.51	12.25	63.12	5.44	12.24
Fe(6666)OAc	178-180	64.34	6.02	11.54	64.09	6.11	11.40
Fe(6565)Br	256-258	55.26	4.64	11.72	55.43	4.78	11.95
Fe(6566)Br	236-238	56.12	4.92	11.38	56.04	5.14	11.28
Fe(6666)Br	221-222	56.94	5.18	11.06	56.78	5.24	11.06
Fe(6666)O$_2$CPh	208-210	68.01	5.71	10.23	67.83	5.55	10.19
Fe(6565)Cl	283-285	60.92	5.10	12.92	60.98	5.03	12.95
Fe(6565)I	273-275	50.31	4.22	10.67	50.27	4.18	10.66
Fe(6566)Cl	223-225	61.70	5.40	12.51	61.88	5.49	12.51
[Fe(6666)]$_2$O	225-227	66.37	6.03	12.90	66.28	5.94	12.92

[a]Sealed tube, uncorrected

Insertion of Fe(III) Into Macrocycles Using Ferric Acetate

Macrocyclic ferric acetates (Fe(III)N_4OAc) are convenient starting compounds in the synthesis of other Fe(III)N_4X complexes. The insertion of Fe(III) directly into macrocycles and porphyrins using ferric acetate potentially gives Fe(III)N_4OAc complexes in a single step. Ferric acetate has not been previously used for the incorporation of Fe(III). Ferric acetate was obtained by heating ferrous acetate in acetic acid in the air. The brick-red material obtained was assumed to have the "basic ferric acetate", $Fe_3O(OAc)_7$, formulation[32,87] The reaction of ferric acetate with the 14-, 15-, and 16-membered tetraaza macrocycles, 1, 2, and 3, in suitable solvents gave the Fe(III)N_4OAc 7, 8, and 9 in fair to good yields. The syntheses were quite solvent dependent. The reaction of H_2(6565) and ferric acetate in ethanol gave Fe(6565)OAc, while in DMF, Fe(6565) was obtained in high yield. The reaction of H_2(6666) with ferric acetate in DMF gave Fe(6666)OAc; in ethanol no produce was formed. Fe(6566)OAc could not be obtained in an analytically pure form. It was used in crude form in the synthesis of other Fe(6566)X complexes, which were obtained in analytical purity. Ferric acetate was used for the incorporation of Fe(III) in porphyrins and other complexes as will be discussed in Chapters 3 and 4.

Oxidative Addition Reaction of Ferrous Macrocycles

From the discussion of the polarographic measurements in Chapter 1, it is not surprising that the Fe(II) tetraaza 14-, 15-, and 16-membered macrocycles (4, 5, and 6) react readily with a variety of oxidizing agents. The general reaction (1) is of the oxidative addition type.

$$Fe(II)N_4 + 1/2\ X_2 \rightarrow Fe(III)N_4X \tag{1}$$
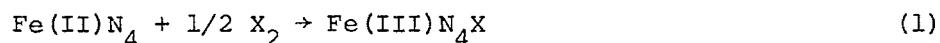
X_2 oxidatively adds to the 4-coordinate Fe(II) complexes to give 5-coordinate Fe(III) complexes. Fe(6565) (4), Fe(6566) (5), and Fe(6666) (6) were reacted with bromine to afford the corresponding 5-coordinate Fe(6565)Br (10), Fe(6566)Br (11), and Fe(6666)Br (12) in good yields. Dibenzoyl peroxide oxidized 6 to Fe(6666)O$_2$CPh (15), which is quite similar in chemical behavior to Fe(6666)OAc. The Fe(II)N$_4$ complexes (4, 5, and 6) react with chlorinated solvents, such as CHCl$_3$ and CH$_2$Cl$_2$, to give the corresponding Fe(III)N$_4$Cl complexes. The reaction of (4) with chloroform was a good route for the synthesis of Fe(6565)Cl (13). The oxidation of 4, 5, and 6 with disulfides will be discussed in the next chapter.

The reaction of 4, 5, and 6 with oxygen does not lead to the expected μ-oxo dimers[33]. Instead what is observed is a general decomposition of the macrocycle complexes. A similar decomposition reaction was observed on exposure of all the Fe(III)N$_4$X complexes to dry air. The Fe(III)N$_4$X complexes react immediately with oxygen in solution and more slowly in the crystalline solid state. The Fe(6666)X complexes are more reactive in the solid state than Fe(6565)X or Fe(6566)X. The sensitivity of the ferric macrocycle complexes to oxygen was an unexpected observation considering the known stability of Fe(III) porphyrins and similar complexes. The reactivity can be understood by considering the polarographic results obtained for the Fe(II)N$_4$ complexes 4, 5, and 6 as were discussed in Chapter I. For each complex there was observed a single, one or two electron, irreversible oxidation at +0.4 V, which were ascribed to the ligand oxidation of the Fe(III)N$_4$ species (similar ligand oxidations were also observed for some Fe(III)N$_4$SR complexes discussed in Chapter 3). These ligand oxidations are well within the oxidizing potential range of oxygen. Similar polarographic ligand

oxidations have been found for Ni(II) and Cu(II) complexes of 1, 2, and 3,[12,43] and for the Ni(II), Cu(II), and Zn(II) complexes of a similar bis(β-imino amine) macrocycle[8]. These complexes, however, are quite stable to oxygen. In the case of the Fe(III)N_4X complexes, Fe(III) might activate the oxygen, which causes the oxidative destruction of the ligands. In no examples, were any products identified from the reaction of excess oxidizing agents with the Fe(II) or Fe(III) macro-cyclic complexes. Because of the known oxidative dehydrogenation reactions of 1, 2, and 3 complexed with Ni(II), Cu(II), and Co(II),[34] the reactions of the Iron complexes should be more carefully investigated. The reaction of Fe(6666) with a limited amount of oxygen gave the μ-oxo dimer [Fe(6666)]$_2$O. Its polarography was examined in Chapter 1. [Fe(6666)]$_2$O is decomposed on exposure to excess oxygen.

Substitution Reactions of Macrocyclic Ferric Acetates

Fe(III)N_4OAc complexes are the reactants in the general synthesis of Fe(III)N_4X complexes (2).

$$Fe(III)N_4OAc + HX \rightarrow Fe(III)N_4X + HOAc \qquad (2)$$
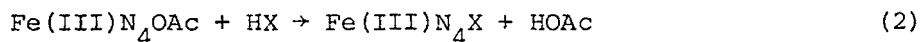
The reaction depends on two factors, the acid strength of HX versus HOAc and the Fe-X versus Fe-OAc bond strength. Fe(6565)X, X = Cl (13), I (16), and Fe(6566)Cl (14) were synthesized by this method. Fe(6565)Cl obtained from the reaction of Fe(6565)OAc with HCl was identical to the complex obtained by the previously described chloroform oxidation of Fe(6565). The reaction of Fe(6666)O_2CPh with aqueous NaOH gave the μ-oxo dimer, [Fe(6666)]$_2$O, which is identical to the product obtained from the reaction of Fe(6666) with oxygen. The reactivity of the macro-cyclic ferric carboxylates with mercaptans will be considered in the next chapter.

Magnetic Susceptibilities of Fe(III)N$_4$X Complexes

The magnetic moments, measured for the synthesized ferric macro-
cyclic complexes, are shown in Table II. The complexes from the 14-
membered ring macrocycle Fe(6565)X (10, X = Br; 13, X = Cl; 16, X = I;
7, X = OAc) have solid-state magnetic moments close to the spin-only
value of 3.88 BM expected for intermediate spin (S = 3/2). The magnetic
susceptibility was measured as a function of temperature for a repre-
sentative member of the series, 10. Fe(6565)Br gave strictly Curie-
Weiss behavior (χ_M^{corr} = 1.957/(T + 7.92), 295-17°K, μ = 3.91 BM
(295°K)),[*] confirming the intermediate-spin ground state. The complexes
for the 15-membered ring macrocycle, Fe(6566)X (11, X = Br; 14, X = Cl) also
have magnetic moments in accord with three unpaired electrons. The
intermediate-spin ground state was established by the variable tempera-
ture magnetic susceptibility for 11 (χ_M^{corr} = 2.110/(T + 4.60), 295 to 17°K,
μ = 4.08 BM (295°K))[*]. The ground state changed to high spin (S = 5/2)
for the complexes of the 16-membered macrocycle, Fe(6666)X (12, X = Br;
9, X = OAc; 15, X = O$_2$CPh), with magnetic moments close to the spin-
only value of 5.92 BM. The high-spin designation was confirmed by
variable temperature measurements for 9 (χ_M^{corr} = 4.225/(T + 0.06), 295-17°K,
μ = 5.82 BM (295°K))[*].

As expected due to antiferromagnetic coupling, the magnetic moment
for [Fe(6666)]$_2$O was reduced[33]. Since neither magnetic susceptibility
measurements as a function of temperature nor Mössbauer measurements were
performed, it is not possible to assign ground states to the individual
Fe(III) atoms. It is interesting to note that there are no examples of
μ-oxo dimers with S = 1/2 or S = 3/2 ground states.[33] The μ-oxo dimers
of the 14- and 15-membered macrocycles have not as yet been synthesized.

----

[*]Figure 1

Table II. Magnetic and Electronic Spectral Data for Fe(III)N_4 Complexes

Compound	μ_{eff} (BM)[a]	λ_{max}[b], cm^{-1} (ε)[c]
Fe(6565)Br	3.91 Solution[b] 4.08 BM (27°C) 4.05 BM (-25°C) 4.06 BM (-49°C)	17,500(6480); 14,600(Sh,4530); 28,300(7,700); 33,900(28,300); 35,500(Sh,26,600)
Fe(6565)Cl	3.98	18,000(6540); 20,000(Sh,5350); 28,600(8100); 34000(24,400); 35,200(Sh,28600)
Fe(6565)OAc	3.92	20,200(6530); 28,800(9000); 34,000(29,400); 35,700(Sh,27,600)
Fe(6565)I	3.88	16,800(7150); 18,900(Sh,6000); 28,400(10,700); 33,900(23,300); 35,700(Sh,22,900)
Fe(6566)Br	4.08 Solution[b] 4.18 (25°C)	16,300(4840); 21,000(2030); 29,000(Sh,8580); 34,500(27,200)
Fe(6566)Cl	4.10	16,800(5100); 21,000(2950); 29,000(Sh,7090); 34,700(19,900)
Fe(6666)Br	5.80	d
Fe(6666)OAc	5.82	13,800(4110); 22,100(1980); 29,900(Sh,7310); 34,500(13,500)
Fe(6666)O_2CPh	5.88 Solution[b] 5.91 (27°C)	14,200(3420); 21,800(1510); 29,900(Sh,7620); 35,100(16,200)
[Fe(6666)]$_2$O	2.66; 1.88/Fe	12,900(4130); 17,500(Sh,7140); 19,300(8160); 22,900(8920); 29,000(Sh,24,100); 32,900(36,800)

[a]Solid state (∿25°C). [b]Dichloromethane. [c]Apparent values, uncorrected for underlying absorption.
[d]Not measured.

Magnetic susceptibilities in solution were measured for Fe(6565)Br, Fe(6566)Br, and Fe(6666)O$_2$CPh as shown in Table II. Solution magnetic moments were quite similar to the solid moments. Fe(6565)Br showed Curie dependence in solution from 27° to -49°C, consistent with S = 3/2. Solid-state effects are therefore not responsible for observed magnetic behavior. The electronic spectra and other solution measurements thus can be related to the ground states determined by the solid-state susceptibility measurements.

The epr spectrum of Fe(6666)O$_2$CPh, a representative high-spin complex, was examined in a DMF/dichloromethane glass at 95°K. It displayed a rhombic signal with g-values, 7.6, 4.4, 1.9. This spectrum is in accord with theoretically predicted spectrum for a high-spin ground state with a substantial zero field splitting.[65,66] The epr spectra (DMF/dichloromethane, 95°K) of Fe(6565)Br and several other S = 3/2 compounds are complex. They consist of a broad resonance centered at g = 4.5 and several sharp resonances around g = 2. No attempts have been made to analyze these spectra.

The electronic spectra for the synthesized complexes, 7 - 17, are listed in Table II. All complexes show intense bands in the UV which appear to be ligand based transitions. The visible bands are of moderate intensity, most likely charge transfer bands involving metal and ligand. An analysis of the spectra did not lead to any systematic or characteristic features that indicate spin state or even macrocycle ring size.

Previous to this work, Fe(III) complexes with intermediate-spin ground states were considered rare. The only well established class is the ferric bis dithiocarbamate halides and pseudohalides complexes, Fe(III)(S$_2$CNR$_2$)$_2$X[35,36]. Chloro ferric phthalocyanine, on the basis of

FIGURE 1

Solid state variable temperature magnetic susceptibilities for

Fe(6565)Br, Fe(6566)Br, Fe(6666)OAc.
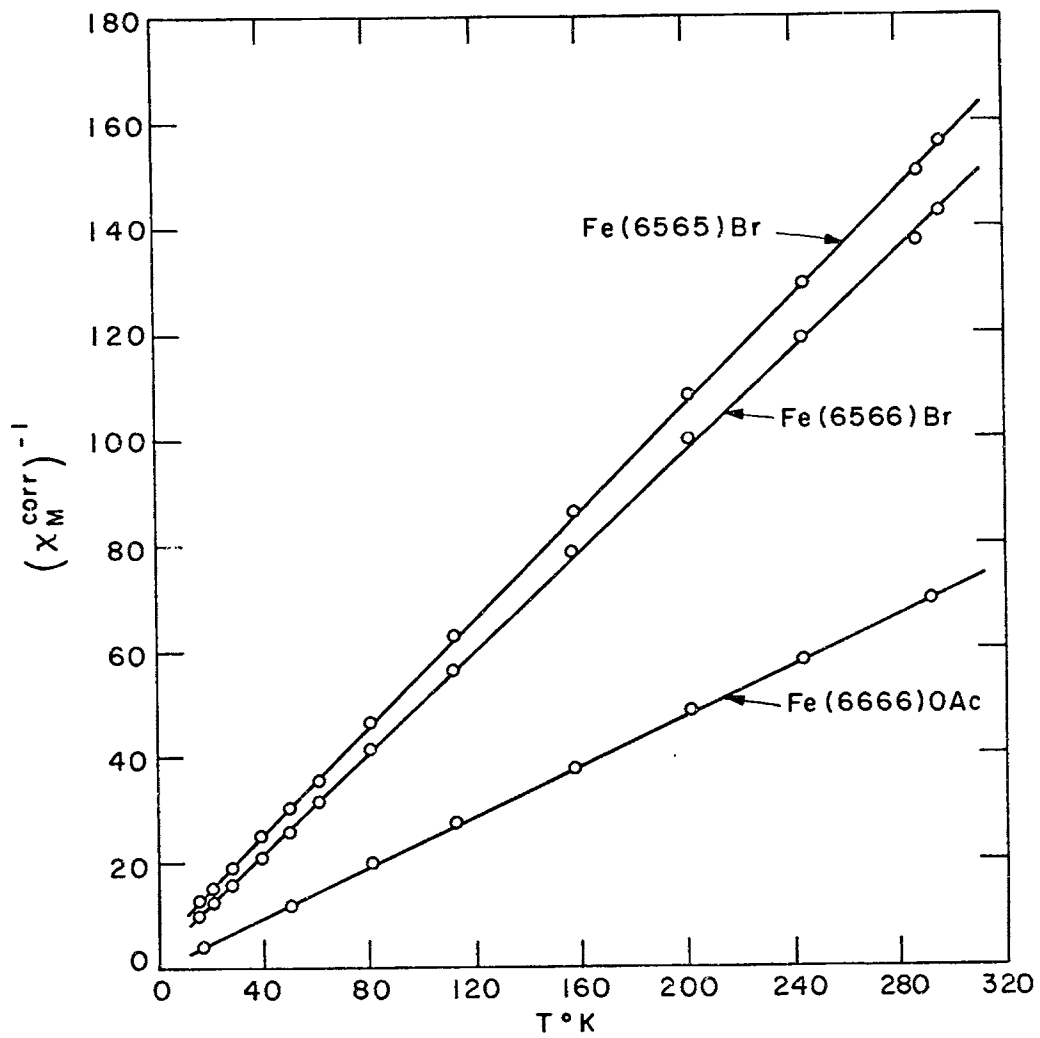
an epr spectral measurement,[37] has been reported to have an intermediate-spin quartet ground state.[38] More recent work has questioned the existence of "chloro ferric phthalocyanine" formulating it instead as the hydrochloride of ferrous phthalocyanine[39]. In this work both the 14- and 15-membered macrocycle complexes possess intermediate spin in both the solid-state and solution. The previous scarcity of the spin quartet case is due possibly to the limited number of examples of low symmetry tetragonal ferric complexes.

Recently the intermediate-spin ground state has made an appearance in the biological realm. Studies on cytochrome c',[40,41] a heme-protein isolated from photosynthetic and denitrifying bacteria, indicate that its oxidized form can be explained as arising from a ground state electronic configuration consisting of quantum mechanical admixtures of an intermediate (S = 3/2) spin state and a high-spin (S = 5/2) state.[42] No ferric porphyrin complex has yet been found to exhibit an intermediate-spin ground state.

The stabilization of the high-spin ground state in complexes of the 16-membered macrocycle was not unexpected. The increased size of the cycle should bring about an increased Fe-N distance with an attendant decrease in the strength of the ligand field provided by the four tetragonal nitrogens.[67] It is interesting that the 16-membered ring complexes show high-spin behavior as do 5-coordinate ferric porphyrins, whose inner structure is also a 16-membered ring. In the absence of X-ray crystallographic information on the structures of these complexes, it is not possible to detail the changes in geometry around the metal as the macrocycle ring size changes. Particularly difficult to estimate are possible deviations from macrocycle planarity.

Chapter 3

Synthetic and Ground State Electronic Properties

of Macrocyclic Ferric Thiolates, Fe(III)N$_4$SR

Introduction

Heme proteins and enzymes are largely dependent in structure,
electronic properties, and reactivity on the interactions of the heme-
iron with its axial ligand(s). Sulfur coordination, via the amino
acid residue cysteine, has been suggested as a possible explanation
for the unusual electronic properties of several of the reaction states
of cytochrome P-450 enzymes.[44,45] There have been reports of the in
situ generation of ferric porphyrin thiolates. However, in no case
has stable thiolate complexes of ferric macrocycles or porphyrin been
isolated.[1,44-48]

In this chapter, the synthesis and electronic properties of the
first stable isolatable macrocyclic complexes containing the Fe(III)N$_4$SR
coordination unit and their 6-coordinate pyridine adducts are described.
This work is an extension of the study discussed in the previous
chapter, on the effects of axial ligand and macrocycle ring size on the
chemical and electronic properties of the ferric complexes of the 14-,
15-, and 16-membered tetraaza macrocycles.

Experimental Section

All manipulations were performed with degassed solvents under a
pure nitrogen atmosphere. Uncorrected melting points were measured in
sealed capillary tubes.

Fe(6565)SPh (18). Method I. Benzenethiol (0.48g, 4.4 mmol) was added
to a suspension of Fe(6565)OAc (2.0g, 4.4 mmol) in 35 ml of ethanol.

The solution went immediately from red-purple to red-brown, and green crystals of starting material were replaced by red-brown crystals of the product. The product was filtered and washed with ethanol. The crude product was dissolved in 25 ml DMF, 150 ml of methanol was added slowly to the filtered DMF solution. The resulting brown fibrous crystals were collected to give (1.9g, 86% yield); mp. 178-180°. _Anal_. Calcd. for $C_{28}H_{27}N_4SFe$: C, 66.27; H, 5.36; N, 11.04; S, 6.32; Found: C, 66.12; H, 5.41; N, 11.08; S, 6.18.

Method II. Fe(6565) (0.60g, 1.5 mmol) and diphenyl disulfide (0.20, 0.92 mmol) were suspended in 40 ml DMF/ethanol (1/1 v/v). Benzenethiol (.08 ml) was added and the solution was warmed to 35°. The product crystallized and was collected. The fibrous crystals (0.55g, 72% yield) isolated were identical to the product obtained by Method I.

Fe(6566)SPh (19). Fe(6566) (0.90g, 2.2 mmol), diphenyl disulfide (0.30g, 1.4 mmol), and benzenethiol (0.05 ml) were stirred in 10 ml of DMF for one hour at room temperature. Ethanol was added slowly to crystallize the product. Recrystallization from DMF/isopropanol at room temperature afforded a black crystalline product (0.55g, 50% yield); mp. 148-152°. _Anal_. Calcd. for $C_{29}H_{29}N_4SFe$: C, 66.79; H, 5.61; N, 10.74; S, 6.15. Found: C, 66.88; H, 5.50; N, 10.69; S, 6.06.

Fe(6666)SPh (20). Fe(6666) (1.7g, 4.1 mmol), diphenyl disulfide (0.50g, 2.3 mmol), and benzenethiol (0.05 ml) were stirred in 50 ml of DMF/ethanol (1/1 v/v) at room temperature. The solution gradually turned a deep blue. Crystallization occurred on stirring over night. The filtered reaction product was dissolved in 80 ml of warm DMF (35°); ethanol (150 ml)

was added dropwise to the filtered DMF solution. Crystallization

occurred on cooling. Filtering and washing with ethanol gave purple-

black crystals (1.3g, 59% yield); mp. 172-174°. <u>Anal</u>. Calcd. for

$C_{30}H_{31}N_4SFe$: C, 67.29; H, 5.84; N, 10.46; S, 5.99. Found: C, 66.89;

H, 5.77; N, 10.61; S, 6.04.

<u>Fe(6666)SCH$_2$Ph</u> (<u>21</u>). Benzylmercaptan (0.4 ml) was added to a suspension

of Fe(6666)O$_2$CPh (1.7g, 3.1 mmol) in 20 ml of DMF. The reaction mixture

immediately went to an intense blue solution. Ethanol (150 ml) was

added dropwise to induce crystallization. The reaction mixture was

cooled and the product filtered. Recrystallization from DMF/isopropanol

afforded black crystals (1.6g, 88% yield); mp. 149-152°. <u>Anal</u>. Calcd.

for $C_{31}H_{33}N_4SFe$: C, 67.76; H, 6.05; N, 10.20; S, 5.84. Found: C,

67.59; H, 5.82; N, 10.04; S, 5.85.

<u>FeIII(Salen)OAc</u>[49,50]. The reaction was not done under a nitrogen

atmosphere.

Ferric acetate (1.9g, 9.6 mmol) and H$_2$(Salen) (2.5g, 9.3 mmol)

were heated in boiling ethanol for 1/2 hour. The filtered red crystals

were dried under vacuum.

<u>Fe(Salen)SPh</u>[49]. Benzenethiol (0.60g, 5.4 mmol) was added to a suspension

of Fe(Salen)OAc (2.0g, 5.3 mmol). The reaction mixture immediately

turned into a fibrous mass which gradually changed to black-purple

crystals on stirring. The filtered product was recrystallized from

DMF/isopropanol (25°). Brown fibrous crystals (1.7g) were obtained in

74% yield. Recrystallization from DMF/methanol gave purple-black

crystals in reduced yield; mp. 169 (dec). <u>Anal</u>. Calcd. for $C_{22}H_{19}N_2O_2S$:

C, 61.26; H, 4.44; N, 6.50; S, 7.43. Found: C, 61.54; H, 4.23; N, 6.63;

S, 7.44.

Fe(6565)SPh(Py). Pyridine (1.5 ml) was added to Fe(6565)SPh (0.50g, 0.99 mmol) dissolved in 30 ml of DMF. Crystalline product precipitated, was filtered, washed with ethanol, and dried under vacuum for 24 hours. (0.4g, 69% yield); mp. 160° (dec). Anal. Calcd. for $C_{33}H_{32}N_5SFe$: C, 67.57; H, 5.50; N, 11.94; S, 5.47. Found: C, 67.59; H, 5.63; N, 12.02; S, 5.59.

Fe(6566)SPh(Py). Fe(6665)SPh (0.25g, 0.54 mmol) (recrystallized and checked for purity by epr) was dissolved in 20 ml of DMF. On the addition of pyridine (0.5 ml), crystals began to separate immediately. Filtering the cooled reaction mixture afforded a brown-black crystalline product (0.25g, 78% yield); mp. 167-170°. Anal. Calcd. for $C_{34}H_{34}N_5SFe$: C, 68.00; H, 5.71; N, 11.66; S, 5.34. Found: C, 67.93; H, 5.74; N, 11.53; S, 5.27.

Physical Measurements. All measurements were performed as described in Chapter 1.

Results and Discussion

Synthesis of Macrocyclic Ferric Thiolates. The successful synthesis of $Fe(III)N_4SR$ complexes was achieved by the substitution reaction (1) and the oxidative addition reaction (2).

$$Fe(III)N_4OAc + RSH \rightarrow Fe(III)N_4SR + HOAc \qquad (1)$$

$$Fe(II)N_4 + 1/2\ RSSR \rightarrow Fe(III)N_4SR \qquad (2)$$
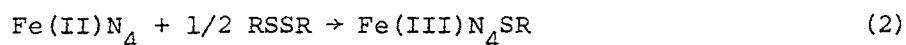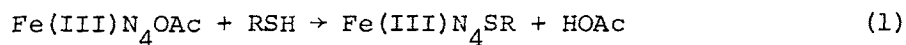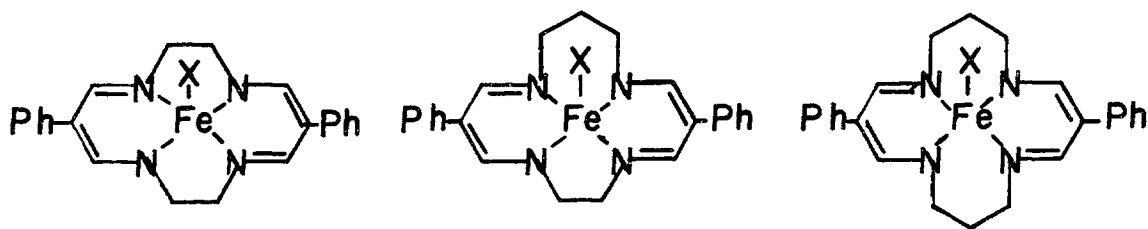
Fe(6565)X

X = OAc ($\underline{7}$)

= SPh ($\underline{18}$)

Fe(6565) ($\underline{4}$)

Fe(6566)X

X = OAc ($\underline{8}$)

= SPh ($\underline{19}$)

Fe(6566) ($\underline{5}$)

Fe(6666)X

X = OAc ($\underline{9}$)

= O_2CPh ($\underline{15}$)

= SPh ($\underline{20}$)

= SCH_2Ph ($\underline{21}$)

Fe(6666) ($\underline{6}$)

The Fe(III)N_4 carboxylates $\underline{7}$, $\underline{8}$, $\underline{9}$, and $\underline{15}$ were reacted with benzenethiol in either ethanol or DMF at room temperature to give the stable macrocyclic ferric benzenethiolates, Fe(III)N_4SPh ($\underline{18}$, $\underline{19}$, $\underline{20}$). The oxidative addition reactions using diphenyl disulfide and the ferrous macrocycles Fe(II)N_4 ($\underline{4}$, $\underline{5}$, $\underline{6}$) also gave $\underline{18}$, $\underline{19}$, and $\underline{20}$ in good yields. The addition of small amounts of benzenethiol catalyzed the oxidative addition reactions.

The substitution reaction using benzylmercaptan, an alkylthiol, was macrocycle-dependent. The reaction of benzylmercaptan with Fe(6666)O_2CPh gave Fe(6666)SCH_2Ph ($\underline{21}$) in good yield, while its reaction with Fe(6566)OAc resulted in complete reduction to Fe(6566). The benzylmercaptide complex of Fe(III)(6565) is stable to reduction, but has not yet been isolated in an analytically pure form. Partial reaction of dibenzyl disulfide with Fe(6666) was observed, but the intense blue color of $\underline{21}$ never developed. Stable 5-coordinate thiolate complexes

were not limited to the 14-, 15-, and 16-membered tetraaza macrocycles;
benezenethiolate complexes of ferric porphyrins (discussed in the next
chapter) and Fe(III)Salen[49] were also obtained. Fe(Salen)OAc (from
H_2(Salen) plus ferric acetate) on reaction with benzenethiol gave
Fe(Salen)SPh in good yield. [Fe(III)Salen]$_2$O in ethanol cleaved with
excess benzenethiol also forming Fe(Salen)SPh. The analogous reaction
using benzylmercaptan gave Fe(II)(Salen). Fe(Salen)SPh is very reactive
with air in solution giving cleanly [Fe(III)Salen]$_2$O,[50] presumably
formed by the following reaction:

$$2 \ Fe(Salen)SPh + 1/2 \ O_2 \rightarrow [Fe(III)Salen]_2O + PhSSPh$$
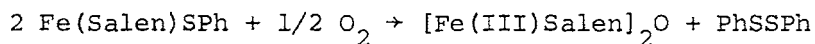
The ferric macrocycle thiolates are more reactive with oxygen than the
previously discussed ferric macrocycle halides and carboxylates
(previous chapter). The ferric thiolates also react rapidly with
chloroform to give the Fe(III)N_4Cl complexes, while reaction with
dichloromethane is very slow at room temperature.

The polarography of the Fe(III)N_4SR complexes (18, 19, 20, 21)
was examined (Table I). Each complex showed a one electron reduction
at -0.7 to -0.8V, which was assigned to Fe(III) → Fe(II). The changes
in macrocycle ring size and the resultant changes in spin state (to be
discussed) did not have an apparent systematic effect on this couple.
These reduction potentials are ~0.4 volts more negative than the
corresponding oxidation potentials for the ferrous macrocycle complexes
(Chapter 1). The complexes displayed a single oxidation (one or two
electrons) quite similar to those ascribed to ligand oxidation in the
Fe(II) macrocycle complexes (Chapter 1).

Electronic Ground States of Ferric Macrocycle Thiolates

The electronic properties of the ferric macrocycle thiolates have

Table I. Polarographic Data

Complex[a]	Couple[b,c]	$E_{1/2}$,v	Slope[d]
Fe(6565)SPh	0/-1	-0.79	74
	0/+1	+0.10	59
Fe(6566)SPh	0/-1	-0.69	72
	0/+2	+0.10	71
Fe(6666)SPh	0/-1	-0.69	69
	0/+2	+0.24	65
Fe(6666)SCH$_2$Ph	0/-1	-0.82	60
	0/+2	+0.14	93

[a] $\sim 10^{-3}$ $\underline{M}$ DMF solution.

[b] Notation used indicates the number of electrons transferred but does not imply strict electrochemical reversibility.

[c] The number of electrons transferred was determined by a comparison of diffusion currents for

$$[Ni(tdt)_2]^{-2} \rightleftarrows [Ni(tdt)_2]^{-1}$$
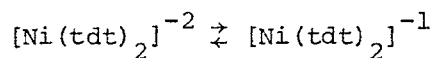
[d] Slope of the plot E versus $\log(\frac{id-i}{i})$.

been thoroughly studied by magnetic susceptibility, Mössbauer and epr

spectroscopy. The spectral data are listed in Tables II and III.

The solid–state magnetic susceptibility results show that the

variations of mercaptide and macrocycle ring size affords representative

complexes of the type $Fe(III)N_4SR$ for all three possible spin states

of Iron(III). The magnetic moment of 1.95 BM for Fe(6565)SPh is

consistent with a low-spin (S = 1/2) ground state. Fe(6566)SPh shows

Curie–Weiss dependence (χ_M^{corr} = 1.973/(T + 3.0), 295-17°K, μ = 3.97 BM

(295°K)) in accord with S = 3/2 intermediate spin. Fe(6666)SPh

deviates slightly from intermediate-spin (S = 3/2) Curie–Weiss behavior[*]

(χ_M^{corr} = 1.944/(T + 5.85), 200 to 17°K) above 200°K; μ = 4.17 BM (295°K)

versus 3.91 BM predicted from the Curie–Weiss equation. This deviation

might be due to an incipient spin equilibrium (S = 3/2 $\rightleftharpoons$ S = 5/2) at

high temperature. The variable temperature magnetic susceptibility for

Fe(6666)SCH_2Ph[*] (χ_M^{corr} = 4.394/(T + 2.0), 295-17°K) μ = 5.91 BM (295°K)

is consistent for a high-spin (S = 5/2) ground state. Fe(Salen)SPh

also shows high-spin behavior μ = 5.90 BM (295°K).

The Mössbauer data[†] are in agreement with the ground states deter-

mined by magnetic susceptibility measurements. The zero-field Mössbauer

spectra (Table II) of the complexes consist of simple quadrupole doublets

with only small variations in isomer shifts (δ) and quadrupole splittings

(ΔE_Q) from room temperature to 4.2°K. The zero-field parameters by

themselves do not lead to unambiguous assignment of ground states.

Particularly informative for ferric complexes with respect to spin state

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[*] Figure 1

[†] All Mössbauer spectra were measured by Richard B. Frankel of the M.I.T.
Francis Bitter National Magnet Laboratory.

Table II. Electronic Properties of Fe(III) Macrocycle Thiolates

Complex	Spin State	Magnetism μ_{eff}(BM)[a]	Mössbauer Spectra	
			Isomer Shift (δ)[b]	Quadrupole Splitting (ΔE_Q)[b]
Fe(6565)SPh	S = 1/2	1.95	0.04	3.60
Fe(6566)SPh	S = 3/2	3.97	0.13[c]	2.55[c]
Fe(6666)SPh	S = 3/2	4.17	0.26	1.93 2.28[c]
Fe(6666)SCH$_2$Ph	S = 5/2	5.91	0.35	0.71
Fe(6565)SPh(py)	S = 1/2	1.82	-0.02[c]	3.22[c]
Fe(6566)SPh(py)	S = 1/2	1.87	d	d

[a] 295°K

[b] mm/sec at 300°K; δ relative to Fe metal

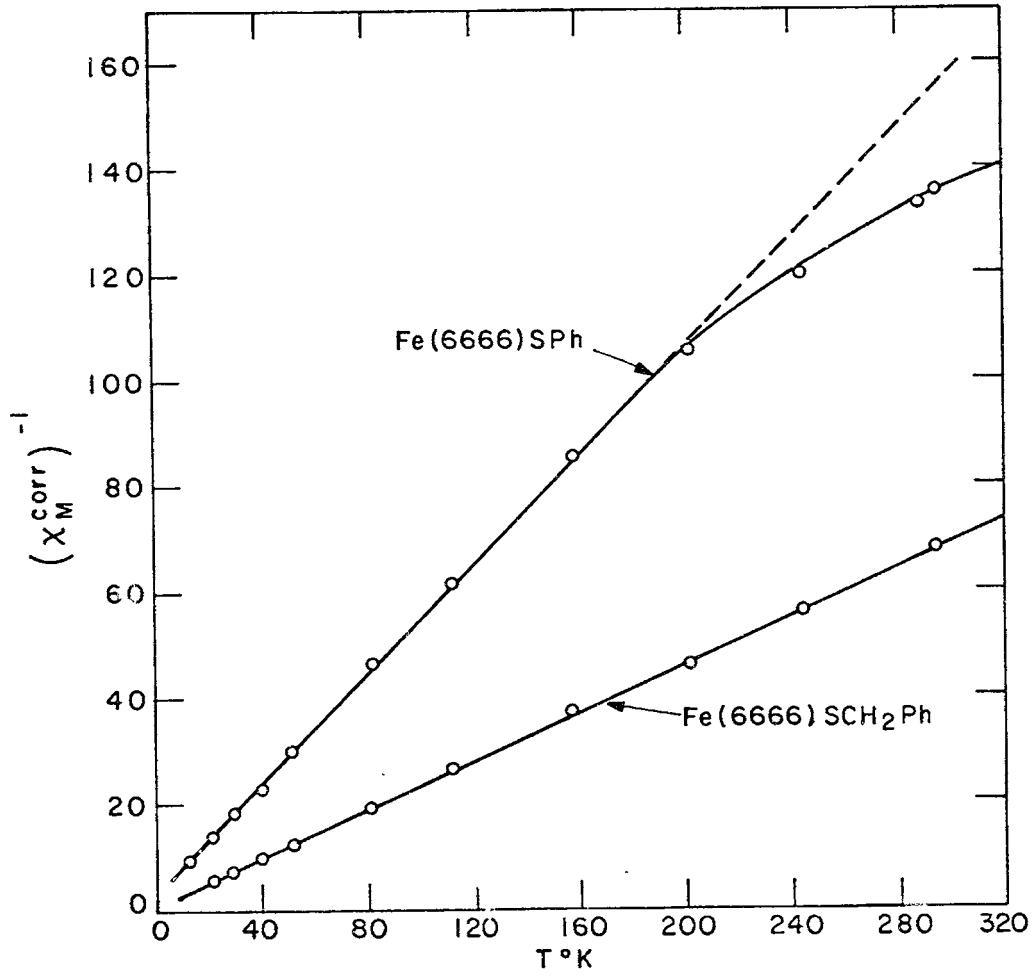[c] mm/sec at 77°K

[d] not measured

FIGURE 1

Variable temperature magnetic susceptibilities for Fe(6666)SCH$_2$Ph
(solid state); Fe(6666)SPh (solid state) - deviation from Curie-Weiss
behavior above 200°K.

is the magnetude of the hyperfine interaction induced on the Mössbauer spectra by large magnetic field. The measured value for the hyperfine interactions is related to the total separation of the two extreme lines of the magnetically perturbed Mössbauer spectra (see Figure 3). For Iron(III) the size of hyperfine interaction, predominated by the core polarization term, is ca. (-200kOe) x (Spin).[74] So that hyperfine fields of 500, 300, and 100kOe are consistent with S = 5/2, S = 3/2 and S = 1/2 ground states, respectively. Deviations from these expected values are due to variations in Fe-ligand covalency.

The values, δ and ΔE_Q, for Fe(6666)SCH$_2$Ph (21) are in good agreement with those of high-spin ferric porphyrin complexes[75]. The S = 5/2 assignment is supported by the large magnetic hyperfine interaction (ca. -450kOe at 4.2°K) induced by the applied field H$_o$ = 80kOe. Fe(6565)SPh (18) and Fe(6565)SPh (py) have markedly different parameters than 21 with δ typical of low-spin Fe(III).[76] Again the magnitude of the hyperfine interaction for 18 (ca. -70kOe, H$_o$ = 80kOe, 4.2°K) confirms the ground state (S = 1/2) assignment. The zero-field parameters for Fe(6566)SPh (19) and Fe(6666)SPh (20) are intermediate between high-spin 21 and low-spin 18. The hyperfine interaction for 20 (ca. -270kOe, H$_o$ = 80kOe, 4.2°K) is also intermediate as expected for a spin quartet (S = 3/2) ground state.

The dramatic changes in the zero-field and the high field Mössbauer spectra, as discussed above, are shown in Figures 2 and 3, as the ground state changes from S = 1/2 (18) to S = 3/2 (20) to S = 5/2 (Fe(OEP)SC$_6$H$_4$NO$_2$). The spectra for Fe(OEP)SC$_6$H$_4$NO$_2$ (a thiolate complex of ferric octaethyl porphyrin; to be discussed in the next chapter) are almost identical to that for Fe(6666)SCH$_2$Ph.

FIGURE 2

Mössbauer spectra of $Fe(OEP)-SC_6H_4NO_2$, $Fe(6666)SPh$, and $Fe(6565)SPh$ at 300°K.

Fe^{III}[OEP]-SC$_6$H$_4$NO$_2$

Fe^{III}[6666]-SC$_6$H$_5$

Fe^{III}[6565]-SC$_6$H$_5$

INTENSITY

VELOCITY (mm/sec)

-3   -2   -1   0   1   2
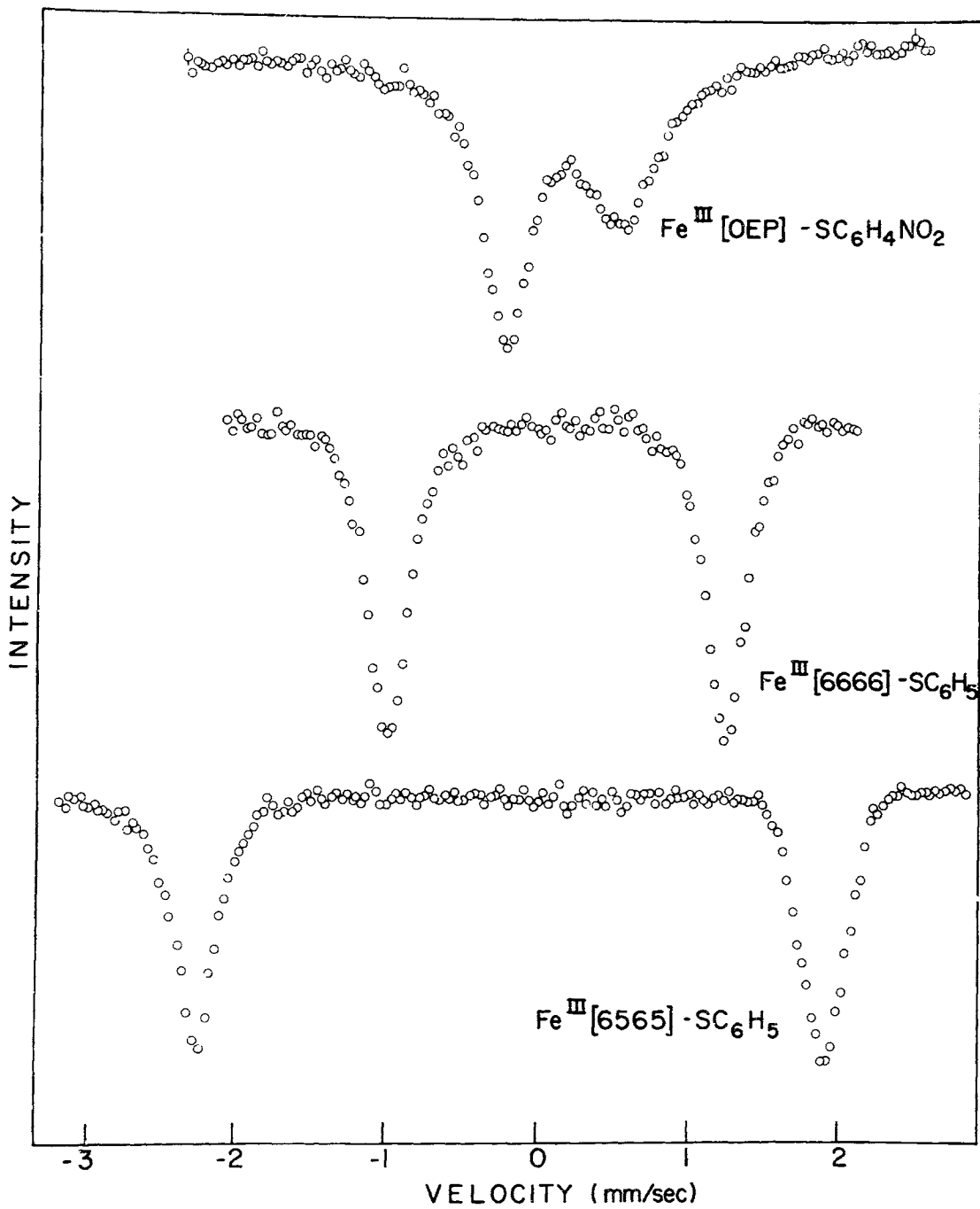
FIGURE 3

Mössbauer spectra of Fe(OEP)SC$_6$H$_4$NO$_2$, Fe(6666)SPh, and Fe(6565)SPh at 4.2°K in an 80 kOe applied field.

T = 4.2 K, H_0 = 80 kOe

$Fe^{III}[OEP] - SC_6H_4NO_2$

$Fe^{III}[6666] - SC_6H_5$

$Fe^{III}[6565] - SC_6H_5$

INTENSITY

VELOCITY (mm/sec)
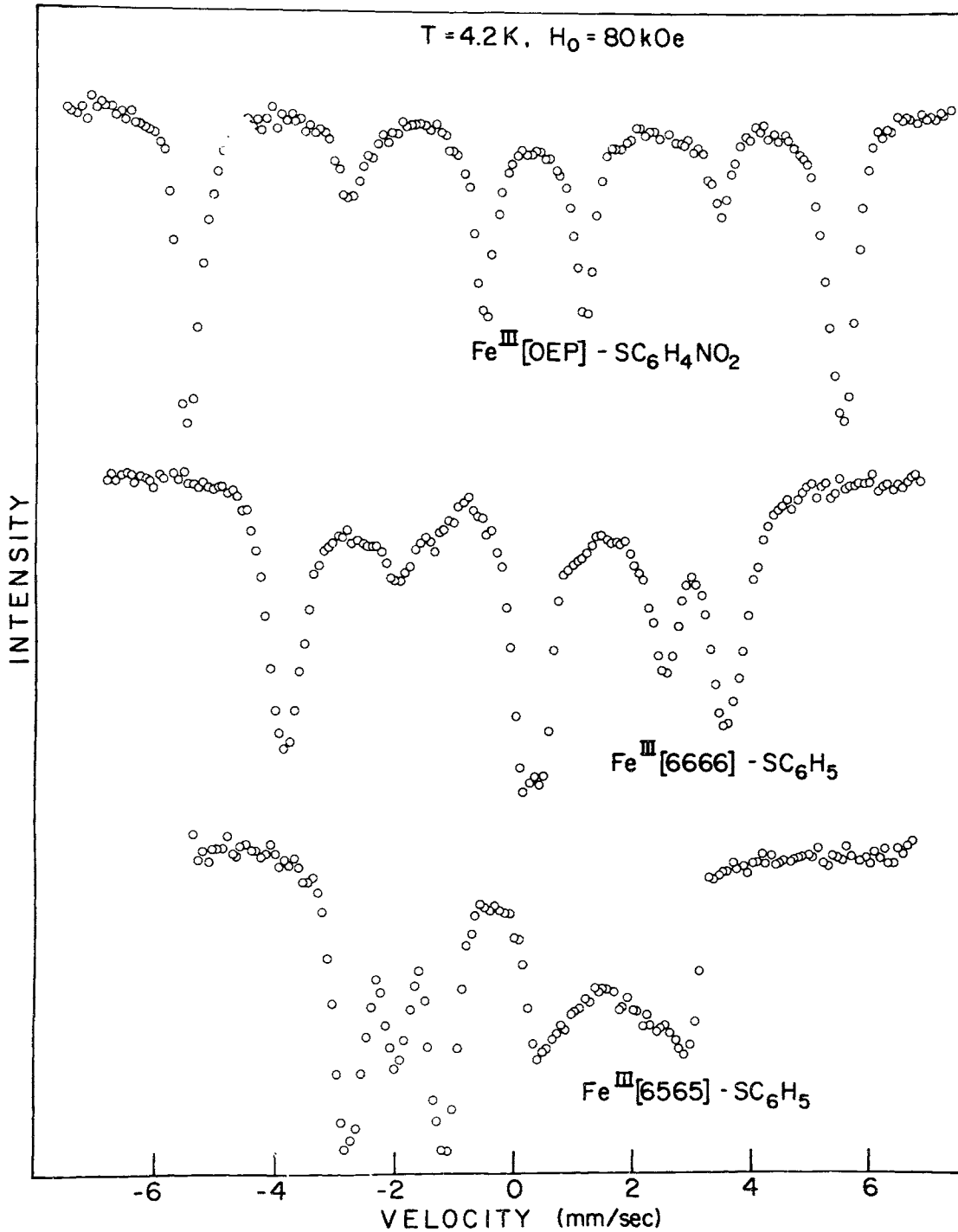
The epr spectra of the ferric macrocycle thiolates were examined in toluene glasses at $\sim$95°K (Table III). Epr spectra of Fe(6565)SPh and Fe(6666)SCH$_2$Ph are consistent with the ground states determined from solid-state measurements. Fe(6565)SPh gave a rhombic epr signal with its three g values close to g = 2, in accord with its S = 1/2 ground state.[48,64]

Fe(6666)SCH$_2$Ph gave a rhombic epr signal with g_x and g_y symmetrically split around g = 6, in agreement with the theoretically predicted spectra for a high-spin ground state.[65,66] Epr spectra for Fe(6566)SPh and Fe(6666)SPh are not consistent with the ground states determined by solid-state measurements. Fe(6666)SPh exhibited an epr spectrum almost identical to the Fe(6666)SCH$_2$Ph spectrum, typical of a high-spin ground state, at variance with its solid-state S = 3/2 ground state. The change in solvent from the non-coordinating toluene to DMF/dichloromethane had no effect on the spectra. Fe(6566)SPh in toluene glass gave a spectrum indicating a low spin S = 1/2 component together with a much weaker broad signal g $\sim$ 4.5 suggesting an S = 3/2 ground state component.[77] Initial solution magnetic susceptibility measurements also indicate deviations from solid-state moments. More work is in progress to understand the solution behavior of these complexes.*

The electronic spectra for 18 - 21 are tabulated in Table IV and displayed in Figure 3. The spectra are similar in general features to the spectra of the Fe(III) macrocyclic halides and carboxylates (Chapter 2).

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* Observations from epr measurements in frozen solutions must be scrutinized carefully as the intensity of signals is not always a good measure of the amount of a species present, also behavior in solution at room temperature can be quite different from that observed at the low temperature needed to observe the epr spectra.

Table III.   Epr Spectra of Ferric Macrocycle Thiolates

Complex	g-values		
Fe(6565)SPh[a]	2.108	2.036	2.007
Fe(6565)SPh(Py)[a]	2.129	2.033	1.997
Fe(6565)SPh(DMF)[a]	2.123	2.036	1.998
Fe(6565)(Py)$_2^+$ [b]	2.078	2.024	1.996
Fe(6565)(N-Me-Im)$_2^+$ [b]	2.100	2.037	1.992
Fe(6566)SPh[a,c]	2.152	2.063	2.009
Fe(6566)SPh(Py)[a]	2.185 2.159	2.063	1.991
Fe(6566)(Py)$_2^+$ [b]	2.094	2.047	1.991
Fe(6566)(N-Me-Im)$_2^+$ [b]	2.119	2.074	1.985
Fe(6666)SPh[a]	7.4	4.6	1.9
Fe(6666)SCH$_2$Ph[a]	7.5	4.5	1.9
Fe(6666)SPh(Py)[a]	2.406	2.096	1.960
Fe(6666)SCH$_2$Ph(Py)[a]	2.319	2.096	1.974

[a]Toluene glass (95°K)

[b]Dichloromethane/DMF (1/1, v/v) glass 95°K

[c]Low spin component, see text

Table IV. Electronic Spectral Data of the

Ferric Macrocycle Thiolate Complexes

Compound[a]	λ_{max} cm^{-1} (ε)[b]
Fe(6565)SPh	15,400(Sh,1380); 18,200(5310); 23,300(Sh,9060); 26,500(14,000); 35,500(20,800)
Fe(6565)SPh(Py)	15,400(Sh,2310); 18,100(6280); 23,300(Sh,9420); 26,500(13,900) 35,500(20,800)
Fe(6566)SPh	17,500(4640); 23,000(4510); 29,400(Sh,10,400); 33,900(25,900)
Fe(6566)SPh(Py)	17,400(4740); 23,000(5220); 29,400(Sh,11,100); 33,900(25,600)
Fe(6666)SPh	14,300(5700); 17,500(Sh,3830); 20,800(2480); 29,400(Sh,12,200); 34,100(24,900)
Fe(6666)SCH$_2$Ph	15,000(5900); 18,200(Sh,4050); 20,700(3170); 29,400(Sh,11,400); 33,700(25,200)

[a]dichloromethane solution at room temperature

[b]apparent values, uncorrected for underlying absorption

FIGURE 4

Electronic spectra of ferric macrocycle thiolates: ———, Fe(6565)SPh

in dichloromethane; —— · —— · ——, Fe(6566)SPh in dichloromethane;

—— —— ——, Fe(6666)SCH$_2$Ph in dichloromethane.
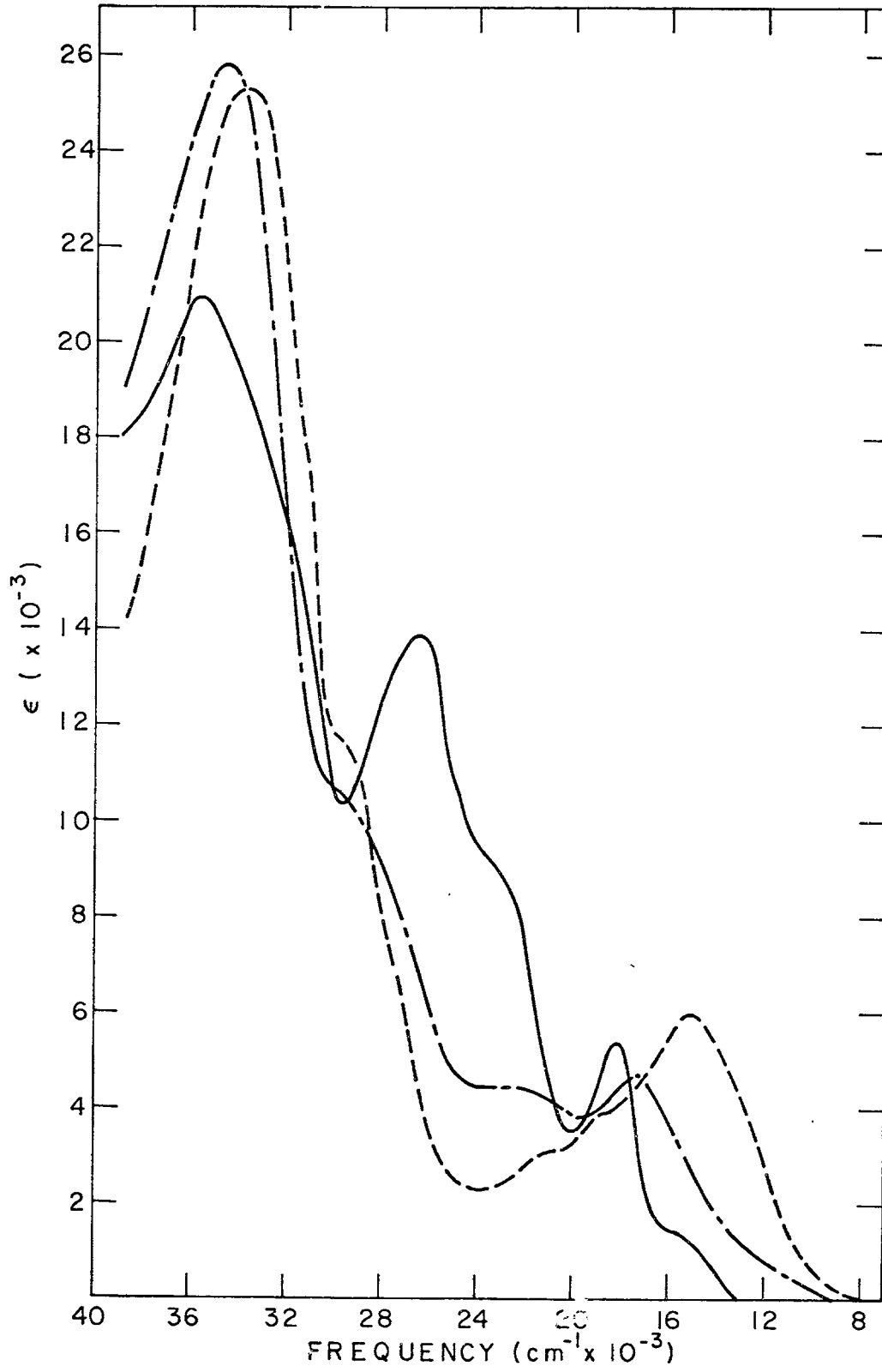
Again for these complexes, the spectra could not be interpreted with regard to the electronic ground states of the complexes.

Ferric Macrocycle Thiolates Base Adducts

The addition of excess pyridine to DMF solutions of Fe(6565)SPh and Fe(6566)SPh resulted in the isolation of 6-coordinate pyridine adducts, Fe(6565)SPh (py) and Fe(6566)SPh (py). Solid-state magnetic susceptibility data (Table II) at room temperature indicate low-spin (S = 1/2) behavior for both complexes. For Fe(6566)SPh, pyridine binding caused a spin change from S = 3/2 to S = 1/2. The electronic spectra (Table IV) of the pyridine adducts were identical to the spectra of the 5-coordinate thiolate complexes. Fe(6565)SPh(py) and Fe(6566)SPh(py) in dichloromethane solution, in the absence of excess pyridine exist in their pyridine-dissociated 5-coordinate forms.

Base adduct formation was studied using epr spectroscopy (Table III). As previously discussed, Fe(6565)SPh in toluene glass (95°K) showed a rhombic epr spectrum consistent with an S = 1/2 ground state. In DMF/ dichloromethane glass a second rhombic epr signal overlapped with the signal assigned to Fe(6565)SPh. The identical behavior was observed on the addition of DMF to the toluene solution of Fe(6565)SPh. The second rhombic signal was therefore assigned to the DMF adduct. The two rhombic signals remained on the addition of large amounts of DMF indicating that the tendency for DMF adduct formation is small even at the low temperature (95°K) at which the epr spectra are observed. On addition of small amounts of pyridine to toluene solution of Fe(6565)SPh, a new rhombic signal replaced the parent signal. The addition of excess pyridine had no further effect. An identical rhombic signal is observed for the isolated Fe(6565)SPh(py) with no detectable signal

FIGURE 5

Epr spectra at ~95°K in toluene glass of

A) Fe(6565)SPh

B) Fe(6666)SCH$_2$Ph

C) Fe(6666)SCH$_2$Ph(Py); generated _in situ_ by the addition of

pyridine to B.

A

2.10   2.04

2.01

100G

B

7.5

1000G

4.5

1.9

C

2.32   2.10   1.97

100G
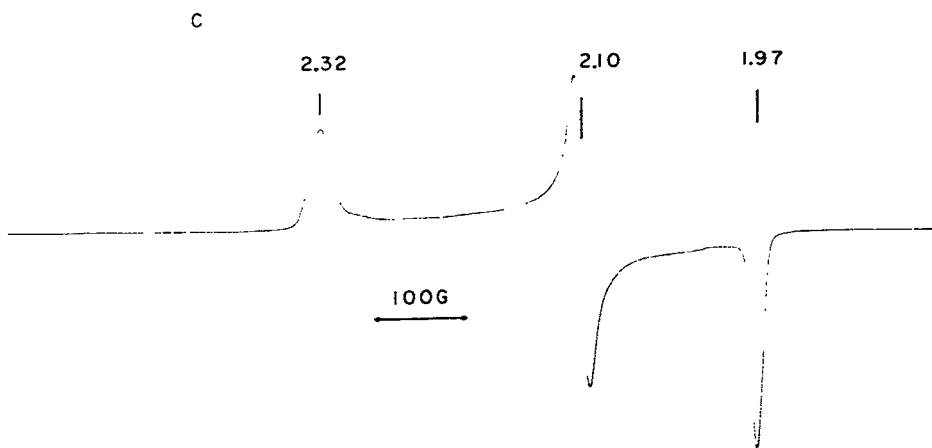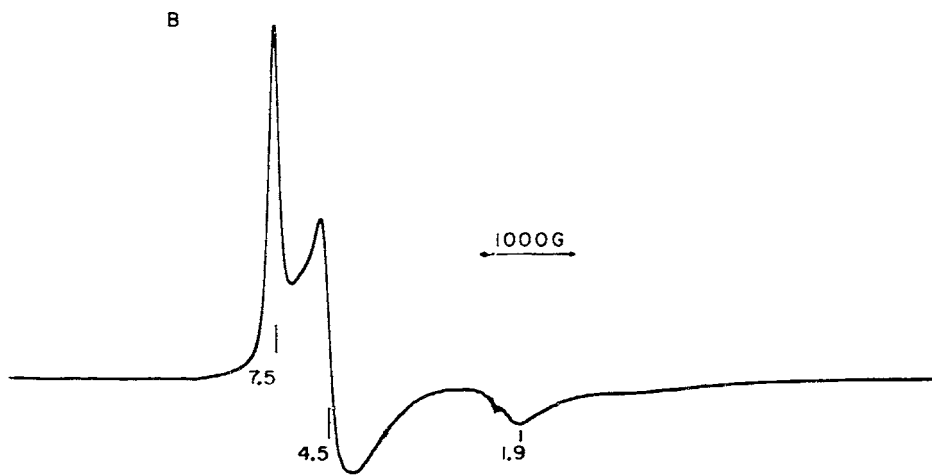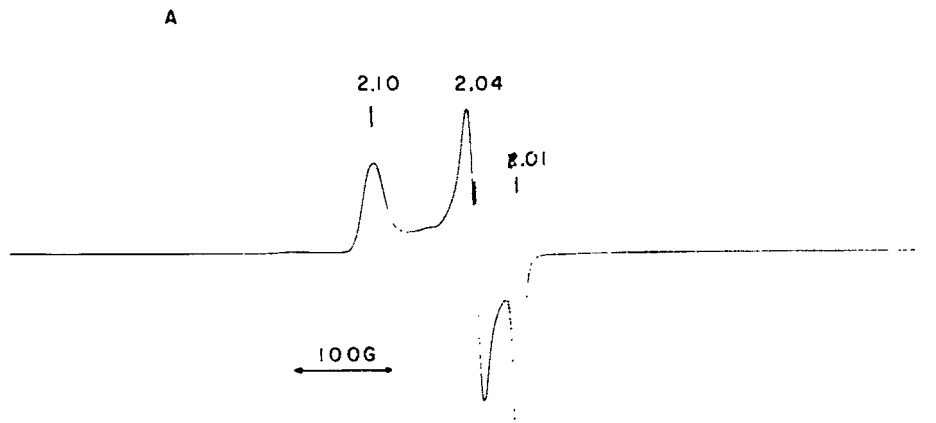
for the 5-coordinate species. This epr spectrum was therefore assigned to the pyridine adduct. In contrast to the dissociative behavior of Fe(6565)SPh(py) at room temperature (electronic spectra), at 95°K (epr) there is complete pyridine binding. There was no evidence of Fe-S bond cleavage by pyridine as the epr signal for Fe(6565)(py)$_2^+$ (Table III independently observed, generated by the addition of pyridine to Fe(6565)Cl) was not observed. Excess N-methyl-imidazole addition in contrast gave an epr spectra identified as the Fe-S bond cleavage product, Fe(6565)(N-Me-Im)$_2^+$.

The epr spectral behavior of pyridine binding to Fe(6566)SPh was similar. The addition of pyridine to Fe(6566)SPh (toluene) gave a low-spin rhombic spectrum identical to that for the isolated Fe(6566)SPh(py) (toluene glass). In both these cases the low field g-value is split into two components. The addition of excess pyridine had no effect on the intensities of these two components. It is possible, due to the low symmetry of the 6566 complexes, that there is more than one stable conformation of the bound pyridine. Excess N-methyl-imidazole again led to Fe-S bond cleavage giving Fe(6566)(N-Me-Im)$_2^+$.

Base adducts have not yet been isolated for Fe(6666)SPh and Fe(6666)SCH$_2$Ph. However, on the addition of small amounts of pyridine, the epr spectra of the low-spin pyridine adducts were observed.

Conclusions

The first stable thiolate complexes of ferric macrocycles have been synthesized and characterized. The series of complexes (18, 19, and 20) with the similar coordination unit, FeN$_4$SR, is unique among tetragonal Fe(III) systems, as it encompasses the three possible spin states.

Some general observations can be made on the effects of axial
ligands and macrocycle ring size on the ferric complexes $Fe(III)N_4X$
of the 14-, 15-, and 16-membered ring macrocycles. A comparison of
ground state determinations for $Fe(III)N_4X$ complexes (previous chapter)
with the $Fe(III)N_4SPh$ complexes (this chapter) indicate that the
axial ligand field component due to SPh is larger than that for
halide or carboxylate. In the 6565 and 6666 complexes replacement
of halide or carboxylate with SPh results in a reduction in the spin
state.

Examples of complexes with intermediate-spin ground state have
been found for each of the three macrocycles. In fact, the previously
considered rare, intermediate-spin state is the one most commonly
found for all the synthesized complexes. High-spin complexes were
confined to the 6666 series, while the only low-spin complex synthe-
sized is from the 6565 series. In no case has it been possible by
suitable choice of axial ligands to achieve 5-coordinate complexes of
a single macrocycle with all three ground states. The complexes of
the 6565 and 6666 series encompass two spin states, while all the
6566 complexes examined possess intermediate-spin ground states.

Chapter 4

Ferric Porphyrin Thiolates; Model

Compounds for Cytochrome P-450

Introduction

The mechanism of action of the cytochrome P-450 mono-oxygenase

enzyme systems has been extensively studied. In particular four

distinct reaction states of the soluble camphor hydroxylase system

from Pseudomonas putida have been identified and characterized by

chemical and physical studies.[44,52-56] It has been suggested that

axial sulfur coordination to heme-iron by means of the amino acid

residue cysteine may provide the explanation for the unusual elec-

tronic properties of several of these reaction states.[44,45] R.J.P.

Williams, et al.,[45-47] were able to simulate the epr spectrum of

substrate-free low-spin Fe(III)P-450 by mixing hemin chloride with

various thiols in the presence of nitrogenous bases. Their epr

results were coupled with their observations that these solutions

quickly reduced to Fe(II).

In order to further evaluate the possibility of sulfur coordina-

tion, the synthesis of ferric macrocycle thiolates (previous chapter)

was extended to porphyrin ligands. The synthesis and characteriza-

tion of stable ferric porphyrin thiolates is described, together with

an assessment of their viability as models for the two ferric reac-

tion states of cytochrome P-450.

Experimental Section

Uncorrected melting points were obtained in sealed capillary

tubes.

<u>Fe(III)Octaethylporphyrin Acetate - FeIII(OEP)OAc.</u>[49,57] The reaction

was not done under a nitrogen atmosphere. Octaethylporphyrin[70] (1.0g,

1.9 mmol) and ferric acetate (0.40g, 2.1 mmol) were heated at 80° in

glacial acetic acid for two hours. The hot solution was filtered, and

the filtrate was allowed to stand at room temperature for 48 hours.

The product was filtered, washed with ether, and air dried, affording

dark purple crystals (0.90g, 74% yield).

<u>[FeIII(OEP)]$_2$O.</u>[57] The synthesis, a modification of the method of

Buchler and Schneehage,[57] was not done under a nitrogen atmosphere.

FeIII(OEP)OAc (2.0g, 3.1 mmol) dissolved in 100 ml of dichloromethane

was stirred vigorously for five hours with 100 ml of aqueous 10% KOH

solution. The dichloromethane layer was separated, washed four

times with water, and dried over sodium sulfate. The product was

purified by dry column chromatography (alumina activity grade III)

with dichloromethane as the eluant. Crystallization was achieved by

dissolving in dichloromethane/benzene and removing almost all the

solvent under vacuum. Purple-black crystals (1.7g) were obtained in

92% yield. Only very small amounts of high-spin Fe(III) impurities

could be detected in the epr spectrum (toluene glass 95°K). Chloro-

form with its 0.7% ethanol stabilizer should not be used as a solvent

for (Fe(OEP)]$_2$O because of its reactivity toward alcohols.

<u>Fe(OEP)SC$_6$H$_4$NO$_2$</u> (<u>1</u>). The reaction was performed under a nitrogen

atmosphere. p-Nitrothiophenol (0.4g, 2.6 mmol) in 10 ml of toluene

(freshly distilled from calcium hydride) was added to a suspension of

[Fe(OEP)]$_2$O (0.6g, 0.50 mmol) in 20 ml of toluene. The reaction

mixture was stirred for one hour at room temperature. Filtering the

cooled reaction mixture, washing with heptane, and drying under

vacuum, afforded dark purple crystals (0.65g, 87% yield); mp. 270° (dec).

Anal. Calcd. for $C_{42}H_{48}N_5SO_2Fe$: C, 67.92; H, 6.51; N, 9.43; S, 4.32.

Found: C, 68.11; H, 6.66; N, 9.30; S, 4.13.

Fe(OEP)SPh(2). The reaction was performed under a nitrogen atmosphere.

[Fe(OEP)]$_2$O (0.2g, 0.17 mmol) and diphenyl disulfide (0.4g, 1.8 mmol)

were suspended in 25 ml of toluene (freshly distilled from calcium

hydride). On the addition of benzenethiol (0.25 ml, 2.4 mmol) all

reactants went into solution, followed by crystallization of the product.

Filtering the cooled reaction mixture, washing with heptane, and drying

under vacuum, gave purple-black crystals (0.19g, 81% yield); mp. 220(dec).

Anal. Calcd. for $C_{42}H_{49}N_4SFe$: C, 72.29; H, 7.08; N, 8.03; S, 4.60.

Found: C, 72.29; H, 7.11; N, 8.07; S, 4.50.

Physical Measurements were done in the same manner as described in

Chapter 1.

Results and Discussion

Synthesis of Ferric Porphyrin Thiolates. Fe(III) octaethylporphyrin

(OEP)thiolates were prepared by the following reaction scheme.

$$H_2(OEP) \xrightarrow[\text{acetic acid}]{\text{ferric acetate}} Fe(OEP)OAc \xrightarrow{KOH} [Fe(OEP)]_2O$$

$$p\text{-}NO_2C_6H_4SH \swarrow \qquad \searrow PhSH$$

$$Fe(OEP)SC_6H_4NO_2 \qquad Fe(OEP)SPh$$

$$\underline{1} \qquad\qquad \underline{2}$$
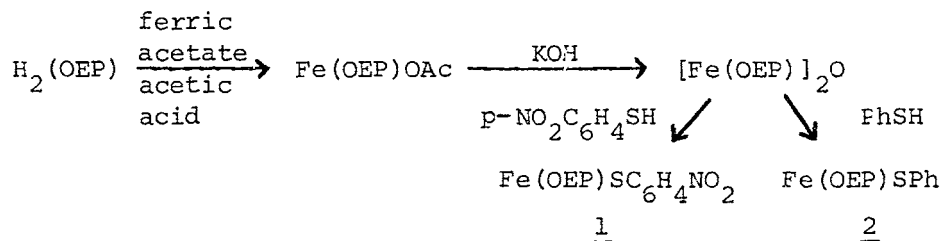
Fe(OEP)OAc[57] was made by the reaction of ferric acetate with octaethyl-

porphyrin[70] (a gift from Professor H. H. Inhoffen) in acetic acid.

[Fe(OEP)]$_2$O was synthesized by a modification of the method of Buchler

and Schneehage[57]. The μ-oxo dimer was chosen as the preferred pre-

cursor to ferric porphyrin thiolates, because it can be obtained in

a very pure state through alumina chromatography. Only very small

amounts of high-spin ferric impurities could be detected in the epr

spectrum of the μ-oxo dimer. It should be noted the $[Fe(OEP)]_2O$ reacts

with the ethanol stabilizer, contained in chloroform, to give Fe(OEP)OEt,

which is easily detected in the epr spectrum. $[Fe(OEP)]_2O$ appears to

be more reactive with alcohols than either $[Fe(PPIXDME)]_2O$[49,71] or

$[Fe(TPP)]_2O$[49,72]. Chloroform should be avoided as a solvent for

$[Fe(OEP)]_2O$.

The reaction of $[Fe(OEP)]_2O$ with a 3-fold excess of p-nitro-

thiophenol in toluene at room temperature gave $Fe(OEP)SC_6H_4NO_2$ (1)

in good yield. The analogous reaction using thiophenol gave a product,

which contained a small amount of Fe(II)OEP impurity (detected by

Mössbauer spectroscopy). High purity Fe(OEP)SPh (2) was obtained by

the addition of eight equivalents of diphenyl disulfide to the reac-

tion mixture. The PhSSPh served to prevent the side reaction:

Fe(OEP)SPh $\rightleftharpoons$ Fe(II)(OEP)+PhSSPh. $Fe(PPIXDME)SC_6H_4NO_2$ was synthesized

in a similar manner by S. C. Tang[58].
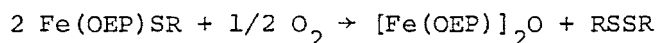
The ferric porphyrin thiolates react in solution immediately

with air to give the μ-oxo dimer. The reaction is slower in the

solid state. Although no attempt has been made to identify the

sulfur-containing product, it is assumed to be the disulfide, a

product of the reaction:

$$2 \ Fe(OEP)SR + 1/2 \ O_2 \rightarrow [Fe(OEP)]_2O + RSSR$$

Attempts to extend these synthetic methods to alkyl thiols failed.

The product isolated from the reaction of $[Fe(OEP)]_2O$ with benzyl-

mercaptan contained no epr detectable ferric porphyrin complexes and

was probably Fe(II)OEP formed by the reaction:

$$1/2[Fe(OEP)]_2O + PhCH_2SH \rightarrow Fe(OEP)SCH_2Ph \rightarrow Fe(II)(OEP) + (PhCH_2S)_2$$
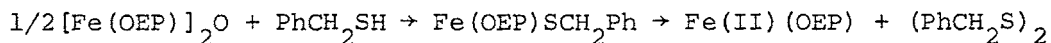
The Fe(OEP)SCH$_2$Ph intermediate was detected by a rapid mixing epr

procedure to be discussed later. The reaction of ferric porphyrin

complexes with alkyl mercaptans is possibly a good synthetic route

to Fe(II) porphyrins. Fe(OEP)OMe and Fe(OEP)OPh were synthesized by

literature methods.[57] Fe(PPIXDME)OC$_6$H$_4$NO$_2$ was synthesized by S. C. Tang.[58]

Characterization of Ferric Porphyrin Thiolates

The electronic ground state of the synthesized ferric porphyrin

thiolates was determined by magnetic susceptibility, Mössbauer, and

epr spectroscopy. These measurements also revealed the complexes to

be magnetically pure, free from detectable impurities. Room tempera-

ture magnetic moments, (Table I) for the ferric porphyrin thiolates

and their oxygen analogs, are all close to the spin-only value ex-

pected for S = 5/2, 5.92 BM. The high-spin susceptibility behavior

for Fe(PPIXDME)SC$_6$H$_4$NO$_2$ was confirmed by the observed Curie behavior

$(\chi_M^{corr} = 4.412/(T + 3.2))$ as a function of temperature (295-20°K).

Mössbauer spectral results[*] (Table I) are also consistent with

the high-spin ground state determination. Symmetric doublets with

small quadrupole splitting are observed at 4.2°K. As the temperature

increases, the quadrupole doublet becomes asymmetric due to a broadening

of the high velocity components. This behavior is quite similar to

that observed and interpreted for hemin chloride.[62] The high-spin

assignment is further supported by the large magnetic hyperfine inter-

action[63] 440kOe at 4.2°K for Fe(OEP)SC$_6$H$_4$NO$_2$ induced by the applied

---

[*]All Mössbauer measurements were done by Richard B. Frankel, M.I.T.
Francis Bitter National Magnet Laboratory.

Table I. Electronic Properties of Ferric Porphyrin Complexes

| Complex | Magnetism μ (BM) [a] | Mössbauer Spectra | | EPR g-values [c] |
		Isomer Shift (δ) [b]	Quadrupole Splitting (ΔE_Q) [b]	
Fe(OEP)SPh	5.87	0.31	0.49	7.2, 4.7, 1.9
Fe(OEP)SC$_6$H$_4$NO$_2$	5.92	0.32	0.66	d
Fe(OEP)OMe	5.94	0.34	e	6.0 [f], 1.9

[a] 295°K

[b] mm/sec at 300°K; δ relative to Fe metal

[c] Toluene glass at ∿95°K

[d] Not measured due to its insolubility in a suitable solvent

[e] Broad asymmetric line

[f] Broadened indicating a small rhombic splitting

field H_o = 80kOe (see Figures 2 and 3 of Chapter 3).

Fe(OEP)SPh in a toluene glass* at 95°K exhibited an epr spectrum with g_x = 7.2, g_y = 4.7, and g_z = 1.9. This epr spectrum is in agreement with theory for a rhombically distorted high-spin ferric complex with a large zero field splitting.[65,66] Most simple high-spin ferric porphyrin complexes give axial epr spectra (g_x = g_y = 6, g_z = 2).[65,66] The cause of the relatively large rhombic splitting (g_x - g_y) for Fe(OEP)SPh is not completely understood. In comparison $g_\perp$ for Fe(OEP)OMe was only slightly split. The electronic spectra of 1 and 2 in dichloromethane and toluene (Table II) are similar to the spectra of other high-spin ferric porphyrin complexes.[1]

The crystal structure of Fe(PPIXDME)$SC_6H_4NO_2$ was determined by Ibers.[58] The structure of the FeN_4SC unit, presently refined to an R index of 0.11 for the 55 non-H atoms, is shown in Figure I. The Fe atom is bonded slightly asymmetrically to the four pyrrole nitrogens and is displaced 0.43 A out of the N_4 mean plane toward the axial sulfur. This displacement is quite characteristic of all the reported structures of high-spin ferric porphyrin complexes[30]; hemin chloride, 0.475 A[54]; Fe(mesoporphyrin IX DME)OMe, 0.455A[60]; Fe(TPP)Cl, 0.383 A[61].

The crystal structure together with the determined high-spin ground state indicate that the ferric porphyrin thiolates are not exceptions to the general statements which summarize the behavior of ferric porphyrins:

1) All 5-coordinate ferric porphyrins are high-spin,

2) All high-spin ferric porphyrins are 5-coordinate.[1,30]

Although the axial ligand field component of SPh was not large enough

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*Solvent purity is essential to prevent the appearance of a low-spin component in the spectrum.

Table II. Electronic Spectra

Compound	Solvent	$\lambda_{max} (\epsilon)^a$
Fe(OEP)SPh	CH_2Cl_2	636(4990); 580(Sh,5260); 513(11,660); 460(Sh,10,500); 381(101,100)
	toluene	634(5420); 520(12,000); 46 460(Sh,10,900); 385(97,600)
Fe(OEP)SC$_6$H$_4$NO$_2$	CH_2Cl_2	641(5040); 580(Sh,4780); 530(Sh,10,500); 510(Sh,11,400); 460(Sh,9680); 371(96,600)
	toluene	640(6510); 580(Sh,6540); 512(13,300); 460(Sh,12,300); 374(110,000)

[a] λ_{max} in nm, ϵ in M^{-1} cm^{-1}

FIGURE 1

Perspective view of the inner coordination geometry of $Fe(PPIXDME)SC_6H_4NO_2$

(phenyl ring omitted). Estimated standard deviations of bonded distance

are $0.01°A$.
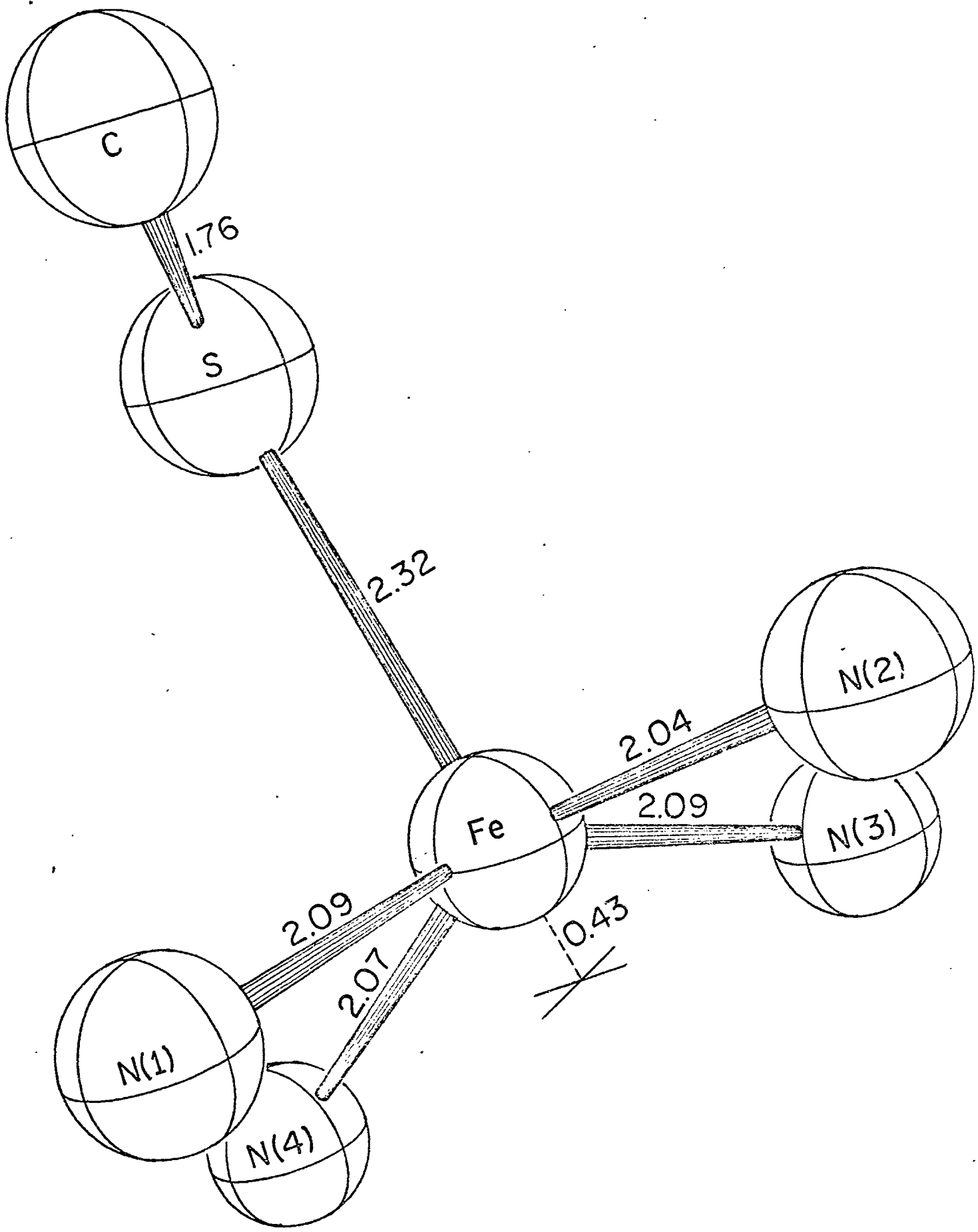
to cause a reduction in spin state as was the case in several of the macrocyclic complexes, its relatively large field strength is reflected in the ease of formation of low-spin base adducts.

Ferric Porphyrin Thiolate Base Adducts

Adduct formation of ferric porphyrin thiolates can be observed by epr spectroscopy for a variety of Lewis bases (Table III).

$$Fe(OEP)SR + Base \rightleftarrows Fe(OEP)SR \ (Base)$$
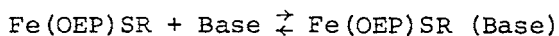
As previously discussed, Fe(OEP)SPh exhibited a high-spin epr spectrum. On addition of a small amount of N-methylimidazole (N-Me-Im), the signal corresponding to the high-spin complex disappeared and was replaced with a single rhombic spectrum, whose three g-values centered around g = 2, is characteristic of a low-spin ferric complex.[48,64] This low-spin epr spectrum was assigned to the 6-coordinate base adduct, Fe(OEP)SPh(N-Me-Im). No signal due to $Fe(OEP)(N-Me-Im)_2^+$ (Table III; generated by the reaction of Fe(OEP)Cl with excess N-Me-Im) could be detected so that there is no indication of Fe-SR bond cleavage upon initial N-Me-Im binding. The epr spectra of the adducts of Fe(OEP)SPh and $Fe(OEP)SC_6H_4NO_2$ with a variety of bases were measured (Table III). In all cases, in the presence of excess base, adduct formation was complete at the temperature that the epr spectra were measured ∿95°K. Fe(OEP)SR (Base) was the only epr-active species detected. The amount of base needed to observe complete low-spin adduct formation followed a qualitative series of decreasing base strength: N-Me-Im < py < CH_3CN < DMF,THF. The epr observations at 95°K should not be taken to imply that adduct formation is large at room temperature. In fact, the electronic spectra of Fe(OEP)SPh in pure THF at room temperature showed no evidence of any adduct formation. Adduct formation was

Table III. EPR Spectra of Ferric Porphyrin Base Adducts[a]

Fe(P)R (Base)

Complex	Base	g-values		
Fe(OEP)SPh	N-Me-Im	2.401	2.261	1.923
	Pyridine	2.402	2.275	1.917
	Acetonitrile	2.409	2.286	1.913
	DMF	2.422	2.270	1.921
	THF	2.351	2.256	1.949
	Tetrahydrothiophene	2.378	2.271	1.933
Fe(OEP)SC$_6$H$_4$NO$_2$	N-Me-Im	2.424	2.264	1.904
	Pyridine	2.427	2.285	1.905
Fe(OEP)OMe	N-Me-Im	2.434	2.148	1.842
Fe(OEP)OPh	N-Me-Im	2.57	2.18	1.86
Fe(OEP)(N-Me-Im)$_2^+$		2.96	2.25	1.53
Fe(PPIXDME)SC$_6$H$_4$NO$_2$	N-Me-Im	2.423	2.261	1.910
Fe(PPIXDME)SCH$_2$Ph[b]	N-Me-Im	2.337	2.226	1.946
Fe(PPIXDME)SCys(Ac)NHMe[b,c]	N-Me-Im	2.371	2.239	1.938
Fe(OEP)SCH$_2$Ph[b]	Tetrahydrothiophene	2.316	2.234	1.954

[a] toluene glass at 95°K

[b] generated in situ as discussed in text

[c] DMF/CH$_2$Cl$_2$ (1/1, v/v)

also observed for Fe(OEP)OMe and Fe(OEP)OPh. For Fe(OEP)OPh only

N-Me-Im was able to form an adduct, while for Fe(OEP)OMe, only N-Me-Im

and pyridine adducts were detectable.

Comparison of the epr spectra of Fe(OEP)SR (Base) shows that

changes in base do not have dramatic effects on the measured g-values.

Larger and more characteristic changes are observed in comparison of

Fe(OEP)SR (Base) with Fe(OEP)OR (Base) and Fe(OEP)(N-Me-Im)$_2^+$. The

epr spectra of corresponding Fe(PPIXDME) complexes[58] indicate that

porphyrin substituents have very little effect on measured g- values.

Epr spectra of the Fe(OEP)SR (Base) decreased in intensity on

repeating measurements after the sample tubes had been standing at

room temperature. The rate of decomposition varied with base according

to the same qualitative series mentioned above. The stronger the

base, the quicker the loss of signal intensity. For the addition of

N-methylimidazole to Fe(OEP)SR the decay product was identified by

electronic spectra to be Fe(II)(OEP)(N-Me-Im)$_2$. The base adducts are

unstable at room temperature with respect to reduction as shown by the

reaction:

$$Fe(OEP)SR + Base \rightleftharpoons Fe(OEP)SR\ (Base) \rightarrow Fe(II)(OEP)\ (Base)_2 + RSSR$$
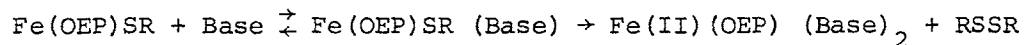
The rate of reduction appears to be proportional to the amount of

Fe(OEP)SR (Base) present at room temperature. Reduction is slowest for

those bases which bind the weakest at room temperature. No base

adducts of Fe(OEP)SR have been isolated. Studies are under way to

examine the electronic and Mössbauer spectra of the base adducts at

reduced temperature, where the rate of reduction is retarded.

It was also possible to obtain the low-spin epr spectra of the

base adducts of ferric porphyrin alkyl thiolate by a rapid mixing

FIGURE 2

Epr spectra at ∿95°K in toluene glass of

      A)   Fe(OEP)OPh (N-Me-Im)

      B)   Fe(OEP)SPh (N-Me-Im)
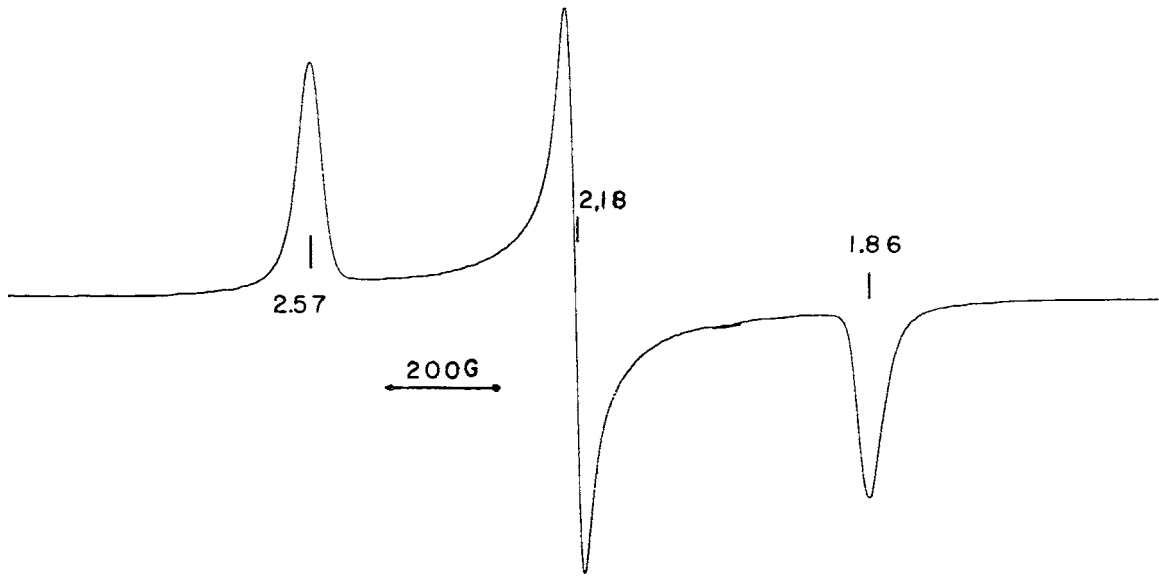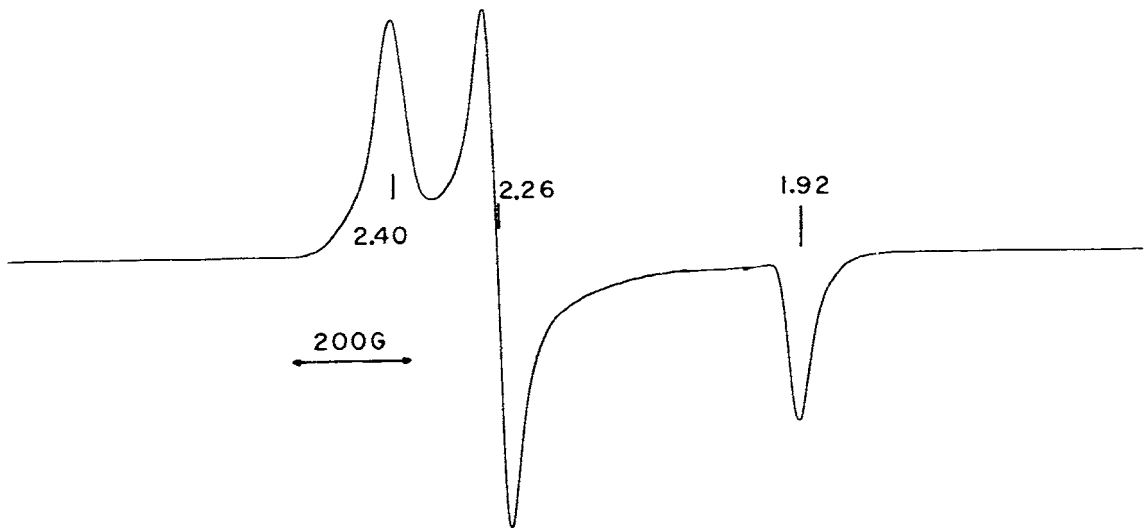
technique. The alkyl thiol was added to an epr tube containing a

solution of the μ-oxo dimer and a potential axial base, the tube was

rapidly frozen in liquid N_2, and the spectrum measured. The epr

spectra of several benzylmercaptan and Ac-L-Cys-NHMe[73] ferric porphyrin

thiolates base adducts were measured in this manner (Table III).

Ferric Porphyrin Thiolates as Models for the Ferric Reaction State of Cytochrome P-450.

Cytochrome P-450 has two characterized ferric reaction states -

a substrate-free form and a substrate bound state.[44]

$$Fe(III)P-450 \quad \overset{+ \text{ substrate}}{\underset{- \text{ substrate}}{\rightleftarrows}} \quad Fe(III)P-450 \cdot S$$
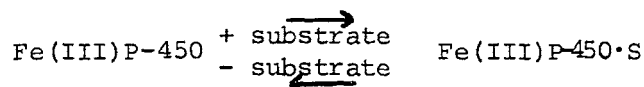
Fe(III)P-450 is low-spin[44,54,55] and presumed 6-coordinate by analogy

to known low-spin ferric compounds.[1,30] On substrate binding Fe(III)P-450

goes to a reaction state which is a spin mixture of mostly high-spin

with a small low-spin component.[44,54,55] Fe(III)P-450·S, with analogy

to known ferric complexes and ferric heme-proteins, is presumed 5-

coordinate or possibly 6-coordinate with a very weakly held sixth

ligand.[1,30]

The chemical and spectroscopic data obtained for the ferric

porphyrin thiolates and their base adducts indicate that they are good

model complexes for the ferric reaction states in P-450.[58] It is not

enough to show that the spectroscopic data obtained for the ferric

reaction states are consistent with sulfur thiolate coordination to

Iron. It is also necessary to evaluate the sensitivity of the spectro-

scopic methods to distinguish sulfur coordination from other biochemically

feasible coordination modes.

Although the isomer shifts and quadrupole splittings (Table I) of

the ferric porphyrin thiolates agree quite well with the values obtained

for the high-spin component of Fe(III)P-450·S (δ = 0.35, ΔE_Q = 0.79 mm/sec,

∿200°K)[55] zero field Mössbauer spectra have not proven sensitive to

differences in axial ligation. Work in progress indicates the magnitude

of the hyperfine field is more diagnostic of changes in the axial

ligand. Fe(III)P-450·S exhibits an epr spectrum with g = 8, 4 and 1.9[54]

consistent with a high-spin ferric heme with a substantial rhombic

character. Although the epr spectrum of Fe(OEP)SPh does not equal

this in rhombic distortion, it has the highest rhombic character of

any known ferric porphyrin complex. The electronic spectrum of

Fe(PPIXDME)SC$_6$H$_4$NO$_2$ is in remarkable agreement in band position and

extinction with that of Fe(III)P-450·S.[58] This is not considered

fortuitous, as the electronic spectra of other 5-coordinate ferric

(PPIXDME) derivatives do not approach this agreement in the position

of their α and Soret bands.[58] The most convincing evidence of sulfur

coordination comes from the close agreement of the epr spectra of

the ferric porphyrin thiolates base adducts (Table III) with the epr

spectra obtained for the low-spin substrate-free Fe(III)P-450 (g = 2.45,

2.26, and 1.91)[54]. Extensive measurements of low-spin ferric porphyrins

and ferric heme proteins have shown that their epr spectra are

characteristically dependent on the fifth and sixth axial ligand.[48,64]

This work leads to the proposal that the substrate-free Fe(III)P-450

has a cysteinyl residue as the fifth ligand and most probably an

imidazole group of a histidine residue as the sixth ligand. Imidazole

is the most likely sixth ligand as the epr of the ferric thiolate base

adducts shows the best agreement with a nitrogenous ligand. Imidazole

is a least one of the axial ligands in every heme proteins where the

axial ligands are known.[48,64] Other possibilities for the sixth

ligands can not be eliminated, however, due to the lack of definitive

evidence. It is further postulated that substrate binding leads to

displacement of the sixth ligand to give the high-spin ferric heme

with cysteinyl coordination. Although this work has not been extended

to Fe(II) porphyrin thiolate, it is considered likely that sulfur

coordination is responsible for the anomalous 450 mm Soret band of

the carbon monoxide adduct of reduced Fe(II)P-450.[68]*

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* During the time this work was in progress, J. P. Collman, et al.,[69]
have synthesized some ferric(TPP)thiolate complexes. Some of their
observations are similar to those reported here (Personal communica-
tions from Professor J. P. Collman to Professor R. H. Holm).

Chapter 5

Some Synthetic Approaches to Bis(β-imino amine) Macrocycles

Introduction

The syntheses of macrocycles and their metal complexes have been
extensively investigated.[2] The work reported in this chapter is
concerned with only bis(β-imino amine) macrocycles. Their general
structure (1) consists of two β-imino amine chelates linked together

1

by saturated carbon chains. Two distinctive features make this type
of macrocycle particularly interesting. First, the diprotic nature
of the macrocycle, similar to that of porphyrins, results in metal(II)
complexes of overall neutral charge. Second, the ring size of the
macrocycle can be systematically varied by changing the length of
the saturated methylene linking chains. This provides a series of
three macrocycles (2, 3, and 4) with 14-, 15-, and 16-membered rings.

2

3

4

The work in this chapter deals with some synthetic approaches to 14-, 15-, and 16-membered ring macrocycles with various substituents (R_1, R_2, R_3) on the β-imino amine chelates. The methods, in this and previous work, have been based on the syntheses of tetradentate ligands of general type 5 and their subsequent closing by nucleophilic attack at X by primary diamines such as ethylenediamine (en) and trimethylene-diamine (tn):

5   6
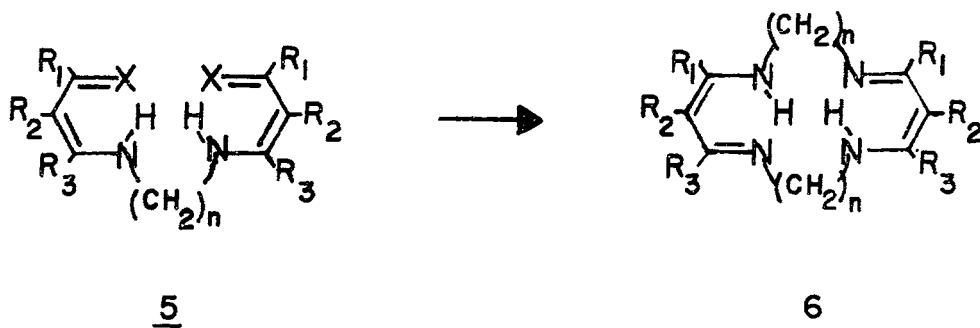
The reaction of bis(acetylacetone)ethylenediamine or its metal complexes with ethylenediamine does not result in macrocycle ring closure.[8] Jager[78] overcame the lack of reactivity of the vinylogous β-amino ketones by utilizing activating group at R_2. The template reactions of the Ni and Cu complexes of 5 (X = O; R_1 = Me or Ph; R_2 = RCO or RCO_2; R_3 = H; n = 2 or 3) with ethylenediamine and trimethylene diamine resulted in the synthesis of the Ni(II) and Cu(II) complexes of 14-, 15-, and 16-membered macrocycles (6).

Truex and Holm[8] have developed at non-template synthesis (Scheme I) of the 14-membered ring macrocycle, H_2(MeHMe(en)$_2$) (10). Their pro-cedure, outlined in Scheme I, was initiated by O-akylation of the β-keto amine 7. The cation 8 underwent nucleophilic attack by ethylene-diamine giving 9, which readily closed by a second equivalent of diamine to yield 10 with expulsion of ammonia.
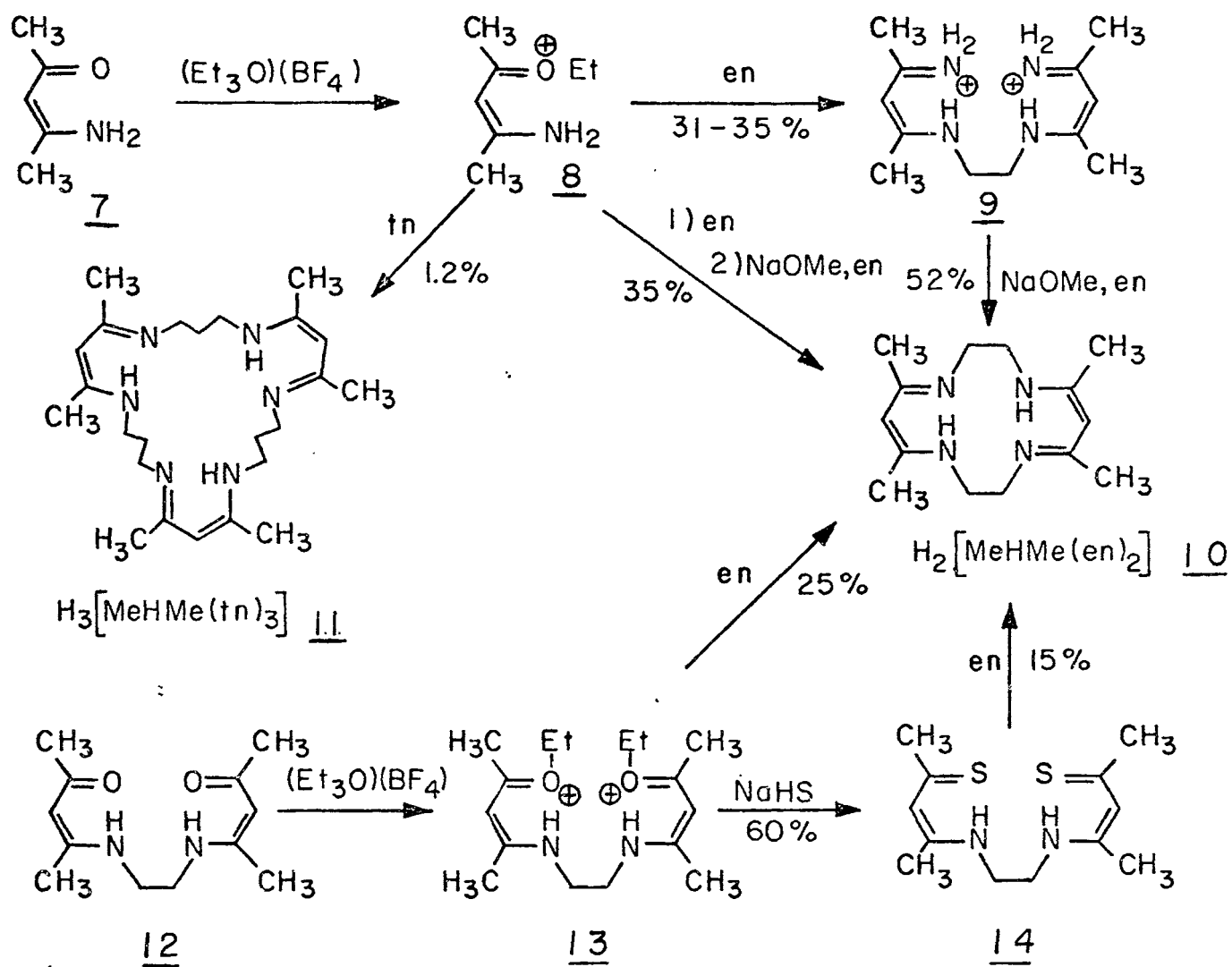
Scheme I Synthesis of macrocycles of the MeHMe series (en = ethylenediamine, tn = trimethylenediamine)
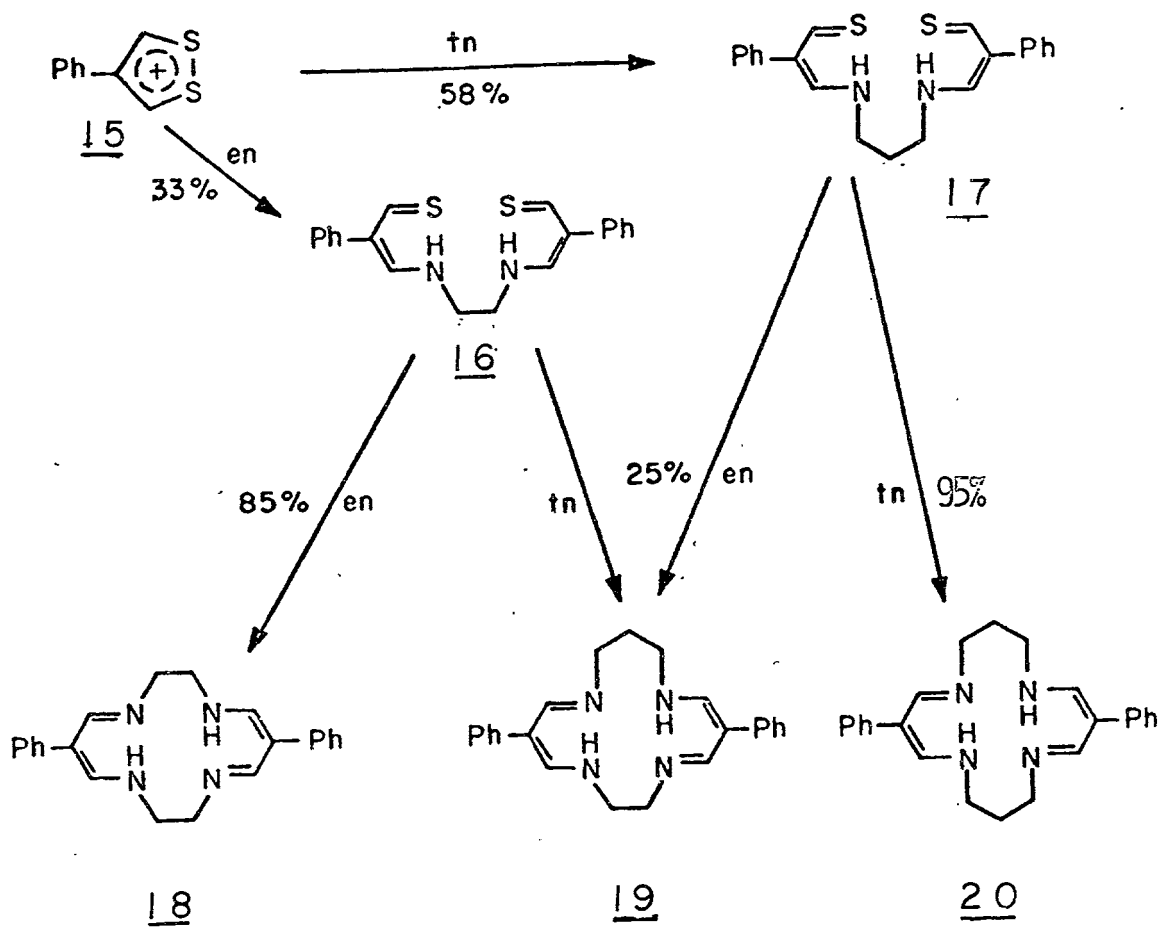
Scheme II   HPhH Series

Concurrent with this work, Tang, Weinstein, and Holm[12] described

a non-template synthesis of 18, 19, and 20 based on the reactivity of

ethylenediamine and trimethylenediamine with 4-phenyldithiolium per-

chlorate. The resultant β-amino-thiones 16 and 17 readily reacted with

a second equivalent of diamine to give the macrocycles. This bis(β-

imino amine) macrocycle series was used in Chapters 1-3, to study the

chemistry of Fe(II) and Fe(III) macrocycle complexes.

Experimental Section

    A. MeHMe Series

    1. 6,8,14,16,22,24-Hexamethyl-1,5,9,13,17,21-hexaazacyclo-

tetracosa-5,7,13,15,21,23-hexaene, H_3[MeHMe(tn)$_3$] (11). To a solution

of 30.0 g (0.30 mol) of 4-aminopent-3-en-2-one[79] in 200 ml of dry

dichloromethane was added 57.0 g (0.30 mol) of triethyloxonium tetra-

fluoroborate dissolved in 150 ml of dry dichloromethane. The solution

was stirred under an atmosphere of dry nitrogen for 30 minutes. Tri-

methylenediamine (11.2g, 0.15 mol) was added over a 30 minute period.

The bright yellow solution was stirred for an additional three hours

at room temperature. Dichloromethane was removed under reduced pressure

and replaced with 400 ml of absolute methanol. To this solution was

added 16.2g (0.30 mol) of sodium methoxide in 150 ml of methanol and

immediately thereafter an additional 11.2 g (0.15 mol) of trimethylene-

diamine was introduced. The reaction was allowed to proceed for four

hours with stirring during which time ammonia was evolved. Half of

the methanol was then removed under reduced pressure and the solution

filtered. No product was recovered from the filtrate. White crystals

were obtained by extracting the residue with 300 ml of hot chloroform,

reducing the volume, and adding methanol. The solid was recrystallized

from absolute ethanol to afford 0.50g of pure product in very low yield

(1.2%); mp. 180-182°. No other product was isolated from the reaction

mixture. Molecular weight: calcd., 414; found 407 (osmometry,

chloroform solution); calcd. for $^{12}C_{24}{}^{1}H_{42}{}^{14}N_6$ parent ion, m/e

414.3470; found, 414,3469. <u>Anal</u>. Calcd. for $C_{24}H_{42}N_6$: C, 69.52;

H, 10.21; N, 20.27. Found: C, 69.56; H, 10.01; N, 20.16.

2. <u>5,7,12,14-Tetramethyl-1,4,8,11-tetraazacyclotetradeca-4,6,11,13-</u>

<u>tetraene, H$_2$[MeHMe(en)$_2$]</u> (<u>10</u>). <u>From H$_2$[O-MeHMe(en)]</u> (<u>12</u>). Triethyl-

oxonium tetrafluoroborate (6.78g, 35.1 mmol) in 200 ml of dichloro-

methane was added under nitrogen to 4.00g (17.8 mmol) of bis(acetyl-

acetone)ethylenediamine[80] (<u>12</u>). After stirring for 30 minutes 1.07g

(17.8 mmol) of ethylenediamine in 40 ml of ethanol was added dropwise

to give a white precipitate. Solvent was removed under vacuum and

replaced with ethanol. A solution of 1.90g (35.1 mmol) of sodium

methoxide in 40 ml of methanol was added with stirring. The resulting

precipitate was filtered and suspended in 100 ml of chloroform. NaBF$_4$

was removed by filtration and the chloroform was evaporated, affording

1.70g of crude product. Recrystallization from ethanol gave 1.10g

(25%) of the pure macrocycle <u>10</u> whose pmr spectrum and mp. are identical

to those of samples prepared by a different route.[8]

3. <u>N,N'-Bis(thioacetylacetone)ethylenediamine, H$_2$(S-MeHMe(en))</u>, (<u>14</u>)[81]

Triethyloxonium tetrafluoroborate (38.0g, 0.200 mol) in 100 ml of

dichloromethane was added under nitrogen to bis(acetylacetone)ethylene-

diamine (22.4g, 0.100 mol) in 200 ml of dichloromethane. The reaction

mixture was stirred for one hour during which time a white product pre-

cipitated. NaHS (11.2g 0.200 mol) in 150 ml of ethanol was added; the

reaction mixture was stirred for 30 minutes. The precipitated product

was collected, washed with water and dried. Recrystallization from hot

ethanol gave yellow crystals (15.0g, 60% yield); mp. 152-154°. <u>Anal.</u>

Calcd. for $C_{12}H_{20}N_2S_2$: C, 56.21; H, 7.86; N, 10.92; S, 25.01. Found:

C, 56.01; H, 8.15; N, 10.86; S, 24.90.

4. <u>N,N'-Bis(thioacetylacetone)trimethylenediamine, H_2(S-MeHMe(tn))</u>

(<u>21</u>). Triethyloxonium tetrafluoroborate (8.00g, 42.0 mmol) in 125 ml of

dichloromethane was added under nitrogen to bis(acetylacetone)tri-

methylenediamine[82] (5.00g, 21.0 mmol). The reaction solution was

stirred for 30 minutes and was added to a solution of NaHS (3.00g,

53.6 mmol) in 125 ml of ethanol. Reaction was stirred for 12 hours at

room temperature. Concentrating the solution resulted in crystalliza-

tion of the product. The filtered product was dissolved in chloroform,

filtered to remove $NaBF_4$, and isolated by removal of solvent. Yellow

crystals (2.10g) were obtained by recrystallization from 25 ml of hot

ethanol in 37% yield; mp. 110-111°. <u>Anal.</u> Calcd. for $C_{13}H_{22}N_2S_2$:

C, 57.73; H, 8.19; N, 10.35. Found: C, 57.98; H, 7.95; N, 10.35.

5. <u>H_2(MeHMe(en)$_2$)</u> (<u>10</u>) From <u>H_2(S-MeHMe(en))</u> (<u>14</u>). Bis(thioacetyl-

acetone)ethylenediamine (3.50g, 13.2 mmol) was refluxed in 200 ml of

benzene with 2.00g (3.3 mmol) of ethylenediamine for four days. Removal

of solvent, addition of methanol, and filtration gave 0.50g of product.

This material was purified by recrystallization from ethanol and

obtained in 15% yield. It was identified as <u>10</u> by mp. and pmr spectrum.[8]

B. <u>HMeH Series</u>

1. <u>N',N'-Bis(2-formyl-2-methylvinyl)ethylenediamine, H_2(O-HMeH(en))</u> (<u>22</u>).

3-Ethoxy-2-methylacrolein[83] (5.00g, 43.8 mmol) and ethylenediamine (1.32g,

43.8 mmol) were refluxed in benzene for 12 hours. The light brown pre-

cipitate was filtered and dried under vacuum. The product was suspended

in 30 ml of isopropanol and stirred for one hour. Filtering and drying

under vacuum gave 2.8g white powder. An analytical sample was obtained

by four recrystallizations from hot isopropanol, mp. 180-184° (sealed

tube). <u>Anal</u>. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27.

Found: C, 61.16; H, 8.21; N, 13.95.

2. <u>N,N'-Bis(2-thioformyl-2-methylvinyl)ethylenediamine, $H_2(S-HMeH(en))$</u>,

(<u>23</u>). Triethyloxonium tetrafluroborate (32.0g, 0.168 mol) in 200 ml of

dichloromethane was added to $H_2(O-HMeH(en))$ (16.0g, 81.5 mmol). After

the reaction mixture was stirred for one hour, it was added to a solu-

tion of NaHS (12.0g, 0.214 mol) in 200 ml of ethanol. The reaction was

stirred at room temperature for 24 hours. Filtering, washing with

water, and drying under vacuum, yielded 16.0g of product. Attempts

at recrystallization using hot solvents led to decomposition. The

addition of 50 ml of ethanol to a filtered solution of 1.5g product

in 15 ml of DMF at room temperature afforded 1.0g of yellow crystals

(57% yield); mp. 160-164°. <u>Anal</u>. Calcd. for $C_{10}H_{16}N_2S_2$: C, 52.59;

H, 7.06; N, 12.26; S, 28.08. Found: C, 52.41; H, 7.26; N, 12.24;

S, 28.19.

C. <u>HPhH Series</u>

1. <u>N,N'-Bis(2-thioformyl-2-phenylvinyl)β-hydroxy-trimethylene-</u>

<u>diamine, $H_2(S-HPH(β-OH-tn))$</u> (<u>24</u>). 4-Phenyl-1,2-dithiolium perchlorate[84]

(10.0g, 35.6 mmol) was suspended in 400 ml of chloroform; 1,3-diamino-

2-propanol (3.20g, 35.6 mmol) was added in small portions over one

hour. The reaction mixture was heated to boiling and was filtered hot.

The filtrate was reduced in volume to 15 ml, and the crude product

was filtered to give 2.35g. Recrystallization from hot chloroform

gave 0.85g of light yellow crystals; mp. 163-164° (sealed tube).

<u>Anal</u>. Calcd. for $C_{21}H_{22}N_2S_2O$: C, 65.94; H, 5.80; N, 7.32. Found:

C, 65.72; H, 5.71, N, 7.17.

2. <u>3,11,-Dihydroxy-7,15-diphenyl-1,5,9,13-tetraazahexadeca-</u>

<u>5,7,13,15-tetraene, H$_2$(HPH(β-OH-tn)$_2$)</u> (<u>25</u>). Crude H$_2$(S-HPhH(β-OH-tn))

(1.70g, 4.45 mmol) was suspended in 60 ml of benzene. 1,3-Diamino-

2-propanol was added in small portions, and the reaction mixture was

heated at boiling for 1 1/2 hours. Benzene was removed under vacuum

and was replaced with 40 ml of ethanol. The resulting oil was titrated,

the ethanol was poured off from the remaining oil. White powder (0.3g)

precipitated from the ethanol. Product was recrystallized from chloro-

form/ethanol to give white crystals (0.15g, 10% yield). The analytical

sample was recrystallized a second time. This product which melts

sharply 201-203°, appears to be one of the two possible isomers.

Physical Measurements

All measurements were performed as described in Chapter 1.

Results and Discussion

Attempts to extend the method of Truex and Holm[8] to the synthesis

of 15- and 16-membered ring macrocycles of the MeHMe substitution type

using trimethylenediamine in place of ethylenediamine resulted in

failure. The desired macrocycles were not isolated. In the case of

the attempted synthesis of H$_2$[MeHMe(tn)$_2$] the only product isolated

was a 24-membered ring macrocycle <u>11</u> (jointly done with G. Weinstein)

whose structure is consistent with analysis, pmr, and mass spectra.

The compound, obtained in very low yield, is relatively strainless

according to CPK space-filling models. The models further indicate

that the large macrocycle can not act as a sexidentate ligand or even

a tetradentate ligand due to steric constraints.

Another synthetic route to MeHMe macrocycles was investigated.

Alkylation of H$_2$(O-MeHMe(en)) <u>12</u> (Scheme I) with triethyloxonium

tetrafluroborate yielded 13 which was reacted without isolation with

ethylenediamine to give $\underline{10}^{8}$ in 25% yield. Here again, attempts to

extend the method to the larger ring systems failed. No product could

be isolated from the reaction of trimethylenediamine with alkylated

H_2(O-MeHMe(tn)). In some cases this alternative route to H_2[MeHMe(en)$_2$]

$\underline{10}$ has proven to be of some synthetic utility.[31]

An attempt was also made to extend the reaction scheme of Tang,

et al.,[12] using alkyl-substituted dithiolium salts. The reaction of

ethylenediamine with 3,5-dimethyl-1,2-dithiolium perchlorate[85] did not

give $\underline{14}$ but gave instead an unidentified purple solid. Similar obser-

vations have been noted in the reaction of ammonia with methyl sub-

stituted dithiolium salts[86]. The acidity of the methyl protons was

proposed for this reaction.[86] Another method was used for the synthesis

of the β-aminothione $\underline{14}$. The reactions of diethylated H_2(O-MeHMe(en))

$\underline{13}$ (Scheme I) and diethylated H_2(O-MeHMe(tn) with NaHS gave $\underline{14}$ and

H_2(S-MeHMe(tn) $(\underline{21})$ in good yields. The reaction of $\underline{14}$ with excess

ethylenediamine for four days at 80° gave a low yield of $\underline{10}$ plus

some recovered starting material. There was no reaction of H_2(S-MeHMe(tn))

with trimethylene diamine under similar conditions. These results

indicate the dramatic change in reactivity of vinylogous thioketones

versus vinylogous thioaldehydes (Tang, et al.,[12]).

Some initial work was done on the HMeH substituted macrocycles.

Ethylenediamine was condensed with two equivalents of 3-ethoxy-2-

methylacrolein to give $\underline{22}$.

$\underline{22}$ X = O
$\underline{23}$ X = S
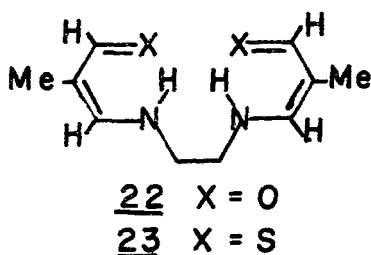
Compound 23 was obtained by alkylation of 22 followed by treatment with NaHS. Closing 23 and dialkylated 22 with ethylenediamine gave white powders which gave the expected pmr for the closed macrocycle. There was no reaction with nickel(II)acetate, which leads to the supposition that the isolated compound was the monomer, 2,3-dihydro-6-methyl-1, 4-diazepine.

In a reaction sequence analogous to Scheme II, 1,3-diamino-2-propanol was reacted with 4-phenyl-1,2-dithiolium perchlorate to afford the β-aminothione (24).
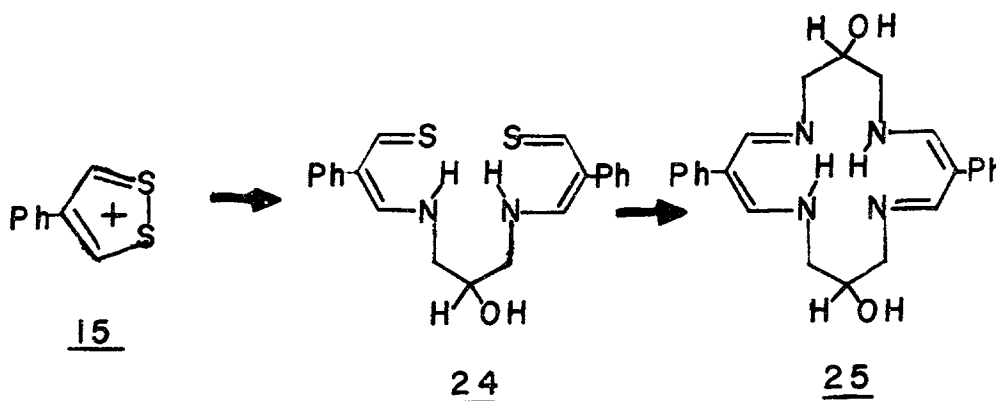
Reacting 24 with another equivalent of 1,3-diamino-2-propanol gave dihydroxysubstituted macrocycle 25. This synthesis is a good indication of the generality of the macrocycle synthesis using the 4-phenyldithiolium cation. The corresponding Jager macrocycle with 1,3-diamino-2-propanol could not be synthesized.

The failure in extending various successful synthetic methods to larger rings and other substitution patterns was disappointing and somewhat confusing. The conditions that effect non-template macrocycle ring synthesis are poorly understood.

Table I. Pmr Data

Compound	Solvent	Bridge[a]		Unsat'd Ring	NH
$H_3[MeHMe(tn)_3]$	$CDCl_3$	$1.88(\beta)^b$	$3.25(\alpha)^c$	$1.88(Me)$, $4.40(\beta)$	11.1
$H_2[S-MeHMe(en)]$	$CDCl_3$	3.67^b		$2.05(Me)^e$, $2.48(Me)$, $6.00(\beta)$	13.9
$H_2[S-MeHMe(tn)]$	$CDCl_3$	$2.20(\beta)^b$	$3.70(\ )^c$	$2.22(Me)$, $2.58(Me)$, $6.14(\beta)$	14.1
$H_2[O-HMeH(en)]$	DMSO-d_6	3.27		$1.52(Me)$, $8.67(H)$, $6.82(H)^e$	f
$H_2[S-HMeH(en)]$	DMSO-d_6	3.52		$1.92(Me)$, $9.67(H)$, $7.38(H)^e$	f
$H_2[S-HPhH(\beta-OH-tn)]$	DMSO-d_6	$3.40-3.90^d$		$7.37(Ph)$, $10.01(H)$, $8.2(H)^e$	15.5
$H_2[HPhH(\beta-OH-tn)_2]$	$CDCl_3$	$3.40-3.90^d$		$7.18(Ph)$, $7.62(H)$	f

[a]Notation for the bridges: $N-\overset{\alpha}{CH_2}-\overset{\beta}{CH_2}-\overset{\alpha}{CH_2}-N$

[b]Multiplet

[c]Apparent quartet

[d]Unresolved multiplet

[e]Adjacent to N

[f]Not located

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49. The following ligand abbreviations are used:
         Salen = N,N'-bis(salicylidene)ethylenediamine dianion
         TPP = tetraphenylporphyrin dianion
         OEP = octaethylporphyrin dianion
         PPIXDME = protoporphyrin IX dimethyl ester dianion

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