SYNTHESES OF SELECTED HEME PROTEIN MODEL COMPOUNDS

BY

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ABSTRACT

Strapped porphyrins may be defined as those compounds in which

some bridging group is covalently attached to opposite edges of the

porphyrin macrocycle. This class of compound has been extensively studied

as models for the active sites of heme proteins such as hemoglobins,

cytochrome P450 etc. Two avenues of approach to the synthesis of

strapped porphyrins have been used. The strap may be covalently

attached to opposite edges of a preformed porphyrin, or the two halves of

the porphyrin macrocycle may be assembled at each end of the strap with

a final intramolecular cyclization fitting the strap into place.

The latter approach has been adopted here to provide a general

route to those strapped porphyrins bearing functional groups in the

bridging straps. Compounds 87a, 87b and 118a, 118b have been prepared

as possible models for cytochrome c and catalase, while the porphyrin-

quinone compounds 143a, 143b may be used to study electron transfer in

donor/acceptor complexes.

The syntheses of the various strapped porphyrins all originate from

the α-free-iodoalkyl pyrroles 44, 64 which are readily available via

Friedel-Crafts acylation of β-free pyrrole 1, followed by reduction and

iodination of the alkyl chain and modification of the α-methyl group.

For the sulfide-strap porphyrins, reaction with sodium sulfide to

give the bis[(pyrrol-3-yl)alkyl]sulfides 75a, 75b formed the strap.

Elaboration to the bis-dipyrromethanes 77a, 77b provided all the units

necessary for porphyrin synthesis. Saponification and decarboxylation

followed by high-dilution acid-catalyzed intramolecular cyclization

yielded the strapped porphyrins 87a (9-19%) and 87b (10-18%). Exposure

to light during work-up is believed to be responsible for the formation

of the corresponding sulfoxide-strap porphyrins 88a, 88b.

1

75a n = 5
b n = 4

44 n = 5
64 n = 4

77a n = 5
b n = 4

87a n = 5
b n = 4

88a n = 5
b n = 4
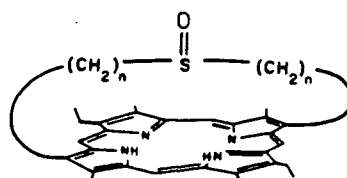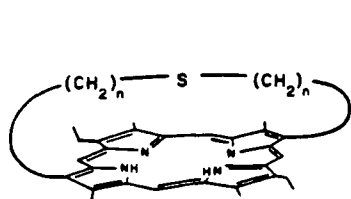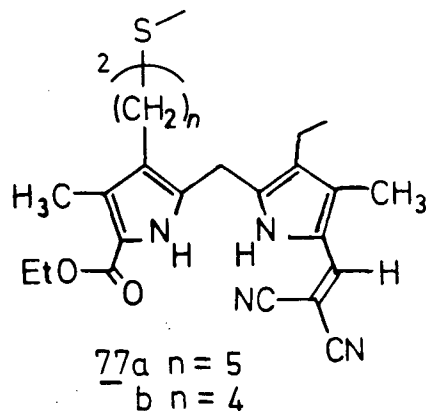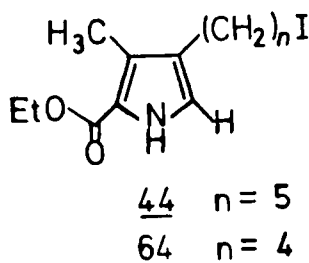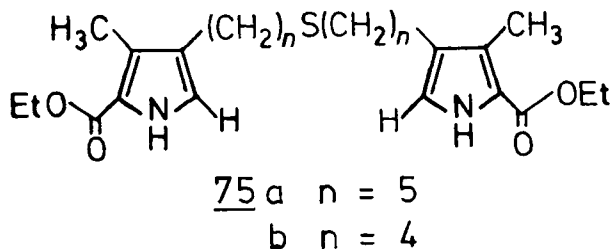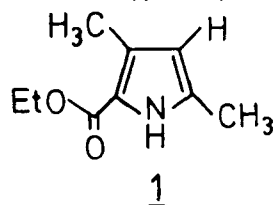
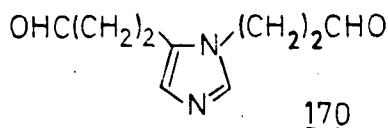Conversion of 44 and 64 to the corresponding phosphonium salts

94a, 94b followed by a double Wittig reaction under phase-transfer

conditions with either of the dialdehydes 95 or 131 gave the bis-alkenes.

Catalytic hydrogenation yielded the bis(pyrrol-3-yl) compounds 113a,

113b and 138a, 138b. Elaboration to the bis-dipyrromethanes was

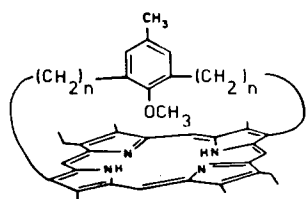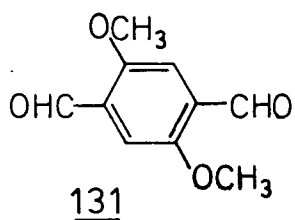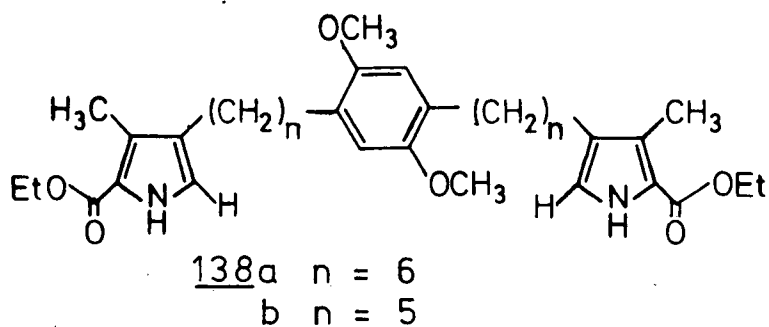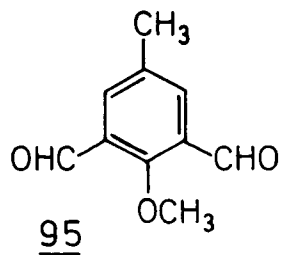followed by saponification, decarboxylation and intramolecular cyclization

to furnish the strapped porphyrins. These relatively unstrained compounds were obtained in good yield: 117a (30-44%), 117b (21-53%), 140a (41-60%), 140b (20-40%).

Treatment of the anisole-porphyrin 117a, 117b with boron tribromide furnished the phenol-strapped porphyrin 118a (76-89%), 118b (89-95%). Demethylation of the dimethoxybenzene-porphyrin 140a, 140b also with boron tribromide yielded the hydroquinone which was oxidized to the quinone-strapped porphyrin 143a (82-87%), 143b (70%).

An attempt was made to incorporate a suitably substituted imidazole into the bridging strap using the same procedure. However production of the required 1,5-disubstituted imidazole intermediates was hampered by low yields and difficulty in purification. The failure to prepare the necessary imidazole bis-aldehyde 170 led to cancellation of this attempt.

All the porphyrins were subjected to elemental analysis, high resolution mass spectrometry, and visible absorption and ^{1}H- and ^{13}C-NMR spectroscopy. A simplistic attempt was made to correlate the spectral characteristics to the structure, length and conformation of the strap.

OHC(CH$_2$)$_2$ $\diagdown$ N $\diagup$ (CH$_2$)$_2$CHO

170

94a n = 5
94b n = 4

95

131

113a n = 6
 b n = 5

138a n = 6
 b n = 5
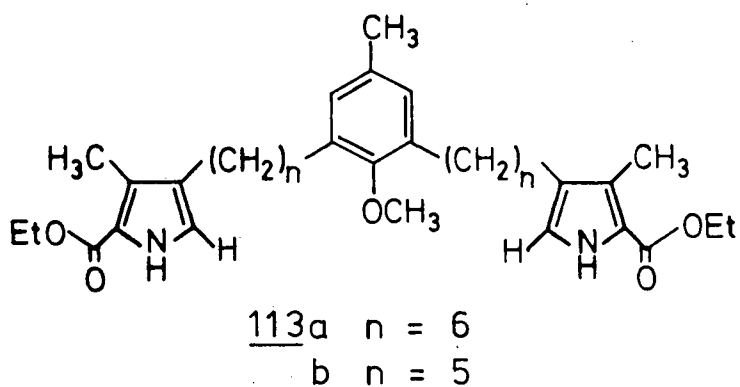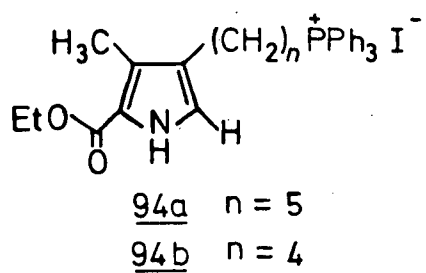
117a n = 6
 b n = 5
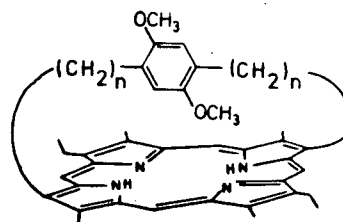
140a n = 6
 b n = 5
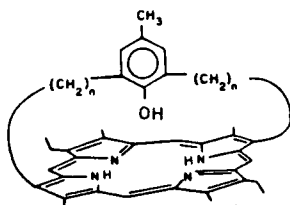
118a n = 6
 b n = 5
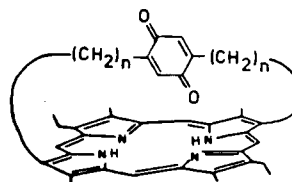
143a n = 6
 .b n = 5

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ABBREVIATIONS

^{13}C-NMR	=	Carbon-13 nuclear magnetic resonance
CH_2Cl_2	=	Dichloromethane
CO	=	Carbon monoxide
DABCO	=	1,4-Diazabicyclo[2.2.2]octane
DDQ	=	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMA	=	N,N-Dimethylacetamide
DMF	=	N,N-Dimethylformamide
DMSO	=	Dimethyl sulfoxide
ee	=	Enantiomeric excess
EPR, ESR	=	Electron paramagnetic (spin) resonance
Et_3N	=	Triethylamine
EtOAc	=	Ethyl acetate
^{1}H-NMR	=	Proton nuclear magnetic resonance
Im	=	Imidazole
KOBu-t	=	Potassium t-butoxide
MCD	=	Magnetic circular dichroism
O_2	=	Oxygen molecule
pyr	=	Pyridine
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran

tlc   =   Thin layer chromatography

TMS   =   Tetramethylsilane

Abbreviations in NMR Assignments

S = singlet   m = multiplet

d = doublet   ·bs = broad singlet

t = triplet   bt = broad triplet

q = quartet

ACKNOWLEDGEMENTS

CHAPTER I

LITERATURE REVIEW

1.1   INTRODUCTION

Because of their ubiquitousness and the variety of functions
which they carry out, heme proteins have been investigated on a multi-
disciplinary level. These proteins, all containing an iron porphyrin
as the prosthetic group, are responsible for oxygen transport and
storage (hemoglobin and myoglobin), electron transport (cytochromes b,
c), oxygen reduction (cytochrome oxidase), hydrogen peroxide utilization
and destruction (peroxidases and catalases), substrate oxidation
(cytochrome P450). The active site in each case contains an iron
porphyrin (usually protoporphyrin IX), the nitrogens of the porphyrin
ring occupying four essentially planar coordination sites of the metal.
The diversity of function of the heme proteins must therefore be
dictated by the number and nature of the axial ligands, the spin and
oxidation state of the iron and the nature of the polypeptide chain.

A basic tenet of bioinorganic chemistry is that the structure
and function of large biomolecules may be simulated using simpler
inorganic complexes to model the active sites. Obviously to fully
understand the mechanisms of heme protein function, a study of iron
porphyrins must be undertaken in which the characteristics of the metal
(spin state, oxidation state and coordination number) and the steric
and electronic effects of the porphyrin and other ligands are
systematically varied.

Historically, much of the research on metalloporphyrins has
focussed on the mechanism of oxygen binding to myoglobin and hemoglobin.
Oxygen binding heme proteins are five-coordinate high spin (S=2) iron(II)
species, which upon oxygenation become six-coordinate low spin (S=0).

TABLE I: Axial Ligands of Selected Heme Proteins[145,146]

PROTEIN	LIGAND	
Hemoglobin		
deoxy	His-F8	a
oxy	His-F8	O_2
carbonmonoxy	His-F8	CO
Myoglobin - deoxy	His-F8	a
Cytochrome P450	Cysteine	a
Cytochrome c - tuna	His-18	Met-80
Cytochrome b_5 - calf liver	His-39	His-63
Peroxidase - horseradish	His	a
Catalase - beef liver	Tyr-357	a

a)   Sixth ligand site vacant or occupied by water

The difficulty in reproducing this behaviour is dominated by two problems:

(i)   irreversible oxidation of iron(II) porphyrins on exposure to oxygen, and

(ii)   the difficulty in obtaining well-defined five-coordinate iron porphyrins.

Simple iron(II) porphyrins cannot reversibly bind oxygen, except at low temperature. At room temperature, and in the absence of a large excess of a sixth ligand, formation of the six-coordinate iron(II)-oxygen species is immediately followed by attack of a second five-coordinate iron(II) complex to give the μ-peroxo dimer. This rapidly breaks down, presumably via the ferryl intermediate to give the μ-oxo dimer in which the iron has been irreversibly oxidized to the ferric form (Scheme 1).[1-4]

Therefore, a major role for the polypeptide backbone of heme-proteins is to sheath the oxygen binding site, preventing the close approach of two heme rings and irreversible oxidation via the μ-peroxo dimer. That irreversible oxidation of iron(II) porphyrins is possible by another mechanism is demonstrated by the fact that the body must provide an enzyme to reduce methemoglobin (the oxidized iron(III) hemoglobin incapable of oxygen transport) to the functional iron(II) form. Even so, hemoglobin exists in the body in the ferric form to the extent of about 3%. This alternative oxidation pathway occurs in aqueous acid or under conditions where μ-peroxo dimer formation is inhibited, and is believed to involve proton assisted formation of protonated super-

SCHEME 1

$$B-Fe^{II}-B \rightleftharpoons Fe^{II}-B + B \tag{1}$$

(showing B axial ligands on Fe)

$$Fe^{II}-B + O_2 \rightleftharpoons B-Fe^{II}-O_2 \tag{2}$$

$$Fe^{II}(B)(O_2) + Fe^{II}-B \rightleftharpoons B-Fe^{III}-O-O-Fe^{III}-B \tag{3}$$

$$B-Fe^{III}-O-O-Fe^{III}-B \longrightarrow 2\ O=Fe^{IV}-B \tag{4}$$

$$B-Fe^{IV}=O + Fe^{II}-B \longrightarrow Fe^{III}-O-Fe^{III} \tag{5}$$
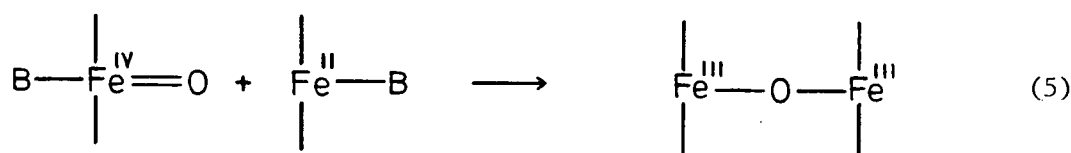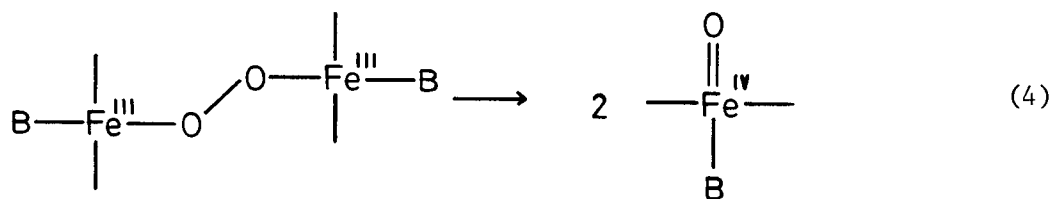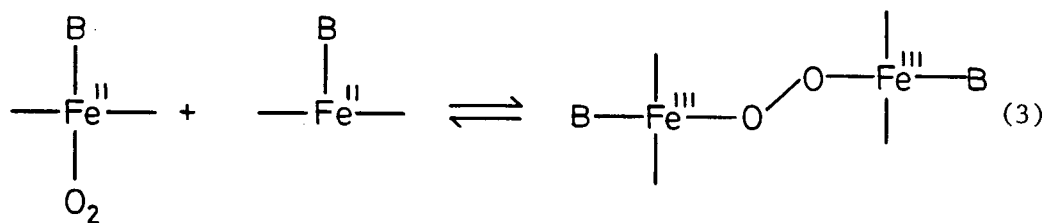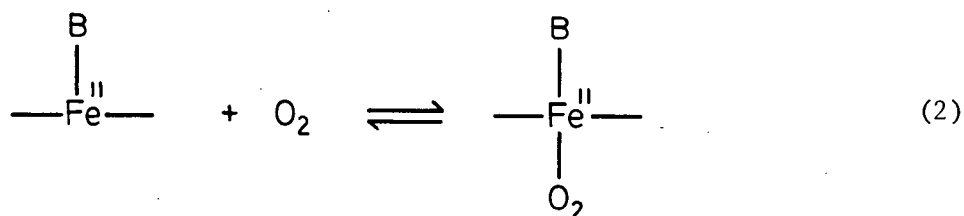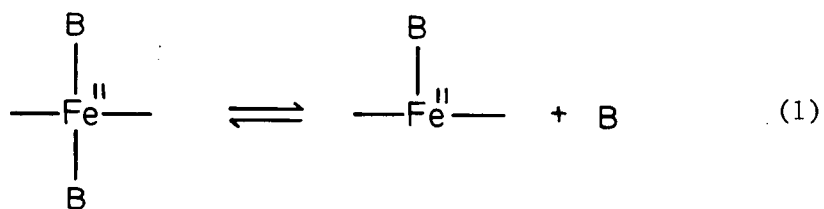
oxide.[5] The peptide chain also stabilizes the Fe(II)-O_2 species by

$$Fe(II) - O_2 + H^+ \longrightarrow Fe(III) + HO_2 \qquad (6)$$

$$Fe(II) + HO_2 + H^+ \longrightarrow Fe(III) + H_2O_2 \qquad (7)$$

$$2Fe(II) + H_2O_2 + 2H^+ \longrightarrow 2Fe(III) + 2H_2O \qquad (8)$$
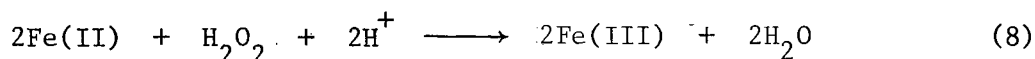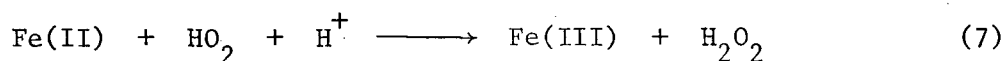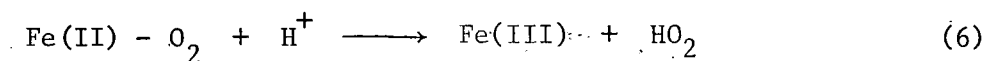
enclosing the porphyrin in a hydrophobic pocket to which access by

protons is inhibited. In addition, recent neutron[7] and X-ray

diffraction[8] studies have indicated that stabilization of the iron-

oxygen bond in oxyhemoglobin and oxymyoglobin may in part be due to

hydrogen bonding between the terminal oxygen atom and the imidazole

of the distal histidine (E7).

The influence of the protein backbone is more pervasive than

simply providing a barrier to oxidation. Conformational changes upon

oxygen binding to the active site are believed to be responsible for

the remarkable cooperativity exhibited by hemoglobin.[6] Similarly,

the arrangement of certain residues on the protein has been postulated

to provide an avenue along which electron transfer may occur in the

cytochromes. But it is the protein's role in maintaining the

coordination sphere of the iron porphyrin which determines the functions

of the various heme proteins.

The second major problem in studying simple iron porphyrins is

the preference of the metal for six-coordination. For example, in

solution containing strongly coordinating N-donor ligands, six-

coordination is favoured over five coordination, i.e., for the equilibria

in equation 9, $K_2 > K_1$ (K_2/K_1 = 10-30 in aprotic solvent at 25°C).[9] In

$$Fe(II)Por + B \overset{K_1}{\rightleftharpoons} Fe(II)PorB + B \overset{K_2}{\rightleftharpoons} Fe(II)Por(B)_2 \qquad (9)$$
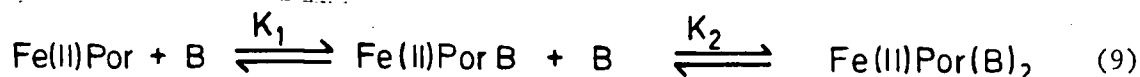
benzene at 25°C, the binding constants of pyridine to Fe(II)(TPP) have

been estimated at $K_1 \sim 1.5 \times 10^3 \text{ M}^{-1}$ and $K_2 \sim 1.9 \times 10^4 \text{ M}^{-1}$. The size

of K_1 and K_2 is obviously controlled by the spin state of the iron. The

four-coordinate iron porphyrin is in an intermediate spin (S = 1) state.

Addition of one ligand gives the high spin (S = 2) five-coordinate

complex which adds a second ligand to form the low spin (S = 0) six-

coordinate species with a gain in crystal field stabilization energy.[10,11]

In contrast, for Co(II), no stabilization is gained on going from five-

to six-coordinate since Co(II) is low spin in both cases, and $K_1 >> K_2$.[12]

A further consequence of this is the difficulty of preparing

mixed-ligand six-coordinate iron porphyrins. A typical example is the

preparation of models for cytochrome c where the iron is coordinated by

an imidazole (His-18) and a thioether (Met-80). The greater ligating

power of imidazole coupled with its tendency to form six-coordinate

bis(imidazole) complexes makes self assembly of the mixed ligand system,

Im-Fe-SR$_2$, difficult. Strategies which control coordination are

essential for preparing a range of heme protein model porphyrins.

Numerous approaches have been used to control oxidation and

coordination in model porphyrin systems.

(i)   Excess Ligand: The presence of excess base (imidazole, pyridine)

will minimize the concentration of five-coordinate heme and reduce

μ-peroxo dimer formation.

$$\underset{\overset{\displaystyle |}{B}}{\overset{\displaystyle B}{\underset{|}{-Fe^{II}-}}} \quad \rightleftharpoons \quad -Fe^{II}- \; + \; \underset{O_2}{\overset{\displaystyle B}{\underset{|}{-Fe^{II}-}}} \quad \rightleftharpoons \quad B-\overset{\displaystyle |}{Fe^{III}}-O\diagdown O-\overset{\displaystyle |}{Fe^{III}}-B \tag{10}$$
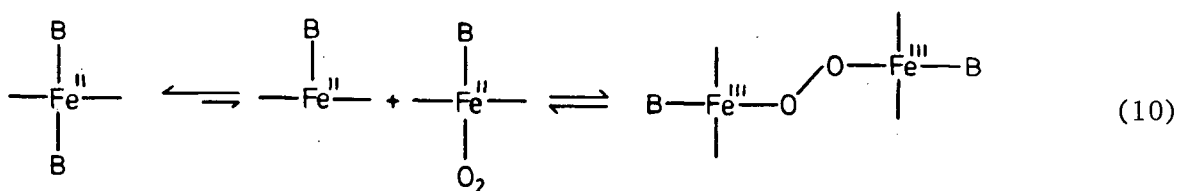
However in this case one is limited to studying competitive oxygen

binding to six-coordinate hemes.

$$\underset{\overset{\displaystyle |}{B}}{\overset{\displaystyle B}{\underset{|}{-Fe^{II}-}}} \; + \; O_2 \quad \rightleftharpoons \quad \underset{O_2}{\overset{\displaystyle B}{\underset{|}{-Fe^{II}-}}} \; + \; B \tag{11}$$
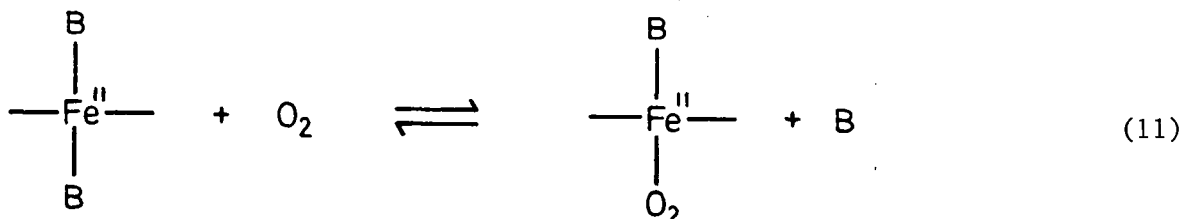
(ii) <u>Low Temperatures</u>:[13-16] Iron(II)-O_2 porphyrin complexes are

stable at low temperatures ($\sim$-60°C), where the irreversible oxidation

reactions are successfully suppressed. Again one is reduced to

studying competitive oxygen binding as K_2/K_1 increases as temperature

decreases.

$$-Fe^{II}- \; + \; B \quad \overset{K_1}{\rightleftharpoons} \quad \overset{\displaystyle B}{\underset{|}{-Fe^{II}-}} \; + \; B \quad \overset{K_2}{\rightleftharpoons} \quad \underset{\overset{\displaystyle |}{B}}{\overset{\displaystyle B}{\underset{|}{-Fe^{II}-}}} \quad \overset{O_2}{\rightleftharpoons} \quad \underset{O_2}{\overset{\displaystyle B}{\underset{|}{-Fe^{II}-}}} \tag{12}$$
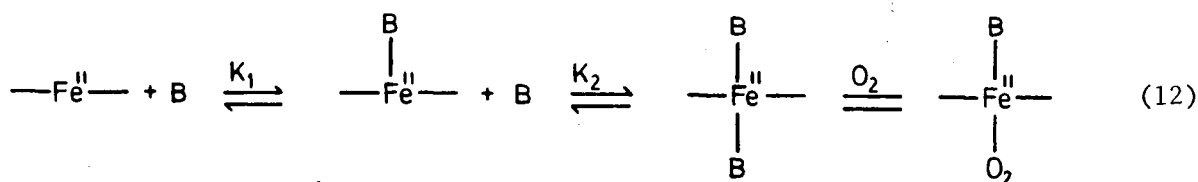
(iii) <u>Kinetic Measurements</u>: Fast spectroscopy methods may be used to

observe reversible oxygen binding even under conditions where irreversible

oxidation will occur. Traylor has exploited the stability of imidazole-

heme-CO complexes towards oxidation.[17] A solution of Im-Hm-CO,

equilibrated with a mixture of oxygen and carbon monoxide, is subjected

to a short laser pulse which completely removes the carbon monoxide.

The deoxy heme then reacts preferentially with oxygen at a fast but

measurable rate ($k_B^{O_2} > 10^7 M^{-1}s^{-1}$). In $10^{-3} - 10s$, the Im-Hm-O_2 complex

dissociates and returns to the Im-Hm-CO complex.

$$
\underset{CO}{\overset{B}{-Fe^{II}-}} \quad \underset{k_B^{CO}}{\overset{h\nu \quad k_B^{-CO}}{\rightleftharpoons}} \quad \overset{B}{-Fe^{II}-} \quad \underset{-O_2 \quad k_B^{-O_2}}{\overset{+O_2 \quad k_B^{O_2}}{\rightleftharpoons}} \quad \underset{O_2}{\overset{B}{-Fe^{II}-}} \tag{13}
$$
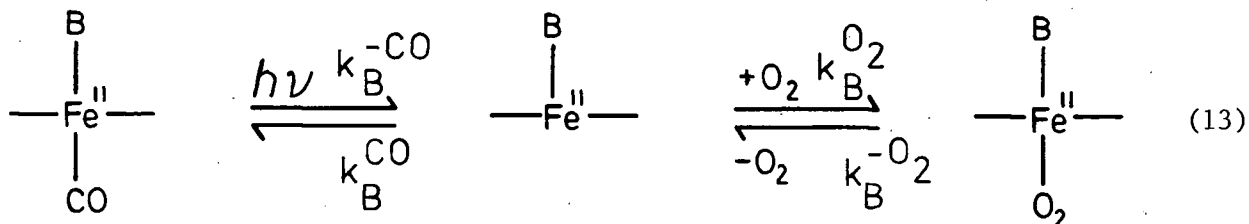
The kinetics are described by:[18]

$$
\frac{1}{k_{return}} = \frac{1}{k_B^{-O_2}} + \frac{K_B^{O_2}[O_2]}{k_B^{CO}[CO]} \tag{14}
$$

Since $k_B^{CO}[CO]$ is the rate of return before O_2 is added, $k_B^{CO}[CO]$ may

be accurately determined in the experiment and $k_B^{O_2}$ and $k_B^{-O_2}$ may be

calculated from a plot of $\frac{1}{k_{return}}$ vs O_2 (pressure).

(iv) Metal Substitution: Replacement of iron with cobalt[19] or

ruthenium[20] leads to metalloporphyrins which are more inert to

oxidation and possess different coordination properties. Such an

approach is applicable since apoproteins may be reconstituted with

Co and Ru porphyrins. In the case of Co, reconstituted Co hemoglobin

exhibits cooperative oxygen binding although to a diminished extent.

(v) Immobilization: This approach attempts to prevent irreversible

oxidation by anchoring the porphyrin to a solid support. In Wang's

classic experiment a heme diethyl ester was embedded in a matrix of polystyrene and 1-(2-phenylethyl)imidazole.[21] The matrix not only prevented close approach of two hemes but also provided a hydrophobic environment. Reversible oxygen uptake was observed. Alternatively, either the porphyrin or the ligand may be covalently attached to a rigid support. Basolo has undertaken the latter approach and prepared a silica gel support which contained 3-imidazolypropyl groups attached to the surface.[22] Reaction with $Fe(II)(TPP)(B)_2$ coordinated the porphyrin and heating in flowing helium removed the sixth axial base (pyridine or piperidine) to give the five-coordinate iron(II) porphyrin. However, attempts to observe reversible oxygen binding were obscured by the physisorption of oxygen by the silica support.

(vi)   <u>Steric encumbrance</u>:   By sterically blocking one or both faces of the porphyrin, close approach of two porphyrin rings and therefore μ-oxo dimer formation may be prevented. The approach most similar to the natural system is to enfold the porphyrin ring in a polymer chain. This approach has been vigorously pursued in an attempt to prepare compounds capable of reversible oxygen binding in aqueous solution at room temperature. However, doubts about the number and nature of the active sites and the reversibility of oxygenation have made this approach less fruitful.

In contrast, porphyrins have been synthesized in which one or both faces of the ring is obstructed by some group(s) covalently bonded to the ring. The function of the steric hindrance is two-fold:

(i)   to direct base binding to the open face, ensuring five-coordina-
        tion, and

(ii)   to allow O_2 to bind on the hindered face, steric hindrance

preventing μ-oxo dimer formation.

Five-coordination may also be ensured in these systems by using bulky

axial bases which cannot bind on the protected face.

This approach has been used by many groups to produce a wide

variety of architecturally different model porphyrins, e.g. picket-

fence, capped, cyclophane, crowned, strapped, basket-handle etc.

(vii) <u>Chelated Hemes</u>:   Covalent attachment of the ligand to the

porphyrin periphery allows one to control the extent of coordination.

For poor ligands such as thiolate, thioether, phenoxide, etc.,

covalent attachment increases the local concentration and the likelihood

of coordination to the metal without the necessity of a large excess of

external ligand. As long as displacement does not occur, addition of

a second ligand allows formation of six-coordinate mixed ligand

systems.

On the other hand, for strong ligands e.g. imidazole, pyridine,

chelation provides a built-in 1:1 base/porphyrin stoichiometry. As

long as dimerization to form mixtures of six- and four-coordinate is

(15)
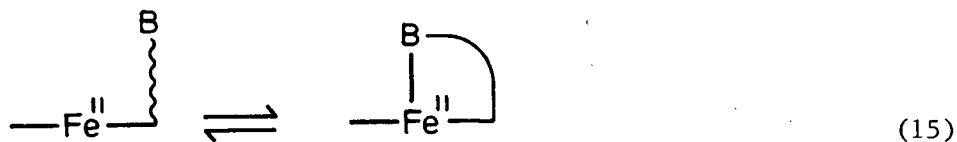
prevented, this approach produces five-coordinate complexes.

In the following sections we will examine those porphyrins

which employ steric encumbrance and chelation as models for heme proteins.

Several excellent reviews exist which discuss the ligand binding

$$2 \quad -\text{Fe}^{\text{II}}- \quad \rightleftharpoons \quad -\text{Fe}^{\text{II}}- \qquad\qquad (16)$$
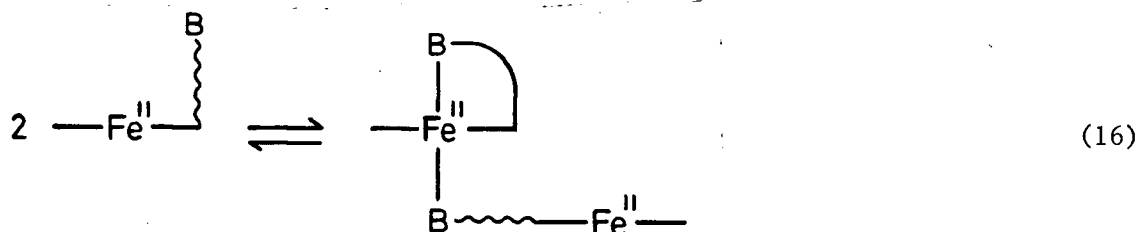
properties of these models and their congruency with the natural

systems.[11,23-28]   Instead, here we will concentrate on the strategy

and synthetic details of model porphyrin production. To that end, the

compounds have been grouped together more in terms of structure than

of function.

1.2   PORPHYRINS WITH APPENDED PEPTIDES

Perhaps the most obvious approach to the synthesis of heme protein models is to reproduce the local environment of the heme active site by covalently attaching various peptide fragments to a suitable porphyrin. If the peptide fragments contain suitable amino acids (e.g. histidine, methionine), reproduction of the coordination sphere of the heme protein may be possible.

An early example of this approach was that of Lautsch et al.,[29] who coupled various histidine-containing tripeptides to the propionic acid side-chains of mesoporphyrin IX 1a (Scheme 2). After metal insertion into the porphyrin, intramolecular coordination by the histidyl imidazole was possible depending on the length of the peptide chain. Similarly, histidine-containing peptides were attached to the ethyl side chains of mesoporphyrin IX via sulfide linkages to give 2, a situation similar to that in cytochrome c. Losse and Muller[30] coupled L-histidine methyl ester and protohemin 3 with dicyclohexylcarbodiimide in N,N-dimethylformamide. However, models indicated that, with a single histidine bound to the porphyrin propionic acid, the length of the side chain was too short for coordination of the imidazole to the iron centre. Van der Heijden et al.,[31] coupled various di- and tri-peptide fragments (e.g. β-Ala-His; Gly-L-His; L-Ala-L-His; Gly-L-His-Gly-OEt) to protohemin 3 in DMF in the presence of triethylamine and ethyl chlorocarbonate (Scheme 3). At the same time Warme and Hager[32] prepared porphyrins containing appended histidine and methionine groups. The reaction of mesohemin 6 with a SO_3/DMF complex 5 yielded the mesohemin sulfuric anhydride, in which one or both of the propionic

SCHEME 2

(a) R = H

(b) R = L-His-Gly-Gly-OH

(c) R = L-Ala-His-Gly-OH

(d) R = L-Ala-Gly-L-His-OH

1

2

SCHEME 3

(a) R = β—Ala—His—OMe

(b) R = Gly—L—His—OMe

(c) R = L—Ala—L—His—OMe

(d) R = Gly—L—His—Gly—OEt
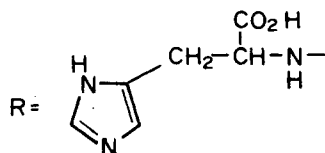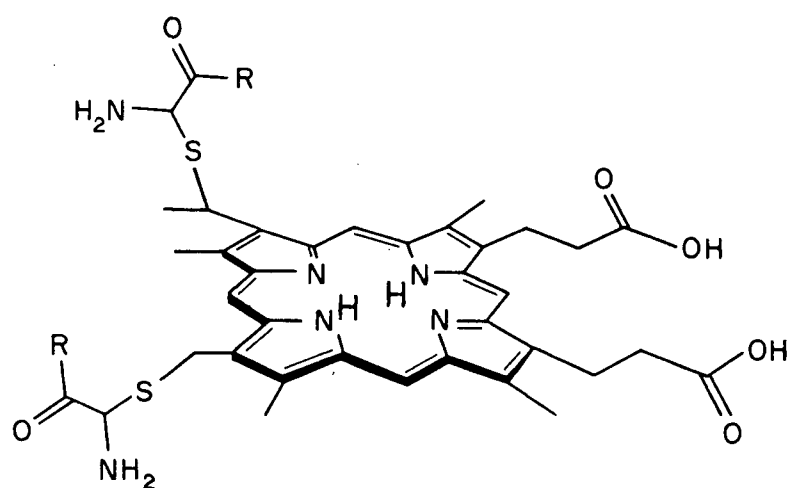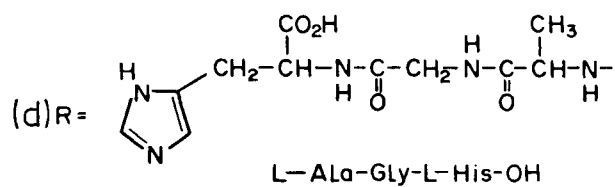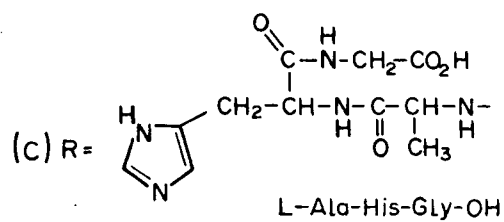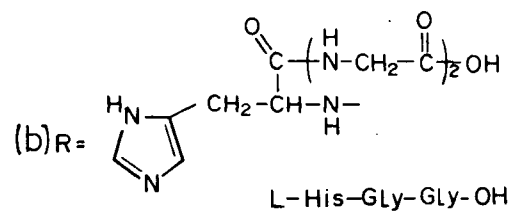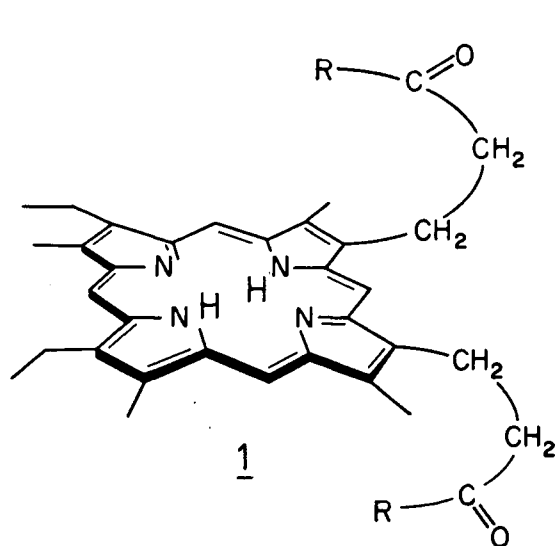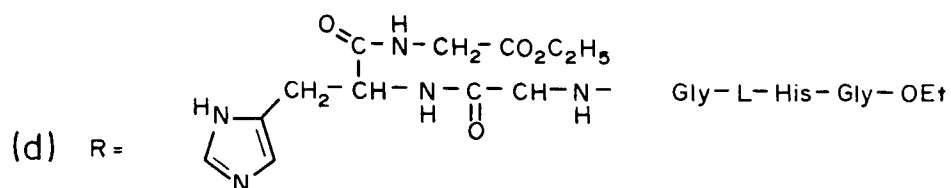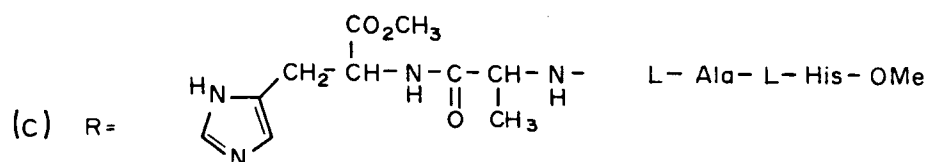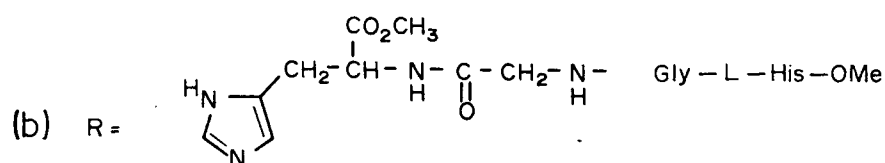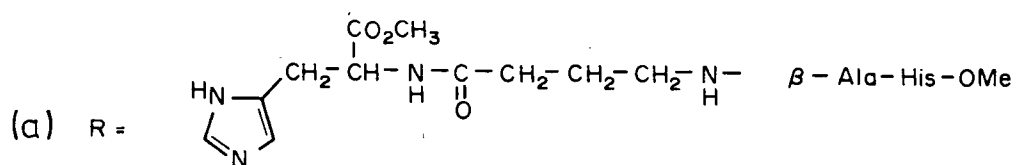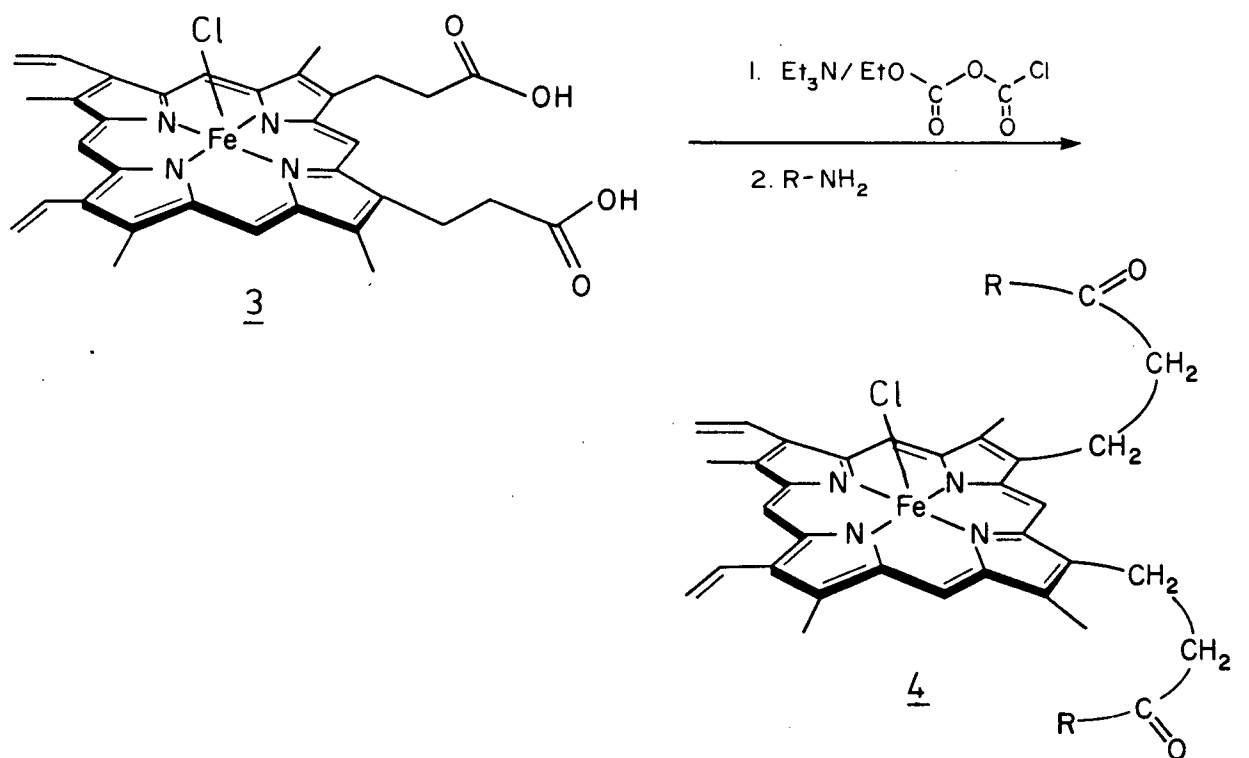
acid side chains had been converted into a sulfuric anhydride. Subsequent reaction with amino acids such as histidine or methionine methyl ester, yielded either mono- or disubstituted hemins (Scheme 4). A potential cytochrome c model 7e, containing both histidine and methionine covalently attached to the porphyrin was also prepared. Unfortunately preparation and isolation of the products was quite tedious and yields were low. It was also recognized that the peptide-containing side arms were too short to allow unstrained intramolecular coordination. Momenteau et al.,[33] have synthesized and characterized the coordinating properties of a five-coordinate iron porphyrin. Treatment of deutero-hemin 8 with equimolar quantities of ethylchloroformate and triethylamine, followed by L-histidine methyl ester dihydrochloride and more triethyl-amine gave, after purification, a mixture of three compounds 9a-c. The desired deuterohemin 6(7) mono-histidine methyl ester 9c was separated from unreacted deuterohemin and deuterohemin 6,7-bis(histidine methyl ester) 9b, and was obtained in 16% yield as a mixture of isomers (Scheme 5). The reduced iron(II) species was capable of binding oxygen reversibly at low temperature but oxidized irreversibly at room temperature. Furthermore, extensive dimerization of the 5-coordinate species occurred at low temperature (-60°C), complicating oxygen binding studies.

$$2 \quad \overbrace{}^{His} \!\!\!\!-Fe^{II}\!\!- \quad \rightleftharpoons \quad \overbrace{}^{His} \!\!\!\!-Fe^{II}\!\!- \qquad (17)$$

SCHEME 4

$$SO_3 + Me_2N-\underset{H}{\overset{O}{C}} \longrightarrow Me_2\overset{\oplus}{N}=\underset{H}{C}-O-\underset{O}{\overset{O}{S}}-O^-$$

$$\underline{5}$$

$$\underline{6}$$

1. SO_3/DMF
2. Et_3N
   · $R-NH_2$

$$\underline{7}$$

(a) $R = R' = $

(b) $R = \; " \; , R' = OH$

(c) $R = R' = CH_3-S-CH_2-CH_2-\underset{CO_2CH_3}{\overset{}{CH}}-\underset{H}{N}-$

(d) $R = \; " \; , R' = OH$

(e) $R = $, $R' = CH_3-S-CH_2-CH_2-\underset{CO_2CH_3}{\overset{}{CH}}-\underset{H}{N}-$
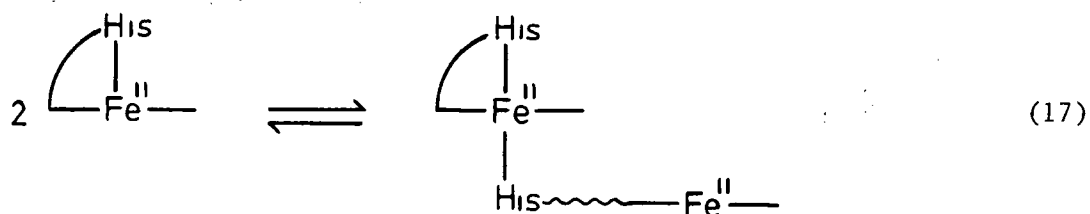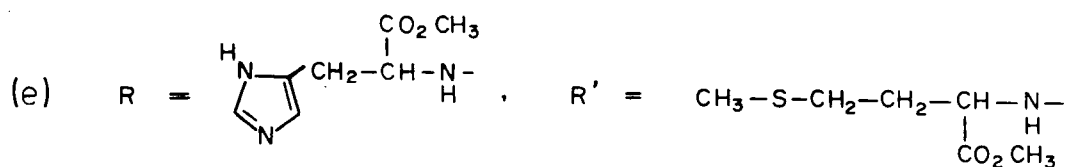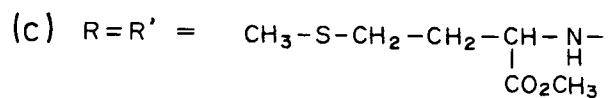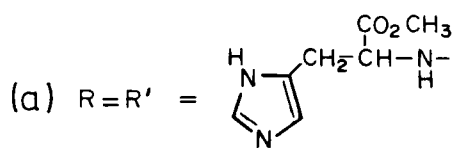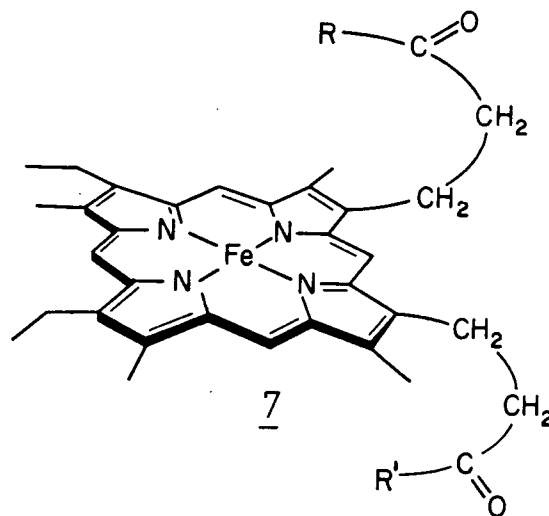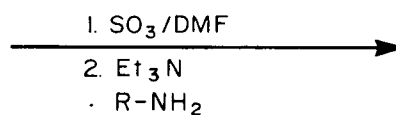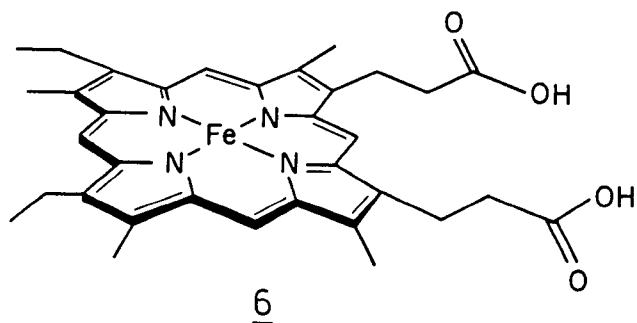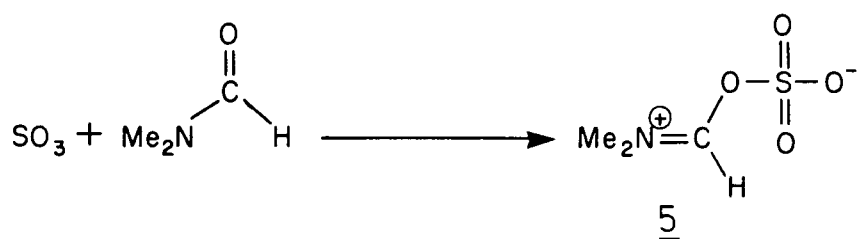
SCHEME 5

(a) $R^1, R^2 = OCH_3$

(b) $R^1, R^2 = $ ...

(c) $R^1 = $ ... , $R^2 = OCH_3$

SCHEME 6

$1a$ R = H
8 R = CH$_2$CH$_3$
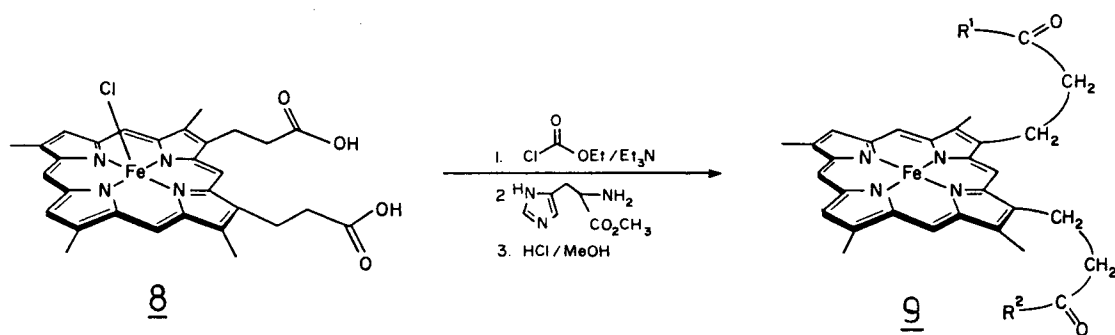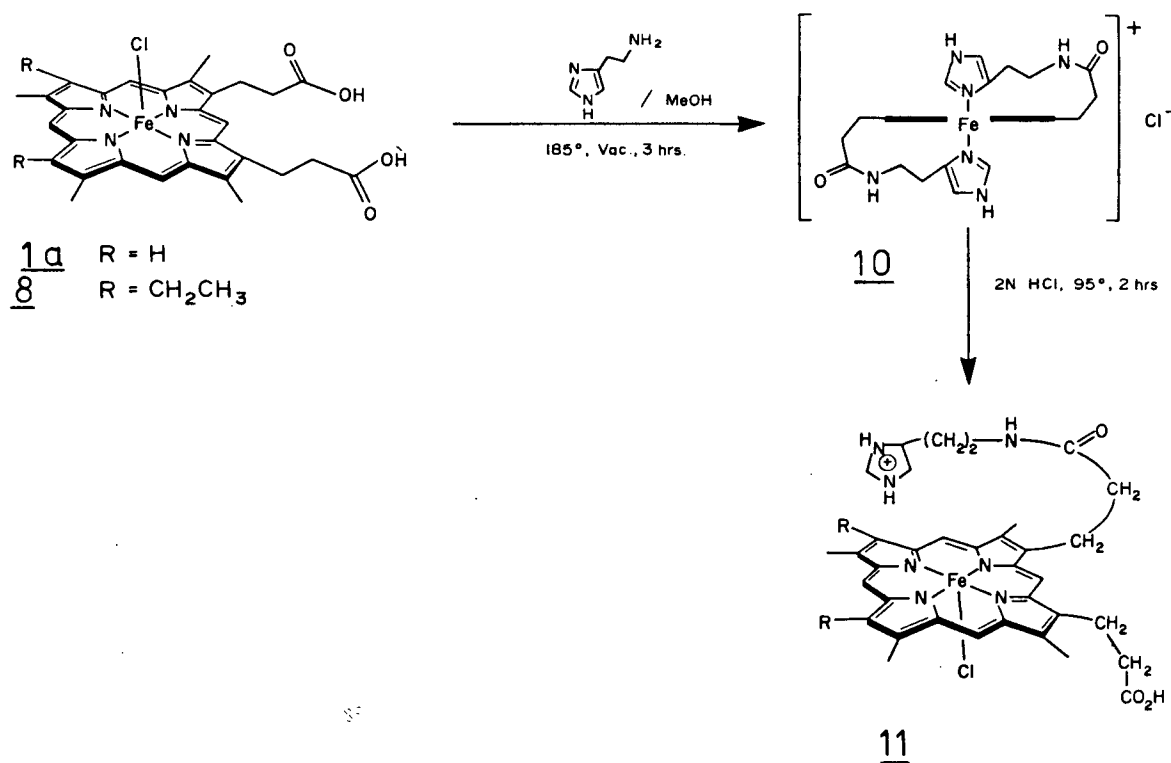
A similar dimerization was observed for the iron(III) species at room temperature in concentrated solutions.

To this stage all the syntheses have yielded model systems which are 6-coordinate, or mixtures of the 5- and 6-coordinate species, separation of which could be tedious. Castro prepared porphyrin derivatives having two covalently attached imidazoles, by heating deuterohemin 8 or mesohemin 1a with excess histamine in vacuo in the absence of solvent for three hours.[34] The bis-chelated product 10 was obtained in up to 50% yield after purification. Controlled hydrolysis with 2M hydrochloric acid gave a 20% yield of the monochelated hemin II, again as a mixture of isomers (Scheme 6).

More recently, Molokoedov et al.,[35] have used protohemin mono-benzyl ester 13, (obtained from protohemin dibenzyl ester 12 in 61% yield by partial hydrolysis), to prepare a series of histidine-containing peptide derivatives 14a-e. Coupling of peptide and hemin was completed by the mixed anhydride method using ethyl chloroformate and triethylamine. The yields of product decreased from 47% to 25% as the length of the peptide chain increased, the products being obtained as a mixture of the 6 and 7 isomers (Scheme 7). The reduced penta-peptide 14d and hexapeptide 14e heme derivatives were reported to be stable for 35-40 minutes at room temperature in chloroform solution in the presence of air.

There have been two attempts to model the active site of cyto-chrome c using heme-peptide compounds. Sequencing of various cytochromes c reveal the segment 14-18 to be invariant, with structure 14-Cys-X-X-Cys-His-18. The heme active site is bound to the polypeptide via sulfide bonds to the two cysteine residues 14 and 17, while the

SCHEME 7

(a) R= Ala-OMe

(b) R= His-OMe

(c) R= Leu-His-OMe

(d) R= Leu-His-Leu-Gly-Cys-OBz
                                    Bz

(e) R= Leu-His-Ala-Gly-Cys-OBz
                                    Bz
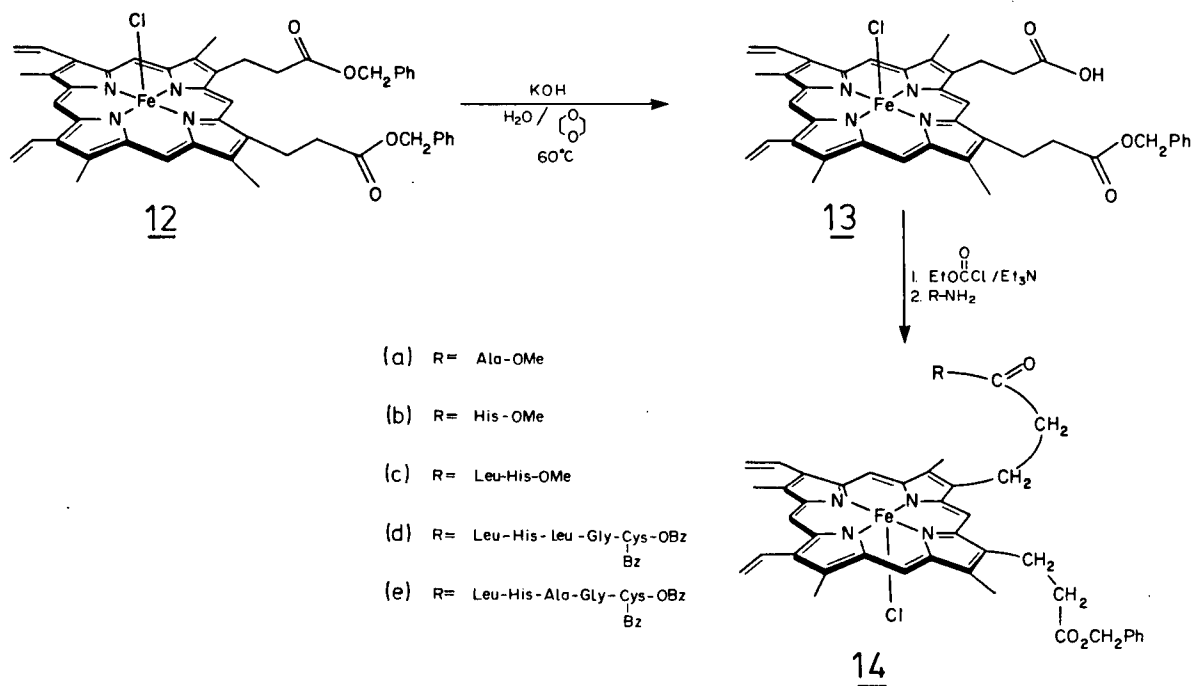
SCHEME 8
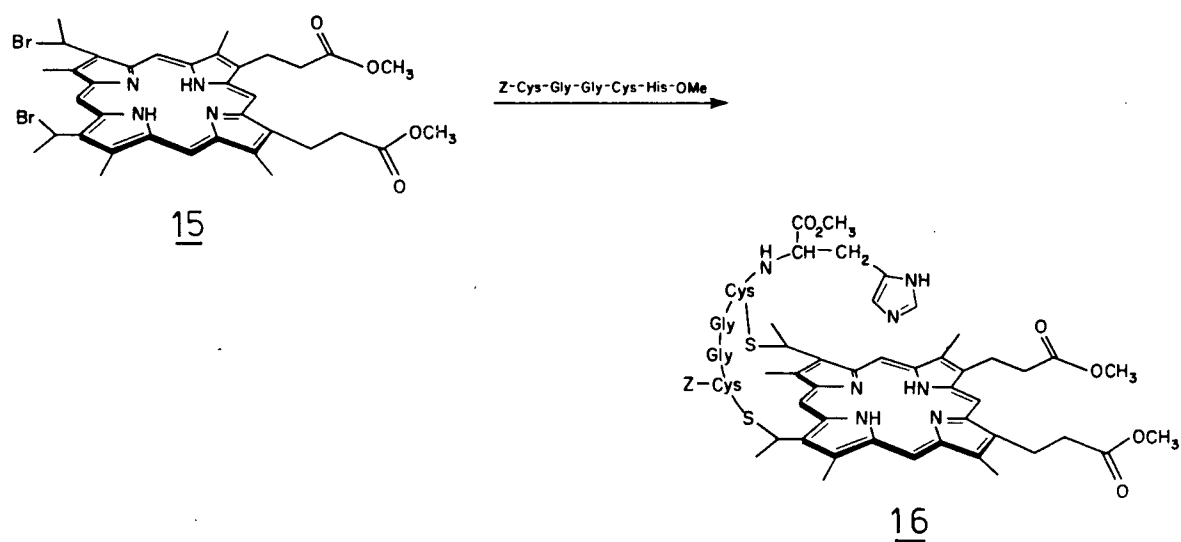
imidazole of His -18 provides one of the ligands for the iron atom of the heme. Momenteau and Loock,[36] with a strategy similar to that of Lautsch,[29] attached a protected pentapeptide (Cys-Gly-Gly-Cys-His) to the ethyl side chains of 2,4-α,α'-dibromomesoporphyrin IX $\underline{15}$. (Scheme 8). After iron insertion, optical spectra indicated that the imidazole of the histidine could bind to the metal centre. Binding of a methyl thioether e.g. methionine, to the iron would then mimic the coordination sphere observed in the natural cytochrome c. However thioethers are poor ligands for iron. An attempt was made to overcome this poor binding by covalently attaching the thioether to the porphyrin. In this case the synthetic porphyrin, tetraphenylporphyrin (TPP) $\underline{17}$ was used. Various cysteine dipeptides were condensed with a TPP derivative bearing a propenoic acid side chain at a β-pyrrole position.[37-40] Reaction of a dipeptide containing a terminal S-alkyl cysteine residue with cis-meso-tetraphenylporphyrin-3-propenoic acid, gave a mixture of two atropisomers, cis-endo $\underline{18}$ and cis-exo $\underline{19}$ (Scheme 9). In the cis-endo case, substituents on the peptide chain are disposed in a favourable conformation for binding to a metal in the porphyrin. When the dipeptide chain was Gly-(SR)Cys-OEt (R = Me, trityl), ^{1}H-NMR and magnetic circular dichroism suggested that a metal sulfur bond involving the cysteine residue might be occurring. However, recent EXAFS data indicated that for the substituted Zn porphyrin, the Zn-sulfur interaction could only be weak and long range, if it occurred at all.[40]

SCHEME 9

(a) R=Me
(b) R=CPh₃

17

18 Endo-Zn-Gly-(SR)CysOEt

I. Zn(OAc)₂

2. KOH

3. H₂N-Gly-(SR)CysOEt

19 Exo-Zn-Gly-(SR)CysOEt

SCHEME 10

21

1. SOCl₂

2. [structure] 20

3. FeSO₄/AcOH

4. Na₂S₂O₄

22

SCHEME 11

23

HCl
H₂O

24

1. t-BuCOCl

2. R-NH₂

25
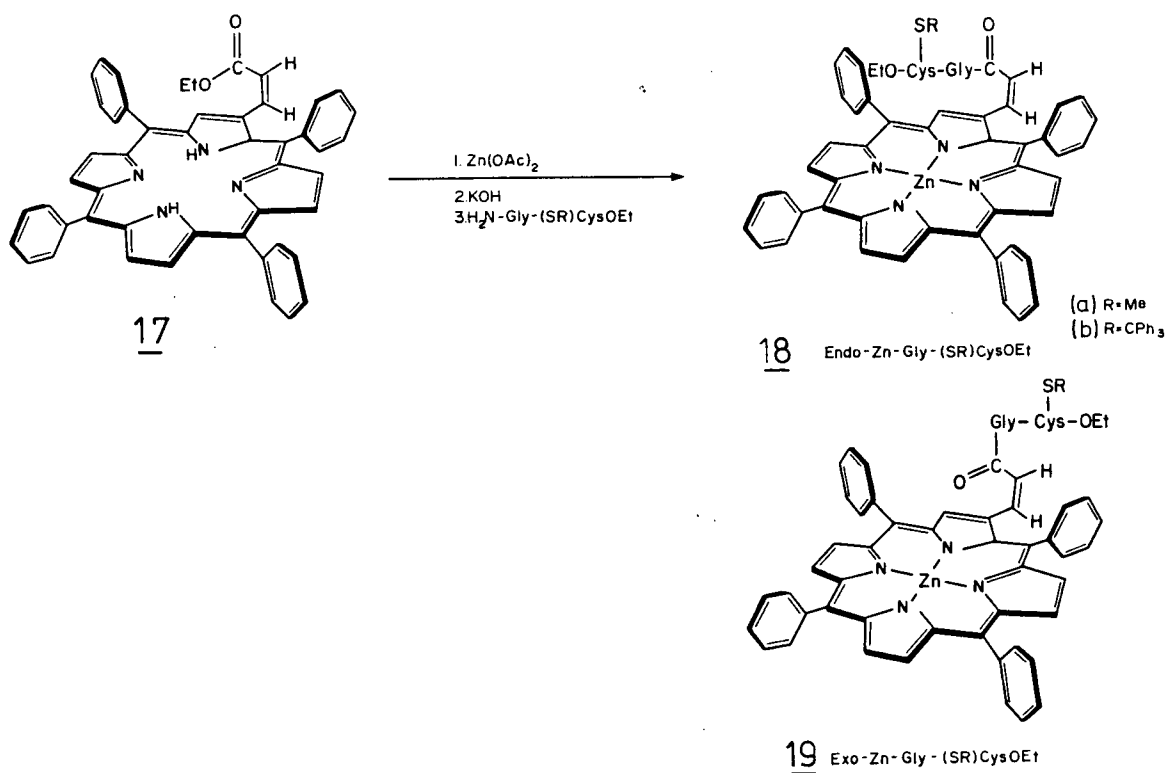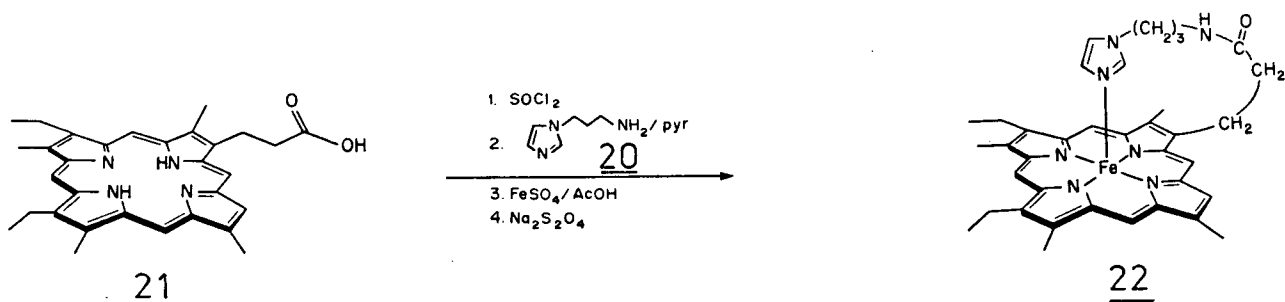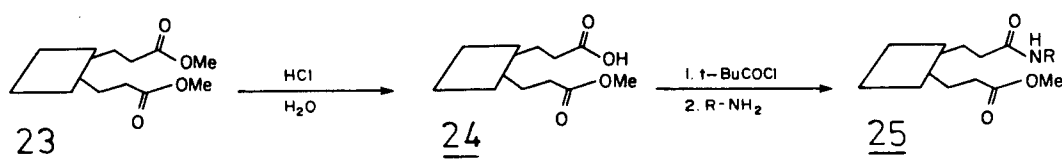
1.3   CHELATED HEMES

1.3.1   Porphyrins having Covalently Attached Imidazole or Pyridine

       Ligands

Traylor argued that in heme-peptide models the side chains containing the imidazole had either too few or too many atoms to achieve a strain-free iron-imidazole bond.[41]   On the other hand he argued that condensation of 1-(3-aminopropyl)imidazole 20 with the acid chloride of pyrroporphyrin XV 21 followed by insertion of iron would give a strain-free five coordinate system 22 (Scheme 10).   This "chelated" heme was capable of binding dioxygen in a reversible manner in the solid state or when dissolved in a polystyrene film.   While capable of binding oxygen reversibly in solution at -45°C, only irreversible oxidation occurred at room temperature.[42]   A series of derivatives of pyrro-, proto- and mesoheme having pyridine or imidazole covalently bound to the porphyrin ring through ester or amide linkages were investigated.[43-46]   For proto- and mesoheme, the monochelated hemes were easily prepared as shown in Schemes 11, 12.[46]   In one approach the porphyrin dimethyl ester 23 was partially hydrolyzed.   The purified monoacid 24 was then coupled to a primary amine or alcohol containing an imidazole or pyridine base using pivaloyl chloride.   Alternatively commercially available protohemin 3 was treated with excess pivaloyl chloride followed by one equivalent of the base-containing primary amine.   The reaction mixture was then quenched with water or methanol. The monochelated products 26, 27 were isolated by chromatography as a mixture of isomers in up to 30% yield.   The dichelated compounds were

SCHEME 12

3

mixture

MeOH

26

SCHEME 14

28

Neighbouring
Group Effect
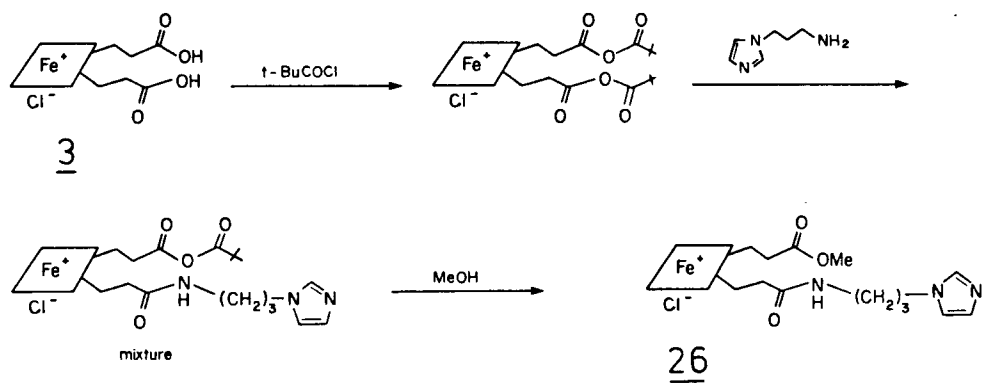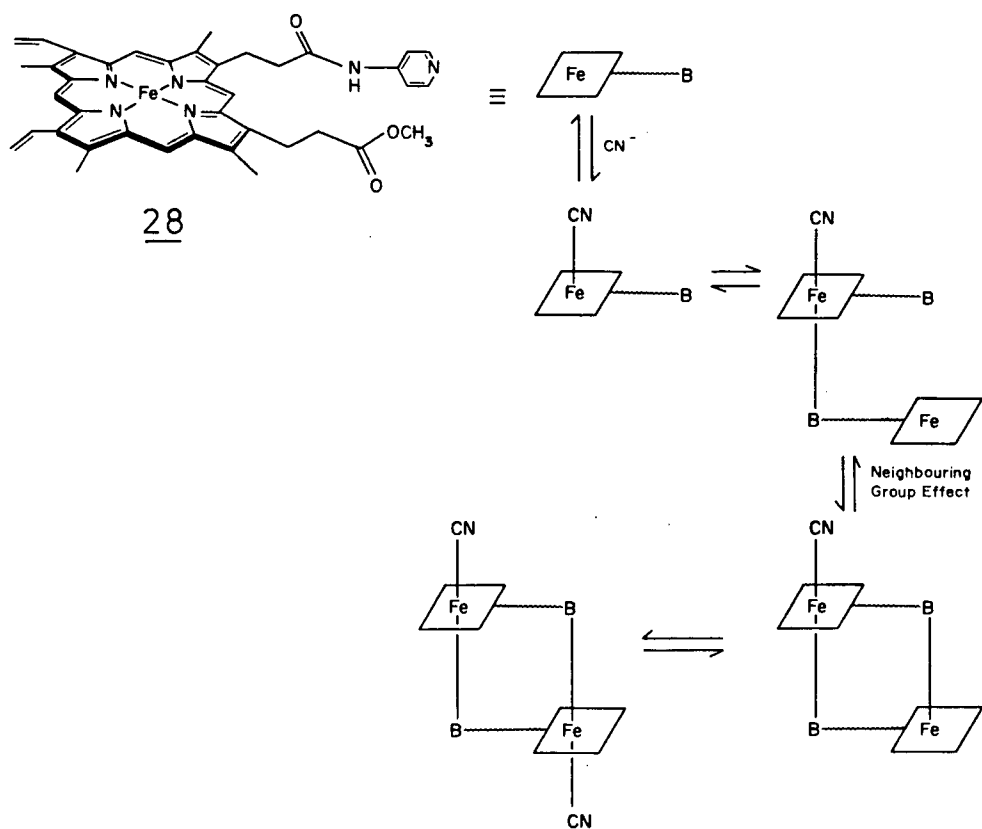
prepared similarly.

The versatility of the chelated heme approach has allowed the systematic study of the kinetics of O_2 and CO binding to these compounds. Changes in solvent, porphyrin side chains, the chelated base, and the length and nature of the chelation arm have been correlated with changes in the association and dissociation rates of O_2 and CO.[47,48]

Unlike the "chelated-histidine" system of Momenteau[33] which underwent dimerization at low temperatures, Traylor argued against the presence of any polymeric forms (Scheme 13) at the temperatures and concentrations used in his studies.[46] Indeed, Traylor exploited such

SCHEME 13
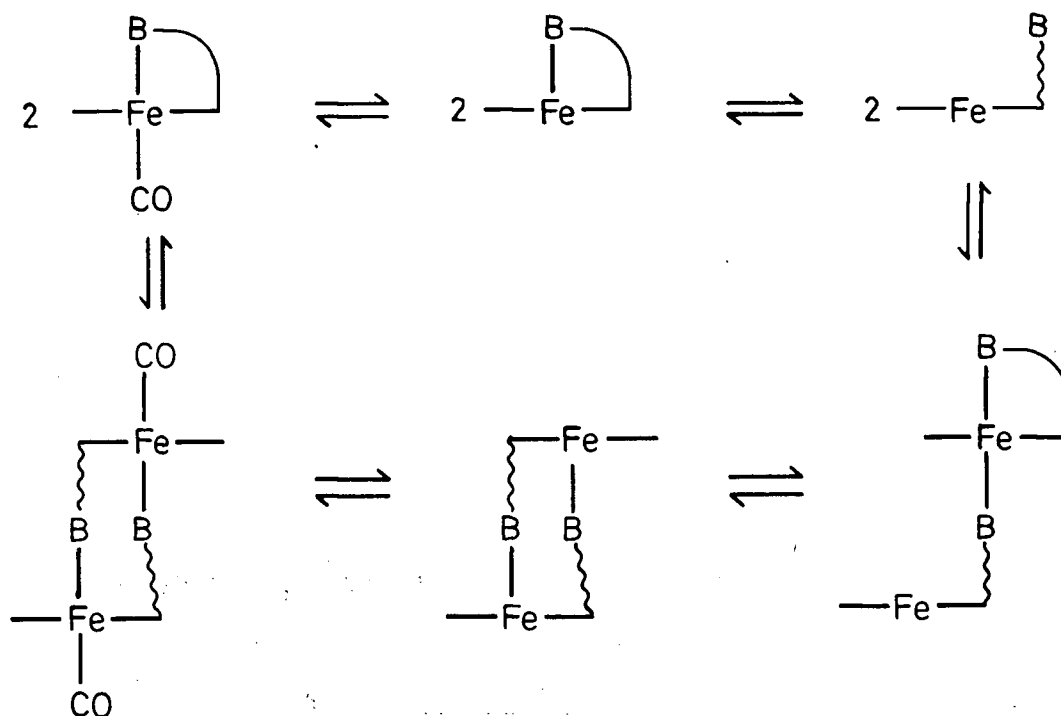
dimerization to design a system exhibiting cooperativity.[49] For the iron(III) protoporphyrin IX derivative 28, the side chain is too short to allow intramolecular binding of the pyridine (Scheme 14). While

pyridine binds very poorly to hemin, addition of cyanide greatly

increases pyridine affinity and vice versa. Therefore titration of

the side-chain pyridine protohemin 28 with cyanide leads to clean

conversion to the pyridine-hemin-CN⁻ dimer 29. A Hill plot (log Y/1-Y vs.

log [CN]) for this titration gave a straight line of slope n = 2.1,

indicating cooperativity between the metal centres.

Axial base chelation was similarly used to prepare a symmetric

diheme.[50] Meso-1,2-di-(3-pyridyl)ethylenediamine 30 was coupled with

mesoporphyrin monomethyl ester 31 through the pivaloyl anhydride, follow-

ed by iron insertion to give the diheme 32 (Scheme 15). The reaction

with CO exhibits two rate constants, indicating either two environments

or a sequential change of environment due to cooperativity.

The paramagnetic ¹H-NMR spectra of the imidazole-cyanide complexes

of dichelated protohemins 33 and 34 were studied.[51] Chelation of the

imidazole maintains a fixed orientation of the base with respect to the

porphyrin ring, causing different chemical shifts for the methyl and

vinyl protons. Comparison of these shifts with the values published

for various heme proteins provided confirmation for the heme-imidazole

orientations proposed in the natural systems.

The ¹H-NMR analysis of chlorophyll is often complicated by its

tendency to form dimers or higher aggregates. Sanders and Denniss[52]

removed the phytyl group of chlorophyll-a and converted it to the mixed

anhydride with triethylamine/ethyl chloroformate. Reaction with 1-(3-

hydroxypropyl)imidazole 35 resulted in the chelated chlorophyll

derivative 36 (Scheme 16). Intramolecular binding of the imidazole to

the magnesium prevented aggregation and gave well resolved ¹H-NMR

spectra. A similar "chelated chlorophyll" 37 used by Boxer to model

SCHEME 15

31

30

32

33 n = 3
34 n = 4

SCHEME 16

1. EtOCOCl, Et$_3$N

2. HOCH$_2$CH$_2$CH$_2$N

35

36

37
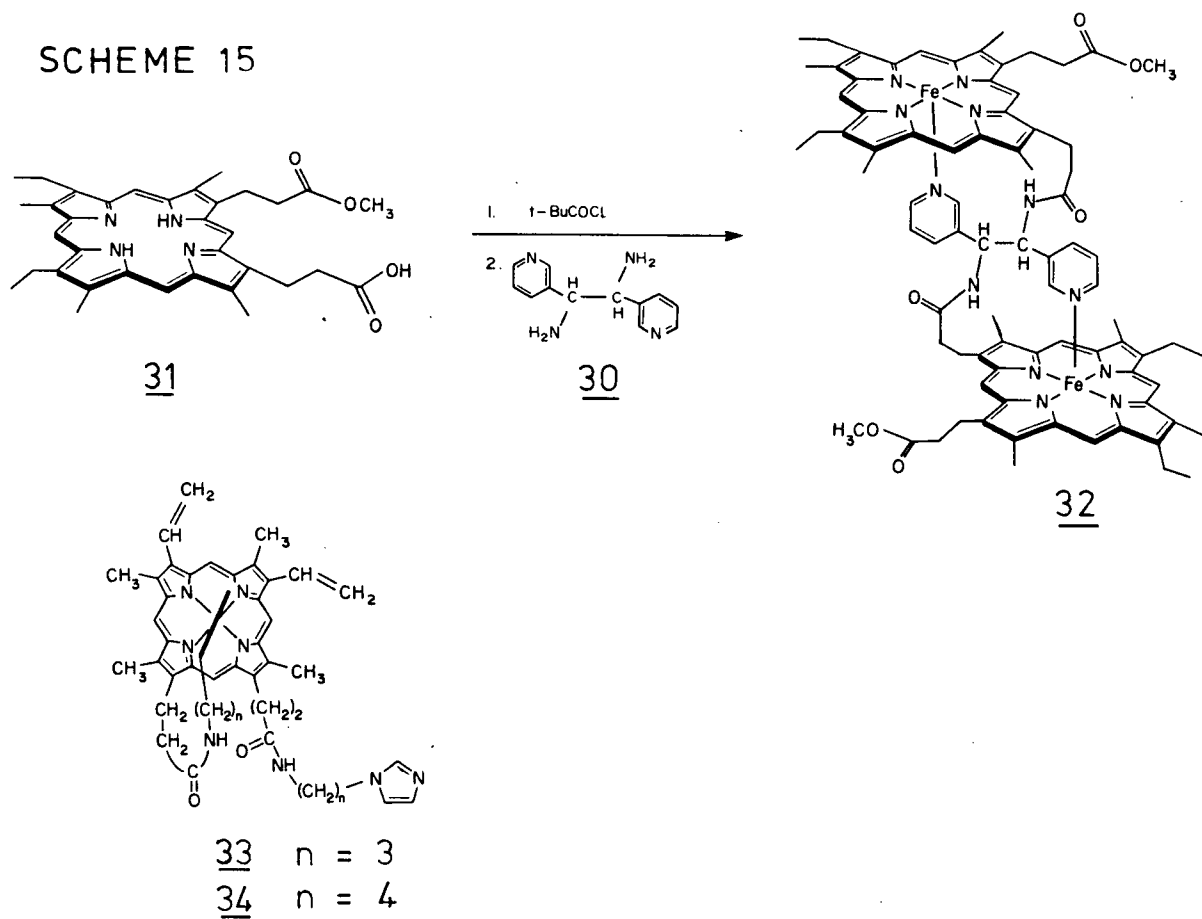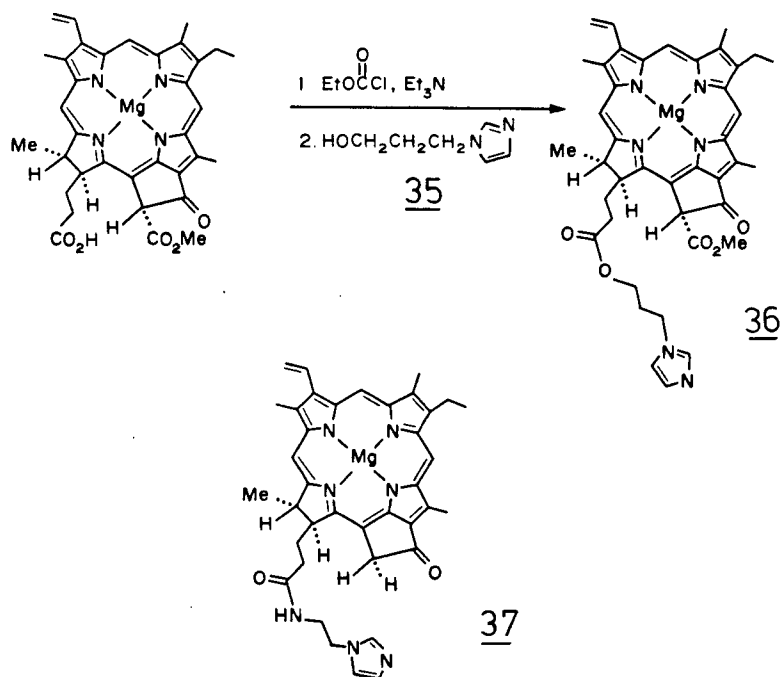
the complex formed when apomyoglobin is reconstituted with chlorophyll derivatives.[53]

Momenteau has synthesized a similar series of chelated heme compounds.[54] In this series the base is attached to the β-pyrrole position of a tetraphenylporphyrin (TPP) ring, via amide or ester linkages (Scheme 17). Vilsmeier formylation of CuTPP 38[55] afforded the monoformyl derivative 39, which was elaborated by a Wittig condensation to yield the acrylate 41 as a mixture of cis and trans isomers. Demetallation, hydrogenation and saponification gave the propionic acid derivative. Treatment of the corresponding acid chloride 42 with 1-(3-aminopropyl)imidazole 43 or 3-(3-hydroxypropyl)pyridine 44 resulted in the appropriate chelated porphyrin (70% and 60% respectively) (Scheme 17). These models were used to study the kinetics of base binding to 4- and 5-coordinated iron(II) TPP,[56] and also to study the transient oxygenation of iron(II) carbonmonoxy TPP after photolytic displacement of CO.[57]

The same TPP-acrylic acid system was used by Eaton et al.[58,59] Treatment of the acid chloride of Cu-TPP acrylic acid 42 with a nitroxyl resulted in the appropriate spin-labelled Cu-TPP derivatives 47 (Scheme 18). The extent of metal-nitroxyl interaction was investigated by EPR by varying the nature of the nitroxyl, the linkage (amide or ester), and the geometry of the complex (cis or trans). A similar study was carried out on a vanadyl porphyrin.[60]

Collman et al.,[61] have prepared chelated TPP compounds where the chain is attached to the ortho position of a meso-phenyl ring. Condensation of o-nitrobenzaldehyde 48, benzaldehyde 49 and pyrrole 50 in hot glacial acetic acid gave a 2% yield of the meso-mono-(o-nitrophenyl)-

SCHEME 17

38

POCl₃

DMF

39 R = CHO
41 R = CH=CH—CO₂C₂H₅ (cis)
(trans)

1. HCl gas
2. H₂ /Pd /C
3. KOH /H₂O
4. (COCl)₂
5. RNH₂

45 B = —NH—(CH₂)₃—N
46 B = —O—(CH₂)₃

SCHEME 18

47

(a) M = Cu, R = N

(b) M = Cu, R = O

(c) M = Cu, R = N

(d) M = Cu, R = OCH₂

triphenylporphyrin 51 after chromatography. Reduction with stannous

chloride produced the mono-o-amino-TPP 52 which was coupled with

various imidazole chains (Scheme 19). Collman merely used these compounds

as substitutes for the less readily accessible "tailed -picket fence"

porphyrins which are discussed in Section 1.4.2. Reed et al.,[62] used

the same chelated TPP compounds to control coordination in a mixed

ligand system. Attempts to prepare models for cytochrome c, which

contains histidine and methionine as the axial ligands, are frustrated

by the greater affinity of heme iron for imidazole rather than thioether.

By covalently attaching the imidazole to the porphyrin ring a stoichio-

metric amount of ligand was provided; addition of thioether then

furnished the mixed six-coordinate system. Reed prepared several

complexes with different tail lengths and various thioethers. For the

C_5 tail with tetrahydrothiophene as the thioether, a crystalline

iron(II) complex, Fe(II)(C_5Im)(TPP)(THT) 54, was obtained and its

crystal structure determined (Scheme 20). Efforts to obtain the corres-

ponding iron(III) complex were defeated by "head-to-tail" dimerization.

A similar chelated TPP compound 55 was used by Walker to study

the effect of axial ligand plane orientation on the ^{1}H-NMR shifts

of the pyrrole protons in iron(III) TPP-bis(imidazole) complexes.[63] In

this case the tail was much shorter to also study the effect of axial

ligand bond strain. In addition Walker and Benson have used mono-

(o-aminophenyl)triphenylporphyrin 52 to prepare a series of derivatives

56a-e containing a pyridine ligand bound to a zinc TPP.[4] ^{1}H-NMR and

visible spectroscopy were used to study the displacement of the 3-

pyridyl ligand by free 3-picoline (Scheme 21).

Ibers[65] used mono-(o-hydroxyphenyl)tritolylporphyrin 57 to

SCHEME 19

(a) R · [imidazole]N—(CH₂)₄—

(b) R · [imidazole]N—(CH₂)₃—

(c) R · [imidazole]N—(CH₂)₃NH—

SCHEME 20

Fe(II)(C₅Im)(TPP)(THT)

54

SCHEME 21

R—COCL →

52

55

B = [imidazolyl]N—CH₂—CH₂—O—C(=O)—N(H)—

↓

56

(a) B = [pyridyl]CH₂C(=O)NH—

(b) B = [pyridyl]CH₂CH₂C(=O)NH—

(c) B = [pyridyl]CH₂CH₂NHC(=O)NH—

(d) B = [pyridyl]CH₂CH₂CH₂OC(=O)NH—

(e) B = [pyridyl]CH₂OC(=O)CH₂CH₂CH₂C(=O)NH—

SCHEME 23

57

1. Br(CH₂)ₙBr **63**

2. [imidazole]
   K₂CO₃ / Et₃N
   DMF

→

65

(a) n = 3
(b) n = 4

SCHEME 22

57

61

62

59

58

(a) n=2
(b) n=3

Br(CH₂)ₙCO₂CH₃

1. KOH
2. (COCl)₂
3.

C—(CH₂)ₙBr
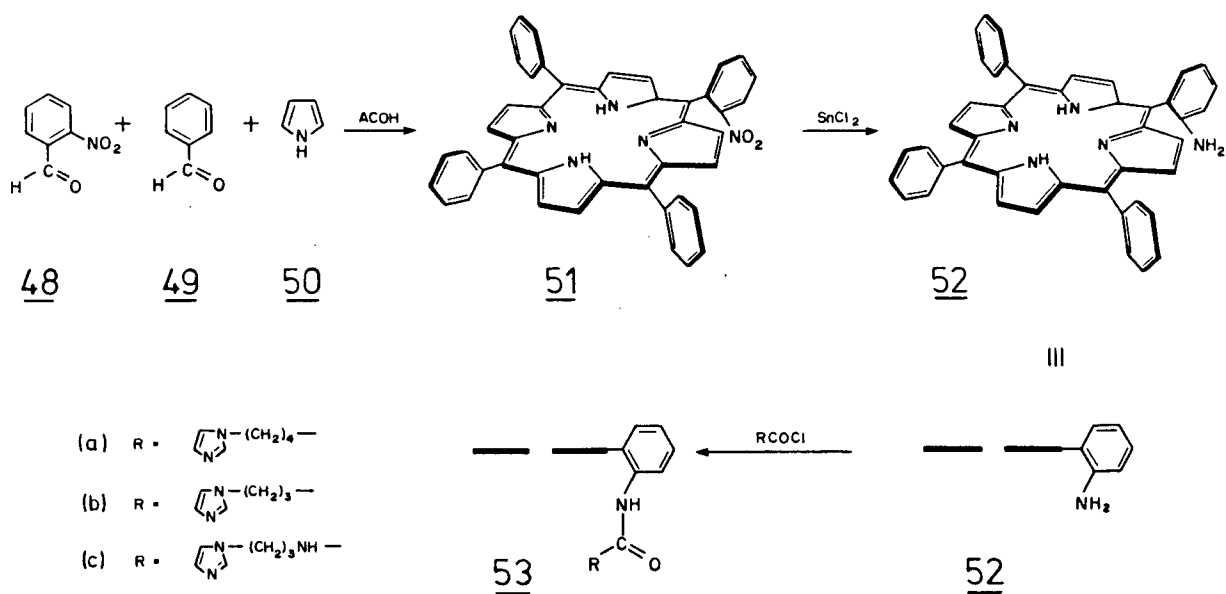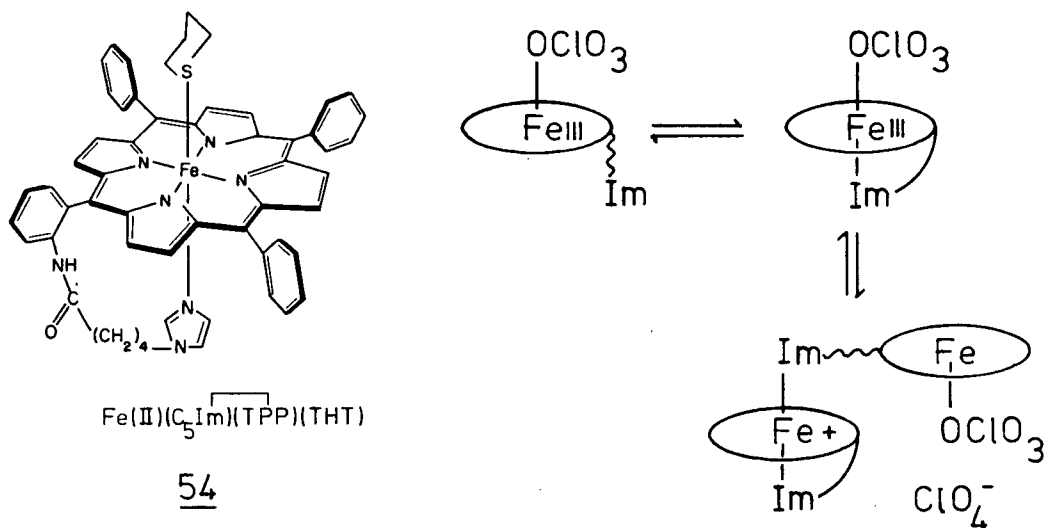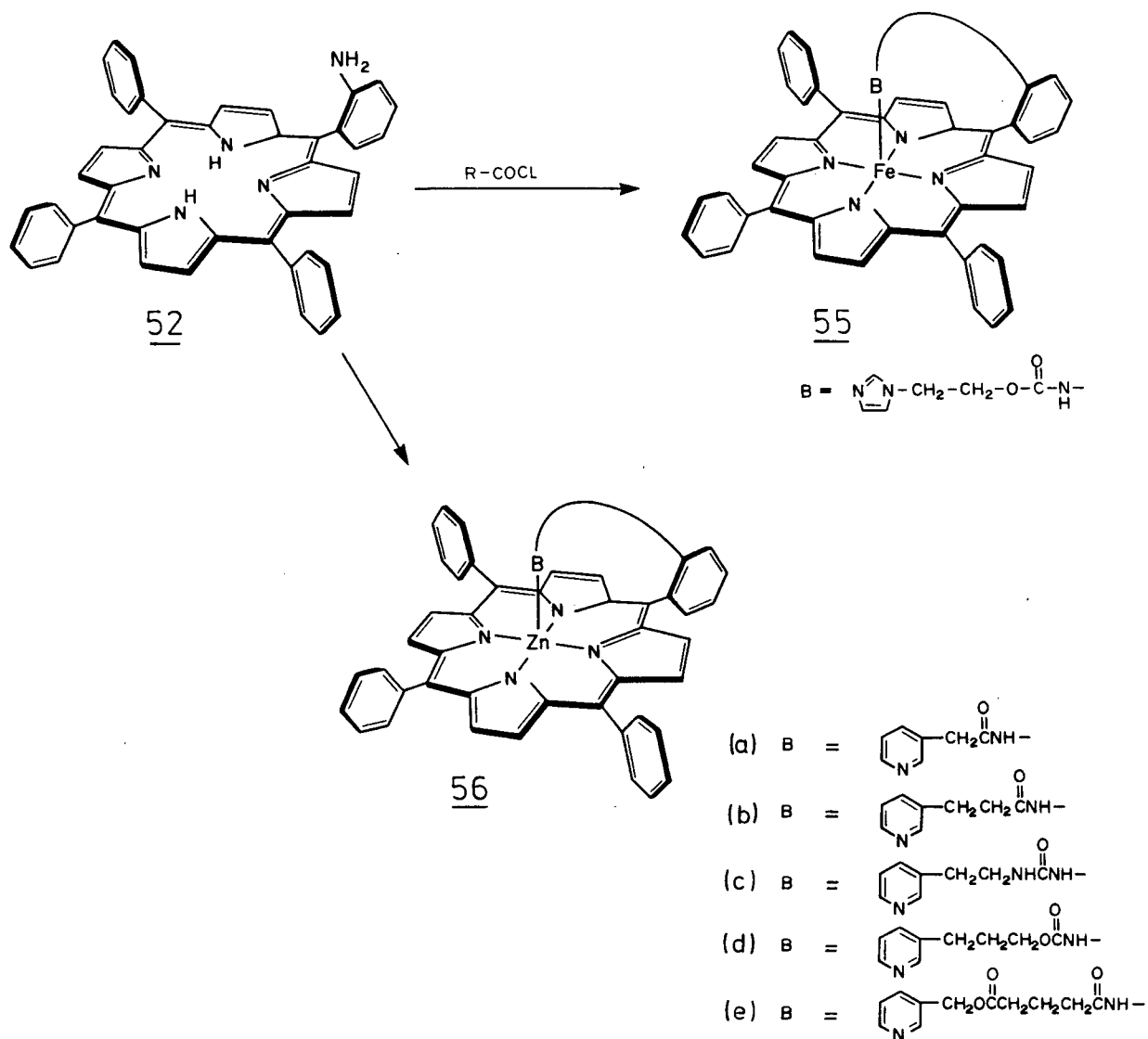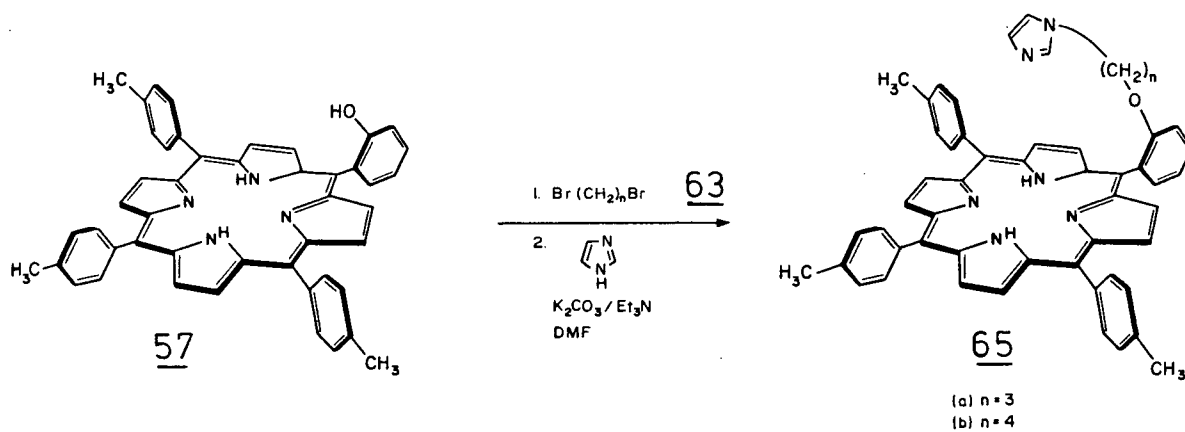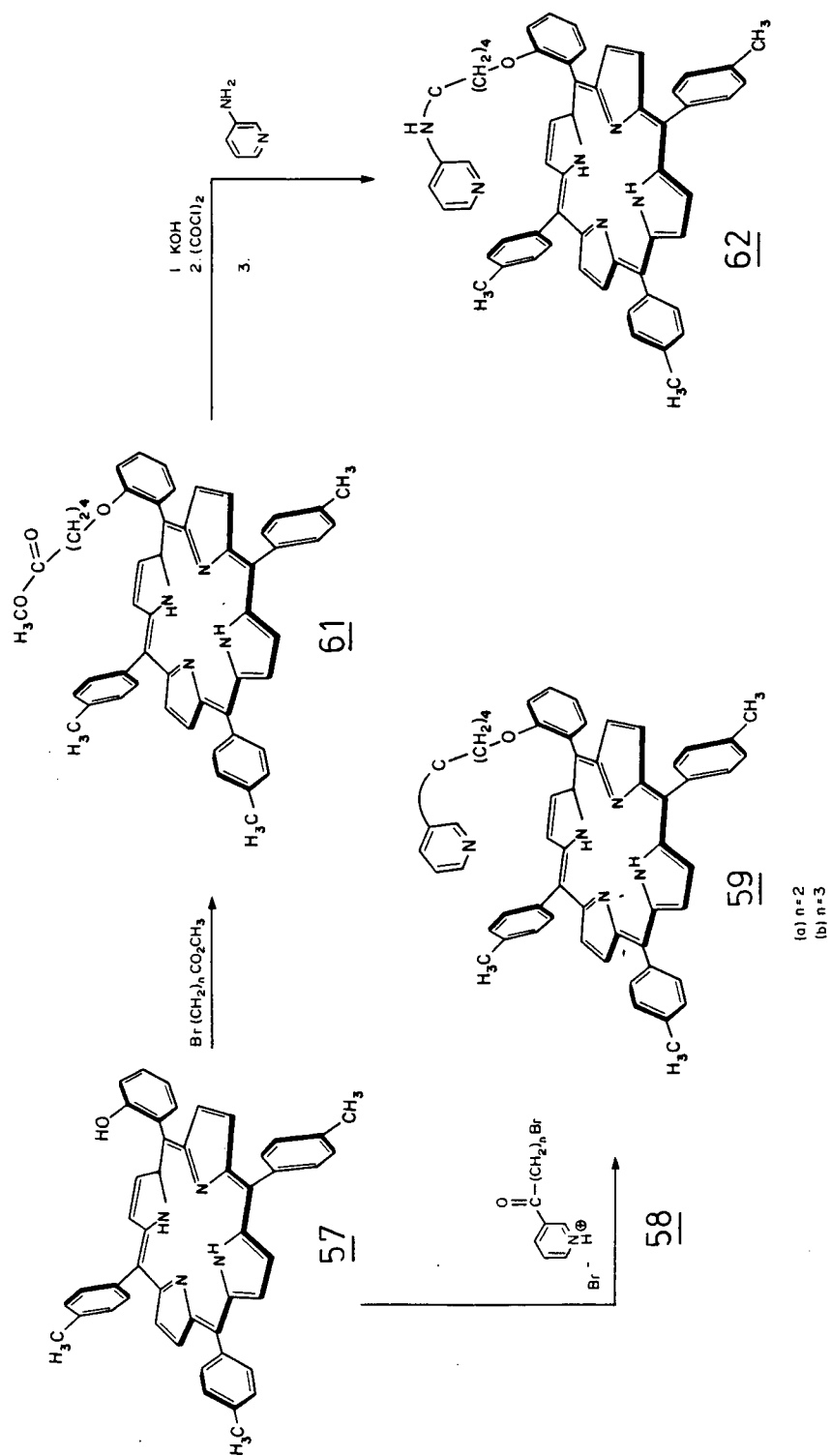
covalently attach a series of pyridine ligands to the porphyrin ring via an ether linkage. Reaction of o-hydroxyphenyl-TTP with 3-(bromo-alkyl) pyridine hydrobromide 58 furnished the chelated porphyrin in 40% yield. The longer chain pyridine compound 62 prepared through the porphyrin butoxy ester 61 was obtained in 27% yield (Scheme 22). The cobalt derivatives reacted reversibly with oxygen at low temperatures (-50°C to -80°C) but the presence of the axial base did not enhance oxygen affinity. Goff used the same synthetic strategy to prepare porphyrins with appended imidazoles.[66] Reaction of o-hydroxyphenyl TTP 57 with a dibromoalkane 63 forms the corresponding ether, which, when allowed to react with imidazole in DMF solvent (using K_2CO_3 or Et_3N), gives the required chelated TTP derivative 65 (Scheme 23). By varying the length of the alkane chain, "tension" may be introduced into the molecule in the form of tilting or elongation of the iron-imidazole bond. This was found to have an effect on the splitting and shift of the pyrrole resonances in the ^{1}H-NMR spectrum.

1.3.2 Porphyrins having Covalently Attached Sulfur Ligands

Because of the poor affinity of iron(II) porphyrins for mercap-tide anion, models of cytochrome P450 have usually consisted of solutions of porphyrins in the presence of large concentrations of excess mercaptide ion. However, Traylor[67] has used the chelated heme approach to covalently attach mercaptide to the porphyrin periphery, making it available for binding to the metal without the necessity of excess external ligand (Scheme 24). Protohemin chloride monodimethyl-

SCHEME 24

III

amide monoacid 66 was coupled to 1-amino-3-mercaptopropane benzoyl

ester 67. Addition of sodium hydride and warming removed the benzoyl

group and addition of CO resulted in formation of the carbonmonoxy-

mercaptide complex 70. A similar compound 71, containing two masked

mercaptides was also prepared and deprotected to give the analogous

CO complex 72. Protection of the mercaptide as the benzoylthio

derivative before reduction of Fe(III) was necessary because of the

reducing ability of mercaptans.

$$2\ Fe(III)\ +\ 2\ RSH\ \rightleftharpoons\ 2\ Fe(II)\ +\ RSSR\ +\ 2\,H^+ \tag{18}$$
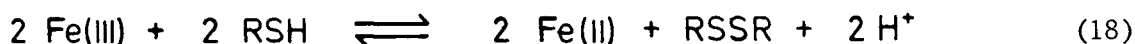
Alternatively protohemin was coupled with bis(3-aminopropyl)-

disulfide 73. The resultant disulfide 74 was treated with sodium

dithionite, the iron being reduced more quickly than the disulfide.

Addition of CO then furnished the carbonmonoxy complex 72.

^{1}H-NMR of the CO complexes indicated that the sulfide underwent

intramolecular binding without appreciable dimer formation.

$$\tag{19}$$
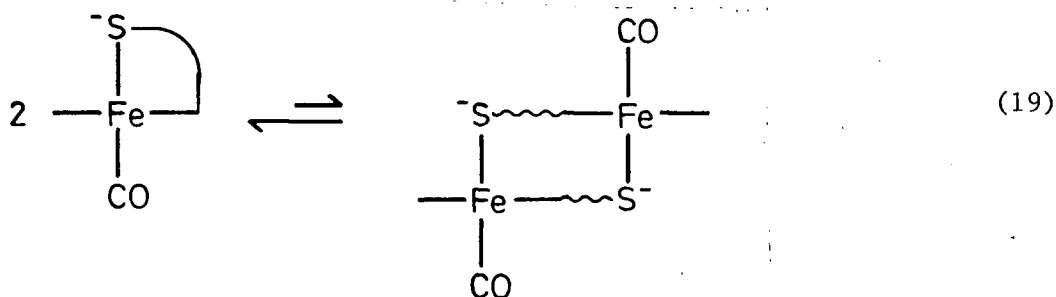
UV/visible spectroscopy in DMSO solution or aqueous suspension showed

a split Soret (384/460 or 363/446 nm) which was similar to the spectrum

of cytochrome P450-CO.

A series of alkyl and aryl "mercaptan-tail" porphyrins has been

prepared by Collman and Groh (Scheme 25).[67] The C_6 alkyl chain may be

SCHEME 25

prepared directly by treating mono-(o-aminophenyl)triphenylporphyrin 52

with S-acetyl- or S-tritylthiohexanoyl chloride 75. Since the S-

protected pentanoic acid derivatives were more difficult to obtain, the

bromoalkyl chain was first attached to the porphyrin and the thio

group introduced by treatment with either TrS^-K^+ or AcS^-K^+. Deacetylation

(MeOH/NH$_3$) or detritylation (Hg(II)/H$_2$S) gave the free thiol. However,

after iron insertion, visible spectra indicated that the alkyl chain

was too flexible to hold mercaptan at the metal site; the spectra, in

toluene, were similar to those of square planar four coordinate iron(II)

species. The introduction of CO does lead to the formation of six-

coordinate low-spin Fe(II)-CO complexes.

$$(20)$$
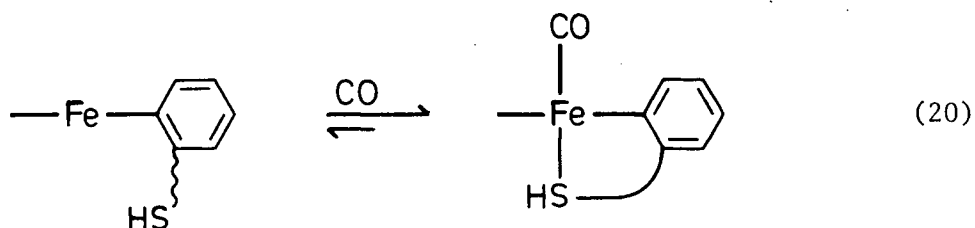
To ensure more rigidity, tails derived from ω-mercaptobenzoic

acid 78 or (m-mercaptophenyl)acetic acid 81 were attached to the

aminoporphyrin. In this case the potential thiol was introduced as the

disulfide which was subsequently cleaved with sodium borohydride to

give the free aryl "mercaptan-tail" porphyrins 82, 83. As in the

alkyl case, the aryl iron(II) species did not show five-coordination.

Furthermore addition of CO gave mixtures of five- and six-coordinate

species, depending on the nature of the mercaptan and the temperature,

suggesting a tail-off/tail-on equilibrium.

Deprotonation of the mercaptan to give the mercaptide was

attempted. The extent of mercaptide formation depended both on the

$$\text{CO}^- \quad | \quad -\text{Fe} - \langle\text{C}_6\text{H}_4\rangle \quad | \quad \text{HS} - \text{CH}_2 \quad \rightleftharpoons \quad \text{CO} \quad | \quad -\text{Fe} - \langle\text{C}_6\text{H}_4\rangle \quad \text{HS}$$

(21)
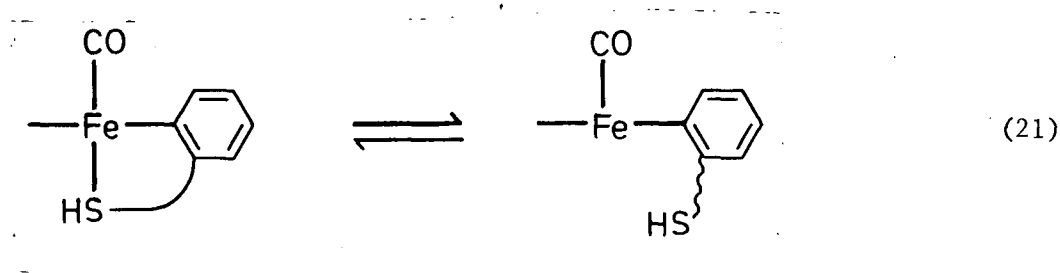
nature of the base and of the tail. Indeed, for most tails only incomplete deprotonation occurred. However for the (m-mercaptophenyl)-acetamide tail system 84, deprotonation to the mercaptide was clean and complete using acetanilide anion as base. In the presence of CO this system gave a six-coordinate iron(II)-mercaptide-CO complex 85 whose visible spectrum exhibited a split Soret absorption at 450 and 380 nm, typical of cytochrome P450.

In section 1.3.1 we referred to Reed's synthesis of Fe(II)-(C_5Im)(TPP)(THT) 54 as a model for cytochrome c.[62] Buckingham and Rauchfuss adopted the alternative strategy of attaching the thioether ligand to the porphyrin periphery.[69] Reaction of (o-aminophenyl)tri-phenylporphyrin 52 with the corresponding anhydrides 86 afforded the tailed porphyrins 87, containing thioether, sulfoxide, or sulfone groups in 60-90% (Scheme 26). After iron insertion and reduction, spectro-photometric titration with base allowed the following ordering of ligand affinities: $R_2SO > R_2S > R_2SO_2$. The easy displacement of sulfide by pyridine or imidazole precluded this system as an effective model for cytochrome c.

Smith and Bisset have also used the chelated heme approach to synthesize a potential P450 model,[70] but in this case the substituents were attached to the meso position of an octalkylporphyrin. A meso-acetoxymethyl substituent is susceptible to nucleophilic displacement

SCHEME 26

52

+

$\left[R(CH_2)_4CO \right]_2 O$

86

$\longrightarrow$

87

(a) R = -SCH_3

(b) R = -$\overset{\displaystyle O}{\underset{}{S}}$CH_3

(c) R = -$\overset{\displaystyle O}{\underset{\displaystyle O}{S}}$CH_3

1. FeX_2
2. Na_2S_2O_4
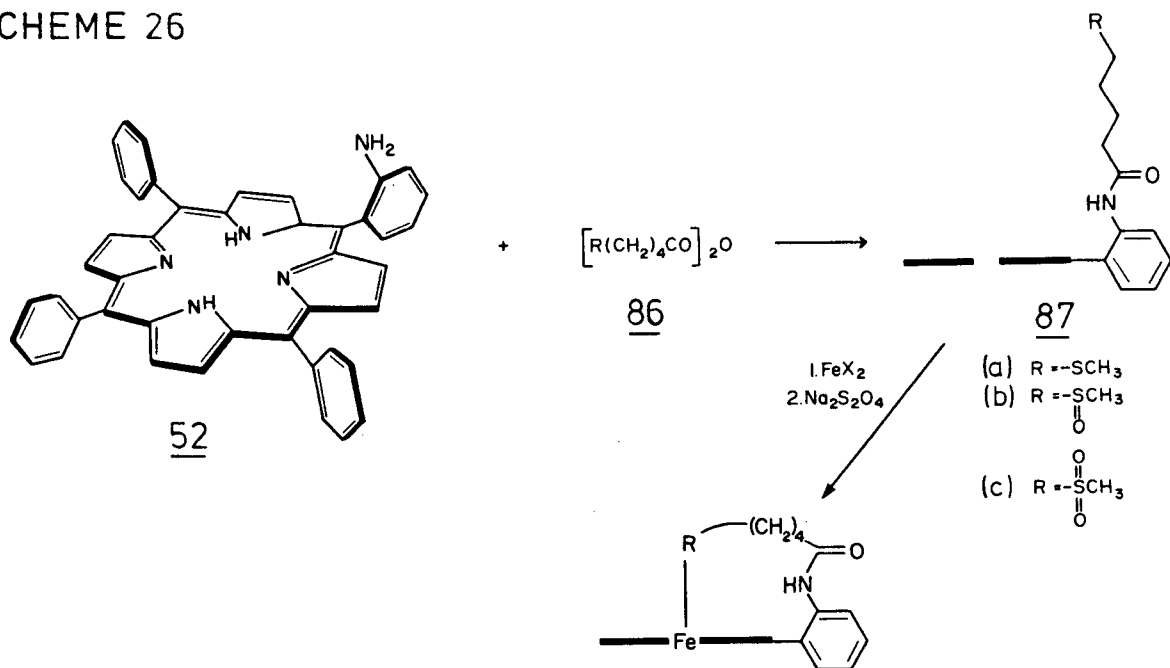
SCHEME 27

at the "benzylic" carbon atom leading to the ready introduction of suitably functionalized chains. Heating the acetoxymethylporphyrin 88 in a melt with 1,6-hexanediol gave the ether 89 with no sign of dimer formation (Scheme 27). Conversion to the bromide followed by refluxing with thiourea afforded the thiouronium salt, the hydrolysis of which was accompanied by oxidation to give the disulfide 91. Unfortunately, attempts to generate the characteristic $RS^--Fe(II)-CO$ spectrum from the iron(III)-disulfide complex were unsuccessful. Alternatively, treatment of acetoxymethylporphyrins with dithiols yielded only the meso-porphyrins. Treatment of meso-acetoxymethyl octaethylporphyrin with excess 1-(3-aminopropyl)imidazole 20 in refluxing tetrahydrofuran containing a suspension of sodium hydride provided the meso-chelated imidazole porphyrin 93, a potential model for T-state hemoglobin.

The success of the chelated heme approach to model heme proteins is due to its ability to control the coordination of a metalloporphyrin. For poorly binding ligands e.g. mercaptide, thioether, covalent attachment to the porphyrin increases the local concentration and enhances binding without the need of excess external ligand. In the case of strongly binding ligands e.g. imidazole, pyridine, chelation can be used to dampen the binding ability. Addition of one equivalent of base to an iron porphyrin results in a mixture of four- and six-coordinate species, since $K_2 > K_1$ in equation 22.

$$—Fe— \; + \; B \; \underset{\longleftarrow}{\overset{K_1}{\rightleftharpoons}} \; \overset{\overset{B}{|}}{—Fe—} \; + \; B \; \underset{\longleftarrow}{\overset{K_2}{\rightleftharpoons}} \; \overset{\overset{B}{|}}{\underset{\underset{B}{|}}{—Fe—}} \tag{22}$$
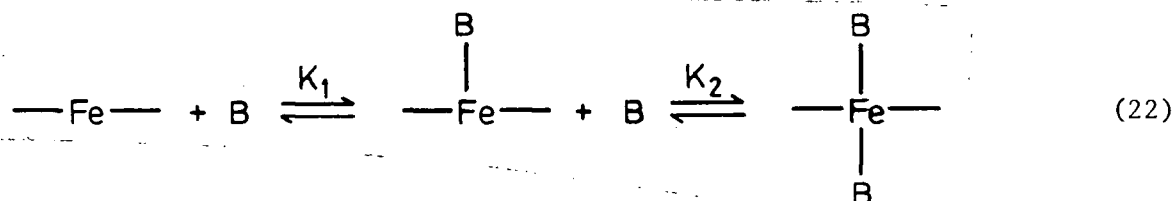
However covalent attachment of the base to the porphyrin provides a stoichiometric equivalent of base which will bind intramolecularly to give the desired five-coordinate species, provided dimerization is not significant.

$$\begin{array}{c} B \\ | \\ | \\ -Fe- \end{array} \rightleftharpoons -Fe\!\!-\!\!\sim\!\!\sim\!\! B \rightleftharpoons \begin{array}{c} B\!\!\sim\!\!\sim\!\!-Fe- \\ | \\ -Fe- \\ | \\ B \end{array} \qquad (23)$$
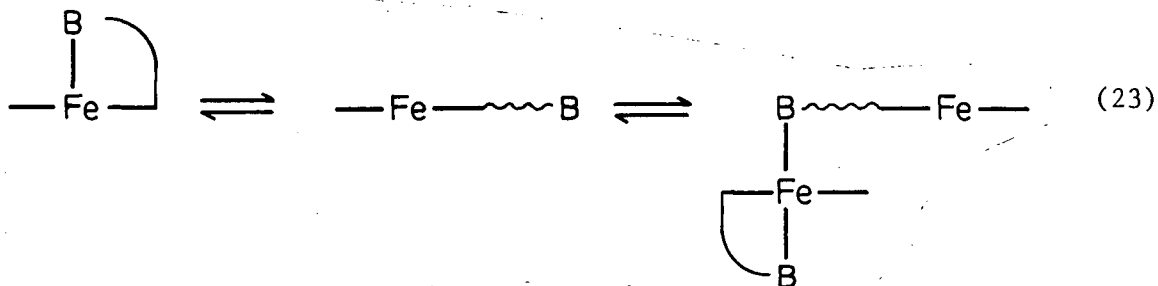
Addition of a second ligand then gives the mixed ligand complex. As models for hemoglobin or myoglobin the chelated hemes of Traylor were found to bind oxygen reversibly in solution at low temperature (-40°C) and the kinetics of oxygen binding at room temperature could be measured. However the oxygen complexes were not stable at room temperature, irreversible oxidation to the μ-oxo dimer occurring.

In an attempt to prepare stable oxygen-binding complexes it was realized that steric hindrance about one face of the porphyrin might prevent irreversible oxidation. If a base bound to the open face and oxygen bound at the sterically hindered face, close approach of two porphyrin rings would be discouraged, preventing μ-oxo dimer formation.

$$B\!\!-\!\!Fe \rightleftharpoons B\!\!-\!\!Fe\!\!-\!\!O_2 \not\longrightarrow B\!\!-\!\!Fe\!\!-\!\!O_2 \quad Fe\!\!-\!\!B \qquad (24)$$
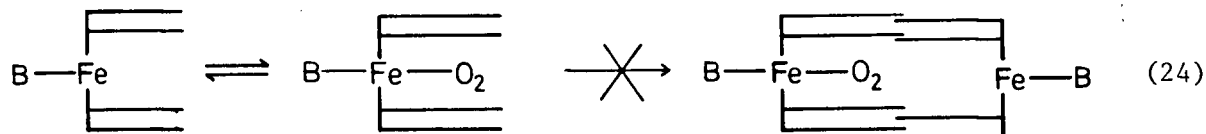
Such an approach has been followed by many groups to produce an array of different model porphyrins e.g. picket-fence, capped, cyclophane, crowned,

strapped, basket-handle etc.

SCHEME 28
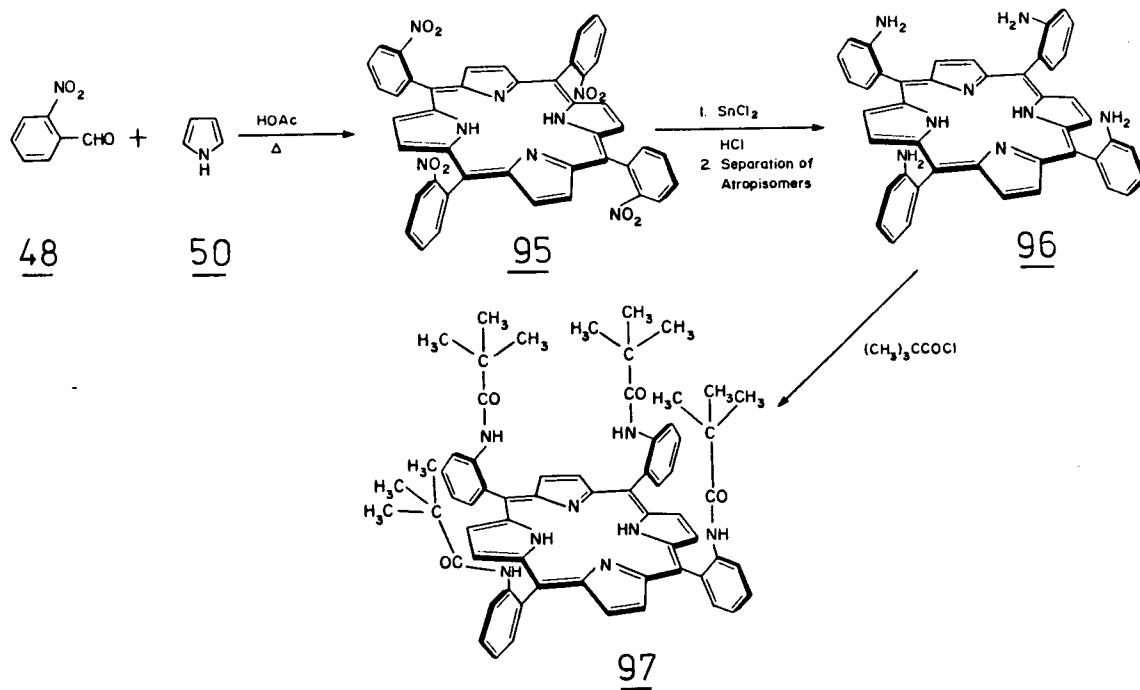
SCHEME 29
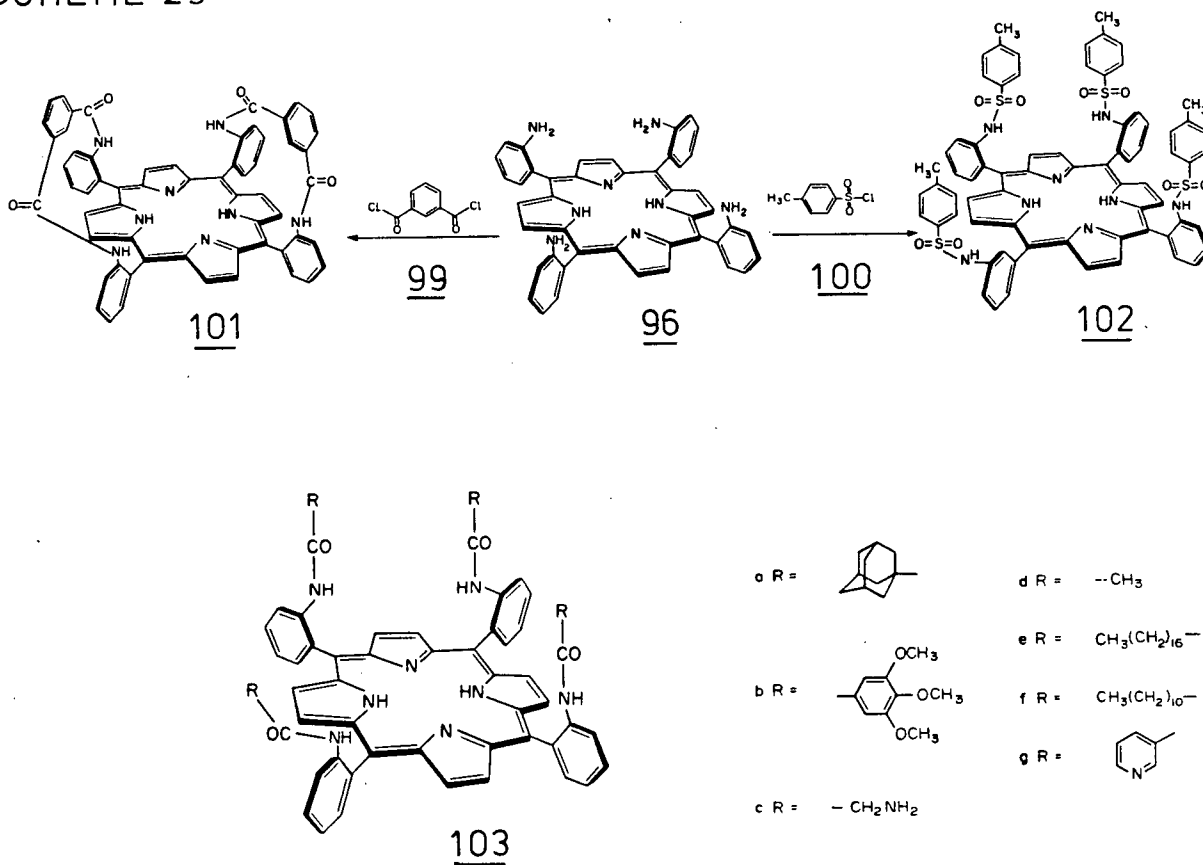
1.4   "PICKET-FENCE" PORPHYRINS

1.4.1   "Picket-Fence" Porphyrins

Perhaps the most successful of the heme protein active site models

is the "picket-fence" porphyrins of Collman. Steric encumbrance about

the metal site of these substituted TPP molecules depends on two factors:

(i)   due to steric repulsion, the TPP will adopt a conformation in

       which the four meso phenyl rings are almost perpendicular to the

       porphyrin ring; substituents at the ortho positions of the phenyl

       rings will lie above and below the porphyrin plane , and

(ii)   for TPP molecules containing mono-ortho-substituted phenyl rings,

       separation and, depending on the bulk of the substituent, inter-

       conversion of the four possible atropisomers may be achieved.

Collman reasoned that synthesis of a substituted iron(II)TPP

having four pivalamido groups located on the same side of the porphyrin

ring would give a "protected pocket". Ligands e.g. imidazole, could

bind to the metal on the unencumbered face but could not penetrate

the pocket, thereby ensuring five-coordination even in the presence of

excess ligand. The much smaller dioxygen molecule would not be sterically

retarded and a six-coordinate complex could form. This oxygenated

complex should be stable since the bulky pivalamido groups would prevent

irreversible oxidation through close approach of two porphyrins to

form a μ-peroxo dimer.

Condensation of pyrrole 50 and four equivalents of ᴏ-nitrobenz-...

aldehyde 48 in acetic acid gave meso-tetra(o-nitrophenyl)porphyrin 95

(25)
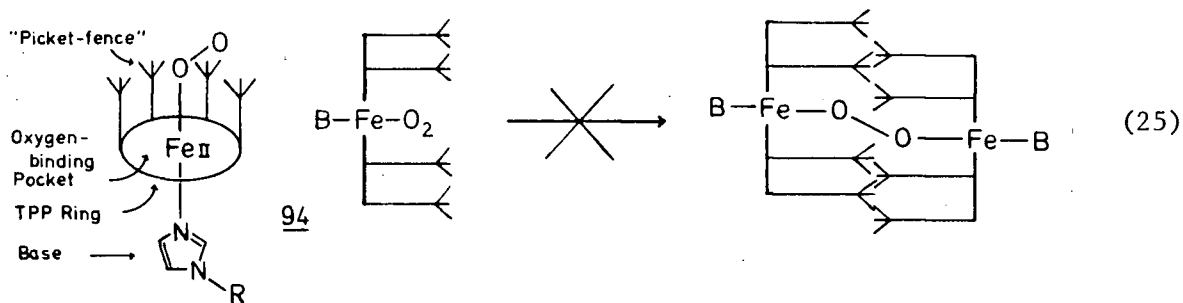
which was reduced by stannous chloride to the meso-tetra (o-aminophenyl)-porphyrin (Scheme 28).[71,72] The four atropisomers ($\alpha\alpha\alpha\alpha$, $\alpha\alpha\alpha\beta$, $2\alpha\alpha\beta\beta$) were separated by chromatography, the slowest moving of which was the desired $\alpha\alpha\alpha\alpha$ isomer 96. Interconversion of the atropisomers was sufficiently slow at room temperature to afford clean separation. Then refluxing the unwanted products in toluene for 20 minutes effected re-equilibration to the statistical mixture allowing further isolation of the $\alpha\alpha\alpha\alpha$ isomer. Reaction of the amino groups with pivaloyl chloride gave the "picket-fence" porphyrin $\alpha,\alpha,\alpha,\alpha$-H$_2$TpivPP 97, in which the configuration is frozen by the bulky substituents, (equilibration required several hours in boiling xylene). Treatment with FeBr$_2$, followed by reduction with Cr(acac)$_2$ gave the Fe(II)($\alpha,\alpha,\alpha,\alpha$,-TpivPP).

Although addition of strong field ligands gave low spin six-coordinate complexes, FeB$_2$($\alpha,\alpha,\alpha,\alpha$-TpivPP), it was suspected that the binding constant of the base on the "picket-fence" side was less than that on the "open" side. A series of six-coordinate compounds were prepared (B = Im, 1-MeIm, 1-n-BuIm, 1-tritylIm, 4-t-BuIm, 1,2-Me$_2$Im, pyridine, piperidine, tetrahydrothiophene, tetrahydrofuran).[72] All of these showed reversible oxygen binding behaviour in benzene solution at 25°C, without appreciable amounts of decomposition. Indeed the

oxygen complexes, Fe(TpivPP)(N-RIm)(O$_2$) were stable for long periods (t$_{1/2}$ 2-3 months) in solution provided 2-4 equivalents of axial base were present to protect the unshielded face. Furthermore, analytically pure,

(26)
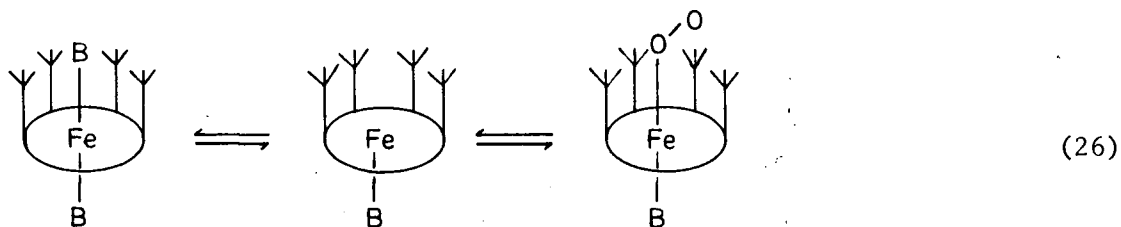
crystalline dioxygen complexes could be obtained.[72] The crystal structures of Fe(II)(TpivPP)(1-MeIm)(O$_2$) 98a,[72,73] Fe(II)(TpivPP)-(2-MeIm)·EtOH and its dioxygen adduct[74] have been determined. Further

a B = 1-MeIm
b B = 1-BuIm
c B = THF
d B = THT

98
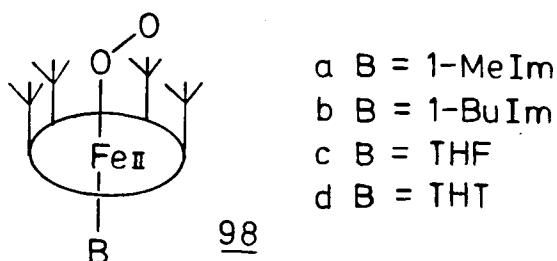
structural information was obtained by I.R.,[73,75-76] and Mossbauer spectroscopy and magnetic susceptibility measurements.[68,73]

Binding of a second base on the "picket-fence" side of the porphyrin prevented determination of oxygen binding to the five-coordinate heme in solution. However, crystals of Fe(II)(TpivPP)(1-MeIM)-(O$_2$) could be deoxygenated under vacuum to give the five-coordinate species which could be re-oxygenated. This cycling between O$_2$ and vacuum produced no observable irreversible oxidation over many cycles.[78] Similar reversible oxygenation was demonstrated by solid samples of Fe(TpivPP)B (B = 2-MeIm, 1,2-MeIm). From the Hill plot (log Y/1-Y vs.

$\log P_{O_2}$) it was observed that solid state oxygen binding for these two compounds showed two regions of non-cooperative binding (at high and low O_2 pressures) and an intermediate region of cooperative binding. Collman rationalized this in terms of a shrinking of the molecules' dimensions on oxygenation as the iron and its bound imidazole move towards the porphyrin ring. As increasing numbers of molecules in the solid oxygenate this change in molecular dimensions presumably induces sufficient strain in the crystallite to induce a conformational change in the solid which enhances the oxygen affinity of the remaining deoxy sites. This behaviour is reminiscent of the cooperative oxygen binding of hemoglobin.

Various other sterically hindered TPP derivatives have been prepared by the condensation of meso-$\alpha, \alpha, \alpha, \alpha$-tetra(o-aminophenyl)-porphyrin 96 and bulky acid chlorides. Collman has also prepared the compounds, $H_2T_{Phth}PP$ 101 and $H_2 T_{Tos}PP$ 102, by reaction of $H_2T_{Am}PP$ 96 with iso-phthaloyl dichloride 99 and p-toluenesulfonyl chloride 100 respectively (Scheme 29). Despite the bulky "picket-fence", the ferrous complexes of both compounds exhibited only irreversible oxidation on exposure to oxygen at 25 °C. This was attributed to the acidic amide protons which were presumably directed into the cavity, allowing protonation of the coordinated dioxygen and consequent heme oxidation.[72] A similar series of TPP derivatives 103a-g have been synthesized under identical conditions by Bogatskii et al.[79,80]

Ortho-substituted TPP derivatives have been used as binuclear ligand systems by choosing suitable substituents on the phenyl rings. For example, treatment of $H_2T_{Am}PP$ 96 with maleic anhydride gave the tetra(o-maleamoylphenyl)porphyrin 104 in 90% yield (Scheme 30). In

SCHEME 30

104

SCHEME 31

96

105

106

7^{2+}

$(ClO_4)_2$

K_1 fast

$+ Cu^{2+}$

CH_2Cl_2/pyr

$Cu(ClO_4)_2$ MeOH

(i) $FeSO_4/HOAc/O_2$
(ii) NaOH
(iii) HCl
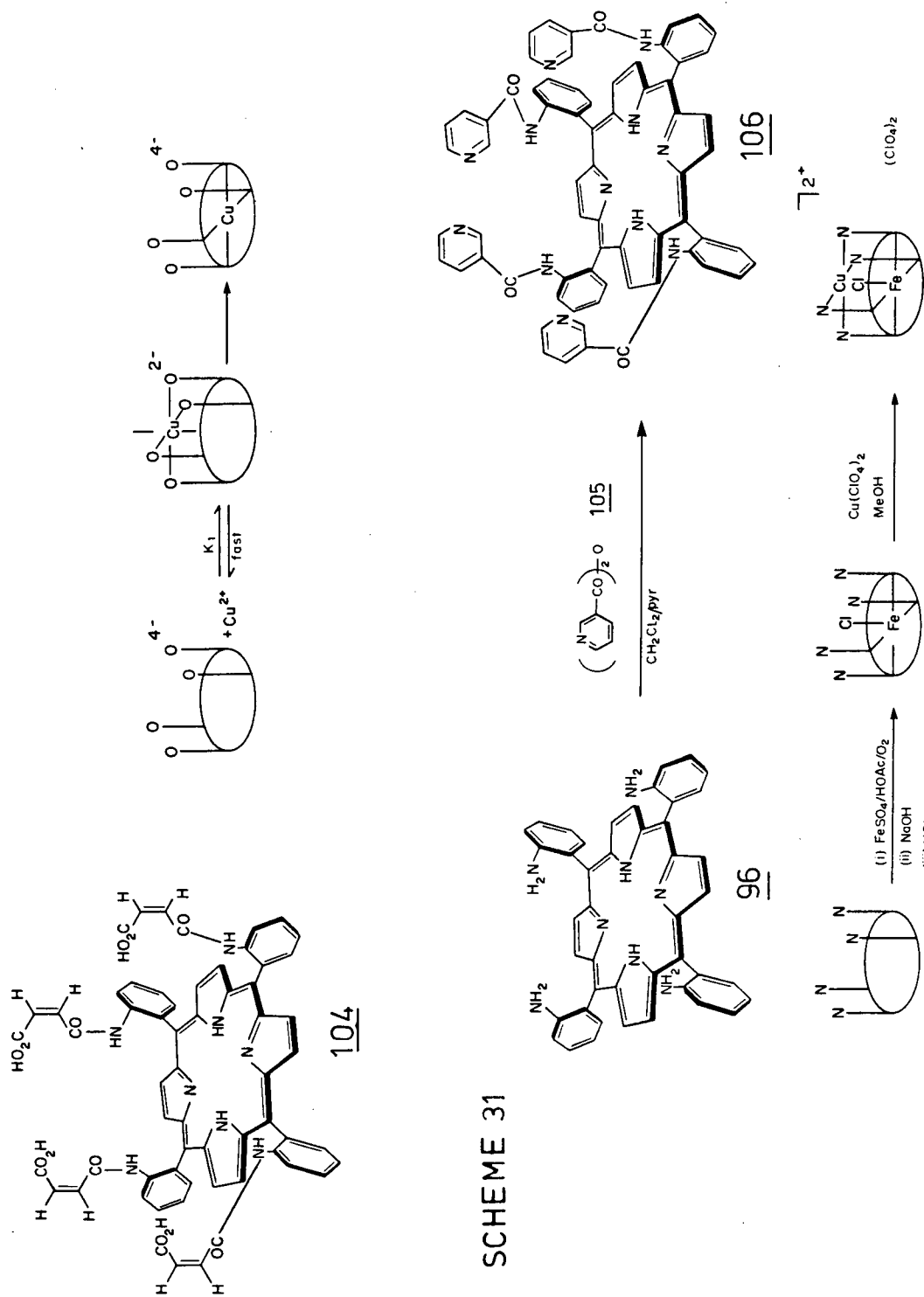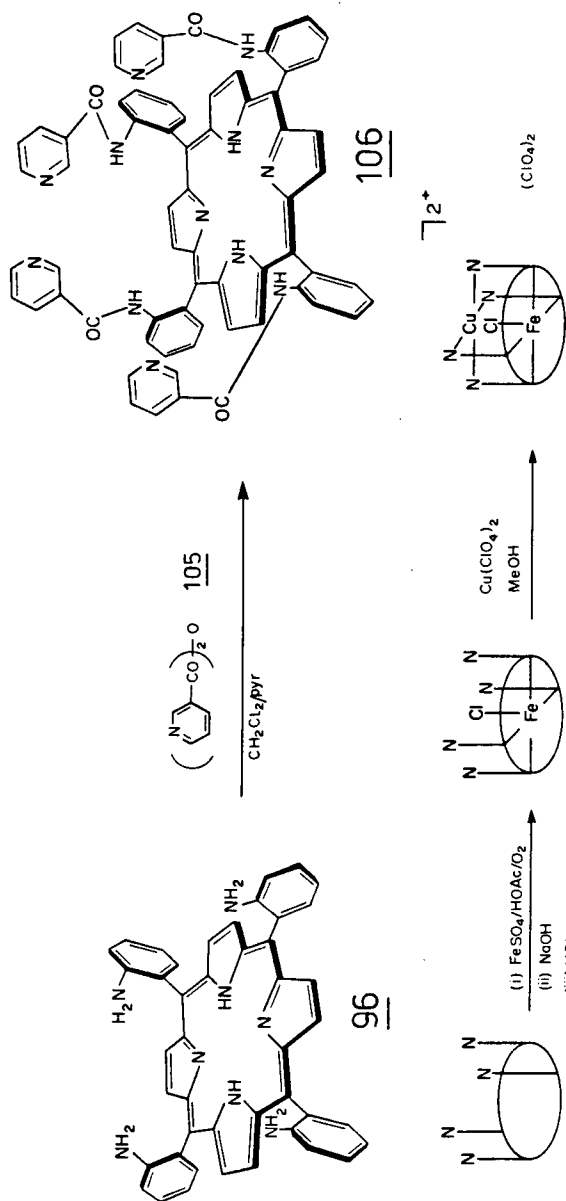
aqueous DMF this porphyrin undergoes copper insertion at a rate much faster than for unsubstituted porphyrins. Rapid complexation of the copper by the carboxylates holds the metal ion in a position favourable for rapid intramolecular transfer to the porphyrin nucleus.[81]

Binuclear porphyrins capable of binding iron and copper have been investigated as synthetic models for the iron/copper site of cytochrome oxidase. One such model 106 consists of a tetraphenylporphyrin ring with a covalently attached tetrapyridine ligand system, obtained by treating $\alpha, \alpha, \alpha, \alpha$-$H_2T_{Am}PP$ 96 with excess nicotinic anhydride 105 (Scheme 31).[82] The mixed metal compound with iron inserted into the porphyrin ring and copper coordinated to the four nicotinamide groups was prepared, and the ESR and magnetic susceptibility of the complex examined.[83] In contrast, Elliott and Krebs claim that the conditions necessary for metal insertion into this complex cause isomerization of the nicotinamide groups.[84] Instead, these authors have coordinated Ru(II) to the nicotin- amide groups, which locks the "pickets" into place allowing more forcing conditions to be used for the introduction of divalent and trivalent first-row transition metals into the porphyrin ring, without fear of isomerization.

Iron porphyrin catalysis of epoxidation and hydroxylation using iodosylarenes as oxidants is believed to proceed via a reactive iron-oxo intermediate. Groves has attempted the catalytic asymmetric epoxidation of olefins using suitably substituted chiral "picket-fence" porphyrins to control the stereochemistry of approach of the substrate olefin to the iron-oxo species.[85] The chiral porphyrins were prepared by stirring $\alpha, \beta, \alpha, \beta$-$H_2T_{Am}PP$ 107 with an optically active acid chloride (Scheme 32). With a (R)-2-phenylpropanamido group as the chiral appendage the

po.

SCHEME 32

(a) R* =

(b) R* =
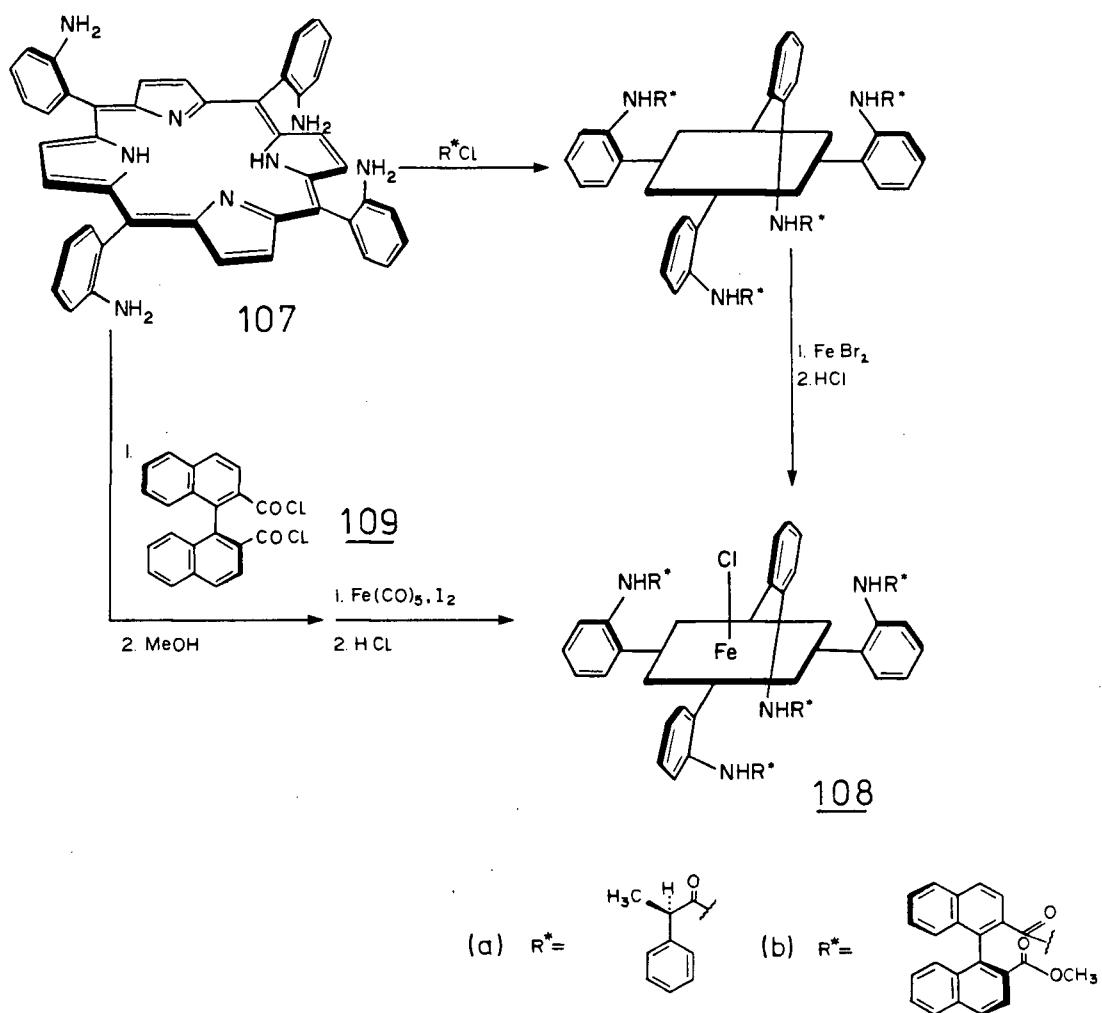
porphyrin 108a was formed in high yield (95%). However, in the epoxidation of various olefins with iodosylbenzene very little selectivity was obtained (%ee, 9-31%). Instead the binaphthyl group was chosen as an appendage which could form a large and relatively rigid chiral cavity about the porphyrin core. The diacid chloride of 1,1'-binaphthyl-2,2'-dicarboxylic acid 109 was reacted with $\alpha,\beta,\alpha,\beta-H_2T_{Am}PP$ 107, followed by methanolysis and iron insertion. This catalyst was more successful and enantiomeric excesses of 20-50% were observed for variously substituted styrenes and aliphatic olefins.

1.4.2 "Tailed Picket-Fence" Porphyrins

While the direct oxygenation of five-coordinate Fe(II) "picket-fence" was observable in the solid state, such studies in solution were not possible since the "picket-fence" could not prevent six-coordination in the presence of excess sterically unhindered base. (Excess base is necessary to ensure complete coordination on the "open" face and prevent μ-oxo dimer formation). To control coordination, Collman et al., adopted the "chelated heme" approach. Dispensing with external ligand, the base was covalently attached to the ortho-phenyl position of TPP, and so constrained into a position promoting intramolecular binding to the porphyrin metal. The other three meso-phenyl rings carry the "pickets" necessary to prevent irreversible oxidation.

Treating $\alpha,\alpha,\alpha,\alpha-T_{Am}PP$ 96 with 3.2 equivalents of pivaloyl chloride gave the "3-picket" α-aminophenylporphyrin 110 (35%) (Scheme 33). Refluxing in benzene solution for 2 hours equilibrated the free

SCHEME 33
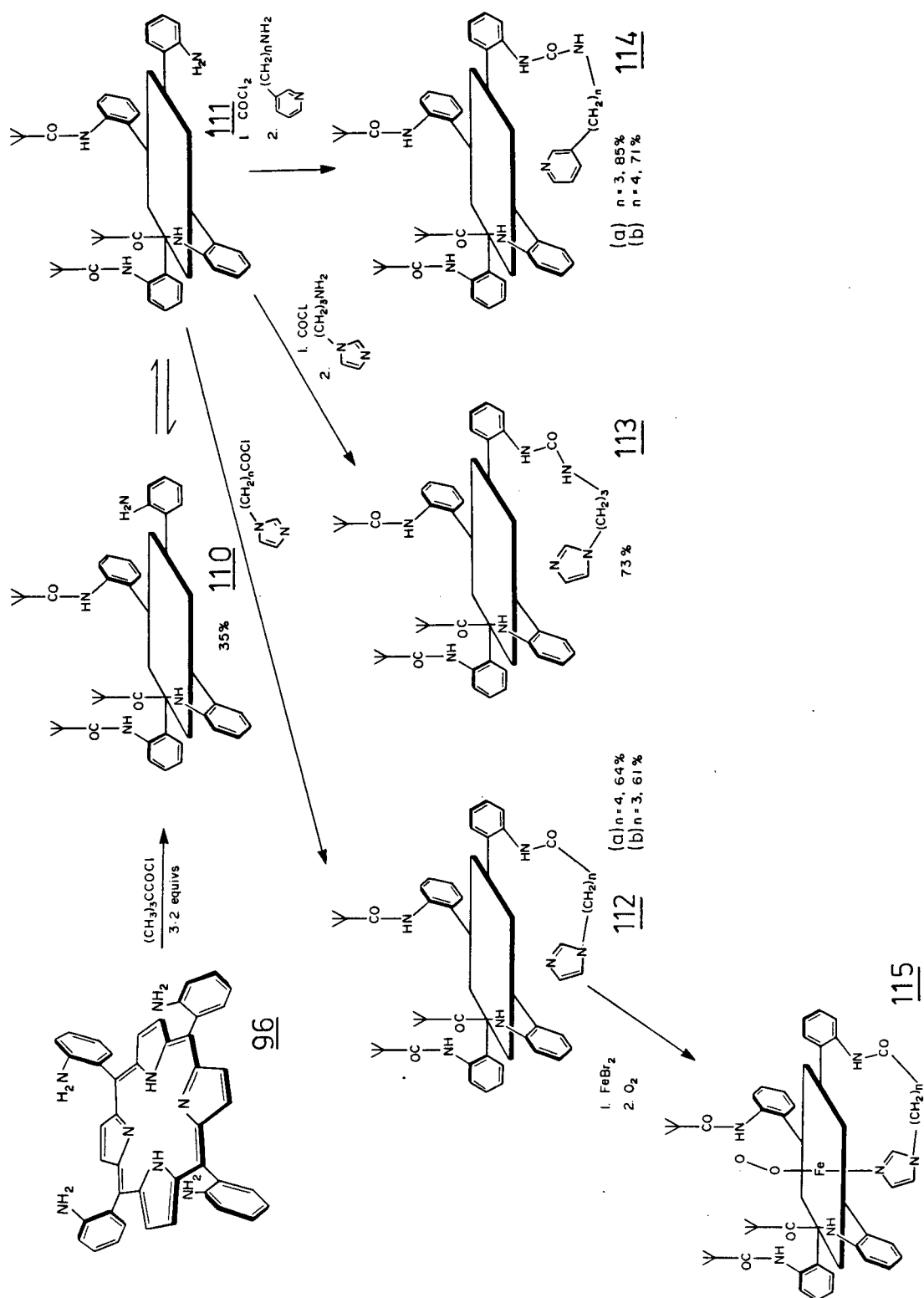
aminophenyl group to a 1:1 mixture of the α and β atropisomers 110, 111

which were separated by chromatography. (The unwanted α- isomer could

be re-equilibrated to increase the yield of the β- product). Using

amide or urea linkages an imidazole was attached to the β-amino porphyrin

by chains of varying length. Direct metal insertion using anhydrous

$FeBr_2$ gave nearly quantitative yields of the five-coordinate iron(II)

"tail picket-fence" porphyrin.[61] ^{1}H-NMR spectra confirmed the proposed

five-coordinate high spin (S = 2) iron(II) formulation, but on decreasing

the temperature (-25°C) peaks due to a diamagnetic (S = 0) complex were

observed, presumably due to a dimerization process. (Momenteau, but not

Traylor, had observed such dimerization in the chelated heme systems).

$$(27)$$
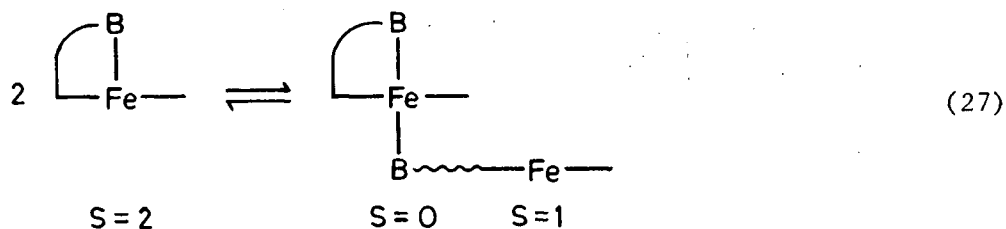
Addition of oxygen to solutions of the high spin five-coordinate

iron(II) compounds gave the expected diamagnetic spectra for the

oxygenated species 115. The peak pattern for the "pickets" suggests

that the oxygen may be ordered in these complexes, presumably towards

the open side of the pocket, a claim which is awaiting confirmation by

X-ray crystallography.

A similar series of "tail picket-fence" porphyrins 114 has been

synthesized with a pyridine covalently attached to the porphyrin periphery

via urea linkages.[86] O_2 and CO binding to both series of porphyrins

has been carried out.[61,86-88]

The use of meso-(o-aminophenyl)triphenylporphyrin 96 to prepare a

series of alkyl and aryl mercaptan-tail porphyrins as cytochrome
P450 models has been described in Section 1.3.2. The same series of
compounds has been prepared by acylation of the tripivalamide-β-amino-
phenylporphyrin 117 to give the alkyl mercaptan "tailed picket-fence"
porphyrins 120 (Scheme 34).[68] A similar compound 121 with an appended
thioether chain has also been prepared and is reportedly capable of
reversibly binding oxygen.[61]

SCHEME 34

117

118

(a) n=5
(b) n=4

Br (CH₂)ₙCOCl

RCOCl

TrS⁻K⁺
or
AcS⁻K⁺

116

3(CH₃)₃CCOCl

96

119

(a) n=5, R=Tr
(b) n=5, R=SAc
(c) n=4, R=Tr
(d) n=4, R=SAc

120

(a) n=5
(b) n=4

121
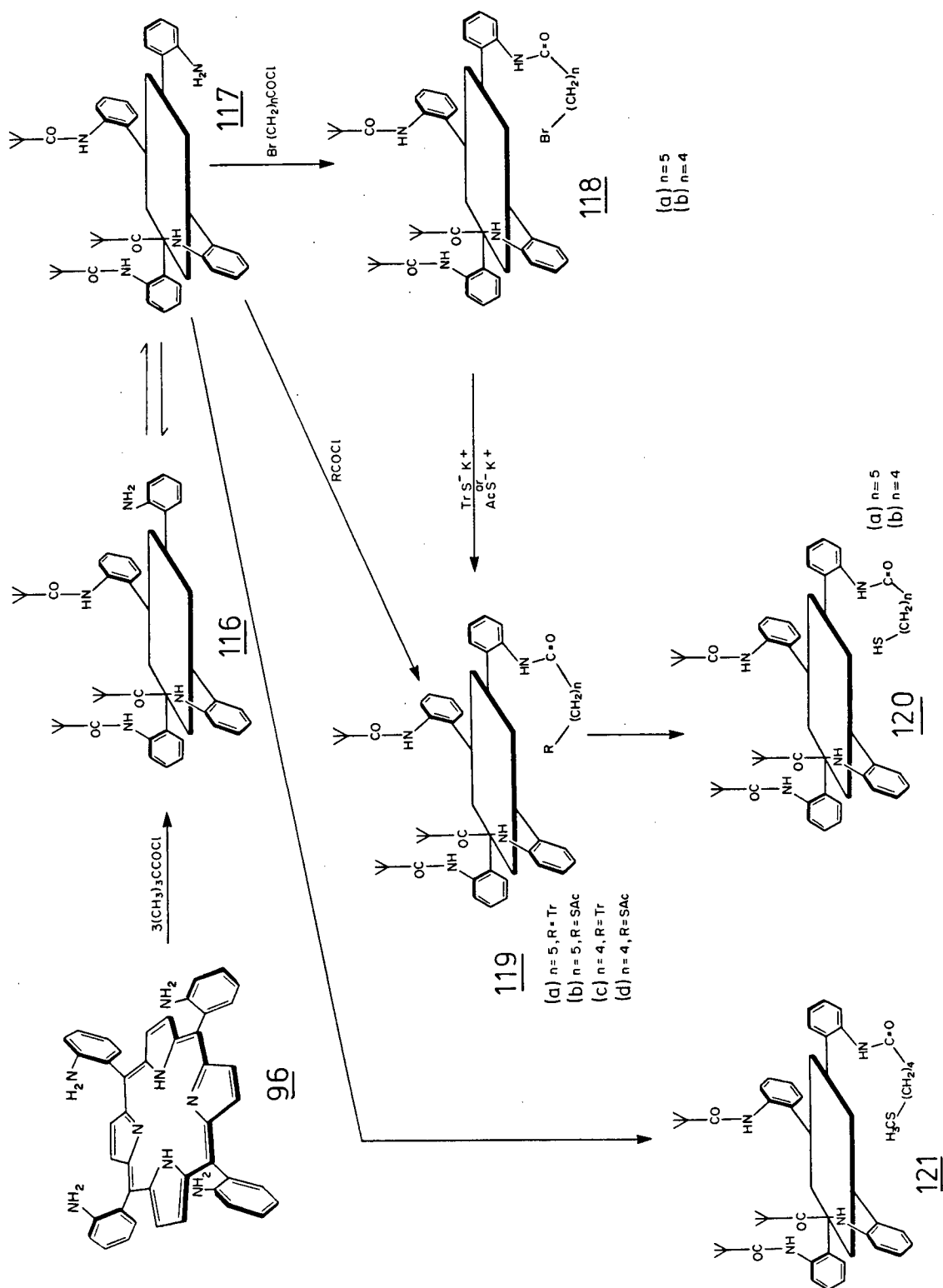
1.5 "CAPPED" PORPHYRINS

1.5.1 "Capped" Porphyrins

The direct condensation of aromatic aldehydes and pyrrole to form tetraphenylporphyrins was exploited by Baldwin and co-workers to prepare a "capped" porphyrin. In this molecule a benzene ring was covalently attached to all four ortho positions of the meso-phenyl rings, enclosing a volume of space above one face of the porphyrin ring. If the cap was sufficiently tight the binding of bases (e.g. alkylimidazoles, pyridine) should be prevented on the enclosed face; binding on the open face would result in a five-coordinate species. On the other hand, the smaller dioxygen molecule would be able to fit under the cap, which would provide a physical barrier to μ-oxo dimer formation. It was recognized that attempts to condense a benzene ring with a porphyrin by four ester linkages would probably result in very low yields. Instead the necessary units were attached to the "cap" to give a tetraaldehyde which was condensed with pyrrole to give the "capped" porphyrin. Unlike the "picket-fence" porphyrin, cyclization of the porphyrin ring is the last step of the synthesis, so chromatographic separation of atropisomers is not required.

The required tetraaldehyde 122 was prepared by alkylation of salicylaldehyde with bromoethanol, followed by condensation with pyromellitoyl chloride 123. Reaction of the tetraaldehyde with pyrrole in refluxing propionic acid yielded the "capped" porphyrin 124 after chromatographic purification (Scheme 35).[89,90] The same reaction sequence using 2-(3-hydroxypropoxy)benzaldehyde yielded the correspond-

SCHEME 35

SCHEME 36

127 R = H
128 R = CHO
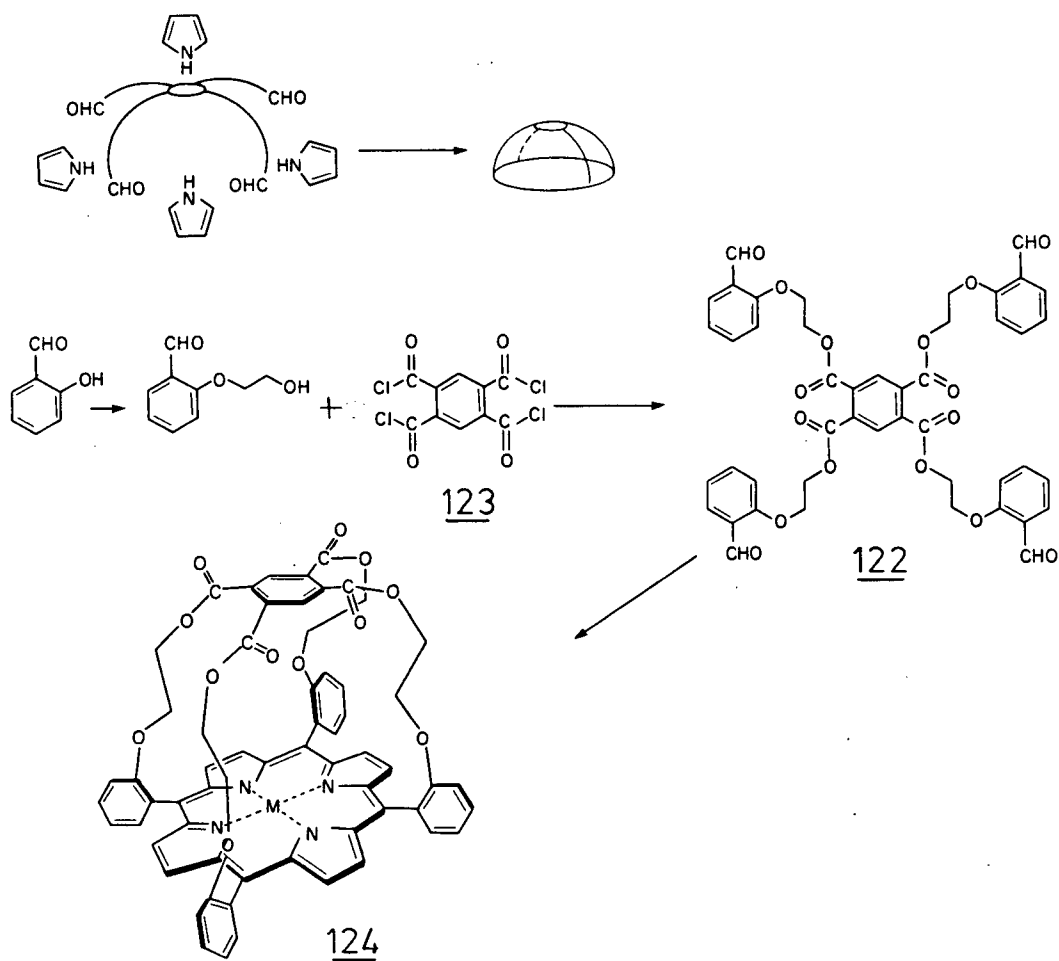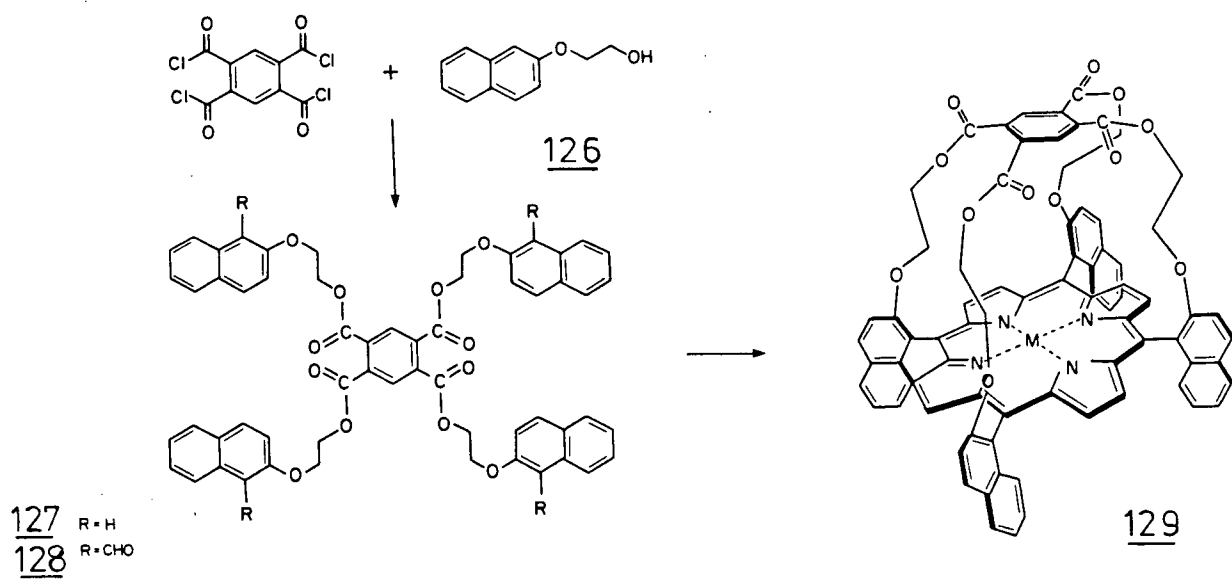
ing "homologous" or "C_3-capped" porphyrin 125 in which there is an extra methylene group in each link of the cap.[90] In this latter case the yield of the cyclization reaction was much lower (5%), probably reflecting the extra entropy factors required to form the larger cap. To provide steric hindrance on the uncapped face a "naphthyl-C_2-capped" porphyrin 129 was similarly prepared (Scheme 36).[90]

Insertion of iron into the "C_2-capped" porphyrin, followed by reduction, gave a crystalline four-coordinate high spin iron(II) porphyrin. In solutions containing excess axial base the five-coordinate heme was formed which was capable of reversible dioxygen binding at 25°C. The stability of the dioxygen adduct depended on the nature and concentration of the axial base and the position of the equilibria in Scheme 37.[89] Unlike the "C_2-capped" porphyrin 124 which could only

SCHEME 37
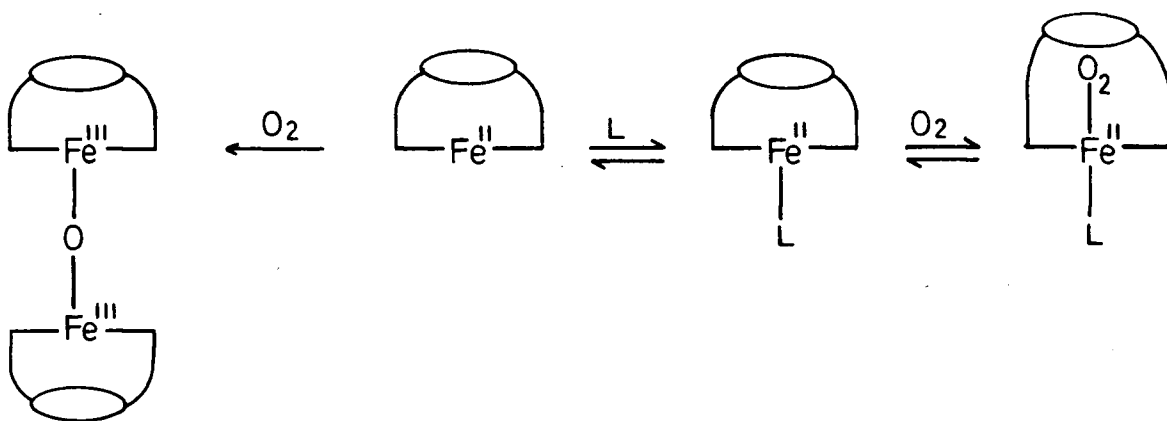
bind a single axial base, the larger size of the "C_3-Cap" 125 permitted binding of two axial bases, provided that they were small, e.g., propyl-amine. For intermediate size bases such as 1-MeIm, it appeared that a second base could weakly coordinate to the iron, probably through the

side of the cap. Oxygen binding was still reported to occur, giving a
pseudo-seven-coordinate complex.[91-93]

(28)
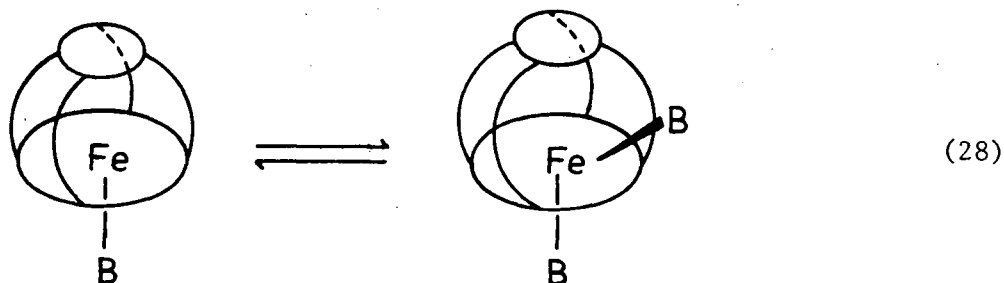
The O_2 and CO affinities of a series of Fe(II) and Co(II) capped
porphyrins have been studied.[90] It was found that O_2 affinities were
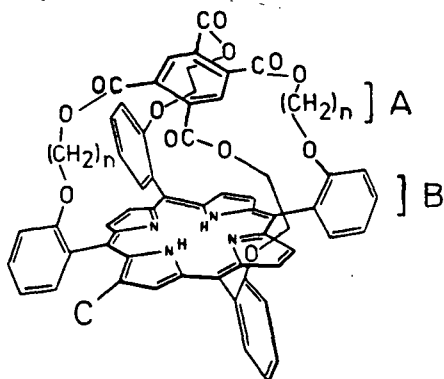
	A	B	C
C_2-Cap 124	n = 2	Phenyl	H
C_3-Cap 125	n = 3	Phenyl	H
C_2-CapNO$_2$ 130	n = 2	Phenyl	NO$_2$
Nap C$_2$-Cap 129	n = 2	Naphthyl	H

much lower than those of natural porphyrins and other synthetic models.

e.g., T(p-OCH$_3$)PP > NapC$_2$ - Cap 129 > C_2 - Cap 124 > C_2 - CapNO$_2$ 130 >

C_3 - Cap 125. In contrast CO bound more quickly than O_2, and the rate

of binding was independent of the cap size and comparable to unhindered

model porphyrins.[96] This was rationalized in terms of a steric effect

of the cap. Although the crystal structures of both $H_2(C_2$-Cap)[97] and

Fe(III)Cl(C_2-Cap)[98] indicated that the phenyl cap-porphyrin separation

was too small to accommodate either CO or O_2, a considerably more

expanded version must exist in solution. That the linear Fe-C-O system could be accommodated under the cap argued against a "central" steric effect. However the bent Fe-O-O system might be destabilized by a "peripheral" steric effect of the methylene chain linkages.

(29)
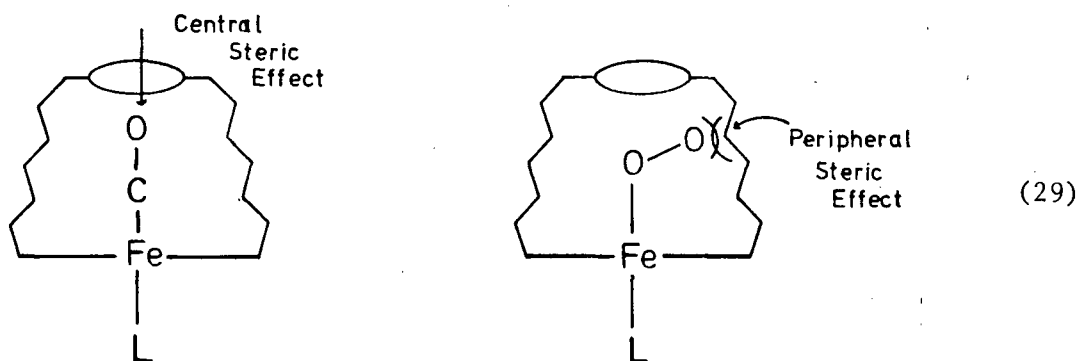
A recent study[99,100] of the paramagnetic shifts in the ^{1}H-NMR of Co(II)Cap porphyrins was used to deduce the cap-porphyrin separation. The relative cavity size was in the order NapC$_2$-Cap>C$_2$-Cap>C$_3$-Cap, which correlates with the relative oxygen affinity of the iron(II) "capped" porphyrins.

1.5.2 "Pocket" and "Tailed Pocket" Porphyrins

To prepare a system which discriminates against the binding of CO relative to that of O$_2$, Collman has used a combination of the "picket-fence" and the "capped" porphyrin approach to prepare a series of "pocket" porphyrins.[101,102] As above, a phenyl ring is used to provide steric encumbrance at one face of the porphyrin, but in this case it is linked to only three meso-phenyl rings, leaving an open side. Oxygen

may bind within the pocket by orientation of the bent Fe-O-O unit toward the open side. Carbon monoxide may only be accomodated by bending and/or tilting of the linear Fe-C-O unit leading to decreased CO affinity.

Treatment of $\alpha,\alpha,\alpha,\alpha\text{-}H_2T_{Am}PP$ 96 with slightly more than one equivalent of pivaloyl chloride formed the "mono-pocket" porphyrin 131 (Scheme 38). Condensation with a phenyl tri-acid chloride 132 under high dilution conditions afforded the pocket porphyrins 133 in good yield (>60%). The volume of the pocket was dictated by the choice of acid chloride and the presence of the single picket provided protection against irreversible oxidation. A similar strategy was employed to prepare the "tailed-pocket" porphyrins 134. However, in these compounds, the remaining ortho-amino group is used to attach the base leaving no protection on the open face of the pocket. In contrast to the "tailed picket-fence" porphyrins, these complexes undergo rapid oxidation to the μ-oxo dimer.[101]

For the iron(II) "pocket" porphyrins, the coordination state of the iron depended on the size of the pocket. Visible absorption and MCD spectral data showed that Fe(II)PocPiv remained five coordinate even in the presence of excess base. Although the medium and large size pockets showed increasing six-coordination, concentration ranges could be determined within which five-coordinate iron(II) was the dominant species. The O_2 and CO binding of the "pocket" and "picket-fence" porphyrins were compared.[103] While the O_2 affinities for both systems were similar, the "pocket" porphyrins showed a reduced CO affinity. Since electronic and solvent effects were similar in the two model systems, the reduction in CO affinity was attributed to the

SCHEME 38
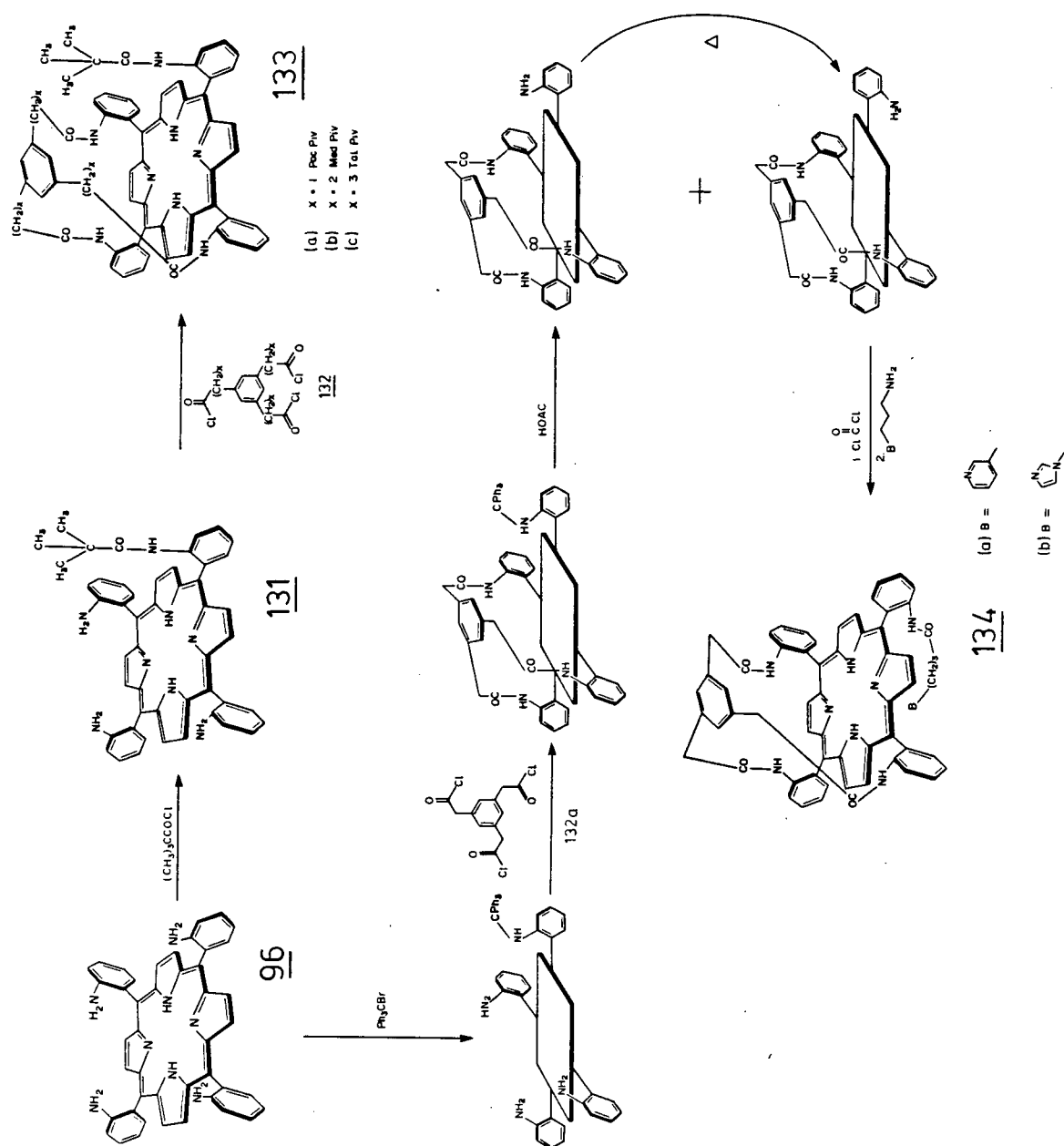
steric hindrance of the cap which distorted the Fe-C-O unit from linearity.

1.5.3 "Bis-Pocket" Porphyrins

Eventual irreversible oxidation of both the "picket-fence" and the "capped" porphyrins occurs because steric encumbrance is present only on one side of the molecule. To avoid this, octa-ortho-substituted TPP compounds have been prepared. By choosing the correct steric bulk for the ortho substituents a protected pocket may be formed on both sides of the porphyrin ring. The pockets could still be penetrated by axial bases and gaseous ligand, but would form a barrier to the close approach of two metal centres, thus stabilizing the oxygenated porphyrin. Vaska and Amudsen have prepared [T-(2,4,6-MeO)$_3$PP]Fe(II)[135] and [T-(2,4,6-EtO)$_3$PP]Fe(II)[136] by condensation of the appropriate tri-substituted benzaldehyde with pyrrole.[104] Balch has shown by ^{1}H-NMR that although the ortho methoxy substituents prevent μ-oxo dimer forma-tion, oxidation at room temperature proceeds to form PFe(III)OH and PFe(III)Cl.[4] A more hindered complex was prepared by Suslick and Fox,[101] who condensed 2,4,6-triphenylbenzaldehyde with pyrrole in refluxing propionic acid to obtain the porphyrin in 1% yield. Metallation and reduction gave the four-coordinate iron(II) species [T-(2,4,6-Ph)$_3$-PP]Fe(II) 137 in 80% yield. Addition of the sterically hindered base, 1,2-dimethylimidazole gave a five-coordinate iron(II) complex which was capable of completely reversible oxygenation in non-polar solvents at 30 °C. However, the oxygen affinity is very low compared

to other model complexes and the natural systems, an observation which was attributed to the non-polar nature of the binding site.

Covalent attachment of a group to the four ortho positions of TPP may also be used to prepare porphyrin complexes having a rigid structure. Such an approach was adopted by Lindsey and Mauzerall[44] to prepare a cofacial porphyrin-quinone system where the separation between the two rings was estimated to be 10Å.[106] The quinone-tetraaldehyde 136 was prepared by alkoxylation of fluoranil 135, and then reacted with $\alpha,\alpha,\alpha,\alpha-H_2T_{Am}PP$ 96. The reversibility and the intramolecular nature of the Schiff base reaction were responsible for the high yield of the reaction; 85% yield of the "capped" porphyrin 137a after stirring at room temperature for 24 hours. Subsequent reduction of the Schiff bases with $NaBH_3CN$ yielded the desired porphyrin-quinone in 80-95% yield. (Scheme 39). Acetylation of the amino groups and metal insertion furnished $ZnPQ(OAc)_4$ 138. The photochemical properties of this compound were investigated and the rate constant for electron transfer from porphyrin to quinone was estimated.[107]

SCHEME 39

135

136

1. CF$_3$CO$_2$H/CH$_3$CN

2. NaBH$_3$CN

+

96

137

138

SCHEME 40

139

1. Cl—CO—,Et$_3$N

2. H$_2$N(CH$_2$)$_n$NH$_2$

140
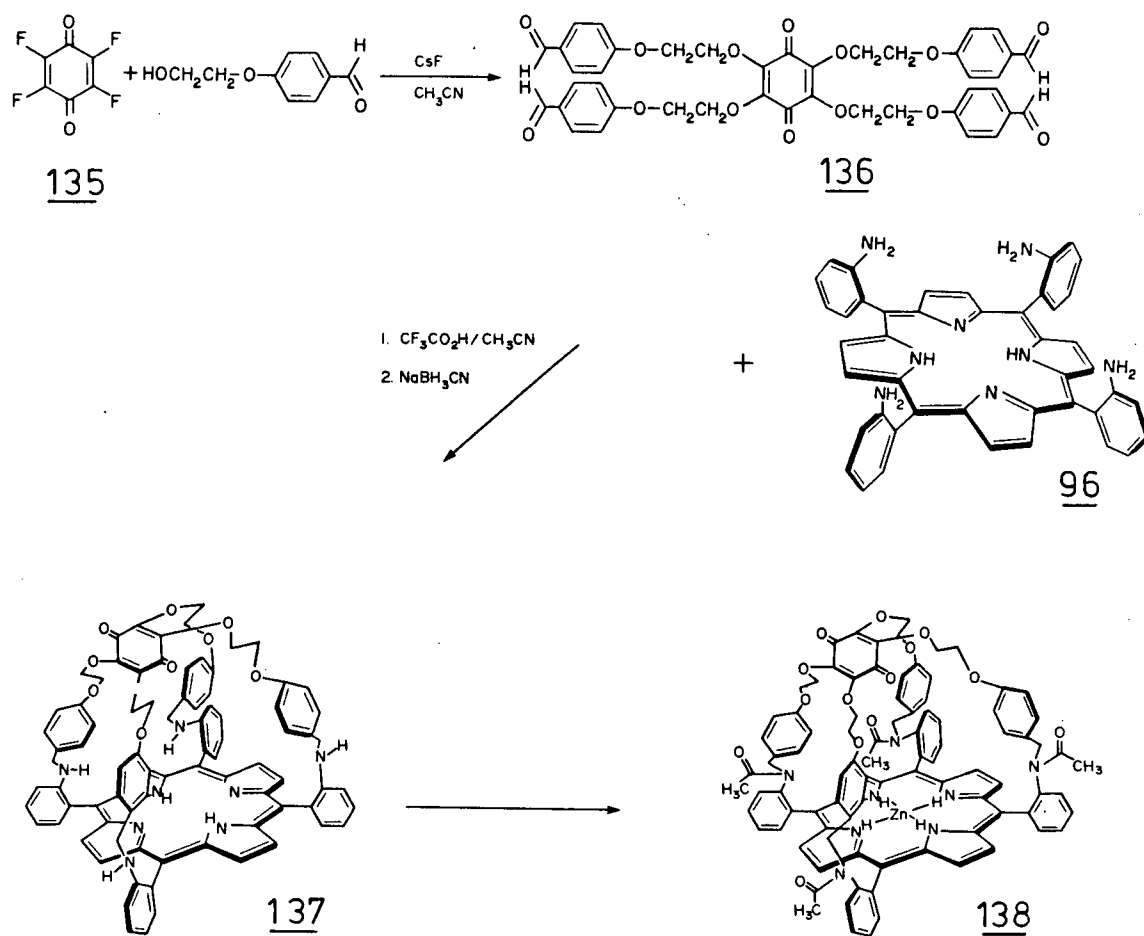
n = 6–10,12
20–30%
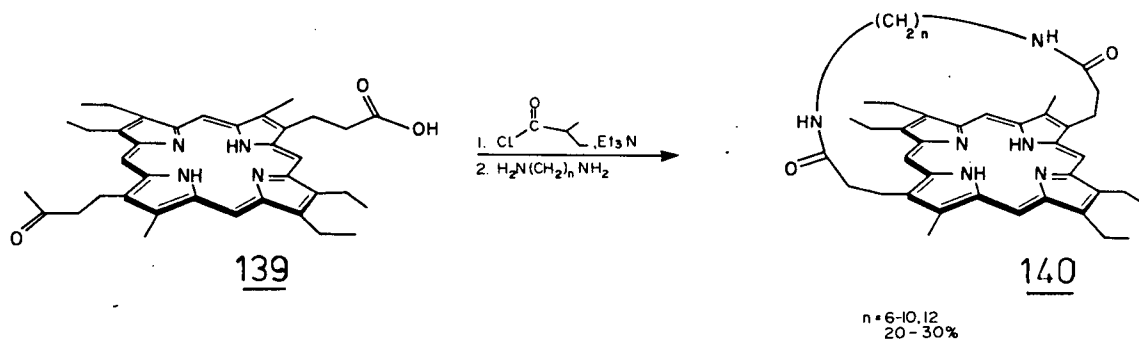
1.6   STRAPPED PORPHYRINS

The strapped porphyrin class of heme protein models embraces all those compounds in which some group is covalently linked to two corners (usually diagonally opposite) of a porphyrin macrocycle. The usual synthetic strategy has been to tie the strap to an already formed porphyrin, thus allowing great versatility in the types of structures made (e.g. cyclophane, crowned, pagoda, basket-handle etc.). The porphyrins may be singly- or doubly-strapped and may be classified according to the nature of the chain:

(i)   · Simple non-functionalized alkyl chains whose role is to span one face of the porphyrin, discouraging μ-oxo dimerization and providing a more hydrophobic environment.

(ii)   Straps incorporating some bulky group which will provide more steric encumbrance than a simple alkyl chain. ·

(iii) Functionalized straps which incorporate some group capable of binding to or interacting with the metal at the porphyrin core. These may be used to maintain five-coordination or to form six-coordinate mixed ligand systems L-M-L', where one ligand binds poorly to the metal.

1.6.1   Non-Functionalized Alkyl Straps

A number of research groups have reported the syntheses of

simple strapped porphyrins. Ogoshi[108-110] condensed long-chain

diamines with a difunctional etio-type porphyrin in the presence of iso-

butyl chloroformate and triethylamine under high dilution to obtain the

strapped porphyrins (n = 6-10,12) in 20-30% yield after chromatography

(Scheme 40). On the basis of visible absorption spectroscopy it was

claimed that, for short straps, binding of a second bulky axial ligand

under the strap was inhibited, giving five-coordinate iron(II) species.

Attempts to observe oxygen binding to the ferrous porphyrins at 15°C

resulted in rapid formation of the μ-oxo dimer. Battersby[111] used the

same strategy, reacting the bis-acid chloride of mesoporphyrin II with

1,12-aminododecane under high dilution to give the bridged porphyrin in

25% yield (Scheme 41). Alternatively, elaboration of the porphyrin

carboxyl side chains by ester or amide formation, followed by intra-

molecular oxidative coupling or Dieckmann condensation gave the ester-,

or amide-linked strapped porphyrins 144, 145 in good yield. Not

surprisingly, attempts to oxygenate the ferrous complexes in THF or

aqueous acetone at 20°C showed only rapid irreversible oxidation to the

ferric state. Chang[112] has also prepared an amide-linked strapped porphyrin

146. In this instance the system was used as a cytochrome P450 model

to investigate the porphyrin-catalyzed hydroxylation of unactivated

alkanes by iodosyl benzene (Scheme 42). A similar series of amide-

linked strapped porphyrins 147 have also been prepared containing 5-7

methylene units in the strap.[113] Such models were prepared in an

attempt to mimic the differentiation of O_2 and CO displayed by the

natural systems. Using resonance Raman spectroscopy a correlation

between increased steric strain (shorter straps) and the Fe-CO stretch-

ing and Fe-C-O bending vibrations has been observed.[114]

SCHEME 41

SCHEME 42

(a) R = H
(b) R = OH

$\text{Ph–IO} + \text{Fe(III)} \longrightarrow \text{Ph–I} + \text{FeO} \xrightarrow{RH} \text{Fe(III)} + \text{ROH}$

146

SCHEME 43

148

149

150 X = CO$_2$CH$_2$Ph
151 X = CO$_2$H

152

SCHEME 44

152

153
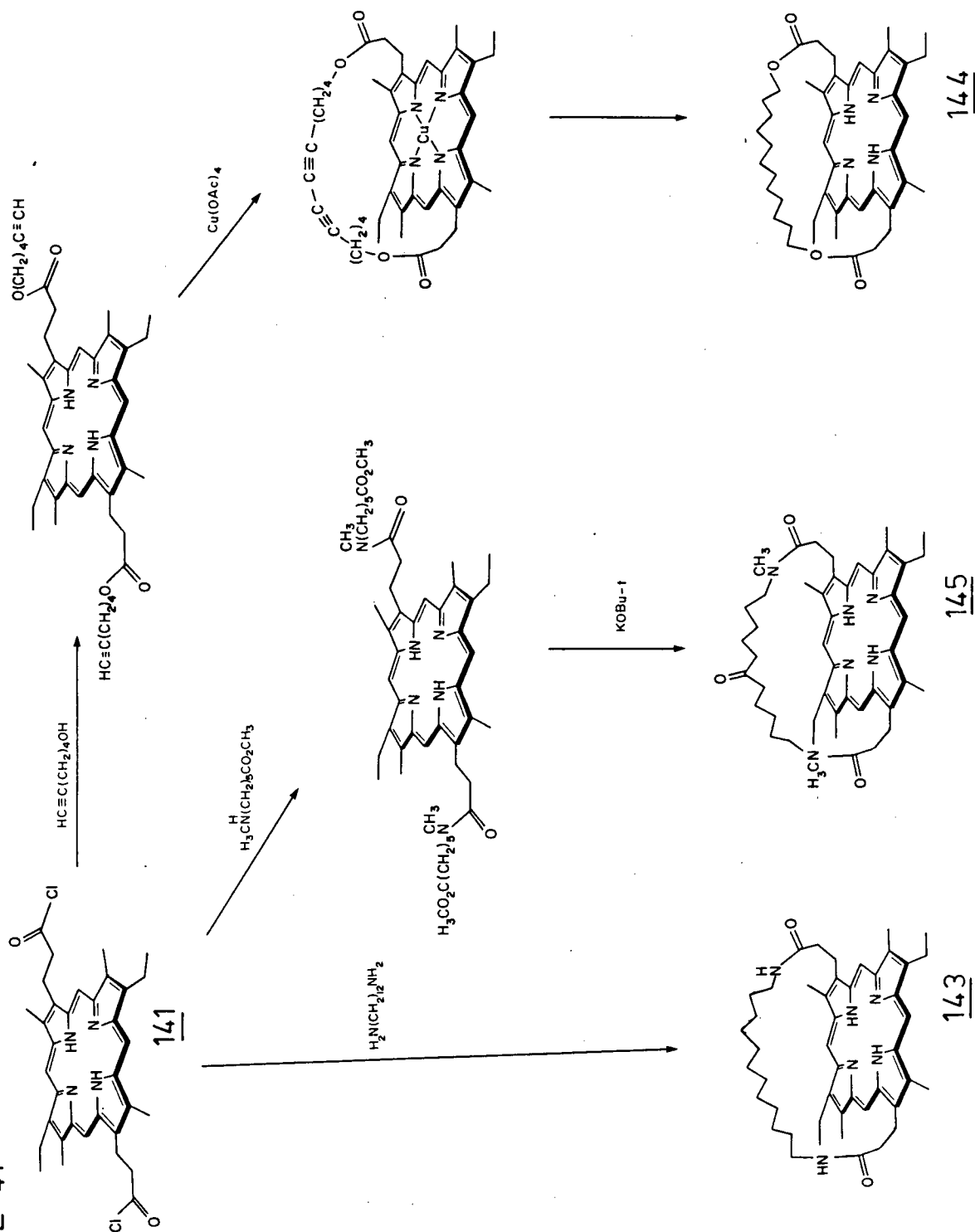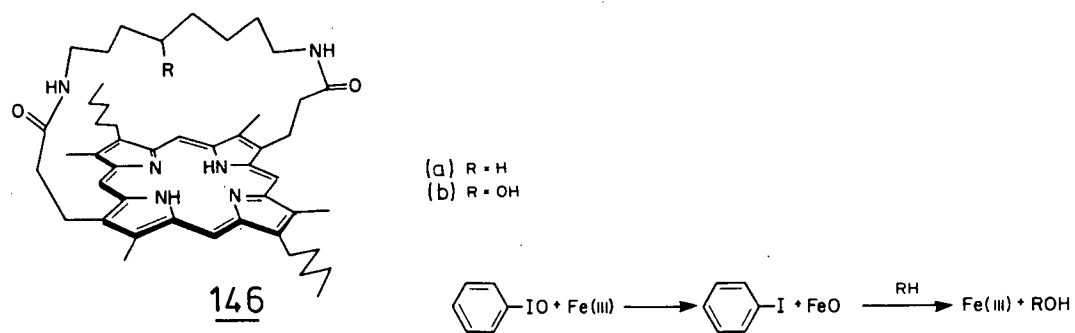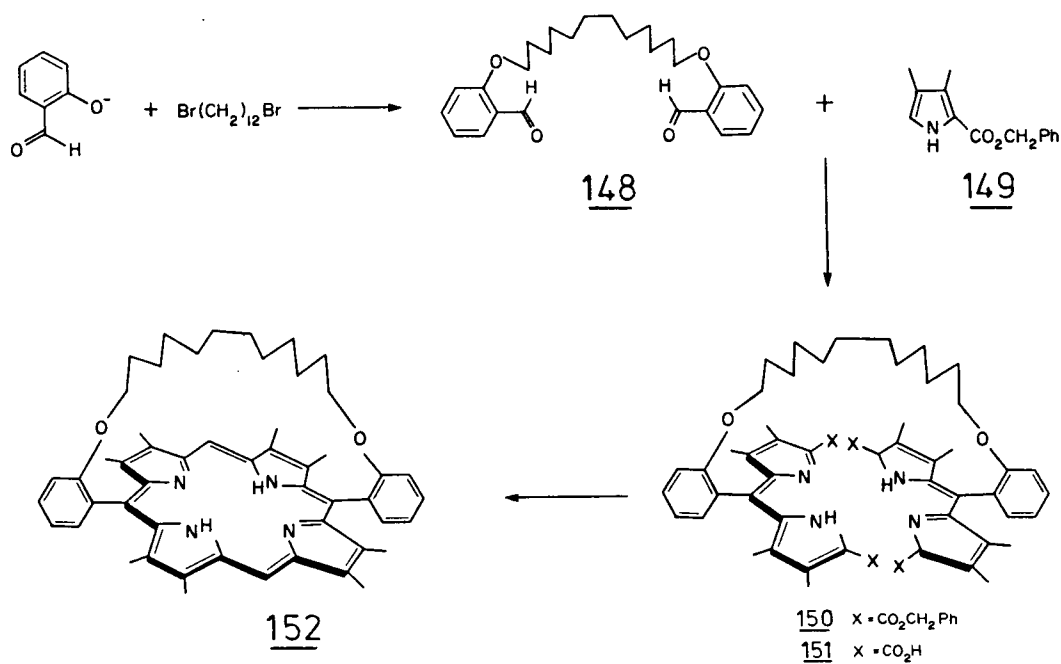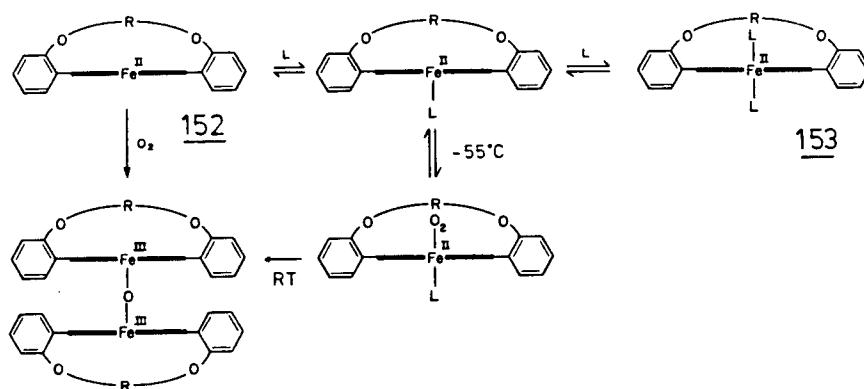
A different synthetic strategy was adopted by Baldwin et al., to prepare strapped porphyrins where the ortho positions of opposite meso-phenyl rings are linked.[115,116] Unlike the previous syntheses, it is the strap which is prepared initially and the two halves of the porphyrin attached to both ends. In the final step the porphyrin ring is formed by intramolecular cyclization and the strap is stretched into position (Scheme 43). Condensation of the anion of salicylaldehyde with 1,12-dibromododecane gave the "strapped-dialdehyde" 148. Acid catalyzed condensation with benzyl 3,4-dimethylpyrrole-2-carboxylate 149 afforded the chain-linked bis-dipyrromethane, which after hydrogenolysis gave the unstable tetraacid 151. This was immediately condensed with trimethyl orthoformate to give the "alkyl-strapped" porphyrin 152 in 23% overall yield. As in the previous examples the alkyl strap was not able to enforce five-coordination of the iron(II) complex. In the presence of excess base the six-coordinate species 153 was formed which did not bind oxygen. Reducing the concentration of base led to an increase of the four-coordinate species 152 which underwent irreversible oxidation. While reversible oxygenation was observed at -55°C as for unhindered porphyrins, warming to room temperature caused μ-oxo dimer formation (Scheme 44).

A similar approach was used by Dolphin and Wijesekera,[117,118] who were attempting to strap a porphyrin with very short alkyl chains – short enough to cause deformation of the porphyrin. Obviously in this case, linking opposite corners of a preformed porphyrin would, at best, give very poor yields. Instead the two halves of the porphyrin were assembled at each end of the strap, and only at the last step was the porphyrin 157 formed by acid-catalyzed intramolecular cyclization under

SCHEME 45

ClOC—(CH$_2$)$_{n-2}$—COCl

154

155

	R
(a)	—CO$_2$CH$_2$CH$_3$
(b)	—CO$_2$CH$_2\phi$
(c)	—CO$_2$H
(d)	—H
(e)	—CH=$\overset{+}{N}$(CH$_3$)$_2$Cl$^-$
(f)	—CHO
(g)	—CH=C(CN)$_2$

156

	R$_1$	R$_2$
(a)	CH$_3$CH$_2$OCO	—CH=C(CN)$_2$
(b)	HOOC—	—CHO
(c)	H—	—CHO

	R
(a)	H
(b)	Cl

157

(a)	n = 11
(b)	n = 10
(c)	n = 9
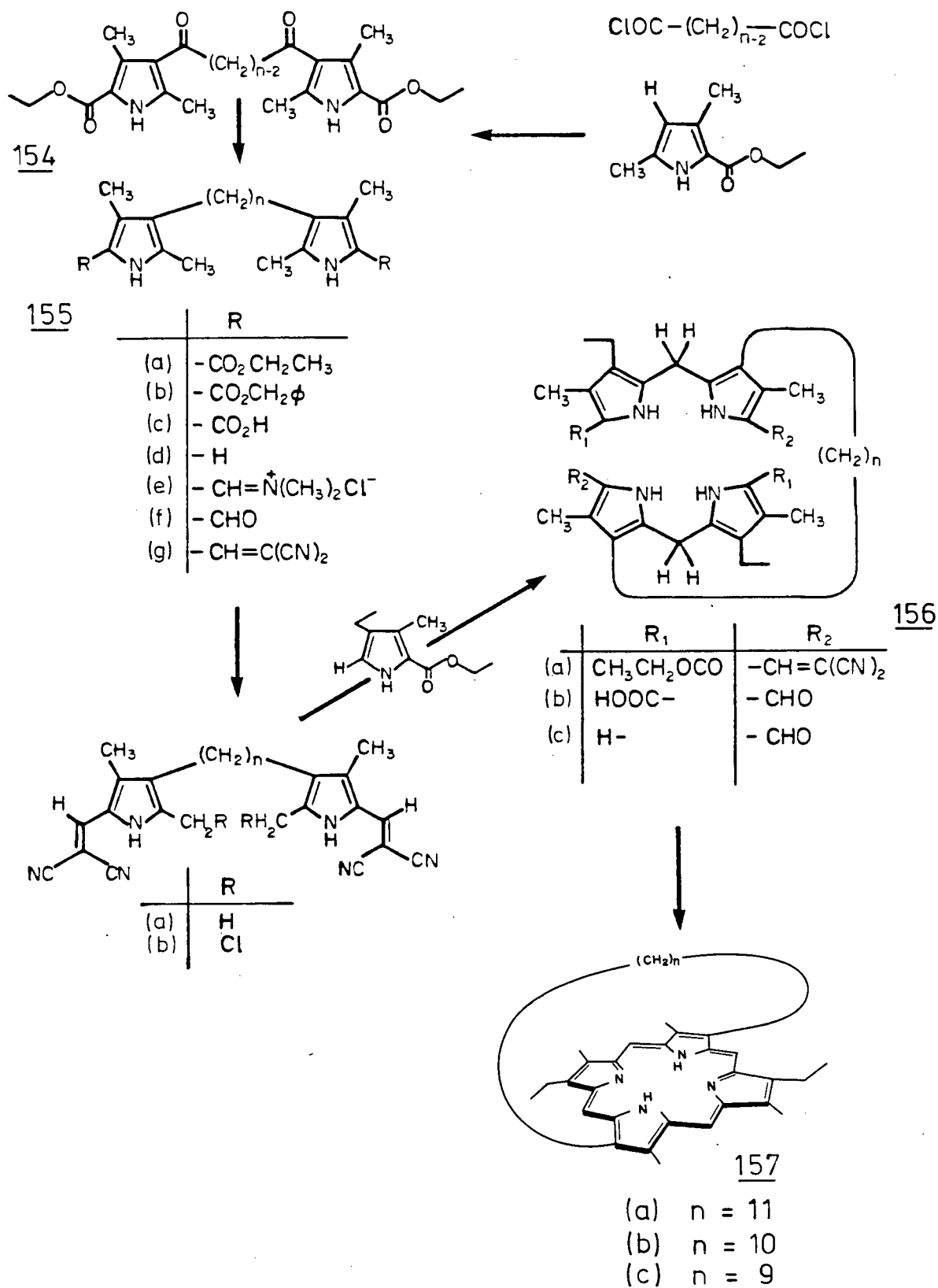
high dilution conditions (Scheme 45). Visible and ^{1}H-NMR spectroscopy

and X-ray crystallography all point to increasing distortion of the ring

as the length of the strap is decreased (n = 11,10,9). A chain length

of nine methylene units appears to be the lower limit; attempts to

prepare even more strained porphyrins with shorter straps were unsuccess-

ful. Ligand binding to the metal complexes showed that the straps

provided no steric protection.

1.6.2   Straps Containing Bulky Blocking Groups

Porphyrins strapped with simple alkyl chains are poor models for

oxygen binding heme proteins. In most cases the strap is too "floppy"

and can be pushed to one side allowing μ-oxo dimer formation. In

addition, base is not prevented from binding under the strap, leading

to oxygen binding on the open face and, consequently, irreversible

oxidation. The logical extension is to incorporate some bulky group

into the strap to increase the steric encumbrance about one face.

One of the initial examples of the strapped porphyrin approach

to heme protein models was the cyclophane porphyrin 160 of Traylor.[119]

In this example steric encumbrance was provided by a biphenyl group in

the strap. To ensure a tightly fitting strap, porphyrin cyclization

was delayed until the final step (Scheme 46). Because of poor yield

(5% for the cyclization step after repeated chromatographic purification)

this porphyrin was not used as a heme protein model. Instead an

anthracene was strapped across a preformed porphyrin 163 by means of

amide linkages (Scheme 47).[120] For the anthracene-heme[6,6]cyclophane

SCHEME 46

158

159

R = COOH
R = Br

160

SCHEME 47

164 the two aromatic rings were estimated to be ∿4.5 Å apart. Performing

a Diels-Alder addition on the anthracene with 1-phenyl-triazine-2,5-

dione 165 gave the "pagoda porphyrin" 166 possessing an even tighter

pocket. Binding of a second axial base underneath the anthracene ring

was not observed, the iron(II) complex being five-coordinate even in

1M 1-MeIm. The anthracene-heme[6,6]cyclophane and the homologous[7,7]

compound were used to study the binding of isonitriles, CO and O_2

within the pocket as models for the distal side steric effects in heme

proteins.[120-122]

Baldwin adapted his strapped porphyrin synthesis to prepare a

system 167 with a phenyl ring above one face (Scheme 48).[116] Although

structurally similar to the "C_2-capped" porphyrin 124, the absence of

the two extra linkages resulted in a "floppy" strap which did not

prevent six-coordination by ligands such as 1-MeIm or pyridine and

which did not prevent μ-oxo dimer formation. An even more bulky strap,

incorporating a naphthalene ring 168, was no more successful.

Dolphin[117,118] has prepared a series of strapped porphyrins with

a durene group protecting one face. Since short chains could be

synthesized by this method it was hoped that a sufficiently rigid strap

could be obtained to enforce five-coordination. While the durene group

did discriminate against bulky ligands such as 1,5-dicyclohexylimidazole,

sterically unhindered ligands (1-MeIm, pyridine) gave six-coordinate

species.

SCHEME 48

(a) | X = CO_2CH_2Ph
(b) | X = CO_2H

167

168
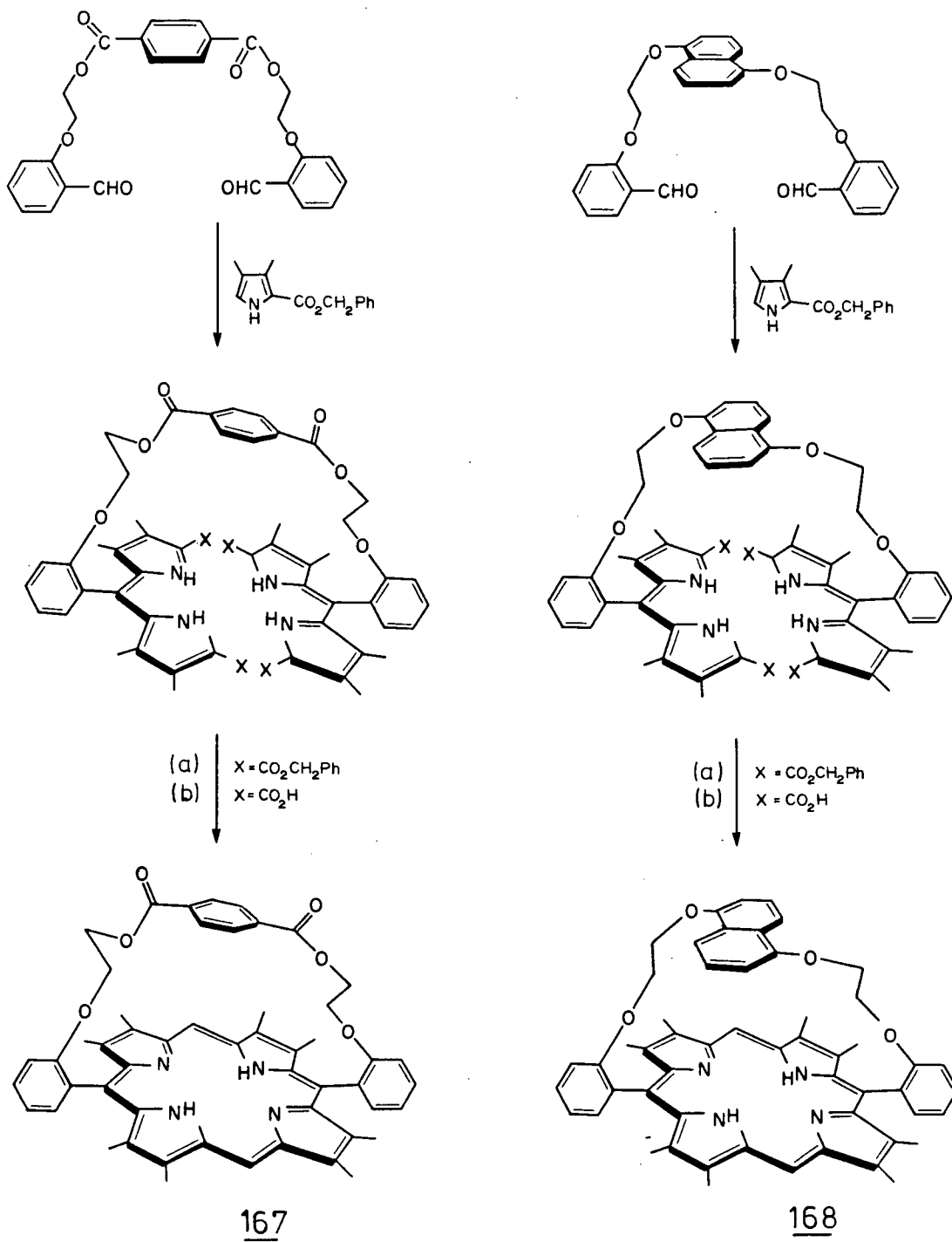
1.6.3 Straps Containing Interactive Groups

The incorporation of potential ligands into the porphyrin strap has three advantages.

(i)   A stoichiometric amount of ligand is built into the system, ensuring five-coordination without the addition of external ligand. In the case of nitrogen bases, mixtures of six- and four-coordinate complexes are not obtained.

(ii)   For ligands which bind poorly to iron(II) (e.g. thiolate), coordination would be favoured by constraining the ligand into a position suitable for binding to the metal.

(iii)   Because the strap is fixed in two positions, complications due to ligand replacement or dissociation will be minimized.

The strapped-porphyrin approach is also useful for orientating other interactive groups (e.g.,metal binding sites, electron donor/ acceptor groups) into specific geometries with respect to the porphyrin.

Battersby has prepared a series of strapped porphyrins bearing variously substituted pyridine ligands.[123] Reaction of the porphyrin bis-acid chloride 141 with the corresponding pyridine diol 169 gave the ester-linked pyridine straps 170 in up to 38% yield (Scheme 49). A cytochrome P450 model was prepared similarly (Scheme 50).[124] A suitably functionalized diol 173 was reacted under high dilution with the bis-acid chloride of mesoporphyrin II 141 to give the strapped porphyrin 174 in 25% yield. The protected-sulfur derivative 175 was obtained by displace-

SCHEME 49
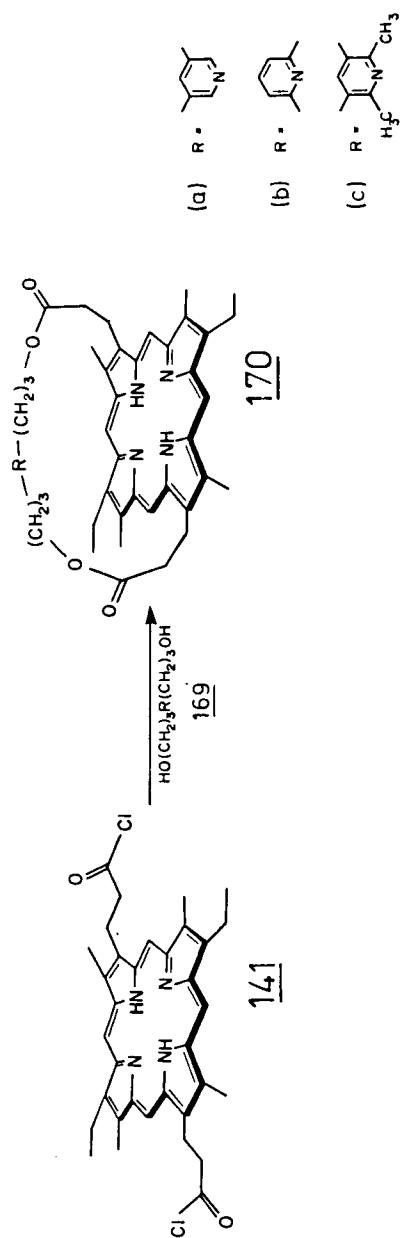
SCHEME 50
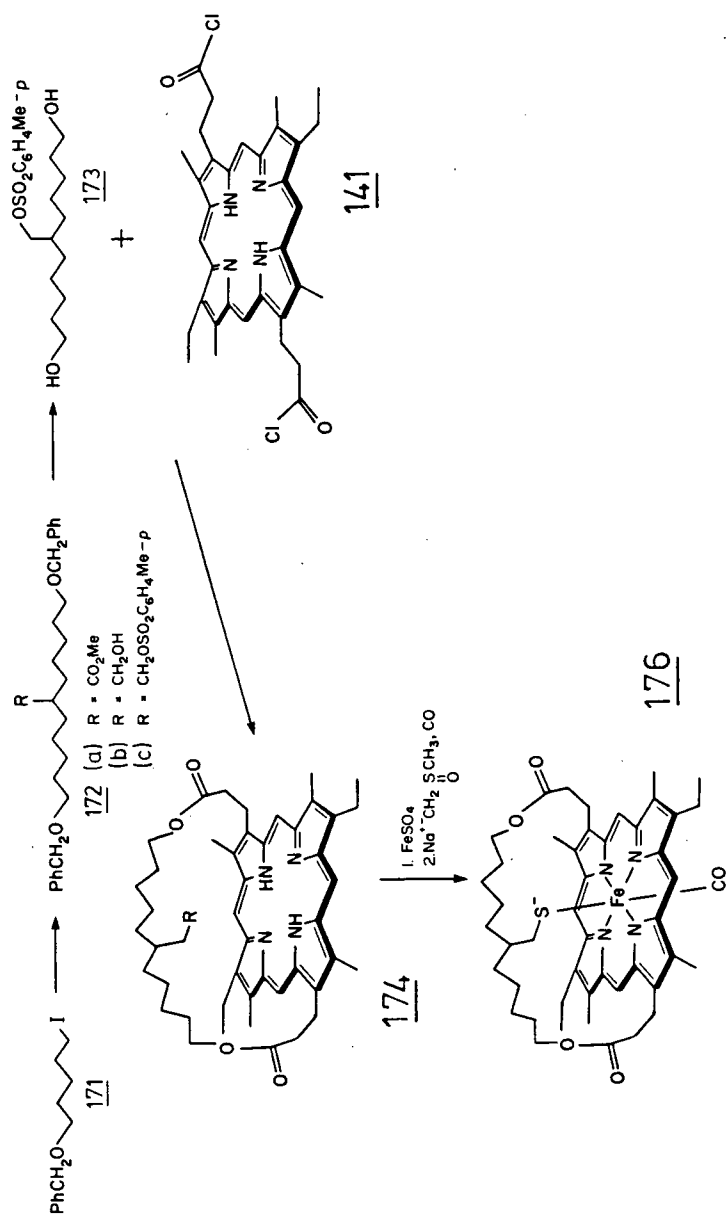
ment of the tosyloxy group with potassium thioacetate. After iron

insertion and reduction to the iron(II) state, the S-acetyl group was

cleaved with dimsyl sodium to produce the five-coordinate iron(II)

species. On exposure to CO a six-coordinate iron(II) species <u>176</u> was

formed whose visible absorption spectrum reproduced the major character-

istics of the carbonmonoxy cytochrome P450 spectrum - a split Soret

band with an intense band at 450 nm. The ^{13}C-NMR spectrum of the ^{13}CO

complex also supported the RS$^-$-Fe(II)-CO formulation.

Several binucleating strapped porphyrins have been prepared, which

are capable of binding two metal ions in close proximity. The "crowned"

porphyrin <u>179</u> of Chang,[125] formed by the addition of a bis-amino crown

ether to the bis-acid chloride of deuteroporphyrin II <u>177</u>, may bind a

transition metal ion (in the porphyrin ring) and a group IA or IIA

cation (in the diaza-18-crown-6 ring) (Scheme 51). Apart from its

metal binding capability the crown ether also exerts some steric control

over one face of the porphyrin. For the iron(II) complexes, bulky

ligands (e.g., 1-triphenylmethylimidazole) bind only on the unhindered

face of the porphyrin to give a five-coordinate species. Oxygen may

then bind under the crown to give a reasonably stable oxygen species

($t_{\frac{1}{2}} > 1$ hr. at 25°C in DMA).

The combination of crown ether and porphyrin has recently been

extended by Lehn.[126] The macrotetracyclic cryptand <u>182</u> was prepared

by condensation of the biphenyl-linked bis-crown ether <u>180</u> with the

di-p-nitrophenyl ester porphyrin <u>181</u> in pyridine at 55°C under high

dilution conditions (45-54% after chromatography). Reduction to the

tetra-amine <u>183</u> was effected by treating the zinc complex with diborane

followed by demetallation. This multisite complexing species is

SCHEME 51

177

178

179

SCHEME 52

180

181 (a) n = 1
(b) n = 2

55°C
PYRIDINE

182 (a) = 1
(b) = 2

1. Zn(OAc)$_2$
2. B$_2$H$_6$
3. HCl
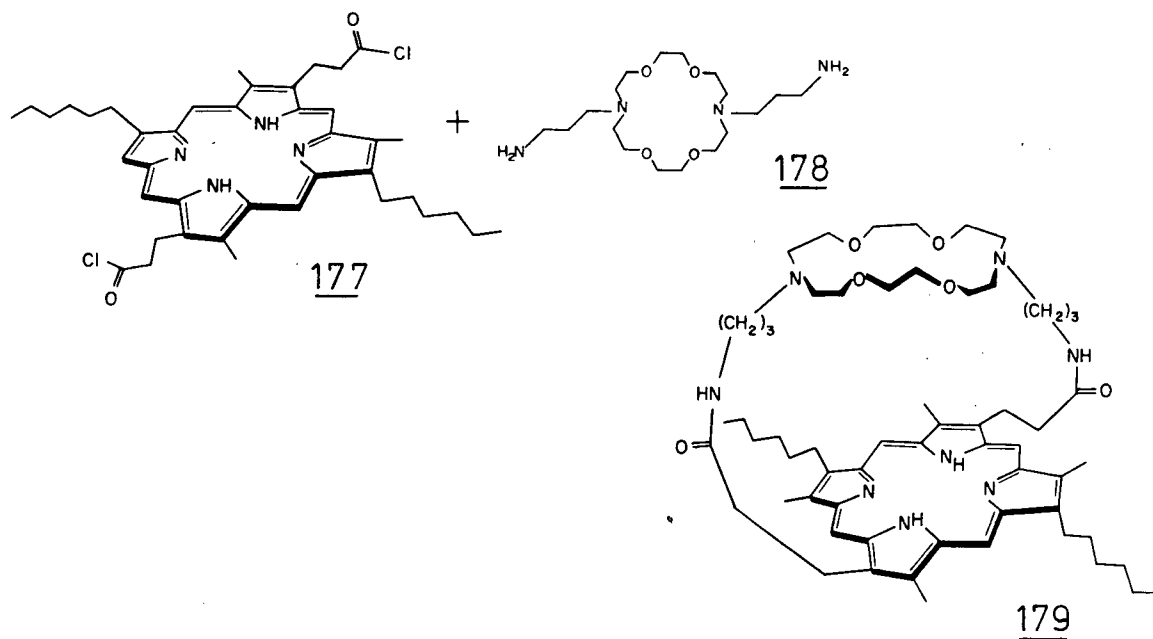
183 (a) = 1
(b) = 2
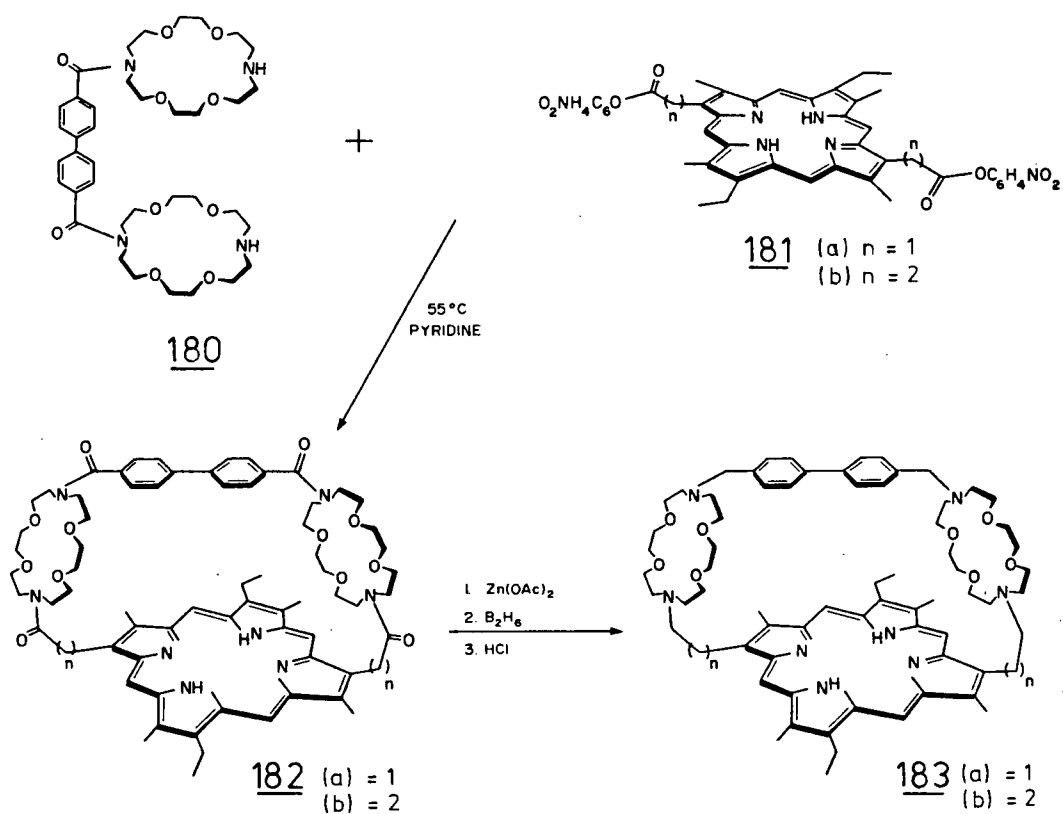
capable of selective substrate binding: transition metal cations are bound by the porphyrin and alkyl diammonium salts, $^+H_3N(CH_2)_n NH_3^+$ (n = 8-10), within the central cavity. That binding within the cavity does indeed occur was evidenced by the large upfield shifts of the methylene protons due to the shielding effects of the porphyrin and biphenyl rings.

A copper binding site has been covalently attached to a porphyrin in an attempt to mimic the ESR characteristics of the iron-copper site of cytochrome oxidase.[127] The copper-binding strap was a bis-thiazole derivative 185, obtainable from phthalylglycine 184 in high yield. Because of the need for a non-square-planar copper binding site, the strap was attached to one side of the porphyrin ring rather than to opposite corners. Condensation of the diamino thiazole sulfide 185 with mesoporphyrin XII bis-acid chloride 186 under high dilution gave the strapped porphyrin 187 in 72% yield after chromatography (Scheme 53). Metal ions could be differentially introduced into the porphyrin and into the strap to give a dinuclear metal complex containing a high spin iron(III) and a copper(II) ion. The extent of coupling between the two metal centres was investigated by ESR. Gunter et al.,[128] used a somewhat different approach to prepare a similar Fe/Cu strapped porphyrin (Scheme 54). Condensation of the tetramethyldipyrromethane 188 with o-nitrobenzaldehyde 48, followed by oxidation afforded the 5,15-meso-(o-nitrophenyl)porphyrin 189. After reduction to the amino derivative the atropisomers were separated by chromatography. The α,α-isomer 189 was finally condensed with 2,6-pyridylbis(4'-thia-5'-pentanoyl)chloride 190, and gave the strapped porphyrin. Insertion of iron and copper and the introduction of bridging ligands gave species of the type 192, whose

SCHEME 53

SCHEME 54

magnetic properties were investigated.[129]

As a model for photosynthetic and electron-transfer systems, Sanders[130,131] has prepared a quinone-capped porphyrin. Using the Battersby group approach, 1,4-dialkoxybenzene 193 derivatives were reacted with mesoporphyrin II bis-acid chloride 141 to give the strapped porphyrins 194 in 7 and 15% yield depending on strap length (Scheme 55). Deprotection with boron trichloride afforded the hydro-quinones which were oxidized to the quinones 195 with lead dioxide. ^{1}H-NMR studies on the magnesium complexes suggest that the quinone carbonyl binds to the metal ion and that therefore the quinone and porphyrin chromophores are perpendicular.[132]

1.6.4 Doubly-Strapped Porphyrins

We have already seen that sterically encumbered porphyrins may still be susceptible to μ-oxo dimer formation if any four-coordinate species in solution binds oxygen on the open face. Steric encumbrance on both faces of the porphyrin, as in the "bis-pocket" porphyrin systems of Vaska[104] and Suslick,[105] may prevent this bimolecular oxidation pathway.

Momenteau has used a combination of approaches to prepare TPP derivatives having two straps on each porphyrin ring.[133] In a strategy reminiscent of Baldwin's "capped" and "strapped" porphyrin syntheses,[115,116] the sodium salt of salicylaldehyde was reacted with a variety of dibromoalkyl and p-(dibromoalkyl)benzene derivatives 193 to give chain-linked dialdehydes 194. The TPP ring was then formed by condensing the

SCHEME 55

141

193

1. BCl₃
   -40°C
2. PbO₂

194

(a) n = 2, R = CH₂OMe 7%
(b) n = 3, R = CH₂OMe 15%
(c) n = 2, R = H
(d) n = 3, R = H

195

(a) n = 2, X = 2H
(b) n = 3, X = H₂
(c) n = 2, X = Mg
(d) n = 3, X = Mg
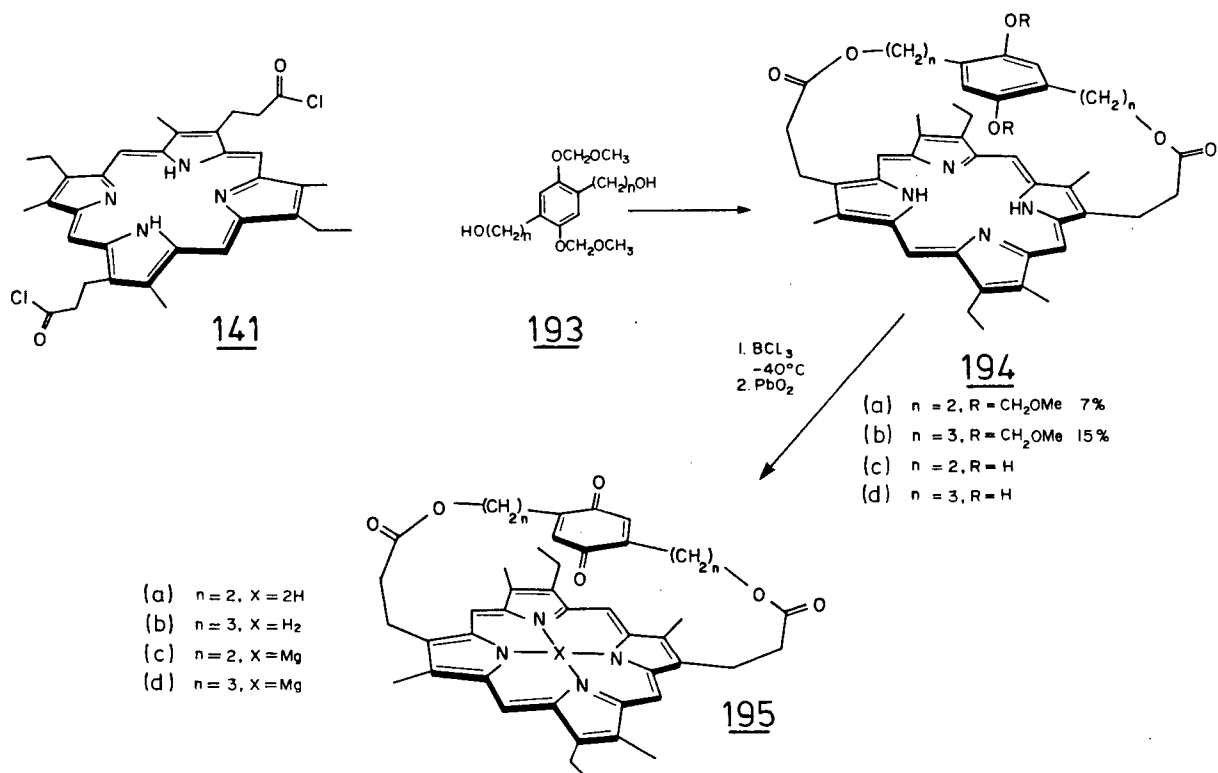
dialdehydes with pyrrole in refluxing propionic acid (Scheme 56).
After removal of polymeric materials, three isomers were obtained by
chromatography in low overall yield. The unwanted adjacent cis-linked
product 195c was often the predominant isomer. To increase the yield
of the more interesting cross trans-linked isomers, formation of the
bridges was delayed until after the porphyrin-forming condensation.
Tetra-(o-methoxyphenyl)porphyrin 196 was obtained from pyrrole and o-
methoxybenzaldehyde (10% yield) and demethylated to provide the tetra-
(o-hydroxyphenyl)porphyrin 197. Alkylation with the dibromo derivatives
193 under high dilution in DMF at 100°C, followed by chromatography led
to the isolation of the three porphyrin isomers 195. In this case the
major product of each reaction was the desired cross trans-linked
isomer 195a (Scheme 57). (The starting T(OH)PP was used as a mixture
of the four possible atropisomers since the conditions of the condensa-
tion would lead to equilibration).

The degree of steric encumbrance is illustrated by the rates of
metallation and oxidation of the various isomers. The adjacent cis-
linked isomer 195c has one face unhindered and is easily metallated.
In contrast the other isomers, where both faces are hindered undergo
iron insertion reluctantly. While not preventing ligation of nitrogenous
bases or gases, the chains do inhibit irreversible oxidation at room
temperature. For the four-coordinate iron(II) cross trans-linked
isomer 195a the $t_{1/2}$ for oxidation to the hematin derivative PFe(III)-OH
is 1.5-10.5 minutes compared to 7-54 seconds for oxidation of the less
hindered isomers to the μ-oxo dimer. Similarly, in toluene at 25°C
under O_2 (1 atm), $t_{1/2}$ for oxidation of the six-coordinate iron(II) complex
is 11-25 minutes for the cross trans-linked isomer compared to 1.5-12

SCHEME 56

Br—R—Br + [2-hydroxybenzaldehyde] → [194]

193

(a) R = —(CH₂)₁₀—

(b) R = —(CH₂)₁₁—

(c) R = —(CH₂)₁₂—

(d) R = —(CH₂)₃—[C₆H₄]—(CH₂)₃—

(e) R = —(CH₂)₄—[C₆H₄]—(CH₂)₄—

195 (a)
cross-*trans*-linked

(b)
adjacent-*trans*-linked

(c)
adjacent-*cis*-linked

SCHEME 57

196

197

195 (a)
cross-*trans*-linked

(b)
adjacent-*trans*-linked

(c)
adjacent-*cis*-linked
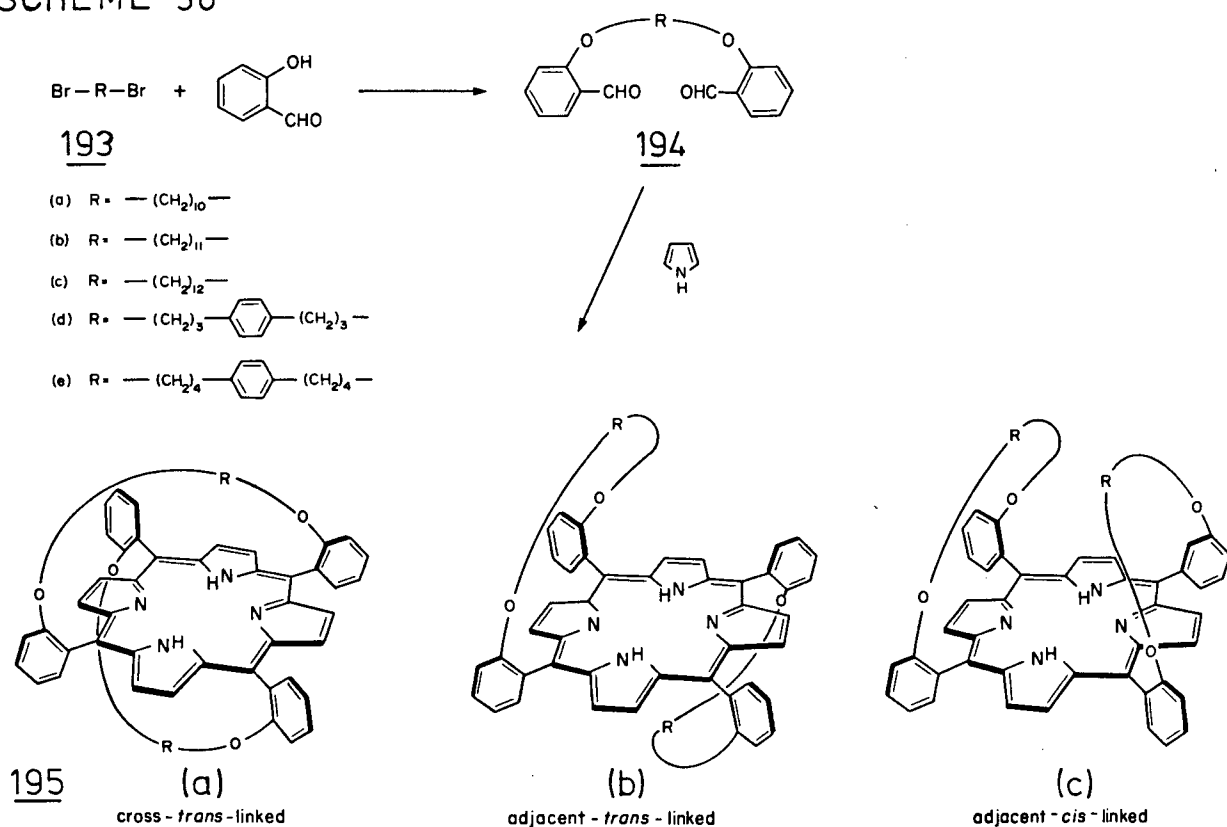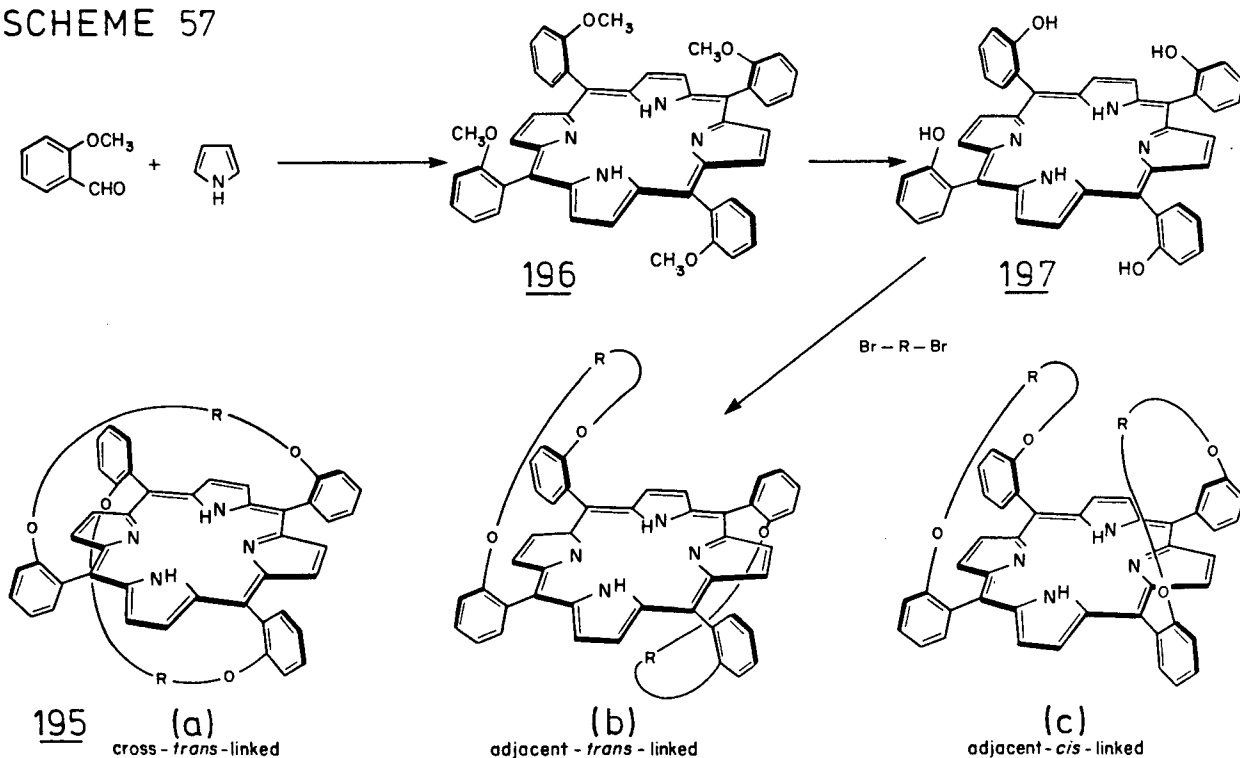
minutes for the other two isomers.[134]

A similar doubly-strapped porphyrin has been reported by
Bogatskii.[135] The $\alpha,\beta,\alpha,\beta$ atropisomer of meso-tetra(o-aminophenyl)porphyrin
107 was acylated with triglycolic dichloride at room temperature in the
presence of pyridine, conditions that do not cause significant isomeri-
zation of the atropisomer. The doubly-strapped porphyrin was obtained
in 32% yield after chromatography (Scheme 58).

A further refinement to the production of heme protein models was
the synthesis of doubly-strapped models containing different straps.
As models for hemoglobin or myoglobin, incorporation of a nitrogen base
into one strap would simulate the proximal face of the natural system
while the steric encumbrance provided by the second strap would be
analogous to the distal, oxygen binding face.

Momenteau's route to doubly-strapped porphyrins was easily adapted
to produce compounds in which an axial base was incorporated into one
of the straps.[136] Condensation of tetra(o-hydroxyphenyl)porphyrin 197
(mixture of four isomers) with one equivalent of 1,12-dibromododecane
gave a mixture of two singly-linked porphyrins, depending on whether
adjacent 199, or opposite 198 meso-phenyl groups were linked. This
mixture was reacted with 3,5-bis(3-bromopropyl)pyridine 200 and the
desired cross trans-linked isomer 201 isolated by preparative tlc (5%
overall) (Scheme 59). A similar porphyrin 203 was prepared from $\alpha,\beta,\alpha,\beta$-
tetra(o-aminophenyl)porphyrin 107; in this case the straps were tied
to the porphyrin skeleton by amide linkages. Following iron insertion
and reduction, both visible absorption and ^{1}H-NMR spectra of both
compounds were consistent with a five-coordinate high spin (S = 2)
iron(II) complex.

SCHEME 58

$$Cl\ C\ CH_2O\ CH_2CH_2\ OCH_2\ C\ Cl$$
$$O \qquad\qquad O$$

THF/ pyr

107

SCHEME 59

197

199

200

Br(CH₂)₁₂Br

198

+

Br(CH₂)₃

Br(CH₂)₃

N

201

Fe

ClCO-(CH₂)₂COCl

(CH₂)₂COCl

N

203

107

THF/Et₃N
R.T.
ClOC(CH₂)₁₀COCl

202
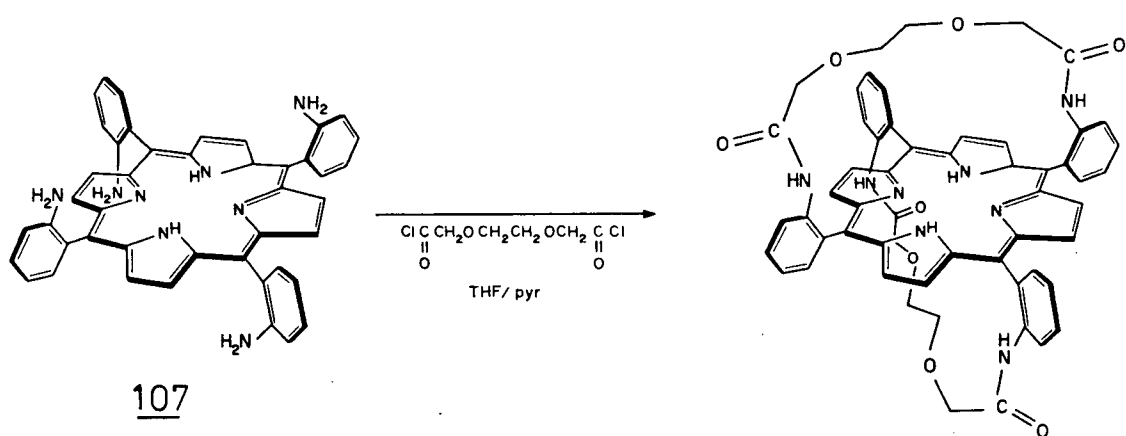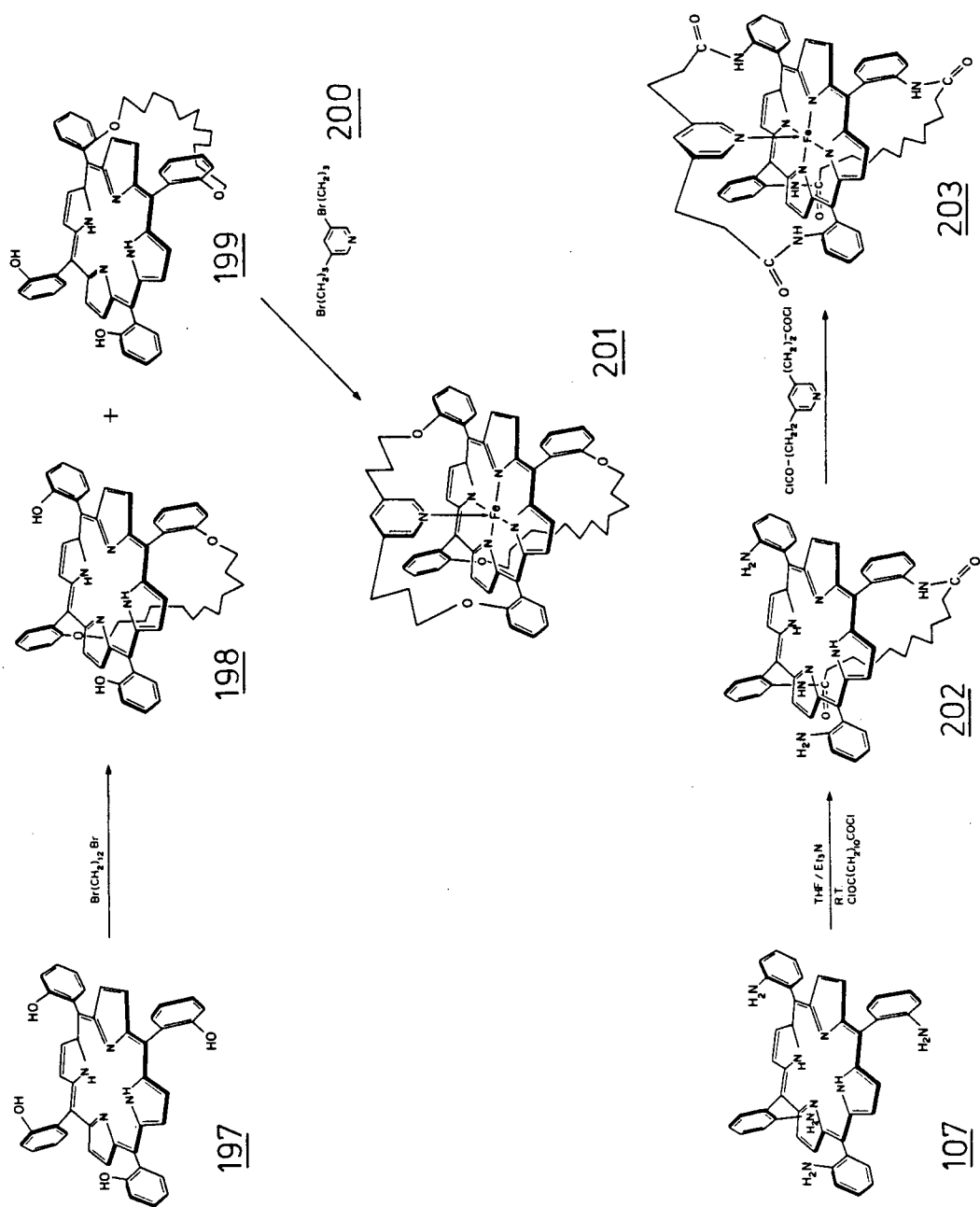
The rate constants for the association and dissociation of O_2 and CO were determined by laser flash photolysis. The O_2 affinity of the "amide" linked system was higher than that of the "ether" linked compound ($P_{\frac{1}{2}}^{O_2}$ 18.6 vs 2) as a result of a difference of a factor of ca. 10 in the O_2 dissociation rates ($k_{off}^{O_2}$ 4 vs 0.5). This increase in stability of the "amide" oxygenated species was attributed to the presence of the N-H group and the possibility of hydrogen-bonding with the terminal oxygen atom. The low temperature (-27°C) ^{1}H-NMR spectrum was used to support this thesis, the observed inequivalence of the pyrrole protons as well as the shifts of the amide protons suggesting a preferred orientation of the oxygen molecule towards the amide N-H's.[137]

To better model the hemoglobin and myoglobin active sites a doubly-strapped porphyrin 204 was prepared incorporating a pendant imidazole (Scheme 60).[138] The iron(II) derivative was capable of binding oxygen to give a relatively stable oxygenated species (lifetime was about one day in dry toluene under 1 atm O_2). The kinetics of O_2 and CO binding have been determined and initial comparisons with the comparable "pendant pyridines" porphyrins show:

(i) O_2 and CO combination rates are practically constant in the three pendant base porphyrins, and

(ii)   a reduction in $k_{off}^{O_2}$ in the imidazole porphyrin due to a combination of hydrogen bonding with the amide N-H and the greater basicity of imidazole over pyridine.

Comparison of the pendant imidazole model with myoglobin or isolated hemoglobin chains shows that the model reacts 10 times faster with O_2

SCHEME 60

107

ClOC(CH₂)₁₀COCl →

202

ClOC(CH₂)₄CH(CH₂)₄COCl

204

SCHEME 61

205

HO(CH₂)₃ ⎯⎯ (CH₂)₃OH →

206

1. H₂, Pd/C
2. (COCl)₂
3.

207

208
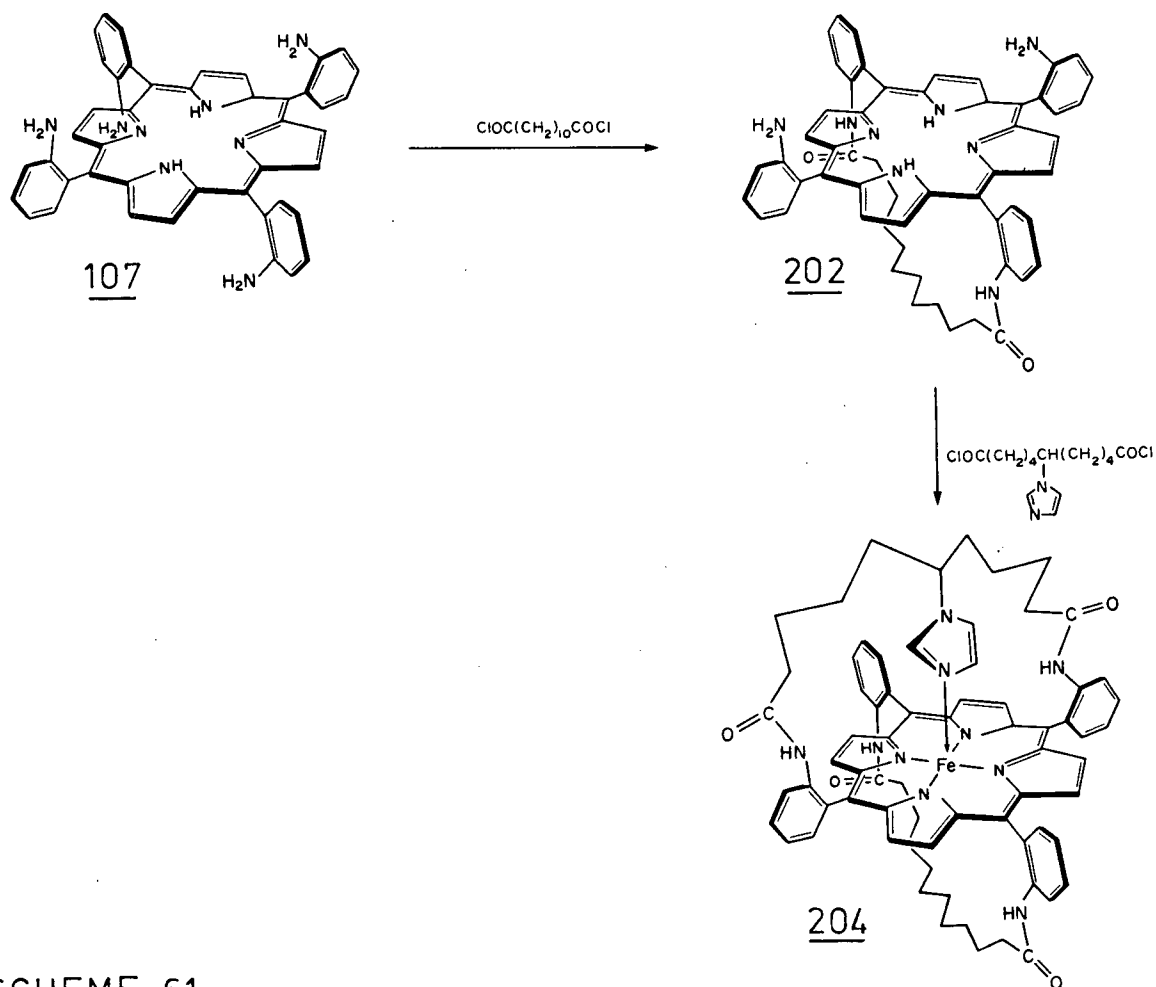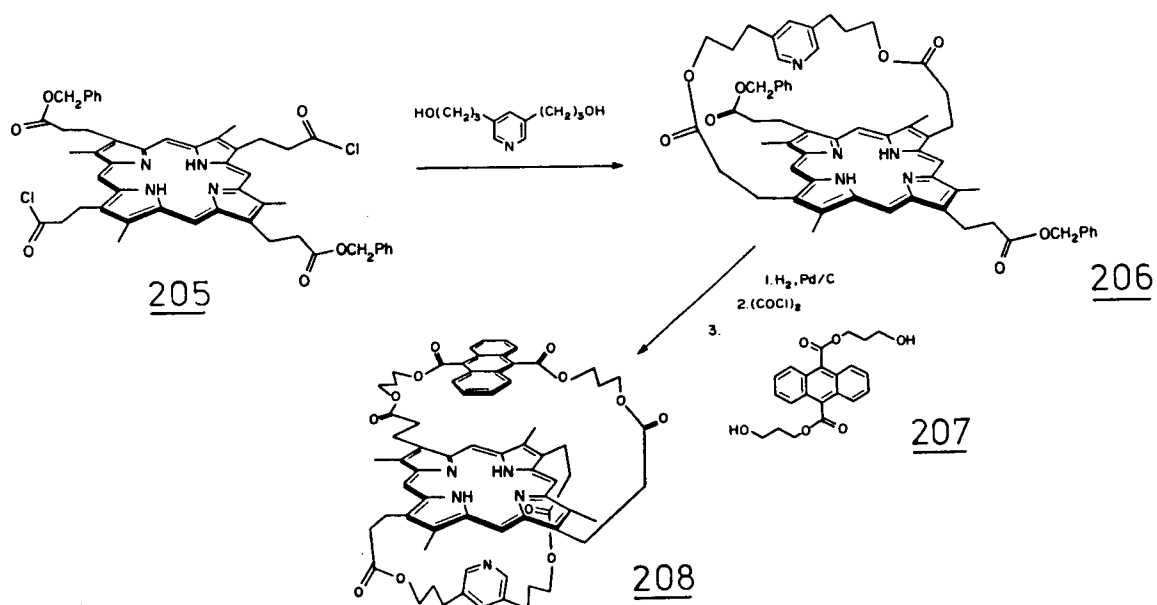
and that the dissociation rate is ∿100 times faster than in the natural systems.

With the availability of the differentially protected copro-porphyrin I 205, Battersby adapted his syntheses to the production of doubly-strapped porphyrins (Scheme 61).[139] Reaction of the bis-acid chloride 205 with 3,5-bis(3-hydroxypropyl)pyridine yielded the pyridine-strapped porphyrin 206 (33%). Hydrogenolysis of the benzyl esters and acid chloride formation was followed by condensation with the anthracene diol 207 to give the doubly-bridged porphyrin 208 (27%). Iron insertion was found to be difficult so the metal was inserted after the introduction of the pyridine strap. Reduction with aqueous dithionite furnished the iron(II) species which on the basis of the visible absorption spectrum was judged to be high spin (S = 2) five-coordinate. Exposure to oxygen gave an oxygenated compound with a $t_{1/2}$ of ∿15 minutes at room temperature in CH_2Cl_2. In DMF a more stable oxygenated species was formed ($t_{1/2}$ ∿2 hr at 20 °C). The O_2 could be displaced by passing CO into the solution, and, surprisingly, regeneration of the oxygenated species was accomplished by passage of O_2. Such O_2-CO cycles could be repeated six times without significant irreversible oxidation. This was in contrast to the resistance of unhindered CO-porphyrin complexes to displacement of CO by O_2.

The further refinement of incorporating an imidazole ligand has been recently reported.[140] As before, the differentially protected coproporphyrin 205 was reacted with the anthracene diol 207 to give the porphyrin 209 (57%). After removal of the benzyl esters and treatment with oxalyl chloride, the bis-acid chloride was reacted with the N-substituted imidazole diol 210. The doubly-bridged porphyrin 211 was obtained

SCHEME 62

209

210

211

207

205

212(a) n = 4
(b) n = 3

213(a) n = 4
(b) n = 3

1. H₂ Pd/c
2. (COCl)₂
3.

1. H₂ Pd/c
2. (COCl)₂
3. HO(CH₂)ₙOH
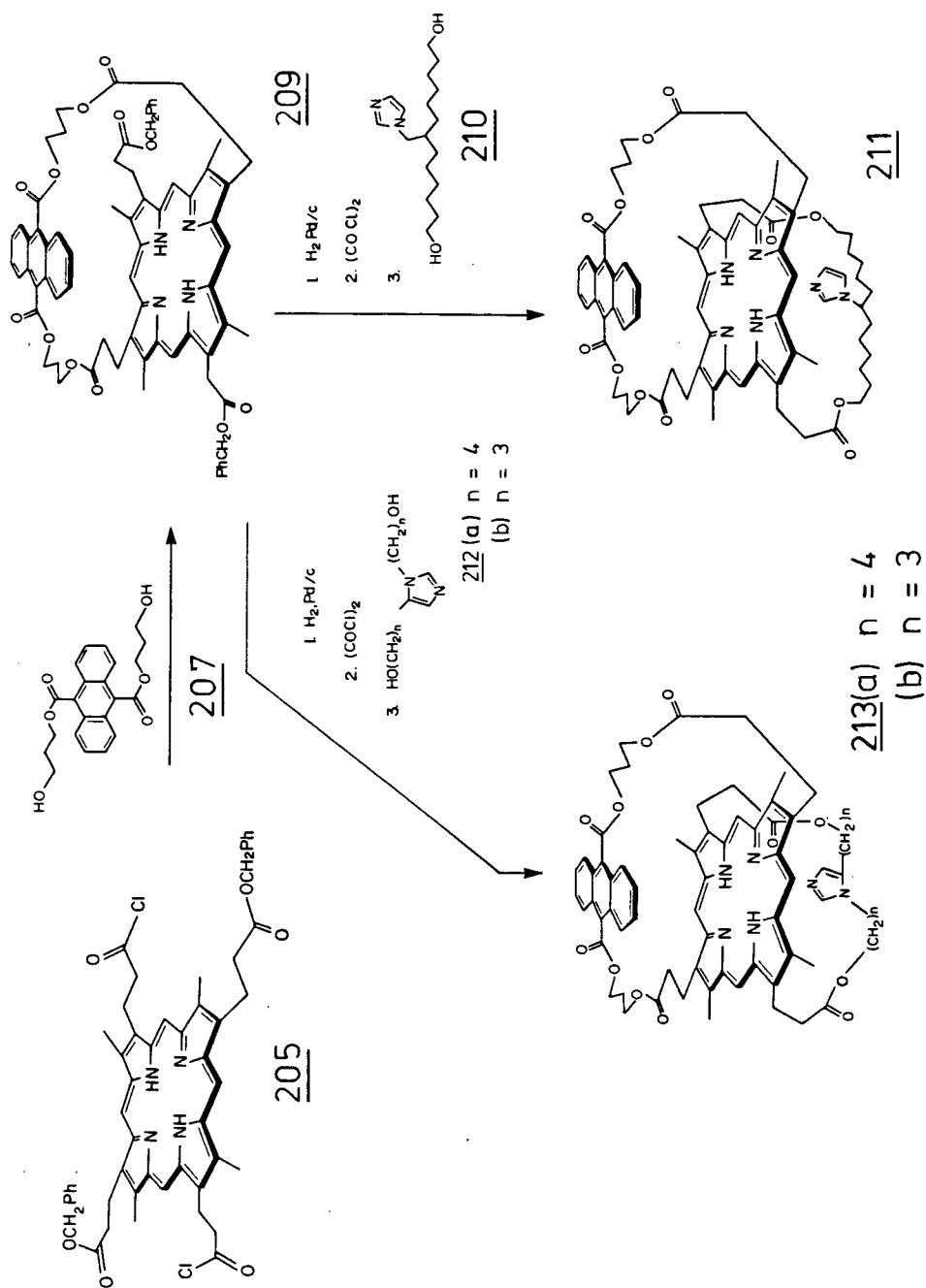
in 22% yield (Scheme 62). The iron(II) complex was capable of reversible oxygen binding, four cycles of oxygenation-deoxygenation (by reducing the pressure) being possible before significant irreversible oxidation occurred. The $t_{1/2}$ for the oxygenated species was ca. 24 hr at room temperature in DMF solution.

Recognizing that the pendant-imidazole strap was still somewhat floppy, more rigid straps containing a 1,5-disubstituted imidazole <u>212</u> were prepared as before (Scheme 62).[140] Coupling 1,5-bis(4-hydroxybutyl)-<u>212a</u> or 1,5-bis(3-hydroxypropyl)imidazole <u>212b</u> with the bis-acid chloride of the anthracene-strapped porphyrin gave the doubly-bridged systems <u>213</u> in 23% and 6% yield. Distortion of the porphyrin ring from planarity to accommodate the shorter strap was held responsible for the low yield in the latter case and also for the lesser stability of the oxygenated iron(II) species. For the n = 4 case, the iron(II) complex could reversibly bind oxygen in DMF solution at ambient temperature. Ten oxygenation-deoxygenation cycles could be performed before irreversible oxidation was significant, and only 20% irreversible oxidation after 2 days in solution.

CHAPTER 2

RESULTS AND DISCUSSION

2.1   INTRODUCTION

Wijesekera has already devised a strategy for the synthesis of porphyrins strapped with non-functionalized hydrocarbon chains, and a durene cap.[117,118] His goal was to make the hydrocarbon straps as short as possible, tying back the porphyrin and distorting the aromatic ring. Such distortion of the porphyrin macrocycle has been suggested to play a role in heme protein functioning e.g. doming of hemes during R ⟷ T state changes in hemoglobin.[141] Clearly any attempt to link opposite corners of a ‚preformed porphyrin with a hydrocarbon chain short enough to cause distortion of the ring was doomed to failure or very low yields. Furthermore, such a chain could probably only be "snapped" in place using ester or amide linkages. For short straps the system would be sufficiently taut that such linkages would be inherently unstable. In addition the amide linkage would make the compound less soluble.

Wijesekera's strategy (Fig. 1) was to synthesize the strap first and attach it to two β-free pyrroles 1 via Friedel-Crafts acylation.[117,118] Modification of the α-methyl and α'-ester groups of the bis-pyrrole 4 enabled the chain-linked bis-dipyrromethane 7 to be formed. With dipyrromethane formation all the elements necessary for construction of the porphyrin were in place. De-esterification and deprotection of the α,α'-functional groups, followed by thermal decarboxylation yielded the chain-linked α-free, α'-formyl bis-dipyrromethane 8. High dilution acid-catalyzed intramolecular cyclization furnished the intermediate porphodimethene 9 which, due to the two sp^3 carbon bridges, was relatively unstrained. In situ oxidation of 9 gave the strapped porphyrin 10, the increase in strain energy being traded off against the resonance stabilization of the aromatic ring. Wijesekera prepared 10
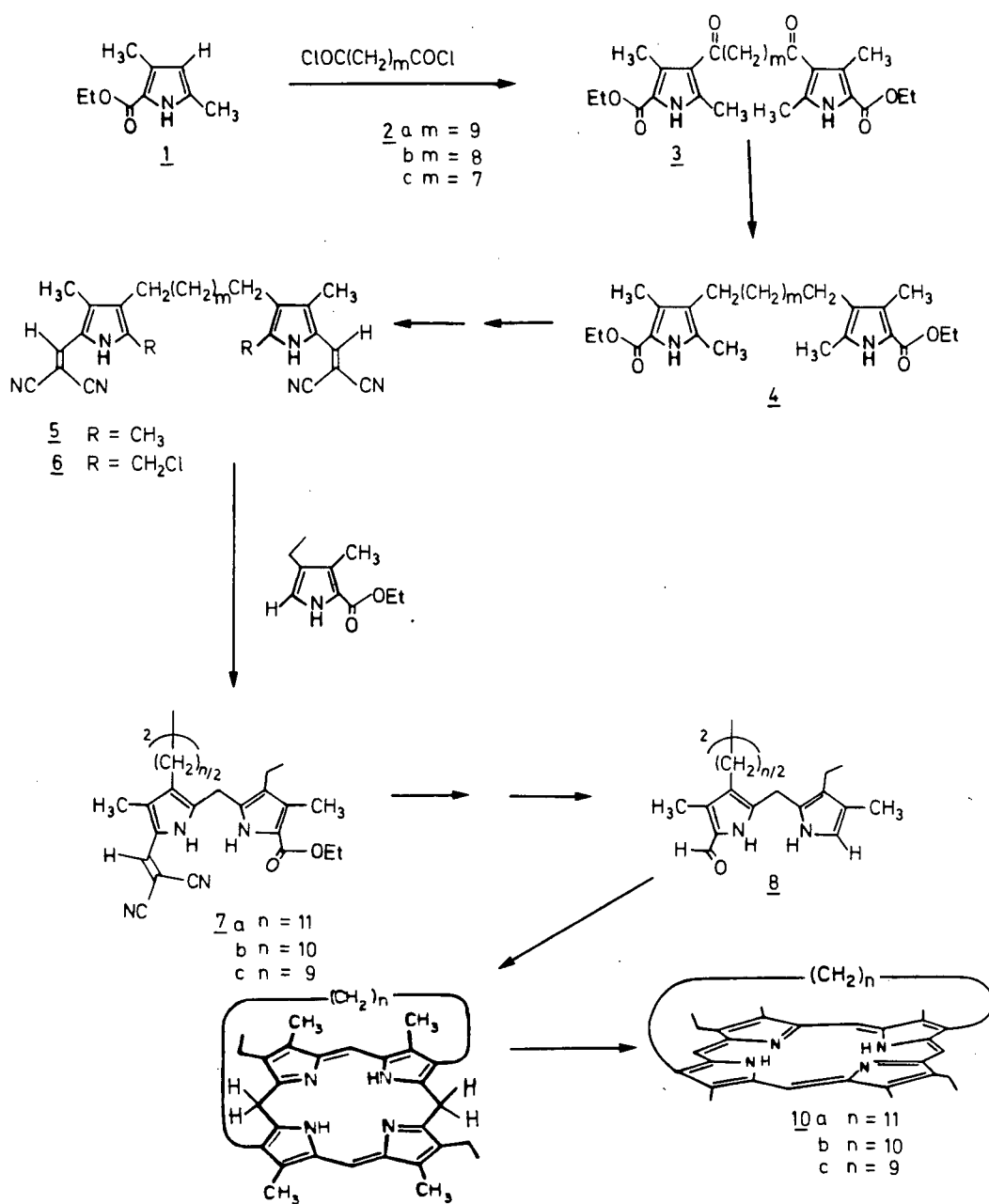
Fig. 1:   Synthesis of the Strapped Porphyrins of Wijesekera et al.[110,111]

in good yield where n = 11 (22-52%), 10 (29-37%), 9 (20-25%). Where

the chain was $-(CH_2)_5$-durene-$(CH_2)_5-$, yields were also good (22-31%)

for the final cyclization step.

With a chain length of eleven methylene units or a $-(CH_2)_5-$

durene-$(CH_2)_5-$ chain, the strapped porphyrin was essentially undistorted

and yields from the cyclization step were similar. Decreasing the

length of the chain led to a corresponding decrease in yield as distor-

tion became more severe.

We anticipated that the above strategy could be used to prepare

a strapped porphyrin containing a $-(CH_2)_5$-S-$(CH_2)_5-$ chain. It was

hoped that this compound would be a good model for cytochrome c. We

have already referred in sections 1.3.1 and 1.3.2 to the difficulty of

preparing the mixed ligand system, N-Fe-S, as a model for the active

site of cytochrome c where methionine 80 and histidine 18 coordinate

to the heme iron. Unless one of the ligands is covalently attached to

the porphyrin periphery only the symmetric complex is obtained. In

our case the sulfide is incorporated into a strap which is slightly

more than eleven methylene units long; long enough to produce a

virtually planar, strain-free porphyrin, yet short enough to ensure

that the sulfur atom would bind to the iron of the corresponding heme.

The series of reactions outlined in Fig. 2 was attempted.

Refluxing 2,4-dimethyl-iodopentylpyrrole 11 with 1.5 equiv. of sodium

sulfide in aqueous THF gave the bis(pyrrol-3-yl)pentyl sulfide 12 in

94% yield. Saponification with potassium hydroxide in aqueous propanol

gave, after 2 hours reflux, the bis(α-carboxypyrrol-3-yl)pentyl sulfide

13. This compound was not purified or characterized but was immediately

decarboxylated in refluxing N,N-dimethylformamide. The course of the
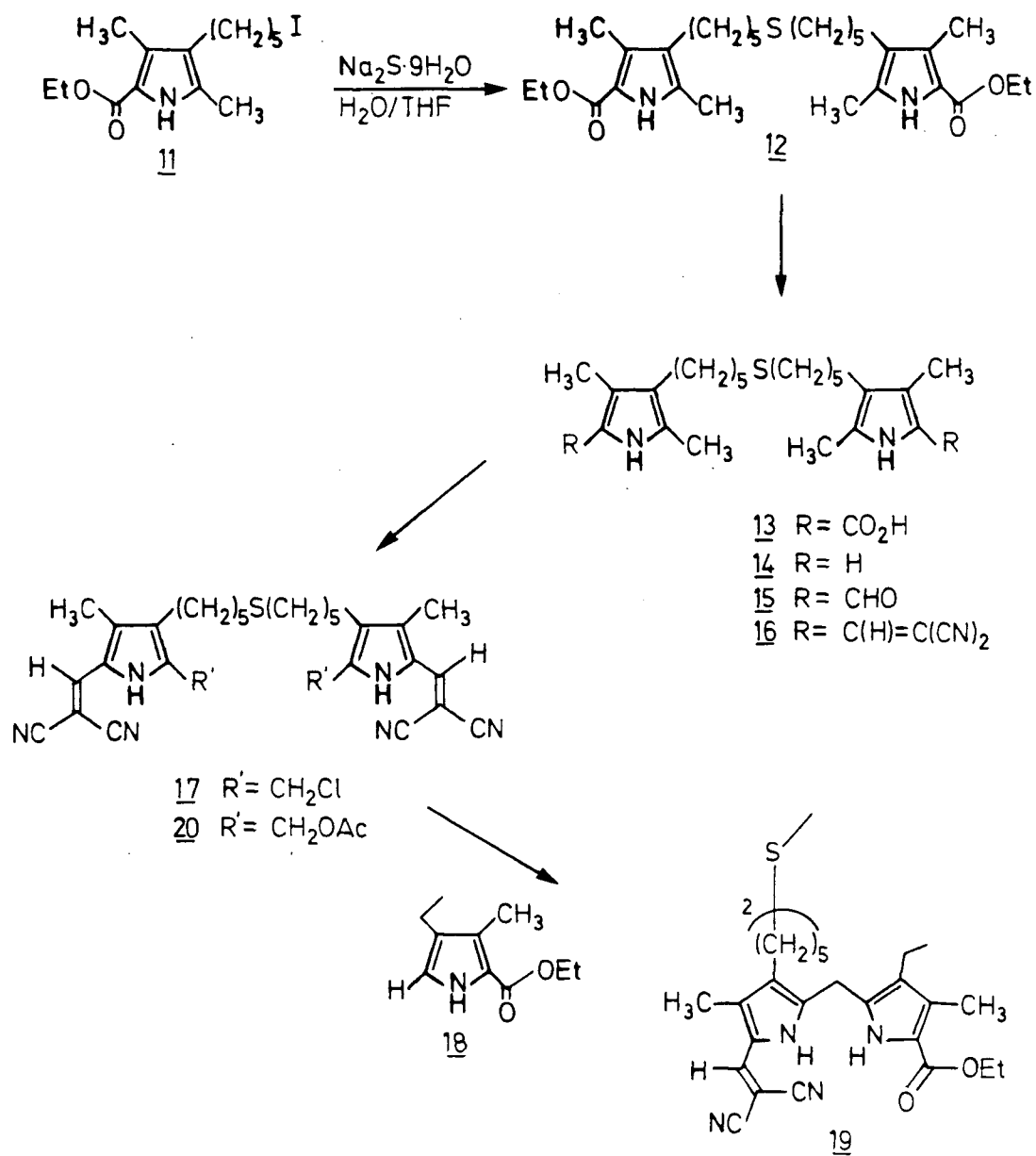
Fig. 2: Attempted Synthesis of the Bis-dipyrromethane 19

reaction was followed by UV spectroscopy, disappearance of the band at
283 nm being indicative of complete decarboxylation. Vilsmeier
formylation of the crude bis(α-free-pyrrol-3-yl)pentyl sulfide 14
was carried out in situ using phosphorous oxychloride and N,N-dimethyl-
formamide. The crude product 15 was treated with malononitrile and
cyclohexylamine, protecting the α-formyl function as the 2,2-dicyano-
vinyl derivative 16. Only at this stage was the product isolated and
purified by column chromatography.

Compound 16 was treated with 2 equivalents of sulfuryl chloride
to form the bis-chloromethyl compound 17, followed by addition of the
α-free pyrrole 18 and refluxing of the reaction mixture. Typically,
dipyrromethanes such as compound 19 show up on tlc as bright yellow
spots which turn violet on exposure to bromine. Tlc of the reaction
mixture, however, showed such a spot only faintly; there were many
other compounds, one being due to unreacted α-free pyrrole 18. ^{1}H-NMR
examination of the crude reaction product showed only a weak signal at
3.92 δ (the bridge $-CH_2$ protons of dipyrromethanes occur at 3.9-4.0 δ),
with a large doublet at 6.53 δ due to the α-H of the unconsumed α-free
pyrrole 18. The failure of this reaction indicated that chloromethyla-
tion of 16 was not occurring as anticipated. This result was not
surprising in view of the known reactivity of sulfides with sulfuryl
chloride to produce α-chlorosulfides.[142] The reaction is believed to
proceed by a mechanism involving chlorosulfonium salts I as inter-
mediates.[143] Such sulfur-chlorine complexes are stable at low
temperatures (-78 to -40°C) and even at 0°C for short periods. However
on warming to room temperature they decompose to give the α-chlorosul-
fides II. Alternatively, hydrolysis at low temperature (-78°C) produces

the corresponding sulfoxide III.[144]

SCHEME 63

$$-CH_2-S-CH_2- \xrightarrow[-70°C]{SO_2Cl_2} \left[-CH_2-\overset{+}{\underset{Cl}{S}}-CH_2- \right] \quad I$$

(95% EtOH, -70°C)

$$-CH_2-\underset{O}{\overset{\parallel}{S}}-CH_2- \qquad -CH_2-S-\underset{Cl}{\overset{|}{CH}}-$$

$$\underline{III} \qquad\qquad \underline{II}$$
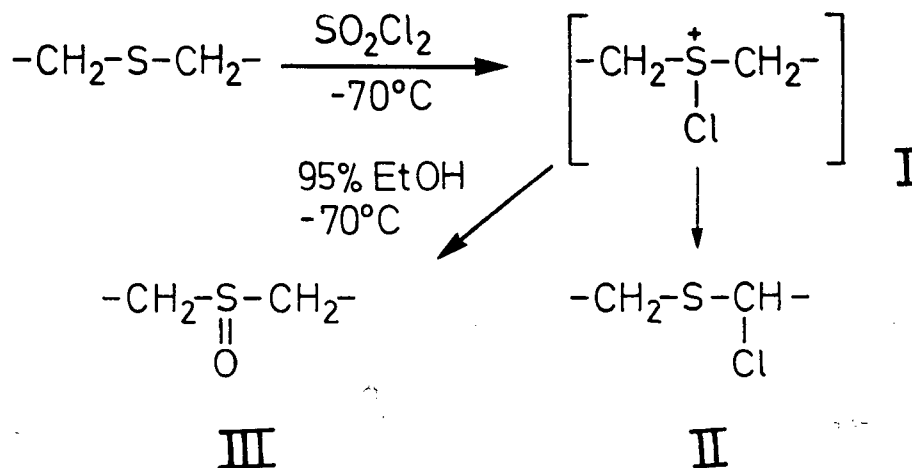
The failure of the chloromethylation reaction of the ιbis(pyrrol-3-yl)pentyl sulfide 16 with 2 equivalents of sulfuryl chloride at room temperature and higher was thought to be due to competing α-chlorination of the sulfide chain. The reaction was repeated at low temperature using 3 equivalents of sulfuryl chloride, one each for the two α-methyl groups and one for the formation of the ·chlorosulfonium salt which would be transformed to a sulfoxide during work-up.

16   R′ = CH₃
17   R′ = CH₂Cl

18
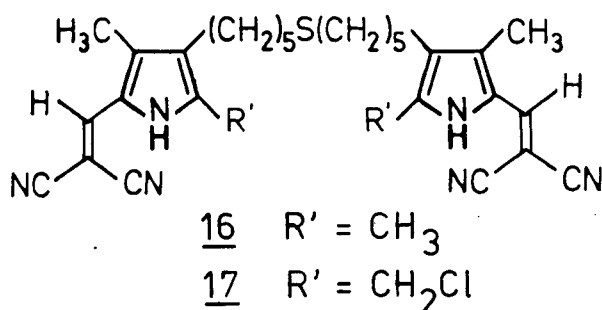
The bis(pyrrol-3-yl)pentyl sulfide 16 was dissolved in dichloromethane and cooled to -60°C. The sulfuryl chloride was added and the

solution stirred at -60°C for 2 hours, then at -40°C overnight. A solution of the α-free pyrrole 18 in dichloromethane and glacial acetic acid was added and the solution allowed to warm to room temperature. After work-up neither ^{1}H-NMR nor tlc showed any significant amount of desired bis-dipyrromethane 19.

Dipyrromethanes may also be synthesized by the condensation of α-acetoxymethyl and α-free pyrroles in the presence of acid. Thus the chain-linked bis-(pyrrol-3-yl)pentyl sulfide 16 was treated with 4 equivalents of lead tetraacetate to give 20. A crude product was isolated and allowed to react with the α-free pyrrole 18. Again examination of the reaction mixture by tlc and ^{1}H-NMR gave no evidence of significant formation of the desired bis-dipyrromethane 19.

$\underline{20}$
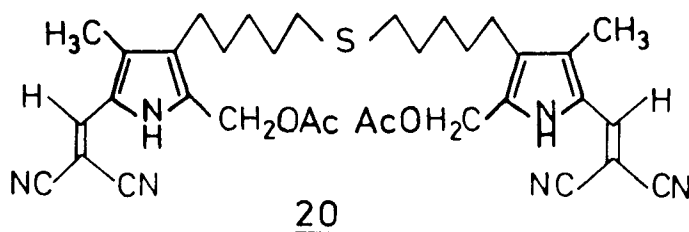
As with sulfuryl chloride, sulfides are attacked by lead tetraacetate. Depending on the nature of the solvent the initially formed acyloxysulfonium cation IV[148] may rearrange to the α-substituted sulfide V or the sulfoxide VI.[149] Likewise the α-acetoxymethyl pyrrole route was not pursued since, if any bis-dipyrromethanes were produced, it would be a mixture of products.

At this stage it was considered that Wijesekera's synthetic strategy might not be directly applicable to the synthesis of strapped porphyrins containing non-inert straps. It was considered that the

SCHEME 64
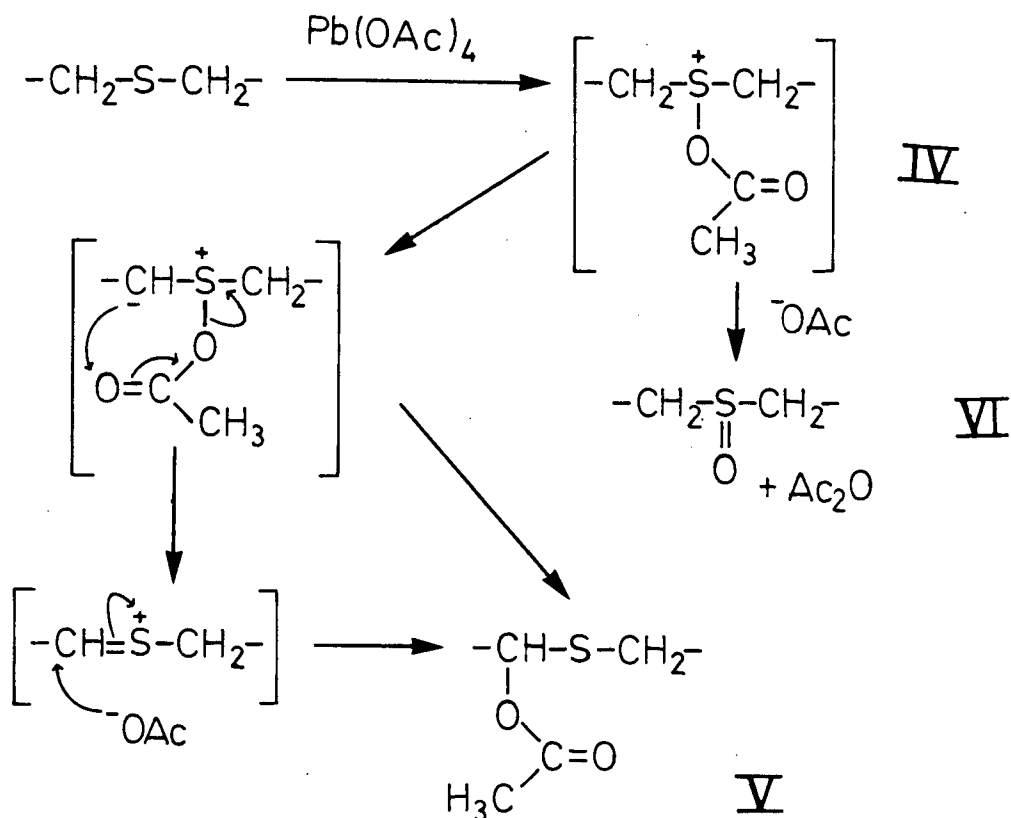
route contained two potentially troublesome steps:

(i)   The Friedel-Crafts acylation of a β-free pyrrole 1 using stannic
      chloride as catalyst, and

(ii) the use of sulfuryl chloride to prepare the chain-linked α-chloro-
      methyl pyrrole dimer, the precursor of the protected bis-dipyrro-
      methane.

Obviously the use of stannic chloride and the necessary formation
of a bis-acid chloride might not be compatible with formation of strapped
porphyrins bearing acid sensitive functionalities in the chain.

Sulfuryl chloride presented two problems. This reagent has been
widely used for the side-chain halogenations of polysubstituted α-methyl

pyrroles.[150] The resulting α-chloromethyl pyrroles have been used as intermediates in the preparation of a number of pyrrole oligomers such as dipyrromethanes, dipyrromethenes and porphyrins. Despite their importance, little attention has been paid to the mechanisms of these halogenations. In one instance, side-chain chlorination with sulfuryl chloride was assumed to occur by a free radical mechanism.[151] Illuminati et al., recently suggested that the mechanism of sulfuryl chloride action might be similar to that of molecular chlorine[152] and bromine,[153] and might proceed by an electrophilic mechanism. They studied the chlorination of specially selected α-methyl pyrroles with molecular chlorine at low temperatures (-28°C) and in the dark. The results suggested that the overall process consists of two main steps, i.e., electrophilic nuclear attack and subsequent rearrangement of the halogen from either the adjacent β- or the vinylogous α'- position to the side-chain. That a radical mechanism did not hold was supported by the fact that the results were unaffected by sunlight and radical scavengers such as galvinoxyl. Furthermore their results provided some analogies with the nonconventional electrophilic substitutions of highly activated methyl substituted aromatics leading to side-chain chlorination.[154]

Unlike the pyrrole case, halogenation of alkylbenzenes has been extensively studied. With less substituted benzene rings and under illumination the reaction proceeds through a free radical mechanism. Lee[155] has studied the light induced chlorination of alkylbenzenes in carbon tetrachloride at 40°C using sulfuryl chloride. The suggested course of the reaction is as follows where hydrogen abstraction is by the chlorosulfinyl radical.[156]

$$R-H \ + \ \cdot SO_2Cl \ \longrightarrow \ R\cdot \ + \ SO_2 \ + \ HCl \qquad\qquad (30)$$

$$R\cdot \ + \ SO_2Cl_2 \ \longrightarrow \ R-Cl \ + \ \cdot SO_2Cl \qquad\qquad (31)$$

$$\cdot SO_2Cl_2 \ \rightleftharpoons \ SO_2 \ + \ Cl\cdot \qquad\qquad (32)$$
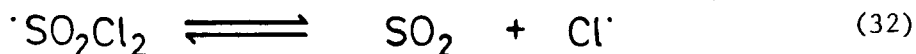
In contrast the dark reaction of polyalkylated benzenes proceeds by an electrophilic mechanism. Thus, reaction of hexamethylbenzene with chlorine involves electrophilic nuclear attack to give the benzene-onium ion which decomposes, via rearrangement of the chlorine from the nucleus to the side-chain, to give the α-chloromethyl benzene.

SCHEME 65
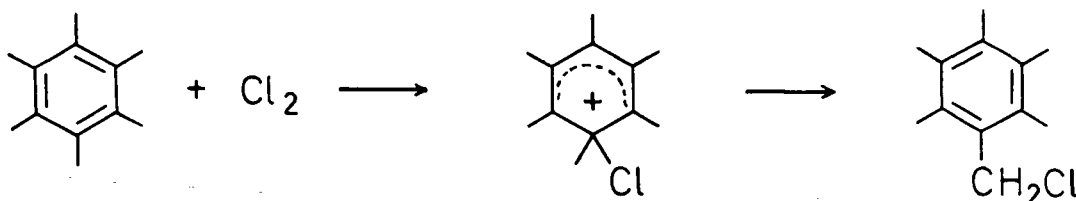
These results suggested that any attempt to monochlorinate the α-methyl groups of compounds 21 and 23 with sulfuryl chloride might also lead to chlorination of the substituted benzene ring (equations 34 and 35). Wijesekera[117] had shown that exclusive pyrrole side-chain chlorination could take place even in the presence of a hexasubstituted benzene in the reaction of compound 25 with sulfuryl chloride in the dark (equation 36). However, although the pyrrole nucleus is known to be highly reactive towards electrophilic attack, the presence of electron donating methoxy groups might make the benzene ring sufficiently reactive to compete with it.

By this time we were aware that sulfuryl chloride could react

SCHEME 66

(33)

(34)

(35)

(36)
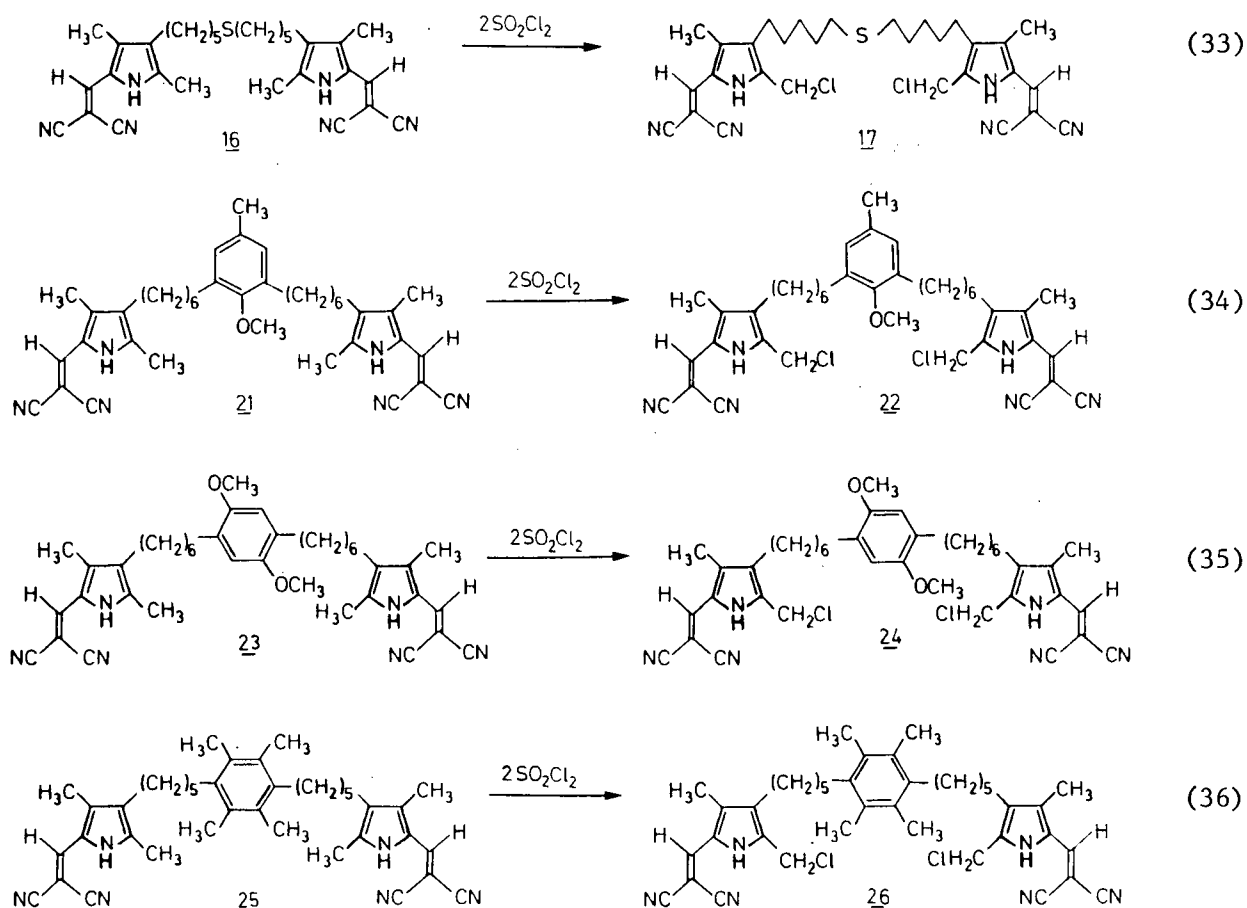
with sulfides to form α-chlorosulfides and/or sulfoxides, depending on reaction conditions. This was demonstrated by our failure to form the bis(α-chloromethyl) pyrrole 17. Furthermore we wished to prepare strapped porphyrins with an anisole or a bis-methoxybenzene ring incorporated into the strap; demethylation would then give a compound with a phenol or a quinone ring respectively, covalently linked to a porphyrin. For this purpose compounds 22 and 24 would be required. However from the above considerations it seemed doubtful if selective chlorination of the α-methyl groups could be effected.

For these reasons it was decided that chlorination of a pyrrole α-methyl function should occur before chains incorporating susceptible groups are set in place. To this end we devised an alternative synthetic route which was a variation on Wijesekera's strategy. In this alternative reaction scheme both the Friedel-Crafts acylation and the modification of the pyrrole α-methyl group are carried out before the strap is set in place (Fig. 3). The various porphyrin syntheses all start from a common intermediate 44 or 64, which is easily obtained in pure form and in large quantities by known reactions.
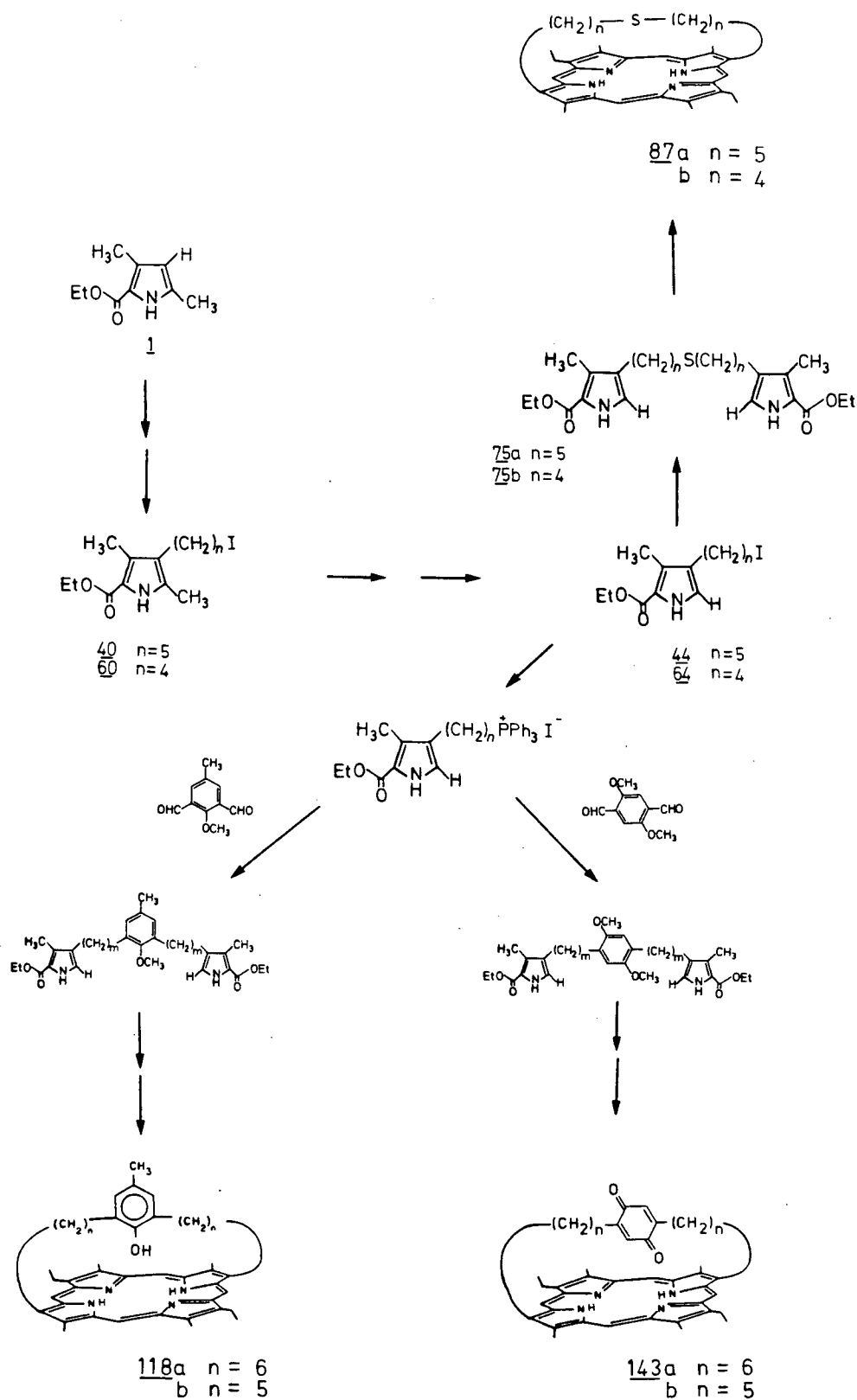
Fig. 3: Proposed Syntheses of Strapped Porphyrins

2.2   SYNTHESIS OF 5-(5-ETHOXYCARBONYL-4-METHYLPYRROL-3-YL)-1-

IODOPENTANE 44 AND ITS LOWER HOMOLOGUE 64

Heating ethyl hydrogen glutarate with excess thionyl chloride

formed the acid chloride 27, which was immediately used in the Friedel-

Crafts acylation of β-free pyrrole 1 (Fig. 4). Stannic chloride was

added dropwise to a cold solution of the crude acid chloride 27 and

the pyrrole 1. When tlc indicated complete consumption of starting

pyrrole the reaction mixture was poured into 2M hydrochloric acid and

the dichloromethane layer separated. Extraction with sodium bicarbonate

solution removed any unreacted acid chloride. The crude keto-ester 28

was recrystallized from aqueous ethanol to give a 84% yield.

Reduction of the keto-ester 28 to the hydroxypentyl pyrrole 30

may be carried out in one or two steps. Thus keto-ester 28 was

dissolved in dry tetrahydrofuran and 2.0 equivalents of sodium boro-

hydride added. Boron trifluoride etherate (2.8 equivalents) was then

added dropwise over a period of 20 minutes. The course of the reaction

was followed by tlc as the starting material was reduced first to the

pentyl ester pyrrole 29 and then to the hydroxypentyl pyrrole 30. The

reaction was carried out without cooling and was complete after stirring

for 2 hours. The excess diborane was quenched by the careful addition

of glacial acetic acid (extreme caution is necessary at this stage

especially if the reaction is being carried out on a large scale).

After work-up and recrystallization a yield of 85% was obtained.

The reduction of the keto group appears to proceed more quickly than

that of the ester group. If the diborane reduction is carried out in a

mixture of tetrahydrofuran and ethyl acetate, reduction of the ester
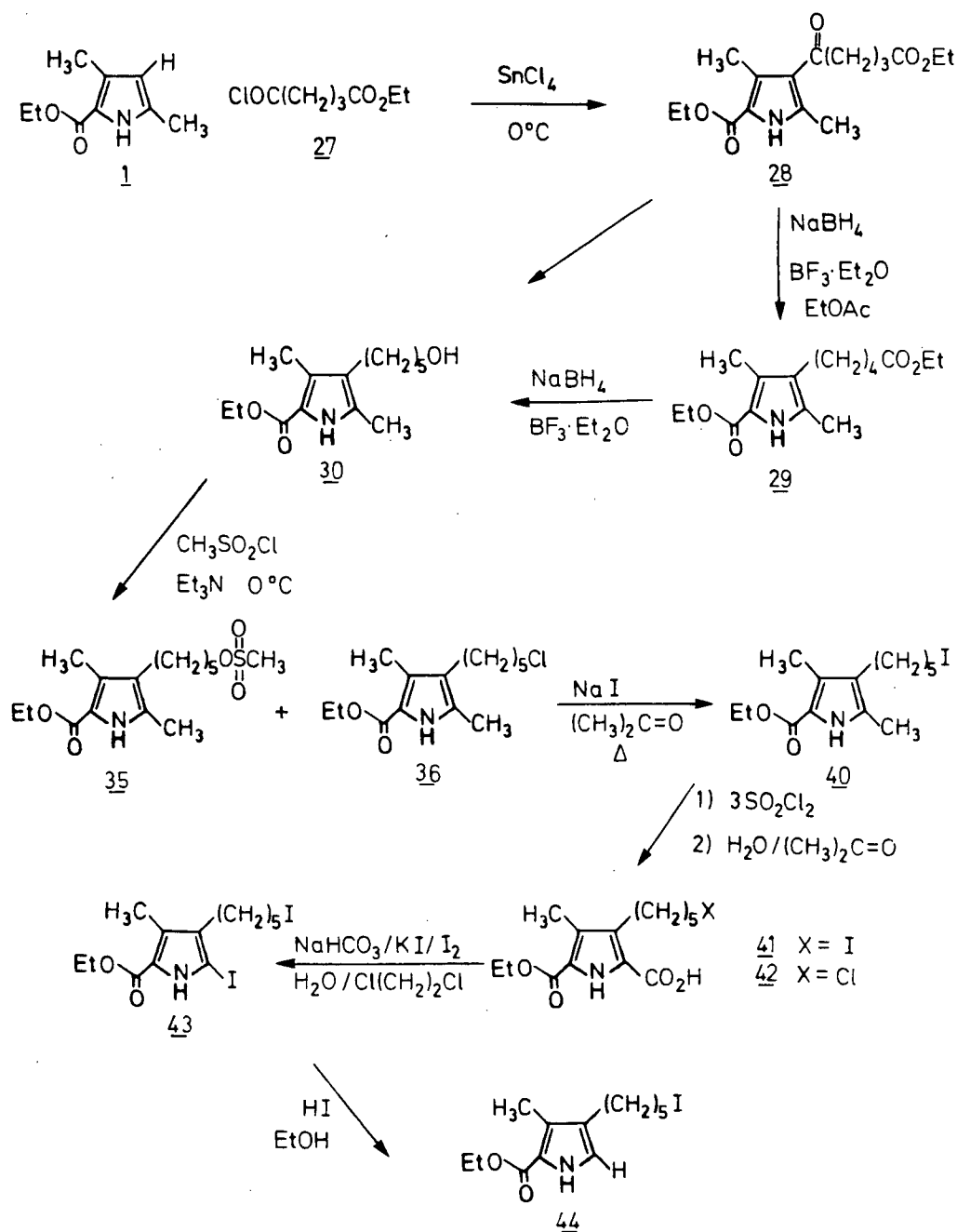
Fig. 4: Synthesis of 5-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-
iodopentane 44

function is suppressed and the product 29, arising from reduction of
the keto group only, is obtained. Reduction of the ester to the
alcohol may then be carried out in THF under the same conditions and
with a similar yield (Fig. 4).

In retrospect, it was realized that it was not necessary to use
the acid chloride of ethyl hydrogen glutarate – the bis-acid chloride
of glutaric acid would have worked equally well. Previous work[157]
had shown that the reaction of β-free pyrrole 1 with succinic and
glutaric acid bis-acid chlorides results in the formation of the
pyrrolyl keto acid 33 as the major product (Scheme 67). Presumably

SCHEME 67
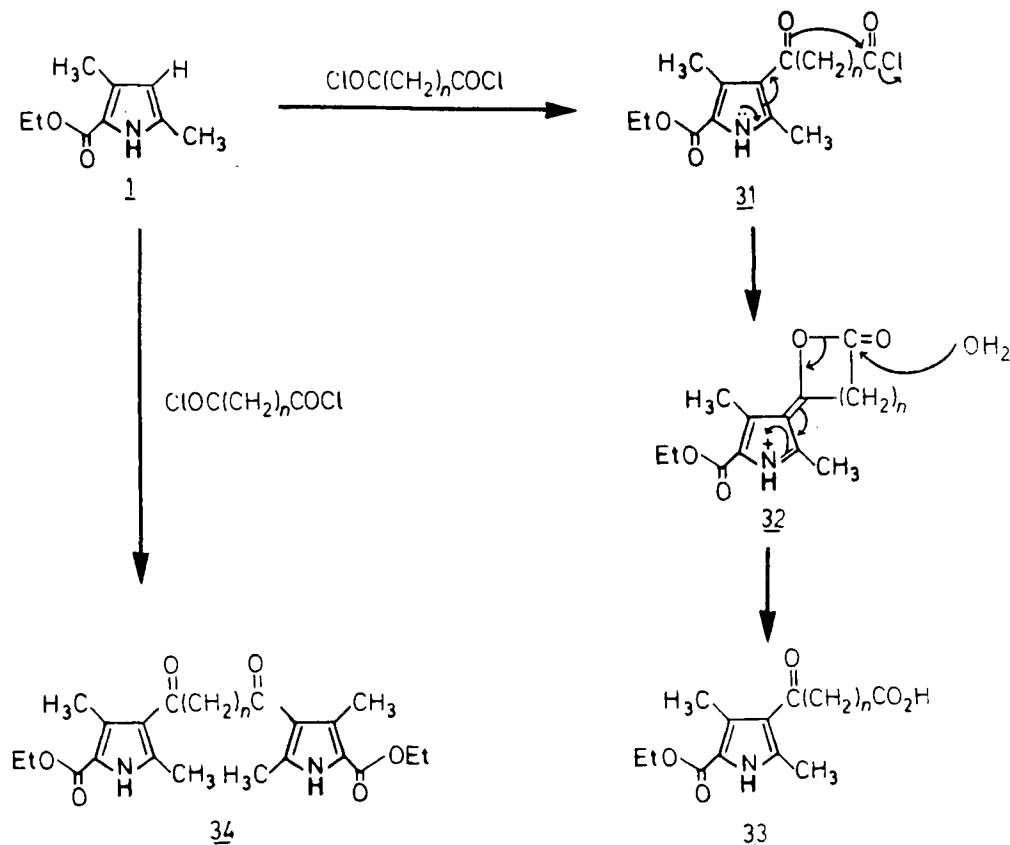
the intermediate pyrrolyl keto acid chloride 31 can cyclize to an enol

lactone 32 which, upon work-up, hydrolyzes to 33. For succinic and

glutaric acids (n = 2 and 3), the lactones are 5 and 6 membered rings

respectively, rationalizing their ease of formation. The product 33

is easily separated from any unreacted bis-acid chloride or β-free

pyrrole 1, and also from the more insoluble bis-acylated product 34.

Reduction of the pyrrolyl keto acid 33 with diborane in the usual way

would give the required hydroxyalkyl pyrrole 30.

The mesylate 35 was prepared by the method of Crossland and

Servis.[158] The hydroxypentyl pyrrole 30 and 1.5 equivalents of triethyl-

amine were dissolved in dichloromethane and cooled to 0°C. Methane-

sulfonyl chloride (1.2 equivalents) was added dropwise and the solution

allowed to warm to room temperature. Work-up included extraction with

dilute acid and saturated sodium bicarbonate to remove excess triethyl-

amine and methanesulfonyl chloride respectively. The crude product was

recrystallized from aqueous ethanol for a 92% yield.
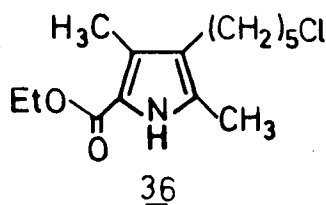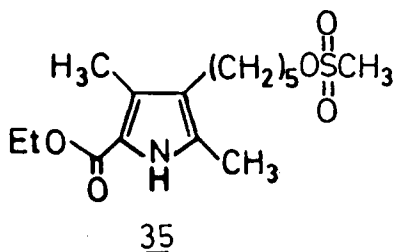
Although tlc of the crude product in several solvent systems

showed only a single spot, the product may have been contaminated with the

corresponding chloropentyl pyrrole 36. If the hydroxyoctyl pyrrole 37

was treated with triethylamine (1.5 equiv) and methanesulfonyl chloride

(1.5 equiv), and the crude product refluxed with potassium bromide in

acetone then a mixture of the bromide 38 and chloride 39 was obtained.
The chloride was presumably formed during the mesylation reaction,
bromide not being sufficiently nucleophilic to effect substitution
during the subsequent S_N2 reaction.

SCHEME 68

$$H_3C\text{—}(CH_2)_8OH\ /\ EtO\text{—}C(O)\text{—}N(H)\text{—}CH_3 \quad \underset{37}{}\ \xrightarrow[\text{2) KBr}]{\text{1) Et}_3\text{N/ CH}_3\text{SO}_2\text{Cl}}\ H_3C\text{—}(CH_2)_8Br\ \underset{38}{}\ +\ H_3C\text{—}(CH_2)_8Cl\ \underset{39}{}$$
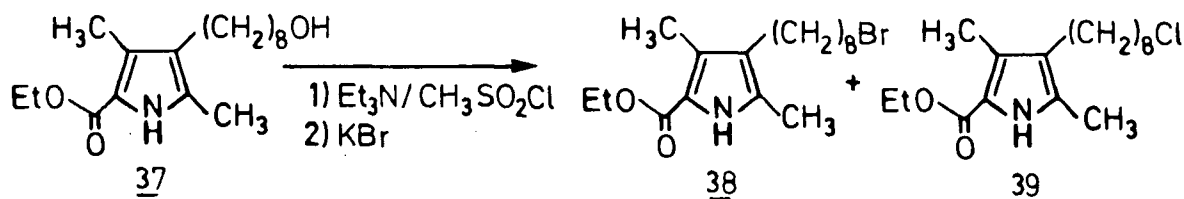
Whether or not the chloropentyl pyrrole 36 was formed in any of
the mesylation reactions was never established since the crude mesylate
was usually carried forward to the next stage without characterization.
Thus refluxing with sodium iodide (4 equiv.) in acetone gave the iodo-
pentyl pyrrole 40. After work-up the crude product was recrystallized
from ethanol to give a first crop yield of 79%; a second crop (13%)
was obtained from the mother liquor. It was found that sodium iodide
was more efficient for the reaction than potassium iodide due to the
greater solubility of the former in acetone. Efficient mechanical
stirring was required for medium-to-large scale reactions as a heavy
gelatinous precipitate was produced which caused severe bumping. Any
chloropentyl pyrrole 36 contaminant present in the crude mesylate would
have reacted with the more nucleophilic iodide ion to give the desired
product 40.

Conversion of the α-methyl-iodopentyl pyrrole 40 to the corres-
ponding α-free pyrrole 44 was effected by trichlorination of the α-methyl

group, hydrolysis to the α-carboxy pyrrole 41, and decarboxylation via
the α-iodo pyrrole 43.
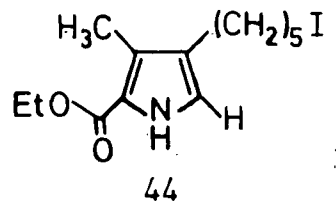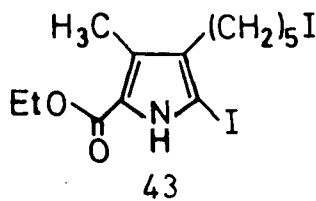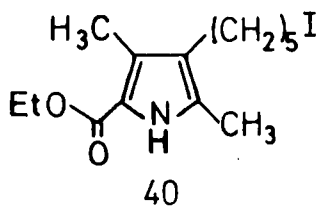
The extent of chlorination can be controlled by the stoichiometry
of the reaction. Mono-, di-, and tri- chlorination may be effected
using one, two and three equivalents of sulfuryl chloride respectively.
Chlorination of the β-methyl group is much more sluggish so there is
little danger of β-chloromethyl pyrrole formation during trichloro-
methylation even if a moderate excess of sulfuryl chloride is used.

Choice of solvent for the trichlorination reaction is important.
It has been reported that the use of chlorocarbon solvents alone leads
to incomplete reaction and impure products.[159] This was attributed to
the hydrogen chloride liberated during the reaction. Use of ether gave
variable results. The ether appears to solvate the liberated hydrogen
chloride preventing reaction with the product, but ether is known to
react with sulfuryl chloride and therefore can compete for reagent.

The reaction was carried out according to the reported method of
Battersby et al.,[160] where a compromise was struck between the desired
solubility of pyrroles in dichloromethane and the solvating property
of ether on the one hand and the adverse reactivity of ether with sulfuryl
chloride on the other. Thus the α-methyl-iodopentyl pyrrole 40 was
dissolved in a 50:50 dichloromethane/diethyl ether mixture. A solution
of sulfuryl chloride (3.3 equiv) in dichloromethane was added dropwise.

Addition was fairly rapid to ensure that the hindered, less reactive
α-dichloromethyl pyrrole could compete with the ether for the oxidant.
The solution darkened and warmed slightly as the reaction proceeded.
After removal of solvents and excess sulfuryl chloride the crude
trichloromethyl pyrrole intermediate was immediately hydrolyzed by
refluxing in 20% aqueous acetone. Removal of most of the acetone led to
the precipitation of the crude α-carboxy pyrrole. Proton nmr of the
crude product showed complete disappearance of the singlet at 2.20 δ
due to the α-methyl group and no evidence of other peaks which might
be attributed to the hydrolysis products of mono- or dichlorination.
However, not only was there a triplet at 3.20 δ due to -CH$_2$I, but in
some cases there was also a significant triplet at 3.56 δ due to -CH$_2$Cl.
This chloride substitution presented only a minor irritation since the
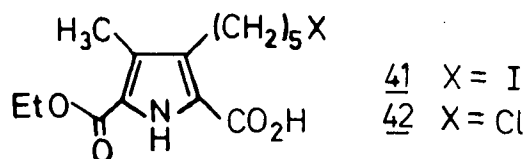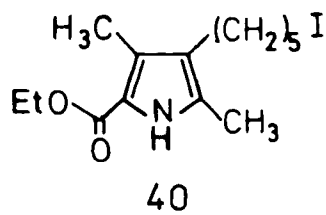
chloropentyl pyrrole 42 may be reconverted to the iodopentyl pyrrole
41 at this or any subsequent stage by refluxing with sodium iodide in
acetone.

Although α-carboxy pyrroles are known to undergo thermal decarboxyla-
tion, it has been accepted that a two step sequence involving iodinative
decarboxylation and de-iodination gives better yields and cleaner
products.[159]

The iodinative decarboxylation was carried out in a two-phase
reaction system (illustrated schematically in Fig. 5). The α-carboxy-
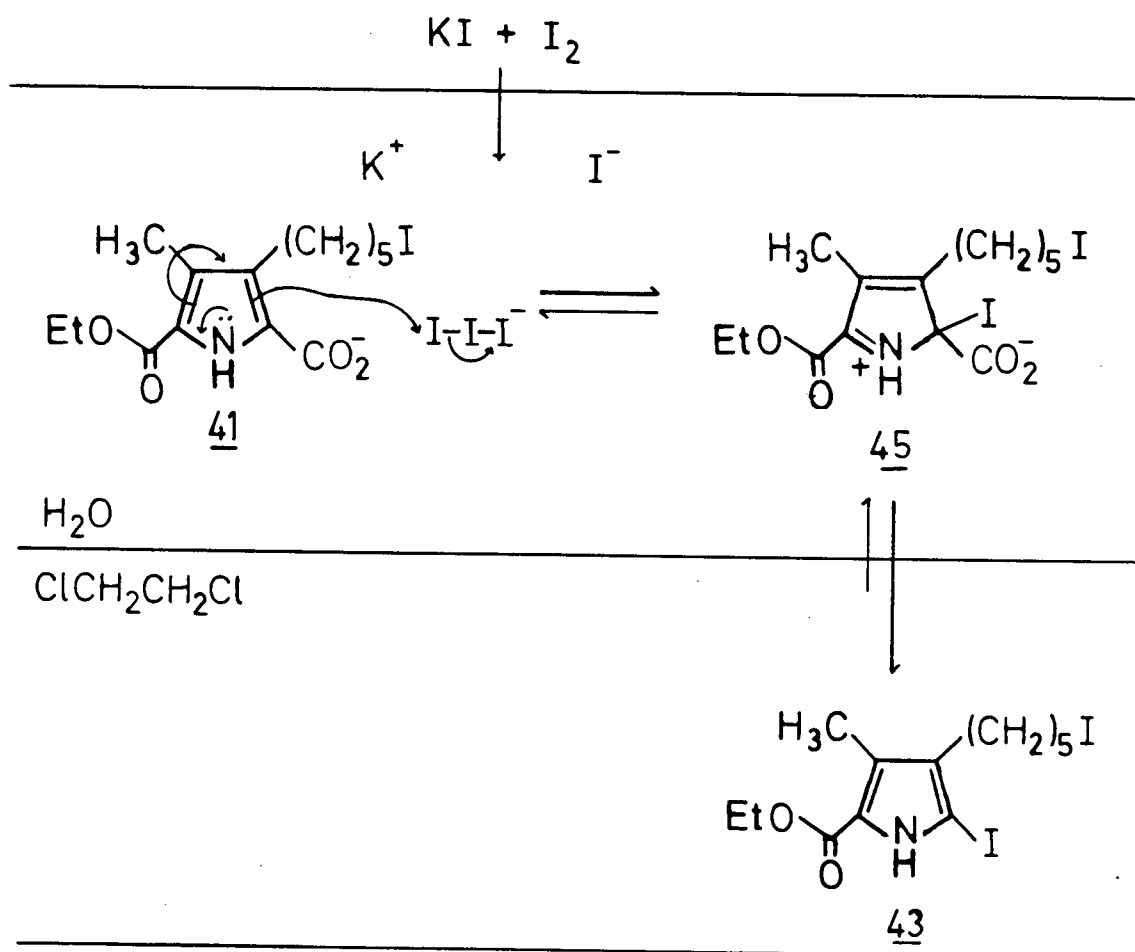
Fig. 5: Schematic Representation of the Iodinative

Decarboxylation of 41

iodopentyl pyrrole 41 was dissolved in the basic aqueous phase of a
water/dichloroethane system. Addition of potassium iodide and iodine
formed KI_3 in the aqueous phase which was subjected to nucleophilic
attack by the pyrrole nucleus to give the sigma adduct 45. This adduct
could break down to regenerate the α-carboxy pyrrole 41, or it could
lose carbon dioxide to form the α-iodo pyrrole 43 which was then
extracted into the lower organic phase, preventing the formation of
solid pyrrole-iodine charge transfer complexes.[161] The reaction mixture
was vigorously stirred and then refluxed, dichloroethane being used rather
than dichloromethane since its higher boiling point gave the optimum
temperature for reaction. Work-up of the reaction was simple. Excess
iodine was destroyed by addition of sodium bisulfite and the two layers
separated. Evaporation of the organic layer yielded the crude α-iodo-
iodopentyl pyrrole 43 which was recrystallized from 50% ethanol/water,
or more frequently carried on to the next stage without purification.
The recrystallized product yield was 78-84%.

De-iodination was accomplished using hydriodic acid. The α-iodo
pyrrole 43 was dissolved in ethanol and the hydriodic acid generated in situ
from potassium iodide and hydrochloric acid. Alternatively the starting
material was dissolved in glacial acetic acid and 47% hydriodic acid
added. Again the equilibrium was pushed to the right by consuming the
liberated iodine with hypophosphorous acid. Neutralization of the acids
and extraction gave the crude product. Chromatographic purification
was carried out at this stage, reactions on a 20 g scale being convenient-
ly purified. The red contaminant (due to bipyrrole by-products) was
retained at the origin and the pure α-free-iodopentyl pyrrole 44 eluted
quickly from the column with dichloromethane as solvent. Evaporation of

the fractions gave a slightly yellow solid (84%). The overall yield
of α-free-iodopentyl pyrrole 44 from the starting 2,4-dimethyl-iodopentyl
pyrrole 40 was 66%.

54
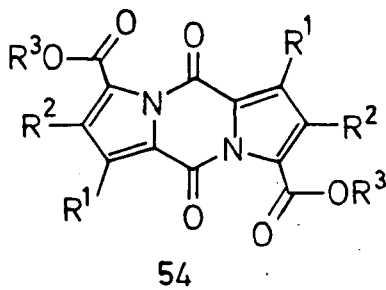
The α-free-iodopentyl pyrrole 44 was also prepared by an alterna-
tive route where the sequence of reactions was changed slightly (Fig. 6).
Thus the hydroxypentyl pyrrole 30 was converted to the acetate 46 which
was used as a protecting group for the trichlorination reaction. Treat-
ment with 3.2 equivalents of sulfuryl chloride followed by hydrolysis with
aqueous acetone produced the α-carboxy pyrrole 48. Unfortunately,
during the hydrolysis stage the reaction mixture was sufficiently acidic
to cause partial removal of the acetate group. This presented only a
minor inconvenience since the acetate could be fully restored after
iodinative decarboxylation, or preferably, at the α-free pyrrole stage.
The trichlorination was also repeated but using a mixture of acetone
and aqueous sodium bicarbonate solution to carry out the hydrolysis
under basic conditions. Under those conditions the acetate remained
intact. However, strongly basic conditions should be avoided for the
hydrolysis reaction since these have been reported to lead to considerable
pyrrocol 54 formation.[162] Iodinative decarboxylation and de-iodination
proceeded exactly as outlined for the corresponding iodopentyl pyrroles.
The crude α-free pyrrole 51 was purified by column chromatography. The
yields for the decarboxylation and de-iodination were 77% and 80%
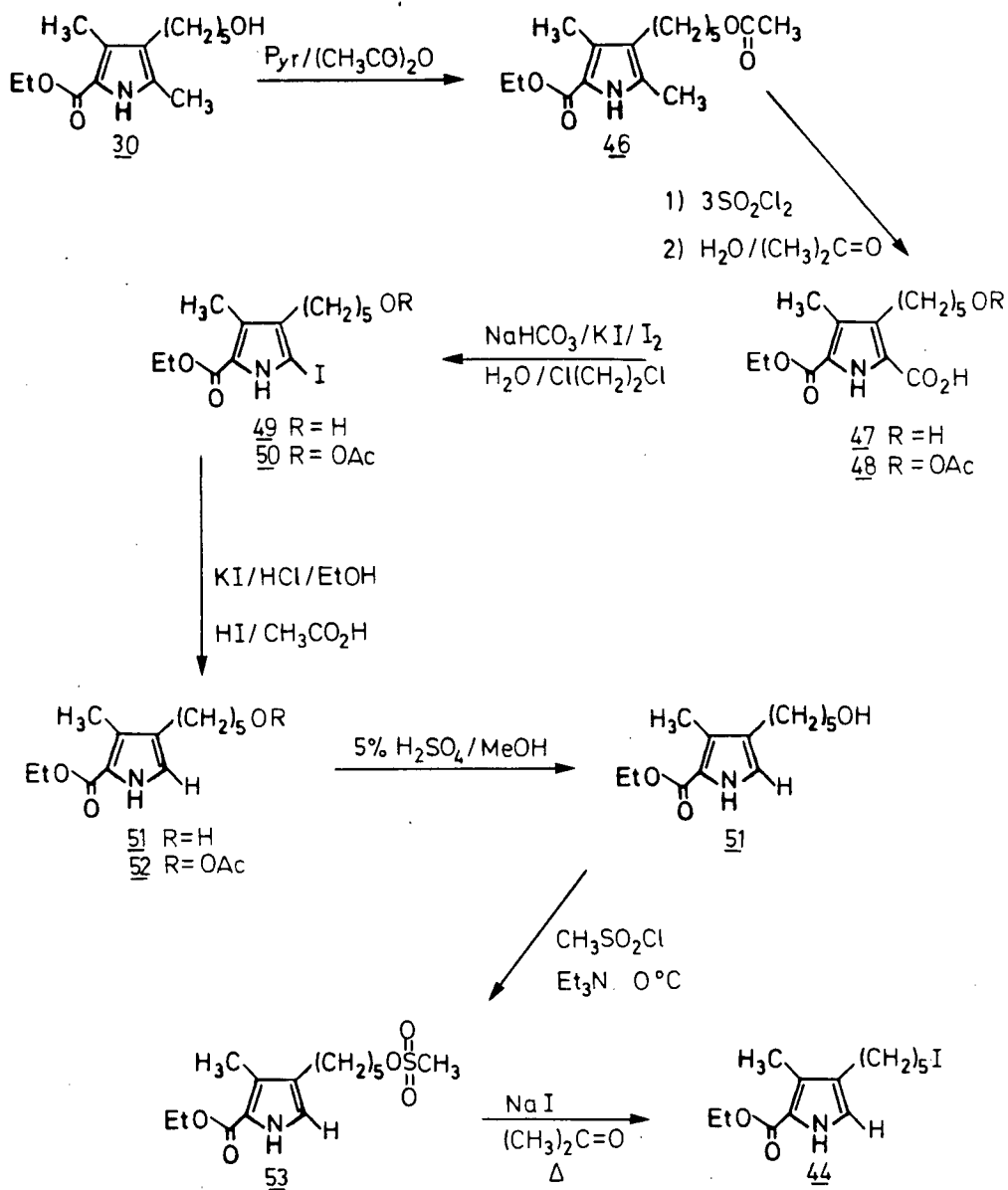
Fig. 6: Alternative Synthesis of 5-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-iodopentane 44

respectively.

The acetate was removed by stirring in 5% sulfuric acid/methanol and the α-free-hydroxypentyl pyrrole 51 converted to the mesylate 53 using the same methanesulfonyl chloride/triethylamine procedure as before. Refluxing the crude mesylate with sodium iodide in acetone gave the desired α-free-iodopentyl pyrrole 44.

The yields in the two reaction sequences were comparable. However due to the lability of the acetate function under the conditions of some reactions and also due to the relative instability of the α-free hydroxypentyl and α-free methanesulfonylpentyl pyrroles, 51 and 53, the reaction sequence using iodopentyl pyrroles was more convenient.

4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-iodobutane 64 was prepared by the same reaction sequence as for its higher homologue 44 (Fig. 7). The acid chloride of ethyl hydrogen succinate 55 was prepared using thionyl chloride and used in the Friedel-Crafts acylation of β-free pyrrole 1 with stannic chloride. After work-up and recrystallization from ethanol a 73% yield of the keto-ester 56 was obtained which was reduced using diborane, generated in situ from sodium borohydride and boron trifluoride etherate. Recrystallization of the crude product from 50% aqueous ethanol yielded the hydroxybutyl pyrrole 57 (72%). The mesylate 58 was obtained using methanesulfonyl chloride/triethylamine and was crystallized from 50% aqueous ethanol (88%, 2 crops). No evidence was observed for the presence of the contaminant chlorobutyl pyrrole 59. Refluxing the mesylate 58 with sodium iodide (4 equivalents) in acetone formed the iodobutyl pyrrole 60, which was recrystallized from 20% aqueous ethanol (88%, 2 crops).

The trichlorination of 60 was carried out exactly as for 40, using
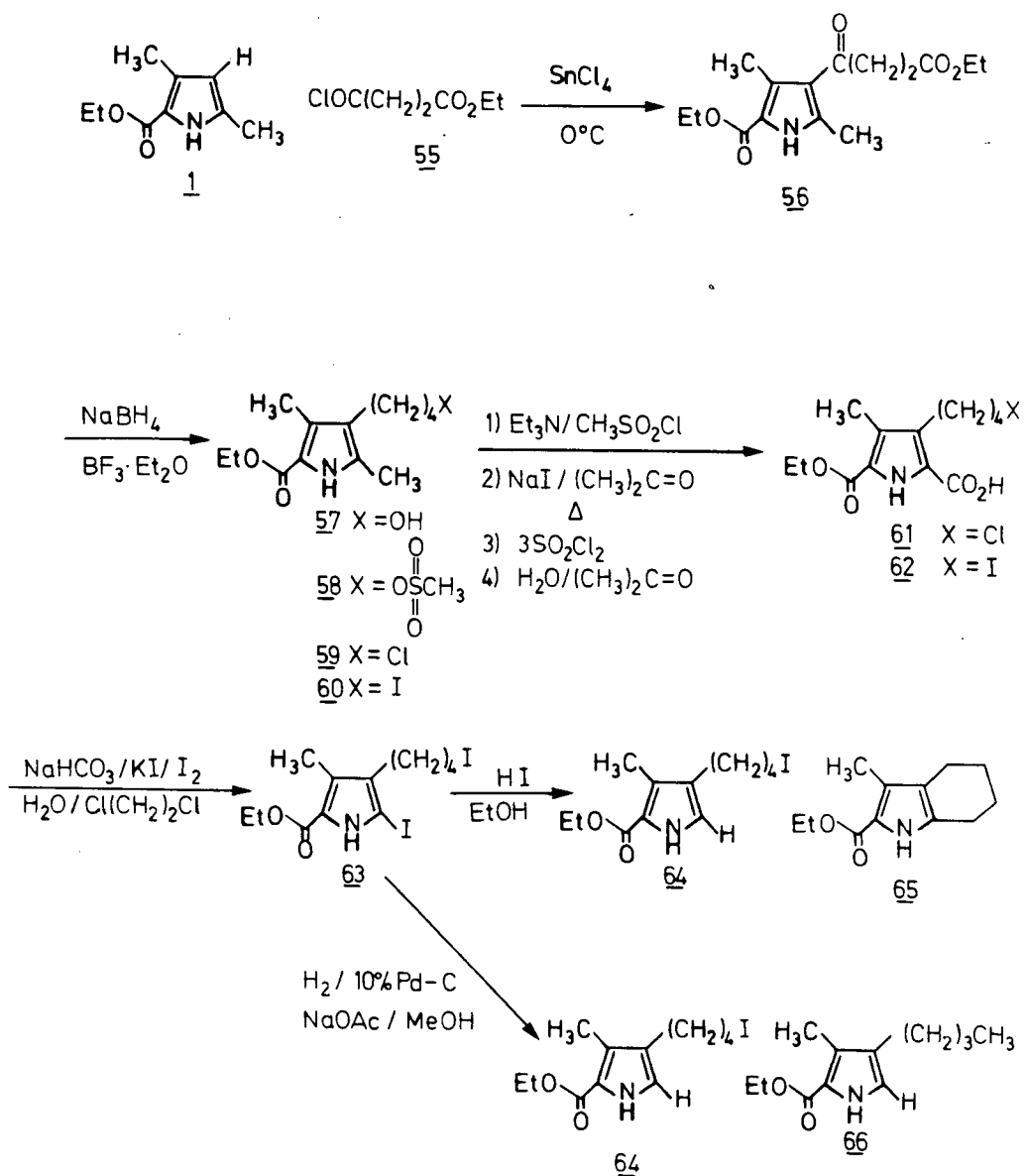
Fig. 7: Synthesis of 4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-iodobutane 64

sulfuryl chloride (3.2 equivalents). In general the "butyl pyrrole" compounds appeared to be less soluble than the corresponding "pentyl pyrrole" compounds. In some trichlorination reactions the starting iodobutyl pyrrole 60 was not completely soluble in a reasonable volume of the reaction solvent, 1:1 dichloromethane/diethyl ether. In those cases the starting material was simply suspended in the solvent mixture and the sulfuryl chloride added. As the reaction proceeded and the mixture warmed the solution became homogeneous. After hydrolysis the crude product was refluxed with sodium iodide in acetone to ensure that none of the chlorobutyl pyrrole 61 was present. The α-carboxy pyrrole 62 was obtained from the reaction mixture in 80-90% yield. Iodinative decarboxylation proceeded as expected under the same conditions as before, the α-iodo pyrrole 63 being obtained in 73-87% yield after recrystallization from ethanol.

Unlike its longer chain counterpart, de-iodination of α-iodo-iodobutyl pyrrole 63 presented some problems. The starting material was dissolved in ethanol by heating gently on a steam-bath. Without further heating hydriodic acid was added, the solution becoming very dark as iodine was liberated, indicating that the reaction was proceeding. The liberated iodine was destroyed by addition of hypophosphorous acid, but tlc indicated incomplete reaction so more hydriodic acid was added. When tlc confirmed complete reaction, water was added and the mixture left standing. The solid which precipitated was collected and dried, and purified by column chromatography. The first fractions from the column comprised pure α-free iodobutyl pyrrole 64, the desired product. However later fractions showed the product to be contaminated with a second compound. This second compound was isolated and identified. ^{1}H-NMR

confirmed the presence of an ester and a 4-methyl group. However the

spectrum displayed no doublet at 6.72 δ due to the α-free proton at

position 2 of the pyrrole ring, nor did it display a triplet at 3.24 δ

due to the $-CH_2I$ group. Mass spectrometry showed a parent peak at 207

and this fact coupled with the ^{1}H-NMR evidence suggested that the

contaminant had the structure 65. This intramolecular cyclization
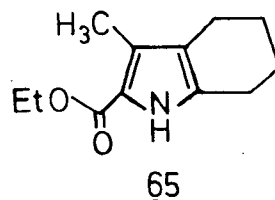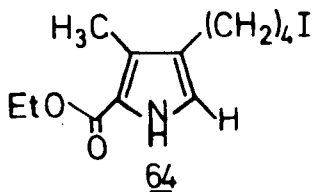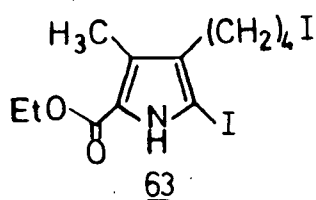
appeared to occur exclusively during the de-iodination reaction

(Scheme 69, equation 39); there was no evidence for the formation of 65

during the iodinative decarboxylation reaction. Similarly there was no

observation of intramolecular cyclization during the de-iodination of

the corresponding α-iodo-iodopentyl pyrrole 43, formation of seven-membered

rings being a less favoured process (equation 40).

De-iodination may also be carried out by catalytic hydrogenation

over palladium on charcoal with sodium acetate present to prevent

poisoning of the catalyst. Accordingly the α-iodo pyrrole was dissolved

in methanol, sodium acetate and 10% palladium on charcoal added, and

stirred under hydrogen overnight. Tlc of the reaction mixture showed a

single spot which was not starting material. However, after work-up,

subsequent reactions showed that the product was not homogeneous but

was a mixture of the two compounds 64 and 66 in approximately equal

amounts. That only two products were obtained from the hydrogenation

SCHEME 69

(37)

(38)

(39)

(40)
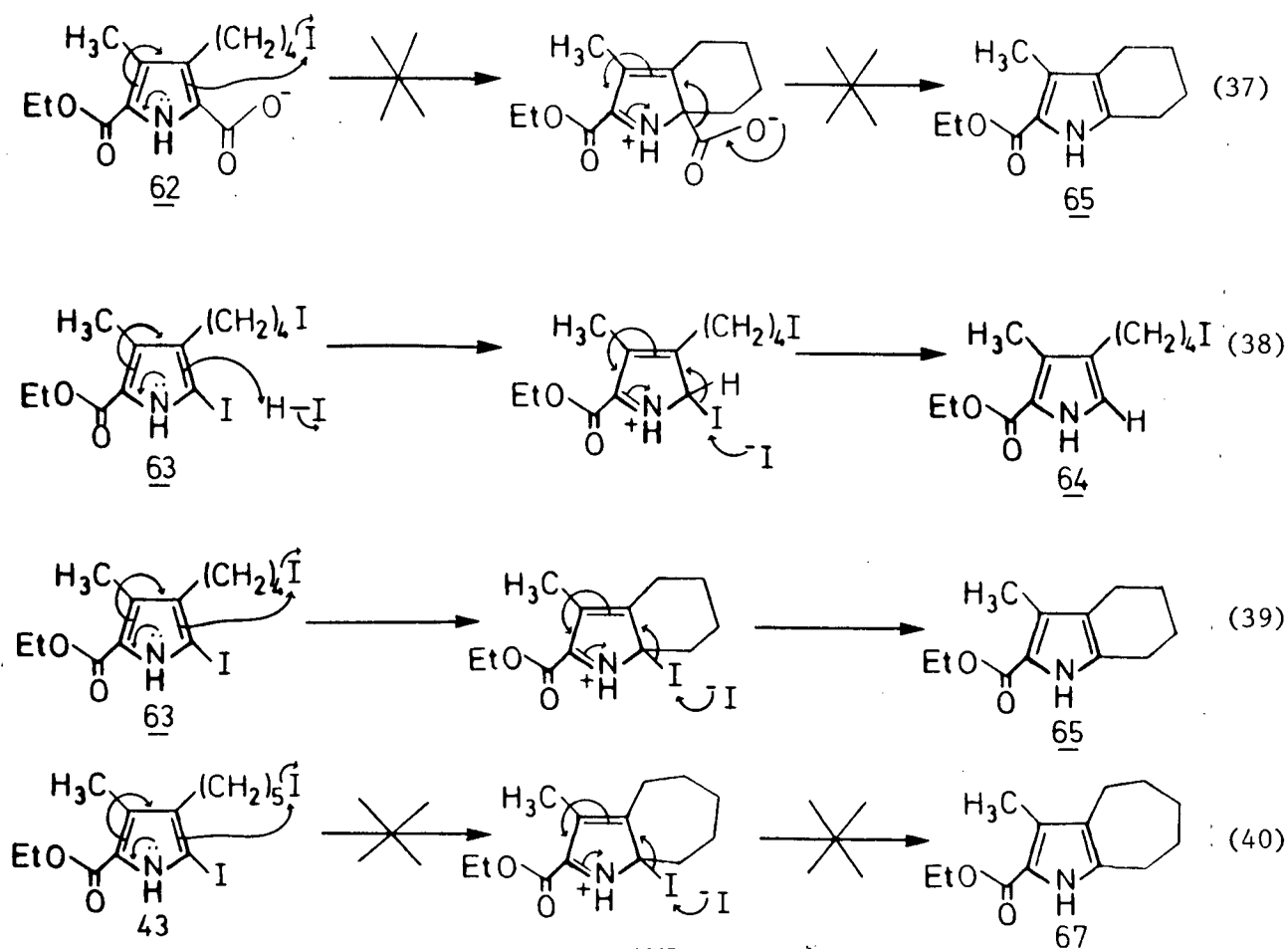
suggested that the pyrrole iodine was more labile than the side-chain

iodine. With careful monitoring it might have been possible to follow

the course of the reaction and interrupt it after all the pyrrolic

iodine had been removed but before any significant de-iodination of the

chain had occurred. Although contaminated with either the butyl

pyrrole 66 or the ring pyrrole 65, samples of the α-free pyrrole 64 were

pushed through to the next steps since the contaminants were easily

removed from subsequent products by chromatography.

To circumvent the problem of de-iodination, the α-free-iodobutyl

pyrrole 64 was synthesized using the acetate route (Fig. 8). The

acetate of 2,4-dimethyl-hydroxypentyl pyrrole 57 was prepared using

pyridine and acetic anhydride (85%). The trichlorination with sulfuryl

chloride was carried out as before and the intermediate trichloromethyl

pyrrole was hydrolyzed by refluxing in aqueous acetone which contained

some sodium bicarbonate. However the NMR spectrum of the crude product

showed it to be a mixture of 68 and 69. This presented no problem as

the mixture of products was carried through the decarboxylation and

de-iodination reactions to give 72 and 73. Before chromatographic

purification the mixture was converted to the acetate 72, then purified

(55% yield from 67). De-iodination of 71 was also carried out by hydro-

genation over 10% palladium on charcoal in the presence of sodium

acetate (91-95%). The acetate group was removed by stirring 72 with 5%

sulfuric acid/methanol and the product was obtained by extraction of

the reaction mixture with ethyl acetate to give a brown solid (93%

crude). The crude hydroxybutyl pyrrole 73 was not purified but carried

on to the mesylation step. Methanesulfonyl chloride was added to a

cold solution of crude 73 and triethylamine in dichloromethane. After
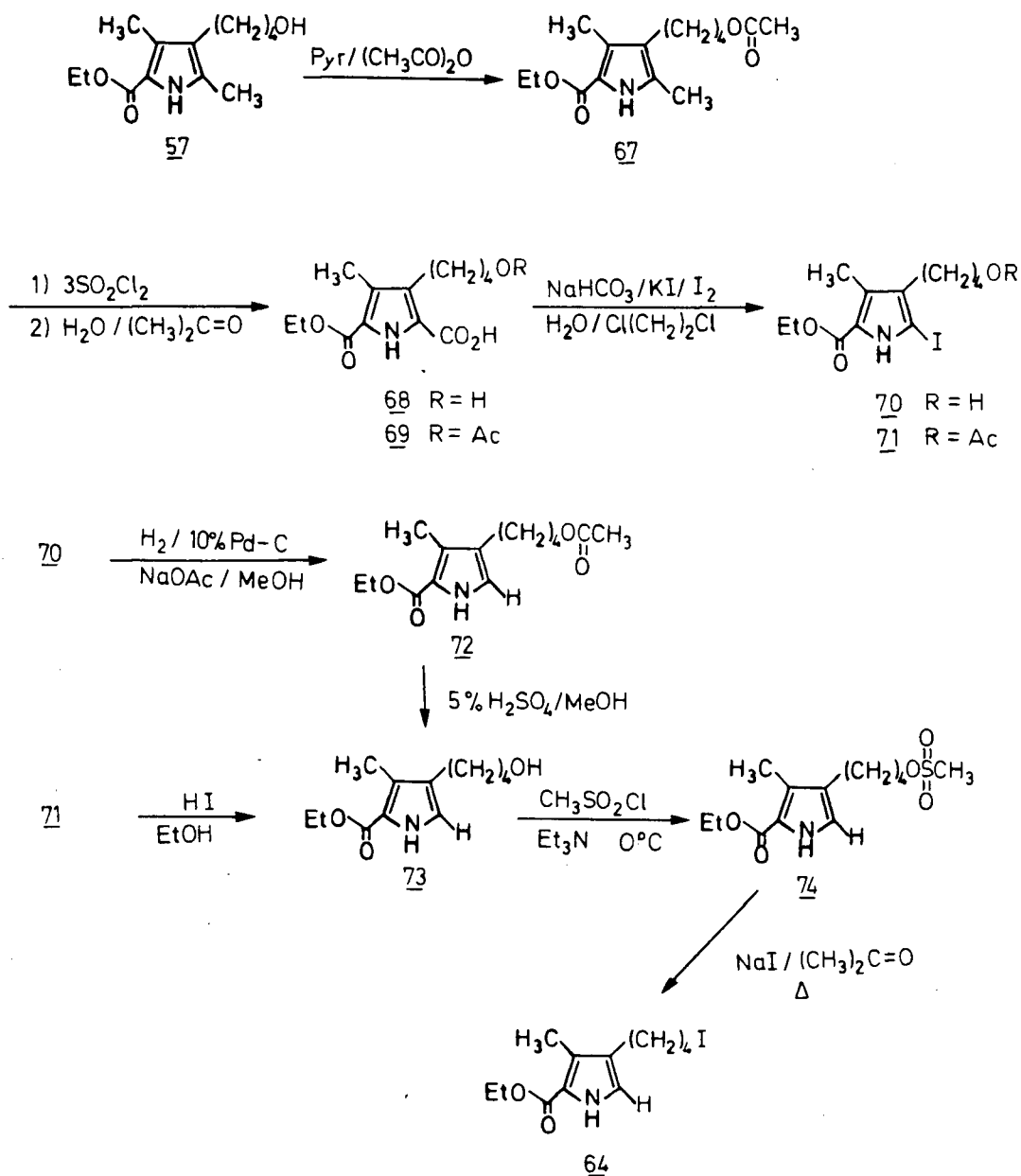
Fig. 8: Alternative Synthesis of 4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-iodobutane 64

30 minutes tlc indicated complete consumption of starting material, the
reaction was terminated and the product 74 isolated as a red oil. This
crude product was dissolved in reagent grade acetone, sodium iodide
(2.0 equivalents) added and the mixture refluxed and stirred for 18.5
hours. Tlc (10% EtOAc/CH_2Cl_2) showed a single spot which was
believed to be the desired α-free-iodobutyl pyrrole 64. The crude
product was obtained from the reaction mixture as a brown solid and
was purified by column chromatography on a silica gel (BDH 60-120; 200 g)
column. The column was eluted first with dichloromethane and then,
since the compound was moving slowly down the column, the polarity of
the eluant was increased to 10% ethyl acetate/dichloromethane. The
first fractions from the column were colorless and were shown to contain
a single compound. Later fractions however contained two compounds,
the desired product 64 and the undesired intramolecular cyclization
product 65. The yield of pure 64 from the hydroxybutyl pyrrole 73 was
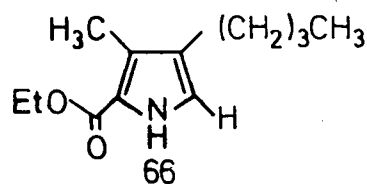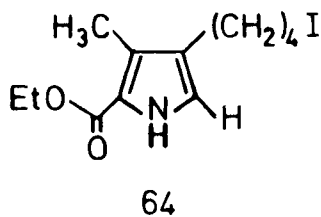
43% and the impure fractions gave a similar quantity of the mixture.
Obviously, in this case, intramolecular cyclization occurred during
mesylate formation or during the subsequent S_N2 reaction of the
mesylate with iodide in refluxing acetone.

Since compound 64 was the branch point for the various porphyrin
syntheses it was important to ascertain where intramolecular cyclization
was occurring and what steps could be taken to avoid it. Formation of

cyclohexyl pyrrole 65 during the de-iodination of 63 with hydriodic

acid was already noted. However de-iodination of the corresponding

acetoxy pyrrole 71 gave no observable amount of 65. Also intramolecular

cyclization occurred during the formation of α-free-iodobutyl pyrrole

64 from the α-free-hydroxybutyl pyrrole 73 via the mesylate 74. Because

mesylate formation was carried out at 0°C it was felt that the cyclo-

hexyl pyrrole 65 was formed during the S_N2 reaction when the mesylate

was heated in refluxing acetone for long periods. Moreover it was

shown that refluxing the α-free-iodobutyl pyrrole 64 in acetone in the

presence of sodium iodide for ∿70 hours produced only a trace of 65,

as indicated by tlc.

The phosphonium iodide 94b was prepared from 64 by treatment with

triphenylphosphine in refluxing toluene for 16-24 hours. It was feared

94a n = 5
94b n = 4
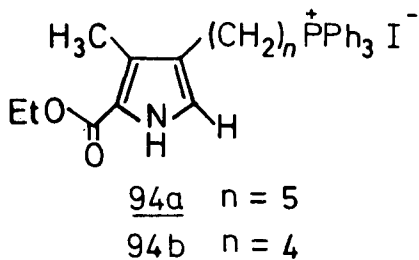
that a major part of either the starting material or the product would

be consumed in the formation of the undesired cyclohexyl pyrrole 65

during the prolonged reflux times. Such a situation was potentially

disastrous, since the phosphonium iodide was a key starting material

for two porphyrin syntheses and relatively large amounts were required.

Fortunately the phosphonium salt appeared to be quite stable under the

conditions of its formation; refluxing a small sample in toluene for

∿30 hours produced only trace of cyclohexyl pyrrole 65 as shown by tlc.

A small sample of α-free-iodobutyl pyrrole 64 was similarly refluxed

in toluene for 24 hours and tlc examination showed only a trace of 65.

Reflux was maintained for a further 70 hours during which time most of

the toluene evaporated and the reaction mixture was concentrated to

∿2 mL. At that stage tlc showed no trace of the starting material 64,

but a major spot due to 65 and a second unidentified material with a

higher Rf value.

SCHEME 70

(41)

(42)

(43)
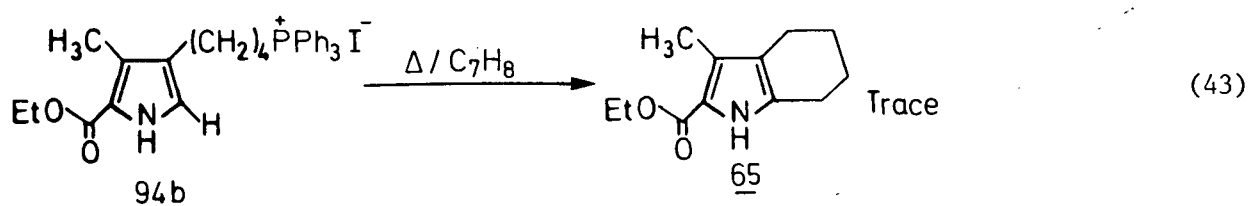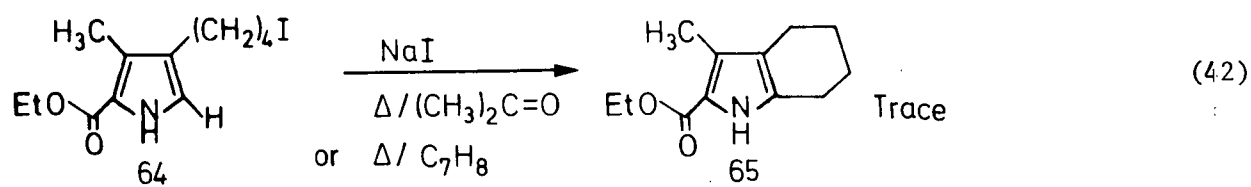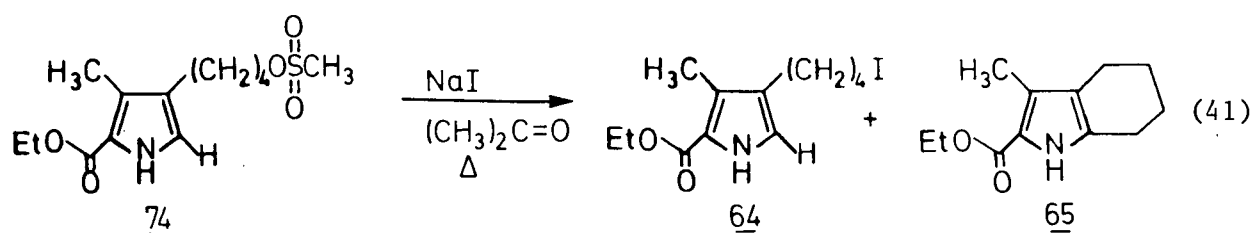
These observations may be rationalized in terms of the leaving

ability of the group at the chain's terminus, and the number and

position of electron-donating and electron-withdrawing groups on the

pyrrole nucleus. Thus, in the de-iodination of 63, the 2-iodo group

renders the pyrrole ring sufficiently electron rich to undertake

displacement of the iodide group at the chain's terminus leading to an

SCHEME 71

(44)

(45)

(46)

(47)

(48)

(49)

(50)
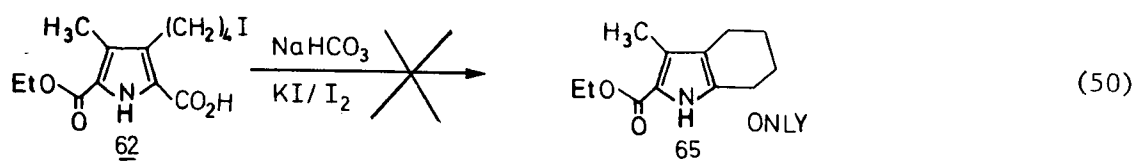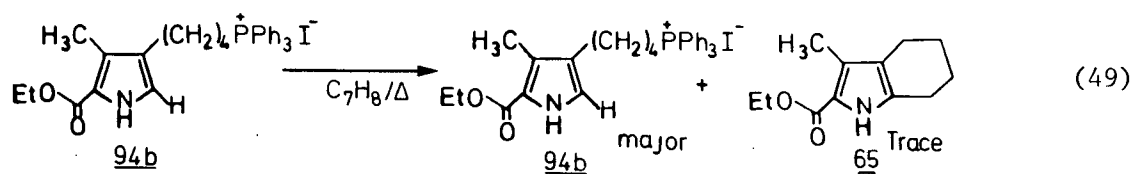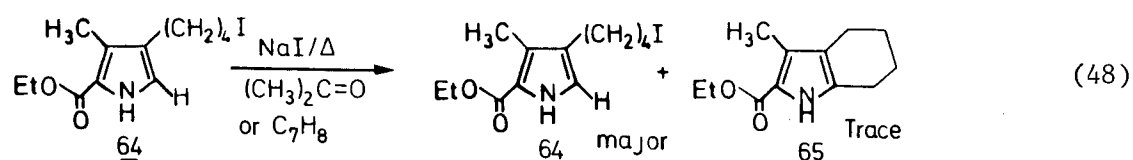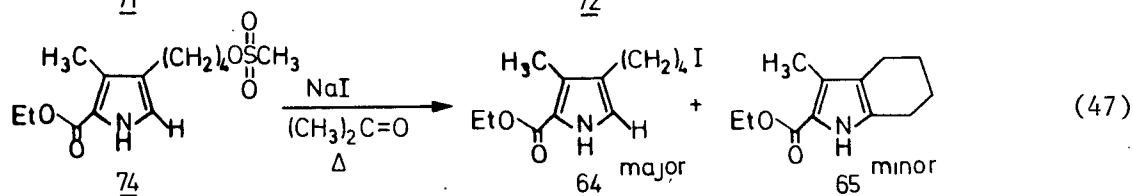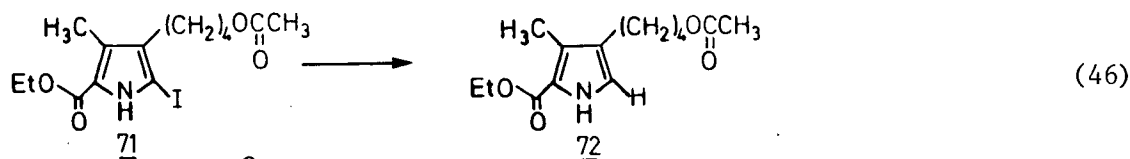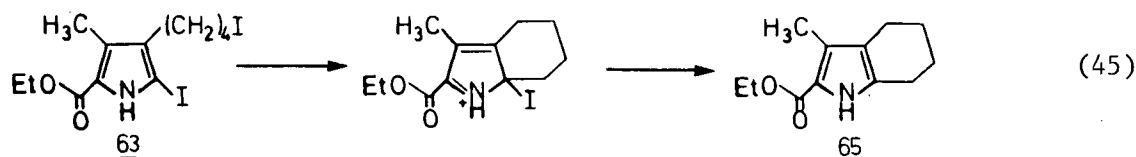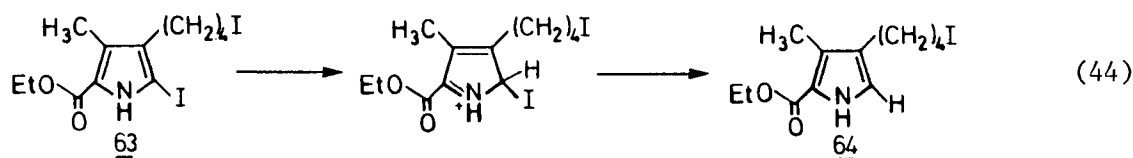
intermediate cyclohexyl-pyrrolonium ion which collapses to the cyclohexyl pyrrole 65 (Scheme 71, equation 45). However, displacement of the poorer leaving acetate group does not occur and de-iodination occurs without formation of 65 (equation 46).

In the case of the α-free butylpyrroles the nucleophilic behaviour of the pyrrole ring is considerably lessened and the qualitative results may be explained by considering the leaving ability of the terminal group. Thus a small but significant amount of the cyclohexyl pyrrole 65 is formed on refluxing the mesylate 61 in acetone with sodium iodide. However extended reflux of iodobutyl pyrrole 64 under the same conditions produces only a trace of 65 as shown by tlc (equation 48). Similarly iodobutyl pyrrole 64 or the phosphonium iodide 94b in refluxing toluene produce only traces of 65. Although one would expect the phosphonium salt to be a good leaving group, steric hindrance by the bulky phenyl groups probably prevents nucleophilic attack by the pyrrole ring.

Introduction of electron withdrawing groups decreases the nucleophilicity of the pyrrole. Therefore no intramolecular cyclization was observed in the decarboxylation of 2-carboxy pyrrole 62 (equation 50).

These observations are analogous to the results reported by Smith et al.,[169] who showed that the transformation of certain 2-hydroxyethyl pyrroles into the corresponding 2-haloethyl pyrroles proceeded with scrambling of the two carbons in the side-chain (Scheme 72). A mechanism was suggested involving neighbouring group participation by the electron-rich pyrrole nucleus to give an ethylenepyrrolonium ion, the course of the reactions depending on the leaving ability of the group at the chain's terminus and the substitution pattern on the

SCHEME 72

(51)

(52)

(53)

(54)
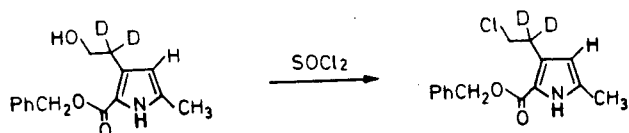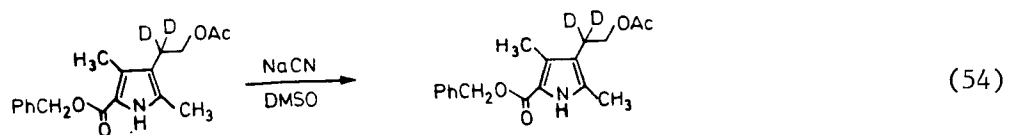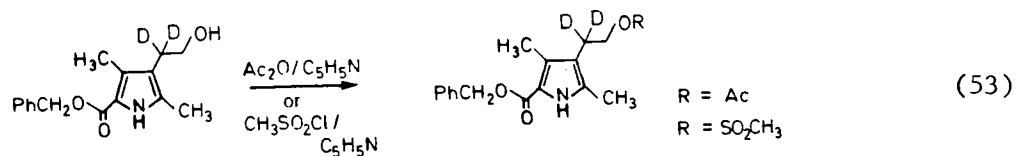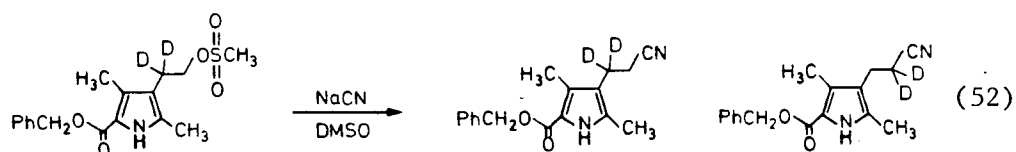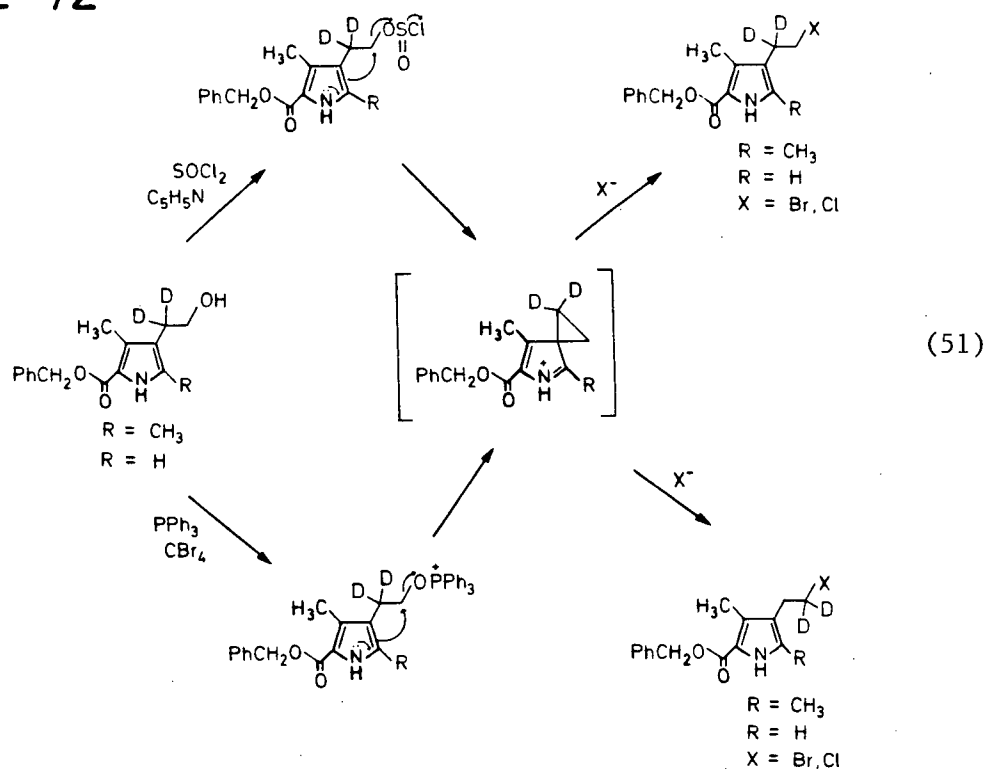
pyrrole ring.

Contamination of the desired α-free-iodobutyl pyrrole 64 with cyclohexyl pyrrole 65 was a major problem. In all the solvent systems
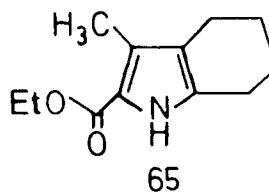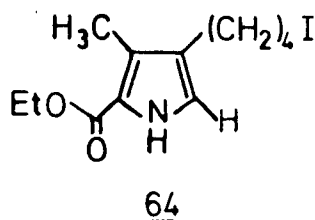
tested the two compounds had similar Rf values so that complete chromato-graphic separation was not possible. Separation of the two compounds by crystallization was not attempted since there was no obvious difference in their solubilities. Indeed, it was more convenient to carry the crude α-free-iodobutyl pyrrole 64 to the next stage, formation of either the phosphonium iodide 94b or the bis(pyrrol-3-yl)butyl sulfide 75b. At this stage the unwanted cyclohexyl pyrrole 65 was easily separated from the desired products.

2.3. SYNTHESIS OF PORPHYRINS CONTAINING A THIOETHER STRAP

With the availability of the key intermediates 44 and 64, the
thioether strapped porphyrins 87a and 87b are conveniently produced in
several steps (Fig.9). Dimerization of 44 or 64 produces the chain-linked
bis-pyrrole 75 which incorporates not only the strap and rings A and
C of the porphyrin, but also two α-free positions to which the eventual
pyrrole rings B and D of the porphyrin may be attached. Therefore with
76 and 44 (or 64) in hand, all the units necessary for porphyrin
construction are available.

Refluxing the α-free-iodopentyl pyrrole 44 with sodium sulfide
(1.5-2.0 equivalents) in aqueous tetrahydrofuran (THF/H$_2$O 100:40) for
14-28 hours gave the bis((pyrrol-3-yl)pentyl sulfide 75a in high yield.
In the initial experiments 44 was inadvertantly contaminated with the
corresponding chloropentyl pyrrole which did not react with the sodium
sulfide. In those cases the tetrahydrofuran was removed and the crude

product isolated by extraction with ethyl acetate. The unreacted
chloropentyl pyrrole 36 was easily removed by column chromatography and
the desired product was obtained as a white solid (72-89%). When pure
starting material was used the chromatographic purification was
unnecessary. Removal of the tetrahydrofuran led to the separation of
a yellow oil which was redissolved by addition of acetone. Addition of

Fig. 9:   Synthesis of Porphyrins Containing a Sulfide Strap

water precipitated a white solid which was collected and dried (81-97%).
Although the thioether 75a was formed under basic conditions, saponifi-
cation of the pyrrole ethyl esters was not observed. However it had
been previously demonstrated that the conditions of this reaction were
sufficient to hydrolyze a dicyanovinyl protecting group, and therefore
the thioether chain was set in place before formation of the dipyrro-
methane 77a.

Unsymmetric dipyrromethanes may be prepared by the reaction of an
α-free pyrrole 80 with a pyrrylcarbinyl cation 79 which may be derived
from a variety of precursors 78 (Scheme 73). Procedures using bromo-

SCHEME 73

X = Br, Cl, OCH₃,
OAc, etc.
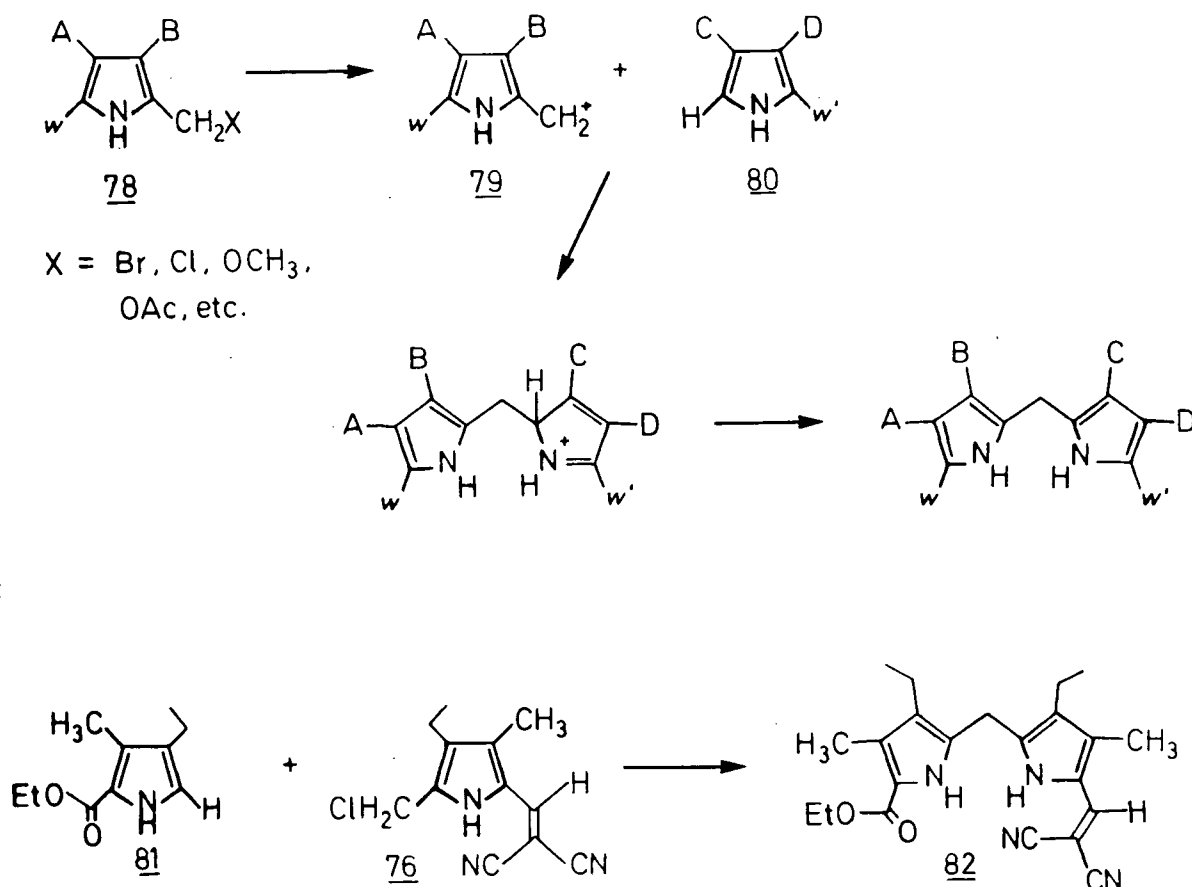
methyl-, chloromethyl-, and acetoxymethyl pyrroles under a variety of conditions and solvents have already been published.[159] Wijesekera,[117] using the α-free pyrrole 81 and the chloromethyl-dicyanovinyl pyrrole 76 as a model system, had evaluated these procedures and had found that the yields were low (<46%) and/or the products required chromatographic purification. On the other hand he found that simply heating 81 and 76 in glacial acetic acid at 70°C for 20 minutes under nitrogen produced the required dipyrromethane 82 in high yield (>87%). The product was recovered from the reaction mixture by crystallization after concentration and addition of methanol. Tlc indicated that only a single dipyrromethane had been formed; no rearrangement products were observed.

The bis-dipyrromethane 77a was prepared by Wijesekera's method. The bis(pyrrol-3-yl)pentyl sulfide 75a and the α-chloromethyl pyrrole 76

77a n = 5
  b n = 4

76
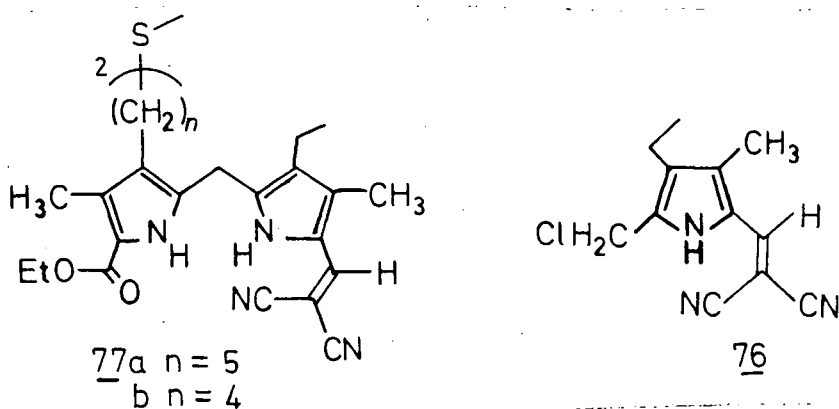
(2.05 equivalents) were suspended in glacial acetic acid (5 mL) and heated at 70°C under nitrogen. After 10-20 minutes all the solids dissolved to give a deep red solution. The solution was cooled, methanol (15-25 mL) added and the mixture stored in the freezer overnight. The orange-red solid which precipitated was collected and dried (81-84%). Tlc exhibited a single major yellow spot which turned purple when the

plate was exposed to bromine vapour. (This test is diagnostic for dipyrromethanes on tlc plates as exposure to bromine oxidizes any dipyrromethane spots to the more highly coloured dipyrromethene). The crude product was also contaminated with small amounts of unidentified pyrrole compounds but there was no sign of any unreacted 75a.

In an alternative work-up procedure the cooled reaction mixture was poured into aqueous sodium bicarbonate to neutralize the acetic acid. The orange solid which precipitated was filtered, washed with water and dried. Recrystallization from dichloromethane/methanol gave an orange/ red solid (74%). As before tlc of this product showed a single major spot due to the dipyrromethane 77a with smaller amounts of pyrrole contaminants.

The chain-linked bis-dipyrromethane 77a contained all the features necessary for the synthesis of the strapped porphyrin (Fig. 9). Since compounds 83a and 84a were neither isolated nor characterized, compound 77a was the direct precursor for the strapped porphyrin 87a. Hydrolysis under strongly basic conditions to remove the dicyanovinyl protecting group and saponify the ester, followed by thermal decarboxylation yielded the α-free,α'-formyl bis-dipyrromethane 84a. This was then cyclized using an acid catalyst, the cyclization being carried out under conditions of high dilution to encourage intramolecular rather than intermolecular cyclization and to minimize the formation of polymeric by-products.

Esters at the 2-pyrrole position are more difficult to hydrolyze than the corresponding aliphatic esters. This was exemplified in the formation of the bis(pyrrol-3-yl)pentyl sulfide 75a where the ester groups survived intact the basic conditions of the reaction. However in the

aliphatic analogue 85 reaction under the same conditions led to complete

SCHEME 74

(55)
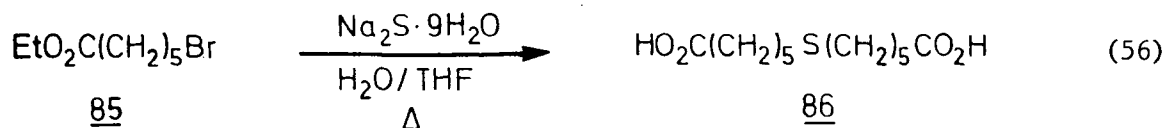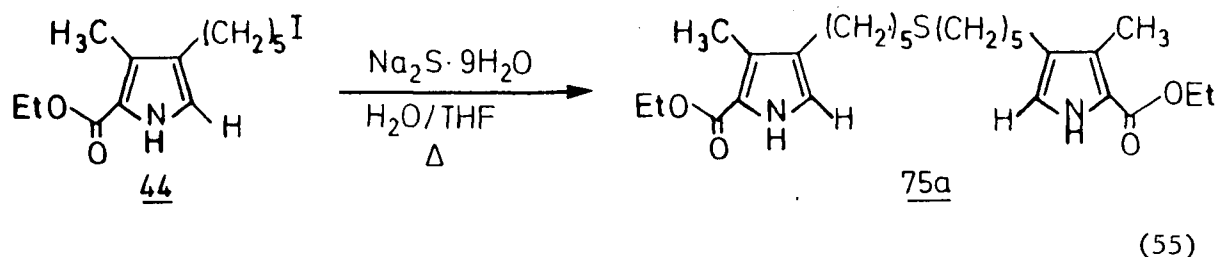
saponification. Moreover it had already been demonstrated that the hydrolysis of the 2-ester group of dipyrromethanes was sluggish in aqueous ethanol.[117] To ensure complete saponification extended refluxing was required providing the opportunity for decarboxylation and material-consuming side reactions to occur. In an attempt to decrease the length of reaction by increasing the reaction temperature but at the same time retain some miscibility, the ethanol was replaced by the higher boiling n-propanol. It was then found that deprotection and saponification of α-ester,α'-dicyanovinyl dipyrromethanes was complete in ∿3 hours and no major side reactions occurred.

The protected dipyrromethane 77a was stirred in n-propanol (50 mL)

77a	R = CO$_2$Et,	R' = CH=(CN)$_2$
83a	R = CO$_2$H,	R' = CHO
84a	R = H,	R' = CHO
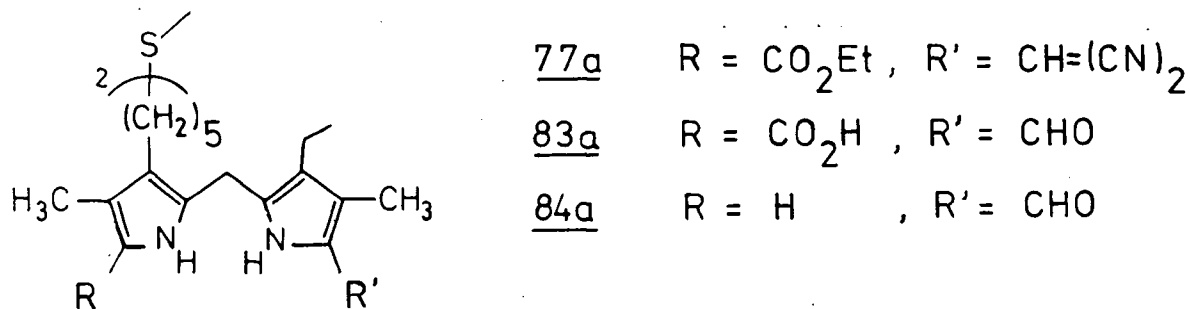
and a solution of potassium hydroxide (14 g, ~160 equivalents) in
water (100 mL) was added. The reaction was stirred and refluxed under
argon, the course of the reaction being monitored by UV/visible
spectroscopy. A spectrum of the starting dipyrromethane in methanol
showed two major bands at 406.0 and 276.8 nm with a shoulder at 250 nm.
The band at 406.0 nm was believed to be due to the pyrrole ring containing
the dicyanovinyl group while the band at 276.8 nm was due to the pyrrole
ester group. As the reaction proceeded the band at 406.0 nm decreased
in intensity and a new band grew in at 316.8 nm, due to the pyrrole
aldehyde; the band at 276.8 nm moved to 268.4 nm. Typically, after
3 hours reflux no further spectral change was observed and the reaction
was deemed complete. The n-propanol was boiled off and the reaction
mixture cooled down. At this stage a brown oily solid precipitated
from solution, presumably the potassium salt of the α-carboxy dipyrro-
methane 83a. For smaller scale reactions this solid could be redissolved
by addition of more water. However for larger scale reactions the most
convenient procedure was as follows. The cooled reaction mixture
containing the precipitated solid was filtered and the brown solid which
was retained on the filter paper was washed with copious amounts of
water until it all redissolved. Typically, by this stage the volume
of solution was ~500 mL. Acidification with glacial acetic acid (15 mL)
formed the α-carboxy,α'-formyl bis-dipyrromethane 83a which separated
from solution as a brown gelatinous solid. This was collected by
filtration and dried overnight in vacuo. The crude product was neither
characterized nor purified but carried on to the penultimate step –
thermal decarboxylation of the α-carboxy group.

Thermal decarboxylation was carried out by refluxing the

α-carboxy,α'-formyl dipyrromethane <u>83a</u> in N,N-dimethylformamide under argon for 3 hours. Since the product <u>84a</u> undergoes indiscriminate acid catalyzed reaction, care must be exercised to ensure that the product does not come into contact with acid before the high dilution intra-molecular cyclization step. Therefore only spectral grade DMF should be used for the decarboxylation reaction. In one instance reagent grade DMF was used, leading to premature cyclization due to traces of formic acid in the solvent; after work-up no strapped porphyrin was obtained. Furthermore, all glassware used in the decarboxylation should be given an alkali rinse.

The course of the reaction may be monitored by UV spectroscopy although it was found that the reaction was complete after 3 hours reflux. The spectrum of the starting material <u>83a</u> in dichloromethane exhibited two bands at 320.0 and 280.0 nm due to the pyrrole aldehyde and pyrrole carboxylic acid respectively. During the course of the decarboxylation the band at 280.0 nm steadily declined and the band at 320.0 nm moved slightly to the blue. The spectrum of the product showed a single major band at 312.0 nm and a shoulder at 272.8 nm. The reaction mixture was then cooled down under argon and the DMF was removed using a rotary evaporator attached to a vacuum pump (bath temperature 50°C). α-Free,α'-formyl dipyrromethanes are known to be unstable so the compound was not evaporated to dryness. When almost all the DMF was removed the residue was immediately dissolved in dichloromethane. This solution was extracted with water to remove the remaining DMF, then dried over anhydrous sodium sulfate, filtered and diluted with dichloromethane to a predetermined volume depending on the scale of reaction.

<u>77a</u>	R = CO$_2$Et ,	R' = CH=(CN)$_2$
<u>83a</u>	R = CO$_2$H ,	R' = CHO
<u>84a</u>	R = H ,	R' = CHO
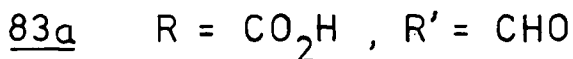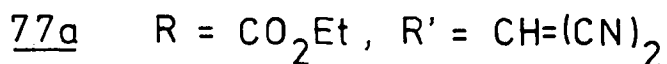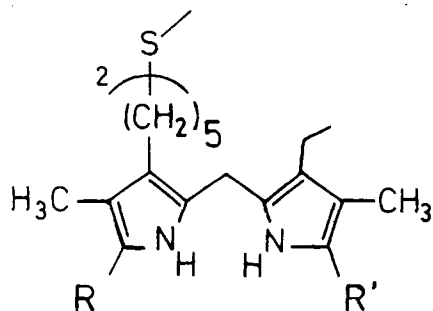
The whole strategy of the strapped porphyrin synthesis depended on delaying the formation of the porphyrin ring until the last step. Having assembled all the necessary subunits in the precursor bis-dipyrromethane 77a the success of this scheme depended on three factors:

(i) Clean and complete removal of the ester and dicyanovinyl protecting groups. Even if only a small percentage of the product 83a contained an unhydrolyzed α-group, such blocked molecules would react with viable molecules to form large amounts of polymeric products and decrease the yield.

(ii) Clean and complete decarboxylation of 83a to 84a. Furthermore 84a required protection from exposure to acid otherwise intermolecular cyclization would occur.

(iii) The acid-catalyzed reaction of 84a had to be performed in a manner that promoted intramolecular 2 + 2 cyclization. If only one of the four reactive α-positions reacted in an intermolecular fashion ring closure to the strapped porphyrin would be impossible and polymeric materials would result.

Clearly it was necessary to effect the final cyclization to the strapped porphyrin under conditions of high dilution. Typically the

reactions were carried out on a 1.2 - 17.0 x 10^{-4} mole scale. After

decarboxylation the solution of the crude α-free,α'-formyl bis-dipyrro-

methane 84a in dichloromethane was diluted to 250 mL for reactions on

a 1.2 - 8.0 x 10^{-4} mole scale, and to 500 mL for 1.0 - 1.7 x 10^{-3} mole

reactions. The solution was loaded into 4 gas-tight syringes each

capable of holding 50-60 mL. The contents of the syringes were then

injected into four Erlenmeyer flasks each containing a solution of

p-toluenesulfonic acid (4 g) in methanol (25 mL) and dichloromethane

(600 mL).[164] To ensure constant slow addition a syringe pump was used

to empty the syringes. At its slowest speed the pump emptied the

syringes over a period of approximately twelve hours, the contents of

the syringes being delivered to each reaction flask by means of tygon

tubing inserted into a capillary tube which was held just above the

surface of the liquid in the flask. The contents of the syringes were

therefore added drop-wise rather than in a continuous fashion. If the

tip of the capillary was placed below the surface of the liquid in the

flask it generally became blocked, leading to spillage. The degree of

dilution was determined by the concentration of acid in the flask, the

concentration of 84a in the syringe, the speed of the syringe pump and

the diameter of the capillary tube. With the exception of the latter

the other factors were maintained constant. Generally addition was

complete and the reaction work-up carried out within a 48 hour period.

To isolate the product the contents of the reaction flasks were

concentrated, then washed with sodium bicarbonate to neutralize the acid

and convert the protonated porphyrins to their free base forms. This

was accompanied by a change in the colour of the solution from deep

red-purple to a brown-red colour. The organic layer was separated,

dried and then evaporated to dryness to obtain the crude product.

Chromatographic purification was attempted using a variety of types and

activities of silica gel and alumina. The following procedure was found

to be the most convenient. The crude product was placed on a Merck

Kieselgel 60 silica gel column (75-150 g) and eluted with 1% methanol-

dichloromethane as solvent. Several small pink bands, due to metallo-

porphyrin and other unidentified material ran ahead of the main bulk of

material and were discarded. The porphyrin eluted from the column as

a broad dark band and was collected in fractions of ∿150 mL. After

most of the material had been eluted the polarity of the solvent was

increased to 2% methanol-dichloromethane to move any more porphyrin which

might be adhering to the column. The fractions were then examined by

tlc and the initial and later fractions were found to contain large

amounts of brown material. (Interestingly the later fractions were

also found to contain two major porphyrin bands). This impure porphyrin

was crudely purified by means of preparative tlc (2% MeOH/CH_2Cl_2) and com-

bined with the bulk of the product. This was then placed on a column of

Merck neutral alumina 90 (activity III, 40-50 g) and eluted with

dichloromethane. The porphyrin moved quickly down the column, any brown

material being adsorbed at the top of the column. As mentioned above

the porphyrin separated into two bands; a fast running major band followed

by a minor band. By adjusting the flow rate of the column and the

size of the fractions it was possible to separate the two bands with

minimal overlap.

The front running major band was due to the desired thioether

strapped porphyrin 87a as shown by mass spectrometry (m/e 592). The

mass spectrum of the slower moving minor compound displayed a parent

87a   88a
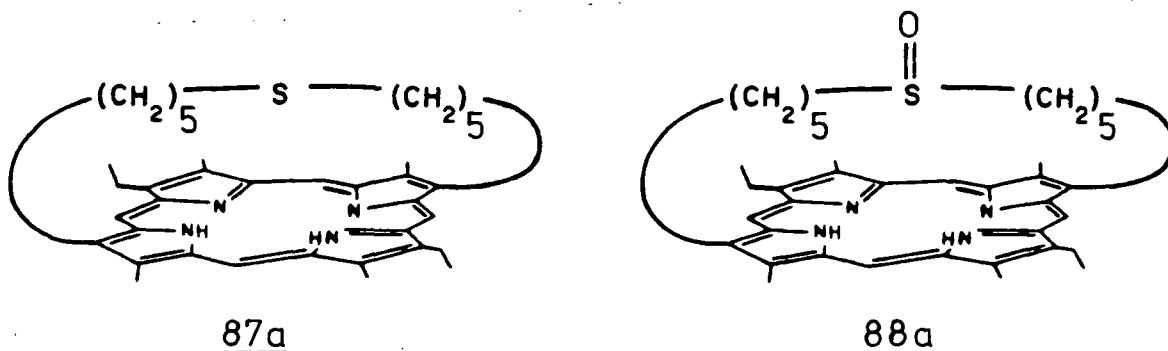
peak at 608 indicating that it was due to a strapped porphyrin in

which the sulfide had been oxidized to a sulfoxide. This was confirmed

by high resolution mass spectrometry, elemental analysis, and ^{1}H and

^{13}C-NMR. The combined yield of 87a and 88a, that is the total

cyclization yield, was 9.5 - 19.5%, based on precursor 77a.

The lower homologue 87b was prepared in exactly the same manner.

The bis-(pyrrole-3-yl)butyl sulfide 75b was obtained from the α-free iodo-

butyl pyrrole 64 by refluxing with sodium sulfide in aqueous THF.

In most cases a yield could not be determined because 75b was contamina-

ted with either the cyclohexyl pyrrole 65 or the butyl pyrrole 66.

75b   65   66
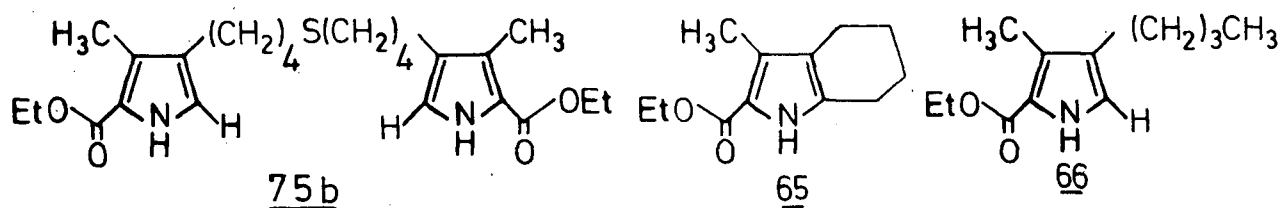
Fortunately these impurities were easily separated from the required

product. In one instance where pure 64 was used the product was

obtained from the reaction mixture as a slightly pink solid (94.4%

crude). The bis-dipyrromethane 77b was prepared as before by heating

75b with 76 (2.1 equivalents) in glacial acetic acid at 80-90°C for

1 hour. After work-up 77b was obtained as an orange solid (82-92%

crude). Again tlc displayed a single major yellow spot which turned

purple on exposure to bromine vapour.

The deprotection-decarboxylation-cyclization sequence was carried

out exactly as described above. Cyclization was carried out under the

same conditions and similar concentrations to those used for 87a. After

work-up tlc of the crude product showed two major purple spots and a

faster running green spot. The crude product was placed on a column

(75-100 g) and eluted with 2% methanol/dichloromethane. As usual faint

bands due to metalloporphyrins and other compounds came off the column

first and were discarded. These were followed by a green band and

then finally by the strapped porphyrin. A visible spectrum of the

green material gave an unrecognizable spectrum totally unlike that of

an etio-type porphyrin. Fractions containing both green material and

strapped porphyrins were stirred in air overnight whereupon tlc indicated

complete disappearance of the green material. Similarly, when fractions

containing only the unknown green material were stirred in air for

48 hours tlc showed the presence of strapped porphyrin. Attempts to

isolate and purify this green material by preparative tlc failed, only

porphyrin and other blue, purple and brown bands appearing on the plate.

The partially purified product was placed on a column of Merck

neutral alumina 90 (activity III) and eluted with dichloromethane. The

first material from the column was an unidentified blue compound,

followed by the thioether strapped porphyrin 87b and the corresponding

sulfoxide porphyrin 88b; all the brown impurities remained at the head

of the column.

87b

88b
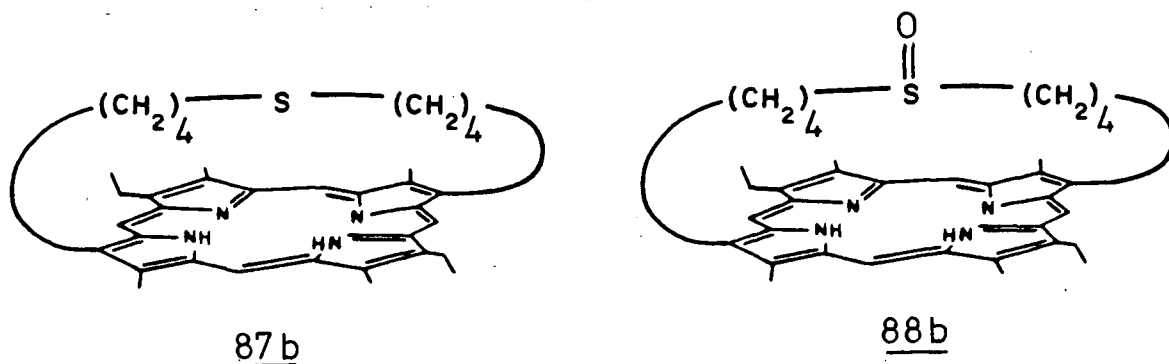
Although no hard evidence was obtained we can speculate as to the identity of the transient green material obtained from the column. The intramolecular cyclization reaction proceeds via a b-bilene 89 to a porphodimethene 90 (Fig. 10). Generally such compounds undergo facile oxidation by air to yield the corresponding porphyrin. However it is conceivable that, if the strap was very short, the molecule might be locked into a conformation where oxidation to the planar porphyrin would be more difficult. Wijesekera, in his preparation of the equally strained porphyrin 91 bearing a 9-carbon chain did not report the occurrence of a possible porphodimethene intermediate. In his purification procedure the crude porphyrin was placed in a silica gel column (Woehlm, activity I) for several hours, a situation which might be expected to enhance oxidation of a porphodimethene to the porphyrin. In our case purification was accomplished by flash chromatography and the crude product was on the column for less than 30 minutes. However in the absence of more evidence the discussion remains merely speculative.

The synthesis of the 8-carbon thioether strapped porphyrin was attempted three times and the total cyclization yield (i.e. yield of
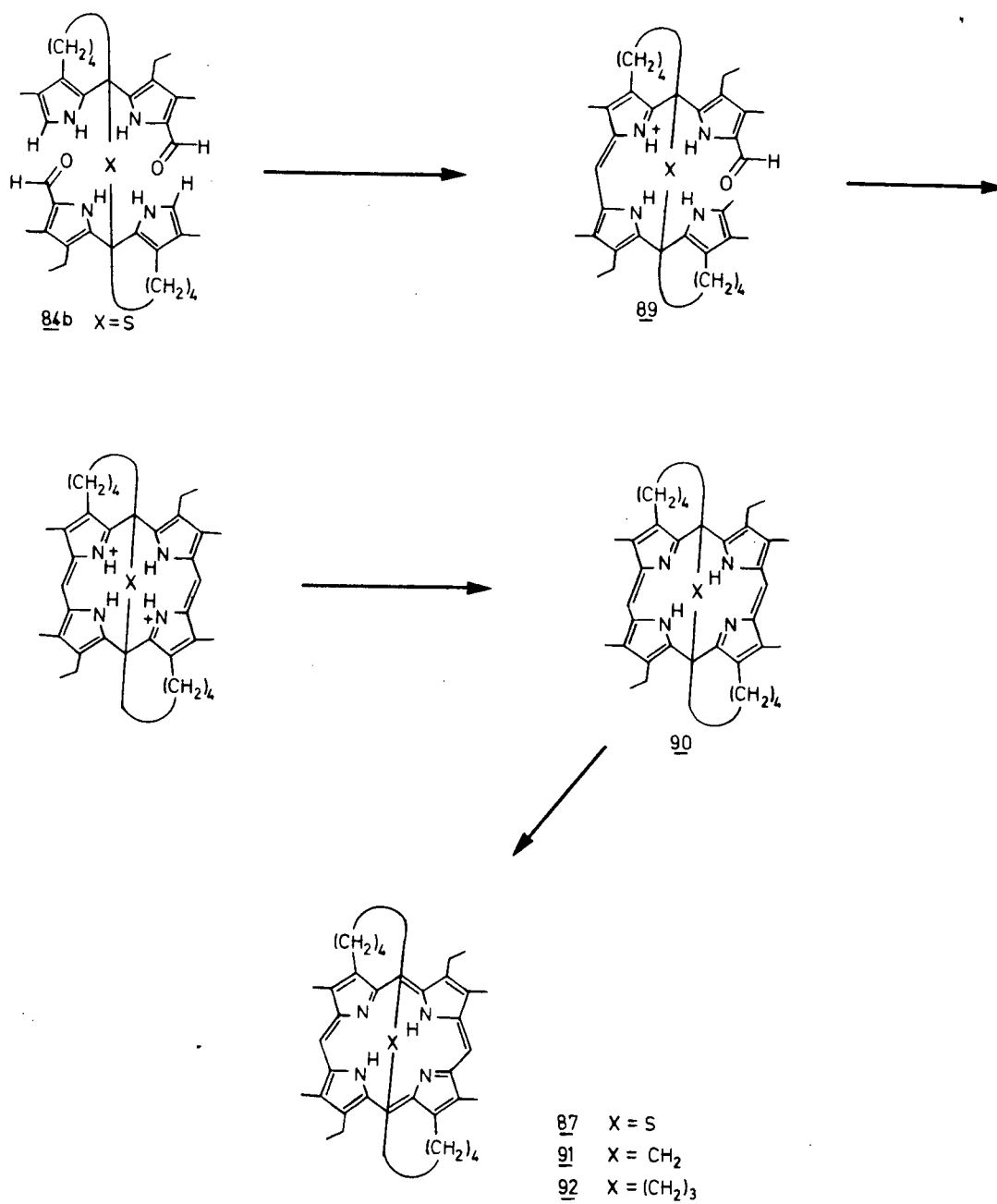
Fig. 10: Synthesis of Sulfide-Strapped Porphyrin 87b via

Intramolecular Cyclization

thioether 87b and sulfoxide 88b) was 12.0, 18.6 and 21.6%. Unexpectedly

the yields were similar to those obtained for the corresponding

homologues 87a and 88a (9.0 - 19.5%). These yields were disappointingly

low when compared to syntheses of similar porphyrins containing only a

methylene strap (92 : 22-52%, 91 : 20-25%). Obviously the purity of the

precursor bis-dipyrromethanes 77a and 77b must be suspected since most

77a n = 5
b n = 4
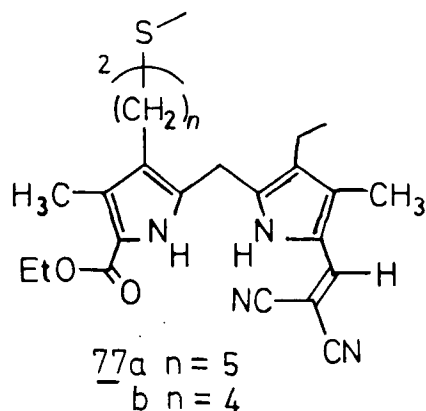
cyclizations were performed using crude samples. However, the samples

would have to be grossly contaminated to bring about the 50% decrease in

yield for 87a. The fact that some sulfoxide was produced may hint that

other reactions besides decarboxylation and hydrolysis are occurring prior

to the intramolecular cyclization. Other reactions, such as breaking of

the thioether chain, would seriously reduce the yield. Wijesekera's

work set the limit on the length of a methylene chain strapping a

porphyrin (91, yield 20-25%). The fact that both 87a and 87b are

produced in similar yields (9-20% and 12-22% respectively) may set the

limit for the more fragile thioether chain, irrespective of its length.

It would be interesting to determine at what stages in Fig. 9,

decomposition and/or oxidation of the sulfide linkage could occur.

Unlike ethers, sulfides are readily reactive.[165] Various aliphatic

sulfur compounds can be decomposed to olefins at 55°C in a KOBu-t/DMSO

medium. Thus Wallace et al.,[166] observed that aryl alkyl sulfides and

sulfoxides undergo base-catalyzed 1,3-rearrangements and subsequent

β-eliminations to stilbene derivatives in dipolar solvents (Scheme 75,

equation 57). However, while Fenton and Ingold[167] have shown that olefin

SCHEME 75

$$\text{Ph-CH}_2\text{SCH}_2\text{-Ph} \xrightarrow{\text{RO}^-} \text{Ph-CH}_2 \overset{S}{\text{CH-Ph}} \longrightarrow \qquad (57)$$

$$\text{Ph-CH-}\overset{\overset{S^-}{|}}{\underset{|}{C}}\text{-Ph} \longrightarrow \text{Ph-CH=CH-Ph} \quad 45\% \qquad (58)$$

$$(CH_3)_3C\text{-S-}C(CH_3)_3 \xrightarrow[\text{HMPA / 80°C}]{\text{KOH}} \text{(CH}_3)_2\text{C=C(CH}_3)_2$$
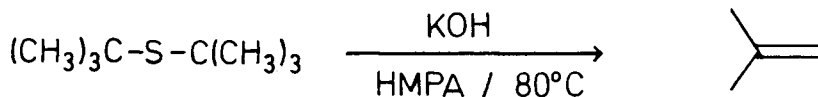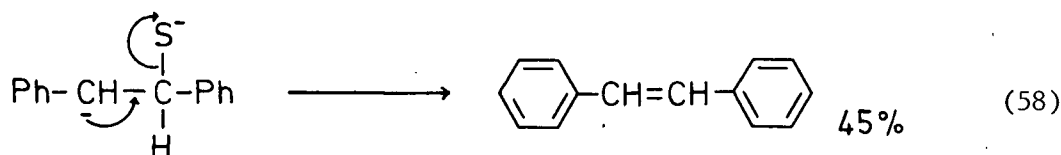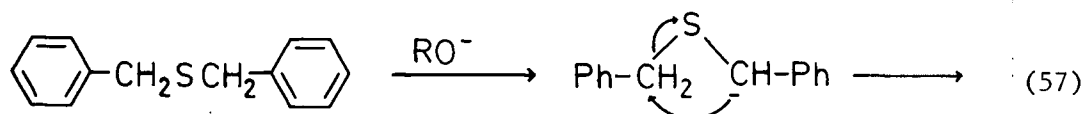
production from simple aliphatic sulfones in the presence of KOH requires

a reaction temperature of 200°C or higher, aliphatic sulfoxides and

sulfides are not decomposed by KOH under these conditions. In contrast,

Wallace et al.,[168] have reported that some aliphatic sulfur compounds

may be decomposed to olefins in the presence of KOH at 80°C in hexa-

methylphosphoramide after extended heating (Scheme 75, equation 58).

Therefore formation of the sulfide 75 and formation of the bis-dipyrro-

methane 77 employ conditions unlikely to lead to decomposition.

Similarly the sulfide bond should be stable under conditions used for

hydrolysis of 77 i.e.,KOH in aqueous propanol at 80°C for 3-4 hours.

However thermal decarboxylation of 83 uses more drastic conditions,

refluxing N,N-dimethylformamide. The cleavage of the C-S bond of

sulfides is known to occur in thermal reactions,[169] but in general the temperature required is quite high. Thus ethyl sulfide decomposes at

$\underline{83}$ a n = 5
   b n = 4
$R = CO_2H$, $R' = CHO$

$\underline{84}$ a n = 5
   b n = 4
$R = $ H , R' CHO
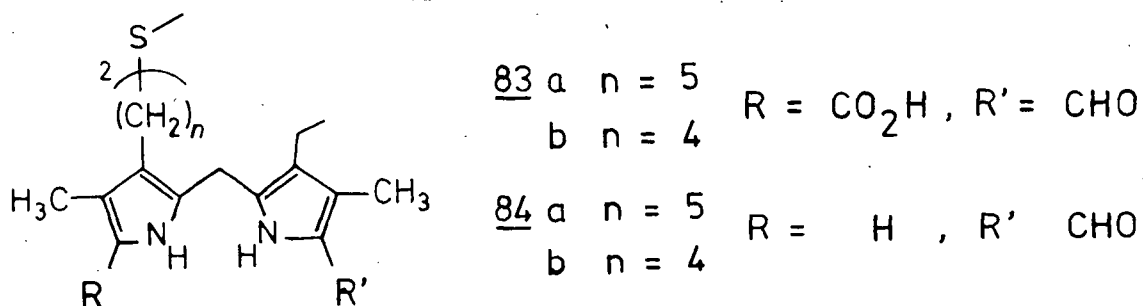
400°C, and, after 2 hours in kerosene at 230°C in the presence of molybdenum sulfide, the decomposition of propyl sulfide was 26%. However the extent of decomposition after 4 hours in N,N-dimethylformamide at 153°C cannot be ascertained without isolation of the unstable α-free, α'-formyl bis-dipyrromethane $\underline{84}$.

Many methods are available for the oxidation of sulfides to sulfoxides.[169,170] Industrially sulfoxides are prepared by the direct air oxidation of sulfides catalyzed by nitrogen dioxide.[171] However samples of $\underline{75}$ and $\underline{77}$ which had been in contact with air for several months showed no evidence for sulfoxide formation. Indeed ^{1}H-NMR and mass spectral analysis seem to indicate that no appreciable amount of sulfoxide is produced prior to hydrolysis of the bis-dipyrromethanes $\underline{77}$, and it is unlikely that sulfoxide formation occurs during the hydrolysis step. Although the thermal decarboxylation of $\underline{83}$ is carried out under argon the high temperatures of the reaction may enable the sulfide to react with traces of oxygen present, or to abstract oxygen from the solvent (Scheme 76, equation 59). The latter would be analogous to the reported oxidation of organic sulfides in dimethyl

sulfoxide at 160-172°C (equation 60).[172]

SCHEME 76

$$\underset{R}{\overset{R}{>}}\!S \;+\; \underset{H}{\overset{O}{\underset{}{\parallel}}}\!\!\overset{}{C}\!\!-\!\!\underset{\underset{CH_3}{|}}{N}\!\!-\!CH_3 \longrightarrow \underset{R}{\overset{R}{>}}\!S\!=\!O \;+\; N(CH_3)_3 \qquad (59)$$

$$\underset{R}{\overset{R}{>}}\!S \;+\; O\!=\!S\!\!\underset{CH_3}{\overset{CH_3}{<}} \longrightarrow \underset{R}{\overset{R}{>}}\!S\!=\!O \;+\; S\!\!\underset{CH_3}{\overset{CH_3}{<}} \qquad (60)$$
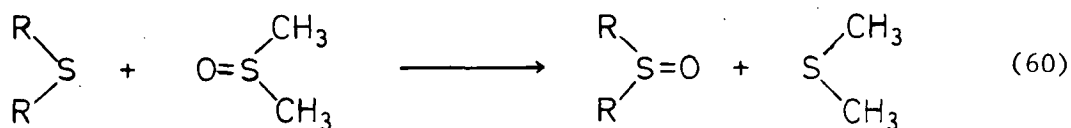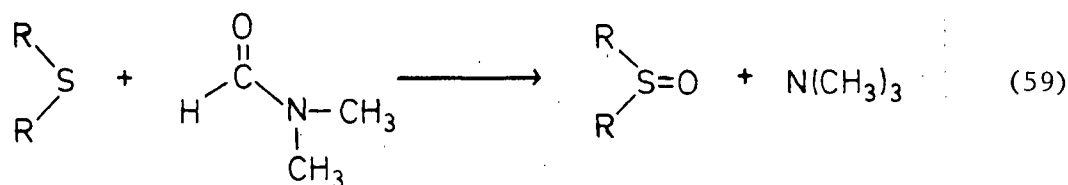
A more attractive proposition is that oxidation of the sulfide

to the sulfoxide does not occur until after formation of the porphyrin

ring. Since most free base porphyrins are good sensitizers of singlet

oxygen it is likely that the sulfoxides 88 are produced by the photo-

oxidation of 87. Schenck and Krauch[173] first reported that dialkyl

sulfides undergo sensitized photooxidation to give 2 mol of sulfoxide

per mol of absorbed oxygen. Recently, Foote et al.,[174] have investi-

gated the singlet oxygen oxidation of diethyl sulfide in various

solvents (methanol, benzene, and acetonitrile), zinc tetraphenylporphyrin

and free base tetraphenylporphyrin being used as sensitizers in the

benzene solution. Sulfide photooxygenation is of particular interest

because methionine is one of the amino acids attacked most rapidly in

photodynamic action (i.e., the destructive action of dye sensitizers,

light and oxygen on organisms),[175] and the photosensitized deactivation

of several enzymes e.g. chymotrypsin, has been correlated with the

photooxidation of methionine to the corresponding sulfoxide.[176] As 87

was synthesized to model the binding of methionine to the heme of
cytochrome č this oxidation was of passing interest.

87a n = 5
  b n = 4

88a n = 5
  b n = 4
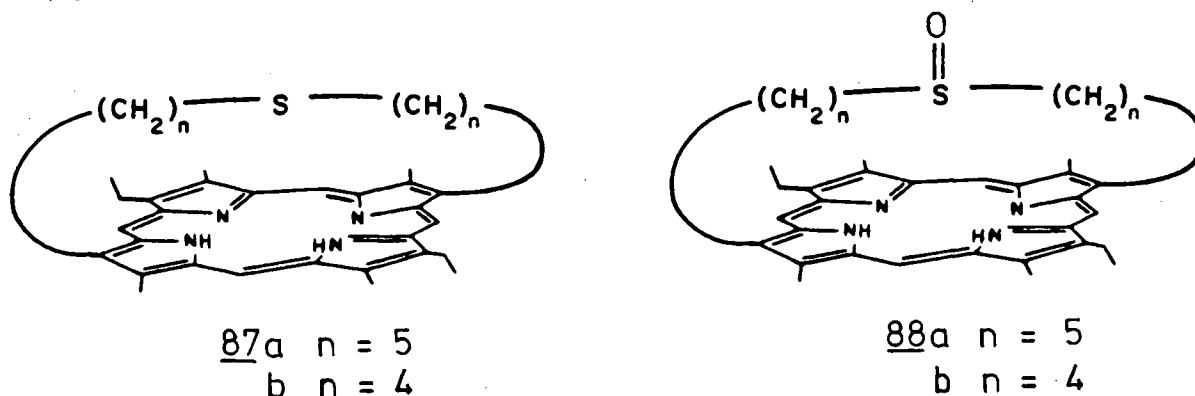
Jori et al.,[177] have carried out a kinetic investigation of the
photooxidation of methionine by irradiation in the presence of a
series of porphyrins. Conversion to the sulfoxide was observed to be
quantitative and a reaction mechanism involving singlet oxygen was
proposed. Whitten and co-workers have studied the photooxidation of
protoporphyrin IX, both in solution and in organized media.[178,179]
The porphyrin activated oxygen mainly by production of singlet oxygen.
While the porphyrin can react with the singlet oxygen to give either
net quenching or photooxidation products, the reactivity is low, so
that protoporphyrin IX can function as a good sensitizer for the photo-
oxidation of other potential substrates.[179] It was also observed that
the photooxidation of protoporphyrin IX in natural membrane systems
yielded products which did not include the "usual" singlet oxygen
products.[180] Whitten and Krieg modelled the kinetic behaviour observed
in the natural membrane systems by using an oil/water microemulsion
as a solvent and adding various amino acids.

The results of this study suggested that porphyrins sensitize
singlet oxygen efficiently but that the singlet oxygen is rapidly

scavenged by substrates such as methionine and other amino acids. The oxygenated amino acids then act as agents to oxidize the porphyrins by attacking the porphyrin ring directly.

To demonstrate that the sulfoxide strap porphyrin 88a is formed by the photooxidation of 87a the following very crude experiment was carried out. Two solutions containing 87a in dichloromethane were prepared and placed in stoppered vials (10 mL). One solution was kept in the dark while the other was subjected to laboratory light. After 3 days the illuminated sample was examined by tlc (2% MeOH/CH$_2$Cl$_2$). It showed no trace of the sulfide strap porphyrin 87a, only a spot due to sulfoxide 88a and a large spot at the origin, presumably due to decomposition products. The sample kept in the dark showed only a spot due to sulfide 87a with no trace of sulfoxide 88a or decomposition.

A further three equimolar solutions of sulfide strap porphyrin 87a in dichloromethane were prepared and stored in stoppered vials. One was stored in the dark, another was subjected to laboratory lighting as before and the third had some diazabicyclooctane (DABCO) added and subjected to laboratory lighting. After 12 hours the dark sample showed no change on tlc. The illuminated sample containing only porphyrin showed no trace of the sulfide 87a, only sulfoxide 88a and decomposition. The illuminated sample containing DABCO showed no trace of sulfoxide 88a formation. This is consistent with the known ability of DABCO to act as a "quenching" agent i.e., it destroys singlet oxygen and the molecular excited states leading to singlet oxygen formation.

The above crude experiments suggest that the porphyrin ring acts as a sensitizer to produce singlet oxygen which can then oxidize the
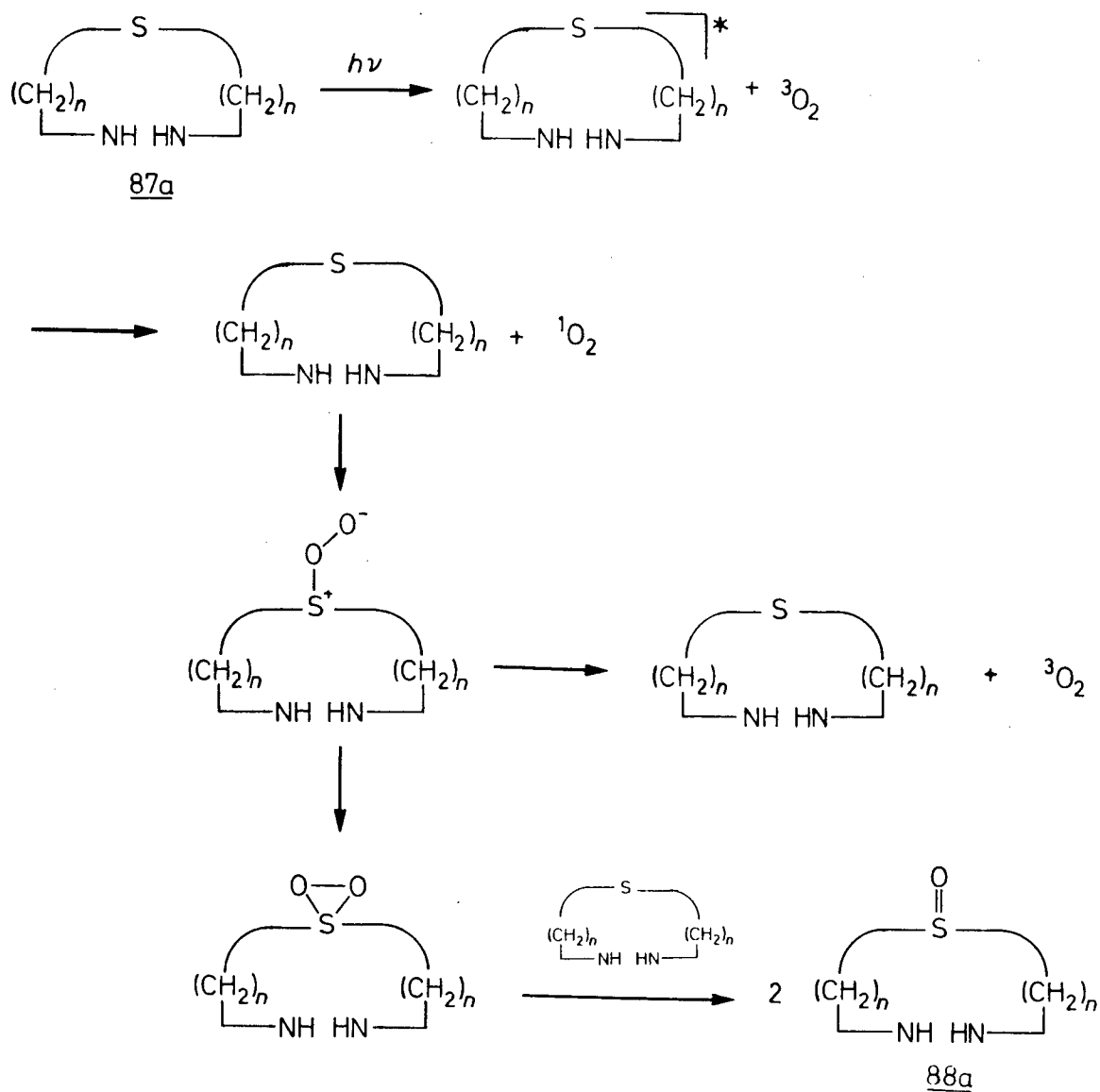
Fig. 11: Proposed Mechanism of Sulfoxide-Strapped Porphyrin 88a Formation

sulfide strap to the corresponding sulfoxide.   Fig. 11, is in analogy

to the mechanism of photooxidation of diethyl sulfide proposed by

Foote et al.[174]

No significance can be attached to the observation that more

sulfoxide appears to be produced during the formation of 87b than

during the formation of the longer chain 87a (Table II). The length

and levels of illumination varied considerably during work-up.

Sulfoxides can be oxidized to sulfones but with a far lower

rate compared to that of sulfides to sulfoxides.[173,174]   No observable

amount of the sulfones 93a and 93b was formed during porphyrin prepara-

tion and purification.
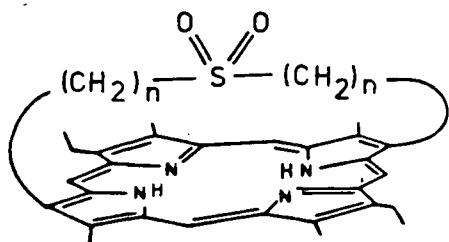
93a   n = 5
  b   n = 4

While formation of the sulfoxide porphyrins 88a, 88b complicated

somewhat the purification of the sulfide porphyrins 87a, 88b the problem

was not a major one since many methods are known for reducing sulfoxides

to sulfides.

As we had already used oxalyl chloride/dimethyl sulfoxide for

the oxidation of alcohols to aldehydes (cf. Section 2.4), a sense of

symmetry prompted us to use an oxalyl chloride/sodium iodide system to

effect the sulfoxide deoxygenation.[181]   The reaction of sulfoxides

with oxalyl chloride occurs to give intermediate VII which can undergo

TABLE II: Yields of the Sulfide-Strapped Porphyrins 87a, 87b and the Sulfoxide-Strapped Porphyrins 88a, 88b

% YIELDS

RUN	87a	88a	87b	88b	% 88a/87a	% 88b/87b
1	9.5	0.8			8.4	
2	14.2	0.9			6.3	
3	18.7	0.8			4.3	
4	8.8	0.7			8.0	
5	13.0	2.6			20.0	
6			10.1	1.9		18.8
7			17.5	4.6		26.3
8			16.5	2.1		12.7

elimination to give chlorinated sulfide. VIII. The presence of sodium iodide prevents chlorination by trapping intermediate VII before elimination occurs or by reducing any chlorine as soon as it is formed (Scheme 77).

SCHEME 77

$$RCH_2\overset{\overset{\text{O}}{\|}}{S}CH_2R \ + \ (COCl)_2 \ \longrightarrow \ \left[\begin{array}{c} \overset{\text{O} \ \text{O}}{\overset{\| \ \|}{O\text{C}\text{C}Cl}} \\ \overset{|}{RCH_2\overset{+}{S}CH_2R} \end{array} \right] \quad \overline{\text{VII}}$$

$$\left[\begin{array}{c} Cl \\ | \\ RCH_2\overset{+}{S}CH_2R \end{array} \right] \qquad \left[\begin{array}{c} \overset{\text{O} \ \text{O}}{\overset{\| \ \|}{O\text{C}\text{C}Cl}} \\ | \\ RCH_2\overset{|}{\underset{I}{S}}CH_2R \end{array} \right]$$

$$\underline{\overline{\text{VIII}}} \quad \overset{Cl}{\underset{}{|}} \\ RCHSCH_2R \qquad\qquad\qquad RCH_2SCH_2R$$
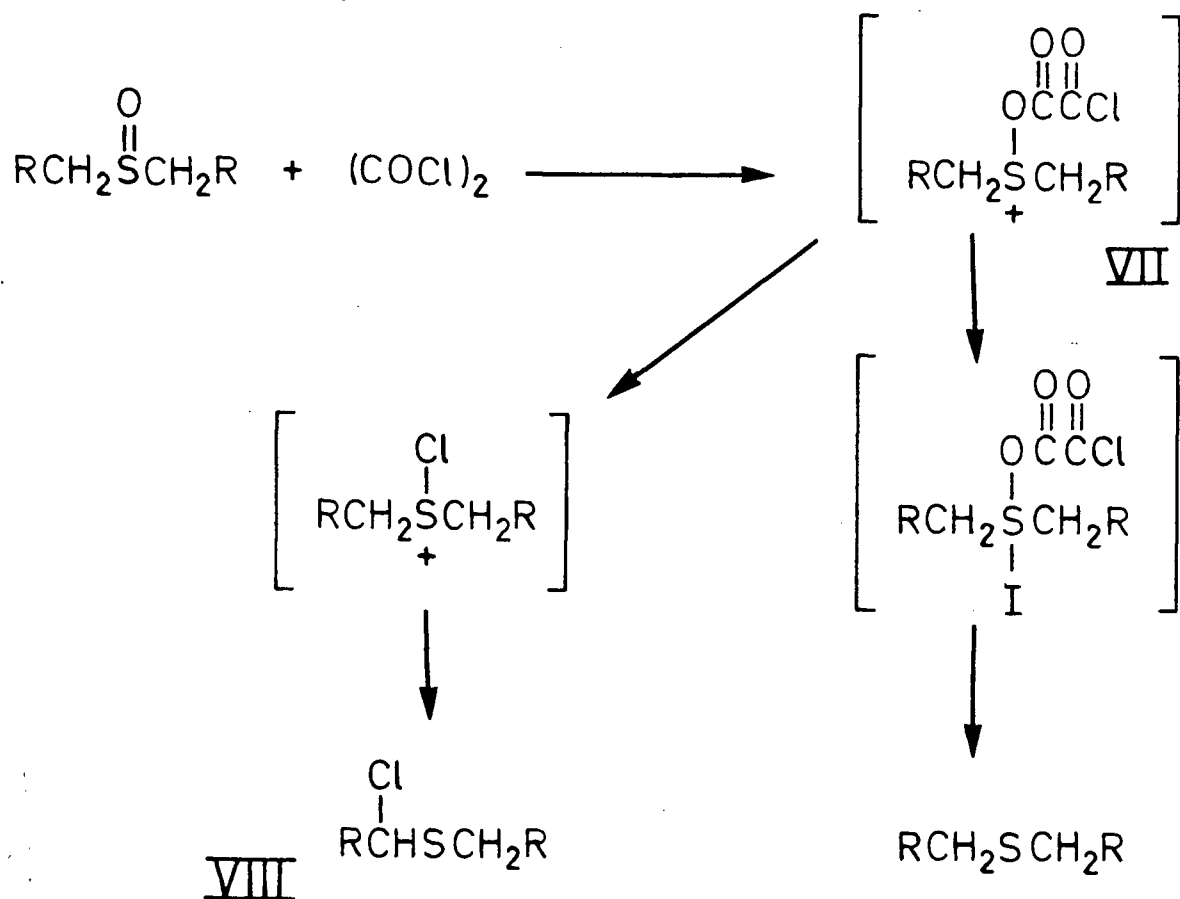
Oxalyl chloride was added dropwise to a solution of the sulfoxide 88a and sodium iodide in cold acetonitrile. There was an immediate evolution of gas and liberation of iodine following which the solution was stirred for a further 20 minutes. After quenching with aqueous sodium thiosulfate and work-up the results were variable. In some instances tlc indicated complete reduction to the sulfide 87a. However

in other cases some sulfoxide 88a still persisted. It was not establish-
ed whether this was due to incomplete reduction or to re-oxidation of
the sulfide 87a on exposure to light during chromatography. Neverthe-
less an alternative reduction method was sought.

Because of its versatility, the use of iodotrimethylsilane was
considered. This reagent was attractive since it could be used not
only for sulfoxide deoxygenation but also for the demethylation of
alkyl aryl ethers (cf Section 2.4).[182] Since iodotrimethylsilane is a
relatively expensive commercial reagent and is subject to decomposition
on standing, several methods for its in situ generation have been
developed. The use of methyltrichlorosilane/sodium iodide as an iodo-
trimethylsilane equivalent has been described by Olah.[183] Addition of
trichloromethylsilane to an acetonitrile solution of anhydrous sodium
iodide gives a yellow solution with precipitation of sodium chloride
and formation of complex IX. Subsequent reaction with a sulfoxide
may proceed through intermediates X-XII resulting in reduction to the
sulfide and liberation of iodine.

Reduction of the sulfoxide strap porphyrin 88a was conveniently
carried out using a large excess of methyltrichlorosilane and sodium
iodide. After stirring for 2 hours the reaction was quenched and the
porphyrin purified by chromatography on an alumina column (70.7%). Tlc
and mass spectrometry indicated complete reduction to the sulfide
strap porphyrin 87a.

For the shorter chain homologue 88b reduction to the sulfide 87b
was more complicated. Addition of 88b to a solution of excess methyl-
trichlorosilane and sodium iodide in acetonitrile was followed by 2
hours stirring before the reaction was quenched by addition of aqueous

SCHEME 78

$$H_3CSiCl_3 \ + \ NaI \ + \ CH_3CN \ \rightleftharpoons \ \left[CH_3C\equiv\overset{+}{N}-\underset{Cl}{\overset{Cl}{Si}}-CH_3 \right] I^- \ + \ NaCl$$

IX

$$RSR$$
$$\overset{\|}{O}$$

$$\left[\underset{\underset{R}{\overset{\|}{S}}\underset{R}{}}{\overset{CH_3}{Cl-\overset{|}{Si}-Cl}} \right] I^-$$

X

$$\left[\underset{\underset{I}{R-\overset{|}{S}-R}}{\overset{CH_3}{Cl-\overset{|}{Si}-Cl}} \right] \longrightarrow \left[\underset{\underset{I}{R-\overset{|}{S}-R}}{\overset{CH_3 \quad CH_3}{Cl_2Si \overset{+}{\underset{O}{}} SiCl_2}} \right] I^- \xrightarrow{-I_2} \begin{array}{c} R-S-R \\ + \\ Cl_2CH_3Si-O-SiCH_3Cl_2 \end{array}$$

XI   **XII**

$$\underline{88}a \ \ n = 5$$
$$b \ \ n = 4$$

$$\xrightarrow[\text{NaI}]{Cl_3MeSi}$$

$$\underline{87}a \ \ n = 5$$
$$b \ \ n = 4$$
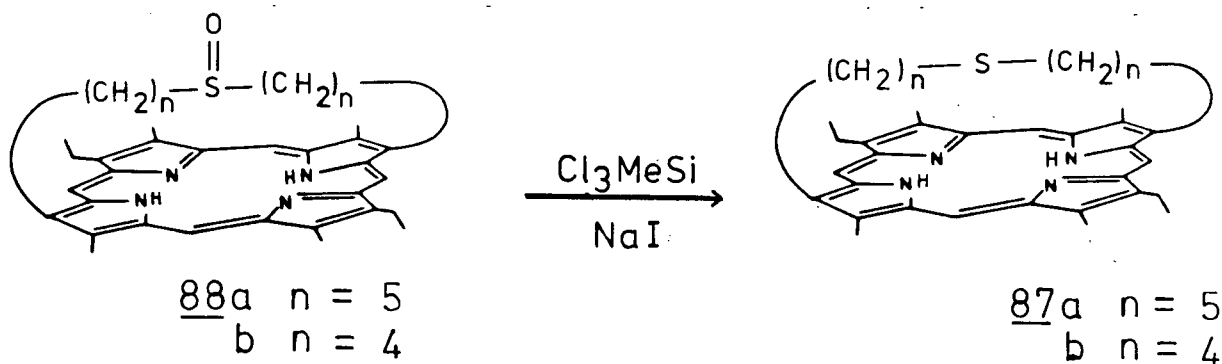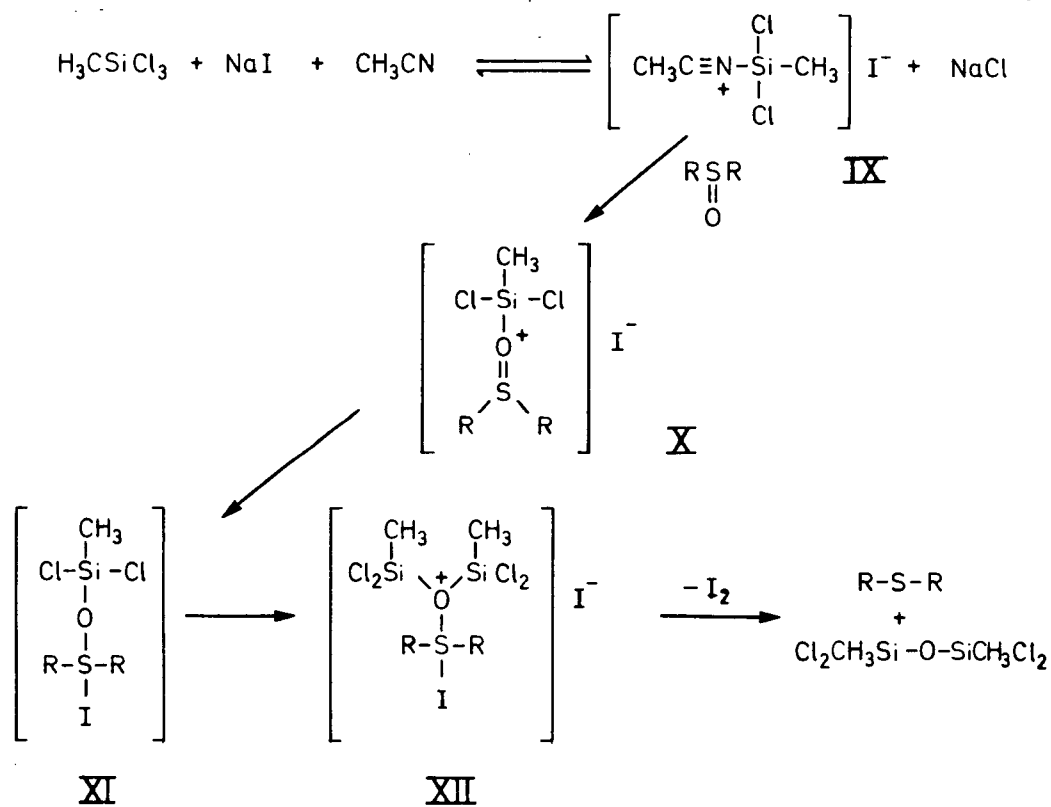
sodium thiosulfate solution. Tlc at this stage showed not only the
presence of the desired porphyrin 87b, but also a pink/brown spot with
a higher Rf value. The crude product was placed on an alumina column
and eluted with dichloromethane. The initial fractions from the
column, when examined by tlc (2% $MeOH/CH_2Cl_2$), were a mixture of a
green and a red/pink material. The optical spectrum of this mixture
displayed a broad band at 590 nm with two more intense bands at 350 and
401 nm. Continued elution with dichloromethane gave fractions
containing only the sulfide porphyrin 87b. The initial fractions were
combined, protected from exposure to light, and stirred overnight in
air. Both tlc and the visible spectrum of the solution showed the
disappearance of both the green and pink/red materials; the strapped
porphyrin 87b was the only material present. All the porphyrin
fractions were combined and further purified by preparative tlc to give
a 74% yield of the sulfide porphyrin 87b.

Previously we had observed the formation of a green material
during the preparation of the sulfide strap porphyrin 87b which, on
stirring in air, was oxidized to the porphyrin. We speculated that the
short strap retarded porphyrin formation and stabilized the intermediate
porphodimethene 90. For the strained C_4-sulfoxide strap porphyrin 88b
it would appear that reduction of the sulfoxide to the sulfide is
accompanied by reduction of the porphyrin ring. That this occurs for
88b but not for the longer chain 88a reflects the highly strained
nature of 88b.

2.4   SYNTHESES OF PORPHYRINS CONTAINING A PHENOL STRAP

Tyrosine plays a role in several hemeproteins, and therefore the

production of suitable porphyrin-phenol models is desirable.

Catalase is an enzyme which protects aerobic organisms from the

toxic effects of hydrogen peroxide by catalyzing reaction 61.

$$2 \, H_2O_2 \longrightarrow 2 \, H_2O \, + \, O_2 \qquad\qquad (61)$$
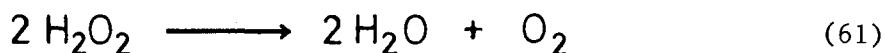
The X-ray crystal structure of beef liver catalase shows that the fifth

proximal ligand of the heme active site is the phenol of Tyr-357,

presumably deprotonated.   There is no sixth ligand but residues on

the distal side include His-74, which is essential for enzyme activity.[184]

Tyrosine also acts as a heme ligand in certain mutant hemoglobins,

where either the proximal or distal histidine is replaced by tyrosine

which binds to the heme iron(III).[185]

In addition, the proximity of a tyrosine (Tyr-67 of horse cyto-

chrome ë) to the heme of cytochrome c has suggested a role for this

residue as a deliverer of electrons to the metal centre.[186]

Porphyrins with coordinated phenoxides have been previously

prepared. Sugimoto and co-workers prepared a series of iron(III)

porphyrins with various 4-substituted phenoxides as axial ligands,

$[Fe(III)(Por)(4-X-C_6H_4O^-)]$ (Por = OEP, TPP).[186] All the compounds were

five-coordinate high spin complexes. A related series of iron(III)

phenoxides, Fe(III)(PPIXDBE)(phenoxide) has been prepared by Ainscough

and co-workers.[185] While the five-coordinate complexes were easily

PROXIMAL
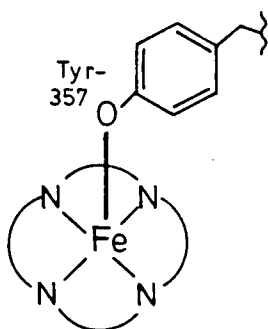
DISTAL
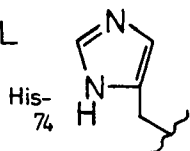
PEROXIDASE
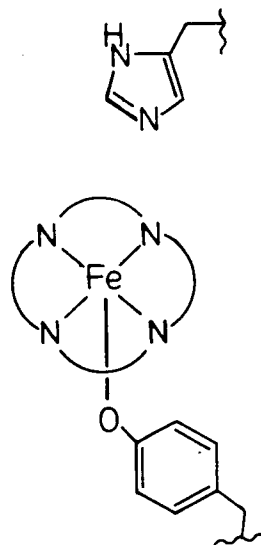
Hb BOSTON

PROXIMAL
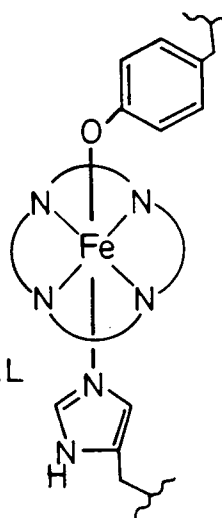
DISTAL
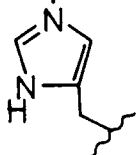
Hb HYDE PARK
Hb IWATE

Tyr-67

Met-80
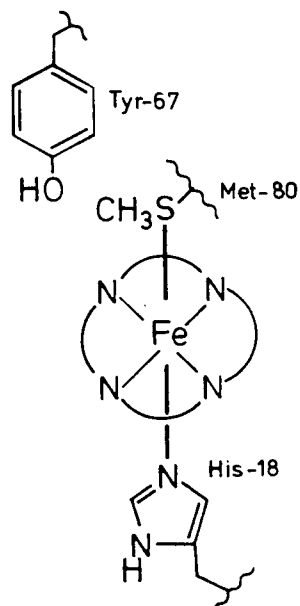
His-18

CYTOCHROME C

Fig. 12:   Schematic Representation of the Active Sites of Peroxidase,

Cytochrome c, and Some Mutant Hemoglobins

prepared as in equation 62, attempts to study the base addition

$$[Fe(III)(PPIXDBE)]_2O + 2HOAr \longrightarrow \qquad (62)$$

$$2\left[Fe(III)(PPIXDBE)(^-OAr)\right] + H_2O$$
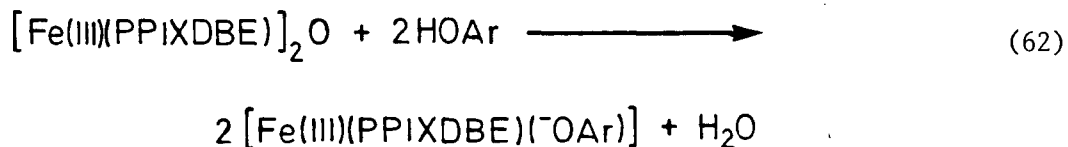
reaction at room temperature were complicated by the formation of

mixtures of $[Fe(III)(PPIXDBE)(^-OAr)]$, $[Fe(III)(PPIXDBE)(^-OAr)(L')]$ and

$[Fe(III)(PPIXDBE)(L')_2]^+$.

$$\left[Fe(III)(PPIXDBE)(^-OAr)\right] + L' \rightleftharpoons \qquad (63)$$

$$\left[Fe(III)(PPIXDBE)(^-OAr)(L')\right]$$

$$L' = 1MeIm, C_5H_5N$$
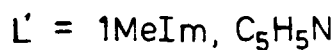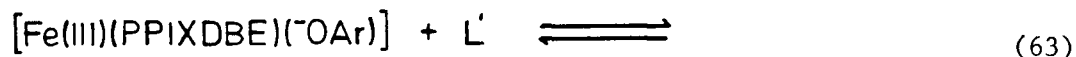
All attempts to prepare the five-coordinate iron(II) phenoxide complexes

failed, spectra attributable to the six-coordinate weak field systems,

$[Fe(II)(PPIXDBE)(^-OAr)_2]^{2-}$, being only observed.

It was hoped that the preparation of a porphyrin with an appended

phenol would give greater control over coordination, leading not only

to the characterization of five-coordinate iron(II) and iron(III)

phenoxides as models for catalase and HbM Boston, but also the mixed

ligand systems, $Fe(Por(^-OAr)(L')$.

As in the synthesis of the sulfide strap porphyrins 87a and 87b, the synthesis of porphyrins containing a phenol strap proceeded from the same building blocks, α-free-iodoalkyl pyrroles 44 and 64 (Fig. 13). This reaction sequence constituted a flexible approach to the synthesis of porphyrins containing functionalized hydrocarbon straps, the method being limited only by the availability of suitable dialdehydes to incorporate into the strap. The key reaction in this route was the double Wittig reaction between the α-free pyrrole phosphonium iodide 94 and the dialdehyde 95.

The dialdehyde 95, 2,6-diformyl-4-methylanisole, was prepared by published procedures (Scheme 79).[187] Treatment of p-cresol 96 with

SCHEME 79
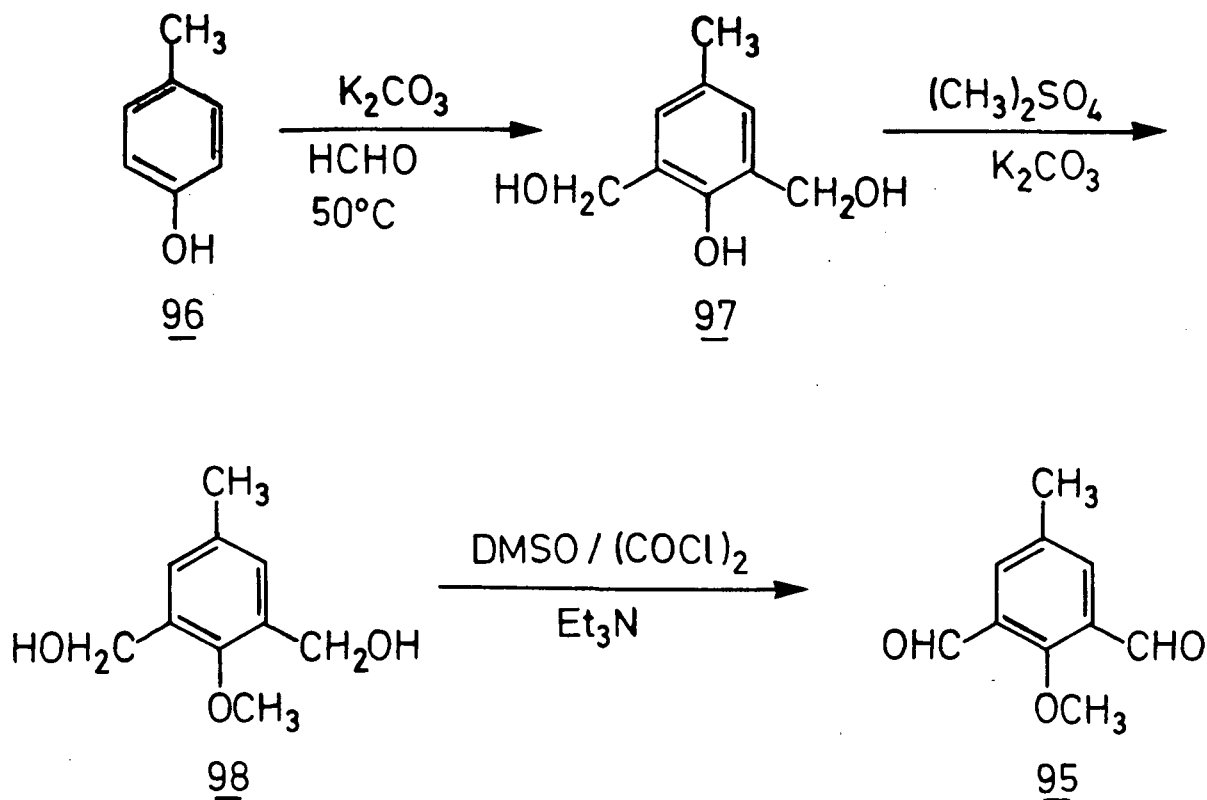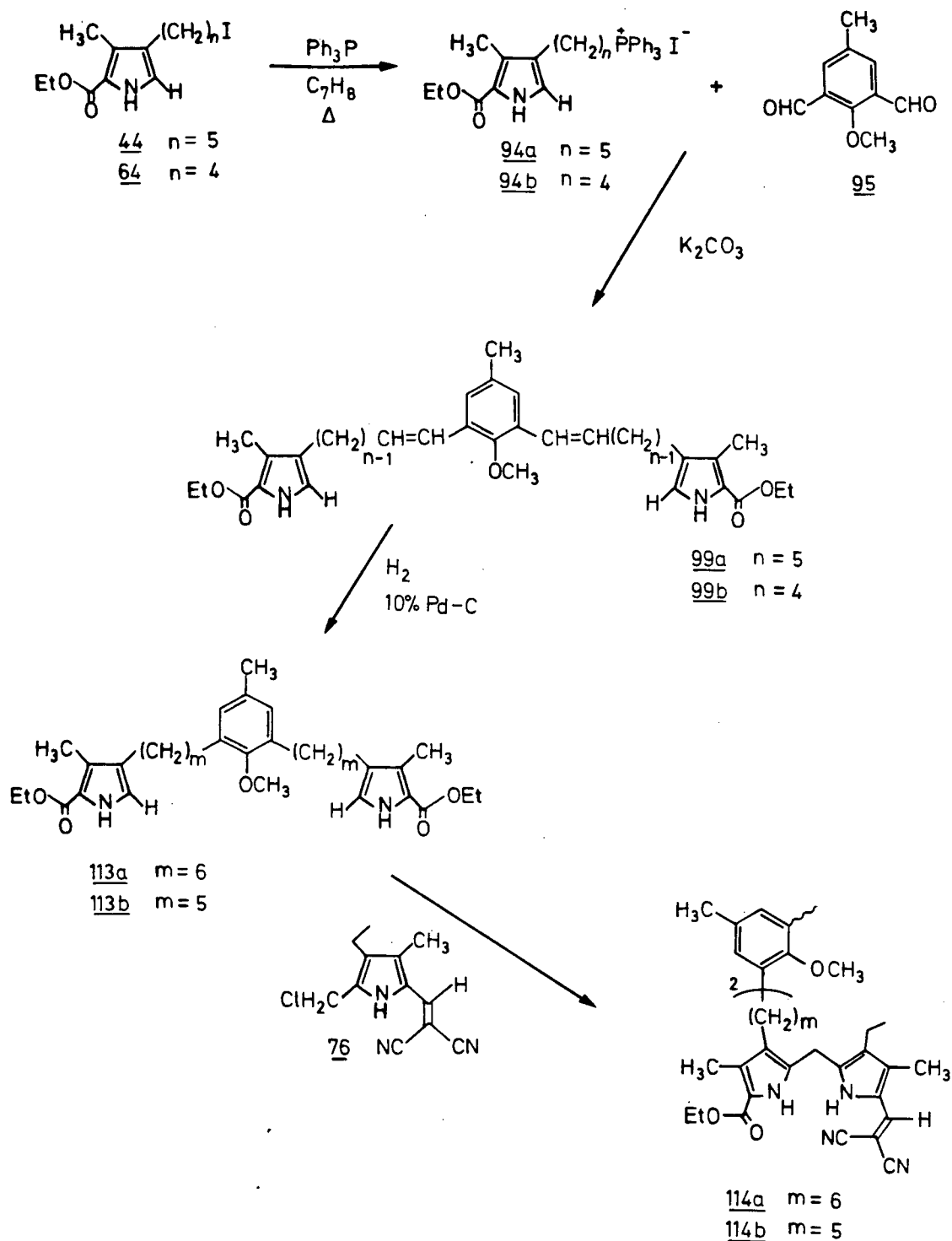
Fig. 13: Synthesis of the Bis-dipyrromethanes 114a and 114b

formaldehyde and potassium carbonate at 50°C gave the desired 2,6-bis(hydroxymethyl)-4-methylphenol 97 in modest yield (34-43%). Despite the low yield the reaction was easily carried out on a large scale using readily available starting materials to give large quantities of pure product.

The phenol 97 was protected as its methyl ether by reaction with dimethyl sulfate. Despite the high published yields (84-95%), Cram's procedure[187] in our hands gave variable yields. Thus 2,6-bis(hydroxymethyl)-4-methylphenol 97 was stirred with dimethyl sulfate (1.1 equivalents) and potassium carbonate in acetone at room temperature for 24 hours. After work-up and recrystallization from chloroform or dichloromethane yields varied from 24-75%. Using sodium hydroxide as base or refluxing the reaction mixture lead to poorer yields. No attempt was made to maximize the yield since sufficient quantities of 98 were obtained for further work.

Oxidation of the hydroxymethyl functions using pyridinium dichromate[188] gave disappointing results (21-53%). However, oxidation using dimethyl sulfoxide/oxalyl chloride/triethylamine gave uniformly good yields (71-93% crude).[189] The crude product was recrystallized from 1:1 (v:v) carbon tetrachloride/cyclohexane to give fine colourless needles.

The α-free pyrrole phosphonium iodide 94a was prepared by refluxing the α-free-iodopentyl pyrrole 44 with excess triphenylphosphine in toluene. In the initial experiments the starting material was contaminated with the corresponding α-free chloropentyl pyrrole which decreased the yield. Furthermore the crude phosphonium iodide 94a separated from solution as a red or brown viscous oil. When the reaction was

H₃C⌒⌒(CH₂)₅Cl
EtO⌒⌒N H
       O H H

H₃C⌒⌒(CH₂)₅P⁺Ph₃ I⁻
EtO⌒⌒N H
       O H H
       94a
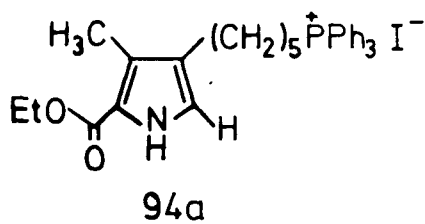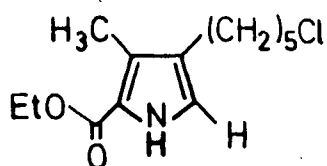
judged complete the solvent was decanted and the viscous product was

triturated several times with diethyl ether to remove unreacted triphenyl-

phosphine and the α-free chloropentyl pyrrole. On drying in vacuo the

viscous oil turned into a hardened foam which was collected. Alter-

natively, trituration with heptane solidified the product but this was

a very tedious process. Although these samples gave poor elemental

analyses they were used without further purification since they were

being used in excess in subsequent reactions. In more recent prepara-

tions, using purer samples of α-free iodopentyl pyrrole 44, the

product phosphonium iodide 94a precipitated from the reaction medium

as a tan powder which was filtered and dried. Yields ranged from

75-97%.

Preparation of the corresponding butyl phosphonium iodide 94b

was complicated by a lack of pure starting material. As mentioned in

Section 2.2, preparation of α-free iodobutyl pyrrole 64 was always

accompanied by formation of the cyclohexyl pyrrole 65 or the α-free-

H₃C⌒⌒(CH₂)₄I
EtO⌒⌒N H
       O H
       64

H₃C⌒⌒
EtO⌒⌒N
       O H
       65

H₃C⌒⌒(CH₂)₃CH₃
EtO⌒⌒N H
       O H
       66
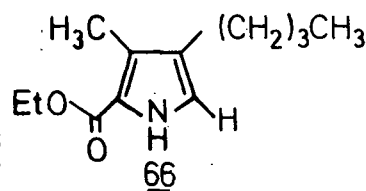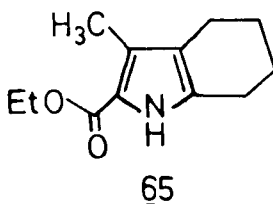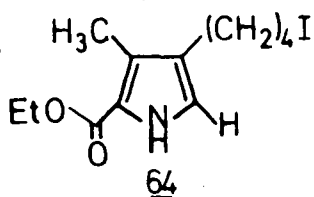
butyl pyrrole 66. Refluxing triphenylphosphine and 64 in toluene

invariably led to the separation of the product 94b as a brown viscous

oil. After trituration with diethyl ether and decanting the supernatant

liquid, the oil was dried on a vacuum line to give a hardened foam

(85-90% crude).

The success of the reactions in Fig. 13 depended upon the yield

and ease of preparation of the bis-alkenes 99. One of the most versatile

reactions for carbon-carbon bond formation is the Wittig reaction.[190]

Thus treatment of a phosphonium salt 100 with base leads to formation of

the ylide 101 which is allowed to react with a carbonyl compound 102

to form the olefinic product 103 and triphenylphosphine oxide 104 via

the intermediacy of the betaine 105. Phosphorous ylides are a unique

form of carbanion in which the charge is modified by possible dπ-pπ

bonding (Scheme 80, 101a ⟷ 101b). The dipolar ylide form 101a gives

the ylide its nucleophilic character which is then modified by the

nature of R^1 and R^2. Thus electron-withdrawing groups will stabilize

the carbanion and reduce the reactivity of the ylide, whereas electron

donating groups will enhance it. For this reason ylides have been

classified as "stable" or "reactive". Similarly the strength of base

required to generate the ylide will depend on the acidity of the

hydrogen on the α-carbon atom. Stable ylides, with electron-withdrawing

groups on the α-carbon are easily deprotonated with dilute aqueous alkai

or neat amines. Reactive ylides, with electron-donating groups on

the α-carbon (e.g. alkyl groups), require metal alkyls or hydrides

to effect ylide formation. Moreover these ylides are oxygen and

moisture sensitive and must be used immediately.

SCHEME 80
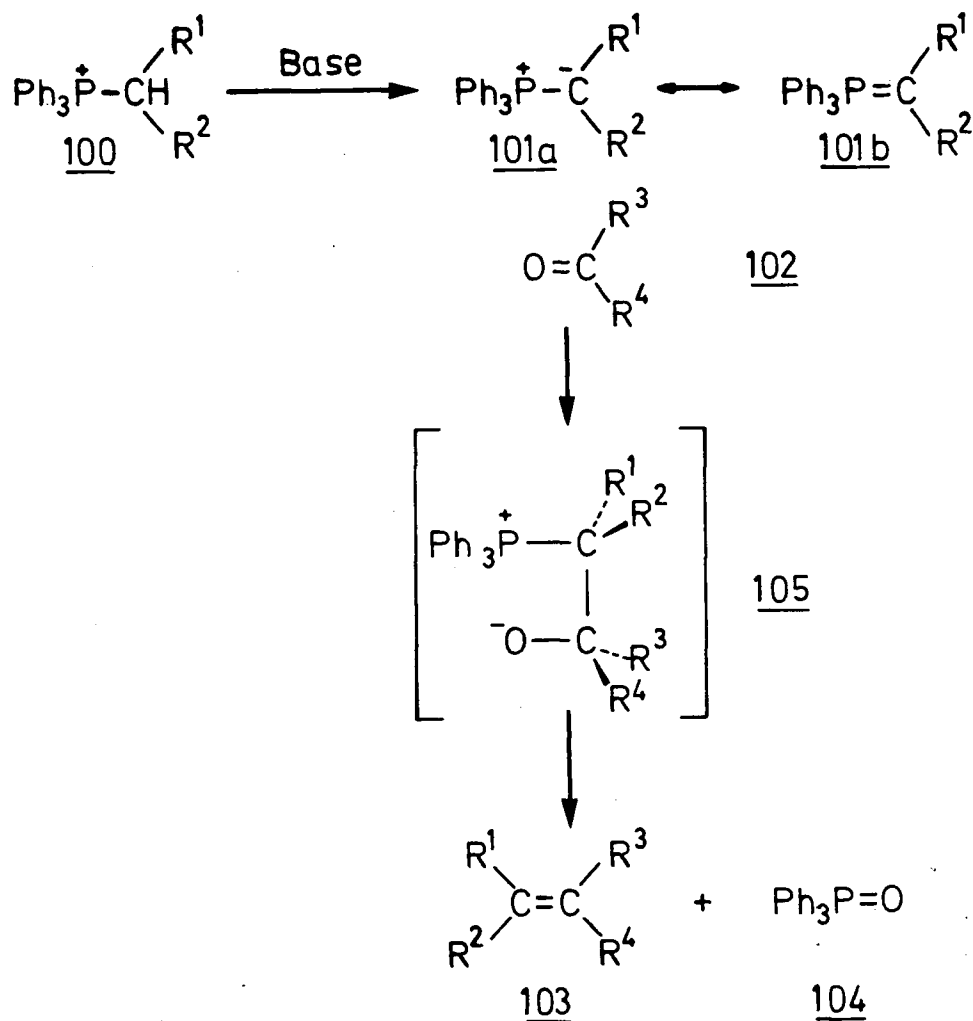
The ylide derived from phosphonium salt 94a was clearly of the reactive kind and, initially, butyl lithium was used for deprotonation of the α-carbon. Thus a solution of 94a in freshly distilled tetrahydrofuran was cooled to -78°C and stirred under argon. n-Butyl lithium was added dropwise via syringe. The solution changed color from clear orange to cloudy white to, finally, a clear orange/red as the

94a

95
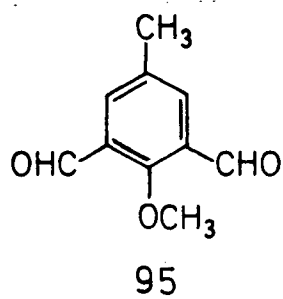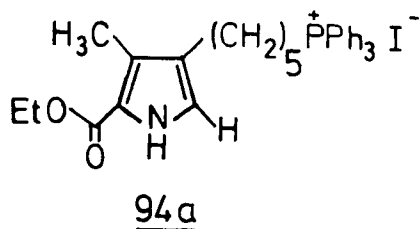
pyrrole nitrogen and then the α-carbon were deprotonated to form the

ylide. Dropwise addition of 2,6-diformyl-4-methylanisole 95 discharged

the orange/red color to give a yellow solution as the ylide reacted.

After warming to room temperature the reaction was quenched and

worked-up. The product was isolated by column chromatography. The

first material from the column was shown by ^{1}H-NMR to be a pyrrolic

by-product. The presence of triplets at 0.90 δ and 5.38 δ suggested

structure 106 which was further confirmed by a parent peak of 277 in

the mass spectrum. The second material from the column was usually

106
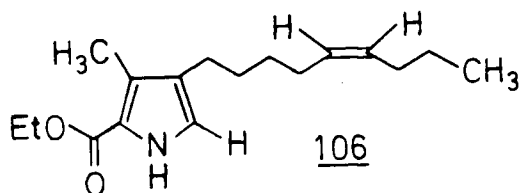
unreacted dialdehyde 95. Unfortunately the desired bis-alkene 99a ran

quite closely after the dialdehyde so care had to be taken to avoid

overlap of the two materials. Optimum yield of product (61-79%) was

obtained when two equivalents of butyl lithium per pyrrole phosphonium

iodide 94a were used. Experiments using 1.5, 3.0 and 4.0 equivalents

of butyl lithium per pyrrole gave lower yields (<42%).

The possibility of using a more convenient reaction which would

avoid formation of by-product <u>106</u> was prompted by the reports of

Delmas, Le Bigot and Gaset who published a simplified Wittig reaction

using a solid-liquid phase-transfer process.[191,192] Phase-transfer

catalysis had previously been applied to the Wittig reaction. Markl

and Merz[193] showed that non-stabilized phosphonium salts could be

deprotonated with aqueous sodium hydroxide in dichloromethane. Thus

addition of 50% caustic soda to a vigorously stirred mixture of

aldehyde and phosphonium iodide led to a weakly exothermic reaction

SCHEME 81

$$R^1CHO + Ph_3\overset{+}{P}CHR^2R^3$$

$$\xrightarrow{\text{NaOH/H}_2\text{O}} \quad Ph_2\overset{\text{O}}{\underset{\parallel}{P}}CHR^2R^3 \quad \underline{107}$$

$$\xrightarrow[\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}]{\text{NaOH}} \quad R^1CH=CR^2R^3 \; + \; Ph_3P=O$$
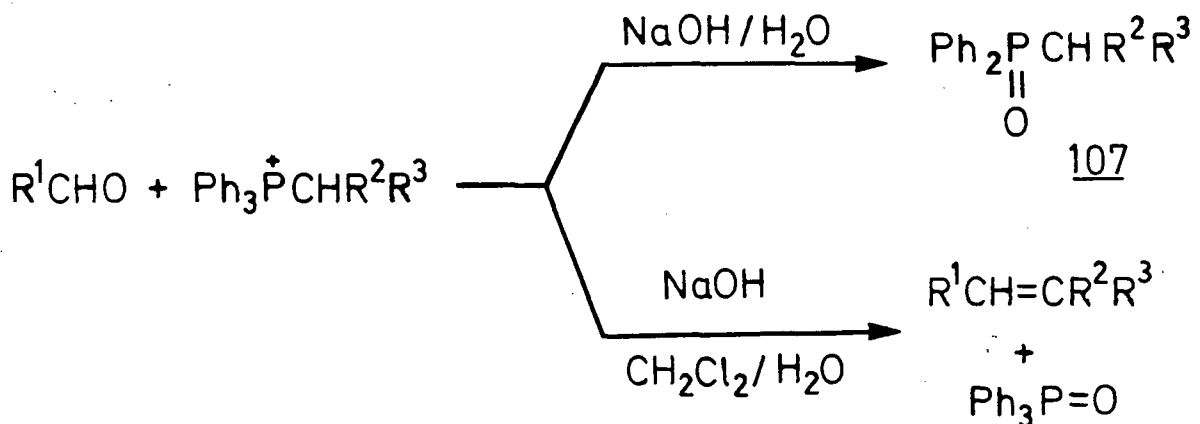
R^1	R^2	R^3	% YIELD	Z/E
ARYL/STYRYL	Ph	H	72 - 88	~1
ARYL/STYRYL	CH_3	H	21 - 51	-

which was complete in ca. 10 minutes. Separation of the organic layer

and removal of the solvent gave the crude product. Since phosphonium

salts are themselves phase-transfer catalysts, no ammonium salt was

necessary. In the presence of aldehydes the Wittig reaction was faster

than the undesired degradation to phosphine oxide 107 (Scheme 81).

Boden[194] was able to introduce some stereoselectivity into the reaction

using a solid-liquid transfer process catalyzed by crown ethers.

Addition of aldehyde and 18-crown-6 to a solution of phosphonium salt

and potassium t-butoxide (or potassium carbonate) in tetrahydrofuran

(or dichloromethane) gave the desired alkene.

SCHEME 82

$$R^1CHO \ + \ Ph_3\overset{+}{P}CH_2R^2 \longrightarrow R^1CH=CHR^2$$

R^1	R^2	SOLVENT	Z/E	BASE	%YIELD
C_6H_5	C_6H_5	THF	22/78	t-BuOK or	96
		CH_2Cl_2	30/70	K_2CO_3	97
C_6H_5	CH_3	THF	85/15	,,	96
		CH_2Cl_2	22/78		93
C_2H_5	C_6H_5	THF	25/75	t-BuOK	82
				K_2CO_3	94
		CH_2Cl_2	46/54	t-BuOK or K_2CO_3	92

In the absence of crown ether little or no product formation was

observed. Delmas, Le Bigot and Gaset[191] found that similar results

(yields, stereochemistry) could be obtained if the crown ether were

replaced by stoichiometric amounts of water (Scheme 83). Similarly

no product was obtained in the absence of added water. Indeed, while

SCHEME 83

$$RCHO \; + \; Ph_3\overset{+}{P}(CH_2)_3CH_3 \; \; B\bar{r} \quad \xrightarrow[\underset{\displaystyle \overset{O}{\underset{O}{\bigcirc}} \; / \; 90°C}{0.03\,mol}]{K_2CO_3} \quad RCH=CH(CH_2)_2CH_3 \; + \; Ph_3PO$$

0.02 mol   0.02 mol
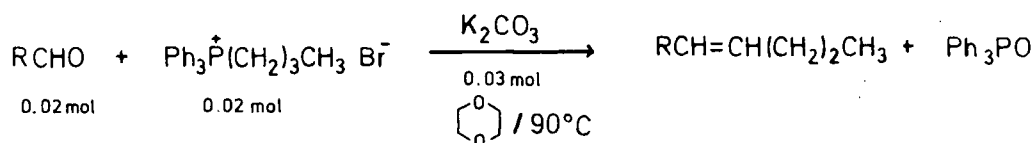
	% YIELD OF ALKENE	
	R = C_6H_5	R = $CH_3(CH_2)_6$
DICYCLOHEXYL-18-CROWN-6	98	67
WATER (0.4 mL)	98	68

$$C_6H_5CHO \; + \; Ph_3\overset{+}{P}(CH_2)_3CH_3 \; \; B\bar{r} \quad \xrightarrow[\underset{\displaystyle \overset{O}{\underset{O}{\bigcirc}} \; / \; 60°C}{0.03\,mol}]{NaOH} \quad RCH=CH(CH_2)_2CH_3 \; + \; Ph_3PO$$

0 02 mol   0.02 mol
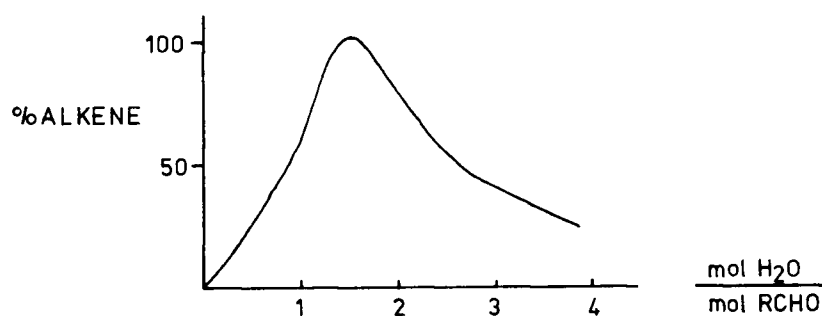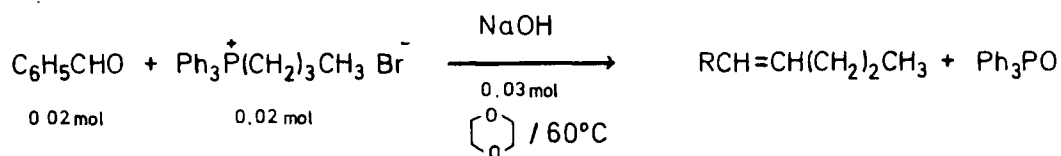
varying amounts of base (sodium hydroxide or potassium carbonate), did not affect the yield or length of the reaction, it was found that maximum yield was obtained when between one and two equivalents of water was used per molecule of aldehyde. The published procedure was extremely simple.[195] A mixture of phosphonium salt (0.02 mol), sodium hydroxide (3 g), water (0.3 mL) and aromatic aldehyde (0.02 mol) was

refluxed in 1,4-dioxane. Filtration, solvent evaporation and flash chromatography yielded the pure alkenes. The simplicity of the reaction and work-up, coupled with the high yields, even for long-chain aliphatic phosphonium salts, recommended this method for our double Wittig reaction.

The initial results were not encouraging. Using sodium hydroxide as base, the phosphonium salt 94a and the dialdehyde 95 were heated in 50:1 dioxane/water (18 equivalents of water per aldehyde) at 70°C. ^{1}H-NMR examination of the crude reaction mixture after work-up gave no indication of alkene formation, nor was any unreacted dialdehyde observed.

Gaset et al.,[195] suggested that potassium carbonate was more suitable as a base in the phase-transfer Wittig reaction since (i) it is a poor catalyst for aldol condensations if aliphatic aldehydes are being used, and (ii) there is less liklihood of a competing Cannizzaro reaction if electron-rich aromatic aldehydes are used. Accordingly, using anhydrous potassium carbonate as base, the phosphonium iodide 94a and the dialdehyde 95 were refluxed in 50:1 dioxane/water (50 equivalents of water per aldehyde) for 20 hours. This time ^{1}H-NMR of the crude reaction mixture indicated some alkene formation. However after chromatography the major product was demonstrated not to be the desired bis-alkene 99a but rather the mono-alkene 108. This was formed in 71% yield. In a similar reaction, using anhydrous potassium carbonate as base, excess phosphonium iodide (4 equivalents) and 2 equivalents of water per aldehyde function, the starting dialdehyde was recovered quantitatively. By contrast, when this reaction was repeated both mono-alkene 108 (74%) and bis-alkene 99a (18%) were obtained; 27% of the

starting dialdehyde 95 was recovered unchanged.

108
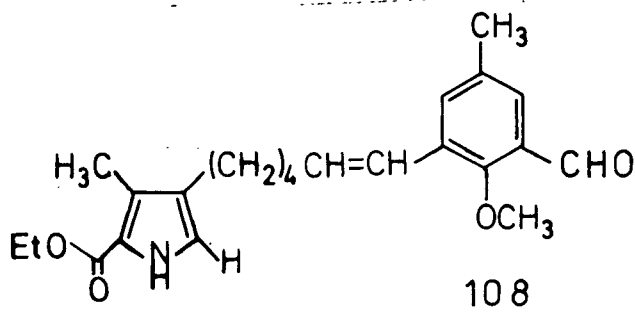
In none of the reactions was any unreacted phosphonium iodide 94a recovered unchanged, even when excess was used. This suggested that some side reaction might be consuming the phosphonium iodide 94a as quickly as it was reacting with the dialdehyde. Accordingly single equivalents each of 94a and potassium carbonate were added to a solution of dialdehyde 95 in refluxing dioxane over a period of time. To avoid any doubt about the amount of water present, hydrated potassium carbonate was used as base, the water necessary for the reaction being present as water of crystallization ($K_2CO_3 \cdot 1\frac{1}{2}H_2O$). The first equivalent of 94a and potassium carbonate was added and the mixture refluxed for 12 hours before the second equivalent was added. After a further 8 hours tlc indicated the complete disappearance of dialdehyde 95 and the presence of both mono-alkene 108 and bis-alkene 99a products. Addition of a third equivalent of 94a and potassium carbonate and a further 18 hours reflux gave essentially complete reaction; the desired

99a
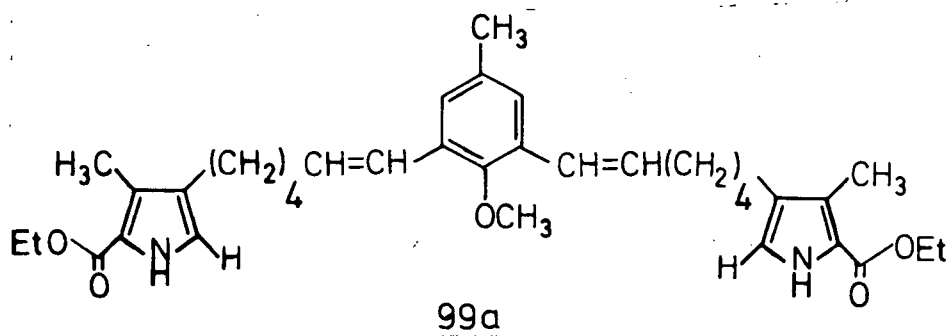
bis--alkene 99a predominated with only a trace of the mono-alkene 108 apparent. Similar reactions using incremental addition of 94a gave the bis-alkene 99a in 60-72% yield after chromatographic purification.

These yields compared favourably with those reported by Gaset et al., for single Wittig reactions on substituted benzaldehydes (73-88%).[195] These authors subsequently confirmed our observations on the

SCHEME 84

OHC—⟨benzene ring⟩—CHO   + $(Ph)_3\overset{+}{P}CH_2R$ Br^-

109

k_1 | K_2CO_3

OHC—⟨benzene ring⟩—CH=CHR

110

k_2 | K_2CO_3

$(Ph)_3\overset{+}{P}CH_2R$ Br^- $(Ph)_3\overset{+}{P}CH_2R'$ Br^-

CH=CHR   CH=CHR
⟨benzene ring⟩   ⟨benzene ring⟩
CH=CHR   CH=CHR'

111   **112**
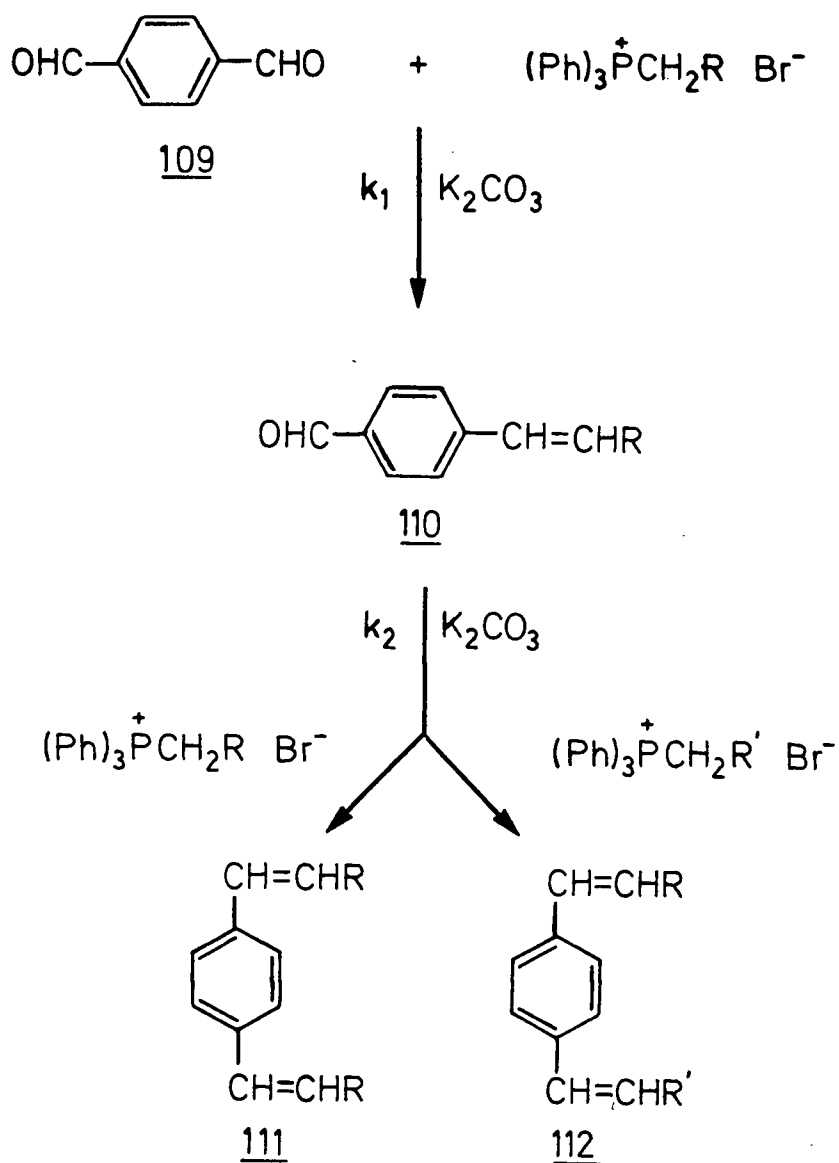
sluggishness of the phase-transfer Wittig reaction when they reported

the reactions of terephthalaldehyde 109 in heterogeneous media.[196]

Because of their higher reactivity in anhydrous homogeneous media,

phosphorus ylides react with dialdehydes to yield exclusively the

di-olefins. In heterogeneous media, however, the reactivity is much

less. Once one of the carbonyl functions reacts to form the mono-

olefin then the electron density on the remaining carbonyl group

increases sufficiently to discourage nucleophilic attack by a second

phosphorus ylide. Gaset et al., were able to exploit the difference

in reactivity of the two carbonyls ($k_1 > k_2$) to isolate and purify the

mono-olefin 110. This could then be reacted with excess of the same, or

a different, phosphonium salt to form symmetric or unsymmetric di-

olefins 111, 112 (Scheme 84). In the case of 2,6-diformyl-4-methyl-

anisole 95 the presence of two electron-donating groups on the benzene

ring may account for the reluctance of the second carbonyl group to

react and the lower yields of di-olefin.

It has been reported that the phase-transfer Wittig reaction in

dipolar solvents yields predominantly the cis isomer (Z/E ~80/20).[192]

Such stereoselectivity is of no consequence for our double Wittig

reactions as three possible isomeric products may be formed (ZZ, ZE,

EE). Since the ^{1}H-NMR chemical shifts and coupling constants in each

isomer are similar, the olefinic protons appear as a doublet and a doublet

of triplets at 6.51 δ and 5.70 δ respectively. However chemical shifts

in ^{13}C-NMR are more sensitive to small changes in molecular geometry.

The presence of three geometric isomers in the pure product gave a more

complicated pattern of peaks in the olefin and aromatic region of the

^{13}C-NMR spectrum.

The stereoselectivity of the Wittig reaction was of no considera-

tion since the next step was hydrogenation of the double bonds.
Stirring the bis-alkene 99a in tetrahydrofuran under hydrogen with 10%
palladium on charcoal as catalyst resulted in complete reduction.
Removal of catalyst and solvent and flash chromatography gave the chain-
linked bis-pyrrole 113a in high yield (85-97%).
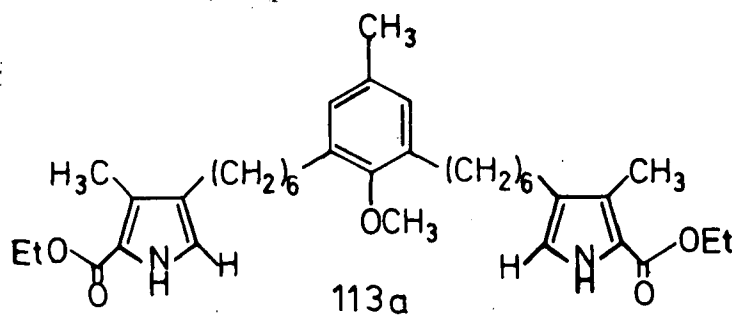
113a

With sufficient quantities of 113a in hand, elaboration to the
corresponding strapped porphyrin 92a followed the same sequence of
reactions as outlined in Section 2.3 for formation of the thioether
strapped porphyrin 87a (Fig. 14).

Heating the bis-pyrrole 113a with the α-chloromethyl-dicyanovinyl
pyrrole 76 (2.1 equivalents) at 80°C in glacial acetic acid for 1 hour
formed the chain-linked bis-dipyrromethane 114a in high yield. Tlc
of the crude product showed a major yellow spot which turned violet on
exposure to bromine vapour (diagnostic for dipyrromethanes). Since tlc
showed the presence of small amounts of other colored materials, the
product was purified by chromatography (84-94%). Hydrolysis of 114a
with potassium hydroxide in a water/n-propanol mixture removed the ester
and dicyanovinyl groups to give the α-carboxy,α'-formyl bis-dipyrro-
methane 115a. Thermal decarboxylation in refluxing N,N-dimethylformamide
yielded the α-free,α'-formyl bis-dipyrromethane 116a. As before this
intermediate was not isolated but used immediately for the porphyrin
synthesis. Slow injection of a dichloromethane solution of 116a into a
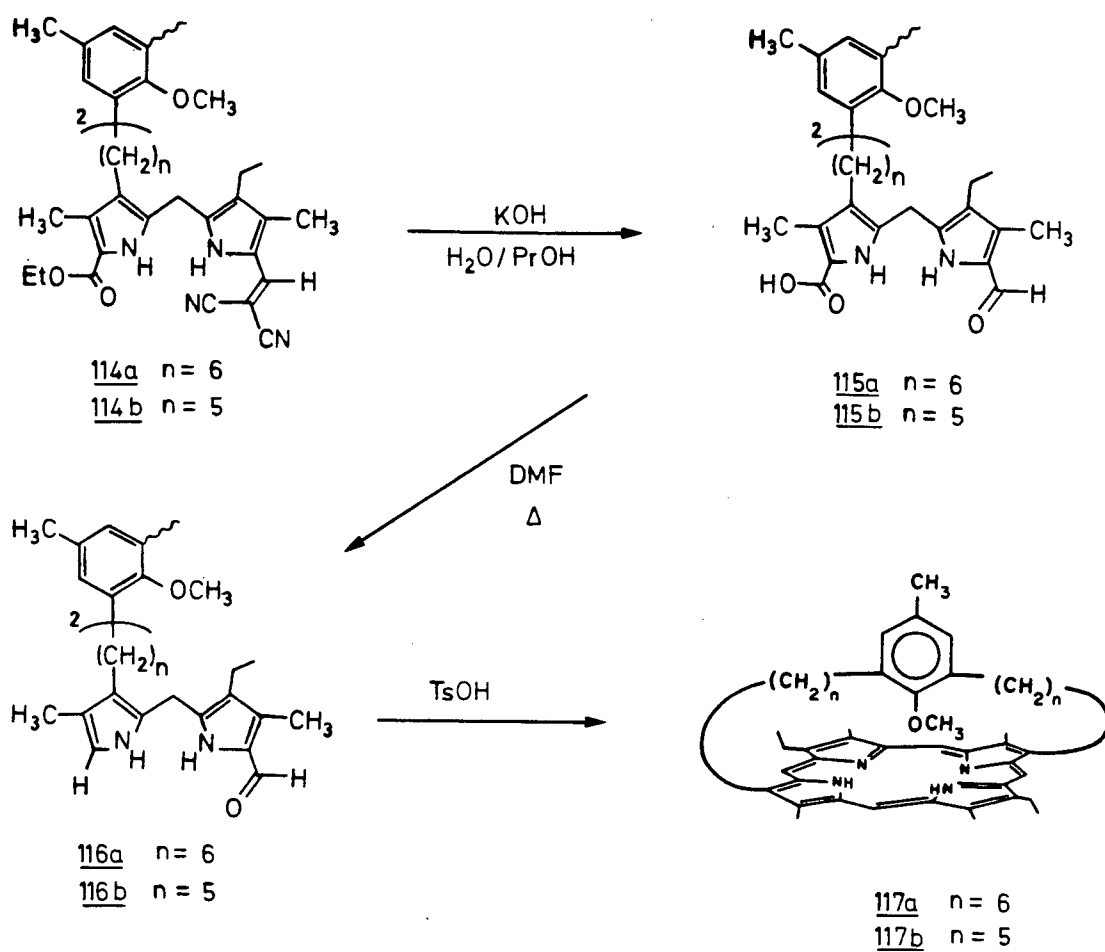
Fig. 14: Synthesis of the Phenol-Strapped Porphyrins 117a and 117b

large volume of dichloromethane containing p-toluenesulfonic acid

favoured intramolecular cyclization to the strapped porphyrin 117a.

In this case the spanning strap is sufficiently long that little

or no deformation of the porphyrin ring is observed. Because of this

yields of the unstrained porphyrin 117a (30-44%) are higher than those

of the more strained thioether strapped porphyrins (10-22%).

Synthesis of the shorter chain homologue 117b followed the same

sequence of reactions as shown in Figs.13, 14. The step-wise double

Wittig reaction of phosphonium iodide 94b and dialdehyde 95 gave lower

yields of the bis-alkene 99b (43-52%) after chromatographic purification.

However, fractions containing impure product were retained and purified

after catalytic reduction of the double bonds. In this way overall

yields of 43-53% were obtained for the two step reaction 94b → 99b →

113b. The bis-dipyrromethane 114b was prepared in 76-95% yield after

chromatography. After deprotection, decarboxylation and intramolecular

cyclization, the strapped porphyrin 117b was obtained in 21-53% yield.

With the formation of the porphyrin ring the final step required

removal of the methoxy group to generate the free phenol. Iodotri-

methylsilane has been used as a mild reagent for the demethylation of

alkyl aryl ethers.[183] Since the iodotrimethylsilane equivalent, $Cl_3MeSi/$

NaI, had already been used to effect the deoxygenation of the sulfoxide

porphyrins 88, this reagent was investigated. Addition of methyltri-

chlorosilane to a solution of sodium iodide in freshly distilled aceto-

nitrile generated the iodotrimethylsilane equivalent, giving a yellow

solution with precipitated sodium chloride. After dropwise addition

of a solution of porphyrin 117a in dichloromethane, the solution was

left stirring for 4 hours before the reaction was quenched and the

product isolated by preparative tlc. Mass spectrometry indicated

complete demethylation. However when the reaction was carried out on a

larger scale under the same conditions a mixture of starting material

117a and product 118a was obtained. Furthermore, two attempts to

demethylate porphyrin 117b under the same conditions led to mixtures

of starting material and product. These variations in results were

attributed to traces of moisture in the system.

117a n = 6
   b n = 5

118a n = 6
   b n = 5
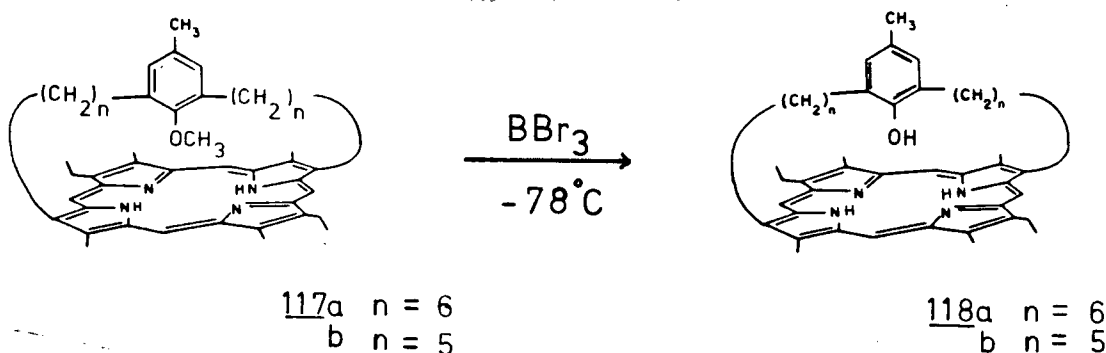
The use of boron tribromide to effect the demethylation gave

more reproducible results. The boron tribromide was added dropwise

to a solution of the anisole porphyrin 117a in dichloromethane at $-78°C$.

The reaction mixture was stirred at $-78°C$ for 30 minutes, allowed to

warm to room temperature and stirred for a further 1 hour. After

work-up and chromatographic purification on an alumina column (Merck

90 neutral, activity III) the phenol porphyrin 118a was obtained in

76-89%. The lower homologue 117b was demethylated under the same

conditions, 118b being obtained in 89-95% after chromatography.

2.5   SYNTHESES OF PORPHYRINS CONTAINING A QUINONE STRAP

Although the exact details of photosynthesis have not all been
elucidated, the essential features of the process are believed to
include the following. Incident light is harvested by a complex
antenna system of chlorophyll (bacteriochlorophyll in photosynthetic
bacteria) and other pigments, and used to excite a special (bacterio)-
chlorophyll center to the singlet state. An electron is then transferred
from the excited (bacterio)chlorophyll through a series of intermediate
compounds [(bacterio)pheophytin, Fe-S clusters] to an acceptor. In
photosynthetic bacteria and in photosystem II of green plants this
electron acceptor is a quinone molecule, ubiquinone and plastoquinone
respectively.[197]   As shown in the simplified scheme (Fig. 15), the net
result is a reduction of NADP and the oxidation of water to oxygen.[198]

Not surprisingly attempts have been made to mimic this light-
induced separation of charge in the laboratory using various porphyrin-
quinone models. The models generally belong to two types. The quinone
may be attached to the porphyrin by a single covalent chain (Fig. 16,
119-125).[197,199-203]   The flexibility of the chain, while discouraging the
formation, will enhance the lifetime of the charge-separated species
by reducing the recombination reaction. The alternative, using
porphyrin with attached "quinone caps" (Fig. 16, 126, 127) is attractive
since the relative orientation and separation of the porphyrin and
quinone may be better controlled.[106,107,130-132]

More sophisticated models have recently been produced allowing
for greater stabilization of the charge separated species. In the
bis-quinone system 128 (Scheme 85) of Sakata and co-workers a two step
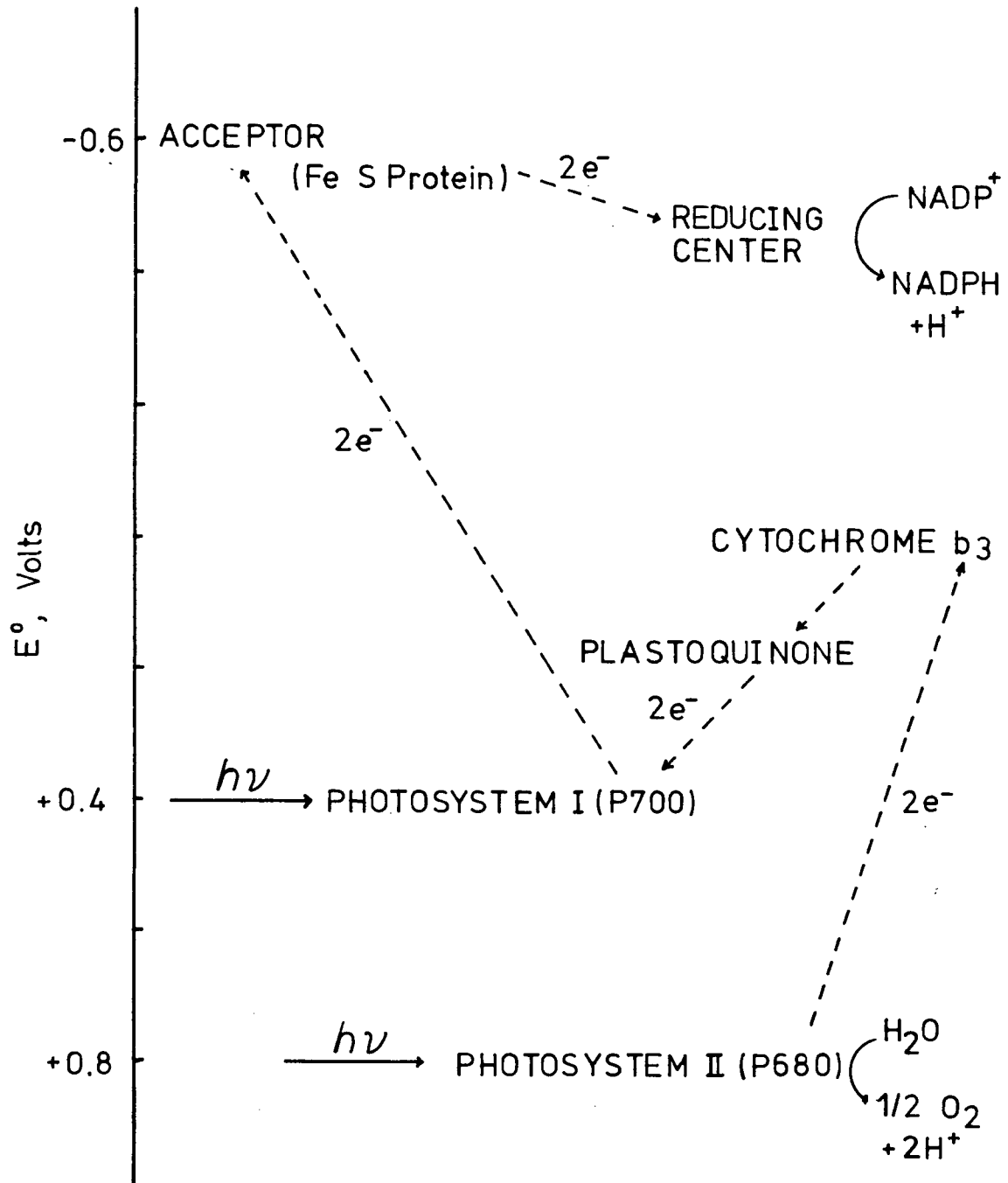
Fig. 15: Simplified Scheme of Photosynthesis in Plants
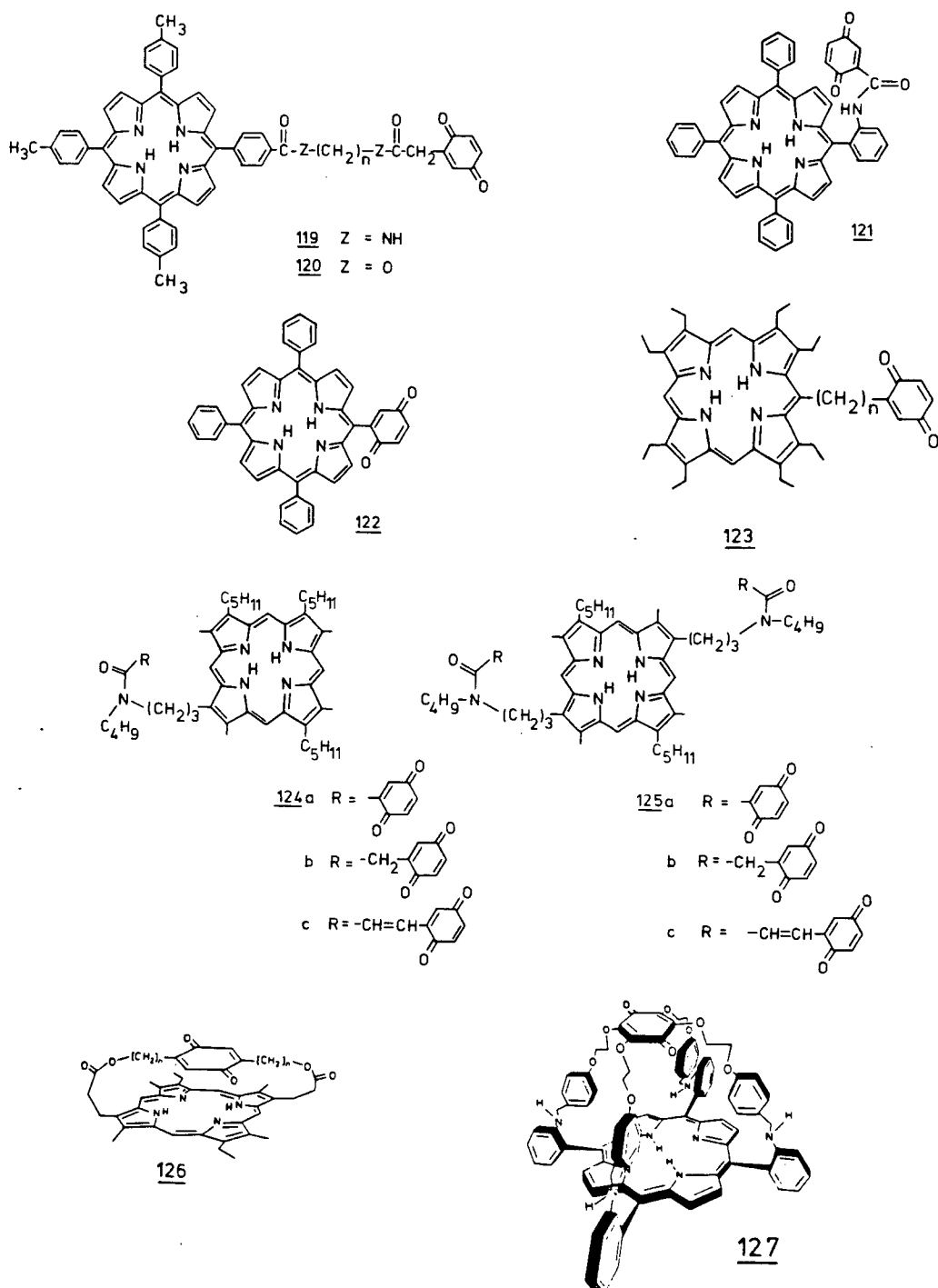
Fig. 16: Representative Covalently Linked Porphyrin – Quinone Molecules

charge transfer is believed to occur to give the long-lived $P^{+ \cdot}4Q4Q'^{- \cdot}$

species, a situation analogous to the multistep electron transfer which

occurs in vivo.[204] The spectroscopic behaviour of the carotenoid-

porphyrin-quinone (CPQ) system 129 of Moore et al.,[205] has been inter-

SCHEME 85

128   P4Q4Q'

$$P4Q4Q' \xrightarrow{\ h\nu\ } P^{+ \cdot}4Q4Q'^{- \cdot}$$
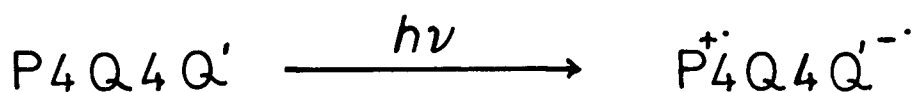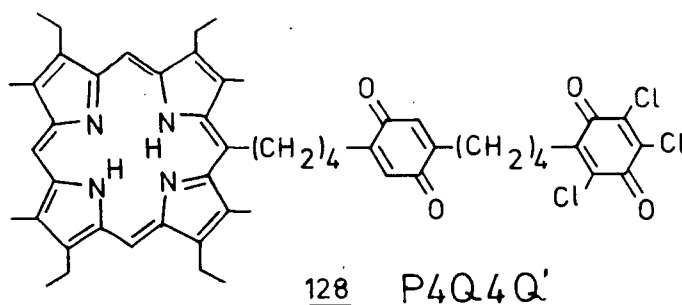
preted as in Scheme 86. Charge recombination is inhibited by electron

transfer from the carotenoid to the porphyrin cation radical, to give

a long-lived (µs scale) $C^{+ \cdot}-P-Q^{-}$ species.

The interest in electron transfer systems and our goal of

preparing porphyrins bearing functionalized straps prompted us to

synthesize a strapped porphyrin in which a quinone was incorporated

into the strap. Sanders and Ganesh had already reported the synthesis

of a strapped porphyrin-quinone 126, using the more common synthetic

strategy of attaching a 2,5-disubstituted-1,4-dimethoxybenzene 144

to a preformed porphyrin ring 145 by ester linkages (Scheme 87).[131]

The authors discovered that demethylation of the subsequent strapped

SCHEME 86

CPQ

129

R =

CPQ $\xrightarrow{h\nu}$ C $-^1$P$-$Q

C$^{+\cdot}-$P$-$Q$^{-\cdot}$ $\longleftarrow$ C$-$P$^{+\cdot}-$Q$^{-\cdot}$
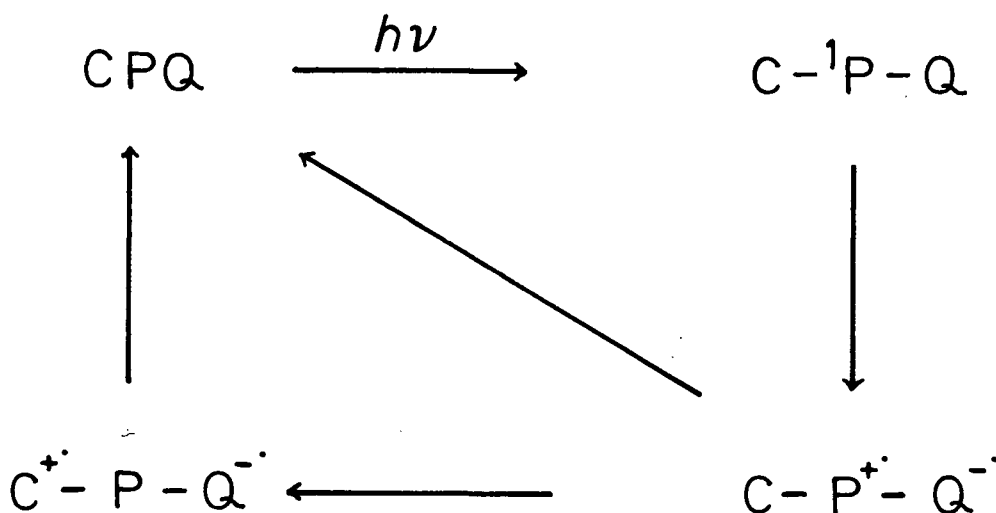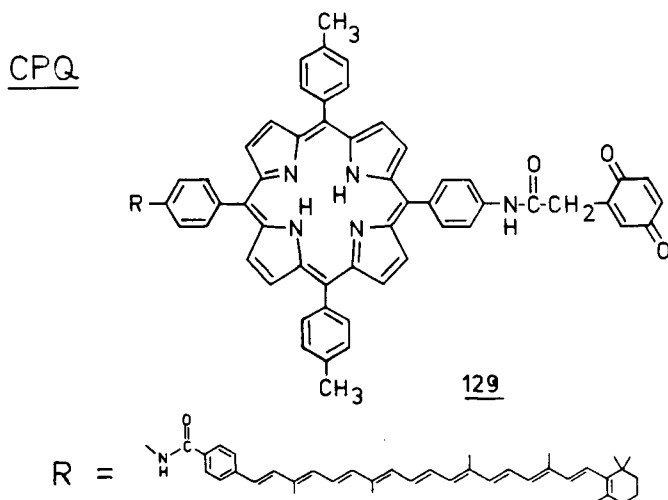
porphyrin 146 failed. Oxidative deprotection using ceric ammonium nitrate gave a meso-nitrated porphyrin, while argentic oxide, amongst other reactions, inserted silver into the porphyrin. Boron tribromide and trimethylsilyl iodide also failed to deprotect without damage. This was not surprising since trimethylsilyl iodide is known to be an extremely efficient reagent for the de-alkylation of esters.[183] They repeated

SCHEME 87
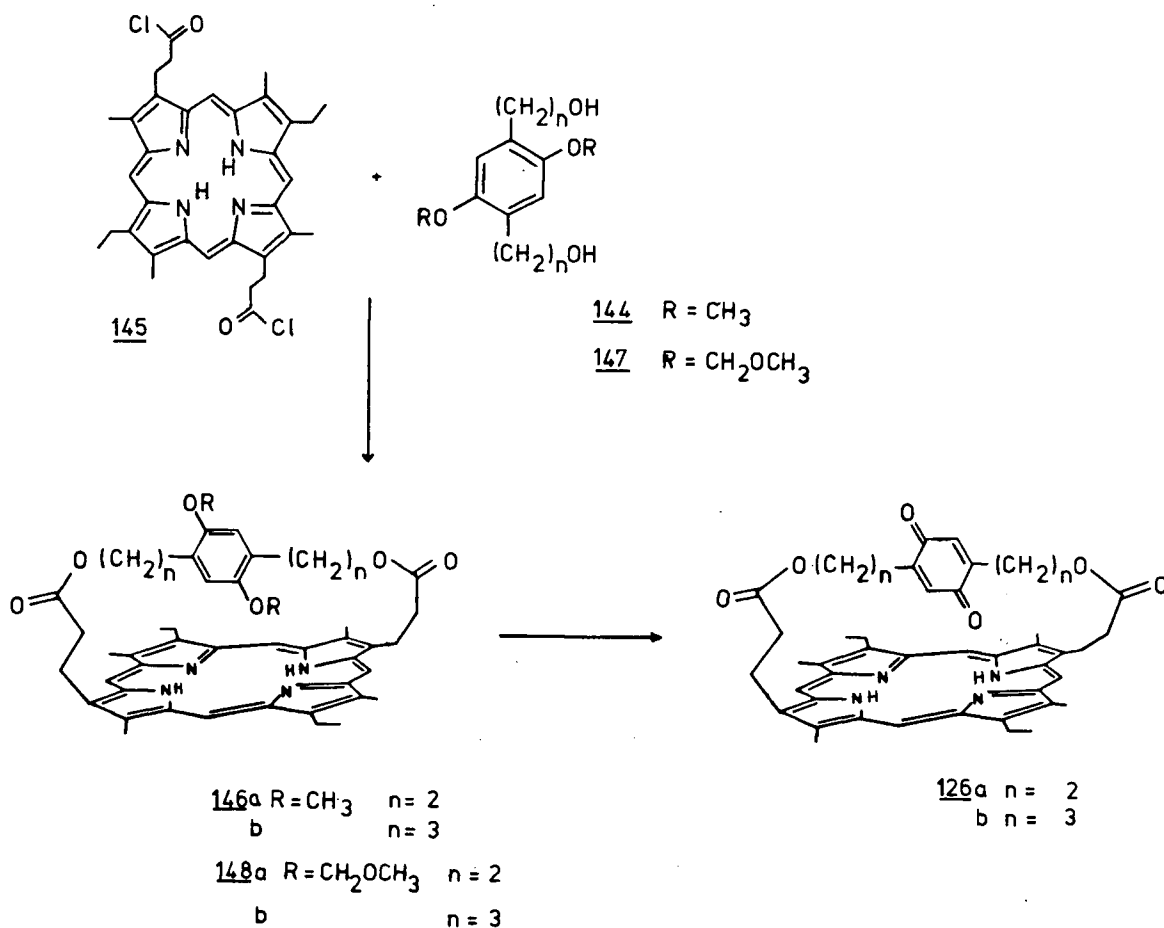
their work masking the quinone with the more labile methoxymethyl ether
(MME = OCH_2OMe) protecting group. In this case they were able to remove
the protecting groups from the strapped porphyrin 148 and oxidize the
cap to the desired quinone 126. Yields for the strapped porphyrin 148
were 7-8% (n = 2) and 15-20% (n = 3).

To demonstrate the versatility of our synthetic strategy we
attempted a synthesis of a similar quinone-strapped porphyrin (Fig. 17).
We decided to protect the quinone as the bis-methoxy ether rather than
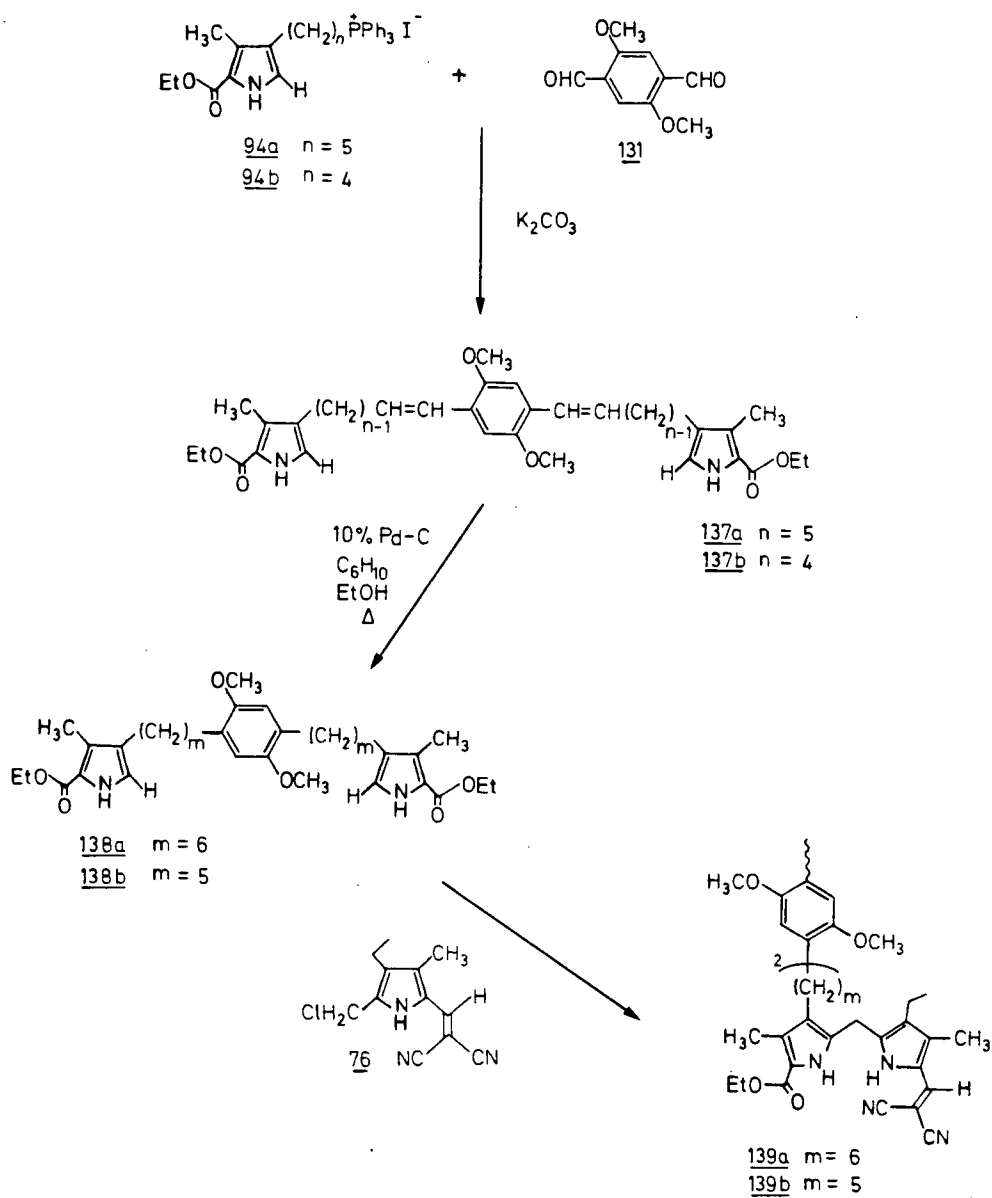
Fig. 17: Synthesis of the Bis-dipyrromethanes 139a and 139b

as the bis-methoxymethyl ether since the former would be more stable

over the reaction sequence. Furthermore, since the product porphyrin

140 would contain only hydrocarbon linkages demethylation might be

easier to effect without damage to the molecule. In addition we

believed that our strategy was more flexible in allowing shorter chain

lengths and higher yields of the strapped porphyrin.

Since the required pyrrole phosphonium iodide 94a and 94b were

already on hand it only remained to synthesize the required   aldehyde

131.

Treatment of 1,4-dimethoxybenzene 132 with formaldehyde, hydrogen

chloride and hydrochloric acid yielded the 2,5-bis(chloromethyl)-1,4-

dimethoxybenzene 133 in good yield (57%) (Fig. 18).[206] This compound

was converted into the corresponding diacetate 134 with sodium acetate
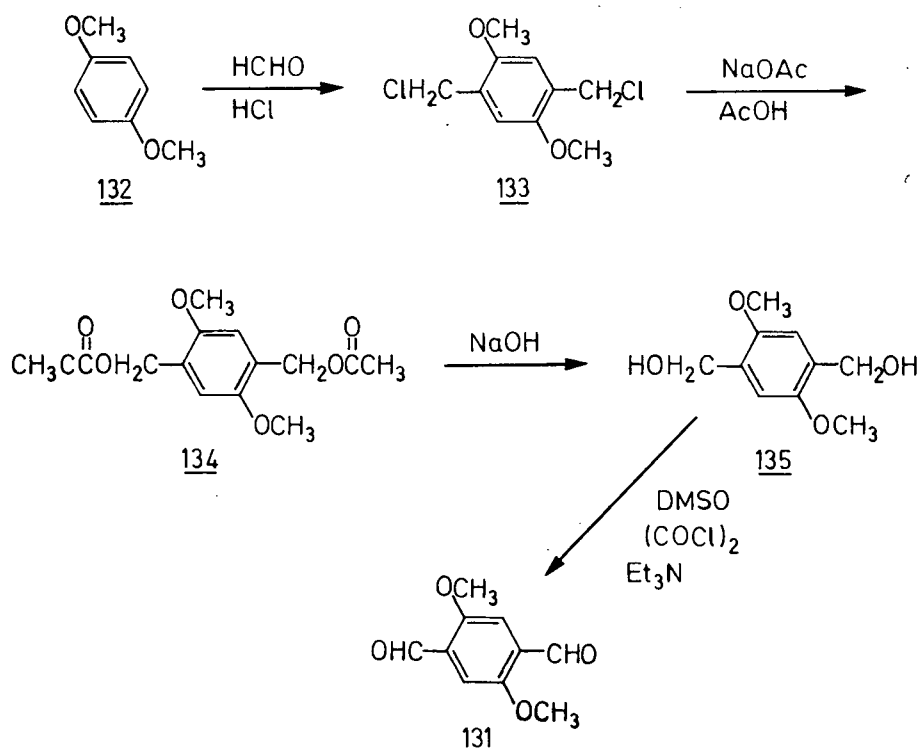
Fig. 18:   Synthesis of 2,5-Diformyl-1,4-dimethoxybenzene

in refluxing acetic acid (72-90%), then saponified with sodium

hydroxide to give the di-hydroxymethyl compound 135.[207] Oxidation with

dimethyl sulfoxide/oxalyl chloride smoothly oxidized both alcohols to

the aldehyde in high yield (94-96% crude). Vacuum sublimation furnished

the pure compound 100 (83-87%) as a yellow solid.

In this case the double Wittig reaction between the dialdehyde

131 and the phosphonium iodide 94 was somewhat more convenient to

follow and work-up. As before the phosphonium iodide 94 and potassium

carbonate were added in one equivalent increments to a refluxing

solution of the dialdehyde 131 in p-dioxane, the course of the reaction

being monitored by tlc. Since 131 is intensely yellow its eventual

consumption is easily noted. The presence of the partially reacted

mono-alkene 136 can be detected since it fluoresces on the plates

under UV light. When tlc indicated that reaction was complete the

$$H_3C \quad (CH_2)_n CH=CH - \text{(OCH}_3\text{)} - CHO \qquad \underline{136}a \quad n = 4$$
$$EtO \quad O \quad N \quad H \qquad OCH_3 \qquad b \quad n = 3$$
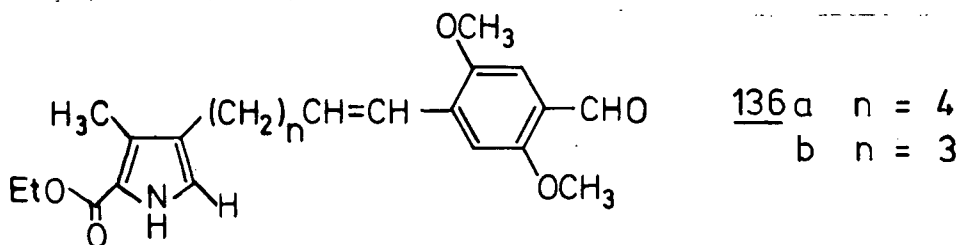
dioxane was removed and the crude reaction product obtained as a yellow

oil. Sometimes on standing this oil solidified. Addition of dichloro-

methane did not completely redissolve it and the white solid which was

filtered off was found to be the required bis-alkene 137. More product

was obtained by chromatographic purification of the filtrate. The

bis-alkene 137 seemed to be unusually insoluble compared to the analogous

anisole compound 99. For this reason room temperature catalytic hydro-

genation was not attempted. Instead, transfer hydrogenation was carried

out where the bis-alkene 137 was refluxed in a mixture of ethanol and

cyclohexene, with 10% palladium/charcoal as catalyst.[208] When the

reaction was complete the hot solution was filtered through a Celite

pad to remove the catalyst. As the filtrate cooled down the product

138 precipitated from solution as a white solid which was collected by

137a n = 4
137b n = 3
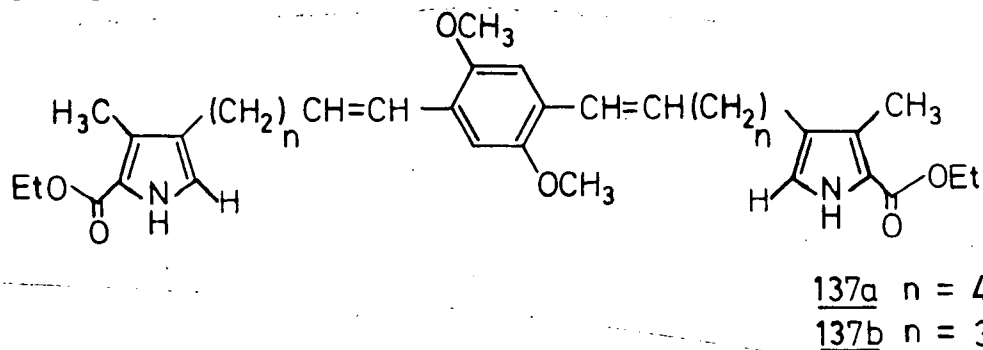
filtration. Further product was obtained from concentration of the

filtrate. For the longer chain bis-pyrrole 138a the combined overall

yields for the two steps 94a → 137a → 138a were excellent (67-84%).

However for the shorter chain 138b the overall yield was much

poorer (42%).

138a n = 6
138b n = 5
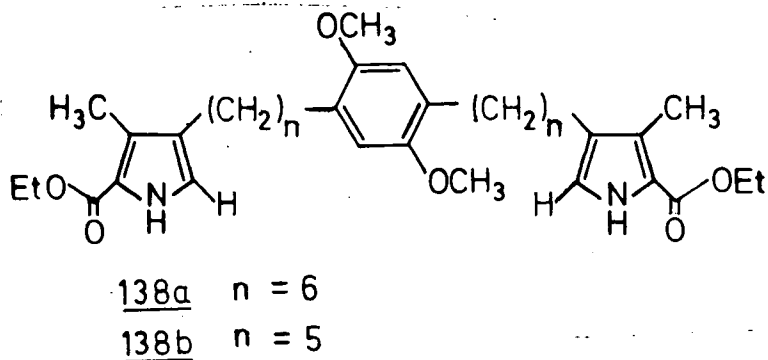
The synthesis of the bis-dipyrromethane 139 was carried out as

usual in hot glacial acetic acid. Compound 139a was obtained in good

yield (76-88%) after chromatography, while the less soluble 139b

precipitated from the reaction mixture in analytically pure form (91%).

Once prepared the bis-dipyrromethanes 139 were subjected to hydrolysis,

decarboxylation and high dilution cyclization under the same conditions
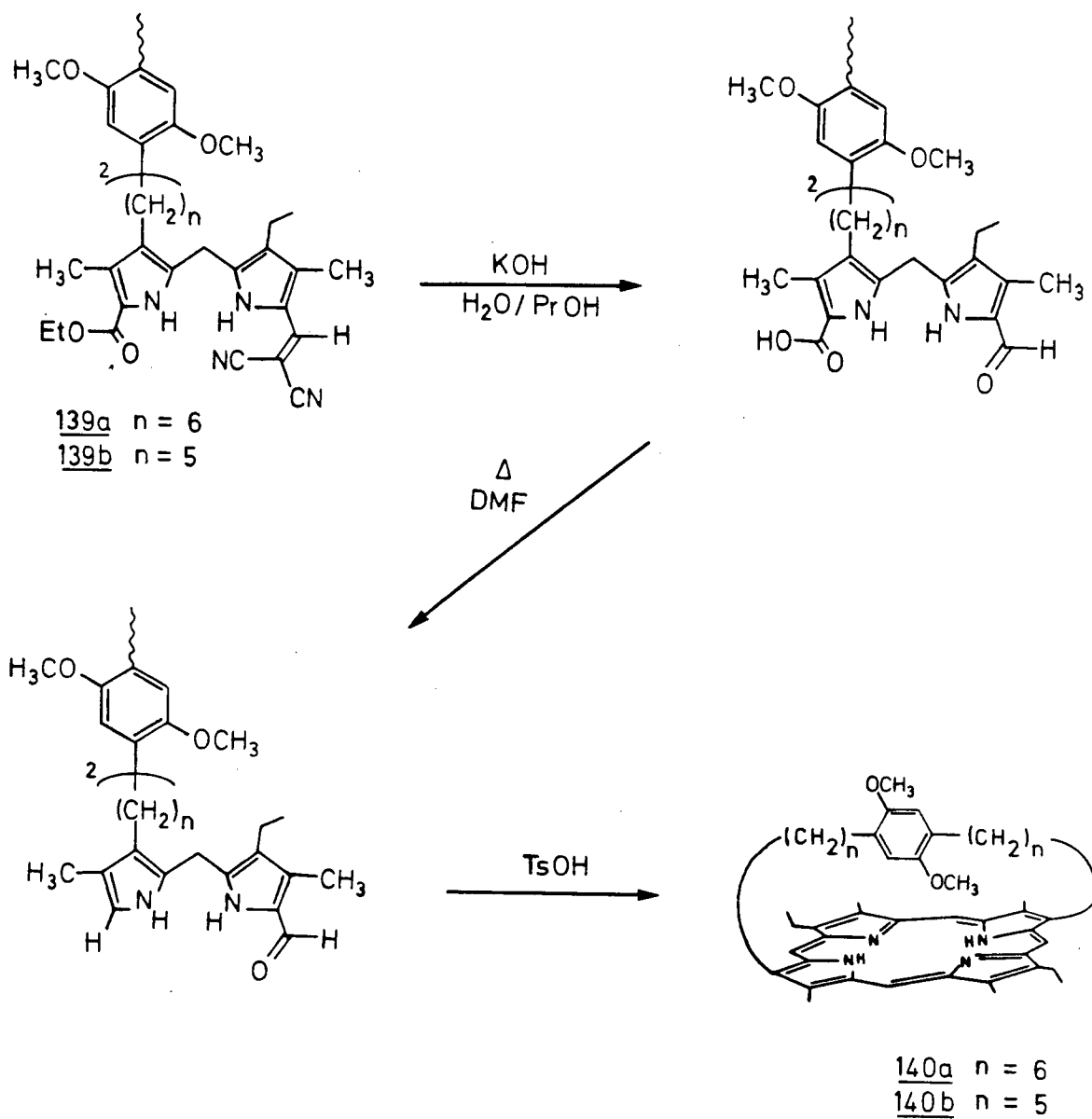
Fig. 19: Synthesis of the Dimethoxybenzene-Strapped Porphyrins 140a
and 140b

as outlined previously (Fig. 19). After work-up and chromatography the strapped porphyrins 140a and 140b were obtained in 41-60% and 20-40% yield respectively.

The methoxy functions were conveniently demethylated using boron tribromide. After stirring 140a with a large excess of boron tribromide at -78°C for 1.5 hours, tlc (10% EtOAc/hexanes) showed the presence of two compounds, neither of which was starting material. They were believed to be the desired porphyrin-hydroquinone 141a and the porphyrin 142a in which only one methoxy group had reacted. This was by analogy to the reports of Loach, who had demonstrated selective demethylation under similar conditions.[199] After warming to room temperature the mixture was stirred for a further hour by which time the reaction was complete. Attempts to purify the crude hydroquinone 141a by chromatography on alumina invariably led to partial oxidation, mixtures of hydroquinone 141a and quinone 143a being obtained. Since the quinone was the desired product, the hydroquinone 141a was oxidized fully to 143a before chromatographic purification. Both DDQ and lead dioxide were used as oxidants, the latter being more convenient as it was easily removed by filtration. The crude porphyrin-quinone 143a was then purified by chromatography on alumina (82-87%). Demethylation of 140b was carried out in exactly the same way. After chromatography, the quinone 143b was recrystallized from toluene for a 70% yield.
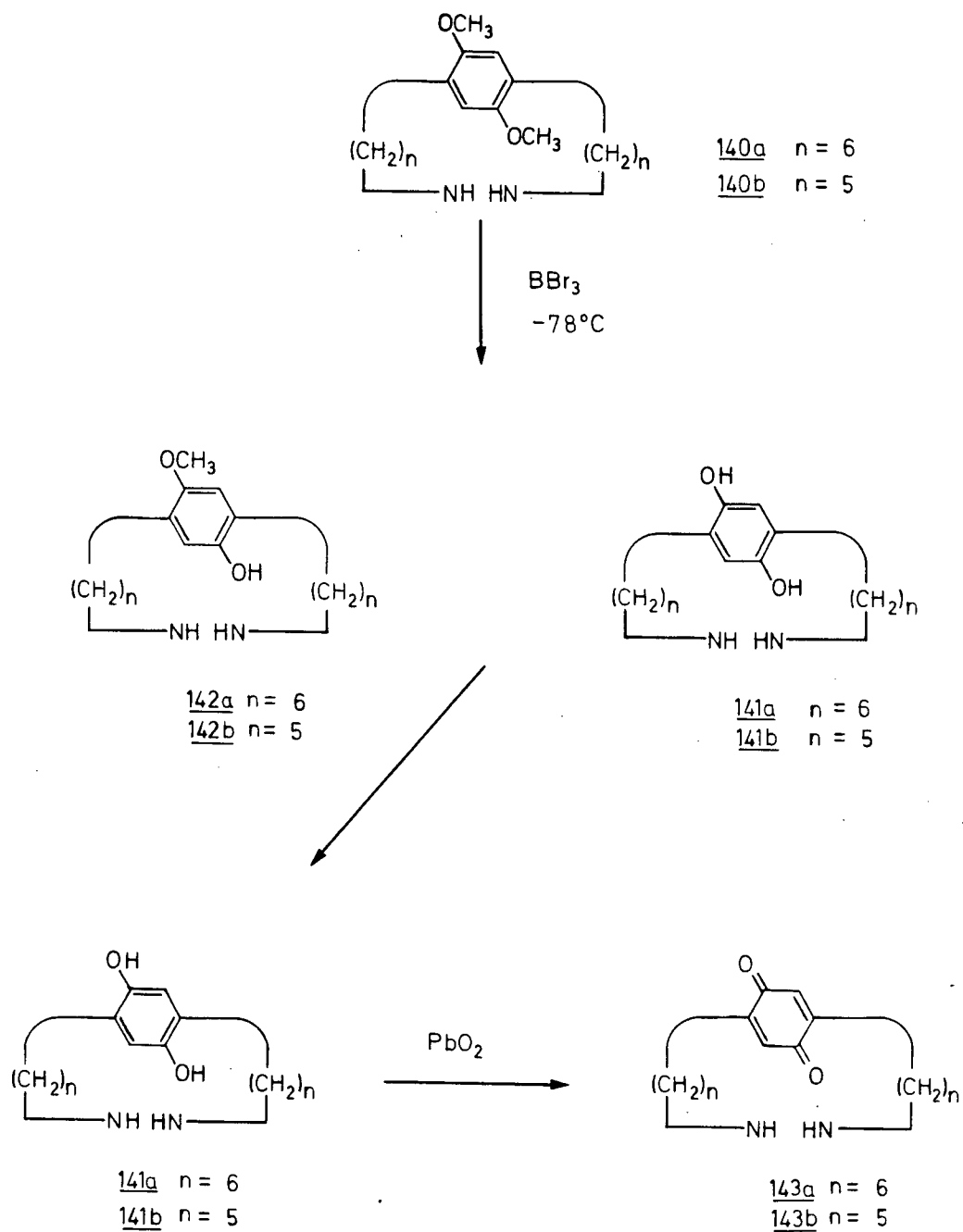
Fig. 20: Synthesis of the Quinone - Strapped Porphyrins 143a and 143b

2.6   ATTEMPTED SYNTHESIS OF A PORPHYRIN CONTAINING AN IMIDAZOLE STRAP

Obviously the most desirable strapped porphyrin would be that

bearing an imidazole ring incorporated into the bridging strap. Such a

model would have widespread applicability since the imidazole of a

histidine residue is a heme ligand in many heme proteins. Incorporation

of the imidazole into the strap would provide a distinct five-coordinate

species, avoiding the problem of six-coordination when using free

imidazole. In addition, if the strap was sufficiently "tight" to

secure the imidazole in place, the problems of dissociation and head-to-

tail dimerization associated with imidazole chelated hemes would

also be avoided.

Examination of molecular models indicated that maximum overlap

would occur betwen the imidazole nitrogen lone pair orbital and

orbitals on the metal at the porphyrin core if the imidazole was attached

to the porphyrin through its 1,5 positions. Strap lengths of 7 or 8

methylene units each would secure the imidazole in place without

causing deformation of the porphyrin ring or allowing excessive motion

of the strap.

Unfortunately, of all the substitution patterns of imidazoles,

the 1,5 disubstituted appears to be the least accessible.[209,210] Our

initial efforts were directed towards preparing the 1,5 disubstituted

imidazole 152, which has the two straps already in place. It was

hoped that the two halves of the porphyrin could be built up at the

chain termini to give, after intramolecular cyclization, the imidazole

strapped porphyrin (Fig. 21). Attempts were made to prepare 152 by a

variation of the Marckwald synthesis,[211] i.e.,condensation of an
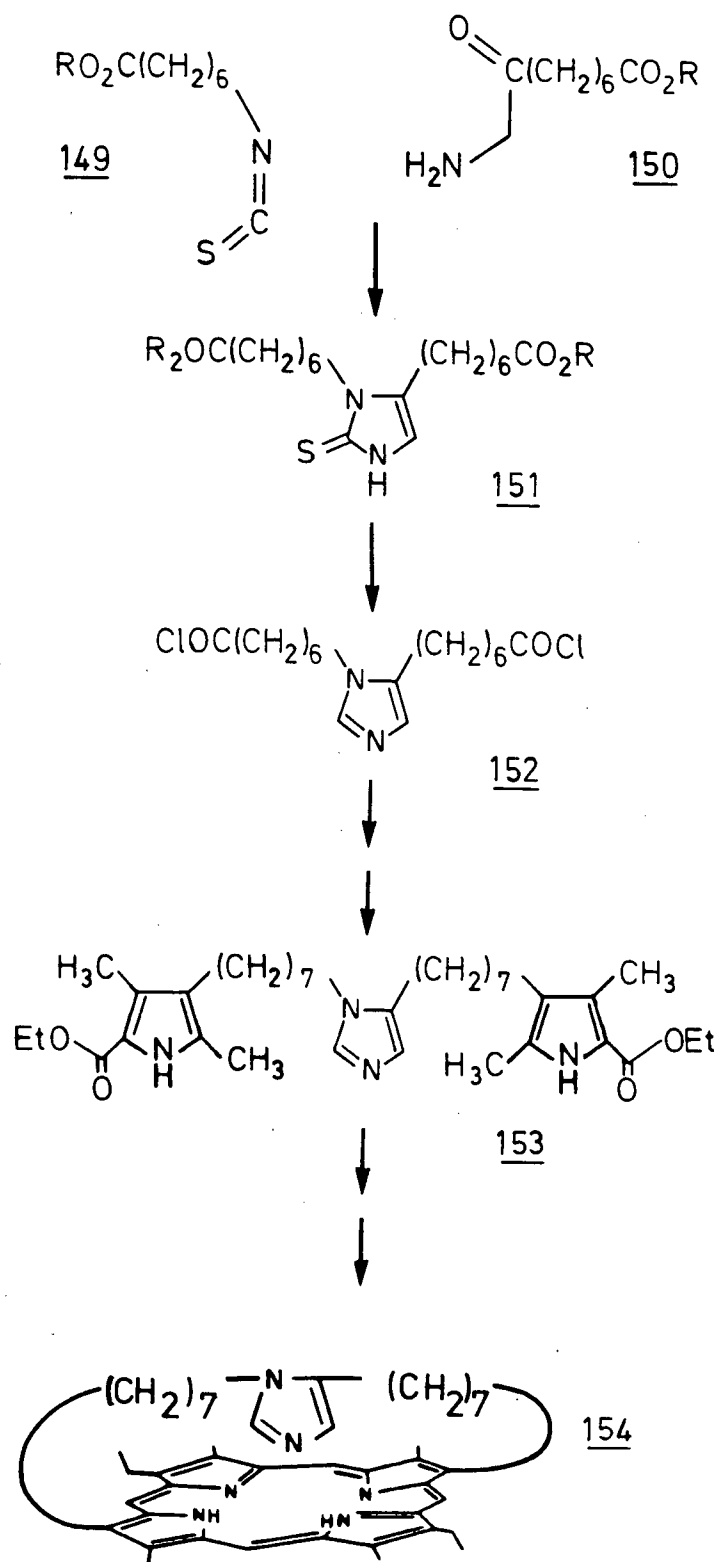
Fig. 21: Proposed Synthesis of the Imidazole - Strapped Porphyrin 154

α-amino ketone 150 and an alkyl isothiocyante 149 to give the

imidazoline-2-thione 151 which could be desulfurized at any subsequent

convenient stage.

The ω-carbalkoxyalkyl isothiocyanates were easily prepared from

the cyclic ketones 155. Beckmann rearrangement to the lactam 156

SCHEME 88
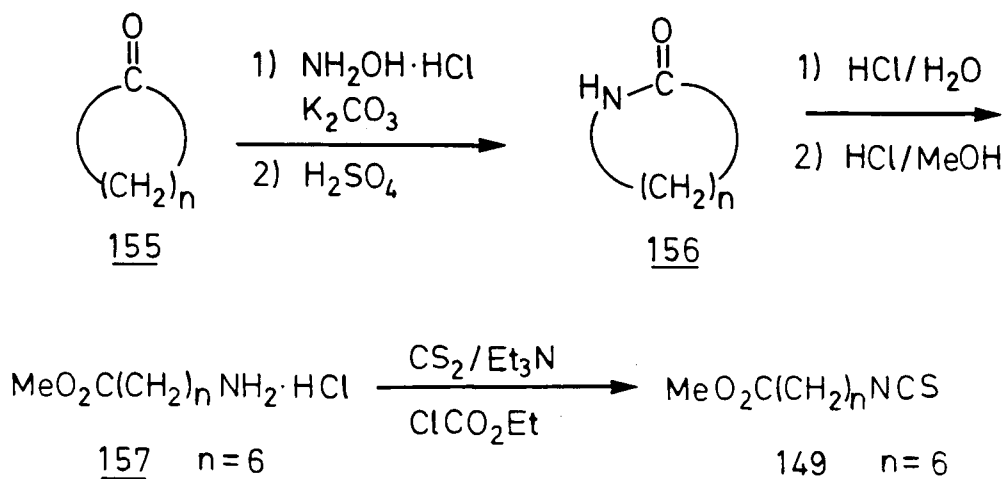
followed by ring opening and esterification furnished the ω-amino

ester 157 (Scheme 88).[212] Condensation with carbon disulfide in the

presence of ethyl chloroformate and triethylamine yielded the isothio-

cyanate 149.[213]

While the isothiocyanate 149 was readily available, convenient

large-scale preparation of the α-amino ketone 150 presented a more

formidable task. Initially the method of Schrecker and Trail was

investigated.[214] Di-t-butyl acetamidomalonate 158 was acylated by

refluxing with sodium hydride followed by treatment with a suitable

acid chloride 159 (Scheme 89). Decarboxylation was effected by

heating the crude reaction mixture with trifluoroacetic acid, the

SCHEME 89
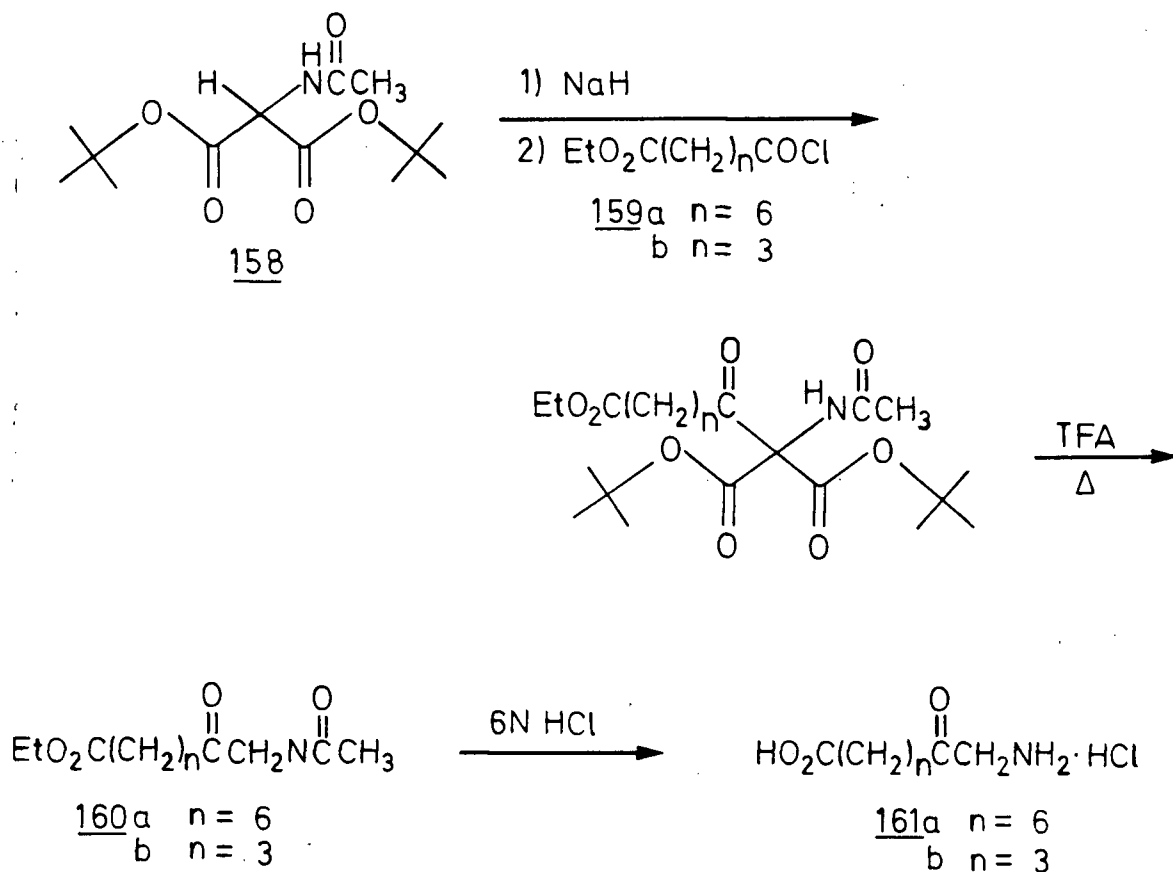
resulting α-acetamido ketone 160 being isolated by column chromato-
graphy before acid hydrolysis furnished the α-amino ketone hydro-
chloride 161 in ∿13% yield overall.

A more attractive route appeared to be that proposed by Evans
and Sidebottom (Fig. 22.).[215] Treatment ·of ethyl hippurate 162a with
two equivalents of lithium diisopropylamide formed the dianion which
was reacted with a series of anhydrides to form the acylated product.
Acid hydrolysis yielded the α-amino ketone hydrochlorides in 40% over-
all yield. In our case reaction of the dianion with the mixed anhydride
163a gave variable results. In a small scale (20 mmol) reaction the
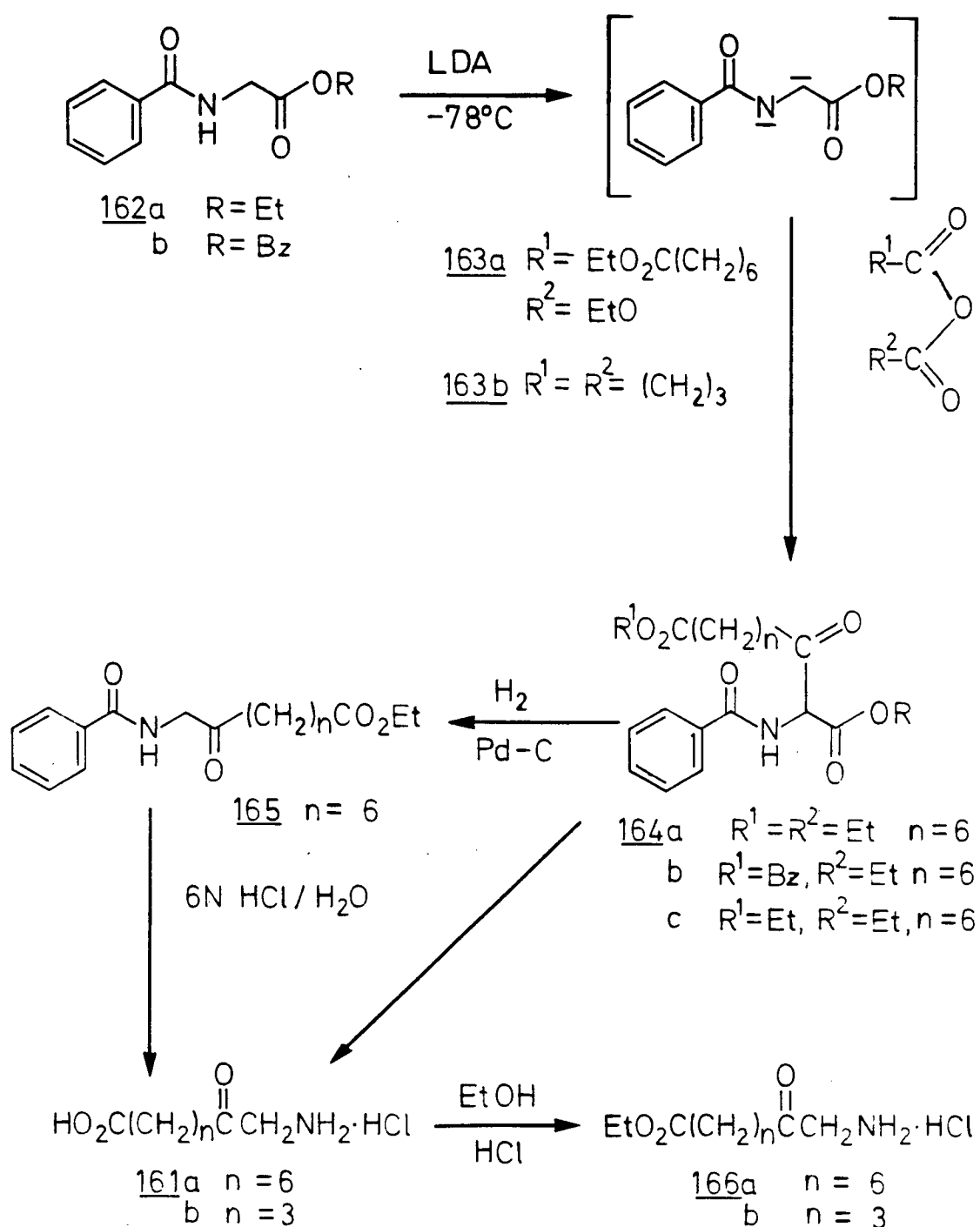
Fig. 22: Synthesis of α-Aminoketones

initial acylated product 164a was isolated by column chromatography (∿20%) prior to the acidic hydrolysis to the α-amino ketone hydrochloride 161a. However, for larger scale (0.2 mol) reactions the products of the acylation step were refluxed in 6M hydrochloric acid without purification. Extraction of the reaction mixture with ethyl acetate removed some of the impurities and the α-amino ketone hydrochloride 161 was precipitated by addition of acetone to the concentrated aqueous phase. The crude yield varied from 20-40%. When glutaric anhydride 163b was used the α-amino ketone hydrochloride 161b was obtained in 21.5% overall yield (33.4% reported yield).[215] In an attempt to simplify work-up the dianion of benzyl hippurate 162b was reacted with the mixed anhydride 163a. Hydrogenation of the crude product brought about deesterification and decarboxylation to give the α-benzamido ketone 165 which was purified by column chromatography (33%). Subsequent hydrolysis provided the α-amino ketone hydrochloride 161a. Re-esterification was accomplished by stirring in ethanolic hydrogen chloride (∿70%).

The formation of the imidazoline-2-thione 151 was carried out by the method of Altland and Doney.[216] Condensation of α-amino ketone 166a and the alkyl isothiocyanate 149a occurred in refluxing toluene in the presence of triethylamine with azeotropic removal of the water formed during the reaction. After work-up and chromatography the desired product was obtained in 27-35% yield (Scheme 90).
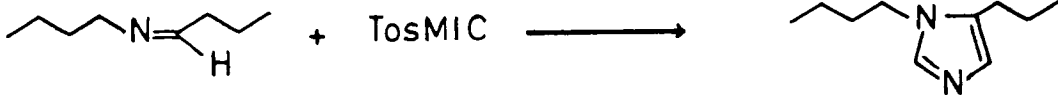
The difficulty of obtaining large quantities of the pure α-amino ketone 166 coupled with the poor yields of the imidazoline-2-thione condensation prompted us to investigate other methods of obtaining 1,5-disubstituted imidazoles. Our attention was focussed on the

SCHEME 90

$EtO_2C(CH_2)_nC\overset{O}{\lesssim}$

166a n = 6
b n = 3

$\overset{|}{NH_2}$
·HCl

$\overset{(CH_2)_nCO_2Me}{\underset{N}{\parallel}}\underset{C}{\lesssim}_S$

149a n = 6
b n = 3

Et_3N
C_7H_8
Δ

$EtO_2C(CH_2)_n$ $(CH_2)_nCO_2Me$

151a n = 6
b n = 3
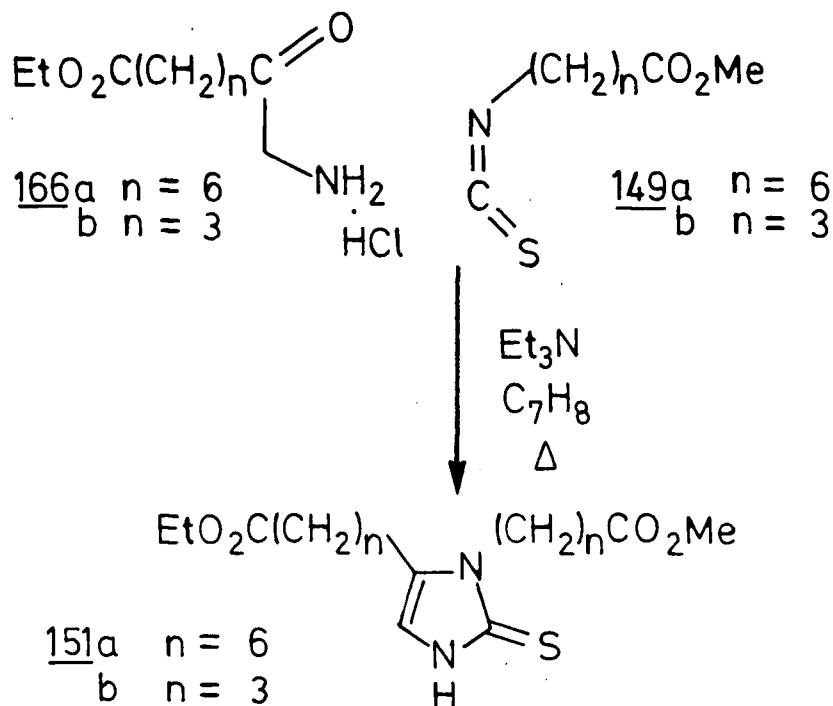
report of Van Leusen et al.[219] These workers had studied the use of
tosylmethyl isocyanide (TosMIC) in the preparation of various hetero-
cyclic ring systems. The reaction of TosMIC with aldimines in the
presence of base (K_2CO_3, t-BuNH$_2$) reportedly provided 1,5-disubstituted
imidazoles in high yield. Following Van Leusen's published procedure
a preformed aldimine 167 was reacted with TosMIC 168 in the presence
of base (Scheme 91). However, despite variation of R^1 and R^2, type
and quantity of base, and stoichiometry and reaction time, the yields
of imidazole 169 were uniformly disappointing (∿40% crude yield).
These low yields were initially attributed to the instability of the
aldimine under the basic condition of the reaction. Aldimines from
primary aldehydes which contain a $-CH_2-C=N-$ group undergo aldol-type
condensations easily to give polymers.[220] It was noted that the high

TABLE III: Preparation of 1-Butyl-5-Propylimidazole

BASE mmol	ALDIMINE mmol	TosMIC mmol	SOLVENT	hrs/°C	% YIELD
n-BuNH$_2$					
2.0	1.1	1.1	MeOH	14/RT	30.3
4.1	1.1	2.2	DME	24/RT	19.0
K$_2$CO$_3$					
2.0	1.1	1.1	MeOH	18/RT	9.7
2.0	1.1	1.1	DME	52/RT	2.5
1.6	1.1	1.1	DME	83/RT	37.3
t-BuNH$_2$					
3.8	1.1	2.2	DME	23/RT	12.5
C$_6$H$_{13}$N					
1.5	1.1	1.1	DME	45/RT	27.0
Et$_3$N					
1.6	1.1	1.1	DME	45/RT	4.5
NaH					
1.4	1.1	1.1	DMSO/DME	4/RT	–
BuLi					
1.0	1.1	1.1	THF	-78°C	–

SCHEME 91
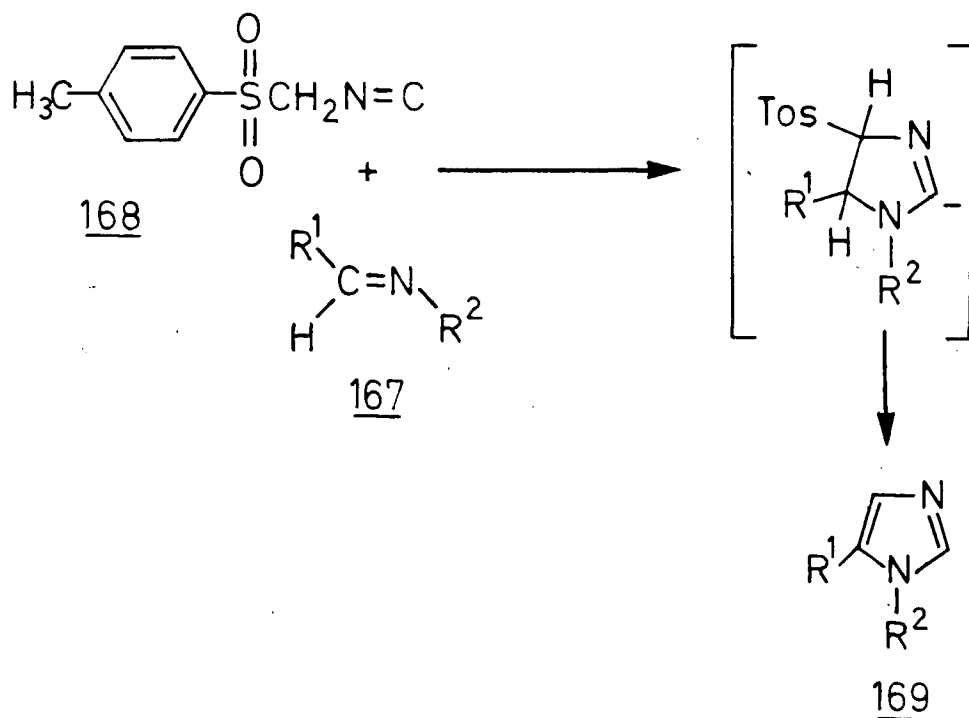
yields reported by Van Leusen et al., were for aldimines containing methyl, isopropyl, or t-butyl groups.

Alternatively, addition of the aldehyde to a solution of TosMIC and excess amine in methanol gave excellent yields of the corresponding imidazole (Scheme 92).[221] Using a stoichiometric amount of the primary amine and triethylamine as base also gave equally good yields.

These results prompted us to attempt the preparation of imidazole bis-aldehyde 170, which could be subjected to a double Wittig reaction with the pyrrole phosphonium iodide 94a and elaborated to form the strapped porphyrin as in the phenol and quinone cases (Fig. 23). Our initial target molecule was the imidazole bis-ester 171 which might be reduced to the bis-alcohol 172 and oxidized to the aldehyde
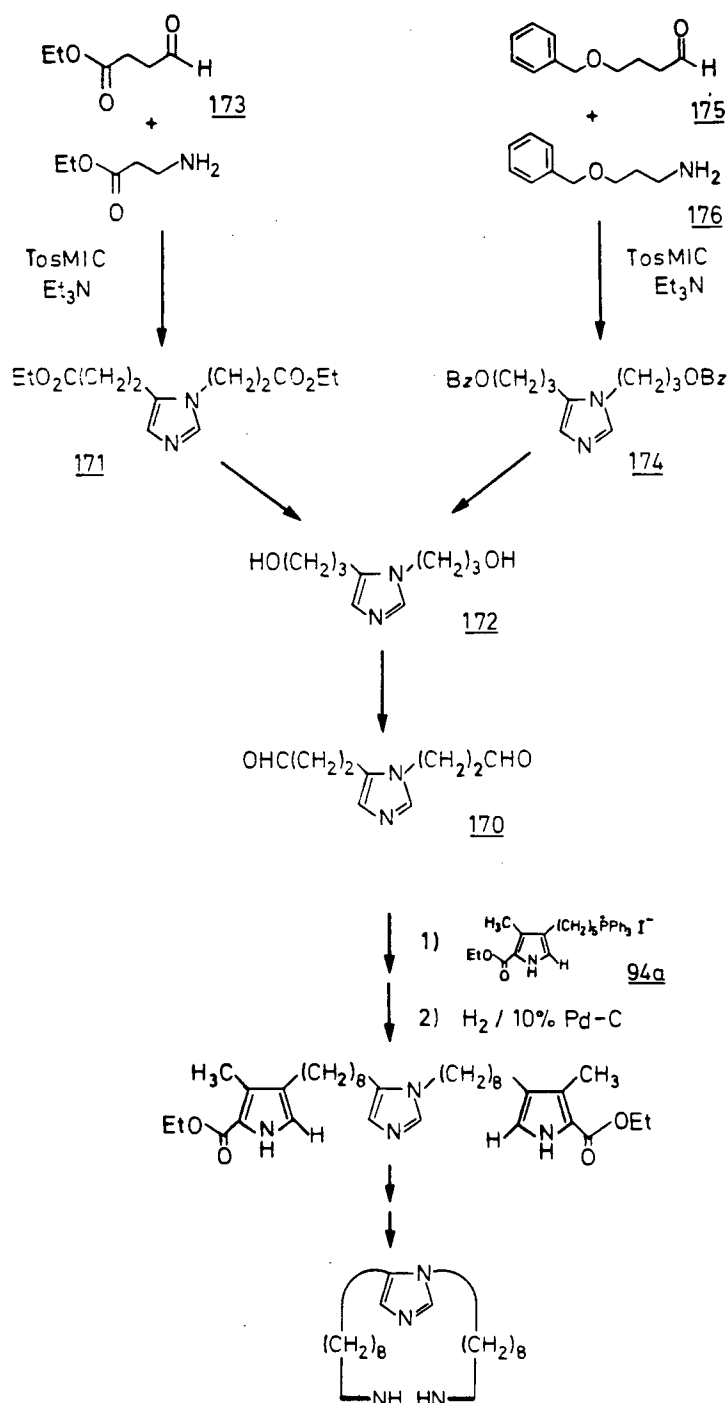
Fig. 23: Proposed Synthesis of Imidazole – Strapped Porphyrin via

1,5-Bis(3-hydroxypropyl)imidazole 172

SCHEME 92

$CH_3(CH_2)_5CHO$ + $CH_3(CH_2)_3NH_2$ $\xrightarrow[\text{TosMIC}]{\text{Et}_3\text{N}}$ [imidazole structure with $CH_3(CH_2)_5$ and $(CH_2)_3CH_3$ substituents] ~90%

$CH_3(CH_2)_5CHO$ + $H_2N(CH_2)_5CO_2Et$ $\xrightarrow[\text{TosMIC}]{\text{Et}_3\text{N}}$ [imidazole structure with $CH_3(CH_2)_5$ and $(CH_2)_5CO_2Et$ substituents] ~77%

$CH_3(CH_2)_2CHO$ + $H_2N(CH_2)_3CH_3$ XS $\xrightarrow[\text{TosMIC}]{\text{Et}_3\text{N}}$ [imidazole structure with CH_3CH_2 and $(CH_2)_2CH_3$ substituents] 90%

CH_3CH_2CHO + $H_2N(CH_2)_3CH_3$ XS $\xrightarrow{\text{TosMIC}}$ [imidazole structure with CH_3CH_2 and $(CH_2)_2CH_3$ substituents] 77%

170. Model reactions on a related system suggested that this was possible (equation 64). However, as we anticipated difficulties in

[imidazole structure with $CH_3(CH_2)_2$ and $(CH_2)_5CO_2Et$ substituents] $\xrightarrow[\substack{2)\ (COCl)_2/DMSO \\ Et_3N}]{1)\ LiAlH_4}$ [imidazole structure with $CH_3(CH_2)_2$ and $(CH_2)_5CHO$ substituents]

$$(64)$$
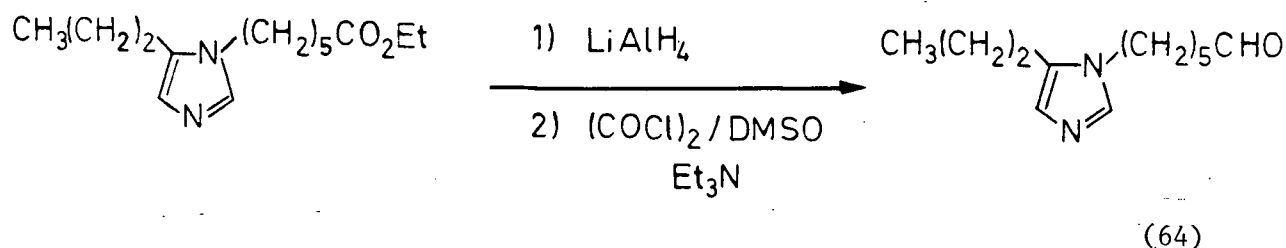
preparing the succinaldehyde 173, we decided to prepare the bis-alcohol 172 from the bis-benzyl ether 174, a route developed by Battersby.[222]

Both the aldehyde 175 and the amine 176 necessary for formation of 1,5-bis(3-benzyloxypropyl)imidazole 174 were easily prepared. Treatment of 1,4-butanediol with 0.5 equivalents of sodium and 0.3

equivalents of benzyl chloride furnished the 3-benzyloxybutan-1-ol 177

in 44-70% yield,[223] which was oxidized to the aldehyde 175 using

dimethyl sulfoxide/oxalyl chloride (65-83% after vacuum distillation).[189]

SCHEME 93

(65)

(66)
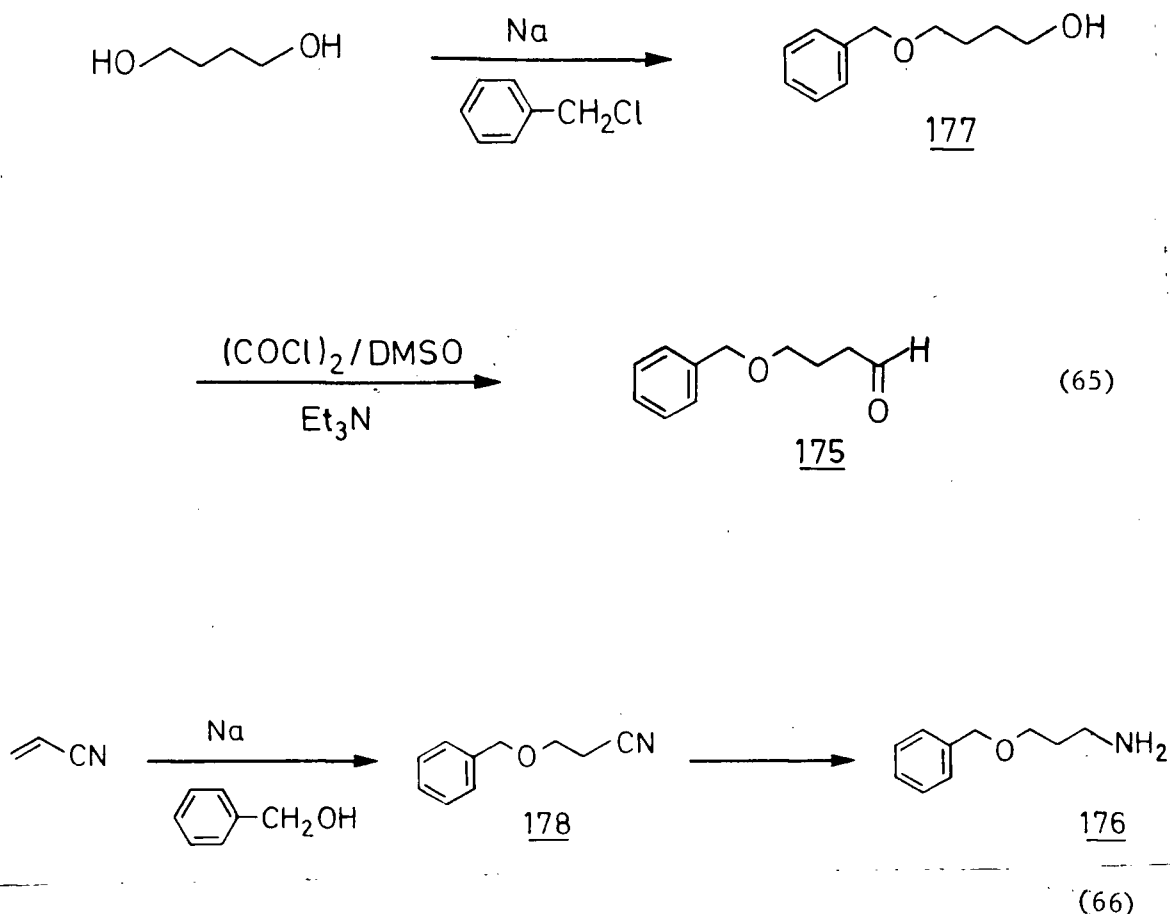
Obtaining the amine 176 proved to be somewhat more difficult. The

nitrile 178 was easily prepared by adding acrylonitrile to sodium

benzylate, the product being obtained by vacuum distillation (67%).[224]

Attempts to reduce the nitrile to the corresponding amine 176 met with

varying success. Both diborane and lithium aluminum hydride reductions

failed, the latter presumably due to removal of the benzyloxy group.[232]

Initially borane/dimethyl sulfide[225] gave reasonable yields (57-66%

crude product) of the amine, but the yield decreased to zero on

repetition for some inexplicable reason.   While tetra-n-butylammonium

borohydride[226] did reduce the nitrile, the crude product was contamina-

ted with tetra-n-butylammonium salts. The yields varied (30-68%)

depending on the scale of the reaction, large scale reactions being

tedious to work-up due to solubility problems. Eventually alane was

found to carry out the reaction in high yield (80-90%).[227]

The imidazole 174 was prepared by stirring equimolar amounts

of the aldehyde 175, amine 176 and TosMIC with 4-5 equivalents of

triethylamine in methanol for 70-168 hours. The solvent was removed

and the residue partitioned between ethyl acetate and 3M hydrochloric

acid. Neutralization of the aqueous layer and back-extraction with

ethyl acetate gave a very crude product, which was purified somewhat

by column chromatography to give a yellow oil. ^{1}H-NMR of the product

at this stage showed all the necessary signals, but the presence of

other resonances and the appearance of other spots on tlc showed it

to be still crude. The imidazole cyclization was judged to have

proceeded in 30-50% yield based on the weight of this crude product

which was carried through to the next stage without further purification.

The low yields of imidazole 174 were both disappointing and

puzzling. The preparation of imidazoles bearing non-functionalized

alkyl chains had, under the same reactions, given excellent yields. Why

the introduction of the benzyl ether functions resulted in such a

lowering of yield remains unclear. Furthermore, reaction of TosMIC

with a pre-formed aldimine 179 under essentially similar conditions

gave equally disappointing yields (Scheme 94).

Hydrogenolysis of the benzyl ethers using palladium-charcoal as

SCHEME 94
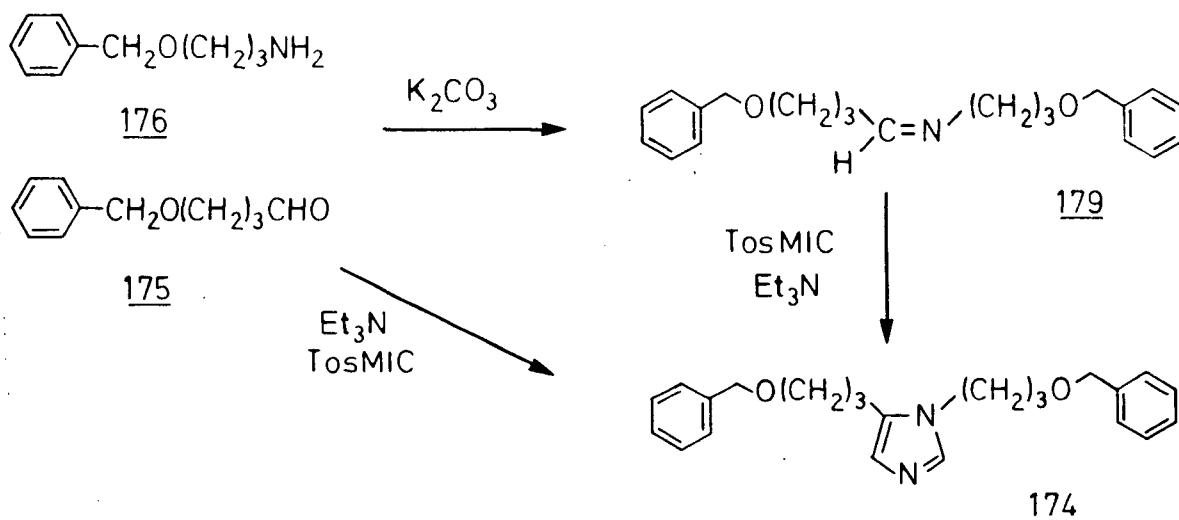
catalyst resulted in, at best, only partial deprotection; presumably

some by-product was poisoning the catalyst. Similarly, transhydro-

genation using cyclohexene and a catalytic quantity of palladium-

charcoal in refluxing ethanol gave a mixture of starting material and

products.[208] Only on addition of stoichiometric amounts of the catalyst

could complete hydrogenolysis be effected.

A more convenient procedure was to carry out a reductive cleavage

of the benzyl ethers using sodium in liquid ammonia.[228] Complete

removal was achieved but isolation of the 1,5-bis(3-hydroxypropyl)-

imidazole 172 was hampered by its low solubility in non-polar solvents.

Using methanol to recover the product led to contamination of the

product with the ammonium chloride used to quench the reduction. Never-

theless samples of the imidazole were obtained by chromatography (60-

70%). ^{1}H-NMR was used to confirm the removal of the benzyl ethers.

With samples of the 1,5-bis(3-hydroxylpropyl)imidazole 172 avail-

able it was decided to push ahead to the oxidation step since only

small quantities of the dialdehyde 170 would be required in the conver-

OHC(CH$_2$)$_2$ ⏤N⏤(CH$_2$)$_2$CHO   HO(CH$_2$)$_3$ ⏤N⏤(CH$_2$)$_3$OH

170   172
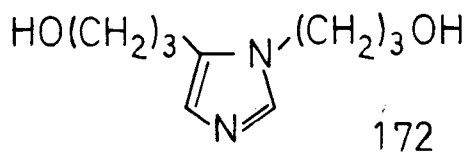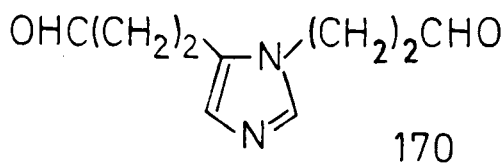
gent porphyrin synthesis. However oxidation of 172 to 170 proved to be

fruitless. Stirring with pyridinium dichromate[188] for 12 hours in

dichloromethane/tetrahydrofuran (10:1) or dichloromethane/pyridine

(1:1), followed by filtration through a short silica gel plug to remove

the chromium salts did not lead to the isolation of any recognizable

product. Similarly refluxing 172 with tetrabutylammonium chromate[229]

in tetrahydrofuran gave no recognizable product after work-up.

Likewise Oppenauer oxidation[230] with aluminum isopropoxide and benzo-

phenone showed no sign of the bis-aldehyde product 170.

Oxidation using DMSO/Et$_3$N/(COCl)$_2$ was examined more closely since

these reagents had previously been used to oxidize a hydroxyalkyl

imidazole 180 to the corresponding aldehyde 181 (equation 67). Addition

of oxalyl chloride to a solution of dimethyl sulfoxide in dichloromethane

CH$_3$(CH$_2$)$_2$ ⏤N⏤(CH$_2$)$_6$OH   →   CH$_3$(CH$_2$)$_2$ ⏤N (CH$_2$)$_5$CHO

180   (COCl)$_2$/ DMSO   181   (67)
Et$_3$N
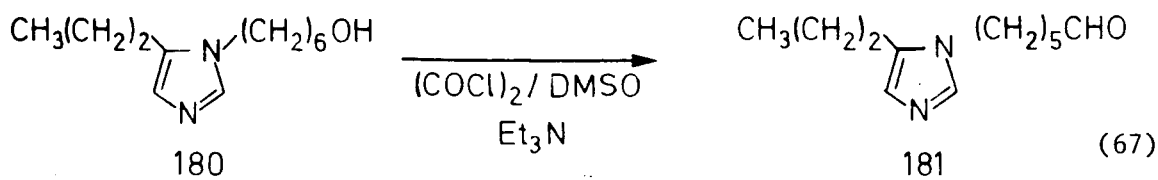
at -78°C was accompanied by an increase in temperature and the evolution

of gas as the initially formed species I decomposed to the dimethyl-

sulfonium chloride II (Scheme 95). On addition of the 1,5-bis(3-hydroxy-

propyl)imidazole 172 in CH_2Cl_2/DMSO solution, a white precipitate

appeared, presumably due to formation of the dimethyl alkoxysulfonium

SCHEME 95
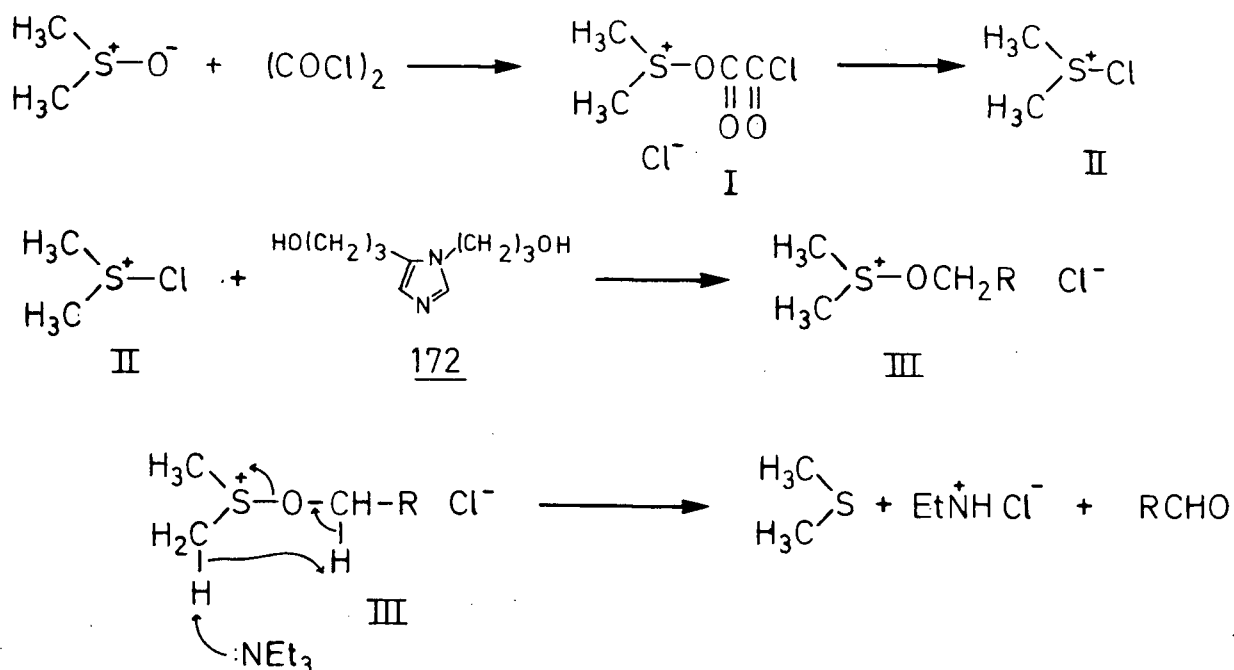
salt III. Subsequent addition of triethylamine led to a temporary

disappearance of the white precipitate, which then returned due to

formation of triethylammonium chloride. The reaction mixture was

allowed to warm to room temperature then quenched by addition of water.

Extraction of the reaction mixture with dilute hydrochloric acid,

followed by neutralization, back-extraction into ethyl acetate and

removal of the solvent gave only a minute amount of material showing

several spots on tlc.

Fearing that the product had been lost in the aqueous phase during work-up, the oxidation was repeated under the same conditions. This time however, after quenching with water, the entire reaction mixture was taken to dryness. Again tlc showed many spots and ^{1}H-NMR of the residue showed no indication of any aldehyde peaks.

Other combinations of conditions were employed. In one instance the reaction was quenched by addition of water while still at -78°C, and in another, the solution containing the dimethyl alkoxysulfonium salt III was allowed to warm to 0°C before addition of triethylamine. In neither case was any of the desired aldehyde observed. Furthermore, improving the solubility of 172 by increasing the quantity of dimethyl sulfoxide, or cancelling the aqueous quench, gave no sign of product. Replacement of triethylamine with diisopropylamine resulted in no improvement.

In only one instance was a recognizable carbonyl product obtained. 1,5-Bis(3-hydroxypropyl)imidazole 172 (0.4 g) was subjected to the usual oxidation procedure and quenched with water. After work-up of both the aqueous and organic layers, tlc showed a large spot for dimethyl sulfoxide which was preceeded by a smaller spot. This material was isolated by chromatography to give an off-white solid. The ^{1}H-NMR

$$HO(CH_2)_3 \diagdown \diagup N \diagup (CH_2)_3OH$$

172
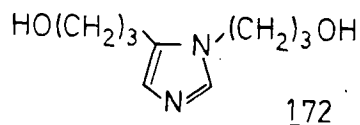
of this product did show a peak in the aldehyde region, but it was

a singlet rather than the expected triplet. This fact, coupled with

the absence of triplets at ~2.6 and 3.8-4.0 δ indicated that the product

was not the desired bis-aldehyde 170. Indeed the pattern of resonances

[2.6-2.9 (m, 2H), 2.9-3.1 (m, 2H), 4.88 (d, 2H), 6.86 (m, 2H), 7.42

(bs, 1H), 9.42 (s, 1H)] was more consistent with the bicyclic imidazole

product 182, formed by intramolecular aldol condensation. The assign-

ment was further confirmed by mass spectrometry (m/e 162) and by two

bands in the infra-red spectrum at 1675 and 1630 cm^{-1}, due to the carbonyl

and imine bonds respectively.
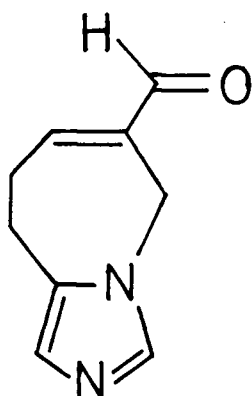
182

These failures led us to believe that suitable conditions could

not be found to produce 170 in satisfactory yields. Since the formation

of the 1,5-disubstituted imidazoles had also been typified by poor

yields and difficulties in purification, further efforts in this field

were postponed. With the publication by Momenteau[138] and by Battersby[140]

of heme models containing a "pendant" and a "strapped" imidazole respectively, our attempts to prepare a strapped imidazole porphyrin were abandoned.

CHAPTER 3

EXPERIMENTAL

3.1   INTRODUCTION

3.1.1 GENERAL METHODS

Melting point determinations were obtained using a Thomas-Hoover Unimelt oil-bath/capillary tube apparatus, and all the quoted results are uncorrected.

A Cary (Model 1756) spectrophotometer was used to record UV and visible spectra.

Elemental analysis was carried out by Mr. P. Borda of the Microanalytical Laboratory, U.B.C.

Mass Spectra were recorded on a Varian MAT CH 4-B spectrometer or a Kratos/AEI MS-902 spectrometer. High resolution measurements were obtained on a Kratos/AEI MS-50 spectrometer. In all cases the ionization voltage was 70 eV.

The ^{1}H NMR spectra of all the monopyrroles were obtained at 100 MHz with a Varian XL-100 spectrometer under Fourier-transform conditions. The spectra of the chain-linked bis-pyrroles were recorded at 270 MHz with a U.B.C. NMR Centre modified Nicolet-Oxford H-270 spectrometer. The spectra of the chain-linked bis-dipyrromethanes and the strapped porphyrins were recorded at 400 MHz on a Bruker WH-400 spectrometer. For the substituted benzene and imidazole compounds the spectra were recorded on a Varian EM-360L or XL-100 spectrometer. The chemical shifts were recorded with tetramethylsilane (TMS) as an internal standard.

Most of the ^{13}C-NMR spectra were obtained with a Varian CFT-20 spectrometer using TMS as the internal standard. Compounds 113b, 138a and 138b were recorded on a Bruker WP-80 instrument operating at 20.15 MHz

and using deuterochloroform (δ = 77.0) as internal standard. Of the strapped porphyrins, 87b, 88b, 117a, 118a and 118b were recorded on a Varian CFT-20 spectrometer; the others were recorded on a Bruker WH-400 spectrometer. The samples were 0.012-0.082M in 10% TFA-CDCl$_3$ with TMS as an internal standard.

Column chromatography on silica gel was performed using BDH silica gel (60-120 mesh), Merck Kieselgel 60H, or Merck Kieselgel 60 (70-230 mesh). For the final purification of the porphyrin samples Merck aluminum oxide 90 (70-230 mesh, neutral, activity III) was used.

Thin layer chromatography (tlc) was performed using precoated silica gel plates (Analtech-Uniplate, 250μ), and the compounds were usually detected by UV light (254 nm) and/or exposure to iodine.

Mixtures of solvents used in chromatography are expressed as volume:volume percentages.

3.1.2 Nomenclature of Porphyrins and Intermediate Compounds

The strapped porphyrins have been numbered in accordance with the IUPAC recommendations on "Nomenclature of Tetrapyrroles" as indicated in Fig. 24.[233] For consistency in the diagrams the strap has been attached to positions 3 and 13 of the porphyrin ring.

For convenience and clarity, all the pyrroles and dipyrromethane compounds have been named as derivatives of the functionalized alkane chain. Numbering of both the pyrrole ring and the alkane chain has been kept constant; thus the alkane chain has been always numbered as attached to position 3 of the pyrrole ring and the ethoxycarbonyl group at position
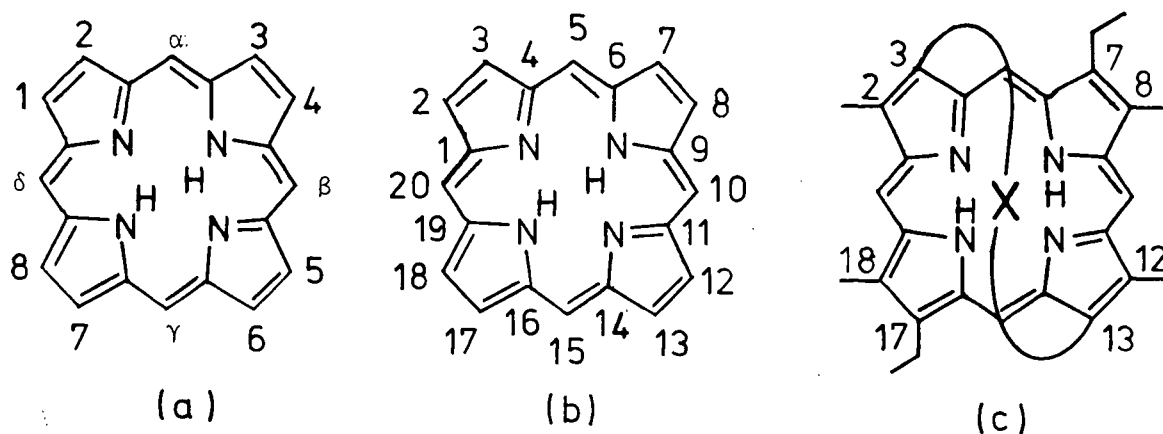
Fig. 24: Fischer (a) and IUPAC (b) Numbering Systems for Porphyrins

5. For example compounds such as 183, (Fig. 25), have been consistently described as 5-(5-ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)pentane derivatives. The chain-linked bis-pyrroles have been numbered in similar fashion. Thus 75a has been named as bis[5-(5-ethoxycarbonyl-4-methyl-pyrrole-3-yl)pentyl]sulfide. This name is more informative and less unwieldy than the corresponding IUPAC or Chemical Abstract names.

In keeping with Chemical Abstracts nomenclature the dipyrromethanes have been named as substituted (pyrrole-2-yl)methylpyrroles 184 (Fig. 26). The pyrrole nuclei were numbered so as to assign 2 and 2' to the methane bridged α-positions. The numbers 2', 3' etc. have been used on one pyrrole ring only for the purpose of distinguishing the analogous positions on the two rings in spectral assignments. Thus the bis-dipyrromethane 77a (Fig. 26) was named as bis[5-(5-ethoxycarbonyl-
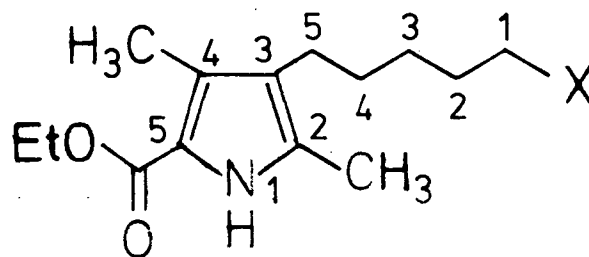
183
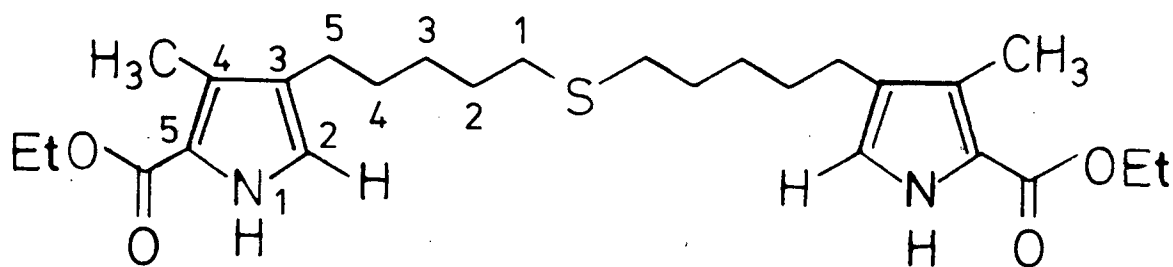
75a

Fig. 25: Numbering System for Pyrrolic Intermediates

-2[(5-(2,2-dicyanovinyl)-3-ethyl-4-methylpyrrol-2-yl)methyl]-4-methyl-

pyrrol-3-yl)pentylsulfide.
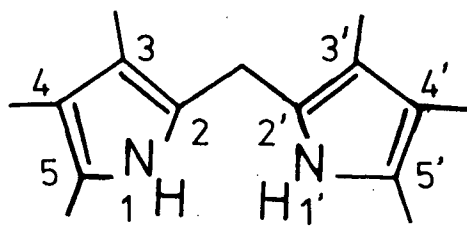
184
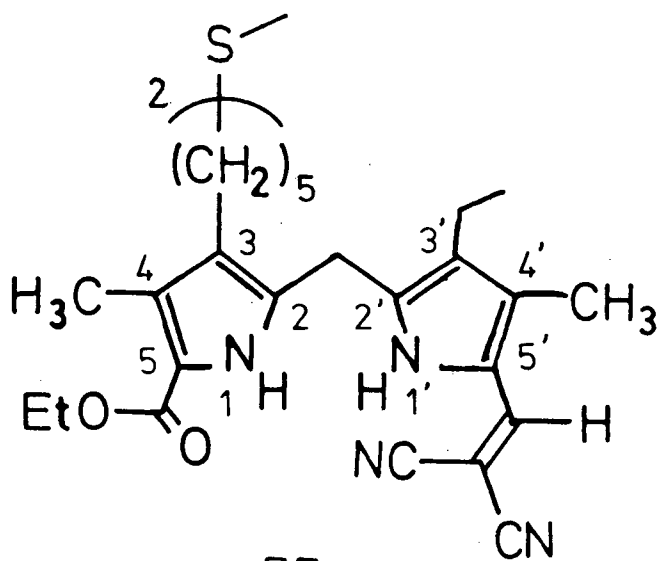
77a

Fig. 26: Numbering System for Dipyrromethanes

3.2 SYNTHESES OF MONOPYRROLES
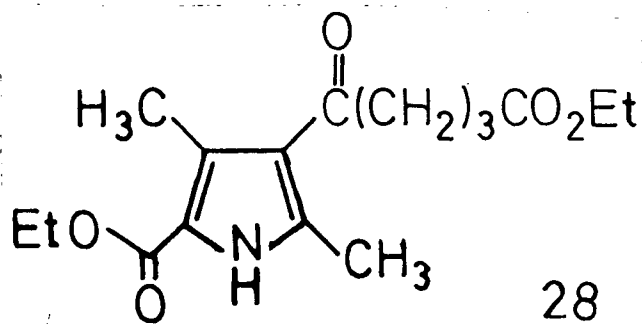
Ethyl 5-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-5-oxopentanoate 28

Ethyl hydrogen glutarate (96.0 g, 0.54 mol) and thionyl chloride (120 mL, 1.6 mol) were placed in a round bottom flask ⌐ equipped with a reflux condenser and a drying tube and heated on a steam bath for 2 hours. The excess thionyl chloride was removed by rotary evaporation with carbon tetrachloride (2 x 100 mL) to give a dark yellow oil. This crude acid chloride was used without purification.

5-Ethoxycarbonyl-2,4-dimethylpyrrole 1 (75.0 g, 0.45 mol) was dissolved in dichloromethane (750 mL) in a 2-liter Erlenmeyer flask equipped with a Claisen adapter, nitrogen inlet, pressure-equalizing dropping funnel and drying tube. The crude acid chloride was added and the mixture stirred under nitrogen and cooled in an ice-bath.

Stannic chloride (58.0 mL, 0.50 mol) was added dropwise over a period of 35 minutes and the solution was then left stirring for 1.5 hours. By this stage tlc (10% EtOAc/CH_2Cl_2) indicated complete consumption of starting material.

The reaction mixture was poured into 2M hydrochloric acid (400 mL) and the dichloromethane layer was separated. This was extracted with

sodium bicarbonate solution to remove unreacted acid chloride, then dried over anhydrous sodium sulfate, filtered and evaporated. The resultant dark red oil was dissolved in ethanol (500 mL). Addition of water precipitated a solid which was collected by filtration and dried to give 116.8 g (84.1%).

The product was contaminated with a trace of starting pyrrole but was used without further purification. An analytically pure sample was prepared by column chromatography on silica gel with 10% EtOAc/CH_2Cl_2 as eluant.

MP: 68.0-70.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.26 (t, 3H, J = 7.0 Hz, chain -OCH$_2$CH$_3$), 1.38 (t, 3H, J = 7.0 Hz, pyrrole -OCH$_2$CH$_3$), 2.08 (q, 2H, J = 7 Hz, chain 3-CH$_2$), 2.43 (t, 2H, J = 7 Hz, chain 2-CH$_2$), 2.54 (s, 3H, 4-CH$_3$), 2.60 (s, 3H, 2-CH$_3$), 2.80 (t, 2H, J = 7 Hz, chain 4-CH$_2$), 4.16 (q, 2H, J = 7.0 Hz, chain -OCH$_2$CH$_3$), 4.37 (q, 2H, J = 7.0 Hz, pyrrole -OCH$_2$CH$_3$), 9.38 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 197.05 (chain 5-C, $\underline{C}$ = O), 173.41 (chain 1-C, $\underline{C}$ = O), 162.10 (pyrrole ester, $\underline{C}$ = O), 138.53 (pyrrole 2-C), 129.16 (pyrrole 4-C), 123.21 (pyrrole 3-C), 118.09 (pyrrole 5-C), 60.28 (pyrrole and chain ester, -OCH$_2$CH$_3$), 41.54 (chain 4-C), 33.57 (chain 2-C), 19.45 (chain 3-C), 14.86 (2-CH$_3$), 14.32 (pyrrole ester, -OCH$_2$CH$_3$), 14.20 (chain ester, -OCH$_2$CH$_3$), 12.71 (4-CH$_3$).

Anal. Calcd. for C$_{16}$H$_{23}$NO$_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.15; H, 7.52; N, 4.59.

Mass Spectrum (m/e, relative intensity): 309 (M$^+$, 28), 264 (24), 222 (10), 209 (7), 194 (83), 148 (100).
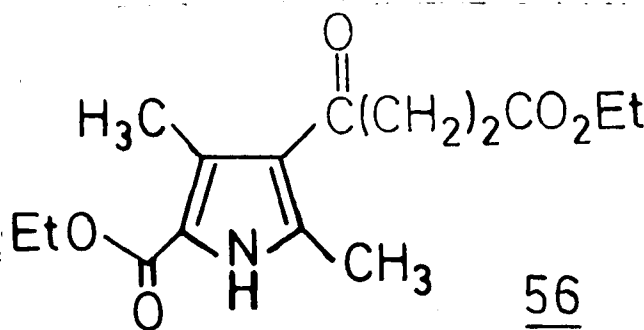
Ethyl 4-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-4-oxobutanoate 56

This was prepared from 5-ethoxycarbonyl-2,4-dimethylpyrrole 1 (20.0 g, 0.12 mol) and ethyl succinyl chloride 55 (23.6 g, 0.14 mol) by the same procedure as for the homologous pyrrole 28.

The crude product was recrystallized from the minimum amount of hot ethanol to give a white crystalline solid as a first crop (25.7 g, 72.8%).

MP: 144.0 - 145.5°C.

^{1}H-NMR (δ, CDCl$_3$): 1.28 (t, 3H, J = 7.0 Hz, chain -OCH$_2$CH$_3$), 1.39 (t, 3H, J = 7.0 Hz, pyrrole -OCH$_2$CH$_3$), 2.55 (s, 3H, 4-CH$_3$), 2.60 (s, 3H, 2-CH$_3$), 2.72 (t, 2H, J = 6 Hz, chain 2-CH$_2$), 3.08 (t, 2H, J = 6 Hz, chain 3-CH$_2$), 4.19 (q, 2H, J = 7.0 Hz, chain -OCH$_2$CH$_3$), 4.37 (q, 2H, J = 7.0 Hz, pyrrole -CH$_2$CH$_3$), 9.14 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 195.49 (chain 5-C, C = O), 173.35 (chain 1-C, C =

0), 162.08 (pyrrol ester, $\underline{C}$ = 0), 138.65 (pyrrole 2-C), 129.32 (pyrrole

4-C), 123.03 (pyrrole 3-C), 118.22 (pyrrole 5-C), 60.55 (pyrrole ester,

-O$\underline{CH}_2$CH$_3$), 60.45 (chain ester -O$\underline{CH}_2$CH$_3$), 37.51 (chain 3-C), 28.42

(chain 2-C), 15.12 (2-CH$_3$), 14.46 (pyrrole ester, -OCH$_2$$\underline{CH}_3$), 14.22

(chain ester, -OCH$_2$$\underline{CH}_3$), 12.86 (4-CH$_3$).

$\underline{Anal}$. Calcd. for C$_{15}$H$_{21}$NO$_5$: C, 61.00; H, 7.17; N, 4.74. Found:

C, 61.06; H, 7.26; N, 4.71.

$\underline{Mass\ Spectrum}$ (m/e relative intensity): 295 (M$^+$, 39), 250 (34), 222

(8), 194 (76), 166 (13), 149 (100).
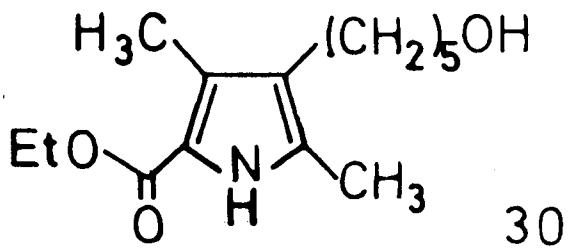
5-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-pentanol   30

Ethyl 5-(5-ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-5-oxopenta-

noate $\underline{28}$ (56.3 g, 0.18 mol) was dissolved in freshly distilled tetra-

hydrofuran (300 mL) and stirred under nitrogen in a 1-liter Erlenmeyer

flask equipped with a pressure-equalizing addition funnel. Sodium

borohydride (14.5 g, 0.38 mol) was added, followed by dropwise

addition of boron trifluoride etherate (62.7 mL, 0.51 mol) over a period

of 20 minutes. No external cooling was applied and the reaction

temperature rose to ∿50°C. The reaction was left stirring for 2 hours.

The reaction was quenched by the slow, careful addition of glacial acetic acid (50 mL) followed by the addition of water until the solution became a clear red. The tetrahydrofuran was removed on a rotary evaporator and the red oil which then separated was extracted with dichloromethane (300 mL). The dichloromethane solution was dried over anhydrous sodium sulfate, filtered and evaporated to give a dark red oil. Dissolving this in ethanol (100 mL) and adding water precipitated a pink solid which was filtered and air-dried to yield 39.2 g (85.0%).

MP: 84.0-85.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.36 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.2-1.7 (m, 7H, chain 2-, 3-, 4-CH$_2$, O-H), 2.21 (s, 3H, 2-CH$_3$), 2.28 (s, 3H, 4-CH$_3$), 2.39 (t, 2H, chain 5-CH$_2$), 3.69 (t, 2H, J = 6 Hz, 1-CH$_2$), 4.32 (q, 2H, J = 7.0 Hz, -OCH$_2$CH$_3$), 8.64 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 162.35 (C = 0), 130.26 (pyrrole 2-C), 127.07 (pyrrole 4-C), 122.06 (pyrrole 3-C), 116.75 (pyrrole 5-C), 62.66 (chain 1-C), 59.62 (-OCH$_2$CH$_3$), 32.74 (chain 2-C), 30.77 (chain 4-C), 25.66 (chain 3-C), 24.04 (chain 5-C), 14.57 (-OCH$_2$CH$_3$), 11.36 (2-CH$_3$), 10.75 (4-CH$_3$).

Anal. Calcd. for C$_{14}$H$_{23}$NO$_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.41; H, 9.12; N, 5.50.

Mass Spectrum (m/e, relative intensity): 253 (M$^+$, 34), 208 (8), 180 (100), 134 (69).
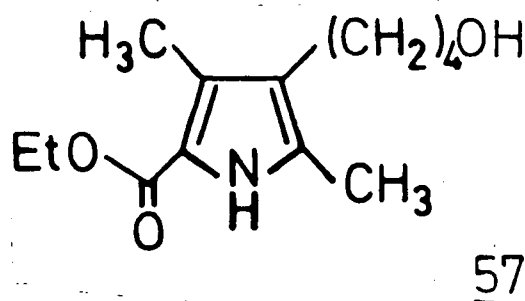
4-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-butanol   57

This was prepared in the same way as 30, from ethyl 4-(5-ethoxy-carbonyl-2,4-dimethylpyrrol-3-yl)-4-oxobutanoate 56 (14.4 g, 0.05 mol), sodium borohydride (7.4 g, 0.2 mol) and boron trifluoride etherate (37.0 mL, 0.3 mol).

After work-up a yellow oil was obtained which slowly crystallized to a white solid. The crude product was recrystallized from 50% water/ethanol (100 mL) to give 8.4 g (72.1%):

MP: 117.0-119.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.36 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.5-1.7 (m, 5H, chain 2-, 3-CH$_2$, O-H), 2.21 (s, 3H, 2-CH$_3$), 2.28 (s, 3H, 4-CH$_3$), 2.40 (t, 2H, chain 4-CH$_2$), 3.67 (t, 2H, chain 1-CH$_2$), 4.32 (q, 2H, J = 7.0 Hz, -OCH$_2$CH$_3$), 8.7 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 162.12 (C = 0), 129.94 (pyrrole 2-C), 127.08

(pyrrole 4-C), 121.87 (pyrrole 3-C), 116.85 (pyrrole 5-C), 62.81
(chain 1-C), 59.65 (-OCH$_2$CH$_3$), 32.49 (chain 2-C), 27.02 (chain 3-C),
23.82 (chain 4-C), 14.60 (-OCH$_2$CH$_3$), 11.45 (2-CH$_3$), 10.71 (4-CH$_3$).

Anal. Calcd. for C$_{13}$H$_{21}$NO$_3$: C, 65.24; H, 8.85; N, 5.85. Found:
C, 65.24; H, 8.86; N, 5.81.

Mass Spectrum (m/e, relative intensity): 239 (M$^+$, 38), 194 (11), 180
(100), 166 (4), 134 (88).
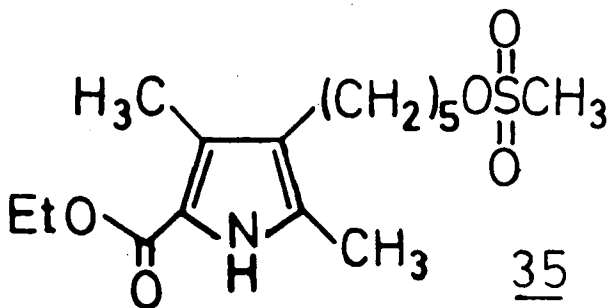
5-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-pentylmethanesulfonate
35

5-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-pentanol 30 (39.2 g,
0.16 mol) and triethylamine (32.3 g, 0.23 mol), were dissolved in
dichloromethane (500 mL) in a 3-neck flask equipped with a nitrogen
inlet, overhead stirrer and pressure-equalizing addition funnel.
The solution was stirred under nitrogen and cooled to 0°C in an
ice-bath.

Methanesulfonyl chloride (18.5 mL, 0.19 mol) was added dropwise
over a period of 10 minutes, and the reaction mixture was then allowed
to warm to room temperature. Tlc (50% EtOAc/CH$_2$Cl$_2$) indicated

complete reaction.

The reaction mixture was extracted in turn with water (200 mL), cold 2M hydrochloric acid (200 mL), saturated sodium bicarbonate solution and finally saturated sodium chloride solution. The dichloromethane solution was dried over anhydrous sodium sulfate, filtered and evaporated. A dark red oil was obtained. Dissolving in the minimum amount of hot ethanol and adding water precipitated a pink solid. This was filtered and air-dried (47.1 g, 91.8%).

The product was carried to the next stage without further purification. An analytically pure sample was prepared by column chromatography on silica gel with 20% EtOAc/CH_2Cl_2 as eluant.

MP: 68.0-70.0°C.

^{1}H-NMR (δ, $CDCl_3$): 1.35 (t, 3H, J = 7.0 Hz, $-OCH_2CH_3$), 1.2-1.9 (m, 6H, chain 2-, 3-, 4-CH_2), 2.20 (s, 3H, 2-CH_3), 2.27 (s, 3H, 4-CH_3), 2.39 (m, 2H, chain 5-CH_2), 2.99 (s, 3H, $-OSO_2CH_3$), 4.23 (t, 2H, J = 7 Hz, chain 1-CH_2), 4.24 (q, 2H, J = 7.0 Hz, $-OCH_2CH_3$), 8.79 (bs, 1H, N-H).

^{13}C-NMR (δ, $CDCl_3$): 162.14 (C = O), 130.11 (pyrrole 2-C), 126.83 (pyrrole 4-C), 121.63 (pyrrole 3-C), 116.90 (pyrrole 5-C), 70.20 (chain 1-CH_2), 59.61 ($-OCH_2CH_3$), 37.22 ($-OSO_2CH_3$), 30.29 (chain 4-C), 29.15 (chain 3-C), 25.19 (chain 2-C), 23.85 (chain 5-C), 14.60 ($-OCH_2CH_3$), 11.36 (2-CH_3), 10.72 (4-CH_3).

Anal. Calcd. for $C_{15}H_{25}NO_5S$: C, 54.36; H, 7.60; N, 4.23; S, 9.68.

Found: C, 54.22; H, 7.66; N, 4.26; S, 9.55.

<u>Mass Spectrum</u> (m/e, relative intensity): 331 (M$^+$, 12), 286 (2), 281 (16), 252 (3), 251 (4), 236 (4), 206 (5), 180 (100), 134 (32).
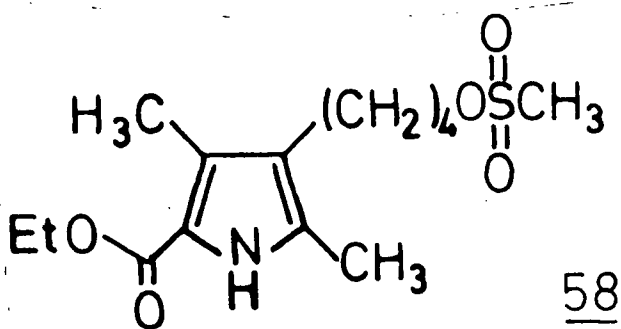
<u>4-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-butylmethanesulfonate</u> <u>58</u>

4-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-butanol <u>57</u> (8.4 g, 35 mmol) in dichloromethane (250 mL) was treated with triethylamine (7.3 mL, 52 mmol) and methanesulfonyl chloride (4.8 mL, 48 mmol) as outlined for the analogous compound <u>35</u> above.

Recrystallization from 50% ethanol/water gave a white flaky solid (8.2 g, 74.0%). A second crop (1.5 g, 13.7%) was obtained from the mother liquors.

<u>MP</u>: 82.0-83.5°C.

<u>^{1}H-NMR</u> (δ, CDCl$_3$): 1.36 (t, 3H, J = 7.0 Hz, -OCH$_2$C$\underline{H}_3$), 1.4-1.9 (m, 4H, chain 2-, 3-CH$_2$), 2.21 (s, 3H, 2-CH$_3$), 2.28 (s, 3H, 4-CH$_3$), 2.43 (t, 2H, chain 4-CH$_2$), 3.00 (s, 3H, -OSO$_2$C$\underline{H}_3$), 4.27 (t, 2H, J = 6 Hz, chain 1-CH$_2$), 4.33 (q, 2H, J = 7.0 Hz, -OC$\underline{H}_2$CH$_3$), 8.58 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 162.00 ($\underline{C}$ = O), 129.98 (pyrrole 2-C), 126.85 (pyrrole 4-C), 121.10 (pyrrole 3-H), 116.99 (pyrrole 5-C), 70.10 (chain 1-C), 59.66 (-O$\underline{C}$H$_2$CH$_3$), 37.32 (-OSO$_2\underline{C}$H$_3$), 28.76 (chain 3-C), 26.56 (chain 2-C), 23.39 (chain 4-C), 14.60 (-OCH$_2\underline{C}$H$_3$), 11.42 (2-CH$_3$), 10.71 (4-CH$_3$).

<u>Anal</u>. Calcd. for C$_{14}$H$_{23}$NO$_5$S: C, 52.98; H, 7.30; N, 4.41; S, 10.10. Found: C, 53.26; H, 7.37; N, 4.32; S, 9.95.

<u>Mass Spectrum</u> (m/e, relative intensity): 317 (M$^+$, 11), 281 (6), 272 (3), 267 (4), 239 (4), 238 (3), 222 (2), 192 (6), 180 (100), 134 (88).
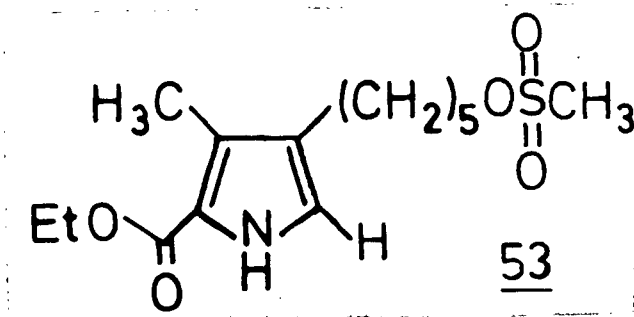
5-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-pentylmethanesulfonate <u>53</u>

This was prepared from 5-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)-1-pentanol <u>51</u> (3.22 g, 13.4 mmol), triethylamine (2.8 mL, 20.1 mmol) and methanesulfonyl chloride (1.61 mL, 16.0 mmol) as outlined for compound <u>35</u> above.

The crude product, after work-up was obtained as a reddish oil which slowly crystallized to a pink solid (4.25 g, 99.5%). This was carried to the next step without purification. A small sample,

recrystallized from 50% ethanol/water, was retained for analysis.

MP: 74.5–76.0 C.

^{1}H-NMR (δ, CDCl$_3$): 1.37 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.4–1.9 (m, 6H, chain 2-, 3-, 4-CH$_2$), 2.30 (s, 3H, 4-CH$_3$), 2.44 (t, 2H, J = 7 Hz, chain 5-CH$_2$), 3.02 (s, 3H, -OSO$_2$CH$_3$), 4.26 (t, 2H, J = 7.0 Hz, chain 1-CH$_2$), 4.34 (q, 2H, J = 7.0 Hz, -OCH$_2$CH$_3$), 6.70 (d, 1H, J = 3.0 Hz, 2-H), 8.8 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 161.84 (C = O), 125.88 (pyrrole 3-C), 125.16 (pyrrole 4-C), 119.84 (pyrrole 2-C), 119.41 (pyrrole 5-C), 70.12 (chain 1-C), 59.82 (-OCH$_2$CH$_3$), 37.32 (-OSO$_2$CH$_3$), 29.75 (chain 4-C), 29.05 (chain 3-C), 25.18 (chain 2-C), 24.79 (chain 5-C), 14.54 (-OCH$_2$CH$_3$), 10.31 (4-CH$_3$).

Anal. Calcd. for C$_{14}$H$_{23}$NO$_5$S: C, 52.98; H, 7.30; N, 4.41; S, 10.10. Found: C, 52.92; H, 7.43; N, 4.28; S, 10.00

Mass Spectrum (m/e, relative intensity): 317 (M$^+$, 31), 272 (7), 244 (11), 238 (10), 222 (6), 208 (2), 192 (17), 180 (4), 166 (100), 120 (88).
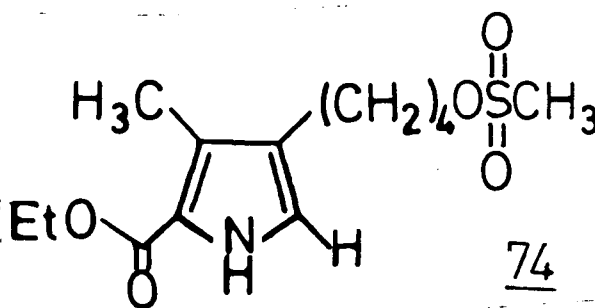
4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-butylmethanesulfonate   74

This was prepared from 4-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)-1-butanol 73 (9.79 mL, 43 mmol), triethylamine (10.0 mL, 72 mmol), and methanesulfonyl chloride (6.0 mL, 60 mmol).

The crude product, obtained as a deep red oil was carried to the next stage without purification. An analytically pure sample was obtained by column chromatography on silica gel with 10% EtOAc/CH_2Cl_2 as eluant.

MP: 46.0-48.0°C.

^{1}H-NMR (δ, $CDCl_3$): 1.36 (t, 3H, J = 7.0 Hz, $-OCH_2CH_3$), 1.5-1.9 (m, 4H, chain 2-, 3-CH_2), 2.29 (s, 3H, 4-CH_3), 2.47 (t, 2H, chain 4-CH_2), 3.00 (s, 3H, $-OSO_2CH_3$), 4.26 (t, 2H, J = 7.0 Hz, chain 1-CH_2), 4.33 (q, 2H, J = 7.0 Hz, $-OCH_2CH_3$), 6.69 (d, 1H, J = 3.0 Hz, 2-H), 8.95 (bs, 1, N-H).

^{13}C-NMR (δ, $CDCl_3$): 161.85 ($\underline{C}$ = 0), 125.85 (pyrrole 3-C), 124.57 (pyrrole 4-C), 119.97 (pyrrole 2-C), 119.46 (pyrrole 5-C), 70.07 (chain 1-C), 59.86 ($-O\underline{C}H_2CH_3$), 37.31 ($-OSO_2\underline{C}H_3$), 28.79 (chain 3-C), 26.16

(chain 2-C), 24.37 (chain 4-C), 14.53 (-OCH$_2$CH$_3$), 10.31 (4-CH$_3$).

Anal. Calcd. for C$_{13}$H$_{21}$NO$_5$S: C, 51.47; H, 6.98; N, 4.62; S, 10.57.
Found: C, 51.50; H, 6.95; N, 4.64; S, 10.39.

Mass Spectrum (m/e, relative intensity): 303 (M$^+$, 22), 267 (18), 258 (7), 253 (18), 224 (13), 208 (7), 207 (7), 206 (4), 178 (22), 166 (100), 120 (100), 134 (20).
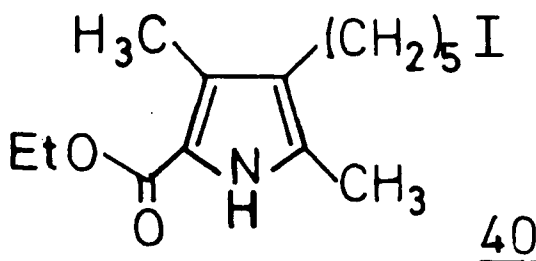
5-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-iodopentane 40

5-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-pentylmethane-sulfonate 35 (46.6 g, 0.14 mol) and sodium iodide (84.0 g, 0.56 mol) were suspended in acetone (750 mL) and, with vigorous stirring, were refluxed for 16 hours. Tlc (10% EtOAc/CH$_2$Cl$_2$) indicated complete reaction.

The reaction mixture was cooled to room temperature and the solid which had precipitated during the course of the reaction was filtered off. The filtrate was reduced in volume to approximately 200 mL, and addition of water (200 mL) precipitated a red solid which was collected by filtration. While still damp the crude product was

recrystallized from hot ethanol to give a pink solid (40.5 g, 79.3%).
A second crop (6.4 g, 12.5%) was obtained by adding water to the mother
liquor.

MP: 79.0-80.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.35 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.3-1.5 and
1.7-2.0 (m, 6H, chain 2-, 3-, 4-CH$_2$), 2.20 (s, 3H, 2-CH$_3$), 2.27 (s, 3H,
4-CH$_3$), 2.2-2.5 (m, 2H, chain 5-CH$_2$), 3.19 (t, 2H, J = 7.0 Hz, chain
1-CH$_2$), 4.31 (q, 2H, J = 7.0 Hz, -OCH$_2$CH$_3$).

^{13}C-NMR (δ, CDCl$_3$): 162.00 (C = O), 129.79 (pyrrole 2-C), 126.82 (
(pyrrole 4-C), 121.75 (pyrrole 3-C), 116.87 (pyrrole 5-C), 59.58
(-OCH$_2$CH$_3$), 33.50 (chain 2-C), 30.34 (chain 4-C), 29.76 (chain 3-C),
23.88 (chain 5-C), 14.61 (-OCH$_2$CH$_3$), 11.47 (2-CH$_3$), 10.71 (4-CH$_3$),
6.78 (chain 1-C).

Anal. Calcd. for C$_{14}$H$_{22}$NO$_2$I: C, 46.29; H, 6.11; N, 3.86; I, 34.94.
Found: C, 46.50; H, 6.17; N, 3.68; I, 34.71.

Mass Spectrum (m/e, relative intensity): 363 (M$^+$, 38), 318 (14), 236
(69), 180 (100), 134 (95).

H₃C / (CH₂)₄ I

EtO — ... NH CH₃   60
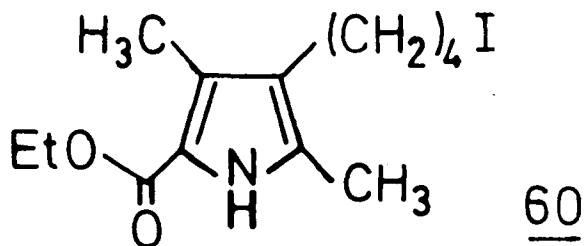
4-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-iodobutane   60

This was prepared from 4-(5-ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-butylmethanesulfonate 58 (9.2 g, 0.03 mol) by the method outlined for compound 40.

The crude product was recrystallized from 20% ethanol/water to give a white flaky solid (8.2 g, 80.2%). A second crop (0.8 g, 7.9%) was obtained from the mother liquor.

MP: 81.0-82.0°C.

^{1}H-NMR (δ, CDCl₃): 1.36 (t, 3H, J = 7.0 Hz, -OCH₂CH₃), 1.4-2.0 (m, 4H, chain 2-, 3-CH₂), 2.22 (s, 3H, 2-CH₃), 2.28 (s, 3H, 4-CH₃), 2.39 (t, 2H, J = 7.4 Hz, chain 4-CH₂), 3.20 (t, 2H, J = 7.2 Hz, chain 1-CH₂), 4.32 (q, 2H, J = 7.0 Hz, -OCH₂CH₃), 8.62 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl₃): 162.07 (C = 0), 129.92 (pyrrole 2-C), 126.86 (pyrrole 4-C), 121.34 (pyrrole 3-C), 116.94 (pyrrole 5-C), 59.64 (-OCH₂CH₃), 33.16 (chain 2-C), 31.57 (chain 3-C), 22.98 (chain 4-C), 14.60 (-OCH₂CH₃), 11.48 (2-CH₃), 10.71 (4-CH₃), 6.77 (chain 1-C).

<u>Anal</u>. Calcd. for C$_{13}$H$_{20}$NO$_2$I: C, 44.71; H, 5.77; N, 4.01; I, 36.34.

Found: C, 44.96; H, 5.87; N, 4.01; I, 36.22.

<u>Mass Spectrum</u> (m/e, relative intensity): 349 (M$^+$, 60), 304 (9), 222 (19), 180 (100), 148 (17), 134 (94).
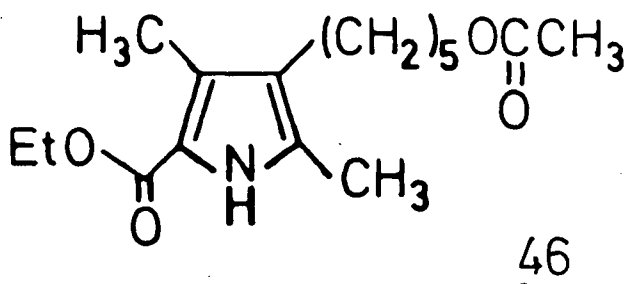
<u>5-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-acetoxypentane</u> <u>46</u>

5-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-pentanol <u>30</u>

(9.2 g, 36 mmol) was stirred overnight in a mixture of pyridine (16 mL)

and acetic anhydride (21 mL). The mixture was then poured into water

(100 mL) and extracted with ethyl acetate (100 mL). The organic

layer was washed with 2M hydrochloric acid (100 mL), saturated

sodium bicarbonate solution and saturated sodium chloride solution.

After drying over anhydrous sodium sulfate and filtering, the solvent

was removed to give a red oil. This was dissolved in ethanol (50 mL)

and addition of water precipitated a pink solid (8.0 g, 74.8%). A

second crop (2.1 g, 19.6%) was also obtained.

<u>MP</u>: 56.5-57.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.36 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.3-1.8 (m, 6H, chain 2-, 3-, 4-CH$_2$), 2.06 (s, 3H, -O$_2$CCH$_3$), 2.20 (s, 3H, 2-CH$_3$), 2.28 (s, 3H, 4-CH$_3$), 2.38 (t, 2H, 5-CH$_2$), 4.08 (t, 2H, J = 7.0 Hz, chain 1-CH$_2$), 4.32 (q, 2H, J = 7.0 Hz, -OCH$_2$CH$_3$), 8.58 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 171.14 (acetate, C = O), 161.79 (pyrrole ester, C = O), 129.39 (pyrrole 2-C), 127.01 (pyrrole 4-C), 121.99 (pyrrole 3-C), 116.92 (pyrrole 5-C), 64.58 (chain 1-C), 59.58 (-OCH$_2$CH$_3$), 30.51 (chain 4-C), 28.64 (chain 3-C), 25.76 (chain 2-C), 23.96 (chain 5-C), 20.96 (-O$_2$CCH$_3$), 14.63 (-OCH$_2$CH$_3$), 11.52 (2-CH$_3$), 10.64 (4-CH$_3$).

Anal. Calcd. for C$_{16}$H$_{25}$NO$_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 65.04; H, 8.61; N, 4.69.

Mass Spectrum (m/e, relative intensity): 295 (M$^+$, 48), 250 (7), 222 (3), 180 (100), 134 (60).
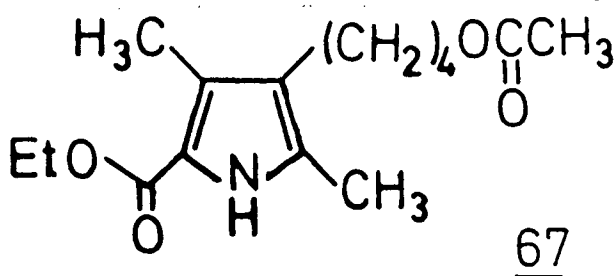
4-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-acetoxybutane 67

4-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-butanol 57 (18.0 g, 75 mmol) was stirred overnight in dichloromethane (100 mL) in the

presence of pyridine (30 mL) and acetic anhydride (35 mL).

The work-up of the reaction was the same as for compound 46 above. The crude product was precipitated from aqueous ethanol to give a white flaky solid (15.8 g, 74.5%). A second crop (2.3 g, 10.8%) was also obtained.

<u>MP</u>: 59.0-60.0°C

<u>^{1}H-NMR</u> (δ, CDCl$_3$): 1.38 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.4-1.8 (m, 4H, chain 2-, 3-CH$_2$), 2.04 (s, 3H, -O$_2$CCH$_3$), 2.21 (s, 3H, 2-CH$_3$), 2.27 (s, 3H, 4-CH$_3$), 2.40 (t, 2H, J = 7 Hz, chain 4-CH$_2$), 4.09 (t, 2H, J = 7.0 Hz, chain 1-CH$_2$), 4.32 (q, 2H, J = 7.0 Hz, -OCH$_2$CH$_3$), 8.78 (bs, 1H, N-H).

<u>^{13}C-NMR</u> (δ, CDCl$_3$): 171.09 (acetate, C = O), 162.11 (pyrrole ester, C = O), 130.00 (pyrrole 2-C), 126.86 (pyrrole 4-C), 121.49 (pyrrole 3-C), 116.96 (pyrrole 5-C), 64.42 (chain 1-C), 59.59 (-OCH$_2$CH$_3$), 28.33, 27.09, (chain, 2-C, 3-C), 23.63 (chain 4-C), 20.90 (-O$_2$CCH$_3$), 14.61 (-OCH$_2$CH$_3$), 11.37 (2-CH$_3$), 10.71 (4-CH$_3$).

<u>Anal</u>. Calcd. for C$_{15}$H$_{23}$NO$_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.11; H, 8.16; N, 4.93.

<u>Mass Spectrum</u> (m/e, relative intensity): 281 (M$^+$, 47), 236 (10), 208 (5), 192 (8), 180 (100), 134 (87).
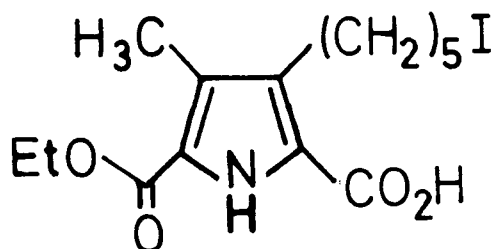
5-(5-Ethoxycarbonyl-2-carboxy-4-methylpyrrol-3-yl)-1-iodopentane 41

5-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-iodopentane 40
(30.0 g, 83 mmol) was dissolved in dichloromethane (250 mL) in a
1-liter Erlenmeyer flask equipped with a magnetic stirrer bar, Claisen
head, pressure-equalizing dropping funnel and nitrogen inlet.
Anhydrous diethyl ether (250 mL) was added. With rapid stirring, a
solution of sulfuryl chloride (21.2 mL, 270 mmol) in dichloromethane
(100 mL) was added dropwise over a period of 15 minutes. The solution
darkened and warmed slightly and was left stirring for a further 15
minutes.

The solvents were removed by rotary evaporation and a 20% water-
acetone solution (300 mL) was added to the residue. The yellow solution
which resulted was refluxed for 45 minutes. After cooling, the acetone
was removed, whereupon the crude product precipitated as a tan solid.

Although tlc (10% EtOAc/CH_2Cl_2) showed no trace of starting
material, ^{1}H-NMR showed that the product was contaminated with the
corresponding "chloropentyl" compound 42. Complete conversion to the
iodide was effected by refluxing the crude product with sodium iodide
(37 g, 0.25 mmol) in acetone (500 mL) for 12 hours. The reaction

mixture was then reduced in volume to approximately half, and addition of water (200 mL) precipitated a brown solid.

The crude product was filtered off, and while still wet, was dissolved in a mixture of methanol (200 mL) and saturated sodium bicarbonate solution (200 mL) by heating on a steam bath. After cooling the solution was extracted with ethyl acetate. The aqueous layer was separated, filtered and acidified with 6M hydrochloric acid which precipitated a cream-colored solid. This was collected by filtration, washed with water and air-dried to give 27.1 g (83.4%).

An analytically pure sample was obtained by one more recrystallization.

MP: 145.0-147.0°C.

^{1}H-NMR (δ, DMSO-d$_6$/CDCl$_3$): 1.37 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.3-2.0 (m, 6H, chain 2-, 3-, 4-CH$_2$), 2.29 (s, 3H, 4-CH$_3$), 2.76 (t, 2H, chain 5-CH$_2$), 3.20 (t, 2H, J = 7.0 Hz, chain 1-CH$_2$), 4.36 (q, 2H, J = 7.0 Hz, -OCH$_2$CH$_3$), 9.52 (bs, 1H, N-H).

Anal. Calcd. for C$_{14}$H$_{20}$NO$_4$I: C, 42.76; H, 5.13; N, 3.56; I, 32.27. Found: C, 42.51; H, 5.11; N, 3.44; I, 32.15.

Mass Spectrum (m/e, relative intensity): 393 (M$^+$, 62), 348 (6), 266 (11), 222 (13), 210 (75), 164 (100), 120 (15).
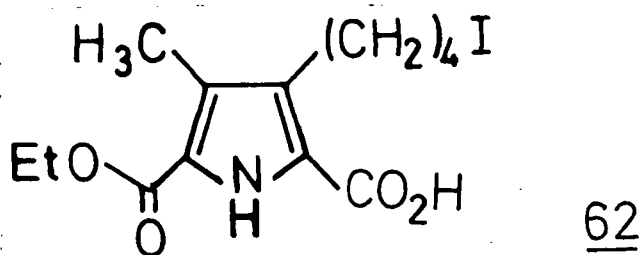
4-(5-Ethoxycarbonyl-2-carboxy-4-methylpyrrol-3-yl)-1-iodobutane   62

This compound was prepared in a similar manner as for compound
41 using 4-(5-ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-iodobutane 60
(8.3 g, 23.6 mmol) and sulfuryl chloride (6.1 mL, 75.6 mmol).

To ensure that the product was not contaminated with any of the
corresponding "chlorobutyl" compound 61, the crude product was dissolved
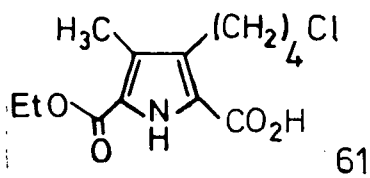
in acetone (250 mL), sodium iodide (4 g, 26 mmol) added and the mixture

refluxed for 13 hours. After cooling, addition of water (200 mL)

precipitated a white solid which was filtered and dried (8.1 g, 90.5%).

The crude product was carried on to the next step without

purification.

MP: 157.0-159.0°C.

^{1}H-NMR (δ, DMSO-d$_6$/CDCl$_3$): 1.30 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.4-

2.0 (m, 4H, chain 2-, 3-CH$_2$), 2.20 (s, 3H, 4-CH$_3$), 2.71 (t, 2H, chain 4-CH$_2$), 3.14 (t, 2H, chain 1-CH$_2$), 4.27 (q, 2H, J = 7.0 Hz, -OCH$_2$CH$_3$), 9.60 (bs, 1H, N-H).

Mass Spectrum (m/e, relative intensity): 379 (M$^+$, 41), 363 (5), 332 (5), 316 (5), 252 (9), 210 (100), 208 (16), 164 (78), 120 (14).
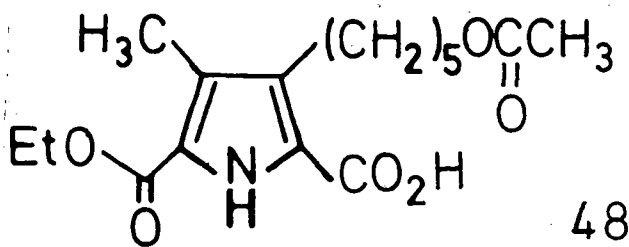
5-(5-Ethoxycarbonyl-2-carboxy-4-methylpyrrol-3-yl)-1-acetoxypentane   48

5-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-acetoxypentane 46 (3.5 g, 12 mmol) was treated with sulfuryl chloride (5.2 g, 38 mmol) as described for compound 41.

After removal of solvents and unreacted sulfuryl chloride, acetone (80 mL) and a solution of sodium bicarbonate (2.8 g) in water (20 mL) were added to the dark red oil residue. The mixture was refluxed for 1 hour then cooled to room temperature. The solution was acidified with acetic acid, water (100 mL) added and the mixture cooled in a freezer. The cream solid which precipitated was collected and dried (3.4 g, 88.0%).

MP: 112.0-115.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.38 (t, 3H, J = 7.0 Hz, -OCH$_2$C$\underline{H}_3$), 1.2-1.9 (m, 6H, chain 2-, 3-, 4-CH$_2$), 2.03 (s, 3H, -O$_2$CC$\underline{H}_3$), 2.28 (s, 3H, 4-CH$_3$), 2.78 (t, 2H, chain 5-CH$_2$), 4.08 (t, 2H, chain 1-CH$_2$), 4.38 (q, 2H, J = 7.0 Hz, -OC$\underline{H}_2$CH$_3$), 9.5 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 171.31 (acetate $\underline{C}$ = O), 160.96 (pyrrole ester $\underline{C}$ = O), 133.68, 126.85, 123.03, 120.46 (pyrrole 2-, 3-, 4-, 5-C), 64.60 (chain 1-C), 60.77 (-O$\underline{C}$H$_2$CH$_3$), 30.14 (chain 4-C), 28.50 (chain 3-C), 25.77 (chain 2-C), 24.40 (chain 5-C), 20.96 (-O$_2$C$\underline{C}$H$_3$), 14.41 (-OCH$_2$$\underline{C}H_3$), 10.04 (4-CH$_3$).

<u>Anal</u>. Calcd. for C$_{16}$H$_{23}$NO$_6$: C, 59.06; H, 7.12; N, 4.31. Found: C, 58.93; H, 7.19; N, 4.31.

<u>Mass Spectrum</u> (m/e, relative intensity): 325 (M$^+$, 100), 309 (6), 307 (7), 281 (26), 265 (27), 236 (21), 220 (30), 210 (80), 192 (23), 166 (38), 164 (100).

<u>5-(5-Ethoxycarbonyl-2-iodo-4-methylpyrrol-3-yl)-1-iodopentane</u> 43

5-(5-Ethoxycarbonyl-2-carboxy-4-methylpyrrol-3-yl)-1-iodopentane

<u>41</u> (13.4 g, 34 mmol) and sodium bicarbonate (11.4 g, 136 mmol) were suspended in a mixture of water (150 mL) and dichloroethane (80 mL) in a 1-liter Erlenmeyer flask, and heated on a steam bath until all the solid dissolved.

The mixture was cooled to room temperature and vigorously stirred while a solution of potassium iodide (16.9 g, 102 mmol) and iodine (9.5 g, 37 mmol) in water (80 mL) was rapidly added dropwise. The solution was refluxed for 30 minutes and the excess iodine was destroyed by the addition of a sodium bisulfite solution. (The color of the solution changed from deep purple to straw yellow).

The solution was cooled and dichloromethane (100 mL) added. The organic phase was separated, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The crude product was dissolved in hot ethanol (100 mL) and water was added until crystallization began. The solid which precipitated was filtered, washed with 50% ethanol/water and air-dried to give a slightly yellow solid (13.6 g, 84.3%).

<u>MP</u>: 92.0-93.5°C.

^{1}H-NMR (δ, CDCl$_3$): 1.38 (t, 3H, J = 7.0 Hz, -OCH$_2$C$\underline{H}_3$), 1.3-2.0 (m, 6H, chain 2-, 3-, 4-CH$_2$), 2.32 (s, 3H, 4-CH$_3$), 2.39 (t, 2H, chain 5-CH$_2$), 3.21 (t, 2H, J = 7.0 Hz, chain 1-CH$_2$), 4.36 (q, 2H, J = 7.0 Hz, -OC$\underline{H}_2$CH$_3$), 8.84 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 160.98 ($\underline{C}$ = 0), 130.23 (pyrrole 3-C), 126.39 (pyrrole 4-C), 124.01 (pyrrole 5-C), 73.46 (pyrrole 2-C), 60.31 (-O$\underline{C}$H$_2$CH$_3$),

33.39 (chain 2-C), 30.17 (chain 4-C), 29.11 (chain 3-C), 26.30 (chain 5-C), 14.55 (-OCH$_2$CH$_3$), 19.98 (4-CH$_3$), 6.70 (chain 1-C).

<u>Anal</u>. Calcd. for C$_{13}$H$_{19}$NO$_2$I$_2$: C, 32.86; H, 4.03; N, 2.95; I, 53.42. Found: C, 32.64; H, 3.84; N, 2.78; I, 53.38.

<u>Mass Spectrum</u> (m/e, relative intensity): 475 (M$^+$, 100), 430 (8), 348 (15), 292 (60), 246 (68), 166 (47).

<u>4-(5-Ethoxycarbonyl-2-iodo-4-methylpyrrol-3-yl)-1-iodobutane</u> <u>63</u>

This was prepared in the same way as for <u>43</u>, from 4-(5-ethoxycarbonyl-2-carboxy-4-methylpyrrol-3-yl)-1-iodobutane <u>62</u> (6.4 g, 17 mmol). After work-up the crude brown product was recrystallized once from hot ethanol to yield 6.6 g (85.5%), which was carried to the next stage without further purification.

^{1}<u>H-NMR</u> (δ, CDCl$_3$): 1.36 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.5-2.0 (m, 4H, chain 2-, 3-CH$_2$), 2.31 (s, 3H, 4-CH$_3$), 2.38 (t, 2H, chain 2-CH$_2$), 3.21 (t, 2H, J = 7.0 Hz, chain 1-CH$_2$), 4.33 (q, 2H, J = 7.0 Hz, -OCH$_2$CH$_3$),

8.86 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 160.92 ($\underline{C}$ = 0), 129.75 (pyrrole 3-C), 126.35 (pyrrole 4-C), 124.04 (pyrrole 5-C), 73.53 (pyrrole 2-C), 60.32 (-O$\underline{C}$H$_2$CH$_3$), 32.94 (chain 2-C), 30.91 (chain 3-C), 25.40 (chain 4-C), 14.52 (-OCH$_2$$\underline{C}H_3$), 10.95 (4-CH$_3$), 6.65 (chain 1-4).
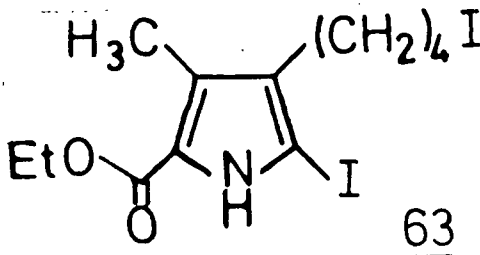
Mass Spectrum (m/e, relative intensity): 461 (M$^+$, 83), 416 (6), 334 (5), 292 (60), 246 (100), 207 (69), 166 (60), 120 (39).
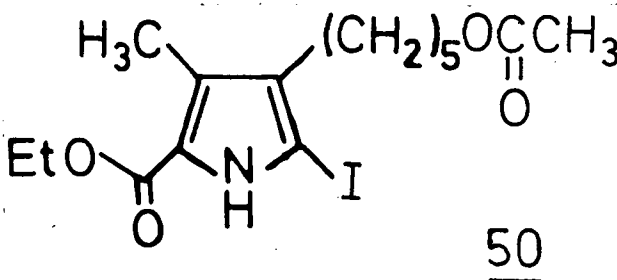
5-(5-Ethoxycarbonyl-2-iodo-4-methylpyrrol-3-yl)-1-acetoxypentane   50

This compound was prepared from 5-(5-ethoxycarbonyl)-2-carboxy-4-methylpyrrol-3-yl)-1-acetoxypentane $\underline{48}$ (3.4 g, 10.5 mmol) exactly as outlined for compound $\underline{43}$. The crude product was recrystallized from 50% ethanol/water (150 mL) to yield pure product (3.3 g, 76.9%).

MP: 79.0-80.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.35 (t, 3H, J = 7.0 Hz, -OCH$_2$C$\underline{H}_3$), 1.2-1.8 (m, 6H, chain 2-, 3-, 4-CH$_2$), 2.00 (s, 3H, -O$_2$CC$\underline{H}_3$), 2.28 (s, 3H, 4-CH$_3$), 2.38

(t, 2H, chain 5-CH$_2$), 4.08 (t, 2H, chain 1-CH$_2$), 4.33 (q, 2H, J = 7.0 Hz,

-OCH$_2$CH$_3$), 8.95 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 171.14 (acetate $\underline{C}$ = O), 160.88 (pyrrole ester

$\underline{C}$ = O), 130.36 (pyrrole 3-C), 126.46 (pyrrole 4-C), 124.01 (pyrrole 5-C),

73.20 (pyrrole 2-C), 64.53 (chain 1-C), 60.24 (-O$\underline{C}$H$_2$CH$_3$), 29.85 (chain

4-C), 28.55 (chain 3-C), 26.40 (chain 2-C), 25.62 (chain 5-C), 20.97

(-O$_2$C$\underline{C}$H$_3$), 14.54 (-OCH$_2$$\underline{C}H_3$), 10.97 (4-CH$_3$).

Anal. Calcd. for C$_{15}$H$_{22}$NO$_4$I: C, 44.24; H, 5.45; N, 3.44; I, 31.16.
Found: C, 44.46; H, 5.43; N, 3.41; I, 31.00.

Mass Spectrum (m/e, relative intensity): 407 (M$^+$, 77), 361 (8), 292

(80), 280 (8), 246 (100), 234 (29), 220 (32), 192 (22), 174 (19), 166

(46), 120 (43).

5-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-iodopentane 44

Method A

5-(5-Ethoxycarbonyl-2-iodo-4-methylpyrrol-3-yl)-1-iodopentane 43

(22.7 g, 47.8 mmol) was dissolved in ethanol (250 mL) by heating on a steam-bath. A solution of potassium iodide (12.7 g, 76.5 mmol) in water (20 mL) and concentrated hydrochloric acid (20 mL) was added, the solution darkening as iodine was liberated. Addition of hypophosphorous acid (20 mL) lightened the color as it destroyed the liberated iodine. Heating was continued for a further 15 minutes.

Water (250 mL) was added and the cloudy pink solution was extracted with ethyl-acetate (100 mL). The organic layer was dried over anhydrous magnesium sulfate, and after filtering and removing the solvent, a pink solid was obtained.

The crude product was placed on a silica gel column (Merck Kieselgel 60H, 120 g) and eluted with dichloromethane. The colored impurities remained at the origin, while the product was obtained as a slightly orange solid (14.6 g, 87.5%).

Method B

5-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-pentylmethanesulfonate 53 (3.6 g, 11.4 mmol) and sodium iodide (6.8 g, 45.4 mmol) were refluxed in acetone (100 mL) for 2.5 hours. About half the volume of acetone was removed by rotary evaporation. Addition of water (50 mL) precipitated a yellow solid which was filtered and dried and used without further purification.

MP: 74.0-75.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.35 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.49 and 1.86 (m, 6H, chain 2-, 3-, 4-CH$_2$), 2.28 (s, 3H, 4-CH$_3$), 2.42 (t, 2H, chain

5-CH$_2$), 3.20 (t, 2H, J = 7.0 Hz, chain 1-CH$_2$), 4.32 (q, 2H, J = 7.0 Hz,

-OCH$_2$CH$_3$), 6.67 (d, 1H, J = 3 Hz, 2-H), 8.76 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 161.85 (C = O), 125.89 (pyrrole 3-C), 125.29

(pyrrole 4-C), 119.73 (pyrrole 2-C), 119.41 (pyrrole 5-C), 59.81 (-OCH$_2$CH$_3$),

33.44 (chain 2-C), 30.28 (chain 4-C), 29.25 (chain 3-C), 24.83 (chain

5-C), 14.55 (-OCH$_2$CH$_3$), 10.31 (4-CH$_3$), 6.78 (chain 1-C).

Anal. Calcd. for C$_{13}$H$_{20}$NO$_2$I: C, 44.71; H, 5.77; N, 4.01; I, 36.34.
Found: C, 44.59; H, 5.66; N, 3.89; I, 36.12.

Mass Spectrum (m/e, relative intensity): 349 (M$^+$, 27), 304 (7), 222

(57), 194 (3), 166 (55), 120 (100).

4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-iodobutane   64

Method A

4-(5-Ethoxycarbonyl-2-iodo-4-methylpyrrol-3-yl)-1-iodobutane 63

(7.3 g, 16 mmol) was dissolved in ethanol (100 mL) by heating on a

steam-bath. The solution was removed from the steam-bath and hydriodic

acid (25 mL) added. The liberated iodine was destroyed by addition

of hypophosphorous acid (10 mL). Tlc (5% EtOAc/Toluene) showed that

about 50% reaction had occurred with no sign of intramolecular cycli-

zation.

More hydriodic acid (20 mL) and hypophosphorous acid (10 mL) was

added, tlc then showing only a trace of starting material. A third

portion of hydriodic acid (10 mL) was added and the solution left stand-

ing for 1 hour. Water (100 mL) was added to the reaction mixture and

the dark red solid which precipitated was filtered and dried.

The crude product was placed on a silica gel column (BDH SiO$_2$ 60-120

mesh, 150 g) and eluted with dichloromethane. At first the eluant was

colorless and was shown by tlc to contain only the desired product 64.

These fractions were combined and evaporated to give 2.3 g (43.4%).

65

Increasing the polarity of the eluant to 10% EtOAc/CH$_2$Cl$_2$ gave

fractions which were orange colored and contained not only the desired

product 64, but also the unwanted contaminant 65. This impure material

(2.1 g) was retained.

Method B

4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-butylmethanesulfonate

74 (14.2 g, 47 mmol) and sodium iodide were dissolved in acetone (200 mL)

and refluxed with stirring for 18.5 hours.

The solution was cooled and the precipitated solid removed by

filtration. The filtrate was evaporated and the resultant dark brown oil was dissolved in ethyl acetate (100 mL). The solution was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated. The crude product was obtained as a brown oil which slowly solidified.

The crude product was placed on a silica gel column (BDH SiO_2 60-120 mesh, 200 g) and eluted with dichloromethane. The first fractions were colorless and contained the desired pure product 64. These were combined and evaporated to give 6.3 g,(40.1%) of a slightly yellow solid.

Increasing polarity to 10% EtOAc/CH_2Cl_2 eluted orange colored fractions. Tlc showed that these contained not only the product 64 but also the unwanted impurity 65. This impure material was collected (5.8 g).

MP: 68.5-70.0°C.

^{1}H-NMR (δ, $CDCl_3$): 1.38 (t, 3H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.5-2.1 (m, 4H, chain 2-, 3-CH$_2$), 2.31 (s, 3H, 4-CH$_3$), 2.47 (t, 2H, chain 4-CH$_2$), 3.24 (t, 2H, J = 7.0 Hz, chain 1-CH$_2$), 4.36 (q, 2H, J = 7.0 Hz, -OCH$_2$CH$_3$), 6.72 (d, 1H, J = 3 Hz, 2-H), 8.8 (bs, 1H, N-H).

^{13}C-NMR (δ, $CDCl_3$): 161.87 (C = O), 125.90 (pyrrole 3-C), 124.85 (pyrrole 4-C), 119.78 (pyrrole 2-, 5-C), 59.86 (-OCH$_2$CH$_3$), 33.16 (chain 2-C), 31.15 (chain 3-C), 23.95 (chain 4-C), 14.54 (-OCH$_2$CH$_3$), 10.34 (4-CH$_3$), 6.68 (chain 1-C).

Anal. Calcd. for $C_{12}H_{18}NO_2I$: C, 43.00; H, 5.41; N, 4.18; I, 37.86.

Found: C, 43.16;   H, 5.31;   N, 4.14;   I, 37.77.

<u>Mass Spectrum</u> (m/e, relative intensity): 335 (M$^+$, 44), 290 (7), 208 (27), 166 (85), 162 (12), 134 (17), 120 (100).

H$_3$C ― (CH$_2$)$_5$OCCH$_3$
EtO ― N ― H   52
O   H

<u>5-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-acetoxypentane</u>   <u>52</u>

5-(5-Ethoxycarbonyl-2-iodo-4-methylpyrrol-3-yl)-1-acetoxypentane <u>50</u> (3.8 g, 9.4 mmol) was dissolved in glacial acetic acid (25 mL). With stirring, hydriodic acid (20 mL) was added, the solution instantly turning dark red due to liberated iodine. The color was discharged by addition of hypophosphorous acid (20 mL) to give a yellow solution which was stirred for 30 minutes. Tlc (10% EtOAc/CH$_2$Cl$_2$) showed two spots – the faster running material due to the desired product and the slower material due to product with the acetate removed.

The reaction mixture was approximately neutralized with potassium hydroxide solution, then extracted with ethyl acetate (100 mL). The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated to get a yellow oil.

The crude product was dissolved in dichloromethane (100 mL) and

acetic anhydride (10 mL) and pyridine (10 mL) added. The mixture was stirred for 3 hours to reconvert all the product to the acetate. After work-up the crude acetate was placed on a column (Kieselgel 60, 150 g) and eluted with 10% EtOAc/CH$_2$Cl$_2$. The product came off cleanly, fractions showing a single spot on tlc were combined and evaporated to give a yellow oil which solidified to a light yellow solid (2.1 g, 80.4%).

MP: 43.0-45.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.35 (t, 3H, J = 7.2 Hz, -OCH$_2$CH$_3$), 1.2-1.8 (m, 6H, chain 2-, 3-, 4-CH$_2$), 2.04 (s, 3H, -O$_2$CCH$_3$), 2.28 (s, 3H, 4-CH$_3$), 2.43 (bt, 2H, chain 5-CH$_2$), 4.08 (t, 2H, J = 6.6 Hz, chain 1-CH$_2$), 4.33 (q, 2H, J = 7.2 Hz, -OCH$_2$CH$_3$), 6.68 (d, 1H, J = 3 Hz, 2-H), 8.83 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 171.15 (acetate $\underline{C}$ = O), 161.77 (pyrrole ester, $\underline{C}$ = O), 125.96 (pyrrole 3-C), 125.54 (pyrrole 4-C), 119.54 (pyrrole 2-C), 119.11 (pyrrole 5-C), 64.54 (chain 1-C), 59.80 (-O$\underline{C}$H$_2$CH$_3$), 29.99 (chain 4-C), 28.55 (chain 3-C), 25.72 (chain 2-C), 24.90 (chain 5-C), 20.97 (-O$_2$C$\underline{C}$H$_3$), 14.55 (-OCH$_2$$\underline{C}H_3$), 10.27 (4-CH$_3$).

Anal. Calcd. for C$_{15}$H$_{23}$NO$_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.29; H, 8.36; N, 4.90.

Mass Spectrum (m/e, relative intensity): 281 (M$^+$, 44), 236 (10), 221 (5), 208 (6), 192 (14), 167 (65), 166 (91), 120 (100).

$$H_3C \overset{\textstyle (CH_2)_4 O \overset{O}{\underset{\|}{C}} CH_3}{\diagdown}$$

EtO $\underset{\underset{O}{\|}}{C}$ N H $\underset{H}{}$ $\underline{72}$
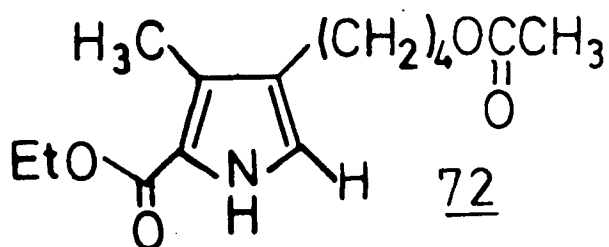
4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-acetoxybutane   72

(a)   Trichlorination

4-(5-Ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-1-acetoxybutane   67

(7.0 g, 24.9 mmol) was treated with sulfuryl chloride (6.4 mL, 79.5 mmol)

and worked-up as described for compound 48.

After refluxing in basic aqueous acetone the solution was cooled

to room temperature and acidified with 6M hydrochloric acid.   The

acetone was removed and the aqueous solution was extracted with dichloro-

methane (200 mL).   The organic layer was separated, dried over anhydrous

sodium sulfate, filtered and concentrated to 20 mL.   Addition of

hexanes (200 mL) precipitated a light tan solid which was collected and

dried.   This crude product was carried to the next stage without

purification or characterization.

(b)   Iodinative Decarboxylation

This step was carried out exactly as for compound 50.   The crude

product was obtained as a dark brown oil which was carried on to the

next stage.

(c) De-iodination

The above product was dissolved in glacial acetic acid (25 mL).
Hydriodic acid (20 mL) was added and the liberated iodine was destroyed
by addition of hypophosphorous acid (20 mL). The reaction mixture was
stirred for 1 hour at which point tlc (10% EtOAc/CH$_2$Cl$_2$) indicated
complete reaction. As before tlc indicated some loss of the acetate
group.

The reaction mixture was roughly neutralized with potassium
hydroxide solution and extracted with dichloromethane (200 mL). The
organic layer was washed with saturated sodium bicarbonate solution and
saturated sodium chloride solution, dried over anhydrous sodium sulfate,
filtered and concentrated to 50 mL. Acetic anhydride (5 mL) and
pyridine (5 mL) were added and the solution stirred overnight.

The solution was extracted with 3M hydrochloric acid (40 mL) and
saturated sodium bicarbonate solution. The organic layer was dried
over anhydrous sodium sulfate, filtered and evaporated to get a dark
brown oil.

The crude product was placed on a column (Kieselgel 60, 150 g)
and eluted with 10% EtOAc/CH$_2$Cl$_2$. Evaporation of the eluant gave a
light brown oil which crystallized (3.7 g, 55.5%).

MP: 48.0-50.0 °C.

^{1}H-NMR (δ, CDCl$_3$): 1.36 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 1.5-1.7 (m, 4H,
chain 2-, 3-CH$_2$), 2.05 (s, 3H, -O$_2$CCH$_3$), 2.29 (s, 3H, 4-CH$_3$), 2.49
(t, 2H, 4-CH$_2$), 4.01 (t, 2H, chain 1-CH$_2$), 4.33 (q, 2H, J = 7 Hz,

-OC$\underline{H}_2$CH$_3$), 6.69 (d, 1H, J = 3 Hz, 2-H), 8.9 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 171.14 (acetate $\underline{C}$ = 0), 161.89 (pyrrole ester $\underline{C}$ = 0), 125.87 (pyrrole 3-C), 125.03 (pyrrole 4-C), 119.48 (pyrrole 20C), 119.10 (pyrrole 5-C), 64.40 (chain 1-C), 59.79 (-O$\underline{C}$H$_2$CH$_3$), 28.36 (chain 3-C), 26.68 (chain 2-C), 24.63 (chain 4-C), 20.91 (-O$_2$C$\underline{C}$H$_3$), 14.56 (-OCH$_2$$\underline{C}H_3$), 10.31 (4-CH$_3$).

<u>Anal</u>. Calcd. for C$_{14}$H$_{21}$NO$_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.18; H, 7.80; N, 5.24.

<u>Mass Spectrum</u> (m/e, relative intensity): 267 (M$^+$, 59), 224 (4), 222 (11), 207 (4), 194 (4), 179 (19), 166 (98), 134 (21), 120 (100).

5-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-triphenylphosphoniumpentane iodide   (n = 5)   94a

A mixture of 5-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)-1-iodo-pentane <u>44</u> (7.2 g, 21 mmol) and triphenylphosphine (16.5 g, 60 mmol) in toluene (250 mL) was refluxed under argon for 25 hours. As the reaction proceeded the product precipitated from solution as a cream

solid. After 25 hours, tlc (25% EtOAc/Tol) showed no trace of the starting pyrrole.

The reaction mixture was cooled to room temperature. The solid product was collected by filtration, washed with diethyl ether and dried to yield 12.2 g (96.6%). This crude product was used without purification. An analytical sample was prepared by chromatography on silica gel with 10% MeOH/CH$_2$Cl$_2$ as eluant.

<u>MP</u>: 191.0-193.0°C.

^{1}<u>H-NMR</u> (δ, CDCl$_3$): 1.34 (t, 3H, J = 7.0 Hz, -OCH$_2$C<u>H</u>$_3$) , 1.4-1.8 (m, 6H, chain 2-, 3-, 4-CH$_2$), 2.21 (s, 3H, 4-CH$_3$), 2.36 (m, 2H, chain 5-CH$_2$), 3.4-3.6 (m, 2H, chain 1-CH$_2$), 4.30 (q, 2H, J = 7.0 Hz, -OC<u>H</u>$_2$CH$_3$), 6.76 (d, 1H, J = 3.0 Hz, 2-H), 7.6-8.0 (m, 15H, C$_6$<u>H</u>$_5$), 8.86 (bs, 1H, N-H).

^{13}<u>C-NMR</u> (δ, CDCl$_3$): 161.61 (<u>C</u> = O), 135.23 (d, J = 2.4 Hz, phenyl 4-C), 138.68 (d, J = 10.4 Hz, phenyl 2-C), 130.67 (d, J = 12.2 Hz, phenyl 3-C), 125.89 (pyrrole 3-C), 124.66 (pyrrole 4-C), 120.52 (pyrrole 2-C), 119.00 (pyrrole 5-C), 118.10 (d, J = 86.0 Hz, phenyl 1-C), 59.65 (-OC<u>H</u>$_2$CH$_3$), 30.46 (chain 4-C), 30.03 (d, J = 17.2 Hz, chain 3-C), 24.47 (chain 5-C), 23.20 (d, J = 51.0 Hz, chain 2-C), 14.61 (-OCH$_2$<u>C</u>H$_3$), 10.32 (4-CH$_3$).

<u>Anal</u>. Calcd. for C$_{31}$H$_{35}$NO$_2$PI: C, 60.87; H, 5.77; N, 2.29; I, 20.75. Found: C, 60.57; H, 5.80; N, 2.27; I, 20.87.

4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-triphenylphosphoniumbutane

iodide   (n = 4)   **94b**

4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-iodobutane __64__ (3.3 g,

9.7 mmol) and triphenylphosphine (10.2 g, 40 mmol) were dissolved in

toluene (70 mL) and refluxed while stirring under nitrogen for 19.5

hours. As the reaction proceeded a purple oil separated from solution.

When tlc (10% EtOAc/Tol) indicated complete consumption of starting

material the solution was cooled to room temperature and the supernatant

liquid was decanted. The oil was triturated with diethyl ether but no

solid developed.

The crude product was placed on a silica gel column (Merck

Kieselgel 60, 200 g) and eluted with 5% MeOH/CH_2Cl_2. The colored

impurities were retained at the head of the column and the product was

collected as a clear oil which was dried under vacuum (5.0 g, 86.2%).

__MP__: 103-106°C.

^{1}__H-NMR__ (δ, $CDCl_3$): 1.36 (t, 3H, J = 7.0 Hz, $-OCH_2C\underline{H}_3$), 1.5-2.0 (m, 4H,

chain 2-, 3-CH_2), 2.18 (s, 3H, 4-CH_3), 2.46 (t, 2H, chain 4-CH_2), 3.5-

3.8 (m, 2H, chain 1-CH_2), 4.32 (q, 2H, J = 7.0 Hz, $-OC\underline{H}_2CH_3$), 6.84

(d, 1H, J = 3.0 Hz, 2-H), 7.6-7.9 (m, 15H, $C_6\underline{H}_5$), 9.00 (bs, 1H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 161.63 ($\underline{C}$ = 0), 135.21 (d, J = 2.2 Hz, phenyl 4-C), 133.67 (d, J = 10.0 Hz, phenyl 2-C), 130.64 (d, J = 12.8 Hz, phenyl 3-C), 125.98 (pyrrole 3-C), 123.73 (pyrrole 4-C), 120.78 (pyrrole 2-C), 119.10 (pyrrole 5-C), 118.09 (d, J = 86.2 Hz, phenyl 1-C), 59.72 (-O$\underline{C}$H$_2$CH$_3$), 30.35 (d, J = 15.4 Hz, chain 3-C), 24.13, 21.74 (chain 2-, 4-C), 22.94 (d, 47.8 Hz, chain 1-C), 14.63 (-OCH$_2\underline{C}$H$_3$), 10.40 (4-CH$_3$).

$\underline{Anal}$. Calcd. for C$_{30}$H$_{33}$NO$_2$PI: C, 60.31; H, 5.57; N, 2.34; I, 21.24. Found: C, 60.47; H, 5.64; N, 2.14; I, 21.10.

3.3 SYNTHESES OF AROMATIC BIS-ALDEHYDES 95, 131 AND THEIR PRECURSORS

2,6-Bis(hydroxymethyl)-4-methylphenol 97

This compound was prepared by the method described by Cram et al.[187]

A mixture of p-cresol (40 g, 0.37 mol) and potassium carbonate (60 g, 0.43 mol) in water (600 mL) was heated to 50°C and stirred under argon. Aqueous formaldehyde solution (37%, 120 mL, 1.48 mol) was added dropwise over a period of 10 minutes. The solution was then maintained at 50°C for a further 3.5 hours.

The heating was removed and carbon dioxide was bubbled through the clear yellow solution until it turned very cloudy. The solution was then extracted with ethyl acetate (2 x 200 mL). The ethyl acetate washings were combined, dried over anhydrous sodium sulfate, filtered and evaporated to give a viscous yellow oil which solidified on cooling. This crude product was recrystallized from ethyl acetate (150 mL) to give a white solid (24.8 g, 39.9%).

MP: 123.0-124.5°C; Lit.[187] 123-124°C.

^{1}H-NMR (δ, Me_2CO-d_6/DMSO-d_6): 2.23 (s, 3H, Ar$\underline{CH}_3$), 3.25 (s, 4H, -$\underline{CH}_2$OH),

4.68 (bs, 2H, -CH$_2$O$\underline{H}$), 6.97 (s, 2H, Ar$\underline{H}$).

<u>Anal</u>. Calcd. for C$_9$H$_{12}$O$_3$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.05.

<u>Mass Spectrum</u> (m/e, relative intensity): 168 (M$^+$, 65), 150 (74), 149 (60), 122 (51), 121 (100), 107 (51), 91 (47), 79 (51), 77 (51).

<u>2,6-Bis(hydroxymethyl)-4-methylanisole</u> <u>98</u>

This compound was prepared by the method described by Cram et al.[187]

A mixture of 2,6-bis(hydroxymethyl)-4-methylphenol <u>97</u> (5.0 g, 29.8 mmol), potassium carbonate (6.2 g, 45 mmol) and dimethyl sulfate (3.3 mL, 35.3 mmol) in spectral grade acetone (100 mL) was stirred under nitrogen at room temperature for 24 hours.

The reaction mixture was filtered and the acetone removed. The residue was dissolved, with difficulty, in ethyl acetate (50 mL) and water (50 mL), and the organic layer was washed with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate and filtering, the solvent was removed to give a white solid. This was

crystallized from dichloromethane (150 mL) to yield colorless needles (4.1 g, 75.5%).

Four other reactions on similar scales and under the same conditions gave yields of 22.5, 37.1, 42.1 and 61.4%.

MP: 105.0-107.0°C; Lit.[187] 103-104°C.

^{1}H-NMR (δ, acetone-d_6): 2.27 (s, 3H, ArCH$_3$), 3.73 (s, 3H, -OCH$_3$), 4.60 (bs, 4H, -CH$_2$OH), 7.17 (s, 2H, ArH).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.83; H, 7.66.

Mass Spectrum (m/e, relative intensity): 182 (M$^+$, 100), 163 (18), 151 (19), 149 (35), 147 (19), 135 (41), 123 (27), 121 (24), 119 (16), 105 (31), 91 (47), 79 (17), 77 (37).

2,6-Diformyl-4-methylanisole 95

Oxalyl chloride (3.5 mL, 10 mmol) was added to freshly distilled

dichloromethane (200 mL) in an oven-dried 3-neck flask equipped with nitrogen inlet, pressure-equalizing dropping funnel and drying tube. The solution was cooled to -78 °C in a dry ice/acetone bath.

A solution of dimethyl sulfoxide (5.2 mL, 73 mmol) in dichloromethane (10 mL) was added dropwise over a period of 5 minutes. The solution was left stirring for 5 minutes. A solution of 2,6-bis(hydroxymethyl)-4-methylanisole 98 (3.01 g, 17 mmol) in dimethyl sulfoxide (5 mL) and dichloromethane (20 mL) was then added dropwise. After stirring for 15 minutes, triethylamine (23 mL, 165 mmol) was added and the reaction mixture was allowed to warm gradually to room temperature.

Addition of water (20 mL) and removal of the dichloromethane on a rotary evaporator led to the precipitation of a waxy solid which was filtered and dried (2.74 g, 93.1%).

The crude product was recrystallized from 1:1 carbon tetrachloride/cyclohexane to yield a first crop of white needles (1.51 g, 51.5%). A second crop (0.57 g, 19.4%) was obtained from the mother liquid.

MP: 91.5-92.5°C: Lit.[187] 88-89°C.

^{1}H-NMR (δ, CDCl$_3$): 2.43 (s, 3H, ArCH$_3$), 4.07 (s, 3H, -OCH$_3$), 7.92 (s, 2H, ArH), 10.42 (s, 2H, CHO).

^{13}C-NMR (δ, CDCl$_3$): 188.54 (C = O), 163.60 (1-C), 135.36 (3,5-C), 134.96 (2,6-C), 129.84 (4-C), 66.71 (-OCH$_3$), 20.52 (-CH$_3$).

Mass Spectrum (m/e, relative intensity): 178 (M$^+$, 100), 150 (35), 149 (35), 132 (38), 119 (27), 105 (35), 91 (43), 77 (57).

$$OCH_3$$

ClH$_2$C— —CH$_2$Cl

133 OCH$_3$

2,5-Bis(chloromethyl)-1,4-dimethoxybenzene 133

This compound was prepared by the method of Wood and Gibson.[206]

A 1-liter three-neck flask was equipped with gas bubbler, dropping

funnel and mechanical stirrer, and was charged with 1,4-dimethoxybenzene

(51.5 g, 0.37 mmol), p-dioxane (300 mL) and concentrated hydrochloric

acid (50 mL). Hydrogen chloride gas was bubbled through the solution

and three portions- (25 mL each) of 37% formaldehyde solution were

added at 30 minute intervals. Stirring and gas addition was continued

for 3 hours after the last formaldehyde addition. The solution was

then left standing overnight.

The white solid which precipitated was filtered and washed with

water, and was recrystallized from acetone (50.1 g, 57.2%).

MP: 158.0–160.0°C; Lit.[206] 167.0–167.5°C.

Anal. Calcd. for C$_{10}$H$_{12}$Cl$_2$O$_2$: C, 51.08; H, 5.15; Cl, 30.16. Found:

C, 50.88; H, 5.14; Cl, 30.05.

Mass Spectrum (m/e, relative intensity): 236 (45), 234 (70), 221 (9),

219 (7), 201 (34), 199 (100), 171 (15), 160 (20), 144 (36), 91 (24).

134

2,5-Bis(acetoxymethyl)-1,4-dimethoxybenzene 134

This compound was prepared by the method of Marx et al.[207]

2,5-Bis(chloromethyl)-1,4-dimethoxybenzene 133 (25.0 g, 0.11 mmol),

anhydrous sodium acetate (32.3 g, 0.39 mol) and glacial acetic acid

(300 mL) were placed in a 1-liter two-neck flask. The mixture was

stirred and refluxed for 18 hours.

After cooling the reaction mixture was poured into water (1.5 L).

The white precipitate was filtered, dried and recrystallized from

methanol (26.9 g, 89.7%).

MP: 114.0-116.0°C; Lit.[207] 116-118°C.

^{1}H-NMR (δ, CDCl$_3$): 2.12 (s, 6H, -O$_2$CC$\underline{H}_3$), 3.83 (s, 6H, -OC$\underline{H}_3$), 5.13

(s, 4H, -C$\underline{H}_2$OAc), 6.88 (s, 2H, Ar$\underline{H}$).

^{13}C-NMR (δ, CDCl$_3$): 170.82 ($\underline{C}$ = O), 151.50 (1,4-C), 125.23 (2,5-C),

113.03 (3,6-C), 61.48 (-OC$\underline{H}_3$), 56.28 (-C$\underline{H}_2$OAc), 20.97 (-O$_2$CC$\underline{H}_3$).

<u>Anal</u>. Calcd. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.85; H, 6.42.

<u>Mass Spectrum</u> (m/e, relative intensity): 236 (45), 234 (70), 221 (9), 219 (7), 201 (34), 199 (100), 171 (13), 169 (20), 144 (36), 91 (24).

<u>2,5-Bis(hydroxymethyl)-1,4-dimethoxybenzene</u> <u>135</u>

2,5-Bis(acetoxymethyl)-1,4-dimethoxybenzene <u>134</u> (15.0 g, 53 mmol) was suspended in methanol (100 mL) and 10% sodium hydroxide solution (60 mL), and the mixture was refluxed for 4 hours. Tlc showed complete consumption of starting material.

The reaction was allowed to cool to room temperature. The solid which crystallized out was filtered and dried (8.6 g, 81.9%) and used without further purification.

<u>MP</u>: 159.0-160.5°C; Lit.[207] 164-165°C.

<u>Anal</u>. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.71; H, 7.12.

(m/e, relative intensity): 198 (M$^+$, 100), 151 (14), 139 (19), 137 (19), 125 (26), 110 (14).

OCH₃ structure

OHC—[benzene ring with OCH₃ top and OCH₃ bottom]—CHO

131

2,5-Bisformyl-1,4-dimethoxybenzene 131

Oxalyl chloride (3.1 g, 24 mmol) was added to dichloromethane (200 mL) in a 3-neck flask equipped with nitrogen inlet, pressure-equaliz-ing addition funnel, magnetic stirrer bar and drying tube. Stirring under nitrogen, the solution was cooled to -70°C in a dry-ice/acetone bath. Dimethyl sulfoxide (3.5 g, 44 mmol) was added dropwise and the solution then left stirring for 5 minutes. Carbon dioxide evolution was observed.

2,5-Bis(hydroxymethyl)-1,4-dimethoxybenzene 135 (2.0 g, 10 mmol) was dissolved in 2:1 dimethyl sulfoxide/dichloromethane (15 mL) and added dropwise to the oxidizing solution over a period of 5 minutes. After stirring for 15 minutes, triethylamine (14 mL, 0.1 mmol) was added, a bright yellow color immediately being formed.

The solution was allowed to warm to room temperature before water (20 mL) was added to quench the reaction. Removal of the dichloromethane precipitated a bright yellow solid, which was filtered and dried (1.83 g, 93.7%). The crude product was purified by vacuum sublimation.

<u>MP</u>: 203.0–205.0°C; Lit. 205–209°C,[207] 205°C.[231]

<u>Anal</u>. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.58; H, 5.20.

<u>Mass Spectrum</u> (m/e. relative intensity): 194 (M^+, 100), 179 (20), 176 (10), 151 (16), 148 (20).

3.4 SYNTHESES OF CHAIN-LINKED BIS-PYRROLES

Bis[5-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)pentyl]sulfide (n = 5) 75a

5-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-iodopentane 44 (6.7 g, 19 mmol) was dissolved in tetrahydrofuran (100 mL). A solution of sodium sulfide (7.0 g, 30 mmol) in water (40 mL) was added and the mixture was stirred and refluxed for 18 hours. At this stage tlc (10% EtOAc/CH$_2$Cl$_2$) showed the presence of some unconsumed starting material. Refluxing was continued and small amounts of sodium sulfide were added until reaction was complete (28 hours).

The tetrahydrofuran was removed on a rotary evaporator causing the product to separate out as a yellow oil. Sufficient acetone was added to obtain a homogeneous solution and addition of an equal volume of water led to the precipitation of a white solid. This was collected and dried (4.4 g, 97%) and used without further purification.

An analytical sample was purified by column chromatography on silica gel (10% EtOAc/CH$_2$Cl$_2$).

MP: 76.0-78.5°C.

^{1}H-NMR (δ, CDCl$_3$): 1.34 (t, 6H, J = 7.0 Hz, -OCH$_2$C$\underline{H}_3$), 1.3-1.7 (m, 12H, chain 2-, 3-, 4-CH$_2$), 2.26 (s, 6H, 4-CH$_3$), 2.39 (t, 4 H, J = 7.0 Hz, chain 5-CH$_2$), 2.49 (t, 4H, J = 7.0 Hz, chain 1-CH$_2$), 4.29 (q, 4H, J = 7.0 Hz, -OC$\underline{H}_2$CH$_3$), 6.62 (d, 2H, J = 2.8 Hz, 2-H), 8.87 (bs, 2H, N-$\underline{H}$).

^{13}C-NMR (δ, CDCl$_3$): 161.93 ($\underline{C}$ = 0), 125.96 (pyrrole 3-C), 125.53 (pyrrole 4-C), 119.84 (pyrrole 2-C), 119.34 (pyrrole 5-C), 59.80 (-O$\underline{C}$H$_2$CH$_3$), 32.21 (chain 1-C), 29.99 (chain 4-C), 29.66, 28.70 (chain 2-, 3-C), 24.91 (chain 5-C), 14.54 (-OCH$_2$$\underline{C}H_3$), 10.33 (4-CH$_3$).

$\underline{Anal}$. Calcd. for C$_{26}$H$_{40}$N$_2$O$_4$S: C, 65.51; H, 8.48; N, 5.88; S, 6.73. Found: C, 65.20; H, 8.54; N, 5.68; S, 6.55.

$\underline{Mass\ Spectrum}$ (m/e relative intensity): 476 (M$^+$, 70), 430 (27), 222 (95), 166 (51), 120 (100).

$\underline{Bis[4-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)-butyl]sulfide}$ (n = 4) $\underline{75b}$

4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-iodobutane $\underline{64}$ (3.0 g, 9 mmol) and sodium sulfide (3.2 g, 13.3 mmol) were refluxed for 22 hours in a mixture of tetrahydrofuran (30 mL) and water (70 mL).

After cooling the tetrahydrofuran was removed on a rotary evaporator and the aqueous solution was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated sodium

chloride solution, dried over anhydrous sodium sulfate, then filtered. Removal of the solvent gave a pink solid (1.9 g, 94.4%) which was used without purification.

An analytical sample was prepared by column chromatography on silica gel (10% EtOAc/CH$_2$Cl$_2$).

MP: 96.5-97.5°C.

^{1}H-NMR (δ, CDCl$_3$): 1.36 (t, 6H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.63 (m, 8H, 2-, 3-CH$_2$), 2.29 (s, 6H, 4-CH$_3$), 2.42 (m, 4H, chain 4-CH$_2$), 2.53 (m, 4H, chain 1-CH$_2$), 4.33 (q, 4H, J = 7.0 Hz, -OCH$_2$CH$_3$), 6.68 (d, 2H, J = 3.0 Hz, 2-H), 8.84 (bs, 2H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 161.91 (C = O), 125.99 (pyrrole 3-C), 125.31 (pyrrole 4-C), 119.78 (pyrrole 2-C), 119.46 (pyrrole 5-C), 59.83 (-OCH$_2$CH$_3$), 32.16 (chain 1-C), 29.48 (chain 2-, 3-C), 24.65 (chain 4-C), 14.55 (-OCH$_2$CH$_3$), 10.32 (4-CH$_3$).

Anal. Calcd. for C$_{24}$H$_{36}$N$_2$O$_4$S: C, 64.25; H, 8.09; N, 6.25; S, 7.15. Found: C, 64.00; H, 7.97; N, 6.21; S, 7.25.

Mass Spectrum (m/e, relative intensity): 448 (M$^+$, 56), 403 (13), 402 (19), 240 (13), 208 (47), 206 (31), 179 (25), 166 (75), 134 (66), 120 (100).

CH₃ structure labeled **99**
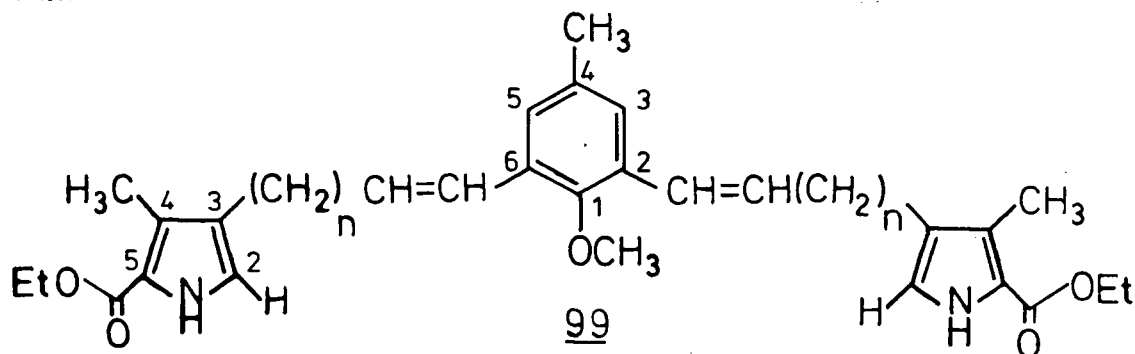
2,6-Bis[6-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)-1-hexenyl]-4-methyl-anisole (n = 4) 99a

Method A

4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-triphenylphosphonium-pentane iodide 94a (1.2 g, 2.0 mmol) was dissolved in freshly distilled tetrahydrofuran (60 mL) in a 3-neck flask equipped with a magnetic stirrer bar, argon inlet and rubber septum. With stirring under argon the solution was cooled to -78°C by placing the flask in a dry ice-acetone bath.

A solution of butyl lithium in hexane (1.45M) was added dropwise to the solution via syringe. The solution changed in color from clear orange to cloudy white, to finally, clear orange/red when 3.0 mL (4.4 mmol, 2 equivalents per pyrrole) of butyl lithium was added. The solution was left stirring at -78°C for 15 minutes.

2,6-Diformyl-4-methylanisole 95 (0.16 g, 0.92 mmol) was dissolved in tetrahydrofuran (10 mL) and added dropwise to the above solution via syringe. When addition was complete the orange/red color was discharged and the resulting yellow solution was allowed to warm to room temperature over a period of 2 hours.

The reaction was quenched by addition of water (20 mL) and the

tetrahydrofuran removed on a rotary evaporator. The residue was
dissolved in ethyl acetate (100 mL) and the solution was washed with
water, dilute hydrochloric acid, saturated sodium bicarbonate solution
and saturated sodium chloride solution. After drying over anhydrous
sodium sulfate and filtering, the ethyl acetate was removed to give a
yellow oil. Thin layer chromatography (25% EtOAc/Tol) showed a major
spot (Rf ∿0.62) which was believed to be the desired product.

The crude reaction product was placed on a silica gel column
(Merck Kieselgel 60H; 100 g). Eluting with dichloromethane washed off
a by-product which was identified by mass spectrometry and ^{1}H-NMR to
be 106.
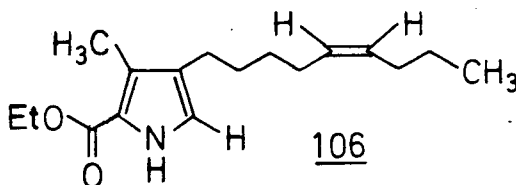
The polarity of the eluant was increased to 2% ethyl acetate/
dichloromethane and the desired product was collected. Removal of the
solvent gave a pink solid (0.34 g, 62.8%).

The reaction was repeated twice on similar scales and under the
same conditions to give yields of 79.3% and 60.9% after chromatographic
isolation.

Method B

4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-triphenylphosphonium-
pentane iodide 94a (0.35 g, 0.58 mmol), 2,6-diformyl-4-methylanisole
95 (0.10 g, 0.58 mmol) and potassium carbonate (0.10 g, 0.59 mmol)
were suspended in p-dioxane (50 mL) and refluxed while stirring under
nitrogen. After 20 hours, tlc (10% EtOAc/Tol) showed two major spots;

the faster running due to unconsumed dialdehyde 95 and the slower spot

due to the "mono-alkene" 108.
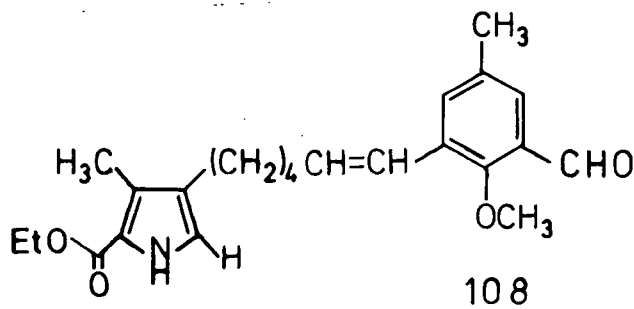
One equivalent each of the phosphonium iodide 94a and potassium

carbonate was added to the mixture and reflux continued for a further

9 hours. By this stage tlc showed complete consumption of the starting

dialdehyde 95, and two major products identified as the "mono-alkene"

108 and the desired "bis-alkene" 99a.

A third equivalent each of phosphonium iodide 94a and potassium

carbonate was added and the solution refluxed for 15 hours. Tlc still

showed a trace of the "mono-alkene" 108. Phosphonium iodide 94a (0.18 g,

0.29 mmol) was added, and after a further 6 hours reflux, the reaction

proceeded to completion.

The reaction mixture was cooled to room temperature and the

p-dioxane removed on a rotary evaporator. The residue was dissolved in

ethyl acetate (50 mL) and water (50 mL). The organic layer was washed

with water, dilute sodium hydroxide solution and saturated sodium

chloride solution. After drying over ahydrous sodium sulfate and

filtering, the solvent was removed to leave a dirty brown oil.

The crude product was placed on a silica gel column (Merck

Kieselgel 60H; 30 g) and eluted with dichloromethane. The first

material off the column was a small amount of an unidentified by-product.

Fractions containing pure product were combined and the solvent removed

to yield 0.21 g (60.4%).

The reaction was repeated three times on similar scales and under the same conditions to give yields of 56.3, 60.1 and 71.8% after chromatographic isolation of the product.

MP: 125.0-128.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.34 (t, 6H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.4-1.6 (m, 8H, chain 4-, 5-CH$_2$), 2.26 (s, 6H, pyrrole 4-CH$_3$), 2.2-2.3 (m, 4H, chain 3-CH$_2$), 2.30 (s, 3H, phenyl 4-CH$_3$), 2.39 (t, 4H, J = 7.0 Hz, chain 6-CH$_2$), 3.60 (s, 3H, -OCH$_3$), 4.30 (q, 4H, J = 7.0 Hz, -OCH$_2$CH$_3$), 5.70 (d of t, 2H, J$_{AB}$ = 8 Hz, J$_{BC}$ = 12 Hz, -CH$_2$CH = CH), 6.51 (d, 2H, J$_{AB}$ = 12 Hz, -CH$_2$CH=CH), 6.62 (d, 2H, J = 3 Hz, pyrrole 2-H), 6.96 (s, 2H, phenyl 3-H, 5-H), 8.74 (bs, 2H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 161.84 (C = O), 153.98 (phenyl 1-C), 133.20 (-CH = CH-CH$_2$-), 132.01 (phenyl 4-C), 130.73 (phenyl 2-, 6-C), 129.56, (phenyl 3-, 5-C), 125.99 (pyrrole 5-C), 125.60 (pyrrole 4-C), 124.62 (-CH = CH-CH$_2$-), 119.69 (pyrrole 2-C), 119.36 (pyrrole 5-C), 60.67 (-OCH$_3$), 59.77 (-OCH$_2$CH$_3$), 29.93, 29.58, 28.57 (chain 3-, 4-, 5-C), 24.87 (chain 6-C), 21.05 (phenyl 4-CH$_3$), 14.56 (-OCH$_2$CH$_3$), 10.30 (pyrrole 4-CH$_3$).

Anal. Calcd. for C$_{36}$H$_{48}$N$_2$O$_5$: C, 73.44; H, 8.21; N, 4.76. Found: C, 73.69; H, 8.33; N, 4.57.

Mass Spectrum (m/e, relative intensity): 588 (M$^+$, 8), 542 (16), 515 (8), 514 (6), 496 (14), 469 (13), 468 (15), 441 (6), 220 (41), 218 (13),

192 (16), 167 (42), 166 (44), 120 (100).

2,6-Bis[5-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)-1-pentenyl]-4-
methylanisole (n = 3) 99b

4-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-triphenylphosphonium-
butane iodide 94b (0.31 g, 0.57 mmol), 2,6-diformyl-4-methylanisole 95
(0.10 g, 0.56 mmol) and potassium carbonate (0.10 g, 0.59 mmol) were
refluxed in p-dioxane (50 mL) under nitrogen for 18 hours. A second
equivalent each of 94b (0.34 g, 0.58 mmol) and potassium carbonate
(0.10 g, 0.59 mmol) was added and reflux maintained for 8 hours. Tlc
(10% EtOAc/Tol) showed complete consumption of the starting dialdehyde
and two major spots due to "mono-alkene" and "bis-alkene" products. A
third equivalent each of 94b and potassium carbonate was added. After
19 hours reflux tlc showed complete reaction.

The reaction mixture was cooled and the p-dioxane removed by rotary
evaporation. The residue was dissolved in ethyl acetate (100 mL) and
water (50 mL) and the organic layer was washed with saturated sodium
chloride solution. Removal of the solvent gave a dirty brown oil.

The crude product was placed on a silica gel column (80 g) and
eluted with 10% EtOAc/CH$_2$Cl$_2$. The front-running by-products were
separated cleanly from the desired product. All the fractions showing
a single spot on tlc were combined and the solvent removed to give a
pink oil (0.15 g, 47.1%).

Later fractions from the column were contaminated with a slower-moving material. This contaminated product was purified after hydrogenation to the reduced product <u>113b</u>.

Repetition of the reaction on similar scales and under the same conditions gave yields in the range 42-52%.

^{1}<u>H-NMR</u> (δ, CDCl$_3$): 1.34 (t, 6H, J = 7.0 Hz, -OCH$_2$C<u>H</u>$_3$), 1.6-1.8 (m, 4H, chain 4-CH$_2$), 2.25 (s, 6H, pyrrole 4-CH$_3$), 2.27 (s, 3H, phenyl 4-CH$_3$), 2.2-2.4 (m, 4H, chain 3-CH$_2$), 2.41 (t, 4H, J = 7.0 Hz, chain 5-CH$_2$), 3.61 (s, 3H, -OC<u>H</u>$_3$), 4.27 (q, 4H, J = 7.0 Hz, -OC<u>H</u>$_2$CH$_3$), 5.69 (d of t, 2H, J$_{AB}$ = 8 Hz, J$_{BC}$ = 11 Hz, -CH$_2$C<u>H</u> = CH-), 6.49 (d, 2H, J$_{AB}$ = 11 Hz, -CH$_2$CH = C<u>H</u>-), 6.54 (d, 2H, J = 3 Hz, pyrrole 2-H), 6.87 (s, 2H, phenyl 3-, 5-H), 8.76 (bs, 2H, N-H).

^{13}<u>C-NMR</u> (δ, CDCl$_3$): 161.87 (<u>C</u> = 0), 154.00 (phenyl 1-C), 132.92 (-<u>C</u>H=CH-CH$_2$-), 132.10 (phenyl 4-C), 130.71 (phenyl 2-,6-C), 129.54 (phenyl 3-,5-C), 126.01 (pyrrole 3-C), 125.60 (pyrrole 4-C), 124.91 (-CH=<u>C</u>H-CH$_2$-), 119.84 (pyrrole 2-C), 119.46 (pyrrole 5-C), 60.70 (-O<u>C</u>H$_3$), 59.80 (-O<u>C</u>H$_2$CH$_3$), 30.45, 28.45 (chain 3-,4-C), 24.70 (chain 5-C), 20.98 (phenyl 4-CH$_3$), 14.56 (-OCH$_2$<u>C</u>H$_3$), 10.31 (pyrrole 4-CH$_3$).

<u>Anal</u>. Calcd. for C$_{34}$H$_{44}$N$_2$O$_5$: C, 72.83; H, 7.91; N, 5.00. Found: C, 73.10; H, 8.02; N, 5.03.

<u>Mass Spectrum</u> (m/e, relative intensity): 560 (M$^+$, 5), 514 (54), 487 (13), 468 (8), 441 (7), 206 (81), 180 (8), 167 (100), 166 (71), 120 (61).

113
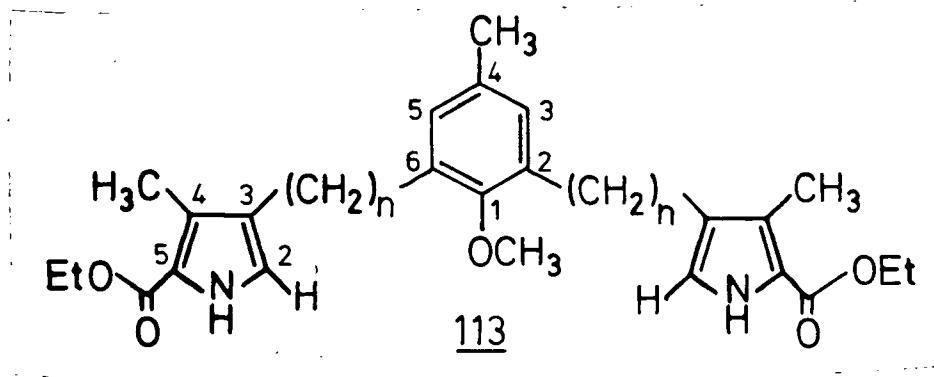
2,6-Bis[6-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)hexyl]-4-methylanisole (n = 6) 113a

2,6-Bis[6-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)-1-hexenyl]-4-methylanisole 99a (0.46 g, 0.78 mmol) was dissolved in tetrahydrofuran (100 mL). 10% Palladium/charcoal catalyst and three drops of triethylamine were added and the mixture was stirred under hydrogen for 24 hours.

The solution was filtered through Celite to remove the catalyst, then evaporated to yield a yellow oil. The crude product was placed on a silica gel column (Kieselgel 60H, 30 g) and eluted with 10% ethyl acetate/dichloromethane. Fractions exhibiting a single spot on tlc were combined and evaporated to yield a colorless oil which slowly crystallized (0.45 g, 96.7%).

Four other reactions on similar scales gave yields of 53.1, 84.7, 88.3 and 95.1%.

MP: 81.0-83.5°C.

^{1}H-NMR (δ, CDCl$_3$): 1.34 (t, 6H, J = 7.5 Hz, -OCH$_2$CH$_3$), 1.2-1.7 (m, 16H, chain 2-, 3-, 4-, 5-CH$_2$), 2.26 (s, 3H, phenyl 4-CH$_3$), 2.27 (s, 6H,

pyrrole 4-CH$_3$), 2.39 (t, 4H, J = 7.6 Hz, chain 6-CH$_2$), 2.57 (t, 4H,

J = 7.9 Hz, chain 1-CH$_2$), 3.70 (s, 3H, -OCH$_3$), 4.31 (q, 4H, J = 7.5 Hz,

-OCH$_2$CH$_3$), 6.66 (d, 2H, J = 2.5 Hz, pyrrole 2-H), 6.84 (s, 2H, phenyl

3-, 5-H), 8.96 (bs, 2H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 161.84 (C = 0), 154.31 (phenyl 1-C), 135.34

(phenyl 2-, 6-C), 133.07 (phenyl 4-C), 128.32 (phenyl 3-, 5-C), 126.04

(pyrrole 3-C), 125.94 (pyrrole 4-C), 119.64 (pyrrole 2-C), 119.37

(pyrrole 5-C), 61.19 (-OCH$_3$), 59.97 (-OCH$_2$CH$_3$), 30.94, 30.34, 29.90,

29.70, 29.36 (chain 1-, 2-, 3-, 4-, 5-C), 25.03 (chain 6-C), 20.89

(phenyl 4-CH$_3$), 14.57 (-OCH$_2$CH$_3$), 10.30 (pyrrole 4-CH$_3$).

Anal. Calcd. for C$_{36}$H$_{52}$N$_2$O$_5$: C, 72.94; H, 8.84; N, 4.73. Found:

C, 73.03; H, 8.83; N, 4.62.

Mass Spectrum (m/e, relative intensity): 592 (M$^+$, 47), 546 (35), 519

(12), 515 (9), 500 (13), 473 (24), 445 (9), 220 (9), 167 (73), 166 (73),

120 (100), 94 (46).

2,6-Bis[5-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)pentyl]-4-methyl-

anisole (n = 5) 113b

2,6-Bis[5-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)-1-pentenyl]-4-

methylanisole 99a was hydrogenated as described for 113a above. Five

reactions were carried out on 0.15-0.32 g scales under the same conditions and with identical work-up and purification procedures. The yields were 79.9, 82.6, 91.7, 97.3 and 97.7% before recrystallization from aqueous ethanol.

MP: 92.0-94.0°C

^{1}H-NMR (δ, CDCl$_3$): 1.33 (t, 6H, J = 7.2 Hz, -OCH$_2$CH$_3$), 1.4-1.5 (m, 4H, chain 3-CH$_2$), 1.5-1.7 (m, 8H, chain 2-, 4-CH$_2$), 2.24 (s, 3H, phenyl 4-CH$_3$), 2.27 (s, 6H, pyrrol 4-CH$_3$), 2.39 (t, 4H, J = 7.7 Hz, chain 5-CH$_2$), 2.56 (t, 4H, J = 8.0 Hz, chain 1-CH$_2$), 3.67 (s, 3H, -OCH$_3$), 4.27 (q, 4H, J = 7.2 Hz, -OCH$_2$CH$_3$), 6.60 (d, 2H, J = 2.8 Hz, pyrrole 2-H), 6.78 (s, 2H, phenyl 3-, 5-H), 8.92 (bs, 2H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 162.40 (C = 0), 154.70 (phenyl 1-C), 135.60 (phenyl 2-, 6-C), 133.40 (phenyl 4-C), 128.58 (phenyl 3-, 5-C), 126.25 (pyrrole 3-C), 126.06 (pyrrole 4-C), 120.00 (pyrrole 2-C), 119.48 (pyrrole 5-C), 61.00 (-OCH$_3$), 59.54 (-OCH$_2$CH$_3$), 30.36, 29.81, 29.40, 29.14 (chain 1-, 2-, 3-, 4-C), 24.45 (chain 5-C), 20.36 (phenyl 4-CH$_3$), 13.96 (-OCH$_2$CH$_3$), 9.73 (pyrrole 4-CH$_3$).

Anal. Calcd. for C$_{34}$H$_{48}$N$_2$O$_5$: C, 72.31; H, 8.57; N, 4.96. Found: C, 72.24; H, 8.59; N, 4.96.

Mass Spectrum (m/e, relative intensity): 564 (M$^+$, 5), 563 (14), 519 (18), 492 (20), 472 (17), 445 (26), 417 (14), 208 (10), 206 (13), 167 (64), 166 (69), 134 (36), 120 (100), 94 (78).
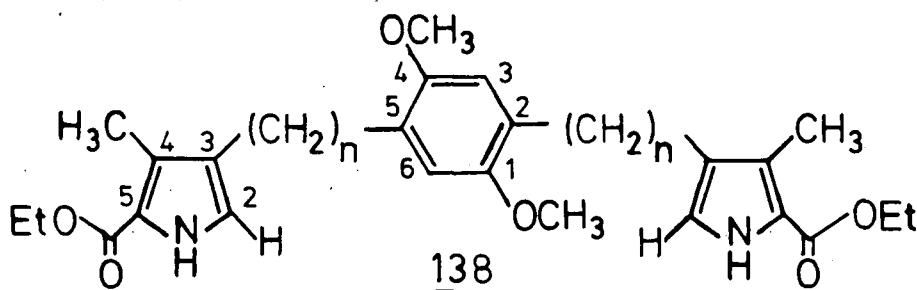
<u>2,5-Bis[6-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)hexyl]-1,4-dimethoxy-</u>
<u>benzene</u> (n = 6) <u>138a</u>

5-(5-Ethoxycarbonyl-4-methylpyrrol-3-yl)-1-triphenylphosphonium

iodide <u>94a</u> (0.65 g, 1.1 mmol), 1,4-diformyl-2,5-dimethoxybenzene <u>131</u>

(0.21 g, 1.1 mmol) and potassium carbonate (0.16 g, 1.0 mmol) were

refluxed in p-dioxane (50 mL) under nitrogen for 6.5 hours. A second

equivalent each of <u>94a</u> and potassium carbonate was added and the

mixture refluxed overnight (16 hours).

By this stage tlc (10% EtOAc/Tol) showed almost complete

reaction. Potassium carbonate (0.05 g, 0.3 mmol) and <u>94a</u> (0.20 g,

0.3 mmol) were added and the solution refluxed for a further 4.5 hours

until tlc indicated complete reaction.

The solution was cooled to room temperature and the p-dioxane

removed. The residue was dissolved in ethyl acetate (100 mL) and

washed with water, dilute sodium hydroxide solution and saturated

sodium chloride solution. The organic layer was dried over anhydrous

sodium sulfate, filtered and evaporated to give a yellow oil which

solidified on standing.

Addition of dichloromethane (~10 mL) did not dissolve all the

crude product. The insoluble material was filtered off and shown by tlc to be almost pure product. The filtrate was concentrated and placed on a silica gel column (Kieselgel 60H, ∿40 g) and eluted with 10% ethyl acetate/dichloromethane. Fractions showing a single product spot on tlc were combined and concentrated to about 50 mL. The solid product was added and the solution diluted with ethanol (150 mL). Cyclohexene (25 mL) and 10% palladium/charcoal catalyst were added and the mixture refluxed for 6.5 hours. While still hot the solution was filtered through Celite and the Celite pad washed well with hot ethanol. As the filtrate cooled down a white solid precipitated which was collected by filtration (0.42 g, 64.1%). Concentration of the filtrate yielded a second crop of product (0.12 g, 18.6%).

Three other reactions, carried out under similar conditions, gave yields of 78.0, 67.3 and 84.8%.

<u>MP</u>: 144.0-145.0°C.

<u>^{1}H-NMR</u> (δ, CDCl$_3$): 1.35 (t, 6H, J = 7.0 Hz, -OCH$_2$C<u>H</u>$_3$), 1.3-1.4 (m, 8H, chain 3-, 4-CH$_2$), 1.4-1.6 (m, 8H, chain 2-, 5-CH$_2$), 2.27 (s, 6H, 4-CH$_3$), 2.39 (t, 4H, J = 7.0 Hz, chain 6-CH$_2$), 2.56 (t, 4H, J = 7.7 Hz, chain 1-CH$_2$), 3.76 (s, 6H, -OC<u>H</u>$_3$), 4.30 (q, 4H, J = 7.0 Hz, -OC<u>H</u>$_2$CH$_3$), 6.64 (s, 4H, pyrrole 2-H, phenyl 3,6-H), 8.75 (bs, 2H, N-H).

<u>^{13}C-NMR</u> (δ, CDCl$_3$): 151.83 (phenyl 1,4-C), 129.61 (phenyl 2, 5-C), 126.38 (pyrrole 3, 4-C), 119.80 (pyrrole 2, 5-C), 113.36 (phenyl 3, 6-C), 59.61 (-OC<u>H</u>$_2$CH$_3$), 56.06 (-OC<u>H</u>$_3$), 29.92, 29.82, 29.08, 28.96 (chain 1, 2, 3, 4, 5-C), 24.48 (chain 6-C), 14.07 (-OCH$_2$C<u>H</u>$_3$), 9.74 (4-CH$_3$).

Anal. Calcd. for $C_{36}H_{52}N_2O_6$: C, 71.02; H, 8.62; N, 4.60. Found: C, 70.70; H, 8.89; N, 4.55.

Mass Spectrum (m/e, relative intensity): 608 (M^+, 100), 562 (6), 535 (6), 516 (8), 489 (14), 340 (6), 220 (9), 167 (35), 166 (37), 134 (12), 120 (52), 108 (10), 94 (22).

2,5-Bis[5-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)pentyl]-1,4-dimethoxy-benzene (n = 5) 138b

This was prepared as described for compound 138a above in 42.4% yield.

MP: 136.0–137.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.34 (t, 6H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.3–1.5 (m, 4H, chain 3-CH$_2$), 1.5–1.7 (m, 8H, chain 2-, 4-CH$_2$), 2.27 (s, 6H, 4-CH$_3$), 2.39 (t, 4H, J = 7.4 Hz, chain 5-CH$_2$), 2.55 (t, 4H, J = 7.7 Hz, chain 1-CH$_2$), 3.74 (s, 6H, -OCH$_3$), 4.28 (q, 4H, J = 7.0 Hz, -OCH$_2$CH$_3$), 6.61 (s, 4H, pyrrole 2-H, phenyl 3, 6-H), 8.76 (bs, 2H, N-H).

^{13}C-NMR (δ, CDCl$_3$): 162.39 ($\underline{C}$ = O), 151.83 (phenyl 1, 4-C), 129.62 (phenyl 2, 5-C), 126.26 (pyrrole 3, 4-C), 119.94 (pyrrole 2-C), 119.60 (pyrrole 5-C), 113.39 (phenyl 3, 6-C), 59.61 (-O$\underline{C}$H$_2$CH$_3$), 56.06 (-O$\underline{C}$H$_3$),

29.80, 29.02 (chain 1, 2, 3, 4-C), 24.52 (chain 5-C), 14.07 ($-OCH_2CH_3$), 9.76 (4-CH_3).

Anal. Calcd. for $C_{34}H_{48}N_2O_6$: C, 70.31; H, 8.33; N, 4.82; Found: C, 70.15; H, 8.19; N, 4.73.

Mass Spectrum (m/e, relative intensity): 580 (M^+, 100), 534 (4), 507 (12), 488 (10), 461 (23), 433 (11), 401 (14), 328 (9), 326 (7), 220 (4), 206 (14), 167 (41), 166 (54), 148 (15), 134 (22), 120 (84), 94 (35).

3.5   SYNTHESES OF CHAIN-LINKED DIPYRROMETHANE DIMERS
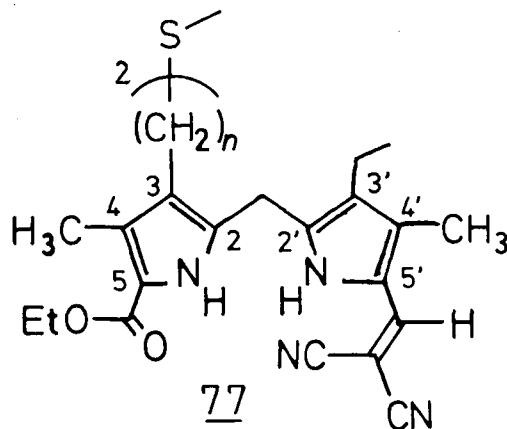
77

Bis{5-(5-ethoxycarbonyl-2-[(5-(2,2-dicyanovinyl)-3-ethyl-4-methyl-
pyrrol-2-yl)methyl]-4-methylpyrrol-3-yl)pentyl}sulfide   (n = 5)   77a

Bis[5-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)pentyl]sulfide 75a
(0.50 g, 1.05 mmol) and 2-chloromethyl-5-(2,2-dicyanovinyl)-3-ethyl-
4-methylpyrrole 76 (0.50 g, 2.15 mmol) were suspended in glacial acetic
acid (5 mL) and stirred under nitrogen. The reaction mixture was
heated at 70°C for 10 minutes whereupon all the solids dissolved to
give a deep red solution.

The solution was cooled to room temperature, methanol (∿15 mL)
added, then cooled in the freezer. A dark oil separated which later
solidified. This solid was triturated with more methanol and an orange
solid (0.77 g, 83.7%) collected by filtration.

MP: 152.0-154.5°C.

^{1}H-NMR (δ, CDCl$_3$): 1.05 (t, 6H, J = 7.6 Hz, 3'-CH$_2$C$\underline{H}_3$), 1.33 (t, 6H,

J = 7.0 Hz, -OCH$_2$C$\underline{H}_3$), 1.30-1.45 and 1.50-1.60 (m, 12H, chain 2-, 3-,

4-CH$_2$), 2.16 (s, 6H, 4'-CH$_3$), 2.29 (s, 6H, 4-CH$_3$), 2.35-2.48 (m, 12H,

chain 1-, 5-CH$_2$, 3'-C$\underline{H}_2$CH$_3$), 3.97 (s, 4H, bridge CH$_2$), 4.29 (q, 4H,

J = 7.0 Hz, -OC$\underline{H}_2$CH$_3$), 7.35 [s, 2H, C($\underline{H}$)=C(CN)$_2$], 8.55 (bs, 2H, 1-N$\underline{H}$),

9.19 (bs, 2H, 1'-N$\underline{H}$).

^{13}C-NMR (δ, CDCl$_3$): 162.14 ($\underline{C}$ = O), 140.74 [$\underline{C}$(H)=C(CN)$_2$], 140.39

(pyrrole 2'-C), 136.01 (pyrrole 4'-C), 127.27 (pyrrole 4-C), 126.61,

126.42 (pyrrole 2-C, 3'-C), 124.16 (pyrrole 5'-C), 123.43 (pyrrole 3-C),

118.89 (pyrrole 5-C), 116.80, 115.96 ($\underline{C}$≡N), 64.15 [C(H)=$\underline{C}$(CN)$_2$], 59.94

(-O$\underline{C}$H$_2$CH$_3$), 32.20 (chain 1-C), 30.48 (chain 4-C), 29.68, 28.79 (chain

2-, 3-C), 24.07 (bridge $\underline{C}$H$_2$, chain 5-C), 17.12 (3'-$\underline{C}$H$_2$CH$_3$), 14.67 (3'-

CH$_2$$\underline{C}H_3$), 14.43 (-OCH$_2$$\underline{C}H_3$), 10.72 (4-CH$_3$), 9.42 (4'-CH$_3$).

<u>Anal</u>. Calcd. for C$_{50}$H$_{62}$N$_8$O$_4$S: C, 68.93; H, 7.17; N, 12.86; S, 3.68.

Found: C, 68.81; H, 7.04; N, 12.82; S, 3.68.

<u>Mol. Wt</u>. Calcd. for C$_{50}$H$_{62}$N$_8$O$_4$S: 870.4615. Found by high resolution

mass spectrometry: 870.4604.

<u>Bis{5-(5-ethoxycarbonyl-2-[(5-(2,2-dicyanovinyl)-3-ethyl-4-methyl-</u>

<u>pyrrol-2-yl)methyl]-4-methylpyrrol-3-yl)butyl}sulfide</u> (n = 4) <u>77b</u>

Bis[5-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)-butyl]sulfide <u>75b</u>

(1.01 g, 2.25 mmol) and 2-chloromethyl-5-(2,2-dicyanovinyl)-3-ethyl-4-methylpyrrole 76 (1.11 g, 4.74 mmol) were suspended in glacial acetic acid (20 mL) and heated at 80°C for 1 hour while stirring under nitrogen. After several minutes heating all the solids dissolved and on continuing heating some product precipitated from solution.

The reaction mixture was cooled, methanol (50 mL) was added and then placed in the freezer overnight. The orange-brown solid which precipitated was filtered and dried (1.71 g, 90.0%). The product was used without further purification but a sample was recrystallized from 50% dichloromethane/methanol for elemental analysis.

MP: 185.0–187.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.04 (t, 6H, J = 7.6 Hz, 3'-CH$_2$CH$_3$), 1.33 (t, 6H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.4–1.6 (m, 8H, chain 2-, 3-CH$_2$), 2.15 (s, 6H, 4'-CH$_3$), 2.26 (s, 6H, 4-CH$_3$), 2.35–2.49 (m, 12H, chain 1-, 5-CH$_2$, 3'-CH$_2$CH$_3$), 3.93 (s, 4H, bridge CH$_2$), 4.26 (q, 4H, J = 7.0 Hz, -OCH$_2$CH$_3$), 7.32 [s, 2H, C(H)=C(CN)$_2$], 8.55 (bs, 2H, 1-NH), 9.19 (bs, 2H, 1'-NH).

^{13}C-NMR (δ, CDCl$_3$): 161.98 (C = O), 140.87 [C(H)=C(CN)$_2$], 139.91 (pyrrole 2'-C), 135.95 (pyrrole 4'-C), 127.31 (pyrrole 4-C), 126.49, 126.23 (pyrrole 2-C, 3'-C), 124.26 (pyrrole 5'-C), 123.23 (pyrrole 3-C), 119.00 (pyrrole 5-C), 116.85, 115.82 (C≡N), 64.59 [C(H)=C(CN)$_2$], 60.04 (-OCH$_2$CH$_3$), 32.13 (chain 1-C), 29.97, 29.41 (chain 2-, 3-C), 23.79 (bridge CH$_2$, chain 4-C), 17.14 (3'-CH$_2$CH$_3$), 14.72 (3'-CH$_2$CH$_3$), 14.48 (-OCH$_2$CH$_3$), 10.70 (4-CH$_3$), 9.45 (4'-CH$_3$).

Anal. Calcd. for $C_{48}H_{58}N_8O_4S$: C, 68.38; H, 6.93; N, 13.29; S, 3.80.
Found: C, 67.71; H, 6.89; N, 13.15. Calculated for $C_{48}H_{58}N_8O_4S \cdot 0.5CH_3OH$
C, 67.80; H, 7.04; N, 13.04.

Mol. Wt. Calcd. for $C_{48}H_{58}N_8O_4S$: 842.4302. Found by high resolution
mass spectrometry: 842.4279.
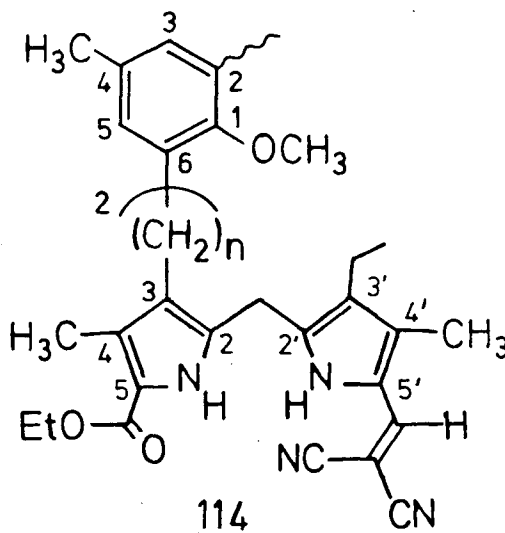
114

2,6-Bis[6-{5-ethoxycarbonyl-2-[(5-(2,2-dicyanovinyl)-3-ethyl-4-methyl-pyrrol-2-yl)methyl]-4-methylpyrrol-3-yl}hexyl]-4-methylanisole
(n = 6) 114a

2,6-Bis[6-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)hexyl]-4-methyl-anisole 113a (0.20 g, 0.34 mmol) and 2-chloromethyl-5-(2,2-dicyanovinyl)-3-ethyl-4-methylpyrrole 76 (0.17 g, 0.73 mmol) were suspended in glacial acetic acid (5 mL) and stirred under nitrogen. The reaction mixture was heated at 80°C for 1 hour.

The solution was cooled to room temperature then poured into

sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried, filtered and evaporated to give a dark red oil.

The crude product was placed on a column (Kieselgel 60, 50 g) and eluted with 10% ethyl acetate/toluene. Many small red and yellow bands eluted off the column initially. These were followed by a bright red band immediately preceeding the product, which eluted off as a broad yellow band. Those fractions displaying a single yellow spot on tlc were collected. The fractions were combined and evaporated to give an orange oil (0.29 g, 85.2%), which was recrystallized from 50% dichloromethane/methanol to give an orange solid.

Three other syntheses on similar scales gave yields of 84.1, 91.2 and 94.2% after chromatographic purification.

MP: 146.5-150.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.04 (t, 6H, J = 7.6 Hz, 3'-CH$_2$CH$_3$), 1.30 (t, 6H, J = 7.2 Hz, -OCH$_2$CH$_3$), 1.25-1.45 (m, 12H, chain 3-, 4-, 5-CH$_2$), 1.48-1.60 (m, 4H, chain 2-CH$_2$), 2.10 (s, 6H, 4'-CH$_3$), 2.26 (s, 9H, 4-CH$_3$, phenyl 4-CH$_3$), 2.32-2.42 (m, 4H, chain 6-CH$_2$), 2.42 (q, 4H, J = 7.8 Hz, 3'-CH$_2$CH$_3$), 2.54 (bt, 4H, chain 1-CH$_2$), 3.67 (s, 3H, -OCH$_3$), 3.97 (s, 4H, bridge CH$_2$), 4.19 (q, 4H, J = 7.2 Hz, -OCH$_2$CH$_3$), 6.80 (s, 2H, phenyl 3-, 5-H), 7.25 [s, 2H, C(H)=C(CN)$_2$], 9.26 (bs, 2H, 1-NH), 9.50 (bs, 2H, 1'-NH).

^{13}C-NMR (δ, CDCl$_3$): 162.10 (C = O), 154.23 (phenyl 1-C), 140.73 [C(H)=C(CN)$_2$], 140.28 (pyrrole 2'-C), 135.93 (pyrrole 4'-C), 135.28 (phenyl 2-, 6-C), 133.07 (phenyl 4-C), 128.26 (phenyl 3-, 5-C), 127.35

(pyrrole 4-C), 126.42 (pyrrole 2-, 3'-C), 124.17 (pyrrole 5'-C),

123.73 (pyrrole 3-C), 118.91 (pyrrole 5-C), 116.81 115.91 ($\underline{C}$≡N), 64.31

[C(H)=$\underline{C}$(CN)$_2$], 61.19 (-O$\underline{C}$H$_3$), 59.95 (-O$\underline{C}$H$_2$CH$_3$), 30.91, 30.27, 29.87,

29.77, 29.45 (chain 1-, 2-, 3-, 4-, 5-C), 24.20, 23.94 (bridge $\underline{C}$H$_2$,

chain 6-C), 20.87 (phenyl 4-CH$_3$), 17.12 (3'-$\underline{C}$H$_2$CH$_3$), 14.69 (3'-CH$_2$$\underline{C}H_3$),

14.46 (-OCH$_2$$\underline{C}H_3$), 10.68 (4-CH$_3$), 9.87 (4'-CH$_3$).

$\underline{\text{Anal}}$. Calcd. for C$_{60}$H$_{74}$N$_8$O$_5$: C, 72.99; H, 7.56; N, 11.35. Found:

C, 73.28; H, 7.42; N, 11.24.

$\underline{\text{Mol. Wt}}$. Calcd. for C$_{60}H_{74}N_8O_5$: 986.5782. Found by high resolution

mass spectrometry: 986.5849.

$\underline{\text{2,6-Bis[5-\{5-ethoxycarbonyl-2-[(5-(2,2-dicyanovinyl)-3-ethyl-4-methyl-}}$

$\underline{\text{pyrrol-2-yl)methyl]-4-methylpyrrol-3-yl\}pentyl]-4-methylanisole}}$

(n = 5) $\underline{\text{114b}}$

This compound was prepared from $\underline{\text{113b}}$ and $\underline{\text{76}}$ exactly as

described for compound $\underline{\text{114a}}$. In four reactions the yields of product

after chromatographic purification were 76.4, 83.9, 91.7 and 95.2%.

$\underline{\text{MP}}$: 181.5-182.5°C.

^{1}H-NMR (δ, CDCl$_3$): 1.05 (t, 6H, J = 7.6 Hz, 3'-CH$_2$$\underline{C}H_3$), 1.34 (t, 6H,

J = 7.2 Hz, -OCH$_2$CH$_3$), 1.3-1.5 (m, 8H, chain 3-, 4-CH$_2$), 1.5-1.6 (m, 4H, chain 2-CH$_2$), 2.14 (s, 6H, 4'-CH$_3$), 2.25 (s, 3H, phenyl 4-CH$_3$), 2.27 (s, 6H, 4-CH$_3$), 2.38 (t, 4H, chain 5-CH$_2$), 2.42 (q, 4H, J = 7.6 Hz, 3'-CH$_2$CH$_3$), 2.54 (bt, 4H, chain 1-CH$_2$), 3.67 (s, 3H, -OCH$_3$), 3.94 (s, 4H, bridge CH$_2$), 4.27 (q, 4H, J = 7.2 Hz, -OCH$_2$CH$_3$), 6.79 (s, 2H, phenyl 3-, 5-H), 7.29 [s, 2H, C(H)=C(CN)$_2$], 8.67 (bs, 2H, 1-NH), 9.17 (bs, 2H, 1'-NH).

^{13}C-NMR (δ, CDCl$_3$): 162.19 (C = O), 154.27 (phenyl 1-C), 140.69 [C(H)= C(CN)$_2$], 140.51 (pyrrole 2'-C), 136.02 (pyrrole 4'-C), 135.19 (phenyl 2-, 6-C), 133.10 (phenyl 4-C), 128.37 (phenyl 3-, 5-C), 127.36 (pyrrole 4-C), 126.60, 126.42 (pyrrole 2-, 3'-C), 124.16 (pyrrole 5'-C), 123.69 (pyrrole 3-C), 118.89 (pyrrole 5-C), 116.76, 116.01 (C≡N), 64.09 [C(H)= C(CN)$_2$], 61.24 (-OCH$_3$), 59.93 (-OCH$_2$CH$_3$), 30.82, 29.86, 29.76 (chain 1-, 2-, 3-, 4-C), 24.16, 23.90 (bridge CH$_2$, chain 5-C), 20.85 (phenyl 4-CH$_3$), 17.10 (3'-CH$_2$CH$_3$), 14.65 (3'-CH$_2$CH$_3$), 14.45 (-OCH$_2$CH$_3$), 10.71 (4-CH$_3$), 9.36 (4'-CH$_3$).

Anal. Calcd. for C$_{58}$H$_{70}$N$_8$O$_5$: C, 72.62; H, 7.36; N, 11.68.   Found: C, 72.84; H, 7.48; N, 11.38.

Mol. Wt. Calcd. for C$_{58}$H$_{70}$N$_8$O$_5$: 958.5469. Found by high resolution mass spectrometry: 958.5511.

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2,5-Bis[6-{5-ethoxycarbonyl-2-[(5-(2,2-dicyanovinyl)-3-ethyl-4-methyl-pyrrol-2-yl)methyl]-4-methylpyrrol-3-yl}hexyl]-1,4-dimethoxybenzene (n = 6) 139a

The compound was prepared from 138a and 76 exactly as described for compound 114a a. .Of five reactions the yield of product oduct after chromatographic purification was 75.9-87.6%.

MP: 165.0-168.0°C.

^{1}H-NMR (δ, CDCl$_3$): 1.04 (t, 6H, J = 7.6 Hz, 3'-CH$_2$CH$_3$), 1.30 (t, 6H, J = 7.0 Hz, -OCH$_2$CH$_3$), 1.25-1.41 (m, 12H, chain 3-, 4-, 5-CH$_2$), 1.45-1.56 (m, 4H, chain 2-CH$_2$), 2.10 (s, 6H, 4'-CH$_3$), 2.25 (s, 6H, 4-CH$_3$), 2.38 (bt, 4H, chain 6-CH$_2$), 2.41 (q, 4H, J = 7.6 Hz, 3'-CH$_2$CH$_3$), 2.51 bt, 4H, chain 1-CH$_2$), 3.74 (s, 6H, -OCH$_3$), 3.94 (s, 4H, bridge CH$_2$), 4.21 (q, 4H, J = 7.0 Hz, -OCH$_2$CH$_3$), 6.62 (s, 2H, phenyl 3-, 6-H), 7.26

[s, 2H, C($\underline{H}$)=C(CN$_2$)], 9.15, 9.19 (bs, 4H, 1-N$\underline{H}$, 1'-N$\underline{H}$).

^{13}C-NMR (δ, CDCl$_3$): 162.12 ($\underline{C}$ = 0), 151.32 (phenyl 1-, 4-C), 140.81 [$\underline{C}$(H)=C(CN)$_2$], 140.21 (pyrrole 2'-C), 136.00 (pyrrole 4'-C), 129.25 (phenyl 2-, 5-C), 127.36 (pyrrole 4-C), 126.39 (pyrrole 2-, 3'-C), 124.19 (pyrrole 5'-C), 123.84 (pyrrole 3-C), 118.92 (pyrrole 5-C), 116.94, 115.89 ($\underline{C}$≡N), 113.14 (phenyl 3-, 6-C), 64.38 [C(H)=$\underline{C}$(CN)$_2$], 60.02 (-O$\underline{C}$H$_2$CH$_3$), 56.27 (-O$\underline{C}$H$_3$), 30.88, 30.27, 29.53 (chain 1-, 2-, 3-, 4-, 5-C), 24.22, 23.97 (bridge $\underline{C}$H$_2$, chain 6-C), 17.16 (3'-$\underline{C}$H$_2$CH$_3$), 14.73 (3'-CH$_2$$\underline{C}H_3$), 14.51 (-OCH$_2$$\underline{C}H_3$), 10.69 (4-CH$_3$), 9.40 (4'-CH$_3$).
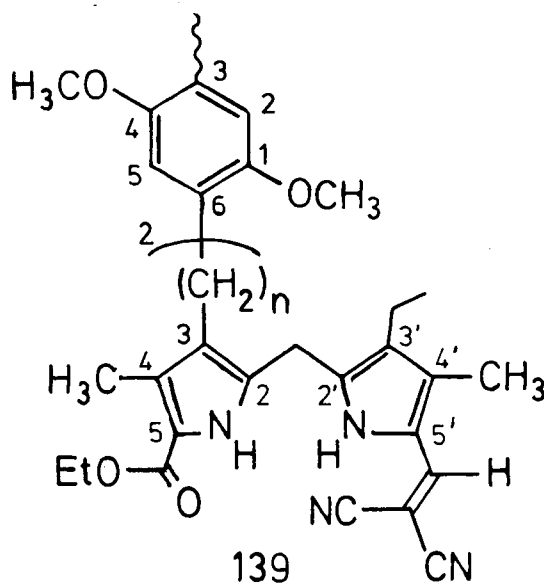
$\underline{Anal}$. Calcd. for C$_{60}$H$_{74}$N$_8$O$_6$: C, 71.83; H, 7.44; N, 11.17. Found: C, 71.91; H, 7.35; N, 11.06.

$\underline{Mol. Wt}$. Calcd. for C$_{60}$H$_{74}$N$_8$O$_6$: 1002.5731. Found by high resolution mass spectrometry: 1002.5728.

$\underline{2,5-Bis[5-\{5-ethoxycarbonyl-2-[(5-(2,2-dicyanovinyl)-3-ethyl-4-methyl-}$
$\underline{pyrrol-2-yl)methyl]-4-methylpyrrol-3-yl\}pentyl]-1,4-dimethoxybenzene}$
(n = 5) $\underline{139b}$

2,5-Bis[5-(5-ethoxycarbonyl-4-methylpyrrol-3-yl)pentyl]-1,4-dimethoxybenzene $\underline{138b}$ (0.24 g, 0.41 mmol) and 2-chloromethyl-5-(2,2-dicyanovinyl)-3-ethyl-4-methylpyrrole $\underline{76}$ (0.20 g, 0.87 mmol) were

suspended in glacial acetic acid (5 mL) and stirred under nitrogen. The mixture was heated at 80°C for 1 hour.

After a few minutes all the solids dissolved to give a dark red solution, but during the course of the reaction an orange solid precipitated from solution. The reaction mixture was cooled to room temperature, methanol (20 mL) added and then cooled overnight in the freezer. The precipitated product was collected by filtration, washed well with methanol and dried to give a yellow powder (0.36 g, 90.0%).

MP: >215° (dec).

^{1}H-NMR (δ, CDCl$_3$): 1.04 (t, 6H, J = 7.6 Hz, 3'-CH$_2$CH$_3$), 1.32 (t, 6H, J = 7.4 Hz, -OCH$_2$CH$_3$), 1.36-1.47 (m, 8H, chain 3-, 4-CH$_2$), 1.47-1.58 (m, 4H, chain 2-CH$_2$), 2.12 (s, 6H, 4'-CH$_3$), 2.25 (s, 6H, 4-CH$_3$), 2.37 (t, 4H, chain 5-CH$_2$), 2.40 (q, 4H, J = 7.4 Hz, 3'-CH$_2$CH$_3$), 2.50 (bt, 4H, chain 1-CH$_2$), 3.73 (s, 6H, -OCH$_3$), 3.93 (s, 4H, bridge CH$_2$), 4.28 (q, 4H, J = 7.3 Hz, -OCH$_2$CH$_3$), 6.71 (s, 2H, phenyl 3-, 6-H), 7.29 [s, 2H, C(H)=C(CN)$_2$], 8.81 (bs, 2H, 1-NH), 9.18 (bs, 2H, 1'-NH).

^{13}C-NMR (δ, CDCl$_3$): 161.94 (C = 0), 151.41 (phenyl 1-, 4-C), 140.87 [C(H)=C(CN)$_2$], 139.81 (pyrrole 2'-C), 135.89 (pyrrole 4'-C), 129.26 (phenyl 2-, 5-C), 127.41 (pyrrole 4-C), 126.48, 126.16 (pyrrole 2-, 3'-C), 124.25 (pyrrole 5'-C), 123.89 (pyrrole 3-C), 119.12 (pyrrole 5-C), 116.79, 115.96 (C≡N), 113.25 (phenyl 3-, 6-C), 64.80 [C(H)=C(CN)$_2$], 60.00 (-OCH$_2$CH$_3$), 56.29 (-OCH$_3$), 30.78, 30.20, 29.56 (chain 1-, 2-, 3-, 4-C), 24.04 (bridge CH$_2$, chain 5-C), 17.14 (3'-CH$_2$CH$_3$), 14.71 (3'-

CH$_2$CH$_3$), 14.54 (-OCH$_2$CH$_3$), 10.65 (4-CH$_3$), 9.39 (4'-CH$_3$).

Anal. Calcd. for C$_{58}$H$_{70}$N$_8$O$_6$: C, 71.43; H, 7.24; N, 11.49. Found: C, 71.19; H, 7.32; N, 11.28.

Mol. Wt. Calcd. for C$_{58}$H$_{70}$N$_8$O$_6$: 974.5418. Found by high resolution mass spectrometry: 974.5402.

3.6   SYNTHESES OF STRAPPED PORPHYRINS
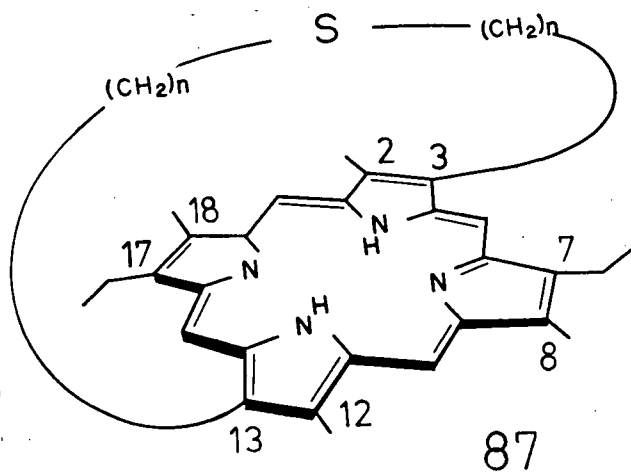
7,17-Diethyl-2,8,12,18-tetramethyl-3,13-[thiobis(pentamethylene)]-
porphyrin   (n = 5)   87a

(i)   Saponification:

Bis{5-(5-ethoxycarbonyl-2-[(5-(2,2-dicyanovinyl)-3-ethyl-4-
methylpyrrol-2-yl)methyl]-4-methylpyrrol-3-yl)pentyl}sulfide 77a (1.312 g,
1.51 mmol) was placed in an Erlenmeyer flask equipped with a Claisen
head and a nitrogen inlet. A solution of potassium hydroxide (14 g) in
water (100 mL) and n-propanol (50 mL) was added and the mixture
stirred. A small quantity of this starting mixture was withdrawn,
diluted with methanol and a uv-visible spectrum recorded. Two major
bands were observed at 406.0 nm and at 276.8 nm. The mixture was heated
to reflux and stirred under nitrogen, the course of the reaction
being followed spectrophotometrically. After 3 hours reflux the reaction
was judged complete. The spectrum of the final solution showed complete
disappearance of the band 406.0 nm and the appearance of a new band at
316.8 nm; the band at 276.8 nm moved to 268.4 nm.

All the propanol was boiled off from the two-phase reaction mixture and more water (200 mL) was added, after which the solution was allowed to come to room temperature. The cooled solution, containing an oily precipitate, was filtered and the material which remained on the filter was washed with water until it all redissolved (final volume 500 mL). The filtrate was acidified with glacial acetic acid which caused the formation of a rust-brown gelatinous precipitate. This crude bis{5-(5-carboxy-2-[(5-formyl-3-ethyl-4-methylpyrrol-2-yl) methyl]-4-methylpyrrol-3-yl)pentyl} sulfide 83a was collected by filtration and dried overnight in a vacuum desiccator.

(ii) Decarboxylation

The crude α-carboxy,α'-formyl bis-dipyrromethane 83a was dissolved in spectral grade N,N-dimethylformamide (150 mL) in an Erlenmeyer flask equipped with a Claisen head and an argon inlet. The uv spectrum of a sample of this solution in dichloromethane showed two bands at 320.0 nm and 280.0 nm in the ratio 1:1.3.

The solution was stirred and refluxed under argon for 3 hours after which no further spectral change occurred. In the final spectrum the band initially at 320.0 nm shifted to 312.0 nm and the 280.0 nm band decreased in intensity and moved to 272.8 nm; the ratio of the two bands was now 1:0.5.

The reaction mixture was cooled under argon then evaporated almost to dryness under reduced pressure. The residue was dissolved in dichloromethane (100 mL) and extracted with water (3 x 200 mL) and saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate, filtered and diluted to 500 mL with dichloro-

methane.

(iii) Cyclization

Four 1-liter Erlenmeyer flasks were wrapped in aluminum foil and each was charged with p-toluenesulfonic acid (4 g), methanol (25 mL) and dichloromethane (600 mL) and stirred in subdued lighting. The solution of the α-free,α'-formyl bis-dipyrromethane 84a was injected slowly into the flasks over a period of 48 hours using a syringe pump.

When addition was complete the four wine colored solutions were concentrated to approximately 250 mL. This was then extracted with saturated sodium bicarbonate solution to neutralize the acid and convert the protonated porphyrin to its free base form (the color of the solution changed from wine to red/brown). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness (a vacuum pump was used to remove any traces of DMF).

(iv) Purification

The crude product was placed on a silica gel column (Kieselgel 60, 150 g). Elution with dichloromethane washed off a small amount of metalloporphyrin and other minor bands which were discarded; most of the material remained at the top of the column. The polarity of the eluant was increased to 1% methanol/dichloromethane whereupon the porphyrin was washed off the column. When the eluant was almost colorless the polarity was increased to ∿5% methanol/dichloromethane.

Tlc (2% MeOH/CH$_2$Cl$_2$) showed that the later fractions, obtained with the most polar eluant, were contaminated with a brown impurity

and the corresponding sulfoxide strapped porphyrin 88a. These later fractions were combined and partially purified on another silica gel column (Kieselgel 60, 50 g) before being combined with the main bulk of the product.

The crude strapped porphyrin was placed on a column of activity III alumina (Merck 90 neutral, 40 g) and eluted with dichloromethane. The brown impurities remained at the head of the column and the porphyrin came off the column in two bands with little overlap. The faster major band was due to the desired sulfide strapped porphyrin 87a, and the slower band was due to the corresponding sulfoxide strapped porphyrin 88a. Combination and evaporation of the various fractions and drying on the vacuum line gave 166.9 mg (18.7%) of porphyrin 87a and 7.5 mg of 88b.

In nine attempts the total overall yield (i.e. yield of sulfide and sulfoxide) for the saponification - decarboxylation - cyclization sequence varied between 9.5% and 19.5%.

MP: 280-283°C.

Mol. Wt. Calcd. for $C_{38}H_{48}N_4S$: 592.3599. Found by high resolution mass spectrometry: 592.3587.

Anal. Calcd. for $C_{38}H_{48}N_4S$: C, 76.98; H, 8.16; N, 9.45; S, 5.41. Found: 76.68; H, 8.07; N, 9.23; S, 5.39.

^{1}H-NMR (δ, CDCl$_3$): 9.93 (s, 2H, methine 10, 20-H), 9.82 (s, 2H, methine 5, 15-H), 4.09 (m, 4H, -C$\underline{H}_2$CH$_3$), 3.97 (m, 2H, chain 5-CH$_2$),

3.63 (s, m, 8H, two CH$_3$, chain 5-CH$_2$), 3.36 (s, 6H, two CH$_3$), 1.86 (t, 6H, -CH$_2$CH$_3$), 1.42 (m, 4H, chain 4-CH$_2$), 0.17 (m, 2H, chain 3-CH$_2$), -0.13 (m, 2H, chain 3-CH$_2$), -1.46 (m, 2H, chain 2-CH$_2$), -1.56 (m, 2H, chain 1-CH$_2$), -1.85 (m, 2H, chain 2-CH$_2$), -2.02 (m, 2H, chain 1-CH$_2$), -3.38 (bs, 2H, N-H).

^{13}C-NMR (δ, 10% TFA-CDCl$_3$): 146.87, 144.79, 143.55, 141.73, 141.07, 140.00, 139.71, 139.47 (16C, α- and β-pyrrolic carbons), 100.52, 99.19, (4C, meso carbons), 29.41, 27.35, 27.06, 26.04, 24.12 (10C, chain carbons), 20.48 (2C, CH$_2$CH$_3$), 16.51 (2C, CH$_2$CH$_3$), 12.28, 11.89 (4C, CH$_3$).

Visible Spectrum (CH$_2$Cl$_2$):

λ_{max} (nm) ,	400.0	502.0	539.0	570.0	624.2
log ϵ ,	5.22	4.03	4.03	3.79	3.52

7,17-Diethyl-2,8,12,18-tetramethyl-3,13-[thiobis(tetramethylene)]-porphyrin (n = 4) 87b

The saponification, decarboxylation and cyclization reactions were carried out on 77b exactly as described for the synthesis of the

thiobis(pentamethylene) porphyrin 87a.

After work-up the crude product was placed on a silica gel column (Kieselgel 60, 100 g) and eluted with 2% methanol/dichloromethane. A small amount of metalloporphyrin came off the column first and was discarded. This was followed by a major green band and then by the purple strapped porphyrin band. The eluant was collected in fractions (100-200 mL) and examined by tlc (2% MeOH/CH$_2$Cl$_2$). Those fractions containing green and purple material were stirred overnight in dichloromethane in air, whereupon tlc indicated disappearance of the green material.

Fractions containing just green material were combined and evaporated. Attempts to purify this by preparative tlc failed. Only strapped porphyrins were obtained from the plate.

The partially purified strapped porphyrin samples were combined and placed on a column of activity III alumina (Merck 90 neutral, 100 g) and eluted with dichloromethane. All brown impurities remained at the head of the column. The porphyrin came off the column in two bands. The first, due to the sulfide porphyrin 87b, was slightly contaminated with a faster running blue material but most fractions (∿5 mL) contained pure sulfide porphyrin. The second, slower moving band was due to the sulfoxide strapped porphyrin 88b. In these preparations the yields of 87b were 10.1%, 17.5% and 16.5%. When the quantity of 88b was included, the total overall yield was 12.0%, 21.6% and 18.6%.

MP: >270°C (dec).

<u>Mol. Wt.</u> Calcd. for C$_{36}$H$_{44}$N$_4$S: 564.3287. Found by high resolution mass spectrometry: 564.3277.

<u>Anal</u>. Calcd. for C$_{36}$H$_{44}$N$_4$S: C, 76.55; H, 7.85; N, 9.92; S, 5.68. Found: C, 76.40; H, 7.58; N, 9.87; S, 5.51.

^{1}<u>H-NMR</u> (δ, CDCl$_3$): 9.72 (s, 2H, methine 10, 20-H), 9.40 (s, 2H, methine 5, 15-H), 3.99 (m, 4H, -C$\underline{H}_2$CH$_3$), 3.56 (s, 6H, two CH$_3$), 3.44 (m, 2H, chain 4-CH$_2$), 3.03 (s, m, 8H, two CH$_3$, chain 4-CH$_2$), 1.83 (t, 6H, -CH$_2$C$\underline{H}_3$), 0.93 (m, 2H, chain 3-CH$_2$), 0.79 (m, 2H, chain 3-CH$_2$), -0.62 (m, 2H, chain 2-CH$_2$), -0.86 (m, 2H, chain 2-CH$_2$), -3.11 (bs, 2H, N-H), -3.74 (t, 4H, chain 1-CH$_2$).

^{13}<u>C-NMR</u> (δ, 10% TFA-CDCl$_3$): 146.96, 145.85, 143.79, 141.71, 139.95, 139.71, 133.91 (16C, α- and β-pyrrolic carbons), 100.99, 98.67 (4C, meso carbons), 29.97, 26.90, 25.72, 23.68 (8C, chain carbons), 20.24 (2C, $\underline{C}$H$_2$CH$_3$), 16.25 (2C, CH$_2\underline{C}$H$_3$), 11.68 (4C, CH$_3$).

<u>Visible Spectrum</u> (CH$_2$Cl$_2$):

λ_{max} (nm),	405.6	512.6	551.0	576.0	630.0
log ε ,	5.16	3.84	4.01	3.79	3.32
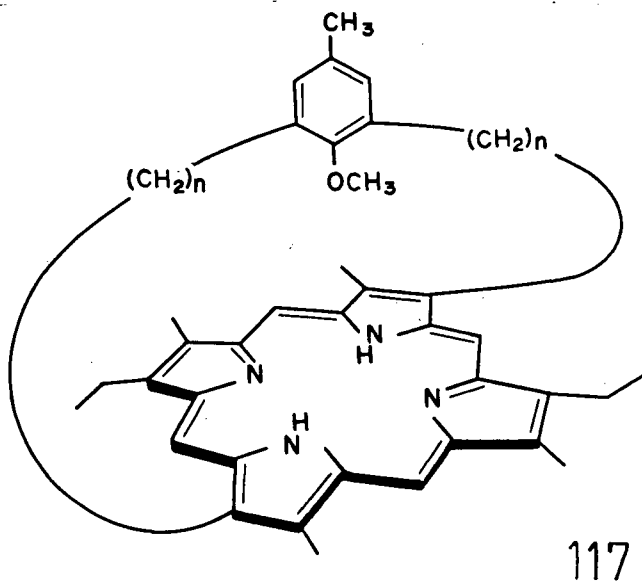
117

7,17-Diethyl-2,8,12,18-tetramethyl-3,13-[2-methoxy-5-methylphenylene-
1,3-bis(hexamethylene)]porphyrin   (n = 6)   117a

The saponification, decarboxylation and cyclization reactions
were carried out on 114a as described for 87a. The product was
purified first on a silica gel column (Kieselgel 60, 100 g), eluting
with 1% methanol/dichloromethane. The partially purified porphyrin
was then placed on an activity III alumina column (Merck 90 neutral,
40 g) and eluted with dichloromethane. The pure porphyrin was
collected and evaporated to dryness. In four preparations the yields
were 30.0%, 39.7%, 40.4% and 43.7%.

MP: 233-234°C.

Mol. Wt. Calcd. for $C_{48}H_{60}N_4O$: 708.4767. Found by high resolution

mass spectrometry: 708.4793.

<u>Anal</u>. Calcd. for $C_{48}H_{60}N_4O$: C, 81.31; H, 8.53; N, 7.90; O, 2.26.
Found: C, 81.21; H, 8.62; N, 7.75; O, 2.35.

<u>^{1}H-NMR</u> (δ, CDCl$_3$): 10.02 (s, 2H, methine 5, 15-H), 10.00 (s, 2H, methine 10, 20-H), 5.60 (s, 2H, phenyl 4, 6-H), 4.36 (m, 2H, chain 6-CH$_2$), 4.13 (m, 2H, -C<u>H</u>$_2$CH$_3$), 4.06 (m, 2H, -C<u>H</u>$_2$CH$_3$), 3.94 (m, 2H, chain 6-CH$_2$), 3.63 (s, 6H, two-CH$_3$), 3.58 (s, 6H, two-CH$_3$), 2.19 (m, 2H, chain 5-CH$_2$), 2.02 (m, 2H, chain 5-CH$_2$), 1.88 (t, 6H, -CH$_2$C<u>H</u>$_3$), 1.69 (s, 3H, phenyl 5-CH$_3$), 0.89 (m, 2H, chain 4-CH$_2$), 0.84 (m, 2H, chain 4-CH$_2$), 0.71 (m, 2H, chain 3-CH$_2$), 0.50 (m, 2H, chain 1-CH$_2$), 0.42 (m, 2H, chain 3-CH$_2$), 0.27 (m, 2H, chain 2-CH$_2$), 0.18 (m, 2H, chain 1-CH$_2$), 0.03 (m, 2H, chain 2-CH$_2$), -2.70 (s, 3H, -OCH$_3$), -3.77 (bs, 2H, N-H).

<u>^{13}C-NMR</u> (δ, 10% TFA-CDCl$_3$): 150.96 (1C, phenyl 2-C), 147.01, 144.07, 143.46, 142.19, 141.37, 141.19, 140.13, 139.97 (16C, α- and β-pyrrolic carbons), 135.09 (2C, phenyl 1, 3-C), 134.76 (1C, phenyl 5-C), 128.76 (2C, phenyl 4, 6-C), 100.42, 99.35 (4C, meso carbons), 60.64 (1C, -OCH$_3$), 31.66, 30.52, 29.59, 29.08, 28.40, 26.36 (12C, chain carbons), 20.39 (2C, <u>C</u>H$_2$CH$_3$), 20.23 (1C, phenyl 5-<u>C</u>H$_3$), 16.65 (2C, CH$_2$<u>C</u>H$_3$), 12.40, 11.80 (4C, -CH$_3$).

<u>Visible Spectrum</u> (CH$_2$Cl$_2$):

λ_{max} (nm)	397.2	497.2	530.6	567.2	620.6
log ϵ	5.21	4.13	3.99	3.82	3.70

<u>117</u>

<u>7,17-Diethyl-2,8,12,18-tetramethyl-3,13-[2-methoxy-5-methylphenylene-</u>

<u>1,3-bis(pentamethylene)]porphyrin</u>   (n = 5)   <u>117b</u>

This was prepared exactly as described for <u>87a</u> and <u>117a</u>.   In

two preparations the yields of porphyrin before recrystallization were

24.1% and 53.0%; a third preparation yielded 20.7% after recrystalliza-

tion from dichloromethane/hexanes.

<u>MP</u>:   253-256 C.

<u>Mol. Wt.</u> Calcd. for $C_{46}H_{56}N_4O$:   680.4454.   Found by high resolution

mass spectrometry: 680.4439.

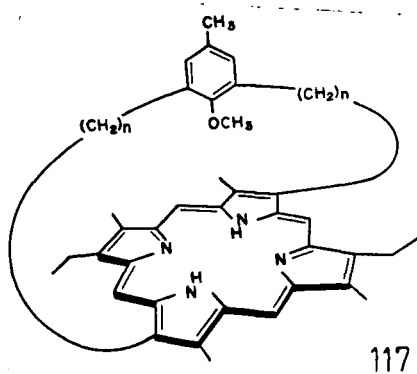<u>Anal.</u> Calcd. for $C_{46}H_{56}N_4O$:   C, 81.13; H, 8.29; N, 8.23; O, 2.35.

Found: C, 81.28; H, 8.20; N, 8.26; O, 2.16.

^{1}H-NMR (δ, CDCl$_3$):   10.04 (s, 2H, methine 10, 20-H), 10.01 (s, 2H,

methine 5, 15-H), 5.20 (s, 2H, phenyl 4, 6-H), 4.23 (m, 2H, chain 5-CH$_2$),

4.16 (m, 2H, -C$\underline{H}_2$CH$_3$), 4.07 (m, 2H, -C$\underline{H}_2$CH$_3$), 3.88 (m, 2H, chain 5-CH$_2$),

3.64 (s, 6H, two -CH$_3$), 3.52 (s, 6H, two-CH$_3$), 2.04 (m, 2H, chain 4-CH$_2$),

1.89 (t, m, 8H, -CH$_2$C$\underline{H}_3$, chain 4-CH$_2$), 1.41 (s, 3H, phenyl 5-CH$_3$),

0.94 (m, 2H, chain 3-CH$_2$), 0.86 (m, 2H, chain 3-CH$_2$), 0.68 (m, 2H,

chain 1-CH$_2$), 0.20 (m, 2H, chain 1-CH$_2$), 0.79 (m, 2H, chain 2-CH$_2$), -1.10 (m, 2H, chain 2-CH$_2$), -2.07 (s, 3H, -OCH$_3$), -3.77 (bs, 2H, N-H).

^{13}C-NMR (δ, 10% TFA-CDCl$_3$): 146.44, 143.87, 143.70, 143.32, 141.44, 141.29, 140.02, 139.58 (16C, α- and β-pyrrolic carbons), 132.93 (1C, phenyl 5-C), 131.81 (2C, phenyl 1, 3-C), 126.45 (2C, phenyl 4, 6-C), 100.04, 99.65 (4C, meso carbons), 58.89 (1C, OCH$_3$), 29.30, 28.65, 27.74, 27.25, 26.97 (10C, chain carbons), 20.22 (2C, CH$_2$CH$_3$), 19.81 (1C, phenyl 5-CH$_3$), 16.34 (2C, CH$_2$CH$_3$), 12.29, 11.59 (4C, CH$_3$).

Visible Spectrum (CH$_2$Cl$_2$):

λ_{max} (nm)	397.2	497.8	533.6	567.2	620.8
log ϵ	5.18	4.07	3.98	3.78	3.63
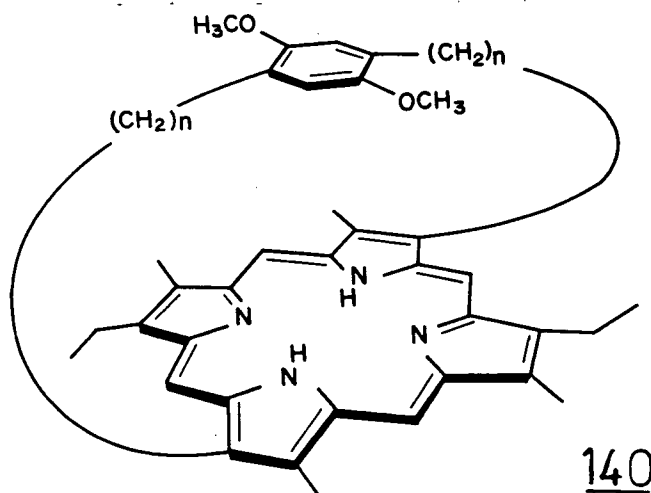
7,17-Diethyl-2,8,12,18-tetramethyl-3,13-[2,5-dimethoxyphenylene-1,4-bis(hexamethylene)]porphyrin   (n = 6)   140a

The synthesis and purification was carried out on 139a as described

for 87a and 117a. Of six preparations the yields before recrystalliza-
tion were 19.2%, 41.3%, 49.2% and 60.2%. The compound was recrystallized
from dichloromethane/hexanes.

MP: 271-274°C.

Mol. Wt. Calcd. for $C_{48}H_{60}N_4O_2$: 724.4716. Found by high resolution
mass spectrometry: 724.4695.

Anal. Calcd. for $C_{48}H_{60}N_4O_2$: C, 79.52; H, 8.34; N, 7.73; O, 4.41.
Found: C, 79.64; H, 8.40; N, 7.64; O, 4.44.

^{1}H-NMR (δ, $CDCl_3$): 10.00 (s, 2H, methine 5, 15-H), 9.98 (s, 2H, methine
10, 20-H), 4.43 (m, 2H, chain 6-CH_2), 4.12 (m, 2H, -CH_2CH_3), 4.04 (m, 2H,
-CH_2CH_3), 3.91 (s, 2H, phenyl 3, 6-H), 3.72 (m, 2H, chain 6-CH_2),
3.60 (s, 6H, two-CH_3), 3.59 (s, 6H, two-CH_3), 2.32 (m, 4H, chain 5-CH_2),
1.87 (t, 6H, -CH_2CH_3), 1.58 (s, 6H, -OCH_3), 1.50 (m, 2H, chain 4-CH_2),
1.22 (m, 2H, chain 4-CH_2), 0.82 (m, 4H, chain 3-CH_2), 0.40 (m, 3H,
chain 1-CH_2), 0.21 (m, 2H, chain 1-CH_2), 0.11 (m, 2H, chain 2-CH_2),
-0.10 (m, 2H, chain 2-CH_2), -3.99 (bs, 2H, N-H).

^{13}C-NMR (δ, 10% TFA-$CDCl_3$): 145.89, 142.96, 142.73, 142.12, 140.92,
139.64, 138.67, 138.28 (16C, α- and β-pyrrolic carbons), 99.00, 97.72
(4C, meso carbons), 31.88, 28.68, 28.43, 26.28 (chain carbons), 20.28
(2C, CH_2CH_3), 16.22 (2C, CH_2CH_3), 12.09, 11.61 (4C, CH_3).

<u>Visible Spectrum</u> (CH$_2$Cl$_2$):

λ_{max} (nm)	397.2	496.6	530.0	565.6	620.8
log ε	5.19	4.11	3.99	3.80	3.72

<u>7,17-Diethyl-2,8,12,18-tetramethyl-3,13[2,5-dimethoxyphenylene-1,4-</u>
<u>bis(pentamethylene)]porphyrin</u>   (n = 5)   <u>140b</u>

The synthesis and purification was carried out on <u>139b</u> as
described for <u>87a</u> and <u>117a</u>. The yield was 39.5%.

<u>MP</u>: 264-267°C.

<u>Mol. Wt.</u> Calcd. for C$_{46}$H$_{56}$N$_4$O$_2$: 696.4403. Found by high resolution
mass spectrometry: 696.4365.

<u>Anal.</u> Calcd. for C$_{46}$H$_{56}$N$_4$O$_2$: C, 79.27; H, 8.10; N, 8.04; O, 4.59.
Found: C, 79.40; H, 8.11; N, 8.02; O, 4.44.

^{1}<u>H-NMR</u> (δ, CDCl$_3$): 9.97 (s, 2H, methine 5, 15-H), 9.93 (s, 2H, methine
10, 20-H), 4.25 (m, 2H, chain 5-CH$_2$), 4.17 (m, 2H, -C<u>H</u>$_2$CH$_3$), 4.07 (m,
2H, -C<u>H</u>$_2$CH$_3$), 3.93 (m, 2H, chain 5-CH$_2$), 3.80 (s, 2H, phenyl 3, 6-H),
3.62 (s, 6H, two-CH$_3$), 3.54 (s, 6H, two-CH$_3$), 2.22 (m, 2H, chain 4-CH$_2$),
1.91, 1.88 (s, t, m, 14H, -OC<u>H</u>$_3$, -OCH$_2$C<u>H</u>$_3$, chain 4-CH$_2$), 1.07 (m, 2H,

chain 3-CH$_2$), 0.96 (m, 2H, chain 1-CH$_2$), 0.88 (m, 2H, chain 3-CH$_2$),

0.53 (m, 2H, chain 1-CH$_2$), -0.31 (m, 2H, chain 2-CH$_2$), -1.13 (m, 2H,

chain 2-CH$_2$), -3.90 (bs, 2H, N-H).

^{13}C-NMR (δ, 10% TFA-CDCl$_3$): 150.01 (1C, phenyl 2,5-C), 146.29, 143.75,

143.45, 143.30, 141.23, 140.91, 140.11, 139.37 (16C, α- and β-pyrrolic

carbons), 128.40 (2C, phenyl 1,4-C), 113.56 (2C, phenyl 3,6-C), 99.94,

99.42 (4C, meso carbons), 57.10 (2C, -OCH$_3$), 29.70, 28.80, 28.15, 28.08,

27.02 (10C, chain carbons), 20.30 (2C, CH$_2$CH$_3$), 16.52 (2C, CH$_2$CH$_3$),

12.34, 11.73 (4C, CH$_3$).

Visible Spectrum (CH$_2$Cl$_2$):

$\lambda\lambda_{max}$ (nm)	398.4	498.4	532.4	567.2	621.8
log ϵ	5.20	4.10	4.01	3.80	3.68

3.7   MODIFICATIONS OF STRAPPED PORPHYRINS
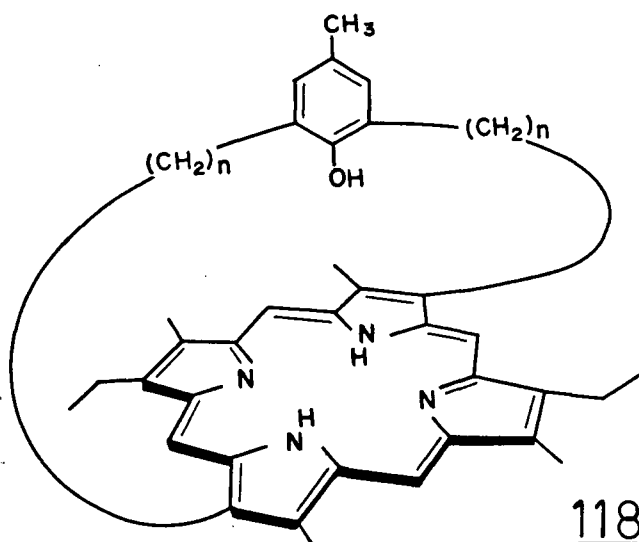
7,17-Diethyl-2,8,12,18-tetramethyl-3,13-[2-hydroxy-5-methylphenylene-

1,3-bis(hexamethylene)]porphyrin   (n = 6)   118a

Anisole strapped porphyrin 117a (153 mg, 0.22 mmol) was dissolved

in dry dichloromethane (10 mL) in an oven-dried 3-neck flask equipped

with magnetic stirrer bar, pressure-equalizing dropping funnel, argon

inlet and drying tube. Stirring under argon, the solution was cooled to

-78°C in a dry ice/acetone bath.

Boron tribromide (0.3 mL, 3.2 mmol) was dissolved in dichloro-

methane (5 mL) in the dropping funnel and was added dropwise to the

porphyrin solution over a period of 5 minutes. The reaction mixture

was left stirring at -78°C for 2 hours, then at room temperature for

a further 1 hour.

The reaction was quenched with water (10 mL) and extracted with

dichloromethane (50 mL). The organic layer was washed with sodium

bicarbonate solution and saturated sodium chloride solution, then dried over anhydrous sodium sulfate, filtered and evaporated to dryness.

The crude product was placed on a neutral alumina column (Merck 90, activity III) and eluted with dichloromethane. Fractions containing a single product were combined and evaporated (123 mg, 82.1%). The product was recrystallized from dichloromethane/hexanes as purple plates (67 mg, 54.3%).

MP: 260–263°C.

Mol. Wt. Calcd. for $C_{47}H_{58}N_4O$: 694.4606. Found by high resolution mass spectrometry: 694.4611.

Anal. Calcd. for $C_{47}H_{58}N_4O$: C, 81.22; H, 8.41; N, 8.06; O, 2.30. Found: C, 81.40; H, 8.47; N, 7.97; O, 2.40.

^{1}H-NMR (δ, CDCl$_3$): 10.04, 10.01 (s, 4H, methine 5,10,15,20-H), 5.51 (s, 2H, phenyl 4,6-H), 4.46 (m, 2H, chain 6-CH$_2$), 4.09 (m, 4H, -CH$_2$CH$_3$), 3.95 (m, 2H, chain 6-CH$_2$), 3.64 (s, 6H, two-CH$_3$), 3.62 (s, 6H, two-CH$_3$), 2.39 (m, 2H, chain 5-CH$_2$), 2.24 (m, 2H, chain 5-CH$_2$), 1.88 (t, 6H, -CH$_2$CH$_3$), 1.51 (s, 3H, phenyl 5-CH$_3$), 1.26 (m, 4H, chain 4-CH$_2$), 0.84 (m, 2H, chain 3-CH$_2$), 0.47 (m, 2H, chain 3-CH$_2$), 0.0 (m, 2H, chain 2-CH$_2$), -0.35 (m, 2H, chain 2-CH$_2$), -0.44 (m, 2H, chain 1-CH$_2$), -0.94 (m, 2H, chain 1-CH$_2$), -2.56 (bs, 1H, phenyl -OH), -3.68 (bs, 2H, -NH).

^{13}C-NMR (δ, 10% TFA-CDCl$_3$): 159.51 (1C, phenyl 2-C), 145.70, 144.79,

142.91, 142.60, 142.13, 140.91, 138.81, 138.10 (16C, α- and β-pyrrolic

carbons), 134.08, 132.61, 127.81 (5C, phenyl carbons), 98.79, 97.61

(4C, meso carbons), 30.89, 30.52, 30.29, 29.64, 28.74, 26.22 (12C,

chain carbons), 20.25 (3C, $\underline{C}H_2CH_3$ and phenyl 5-CH_3), 16.33 (2C, $CH_2\underline{C}H_3$),

11.92, 11.61 (4C, CH_3).

Visible Spectrum (CH_2Cl_2):

λ_{max} (nm)	398.0	498.0	534.8	564.4	618.0
log ε	5.24	4.12	4.00	3.84	3.69

7,17-Diethyl-2,8,12,18-tetramethyl-3,13-[2-hydroxy-5-methylphenylene-

1,3-bis(pentamethylene)]porphyrin   (n = 5)   118b

The demethylation was carried out on a 0.15 mmol scale, exactly

as described for 118a. After work-up the crude product was was

purified by chromatography on a neutral alumina column [Merck 90,

activity III] using dichloromethane as eluant (89.8 mg, 88.9%). The

product was recrystallized from dichloromethane/hexanes (72.9 mg, 72.2%).

MP: 295-298°C

Mol. Wt. Calcd. for $C_{45}H_{54}N_4O$: 666.4298. Found by high resolution

mass spectrometry: 666.4293.

<u>Anal</u>. Calcd. for $C_{45}H_{54}N_4O$: C, 81.04; H, 8.16; N, 8.40; O, 2.40.
Found: C, 78.70; H, 8.27; N, 8.04; O, 4.70.   Calcd. for
$C_{45}H_{54}N_4O \cdot 1H_2O$: C, 78.91; H, 8.24; N, 8.18; O, 4.67.

^{1}H-NMR (δ, CDCl$_3$): 10.22 (s, 2H, methine 5,15-H), 10.08 (s, 2H, methine
15,20-H), 5.33 (s, 2H, phenyl 4,6-H), 4.24 (m, 2H, chain 5-CH$_2$), 4.21,
4.08 (m, 4H, -C$\underline{H}_2$CH$_3$), 4.00 (m, 2H, chain 5-CH$_2$), 3.64, 3.50 (s, 12H,
four-CH$_3$), 2.22 (m, 2H, chain 4-CH$_2$), 1.88 (t, 6H, -CH$_2$C$\underline{H}_3$), 1.61 (m,
2H, chain 4-CH$_2$), 1.24-1.40 (m, 4H, chain 3-CH$_2$), 1.37 (s, 3H, phenyl
5-CH$_3$), -0.15 (m, 2H, chain 1-CH$_2$), -0.48 (m, 2H, chain 2-CH$_2$), -1.60
(m, 2H, chain 1-CH$_2$), -1.94 (m, 2H, chain 2-CH$_2$), -3.84 (bs, 2H, -NH).

^{13}C-NMR (δ, 10% TFA-CDCl$_3$): 158.87 (1C, phenyl 2-C), 146.42, 144.73,
143.42, 143.12, 141.66, 141.37, 140.56, 140.02 (16C, α- and β-pyrrolic
carbons), 131.32, 127.33, 126.52 (5C, phenyl carbons), 100.76, 100.10,
(4C, meso carbons), 29.08, 28.67, 28.13, 27.77, 27.65 (10C, chain
carbons), 20.36 (2C, $\underline{C}H_2CH_3$), 19.42 (1C, phenyl 5-$\underline{C}H_3$), 16.65 (2C,
CH$_2\underline{C}H_3$), 12.31, 11.85 (4C, CH$_3$).

<u>Visible Spectrum</u> (CH$_2$Cl$_2$):

λ_{max} (nm)	397.2	499.2	535.2	563.6	617.6
log ϵ	5.25	4.10	4.01	3.84	3.59

143
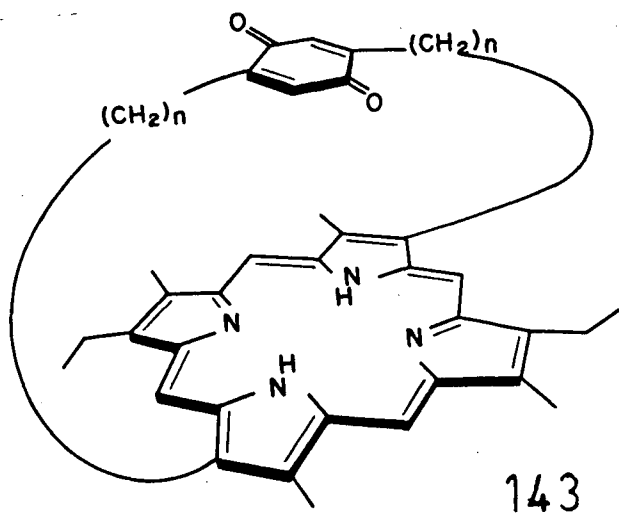
7,17-Diethyl-2,8,12,18-tetramethyl-3,13-[2,5-dioxophenylene-1,4-bis(hexamethylene)]porphyrin   (n = 6)   143a

The bis(methoxy)benzene porphyrin 140a (101 mg, 0.14 mmol) was dissolved in freshly distilled dichloromethane (30 mL) in a 3-neck flask equipped with argon inlet, pressure-equalizing addition funnel, drying tube and magnetic stirrer bar. The solution was stirred under argon and cooled to -78°C in a dry ice/acetone bath.

A solution of boron tribromide (0.5 mL, 5.3 mmol) in dichloromethane (10 mL) was placed in the addition funnel and added dropwise to the porphyrin solution over a period of 10 minutes. The solution was left stirring at -78°C for 1.25 hours, allowed to reach room temperature and stirred for a further 1.5 hours. At this stage, tlc (10% ethyl acetate/hexanes) showed no sign of the starting material.

The reaction was quenched by the addition of water (10 mL) and the mixture extracted with 6M hydrochloric acid, sodium bicarbonate

solution and saturated sodium chloride solution. The organic layer
was dried over anhydrous sodium sulfate, filtered and evaporated to
dryness.

The hydroquinone was oxidized to the quinone by stirring in
dichloromethane with lead dioxide for approximately 10 minutes. When
tlc indicated complete reaction the oxidant was filtered off. The
crude product was placed on a neutral alumina column [Merck 90,
activity III]. Elution with dichloromethane yielded the quinone-
strapped porphyrin 143a (79.8 mg, 82.2%) which was recrystallized
from toluene (58.8 mg, 60.6%).

MP: >260°C (dec).

Mol. Wt. Calcd. for $C_{46}H_{54}N_4O_2$: 694.4247. Found by high resolution
mass spectrometry: 694.4249.

Anal. Calcd. for $C_{46}H_{54}N_4O_2$: C, 79.50; H, 7.83; N, 8.06; O, 4.60.
Found: C, 79.24; H, 8.00; N, 7.94; O, 4.80.

^{1}H-NMR (δ, CDCl$_3$): 10.03 (s, 2H, methine 5,15-H), 10.02 (s, 2H, methine
10,20-H), 4.40 (m, 2H, chain 6-CH$_2$), 4.12 (q, 4H, -CH$_2$CH$_3$), 3.63-3.75
(m, 2H, chain 6-CH$_2$), 3.68, 3.60 (s, 12H, four-CH$_3$), 2.76 (s, 2H,
quinone 3,6-H), 2.51 (m, 4H, chain 5-CH$_2$), 1.89 (t, 6H, -CH$_2$CH$_3$), 1.73
(m, 2H, chain 4-CH$_2$), 1.51 (m, 2H, chain 4-CH$_2$), 1.11 (m, 2H, chain 3-
CH$_2$), 0.95 (m, 2H, chain 3-CH$_2$), 0.27 (m, 2H, chain 1-CH$_2$), 0.05 to
-0.15 (m, 4H, chain 2-CH$_2$), -0.72 (m, 2H, chain 1-CH$_2$), -4.00 (bs, 2H,
-NH).

^{13}C-NMR (δ, 10% TFA-CDCl$_3$): 188.19 (2C, $\underline{C}$ = 0), 148.61 (2C, quinone 1,4-C), 145.71, 142.69, 142.57, 142.21, 141.39, 141.05, 139.39, 138.46 (16C, α- and β-pyrrolic carbons), 132.42 (2C, quinone 3,6-C), 99.14, 98.10 (4C, meso carbons), 31.32, 27.51, 27.28, 27.17, 26.93, 26.29 (12C, chain carbons), 20.30 (2C, $\underline{CH}_2CH_3$), 16.32 (2C, CH$_2\underline{C}$H$_3$), 12.27, 11.68 (4C, CH$_3$).

Visible Spectrum (CH$_2$Cl$_2$):

λ_{max} (nm)	258.4	397.2	497.2	530.4	567.2	621.6
log ϵ	4.72	5.21	4.08	3.94	3.79	3.63

7,17-Diethyl-2,8,12,18-tetramethyl-3,13-[2,5-dioxophenylene-1,4-bis(pentamethylene)]porphyrin   (n = 5)   143b

The bis(methoxy)benzene porphyrin 140b (61.6 mg, 0.09 mmol) was demethylated under the conditions outlined for compound 143a. The crude product was oxidized with lead dioxide and purified by chromatography to give 58.9 mg (98.6%). Recrystallization from toluene afforded 41.2 mg (69.9%) of the quinone-strapped porphyrin 143b.

MP: >270°C (dec).

Mol. Wt. Calcd. for C$_{44}$H$_{50}$N$_4$O$_2$: 666.3934. Found by high resolution

mass spectrometry: 666.3984.

Anal. Calcd. for $C_{44}H_{50}N_4O_2$: C, 79.24; H, 7.56; N, 8.40; O, 4.80.

Found: C, 77.00; H, 7.44; N, 8.00; O, 6.77.

Calcd. for $C_{44}H_{50}N_4O_2 \cdot 1H_2O$: C, 77.16; H, 7.65; N, 8.18; O, 7.01.

^{1}H-NMR (δ, CDCl$_3$): 9.47 (s, 4H, methine 5,10,15,20-H), 4.30 (m, 2H, chain 5-CH$_2$), 4.08-4.25 (m, 4H, -C$\underline{H}_2$CH$_3$), 3.97 (m, 4H, chain 5-CH$_2$), 3.70, 3.57 (s, 12H, four-CH$_3$), 2.94 (s, 2H, quinone 3,6-H), 2.33 (m, 2H, chain 4-CH$_2$), 1.93 (t and m, 8H, -CH$_2$C$\underline{H}_3$ and chain 4-CH$_2$), 1.25 (m, 2H, chain 3-CH$_2$), 1.14 (m, 2H, chain 3-CH$_2$), 0.65 (m, 2H, chain 1-CH$_2$), -0.02 (m, 2H, chain 1-CH$_2$), -0.32 (m, 2H, chain 2-CH$_2$), -1.29 (m, 2H, chain 2-CH$_2$), -3.91 (bs, 2H, N-H).

^{13}C-NMR (δ, 10% TFA-CDCl$_3$): 186.33 (2C, quinone 2,5-C), 147.05 (2C, quinone 1,4-C), 146.15, 142.99, 142.81, 142.05, 141.92, 140.86, 140.17, 139.62 (16C, α- and β-pyrrolic carbons), 131.45 (2C, quinone 3,6-C), 99.85, 98.72 (4C, meso carbons), 28.66, 27.00, 26.86, 25.99, 25.92 (10C, chain carbons), 20.43 (2C, $\underline{C}H_2CH_3$), 16.54 (2C, CH$_2\underline{C}H_3$), 12.20. 11.80 (4C, CH$_3$).

Visible Spectrum (CH$_2$Cl$_2$):

λ_{max} (nm)	260.0	396.8	498.0	534.8	567.2	620.8
log ϵ	4.47	5.21	4.07	3.98	3.82	3.58

3.8   SYNTHESES OF IMIDAZOLE PRECURSORS
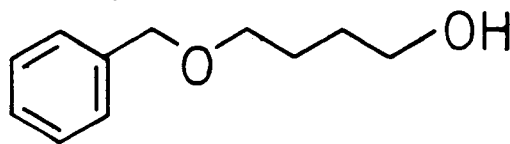
177

4-Benzyloxy-1-butanol 177

Sodium metal (40.1 g, 1.7 mol) was washed in dry xylene and was added in small pieces (~1 g) to a solution of butanediol (476.5 g, 5.3 mol) in dry xylene (160 mL) at 120°C. When all the sodium had dissolved, benzyl chloride (218.1 mL, 1.9 mol) was added dropwise over a period of 3 hours, the temperature of the reaction mixture being maintained at 120°C. The solution was heated at 120°C for a further 1 hour, then allowed to cool to room temperature.

The precipitate was filtered off and the xylene was removed from the filtrate by rotary evaporation. The residue was distilled under reduced pressure (10 mmHg). The unreacted butanediol distilled over first and the product was collected at 152-165°C (10 mmHg) as a clear colorless liquid (179.3 g, 52.5%).

BP: 152-165°C @ 10 mmHg; Lit.[234] 98-107°C @ 1 mmHg

^{1}H-NMR (δ, CDCl$_3$): 1.5-1.8 (m, 4H, 1-, 3-CH$_2$), 2.59 (b.s, 1H, -O$\underline{H}$), 3.51, 3.61 (t, 4H, 1-, 4-CH$_2$), 4.52 (s, 2H, C$_6$H$_5$C$\underline{H}_2$), 7.34 (s, 5H, C$_6\underline{H}_5$).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.12; H, 8.88.

Mass Spectrum (m/e, relative intensity): 180 (M^+, 7), 137 (3), 107 (73), 91 (100), 79 (14), 77 (7), 71 (17).
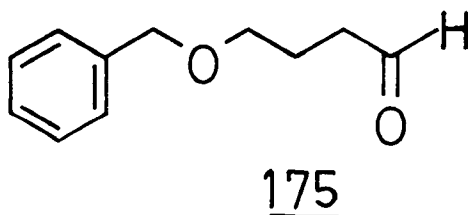
4-Benzyloxybutyraldehyde 175

Oxalyl chloride (27.8 mL, 0.32 mmol) was added to dry dichloromethane (150 mL) in a 3-neck flask equipped with overhead stirrer, nitrogen inlet and pressure equalizing addition funnel. The mixture was cooled to ∿-70°C in a dry ice/acetone bath.

With stirring, a solution of dimethyl sulfoxide (47.2 mL, 0.67 mmol) in dichloromethane (150 mL) was added dropwise, gas evolution being observed.

4-Benzyloxy-1-butanol 177 (50.0 g, 0.28 mmol) was dissolved in dichloromethane (200 mL) and added dropwise to the above solution. The solution was left stirring for 10 minutes while a cloudy white precipitate developed.

Triethylamine (194.4 mL, 1.4 mmol) was added. A dense white precipitate formed and the solution was left stirring at -70°C for 1 hour before warming to room temperature.

The reaction mixture was transferred to a separatory funnel and

washed with 2M hydrochloric acid (200 mL), saturated sodium bicarbonate solution (200 mL), water (200 mL) and saturated sodium chloride solution (200 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to give a slightly yellow oil. The crude product was distilled under reduced pressure. The clear colorless liquid distilling at 105-108°C (4 mmHg) was collected (43.8 g, 88.5%).

BP: 105-108°C @ 4 mmHg.

^{1}H-NMR (δ, CDCl$_3$): 1.7-1.8 (m, 2H, 3-CH$_2$), 2.44 (t, 2H, 2-CH$_2$), 3.42 (t, 2H, J = 6 Hz, 4-CH$_2$), 4.40 (s, 2H, C$_6$H$_5$CH$_2$), 7.24 (s, 5H, C$_6$H$_5$), 9.68 (t, 1H, -C(H)=O).

Anal. Calcd. for C$_{11}$H$_{14}$O$_2$: C, 74.13; H, 7.92. Found: C, 73.94; H, 8.02.

Mass Spectrum (m/e, relative intensity): 178 (M$^+$, 8), 150 (9), 107 (35), 91 (100), 87 (10), 79 (12), 77 (4), 71 (11).

178
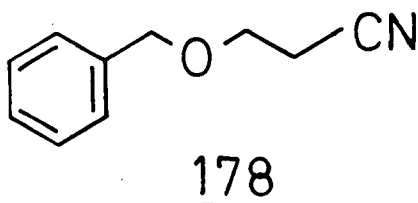
3-Benzyloxypropionitrile 178

Methanol (10 mL) was placed in a 3-neck flask equipped with nitrogen inlet, magnetic stirrer bar, thermometer and pressure-equalizing

addition funnel. With stirring, sodium metal (1.5 g) was added. When hydrogen evolution slowed down, benzyl alcohol (240 mL, 2.28 mol) was added and the solution stirred until all the sodium dissolved. The solution was cooled in an ice-bath to 35°C and acrylonitrile (150 mL, 2.28 mol) added, keeping the temperature at 30-35°C. The mixture was left stirring at room temperature for 1 hour then acidified with glacial acetic acid.

The mixture was distilled through a 1-foot Vigreux column under reduced pressure. The product was collected as a clear colorless liquid distilling in the range 115-123°C @ 5 mmHg (268.1 g, 73.0%).

BP: 115-123°C @ 5 mmHg. Lit.[224] 114-116°C @ 0.5 mmHg.

^{1}H-NMR (δ, CDCl$_3$): 2.50 (t, 2H, 2-CH$_2$), 3.58 (t, 2H, 3-CH$_2$), 4.48 (s, 2H, C$_6$H$_5$CH$_2$), 7.30 (s, 5H, C$_6$H$_5$).

Anal. Calcd. for C$_{10}$H$_{11}$NO: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.50; H, 7.09; N, 8.85.

Mass Spectrum (m/e relative intensity): 161 (M$^+$, 39), 132 (7), 106 (22), 104 (10), 91 (100), 79 (30), 77 (21).
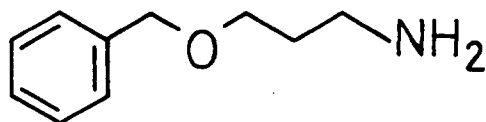
176

3-Benzyloxypropylamine 176

A 1-liter 3-neck flask, equipped with nitrogen inlet and mechanical stirrer, was charged with anhydrous diethyl ether (300 mL) and cooled in an ice-bath. Lithium aluminum hydride (21.2 g, 0.56 mol) was added and the mixture stirred.

Aluminum trichloride (62.0 g, 0.47 mol) was weighed into a 50 mL Erlenmeyer flask which was then attached to one neck of the reaction flask by a length of wide bore Tygon tubing. This enabled the aluminum chloride to be added in small portions. When addition was completed the flask and tubing were replaced with a pressure equalizing dropping funnel.

A solution of 3-benzyloxypropionitrile 178 (50.0 g, 0.31 mol) in anhydrous diethyl ether (200 mL) was added dropwise, and the solution left stirring overnight.

A 30% potassium hydroxide solution (300 mL) was added (slowly at first) and, after briefly stirring, the two layers were allowed to separate. The ether layer was decanted, and the aqueous layer was extracted with more ether (2 x 200 mL). The ether solutions were combined, dried over anhydrous sodium sulfate, filtered and evaporated to obtain a yellow oil.

The crude product was distilled under reduced pressure (96–98°C at 4 mmHg) to yield a colorless liquid (44.8 g, 87.3%).

BP: 96–98°C @ 4 mmHg; Lit.[232] 103°C @ 2 mmHg.

^{1}H-NMR (δ, CDCl$_3$): 1.58 (s, 2H, -NH$_2$), 1.70 (q, 2H, J = 6 Hz, 2-CH$_2$), 2.75 (t, 2H, J = 6 Hz, 1-CH$_2$), 3.50 (t, 2H, J = 6 Hz, 3-CH$_2$), 4.45 (s, 2H, C$_6$H$_5$CH$_2$-), 7.28 (s, 5H, C$_6$H$_5$).

Anal. Calcd. for C$_{10}$H$_{15}$NO: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.89; H, 9.08; N, 8.60.

Mass Spectrum (m/e, relative intensity): 166 (M$^+$, 1), 108 (16), 107 (15), 91 (100), 79 (24), 77 (20), 74 (75).

$$BzO(CH_2)_3 \diagdown \diagup (CH_2)_3OBz$$

174
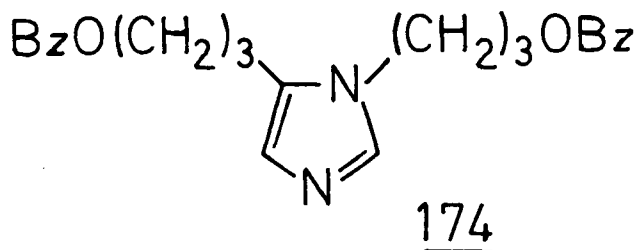
1,5-Bis(3-benzyloxypropyl)imidazole 174

A solution of 3-benzyloxybutyraldehyde 177 (0.54 g, 3.0 mmol) and triethylamine (1.27 g, 12.6 mmol) in dry methanol (25 mL) was added dropwise to a solution of 4-benzyloxypropylamine 176 (0.49 g, 3.0 mmol) and tosylmethyl isocyanide (0.61 g, 3.1 mmol) in dry methanol (40 mL)

over a period of 30 minutes. The mixture was left stirring for 70 hours.

The solvent was removed and the residue placed on a silica gel column (Merck Kieselgel 60H, 20 g). The column was eluted first with dichloromethane but the product only came off when the polarity of the eluant was increased to 10% acetone/dichloromethane. Those fractions in which the desired product predominated were combined and evaporated to give a yellow oil (0.43 g, 39.4%).

^{1}H-NMR (δ, CDCl$_3$): 1.7-2.2 (m, 4H, chain 2-CH$_2$), 2.67 (t, 2H, Im-5C-CH$_2$), 3.40, 3.50 (t, 4H, chain 3-CH$_2$), 3.97 (t, 2H, Im-N-CH$_2$), 4.50 (s, 4H, C$_6$H$_5$CH$_2$O-), 6.77 (bs, 1H, Im-4H), 7.37 (s, 6H, C$_6$H$_5$- and Im-2H).

Mass Spectrum (m/e, relative intensity): 364 (M$^+$, 13), 273 (20), 167 (19), 139 (16), 124 (26), 91 (100).

$$HO(CH_2)_3 \diagdown \diagup N \diagup (CH_2)_3 OH$$

172
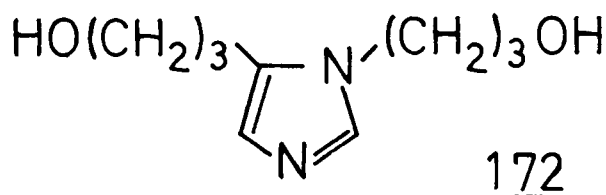
1,5-Bis (3-hydroxypropyl)imidazole 172

A 3-neck flask was equipped with ammonia and nitrogen inlets, pressure-equalizing addition funnel and magnetic stirrer bar. With

cooling in a dry ice/acetone bath, ammonia was introduced into the flask until about 25 mL of liquid had collected.

1,5-Bis(3-benzyloxypropyl)imidazole 174 (0.39 g, 1.1 mmol) was dissolved in freshly distilled tetrahydrofuran (50 mL) and added dropwise to the solution which was stirring under nitrogen. Sodium metal was cut into small pieces and added in portions until the reaction mixture attained a deep blue color. After stirring for 30 minutes the blue color was discharged by the addition of solid ammonium chloride and the solution allowed to warm to room temperature under a stream of nitrogen.

20% Methanol/dichloromethane was added to the solid residue and the insoluble material removed by filtration. The filtrate was placed on a silica gel column (Merck Kieselgel 60, 50 g) and eluted with 20% methanol/dichloromethane. Those fractions containing pure product were combined and evaporated to give a yellow oil (0.11 g, 57.4%).

^{1}H-NMR (δ, CDCl$_3$/DMSO-d$_6$): 1.4-1.8 (m, 4H, chain 2-CH$_2$), 2.40 (t, 2H, Im-5C-CH$_2$), 2.30, 2.39 (t, 4H, 3-CH$_2$), 3.76 (t, 2H, Im-N-CH$_2$), 6.48 (bs, 1H, Im-4H), 7.23 (bs, 1H, Im-2H).

Mass Spectrum (m/e, relative intensity): 184 (M$^+$, 22), 140 (39), 96 (100).

CHAPTER 4

SPECTRAL ASSIGNMENTS AND COMPARISON TABLES

4.1 ^{1}H-NMR DATA OF STRAPPED PORPHYRINS

In this and subsequent sections the strapped porphyrins will be referred to by the trivial names indicated in Fig. 27. Chemical shifts stated without indication of the units refer to ppm on the δ scale.

When compared to their non-strapped analogue, etioporphyrin II 185, the ^{1}H-NMR of the strapped porphyrins display the expected features. Because of its symmetry, etioporphyrin II has a simple spectrum with the four ring methyls at the 2,8,12,18 positions occurring as a singlet at 3.62 and the ethyl groups as a triplet and quartet at 1.87 and 4.11 respectively.[235] Although two signals would be expected, the four meso protons (5,10,15,20) occur as a singlet at 10.11. The inner N-H protons appear upfield of TMS at -3.67 due to extensive shielding by the porphyrin ring current.

Introduction of the bridging strap, which is equivalent to joining the ethyl groups at positions 3 and 13 of etio II, leads to a decrease in symmetry and a splitting of the meso, ring methyl and methylene resonances. It has been already noted that the splitting of the ring methyl signals shows a definite trend depending on strap length.[117] While the unstrapped etio II shows a single methyl resonance at 3.62, the presence of the strap results in a splitting and an upfield shift as illustrated in Fig. 28. In general the two methyl resonances move upfield at differing rates as the strap length is decreased. The resonance at higher field may be assigned to the methyl groups at the 2,12 positions by analogy to N-alkylated porphyrins. Studies have shown that substituents on the N-alkylated pyrrole ring appear upfield relative to similar substituents on the non-alkylated rings. Since the N-alkylated ring is tilted
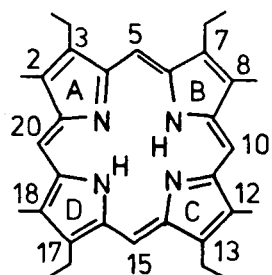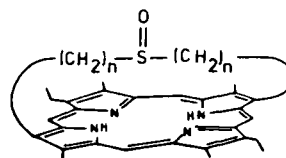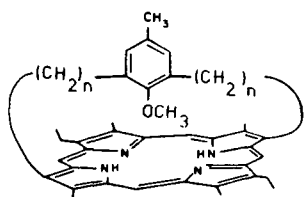
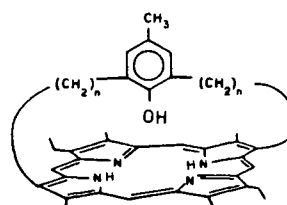**185** Etio II
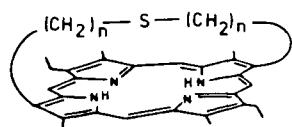
87a n = 5 C_5SC_5

b n = 4 C_4SC_4

88a n = 5 C_5-Sulfoxide

b n = 4 C_4-Sulfoxide

117a n = 6 C_6-OCH_3

b n = 5 C_5-OCH_3

118a n = 6 C_6-OH

b n = 5 C_5-OH
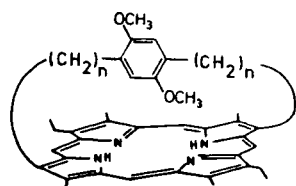
140a n = 6 C_6-$(OMe)_2$

b n = 5 C_5-$(OMe)_2$
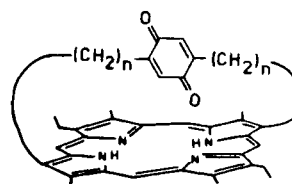
143a n = 6 C_6-Quinone

b n = 5 C_5-Quinone

Fig. 27: Schematic Representation and Abbreciated Names for the
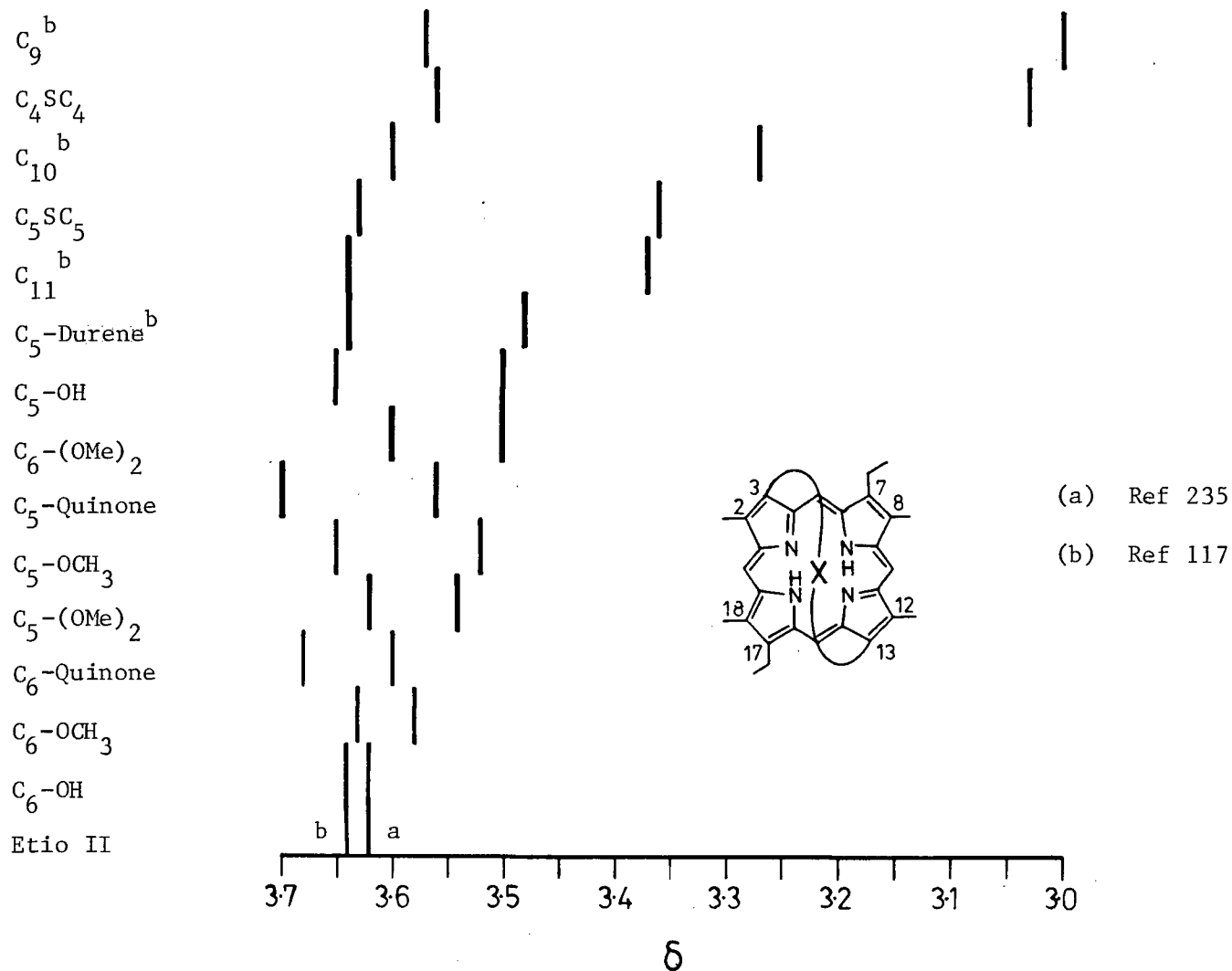Strapped Porphyrins

Fig. 28: Variation of Porphyrin Ring Methyl Chemical Shifts with Strap Length

from the porphyrin plane this difference in chemical shifts reflects

the difference in position of the substituents with respect to the

porphyrin ring current.[235,236] Similarly decreasing the strap length

will tilt rings A and C so that the methyl groups at the 2,12 positions

no longer experience the full deshielding effect of the porphyrin and

move upfield. For the longer straps, the distortion of rings B and D

is minimal and the methyls at the 8,18 positions resonate close to the

position for the unstrained etio II. Only as the strap becomes very

short (10 carbon atoms) is there a significant upfield shift of this

signal.

Two exceptions to this behaviour are noted. When a quinone is

incorporated into the strap the signal for the 8,18 methyl groups

experiences a significant downfield shift. These methyl groups may

experience a deshielding effect from the quinone carbonyls. The methyl

groups at the 2,12 positions also experience this deshielding, but the

effect is overridden by the out-of-plane shift. For the dimethoxybenzene

porphyrins 117a,b the 8,18 methyls experience a slight upfield shift.

From examination of CPK models, conformations of the strap are possible in

which the benzene ring is above rings B and D. In those cases the

deshielding effect of the ring current at the porphyrin periphery may be

opposed by a shielding effect of the benzene ring, resulting in a net

upfield shift.

Introduction of the strap disrupts the coincidence of the meso

proton signals observed in etio II. As with the methyl groups decreasing

the strap length leads to upfield shifts and an increasing separation

between the meso signals (Fig. 29). Individual resonances were assigned

in most cases using decoupling experiments; irradiation of the multiplet
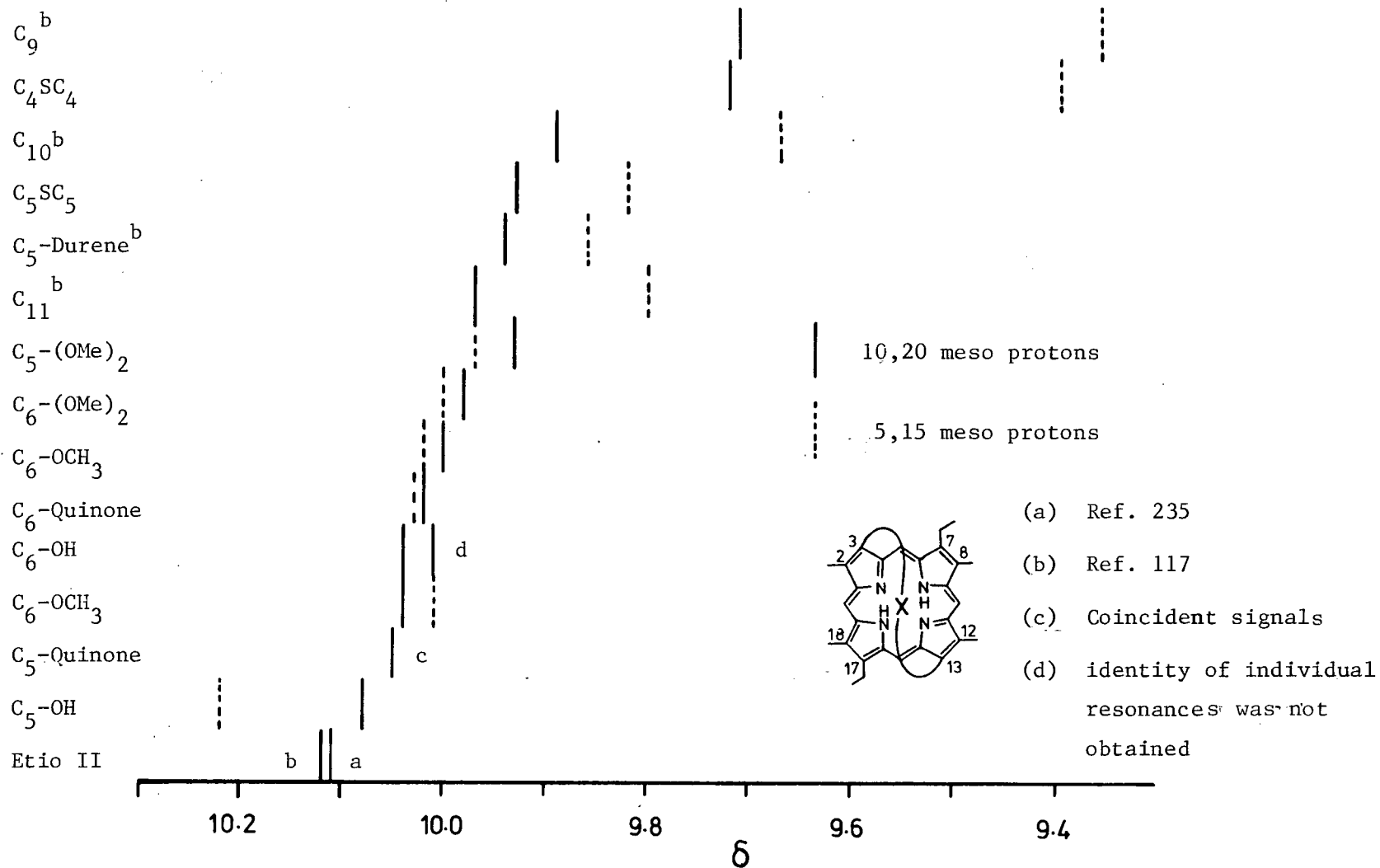
Fig. 29: Variation of Meso Proton Chemical Shifts with Strap Length

due to the ethyl methylene groups results in an enhancement of the
signal for the 5,15 meso protons. In general, for the longer chain, the
upfield shift and the splitting of the signals is quite small, and it is
the 10,20 signal which is further upfield. On decreasing the strap length
both signals continue to move upfield, but at differing rates, so that
eventually it is the 5,15 meso signal which is further upfield. Examina-
tion of CPK models suggests that, when an aromatic ring is incorporated
into the strap, there are conformations of the strap in which the aromatic
ring is directly above the 10,20 meso positions. At these positions the
deshielding effect of the porphyrin ring current is partially offset by
the shielding effect of the aromatic ring, resulting in a slight upfield
shift for these protons compared to the 5,15 protons, whose upfield shift
is determined solely by disruption of the porphyrin ring current. As the
disruption becomes more severe in the shorter straps (11-9 carbon atoms)
and the influence of the phenyl ring is removed, the 5,15 meso protons
experience a greater upfield shift. Some exceptions occur to this
simplistic explanation notably for C_5-OH, where the 5,15 protons display
a unexpected downfield shift and for the C_5-durene and C_5-OMe$_2$ where
the order of the signals is reversed despite the similarity of the
straps. The same reversal of signals is also observed for the C_6-OCH$_3$
and C_5-OCH$_3$ pair. For the C_5-quinone sample the meso signals were
coincident.

If the upfield shift of the porphyrin methyl and meso protons is
the result of the perturbation of the porphyrin π electron cloud on
introduction of the strap, then a corresponding downfield shift of the
N-H protons should be observed due to a decreased shielding at the
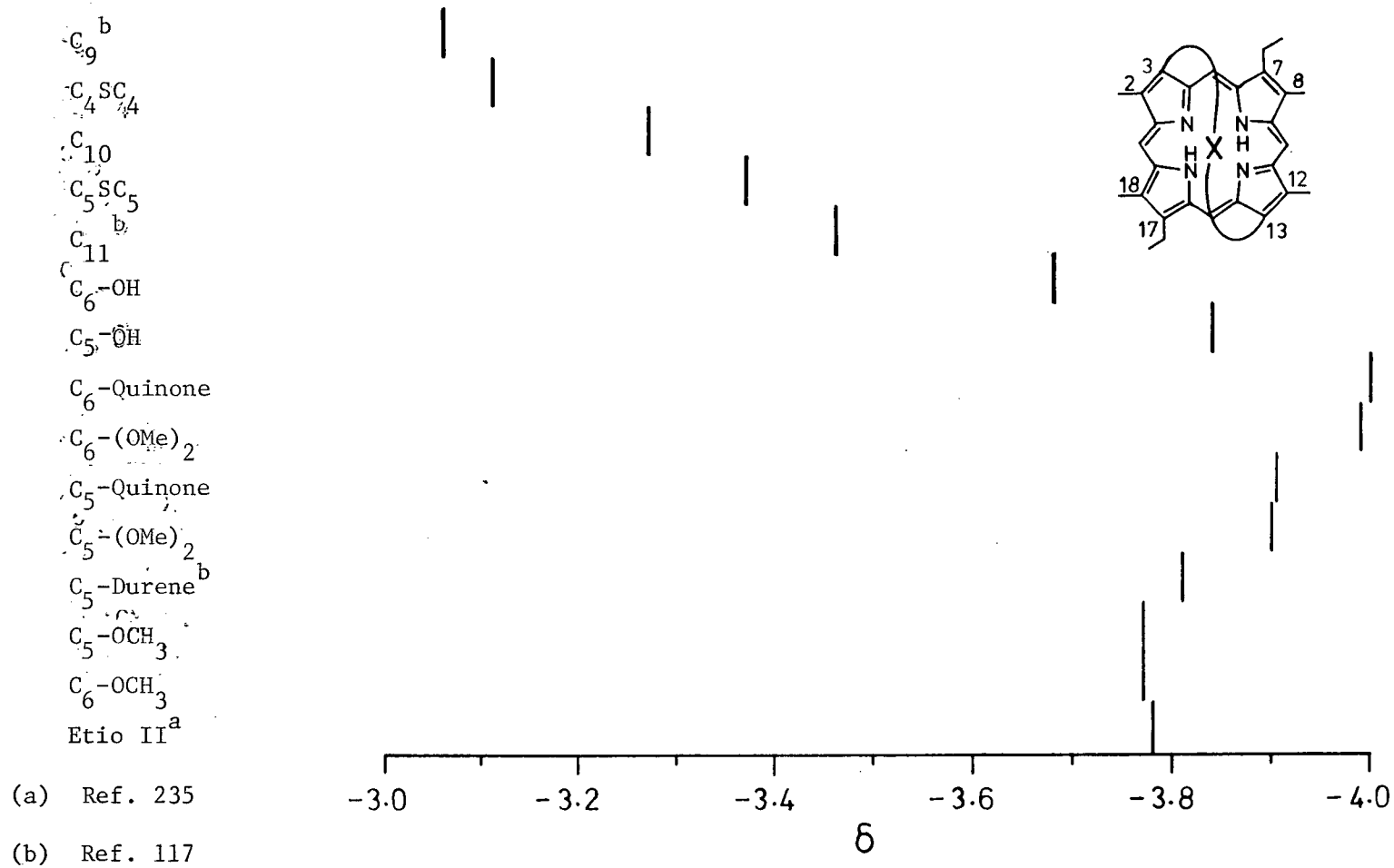porphyrin core. On the whole this is what is observed (Fig. 30). For

C$_9$ [b]

C$_4$SC$_4$

C$_{10}$

C$_5$SC$_5$

C$_{11}$ [b]

C$_6$-OH

C$_5$-OH

C$_6$-Quinone

C$_6$-(OMe)$_2$

C$_5$-Quinone

C$_5$-(OMe)$_2$

C$_5$-Durene [b]

C$_5$-OCH$_3$

C$_6$-OCH$_3$

Etio II [a]

(a) Ref. 235

(b) Ref. 117

-3.0   -3.2   -3.4   -3.6   -3.8   -4.0

δ

Fig. 30:   Variation of Porphyrin Core Protons with Strap Length

straps bearing a dimethoxybenzene 140a,b or quinone ring 143a,b there is

a further upfield shift due to the shielding effect of the rings. With

the anisole porphyrins 117a,b the N-H protons resonate at a similar

position to etio II (3.77), indicating that the phenyl ring may be

perpendicular to the porphyrin. While hydrogen bonding to the phenol may

explain the downfield shift of the N-H protons in C_6-OH, the upfield

shift in C_5-OH is unexpected. When the complicating effect of a benzene

or quinone ring in the strap is removed the downfield shift of the N-H

resonance corresponds directly to the decrease in chain length.

The ethyl methylene protons of etio II appear as a simple quartet

at 4.11. Introduction of the strap, which is equivalent to linking

diagonally opposite ethyl groups, results in a pair of multiplets for the

methylene groups adjacent to the porphyrin. That the protons at the

strap's terminus appear as complex multiplets indicates that flipping

of the strap above and below the porphyrin plane is relatively slow

(Scheme 96). Otherwise the n,n' protons would give simple triplets

from coupling to its adjacent pair.[132] From Fig. 31 it can be seen

that for unstrained porphyrins the signals for the chain terminal protons

are evenly distributed about the resonance position of the ethyl

methylene protons of etio II. As the chain length decreases and rings

A and C are tilted out of the plane, both signals experience similar

upfield shifts. The asymmetry of the strapped porphyrins also results

in an inequivalence of the methylene protons of the 7,17 ethyl groups,

which occur as a pair of complex multiplets. Similar diastereotopic

behaviour by the ethyl methylene protons has been observed in a number

of monomeric and dimeric scandium and thallium porphyrins.[217,218] In

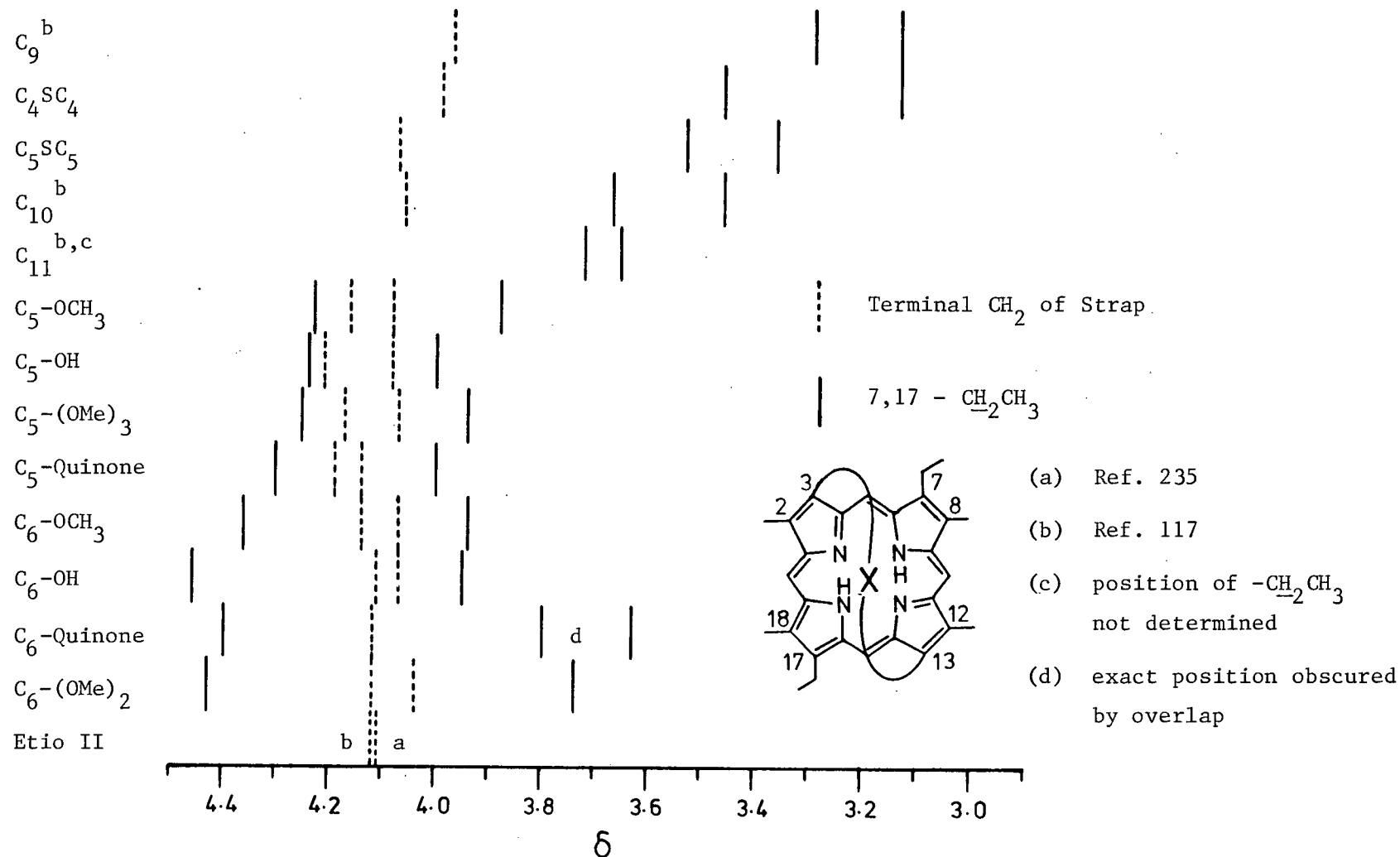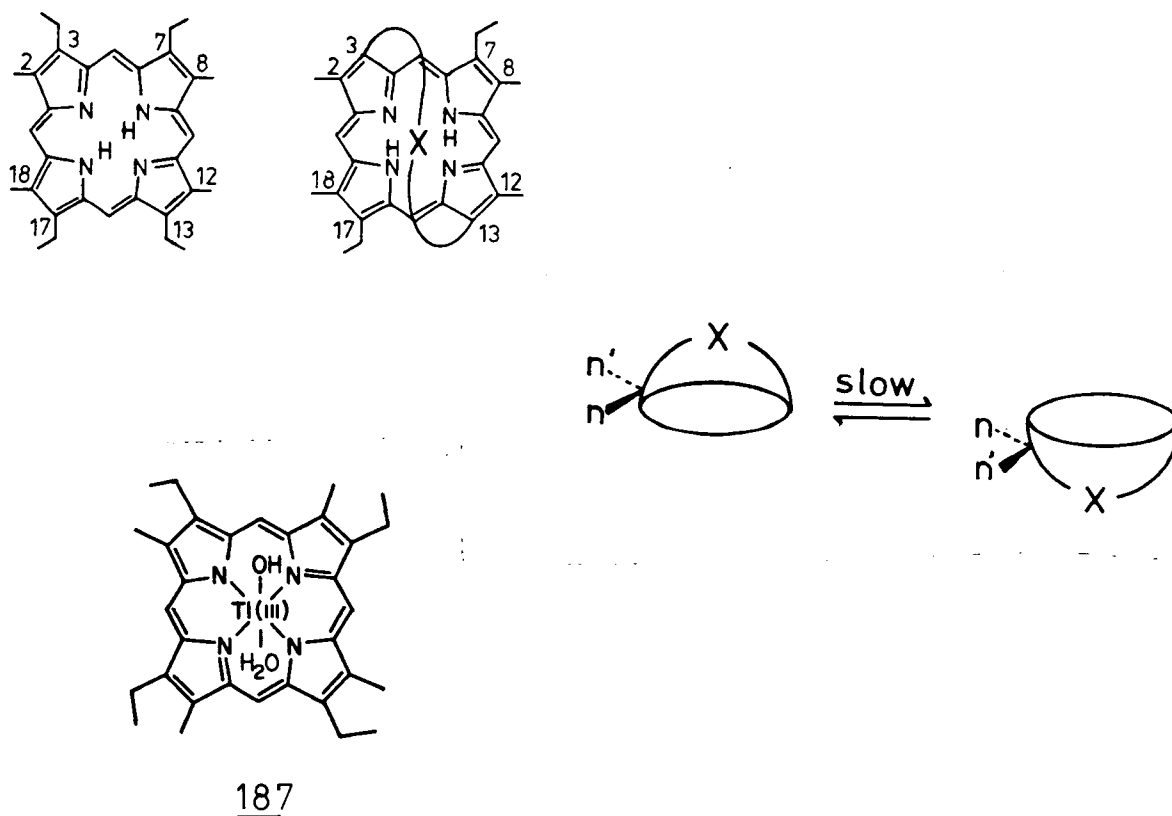the case of the thallium porphyrin 187 the asymmetry results both from

Fig. 31: Variation of Chain Termini and Porphyrin Ethyl Chemical Shifts

The following labels appear along the vertical axis of the chart:

C_9 b
C_4SC_4
C_5SC_5
C_{10} b
C_{11} b,c
C_5-OCH$_3$
C_5-OH
C_5-(OMe)$_3$
C_5-Quinone
C_6-OCH$_3$
C_6-OH
C_6-Quinone
C_6-(OMe)$_2$
Etio II

Legend within the figure:

Terminal CH_2 of Strap

$7,17 - CH_2CH_3$

(a) Ref. 235

(b) Ref. 117

(c) position of $-CH_2CH_3$ not determined

(d) exact position obscured by overlap

Horizontal axis (δ): 4.4, 4.2, 4.0, 3.8, 3.6, 3.4, 3.2, 3.0

SCHEME 96

<u>187</u>

the difference in the axial ligands and from the size of the thallium

ion which is too large to sit in the porphyrin plane. For the strapped

porphyrins irradiation of the triplet at 1.6-1.9, due to the ethyl methyl

protons, leads to the collapse of the multiplets to give an AB quartet.

The only exception to this behaviour was observed in the C_6-quinone case

where the methylene protons appeared as a quartet centered at 4.12.

Irradiation of the triplet at 1.89 then yielded a singlet.

The chemical shifts of each pair of protons in the strap have been

identified by decoupling experiments (Table VII). Having assigned the

two multiplets in the region 3.1-4.5 to the protons at the strap's

terminus, irradiation of each multiplet in turn identified those protons

on the adjacent carbon. Systematic irradiation of each multiplet

TABLE IV: ^{1}H-NMR Data of Sulfide- and Sulfoxide-Strapped Porphyrins
(in $CDCl_3$)
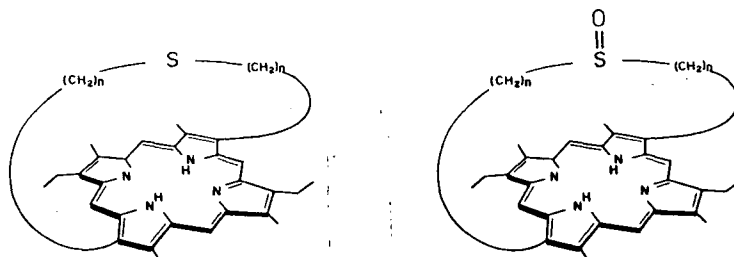
| GROUP	87a (n = 5)	87b (n = 4)	88a (n = 5)	88b (n = 4)
10,20 Methine H's	9.93	9.72	9.98*	9.78*
			9.96	9.50
5,15 Methine H's	9.82	9.40	9.89	9.47
			9.88	
$-CH_2CH_3$	4.09	3.99	4.02	4.01
$-CH_3$	3.63	3.56	3.67	3.58
	3.36	3.03	3.66	3.09
			3.43	3.05
			3.40	
$-CH_2CH_3$	1.86	1.83	1.88	1.87
			1.87	
N-H	-3.38	-3.11	–	–
Chain 1-CH_2	-2.02	-3.74	-3.98*	-5.69*
	-1.56		-3.45	-5.35
			-2.89	-2.49
Chain 2-CH_2	-1.85	-0.86	-1.91	-2.30
	-1.46	-0.62	-0.74	-1.10
Chain 3-CH_2	-0.13	0.79	-0.3 to -0.6	+0.26
	0.17	0.93	-0.07	0.35
			+0.47	0.54
Chain 4-CH_2	1.42	3.08	1.22	1.4 - 1.6
		3.44	1.50	2.90
			1.82	3.3 - 3.5
Chain 5-CH_2	3.63	–	3.6 - 3.7	3.6 - 3.7
	3.97		3.8 - 4.0	

* Resonances not assigned

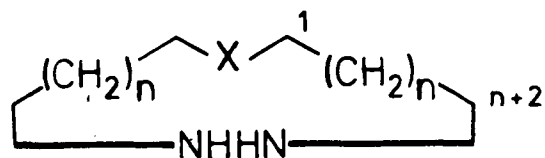TABLE V: ^{1}H-NMR Data of Anisole- and Phenol-Strapped Porphyrins (in $CDCl_3$)
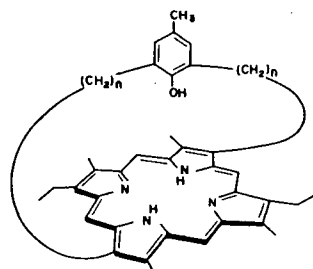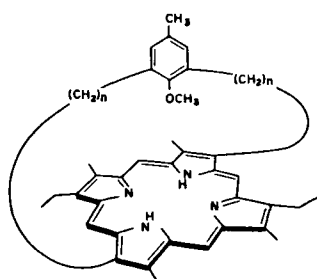
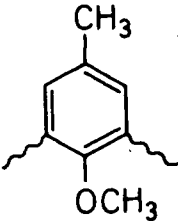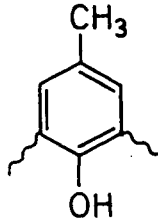| GROUP	117a (n = 6)	117b (n = 5)	118a (n = 6)	118b (n = 5)
10,20 Methine H's	10.00	10.04	10.04	10.08
5,15 Methine H's	10.02	10.01	10.01	10.22
Phenyl 4,6-H	5.60	5.20	5.51	5.33
-$\underline{CH}_2CH_3$	4.13 4.06	4.16 4.07	4.09	4.21 4.08
-CH_3	3.63 3.58	3.64 3.52	3.64 3.62	3.64 3.50
-CH_2CH_3	1.88	1.89	1.88	1.88
Phenyl 5-CH_3	1.69	1.41	1.51	1.37
Phenyl 2-OCH_3	-2.70	-2.07	-	-
N-H	-3.77	-3.77	-3.68	-3.84
Chain 1-CH_2	0.18 0.50	0.20 0.68	-0.94 -0.44	-1.60 -0.15
Chain 2-CH_2	0.03 0.27	-1.10 -0.79	-0.35 0.0	-1.94 -0.48
Chain 3-CH_2	0.42 0.71	0.86 0.94	0.47 0.84	1.24 1.40
Chain 4-CH_2	0.84 0.89	1.89 2.04	1.26	1.60 2.22
Chain 5-CH_2	2.02 2.19	3.88 4.23	2.24 2.39	4.00 4.24
Chain 6-CH_2	3.94 4.36	-	3.95 4.46	-

TABLE VI: ^{1}H-NMR Data of Dimethoxybenzene- and Quinone-Strapped
Porphyrins (in $CDCl_3$)
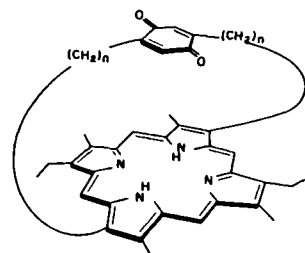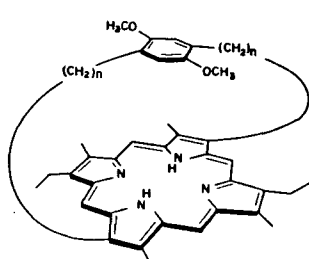
GROUP	140a (n = 6)	140b (n = 5)	143a (n = 6)	143b (n = 5)
10,20 Methine H's	9.98	9.93	10.02	
				10.05
5,15 Methine H's	10.00	9.97	10.03	
$-CH_2CH_3$	4.12 4.04	4.17 4.07	4.12	4.08–4.25
Phenyl 3,6-H	3.91	3.80	–	–
$-CH_3$	3.60 3.59	3.62 3.54	3.68 3.60	3.70 3.57
Quinone 3,6-H	–	–	2.76	2.94
$-CH_2CH_3$	1.87	1.88	1.89	1.93
Phenyl 2,5-OCH_3	1.58	1.91	–	–
N-H	-3.99	-3.90	-4.00	-3.91
Chain 1-CH_2	0.70 0.21	0.53 0.96	0.27 -0.70	0.65 0.0
Chain 2-CH_2	-0.10 0.11	-1.13 -0.31	0.05–0.15	-1.29 -0.32
Chain 3-CH_2	0.82	0.88 1.07	0.95 1.11	1.14 1.25
Chain 4-CH_2	1.22 1.50	1.91 2.22	1.51 1.73	1.93 2.33
Chain 5-CH_2	2.32	3.93 4.25	2.51	3.97 4.30
Chain 6-CH_2	3.72 4.43	–	3.63–3.75 4.40	–
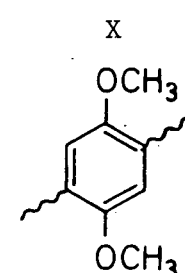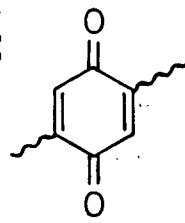
X		1	2	3	4	5	6
	87a (n = 3)	−2.02	−1.85	−0.13	1.42	3.63	
S		−1.56	−1.46	0.17		3.97	
	87b (n = 2)	−3.74	−0.86	0.79	3.08		
			−0.62	0.93	3.44		
CH₃ ... OCH₃	117a (n = 4)	0.18	0.03	0.42	0.84	2.02	3.94
		0.50	0.27	0.71	0.89	2.19	4.36
	117b (n = 3)	0.20	−1.10	0.86	1.89	3.88	
		0.68	−0.79	0.94	2.04	4.23	
CH₃ ... OH	118a (n = 4)	−0.94	−0.35	0.47	1.26	2.24	3.95
		−0.44	0.0	0.84		2.39	4.46
	118b (n = 3)	−1.60	−1.94	1.24	1.61	4.00	
		−0.15	−0.48	1.40	2.22	4.24	

X		1	2	3	4	5	6
OCH$_3$ ... OCH$_3$ (structure)	140a (n = 4)	0.21	-0.10	0.82	1.22	2.32	3.72
		0.70	0.11		1.50		4.43
	140b (n = 3)	0.53	-1.13	0.88	1.91	3.93	
		0.96	-0.31	1.07	2.22	4.25	
O ... O (quinone structure)	143a (n = 4)	-0.70	0.05-0.15	0.95	1.51	2.51	3.63-3.75
		0.27		1.11	1.73		4.40
	143b (n = 3)	0.0	-0.32	1.14	1.93	3.97	
		0.65	-1.29	1.25	2.33	4.30	

C_6-quinone

undecoupled

Simultaneous
Irradiation
at 1.89
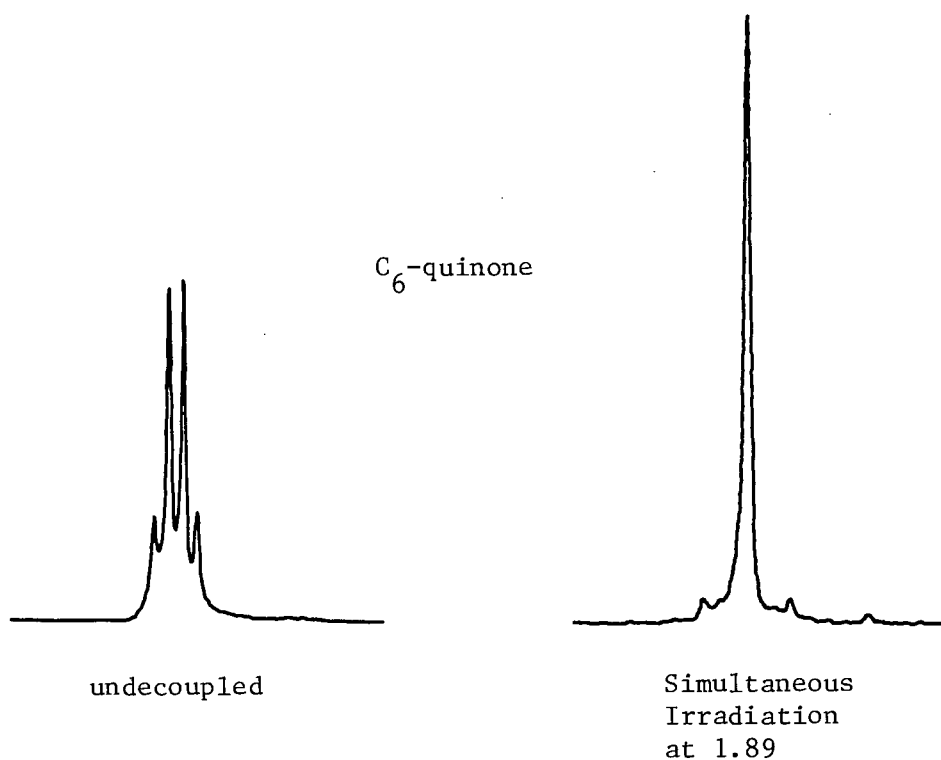
identified each pair of protons on the strap.

Attempts to extract structural information from the chemical

shifts of the strap protons were complicated by the interplay of

several factors. All protons in the strap will experience an upfield

shift due to shielding by the porphyrin ring current. Since this effect

Y

─NH │ HN─

X
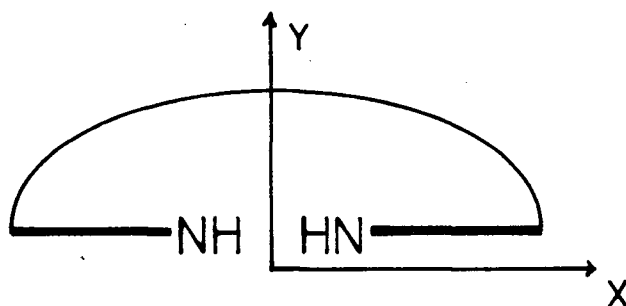
decreases along both x-and y-axes, the largest upfield shift should be experienced by the protons at the center of the strap. However when the strap is functionalized this upfield shift may be opposed by the deshielding effect of the functional group. Thus, for C_5SC_5, the methylene protons adjacent to the sulfur occur further downfield (-1.56 and 2.02) than expected compared to a non-functionalized carbon strap (e.g., C_{10}, -2.23, -5.87). Since the shielding effect of the porphyrin decreases also along the y-axis the conformation of the strap will determine chemical shifts. Those protons which are directed into the cavity bounded by the porphyrin and the strap will experience a greater shielding and upfield shift than those directed away. This has been exemplified by the methylene chain porphyrins where a particular conformation 184 has been invoked to explain the pattern of upfield shifts.[117,132] Although the porphyrin ring current has its greatest
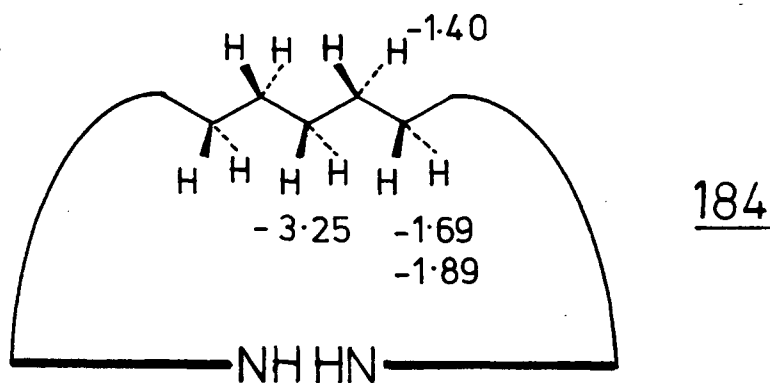

effect at the porphyrin core, local maxima associated with individual pyrrole rings may also account for the alternating pattern of upfield shifts.[132] Therefore for functionalized straps the chemical shifts of the straps' protons depend on the following factors:

(i)   the shielding effect of the porphyrin

(ii)   the deshielding effect of the functional group

(iii)   the conformation of the strap

(iv)   the length of the strap

(v)   the presence of local ring current maxima

Since these factors may reinforce or cancel each other it is difficult to extract useful information from the chemical shift data alone.

For the C_5-quinone porphyrin the C_2 protons appear further upfield than the C_1 protons (Table VII). How much of this can be attributed to the deshielding effect of the quinone, or to a conformation in which the C_1 protons are directed outside the cavity and the C_2 protons inside, is unclear. For the C_6-quinone the C_1 protons are at +0.27 and -0.70 while the C_2 protons both occur at 0.05-0.15. If the influence of the quinone is the same in both compounds then in C_6-quinone the strap has adopted a conformation in which one proton of C_1 is pointing into the cavity while both protons of C_2 are on the outside. However this data does not suggest any order for the porphyrin-quinone separation in the two compounds. Observation of CPK molecular models suggests that the longer, more flexible chain in C_6-quinone can accomodate a shorter porphyrin-quinone separation, which is analogous to Baldwin's "cap" and "homo-cap" porphyrins.[99,100] This is reinforced by the larger upfield shift of the quinone proton in C_6-quinone (2.76) compared to C_5-quinone (2.94). A similar situation was observed by Sanders.[132]

For both dimethoxybenzene porphyrins, C_6-OMe_2 and C_5-OMe_2, the conformation of the chain appears to be similar with the C_1 protons on

C_6-quinone C_5-quinone

$Y_5 > Y_6$
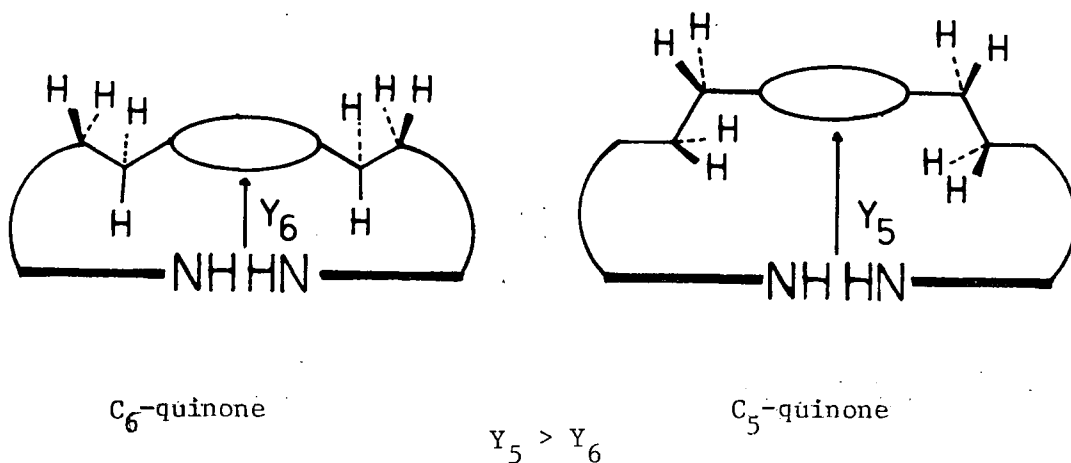
the outside of the cavity and the C_2 protons directed inside. Alternatively, the deshielding effect of the phenyl ring current may cancel the shielding effect of the porphyrin, resulting in a net downfield shift of the C_1 protons compared to those on C_2. In this instance the phenyl proton (C_6 3.91, C_5 3.80) and the methoxy protons (C_6 1.58, C_5 1.88) offer conflicting estimates of the porphyrin-phenyl separation.

Similar arguments may be advanced to explain the more downfield position of the C_1 protons relative to those on C_2 for the anisole porphyrins, C_5-OCH_3 and C_6-OCH_3. If the chemical shifts of the phenyl (C_6 5.60, C_5 5.20) and methyl protons (C_6 1.69, C_5 1.41) may be taken as indicators of separation, then in C_5-OCH_3 the phenyl is closer to the porphyrin than in C_6-OCH_3. That the methoxy group occurs at -2.70 in C_6-OCH_3 compared to -2.07 in C_5-OCH_3 may be ascribed to steric crowding in the latter system. In the more crowded C_5-OCH_3 the methoxy methyl is constrained into positions outside the cavity and experiences a lesser upfield shift compared to the "looser" C_6-OCH_3 which can accommodate the methoxy group within the cavity (Fig. 32).

Removal of the methoxy group to give C_5-OH and C_6-OH results in a dramatic change in the chemical shifts of the C_1 and C_2 protons. One may speculate that formation of the phenol results in either a relief
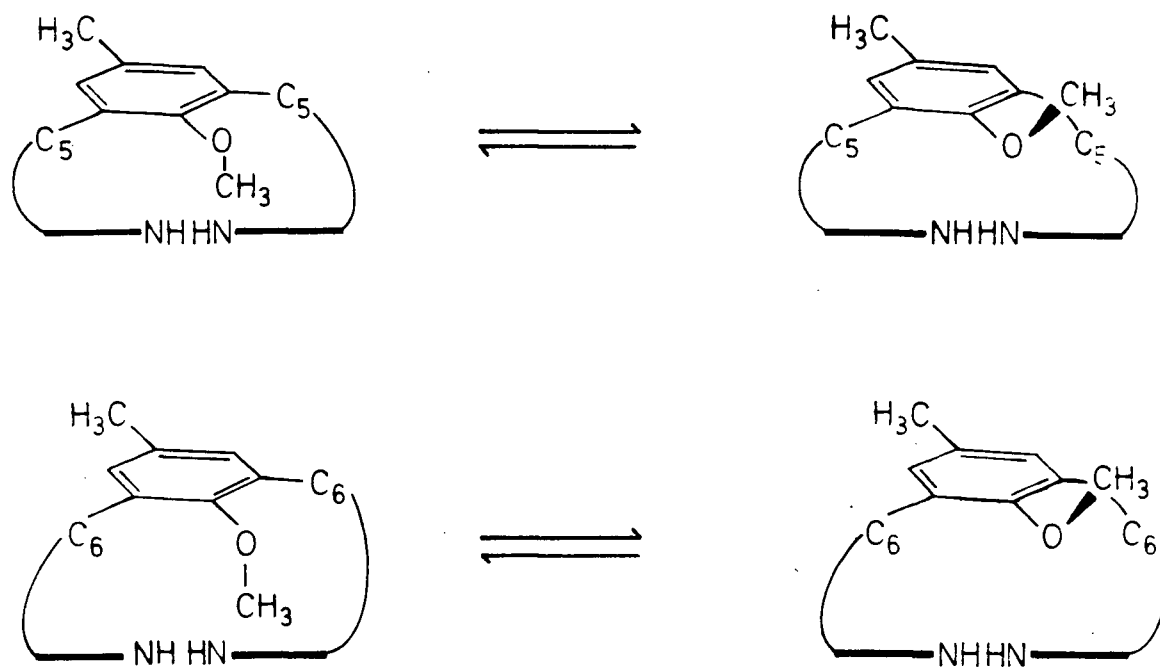
Fig. 32: Schematic Representation of Steric Crowding in 117a and 117b

of steric congestion or hydrogen-bonding between the phenol and N-H protons. The phenyl moves closer to the porphyrin core, and the subsequent conformational change in the strap rotates the C_1 protons inside the cavity, resulting in a large upfield shift. The position of the phenyl (C_6 5.51, C_5 5.33) and methyl protons (C_6 1.51, C_5 1.37) both suggest that the phenyl ring is closer to the porphyrin in the C_5-OH case. One anomaly is the downfield shift of the phenyl proton on going from C_5-OCH$_3$ (5.20) to C_5-OH (5.33). The origin of this effect is unclear.

The pattern of peaks for the C_4SC_4 porphyrin suggests that the

molecule may adopt a conformation similar to that shown in 185, where

the C_1 protons are directed inside the cavity with the sulfur and the

C_2 protons pointing away from the porphyrin. For the C_5SC_5 186 porphyrin

185

186
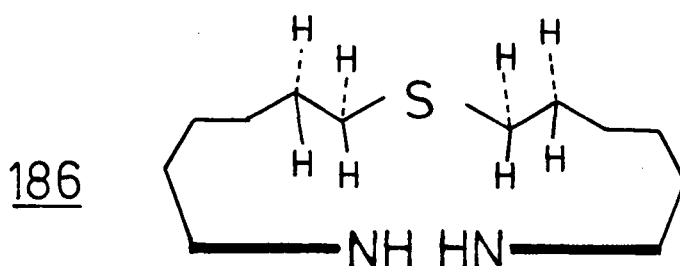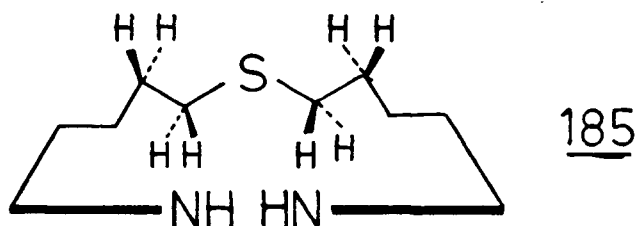
it appears that both C_1 and C_2 have one proton directed inside the

cavity and one outside.

Etioporphyrin II displays C_{2v} symmetry and so we observe a single

resonance for the methyl and ethyl methylene protons and two coincident

signals for the meso protons. Introduction of the strap across one

face of the porphyrin decreases the symmetry of the molecule. The

strapped porphyrins are chiral and occur as a racemic mixture of the two

enantiomers. For the quinone 143a,b and dimethoxybenzene porphyrins

140a,b , all conformations of the strap (except one) render the molecule

completely asymmetric. That only two signals are still observed for

the meso and methyl protons implies that the porphyrin and the quinone or

benzene rings are strictly parallel, or that there is rapid averaging

of a least two conformations. Similarly, for the anisole 117a,b and

phenol porphyrins 118a,b, the porphyrin and the phenyl rings must be

strictly perpendicular or rapid averaging is occurring.

The consequences of molecular symmetry were demonstrated in the ^{1}H-NMR spectra of a series of porphyrins with a sulfur functional group incorporated into the strap. For C_5SC_5 87a the molecule displays effective C_2 symmetry and two signals each are observed for the meso and methyl protons, and ten multiplets for each of the pairs of protons on the strap. On oxidation to the tetrahedral sulfoxide the porphyrin contains no symmetry elements at all. Four signals each are observed for the meso and methyl protons, with two triplets for the ethyl methyl groups and twenty multiplets for each proton of the strap. Further oxidation to the sulfone restores the symmetry of the molecule and only two signals each are observed for the meso and methyl protons and ten multiplets for the strap protons.

Recent X-ray crystal structure determinations of C_5SC_5 87a and C_4SC_4 87b have been carried out. For the shorter chain C_4SC_4 87b the porphyrin ring is significantly distorted from planarity. This distortion, while much less, is still apparent for the longer chain C_5SC_5 87a. These results are in agreement with the conclusions drawn from visible and ^{1}H-NMR spectroscopy. The conformations of the straps in the crystal are also similar to those conformations 185, 186 deduced from a simplistic interpretation of the ^{1}H-NMR case. Thus for C_4SC_4 the strap carbons adjacent to the sulfur are close to the porphyrin ring. The protons on these carbons are directed into the cavity and experience a large upfield shift. For C_5SC_5, the unit $-C_2-C_1-S-C_1-C_2-$ appears to be almost linear, and one proton each from C_1 and C_2 is directed into the cavity experiencing larger upfield shifts compared to the protons directed outside.

C₄SC₄ **87b**
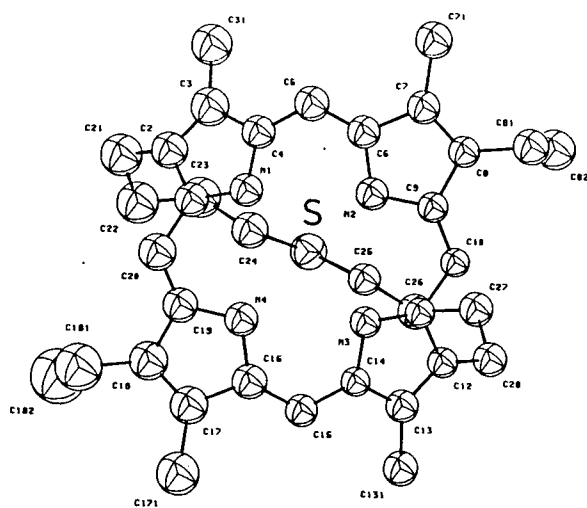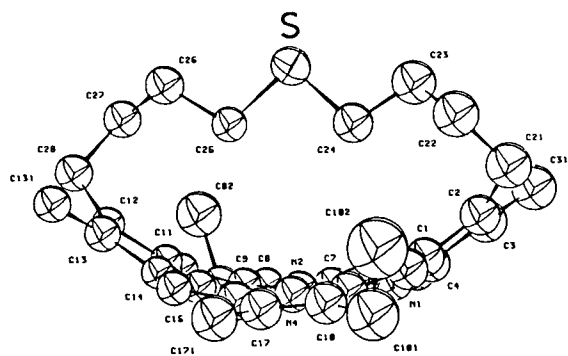
C₅SC₅ **87a**
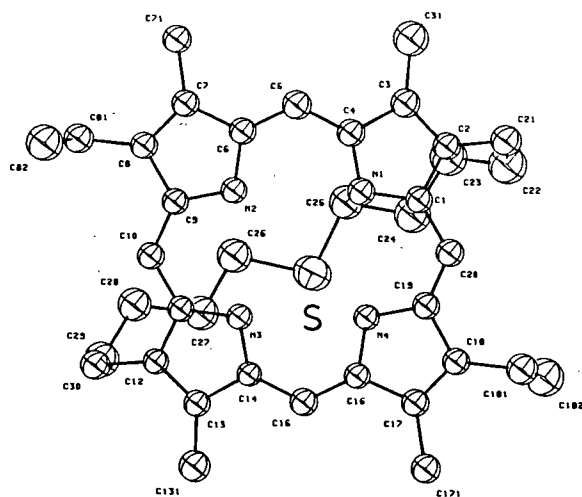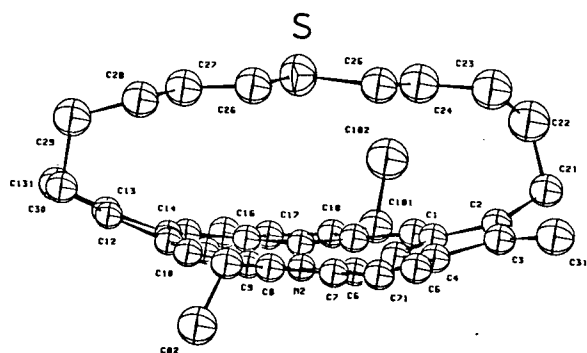
4.2 ^{13}C-NMR DATA OF STRAPPED PORPHYRINS

The ^{1}H-NMR spectra of porphyrins are dominated by the ring current

effects of the macrocycle, the resulting shifts being of the same

magnitude as the observed range of chemical shifts (∿10 ppm).   For ^{13}C-NMR

the ring current shifts are of the same magnitude as for ^{1}H-NMR, but since

the observed range of ^{13}C chemical shifts is about 200 ppm, the effect

is less dramatic.

The ^{13}C-NMR spectra of the strapped porphyrins may be divided

into four regions. Signals for the β- substituents and the methylene

carbons of the strap occurred in the region 10-52 δ. The methoxy groups

of the dimethoxybenzene 140a,b and the anisole porphyrins 117a,b are

located at 57-60 δ. The meso carbons were confined to a narrow region at

97-100 while the α- and β-pyrrolic carbons and the phenyl carbon occurred

from 110-160 δ.

In general the spectra showed small upfield shifts (4 ppm) for

the carbons in the straps functional group compared to the corresponding

bis-dipyrromethanes or bis-pyrroles. Furthermore, for the anisole and

phenol porphyrins this upfield shift was more pronounced in the C_5

rather than the C_6 strap. This supported the arguments based on ^{1}H-NMR

that the phenyl ring is closer to the porphyrin in the shorter strap

molecule. For the quinone porphyrins 143a, 143b the upfield shift

(1-2 ppm) of the quinone carbons on decreasing the strap length from 6

to 5 conflicted with ^{1}H-NMR evidence which suggested that it was with

the longer, more flexible strap that the quinone could approach more

closely to the porphyrin.

For the strapped porphyrins displaying C_2 symmetry there were four

distinct carbons each for the α- and β-pyrrolic positions. When a spectrum of C_5SC_5 was recorded in deuterochloroform no signals were observed for the quarternary α-pyrrolic carbons. This failure to observe sharp resonances had previously been attributed to N-H tautomerization.[237] The use of 10% TFA-CDCl$_3$ as solvent to record the ^{13}C-NMR spectra of the strapped porphyrins was prompted not by solubility considerations alone (indeed the samples appear to be sufficiently soluble in deuterochloroform), but to allow observation of the α-carbons by forming the dication and preventing tautomerization. Under these conditions the full eight signals were observed although it was not possible to assign the individual resonances.

The chemical shifts of the meso carbons are sensitive to the substitution pattern on the porphyrin periphery. These signals were used to confirm the homogeneity of the sample, the observation of only two peaks in the region 98-100 ppm indicating that rearrangement during the acid catalyzed intramolecular condensation had not occurred. Two exceptions were the asymmetric C_5-sulfoxide 88a and C_4-sulfoxide 88b where three (ratio 2:1:1) and four meso signals were observed respectively. These compounds also showed sixteen signals for the α- and β-pyrrolic carbons as expected. Attempts to correlate the chemical shifts of the meso carbons and the strap length met with only limited success. For hydrocarbon and sulfide straps the separation of the two signals increased with decreasing strap length (Fig. 33). Introduction of a phenyl or quinone ring into the strap resulted in no obvious trends.

The positions of the porphyrin ethyl (∿20 and 16 δ) and methyl (∿11 ppm) did not appear to be affected by introduction of the strap, appearing close to the values observed for etioporphyrin II. In most
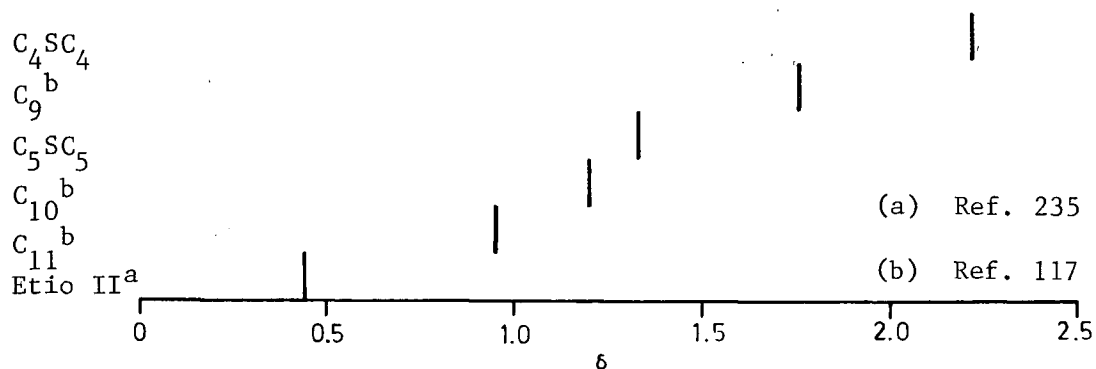
Fig. 33: Separation of Meso Carbon Resonances as a Function of Strap Length

cases two signals were observed for the two distinct methyl groups. For C_4SC_4 the two signals are coincident, while for the asymmetric C_5-sulfoxide four signals were observed.

The spectrum of $C_6-(OMe)_2$ 140a was anomalous. When run in 10% TFA-CDCl$_3$ all the signals for the porphyrin carbons appeared at the expected positions. However none of the dimethoxybenzene signals appeared and for the strap carbons only two sharp signals (31.88, 26.28) were observed with two broad signals at 28.67 and 28.43. Introduction of a 3s pulse delay resulted in no improvement of the spectrum. In contrast, the spectrum of $C_5-(OMe)_2$ 140b in the same solvent displayed all the expected signals.

Three explanations presented themselves:

(i)   the samples of $C_6-(OMe)_2$ were contaminated with some paramagnetic impurity,

(ii)   the dimethoxybenzene ring had been oxidized to the radical, or

(iii)   the dimethoxybenzene ring and the strap were slowly interconvert-

        ing among several conformations leading to broadening of the

        signals.

Possibility (i) was considered unlikely since the absence of the

peaks had been observed using different samples of C_6-(OMe)$_2$ and

different batches of solvents. Furthermore C_5-(OMe)$_2$ 140b, prepared

under identical conditions, showed all the expected peaks.

A high temperature (80°C) spectrum (Fig. 54) was run in 10% TFA-

Toluene-d$_8$ in an attempt to speed up interconversion between the various

conformers leading to sharp signals for an "average" conformation.

Although there was some sharpening for the strap carbons (3 peaks at

32.28, 29.07 and 26.47), the dimethoxybenzene carbons were still very

broad. However, when the spectrum was run in CDCl$_3$ at room temperature,

all the expected resonances were observed (the α-pyrrolic carbons were

broadened due to N-H tautomerization). ^{1}H-NMR displayed complimentary

behaviour. In CDCl$_3$ all the proton resonances were observed, but in

TFA-CDCl$_3$ or TFA-Toluene-d$_8$, there was a broadening or disappearance of

all the dimethoxybenzene protons and some of the strap methylene protons.
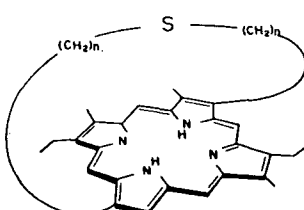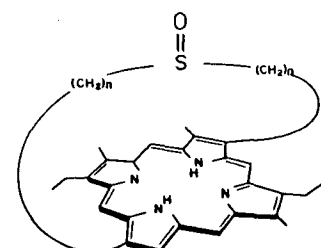
It would appear that for the free-base form the strap of C_6-(OMe)$_2$

can rotate freely among a number of conformations giving rise to sharp

signals for the average conformation. On protonation however, this

rotation is restricted and the signals for the strap are broadened. This

restricted rotation may be due to either or both of the following:

(i)   hydrogen-bonding between the oxygen of the methoxy group and the

(i) N-H, or

(ii) ruffling of the pyrrole rings on protonation may hinder rotation

of the strap.

TABLE VIII: ^{13}C-NMR Data of Sulfide- and Sulfoxide-Strapped Porphyrins (in 10% TFA-CDCl$_3$)
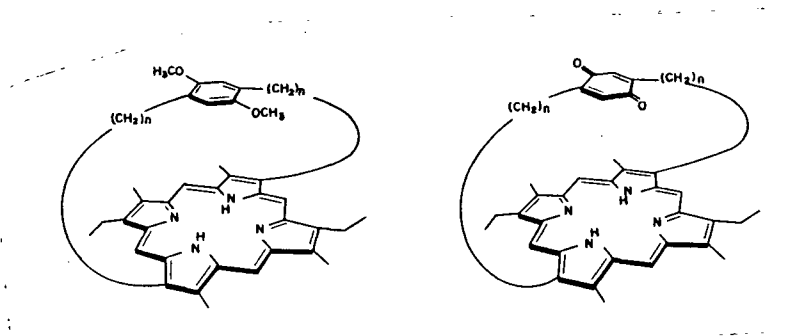

GROUP	87a (n = 5)	87b (n = 4)	88a (n = 5)		88b (n = 4)	
α- and β-pyrrolic carbons	146.87	146.96	145.68	144.17	146.75	146.48
	144.79	145.85	143.44	142.96	146.37	145.51
	143.55	143.79	142.86	142.80	145.00	143.76
	141.73	141.71	142.56	141.56	142.72	142.60
	141.07	139.95	141.20	139.02	141.09	140.78
	140.00	139.71	138.79	138.46	139.44	139.36
	139.91	(139.71)	138.20	137.56	137.59	137.01
	139.47	133.91	136.75		132.60	131.10
Meso carbons	100.52	100.99	99.50		100.78	
	99.18	98.67	(99.50)		99.93	
			98.18		98.37	
			98.14		97.87	
Chain carbons	29.41	29.97	49.56	48.61	51.75	49.35
	27.35	26.90	26.54	26.25	28.78	26.28
	27.06	25.72	26.24	25.65	25.70	25.14
	26.04	23.68	25.47	24.17		
	24.12					
-CH$_2$CH$_3$	20.48	20.24	20.71		20.24	
-CH$_2$CH$_3$	16.65	16.33	16.25		16.09	
		16.27				
-CH$_3$	12.28	11.68	12.06		11.60	
	11.89		11.99		11.37	
			11.77			
			11.70			

TABLE IX: ^{13}C-NMR Data of Anisole- and Phenol-Strapped Porphyrins (in 10% TFA-CDCl$_3$)
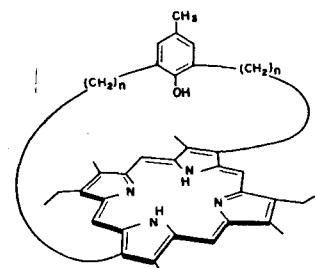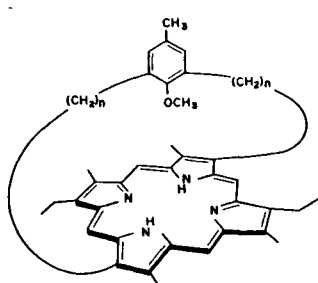
GROUP		117a (n = 6)	117b (n = 5)	118a (n = 6)	118b (n = 5)
α- and β-pyrrolic carbons		147.01	146.44	145.70	146.42
		144.07	143.87	144.79	144.73
		143.46	143.70	142.91	143.42
		142.19	143.32	142.60	143.12
		141.37	141.44	142.13	141.66
		141.19	141.29	140.91	141.37
		140.13	140.02	138.81	140.56
		139.97	139.58	138.10	140.02
Phenyl carbons	2-C	150.96	–	159.51	158.87
	1,3-C	133.09	131.81	134.08	127.33
	5-C	134.76	132.93	132.61	131.32
	4,6-C	128.78	126.45	127.81	126.52
Meso carbons		100.42	100.04	98.79	100.76
		99.35	99.65	97.61	100.16
Phenyl 2-OCH$_3$		60.64	58.89	–	–
Chain carbons		31.66	29.30	30.89	29.08
		30.52	28.65	30.52	28.67
		29.59	27.74	30.29	28.13
		29.08	27.25	29.64	27.77
		28.40	26.97	28.74	27.65
		26.36		26.22	
-$\underline{C}$H$_2$CH$_3$		20.39	20.22	20.25	20.36
Phenyl 5-CH$_3$		20.23	19.81	20.25	19.42
-CH$_2\underline{C}$H$_3$		16.65	16.34	16.33	16.65
-CH$_3$		12.40	12.29	11.92	12.31
		11.80	11.59	11.61	11.85

TABLE X: ^{13}C-NMR Data of Dimethoxybenzene- and Quinone-Strapped
Porphyrins (in 10% TFA-CDCl$_3$)

GROUP		140a (n = 6)	140b (n = 5)	143a (n = 6)	143b (n = 5)
α- and β- pyrrolic carbons		145.90 142.96 142.12 140.92 139.64 138.67 138.28	146.29 143.75 143.45 143.30 141.23 140.91 140.11 139.37	145.71 142.69 142.57 142.21 141.39 141.05 139.39 138.46	146.15 142.99 142.81 142.05 141.92 140.86 140.17 139.62
Phenyl carbons	2,5-C 1,4-C 3,6-C	* 	150.01 128.40 113.56	188.19 148.61 132.42	186.33 147.05 131.45
Meso carbons		99.00 97.72	99.94 99.42	99.14 98.10	99.85 98.72
Phenyl 2,5-OCH$_3$		*	57.10	–	–
Chain carbons		31.88 28.68 28.43 26.28	29.70 28.80 28.15 28.08 27.20	31.32 27.51 27.28 27.17 26.93 26.29	28.66 27.00 26.86 25.99 25.92
-CH$_2$CH$_3$		20.28	20.30	20.30	20.43
-CH$_2$CH$_3$		16.22	16.52	16.32	16.54
-CH$_3$		12.09 11.61	12.34 11.73	12.27 11.68	12.20 11.80

* Resonances not observed
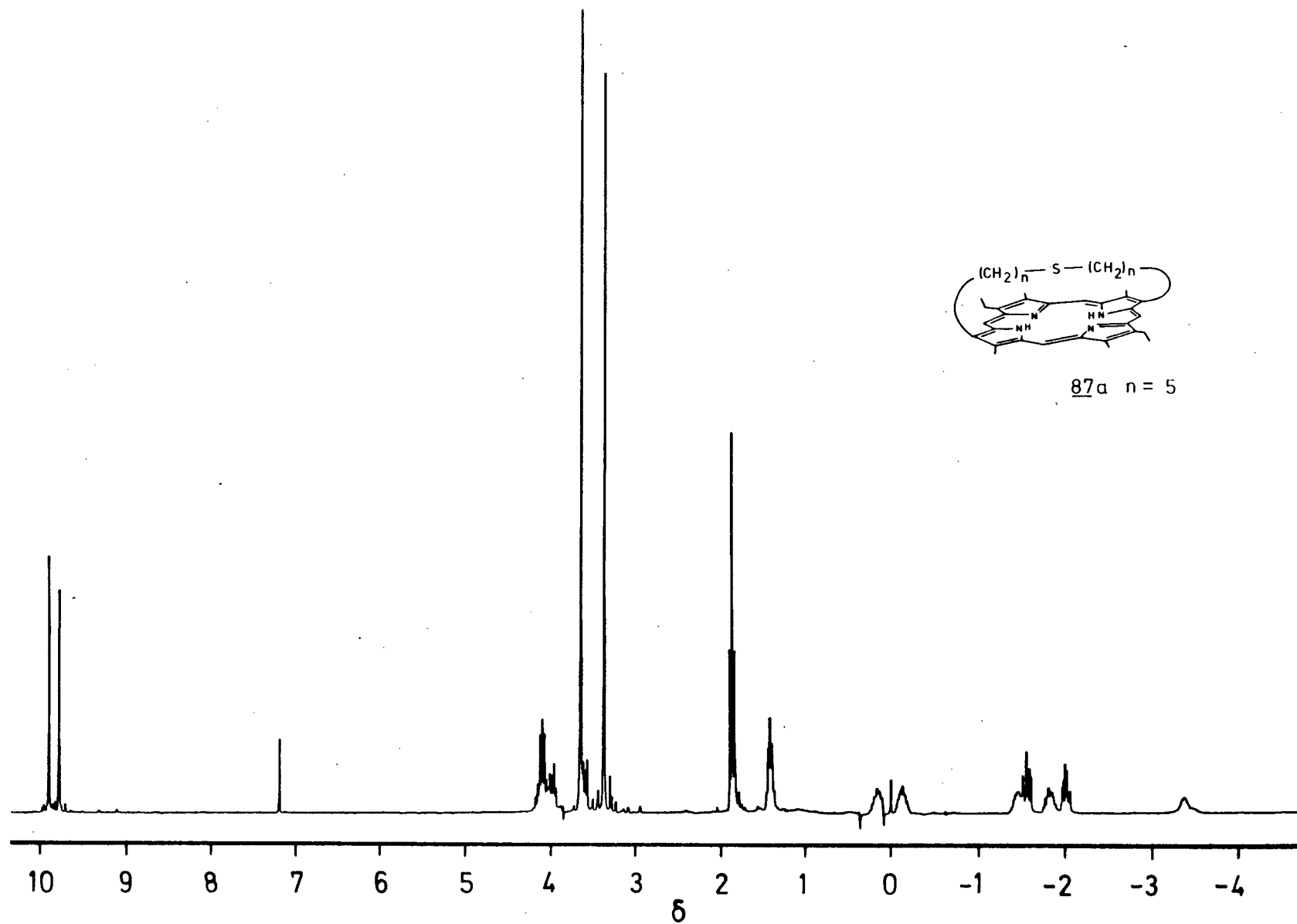
Fig. 34: ^{1}H NMR Spectrum of 87a in CDCl$_3$
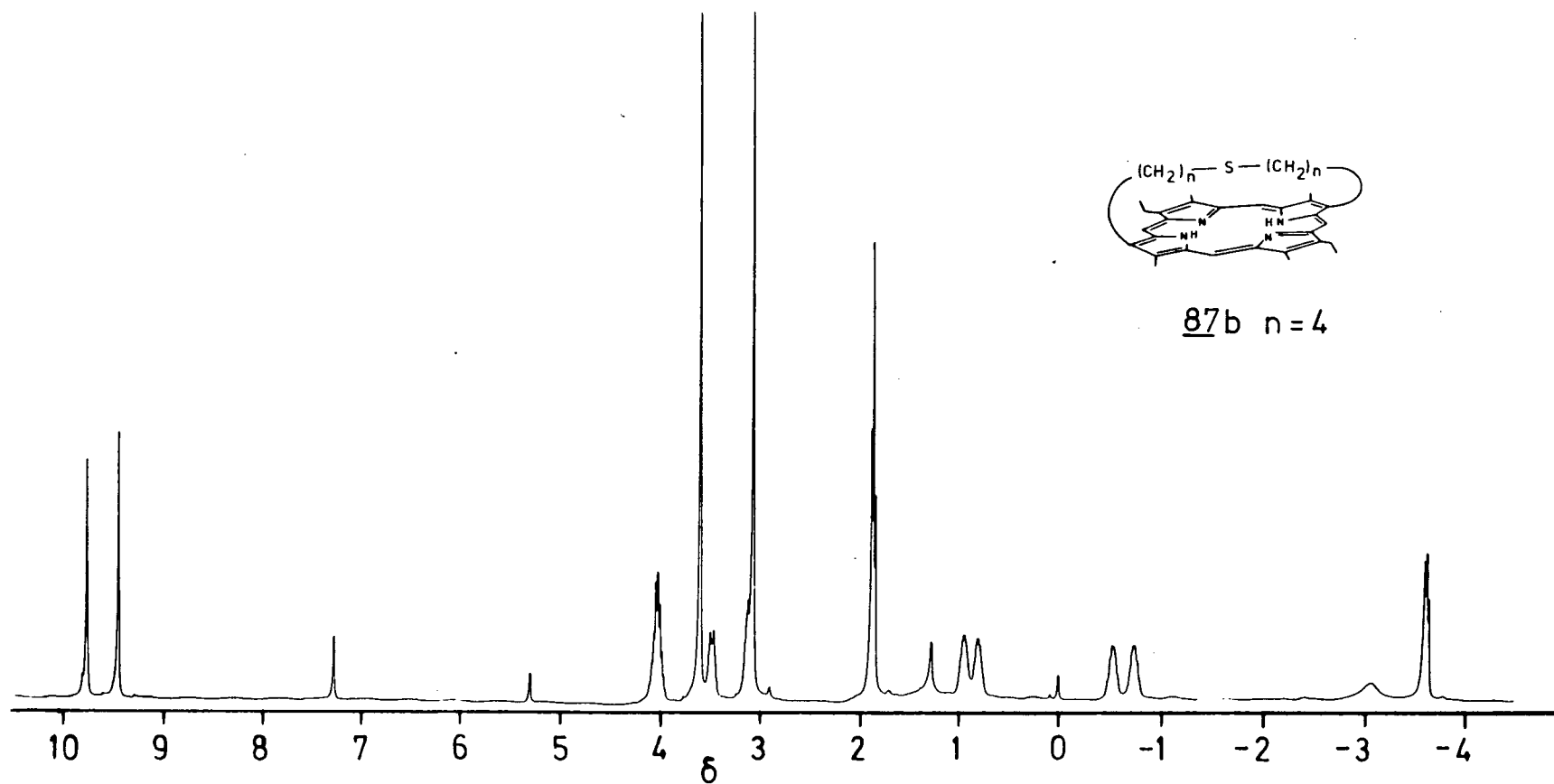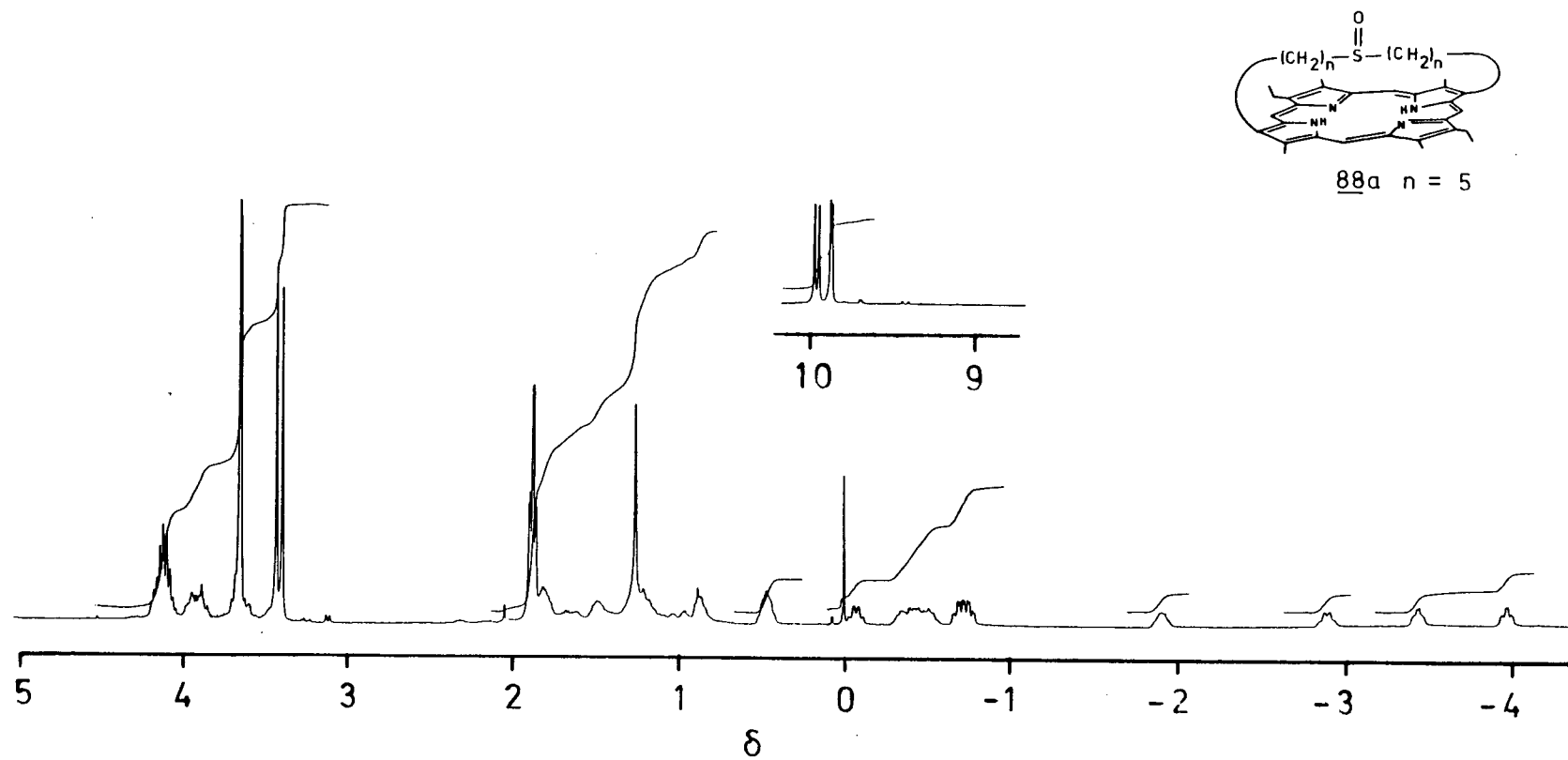
Fig. 35: ^{1}H NMR Spectrum of 87b in CDCl$_3$

87b n = 4
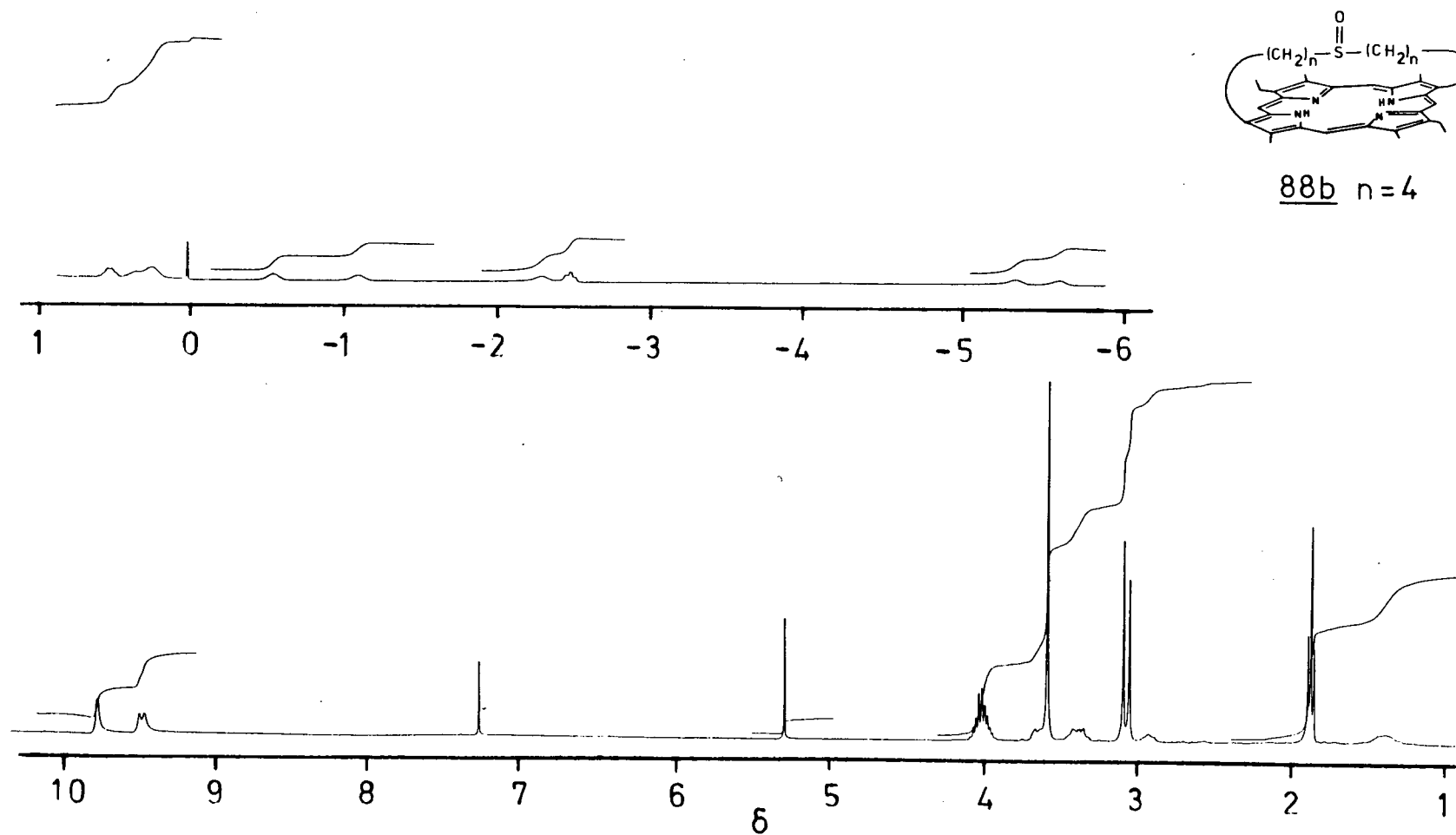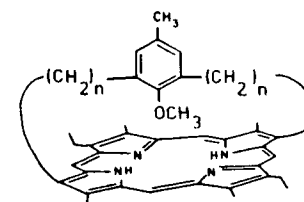
Fig. 36: ^{1}H NMR Spectrum of <u>88a</u> in CDCl$_3$

Fig. 37: ^{1}H NMR Spectrum of __88b__ in CDCl$_3$
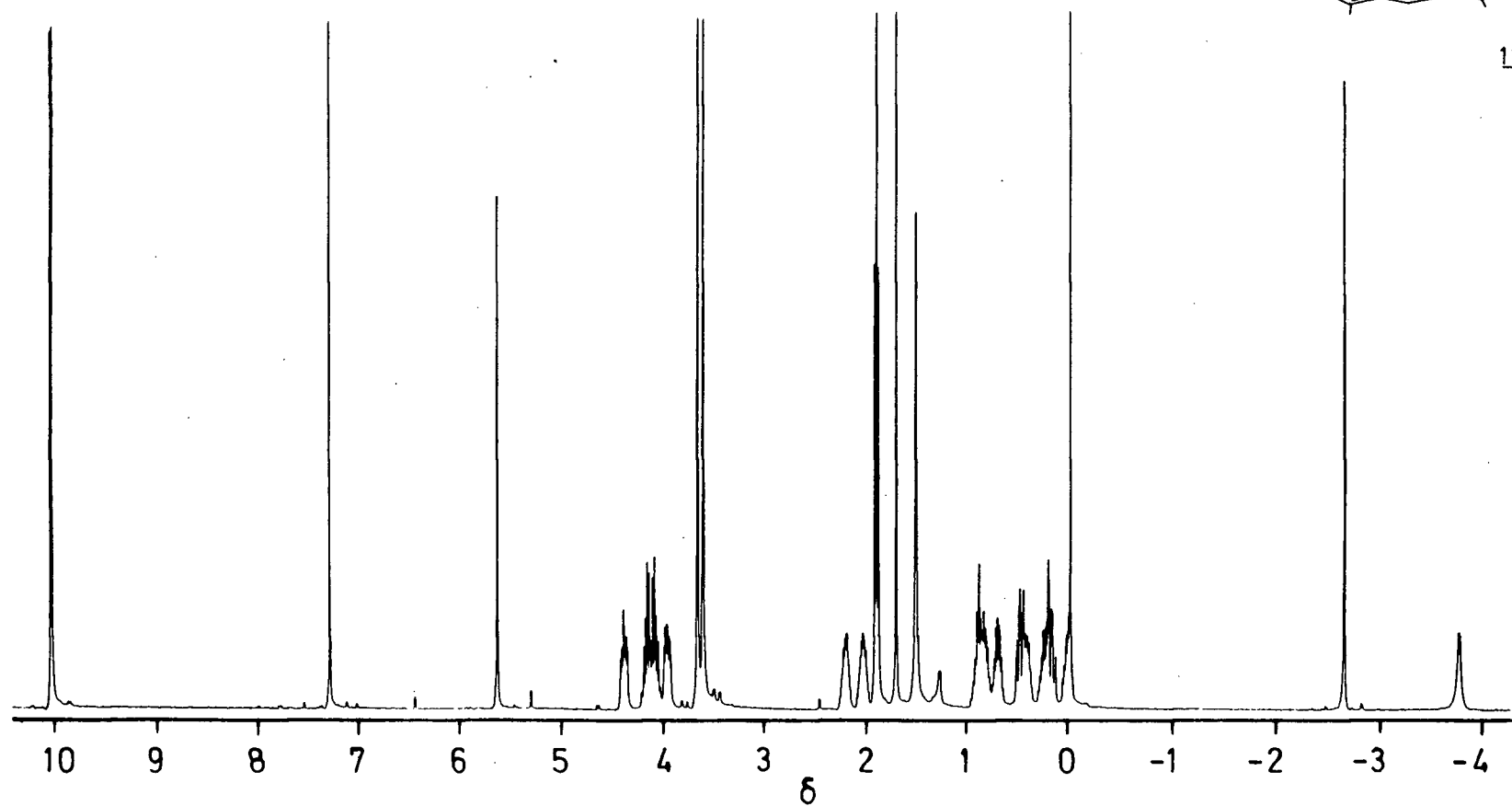
Fig. 38: ^{1}H NMR Spectrum of 117a in CDCl$_3$
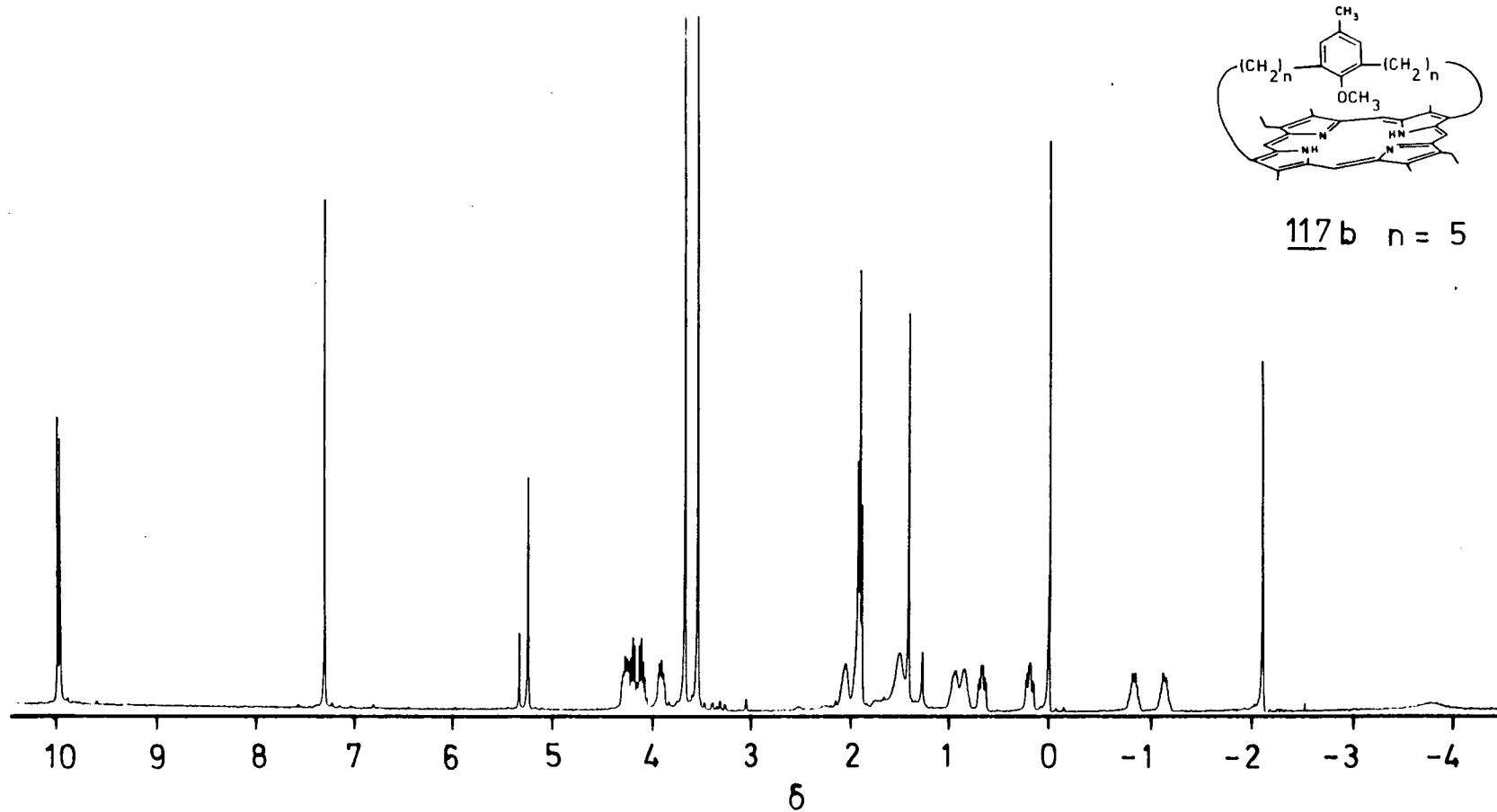
117 b n = 5

Fig. 39: ^{1}H NMR Spectrum of 117b in CDCl$_3$

118a n = 6
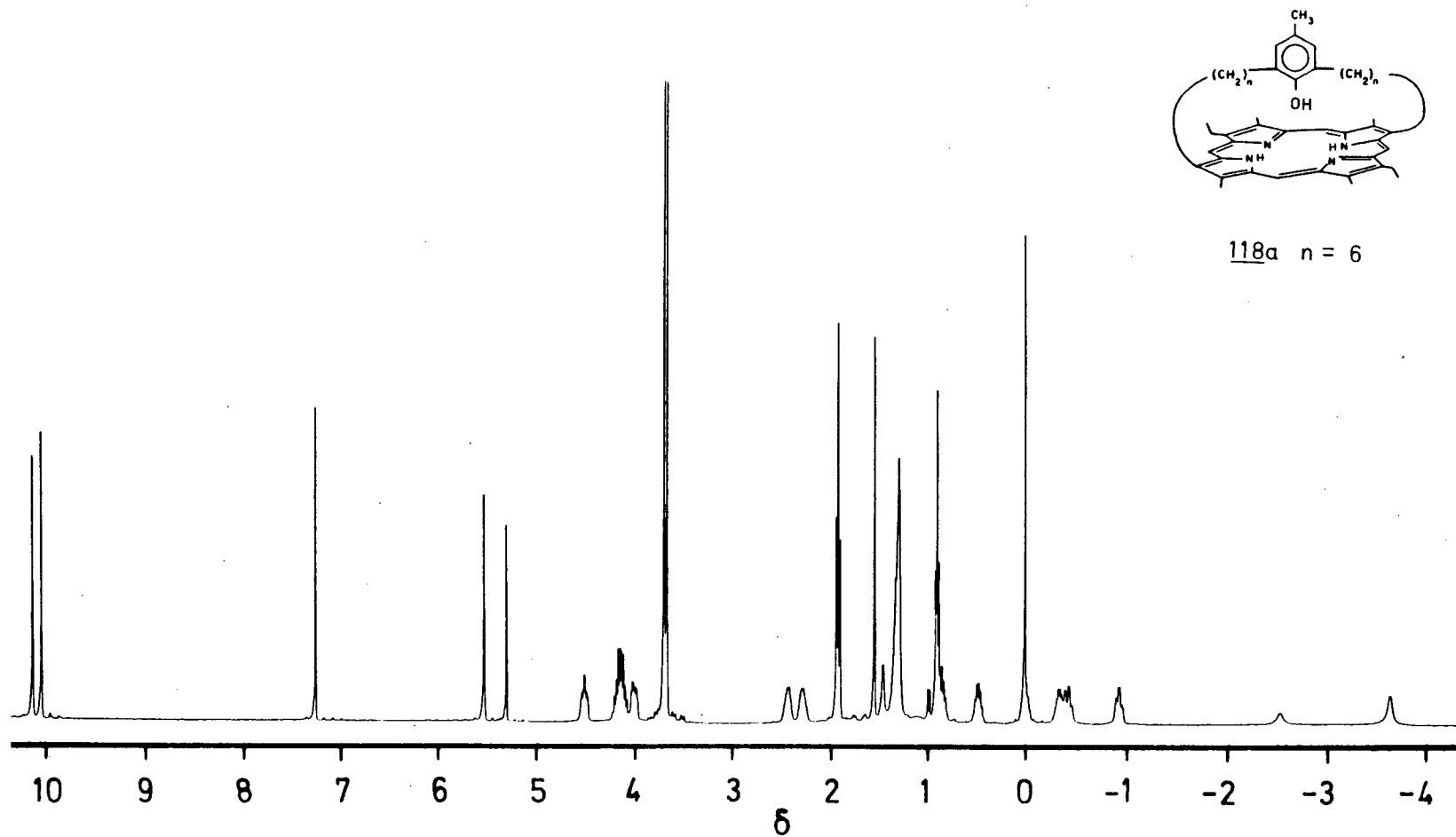
Fig. 40: ^{1}H NMR Spectrum of 118a in CDCl$_3$
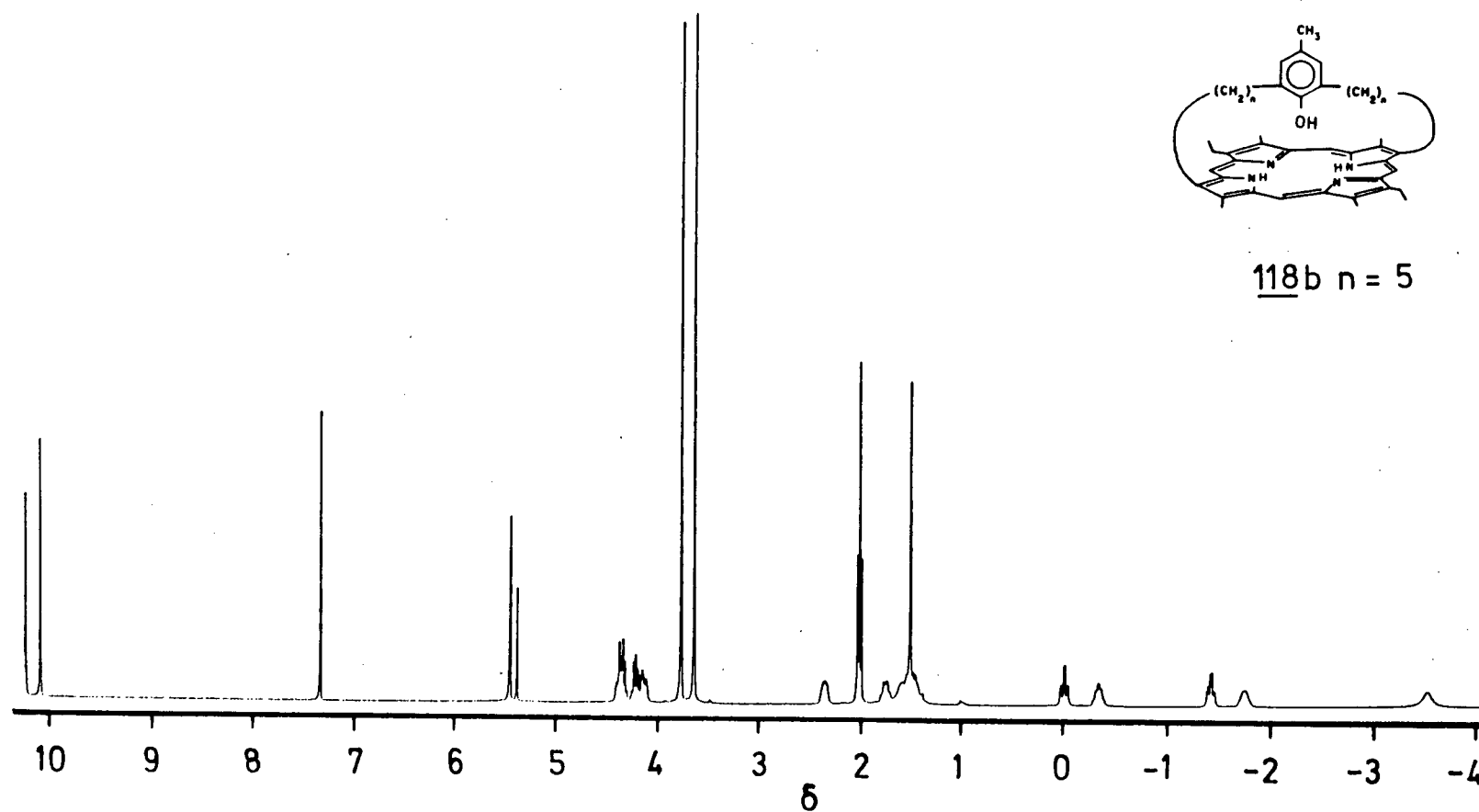
Fig. 41: ^{1}H NMR Spectrum of 118b in CDCl$_3$

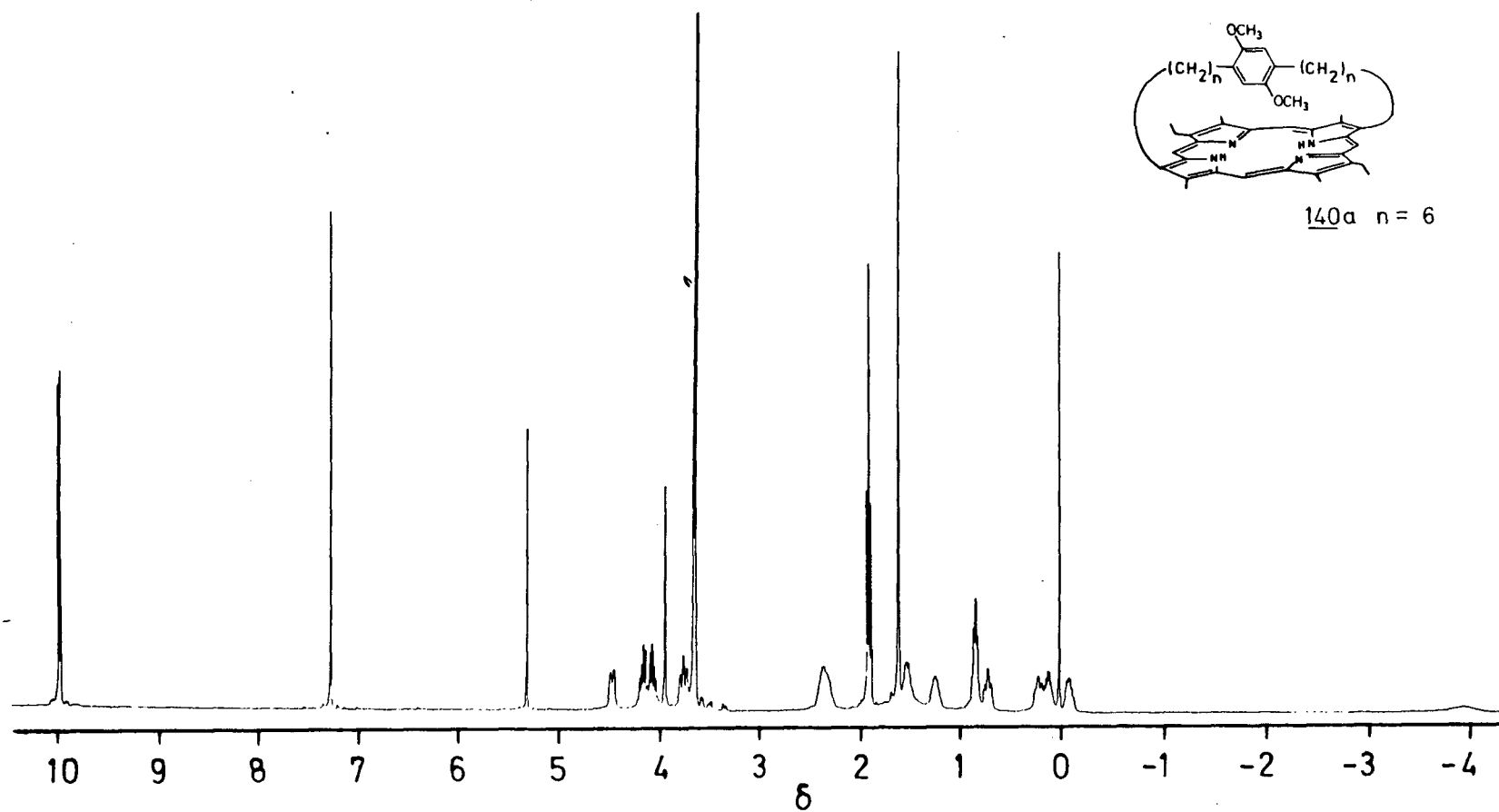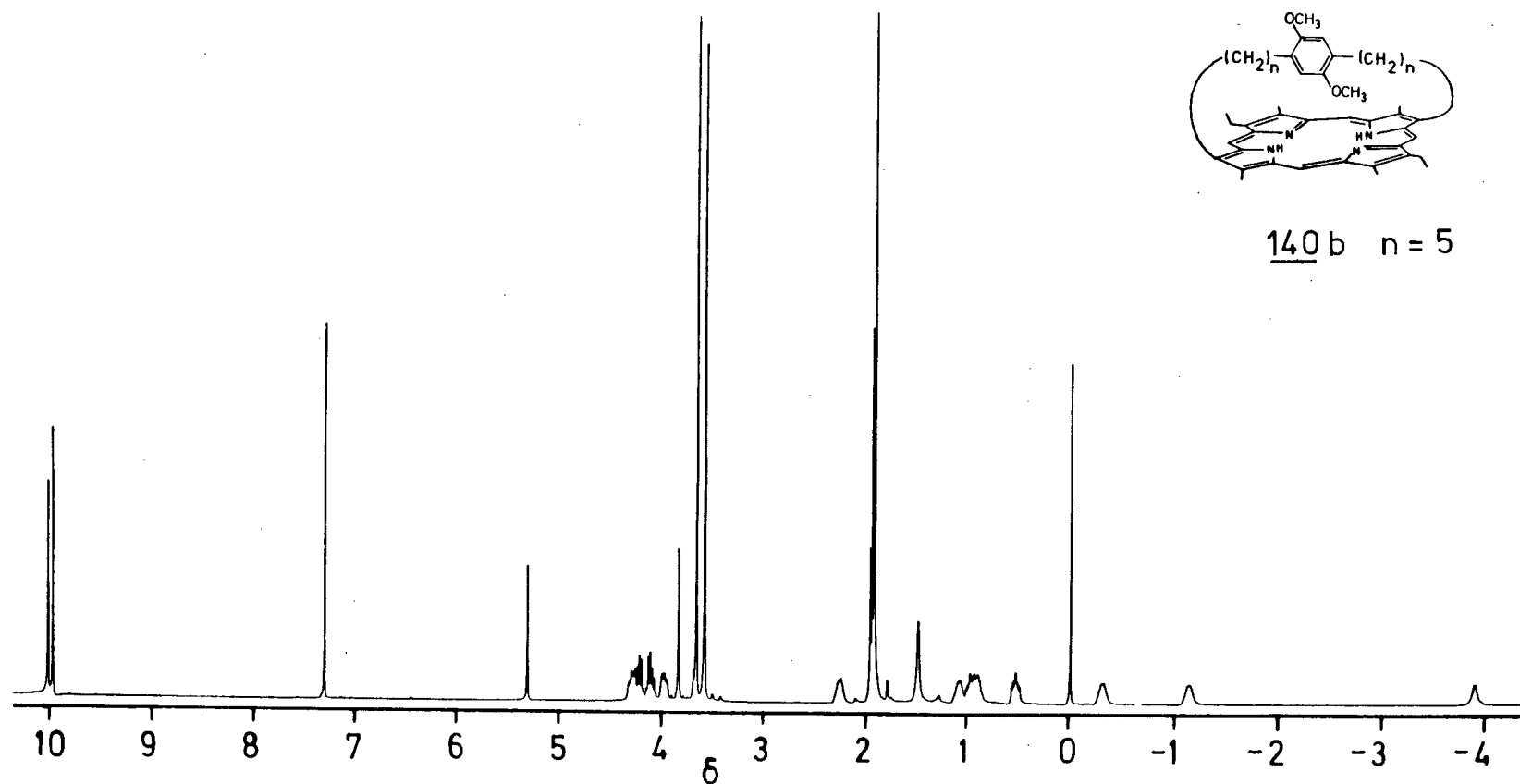140a   n = 6

Fig. 42: ^{1}H NMR Spectrum of 140a in CDCl$_3$
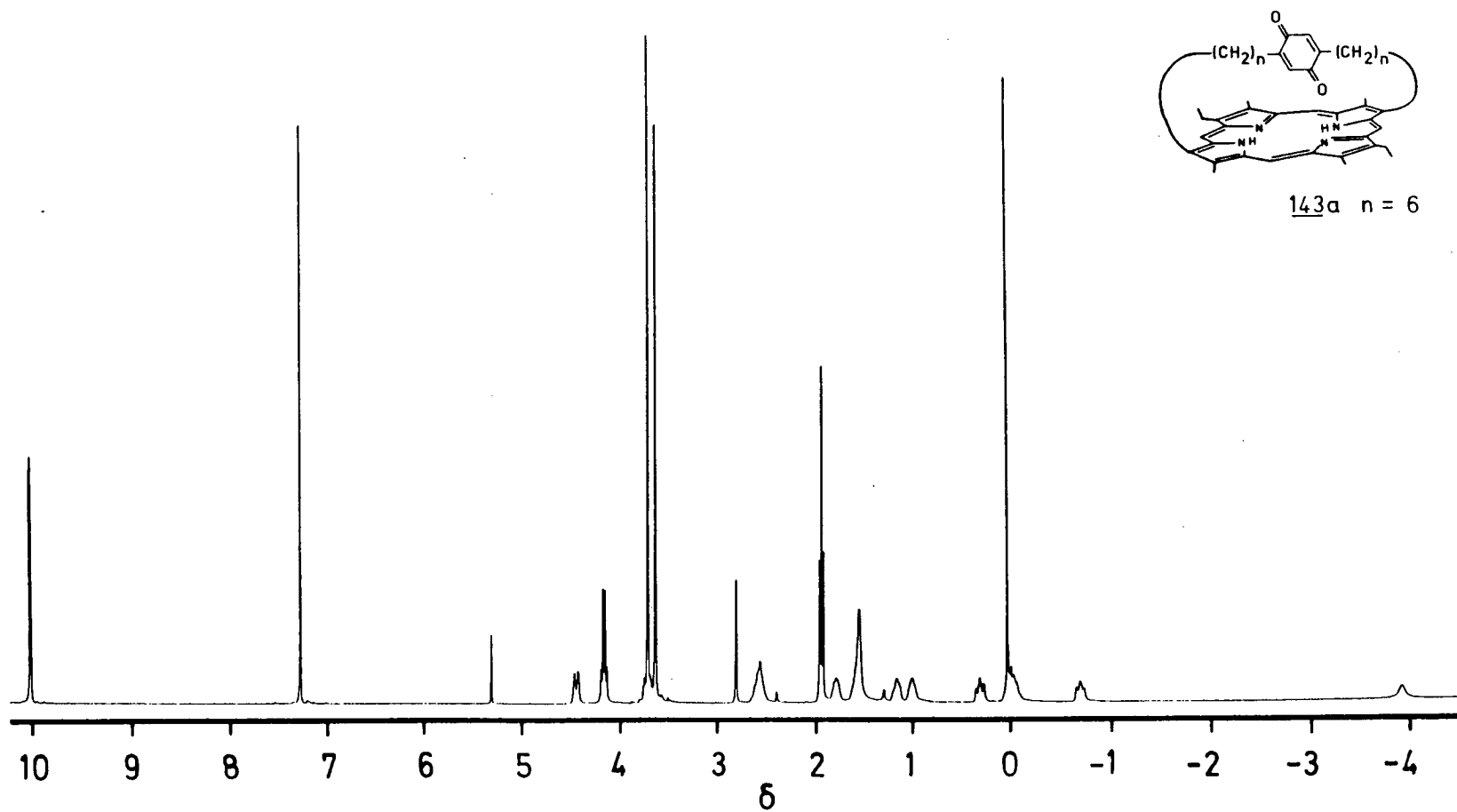
Fig. 43: ^{1}H NMR Spectrum of 140b in CDCl$_3$

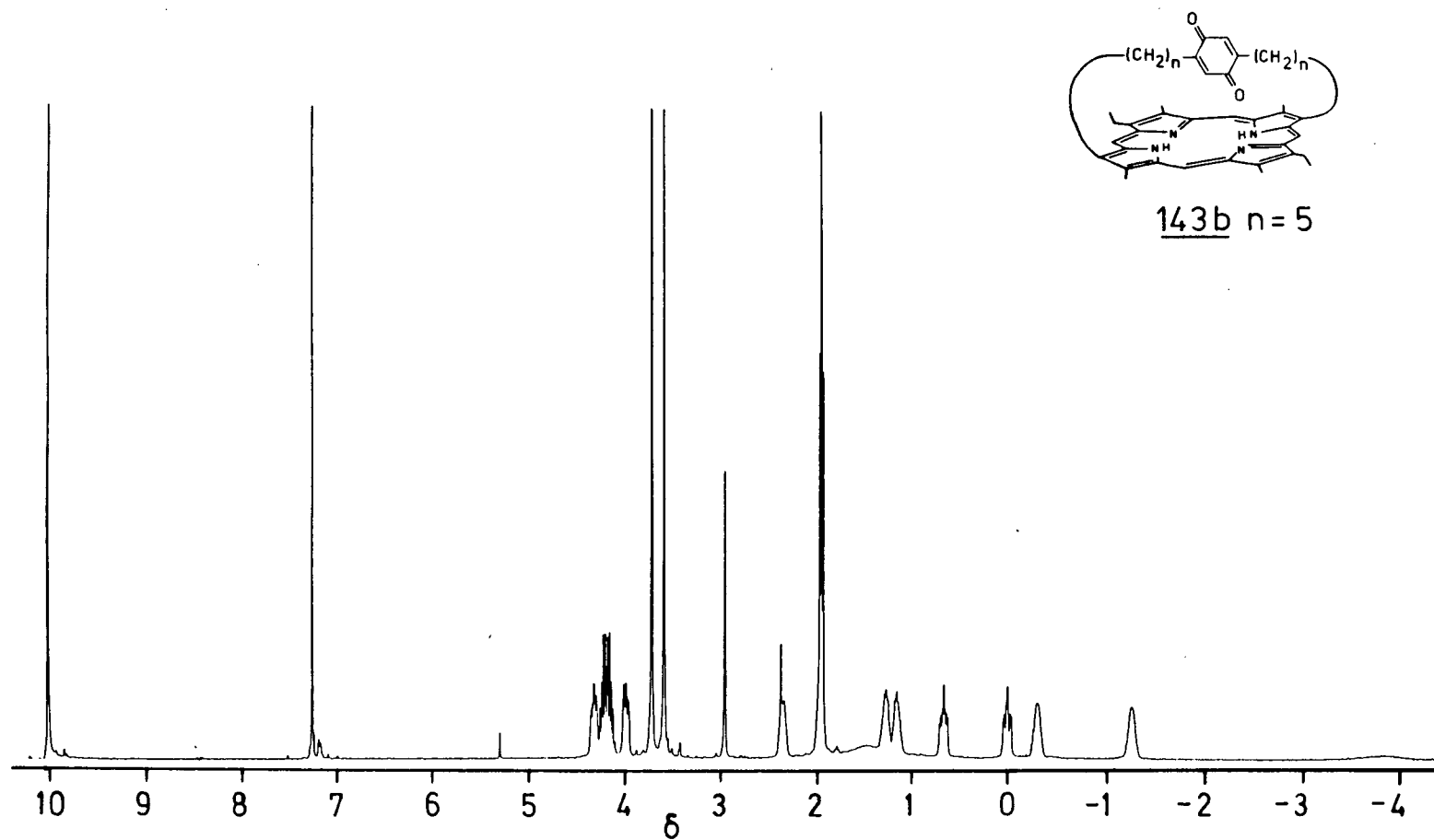Fig. 44: ^{1}H NMR Spectrum of 143a in CDCl$_3$

143b n = 5

Fig. 45: ^{1}H NMR Spectrum of 143b in CDCl$_3$

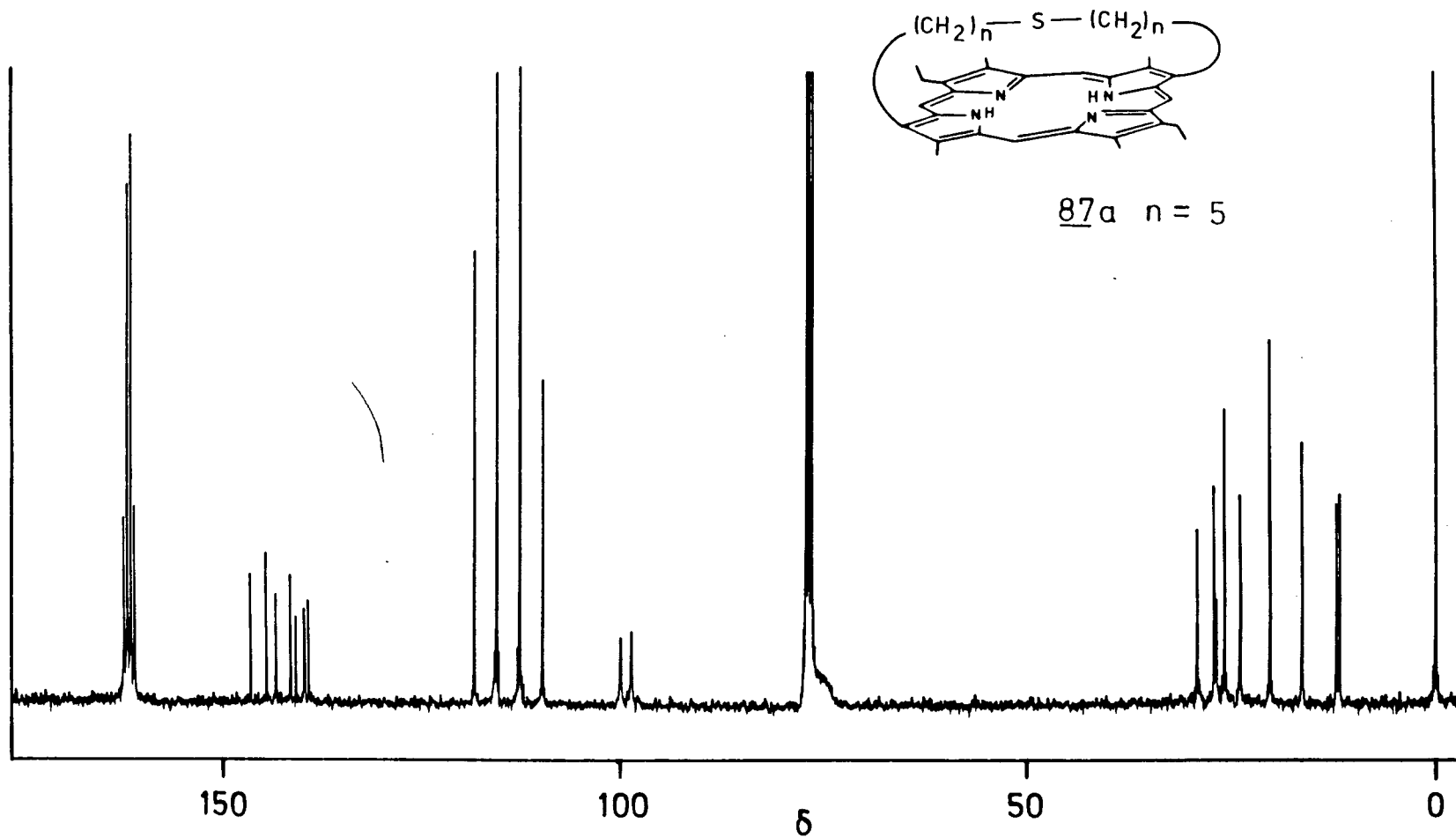Fig. 46: ^{13}C NMR Spectrum of 87a in 10% TFA-CDCl$_3$
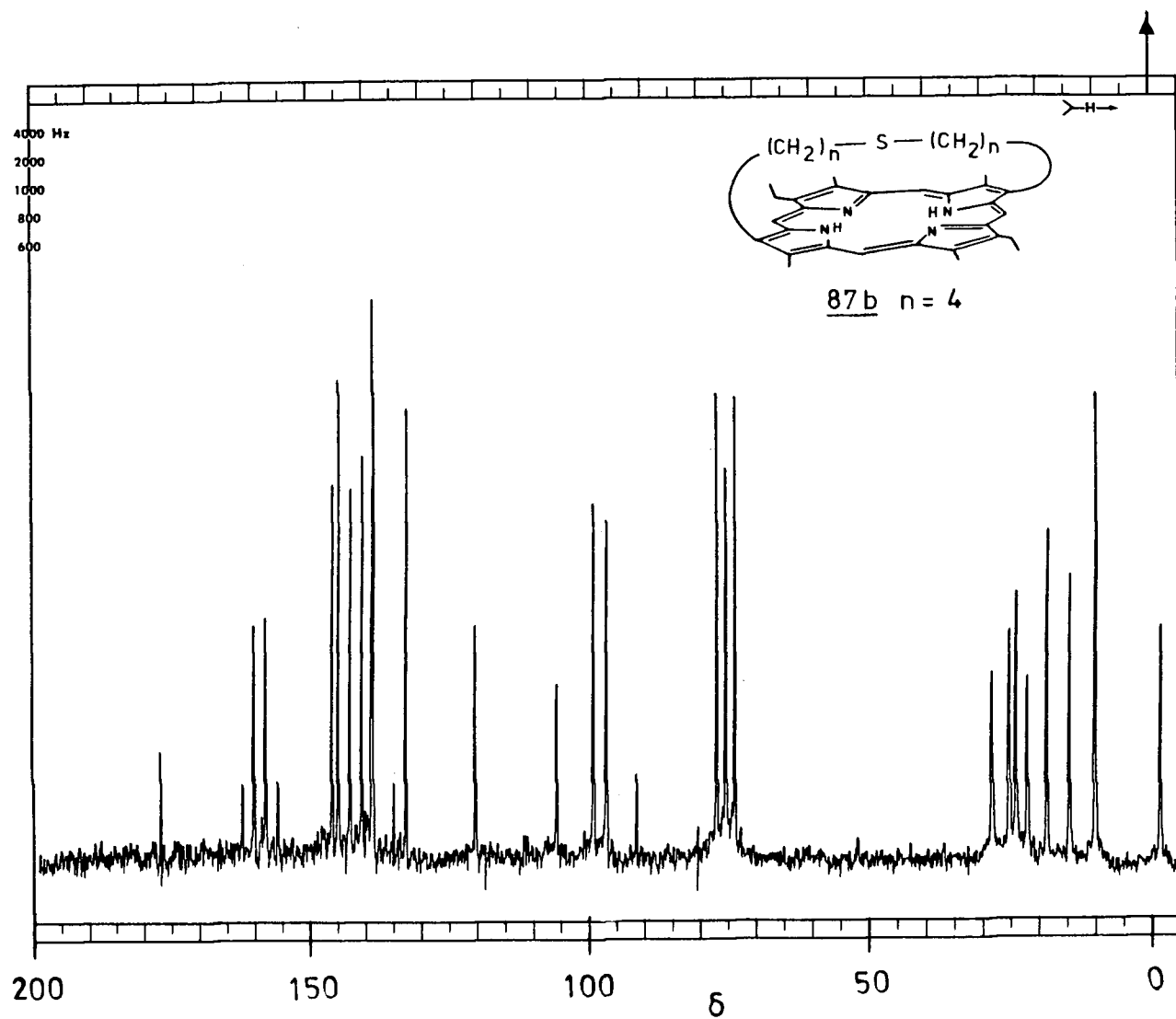
Fig. 47: ^{13}C NMR Spectrum of 87b in 10% TFA-CDCl$_3$
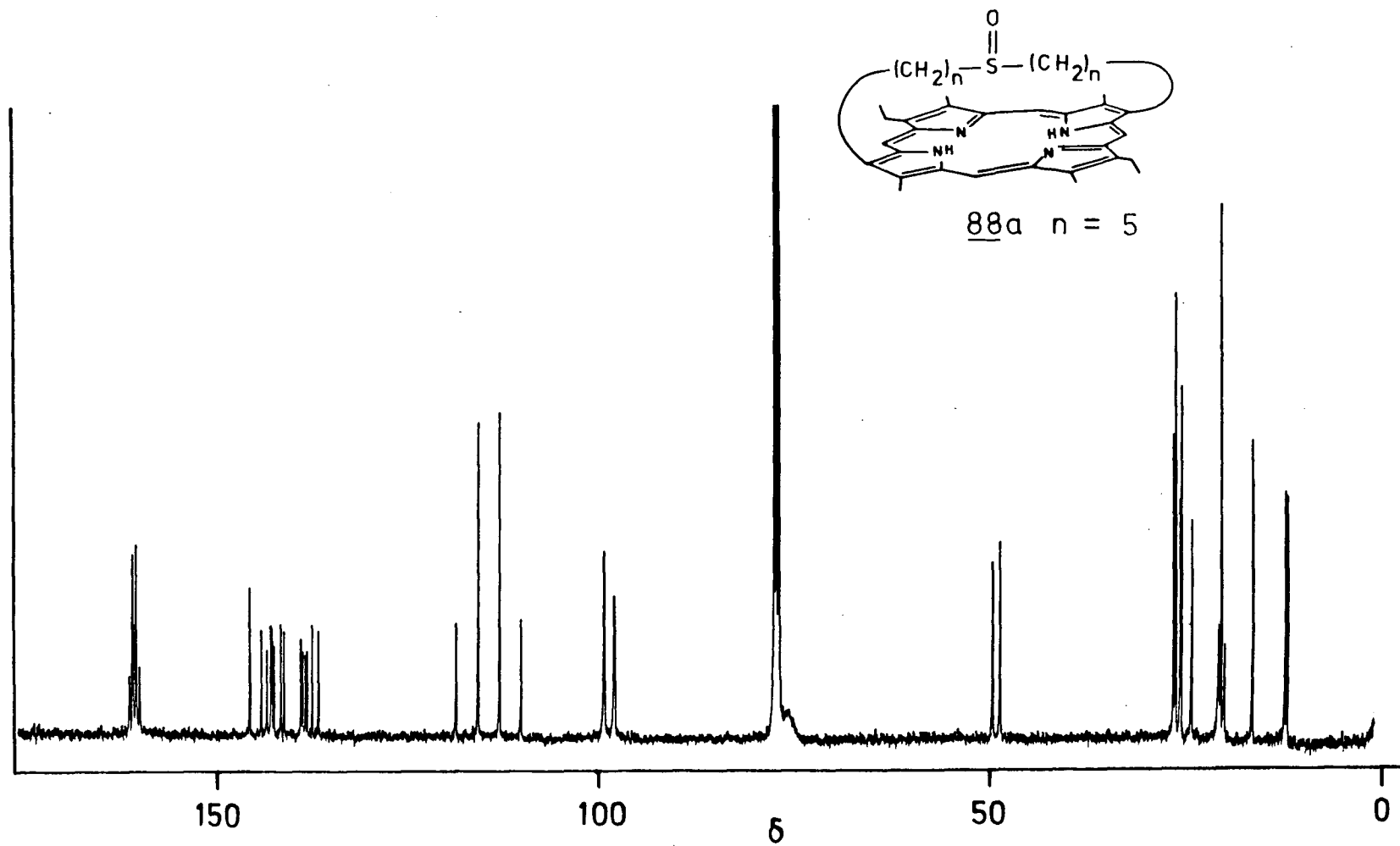
Fig. 48: ^{13}C Spectrum of 88a in 10% TFA-CDCl$_3$

Fig. 49: ^{13}C NMR Spectrum of 88b in 10% TFA-CDCl$_3$

Fig. 50: ^{13}C NMR Spectrum of <u>117a</u> in 10% TFA-CDCl$_3$

Fig. 51: ^{13}C NMR Spectrum of 117b in 10% TFA-CDCl$_3$

Fig. 52: ^{13}C NMR Spectrum of 118a in 10% TFA-CDCl$_3$

Fig. 53: ^{13}C NMR Spectrum of 118b in 10% TFA-CDCl$_3$

Fig. 54: ^{13}C-NMR Spectra of 140a;   A: in 10% TFA-CDCl$_3$ at Room Temperature

B: in 10% TFA-Toluene-d$_8$ at 80°C

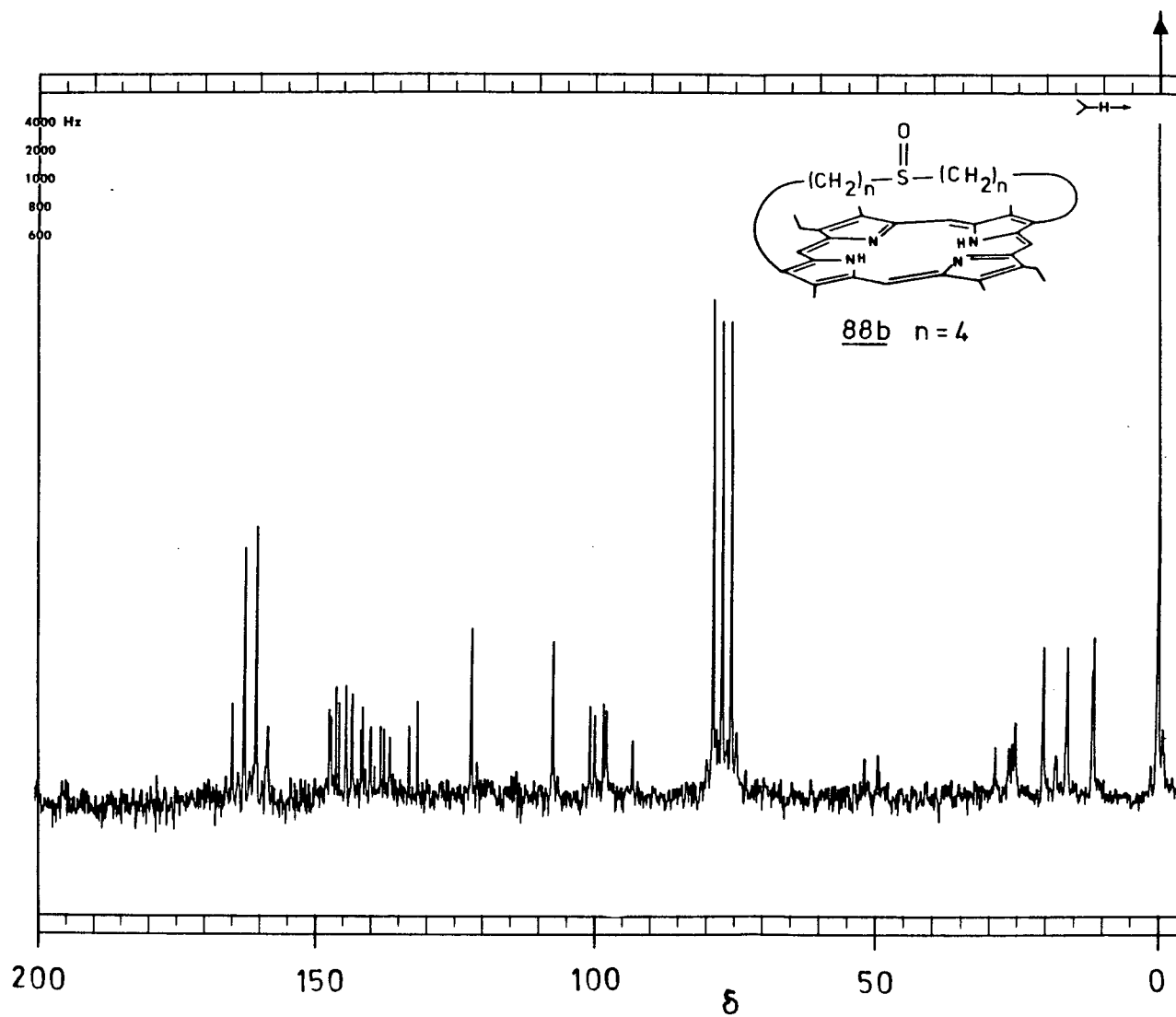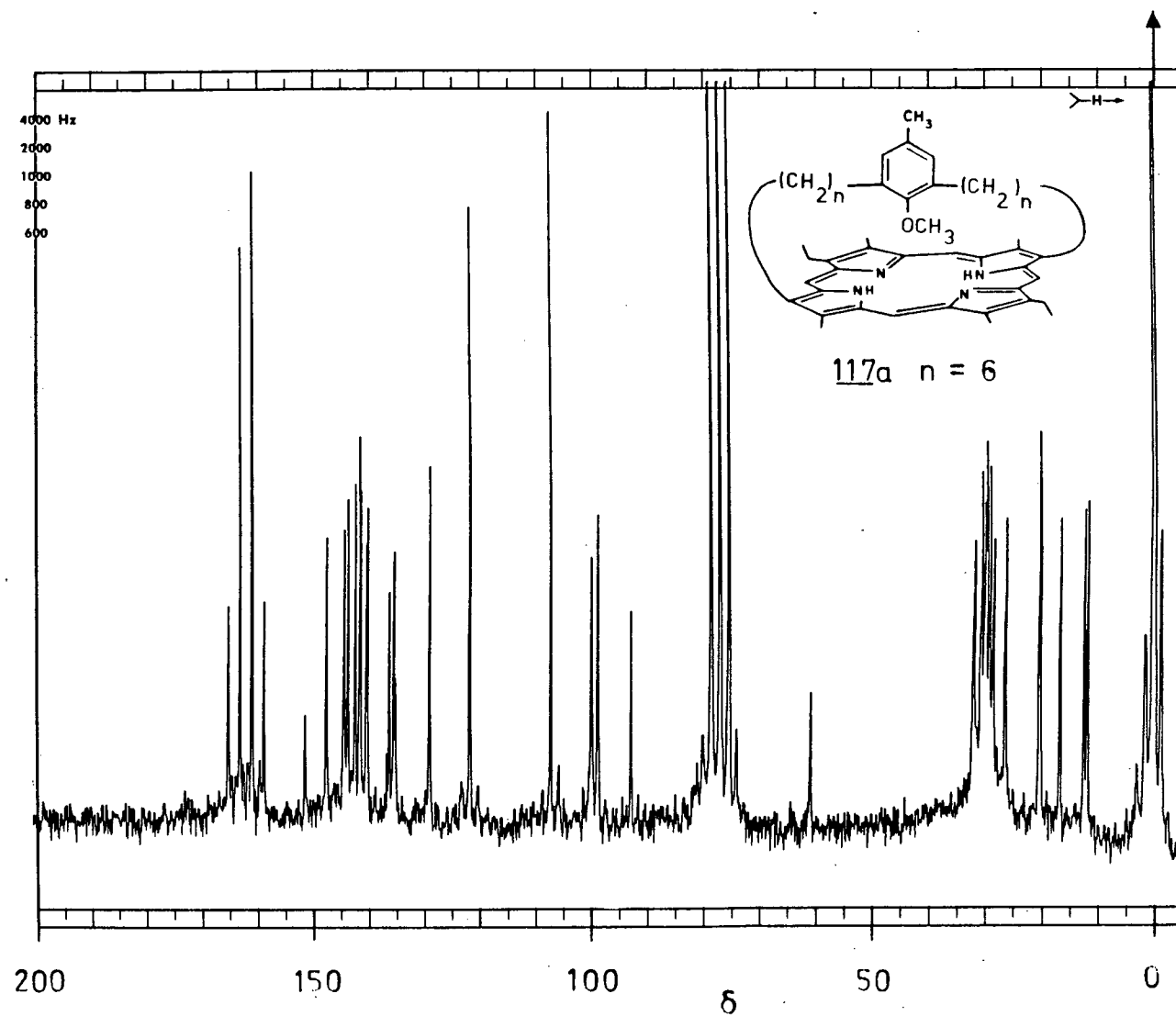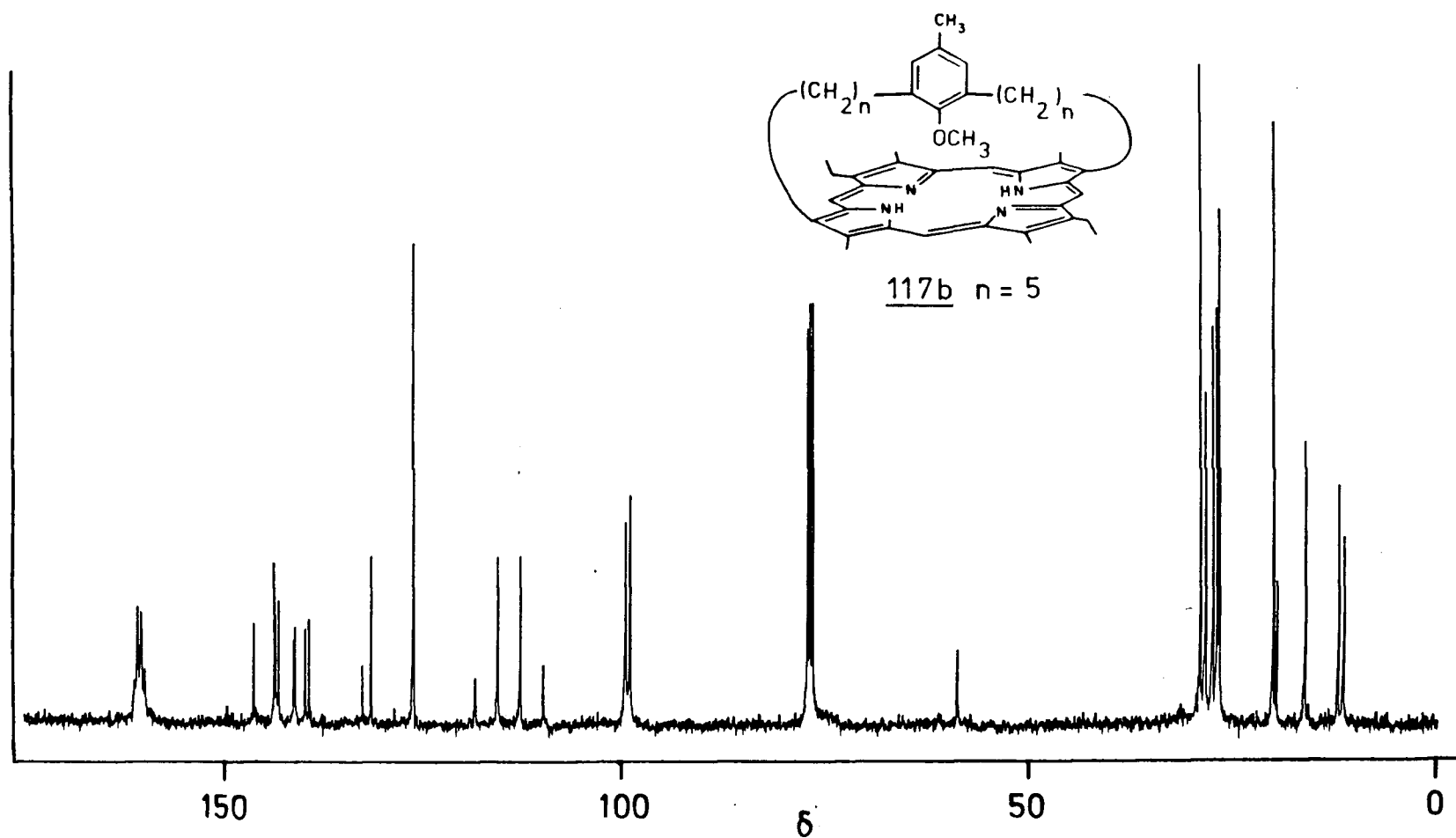C: in CDCl$_3$ at Room Temperature

Fig. 55: ^{13}C NMR Spectrum of 140b in 10% TFA-CDCl$_3$

Fig. 56: ^{13}C NMR Spectrum of 143a in 10% TFA-CDCl$_3$

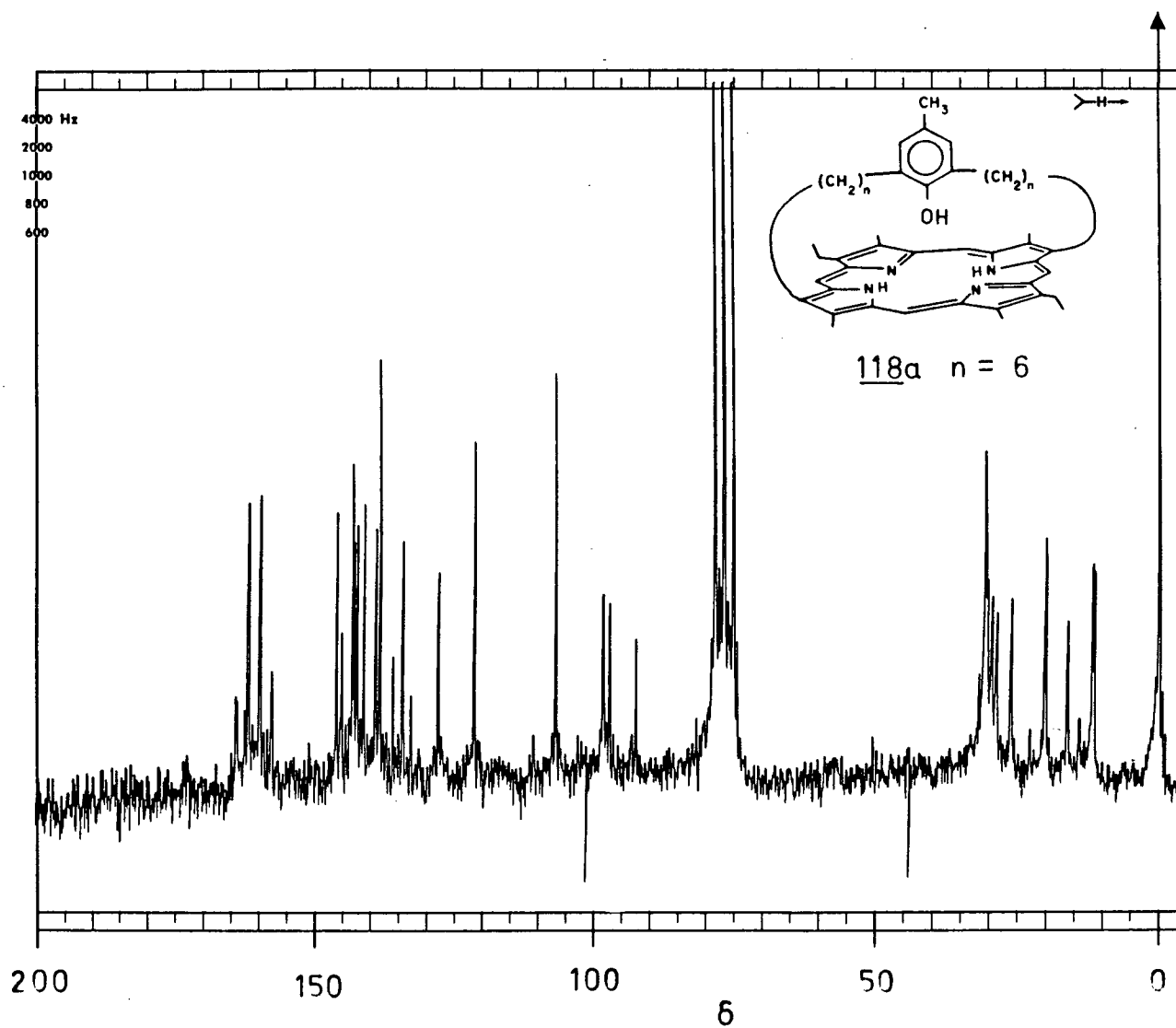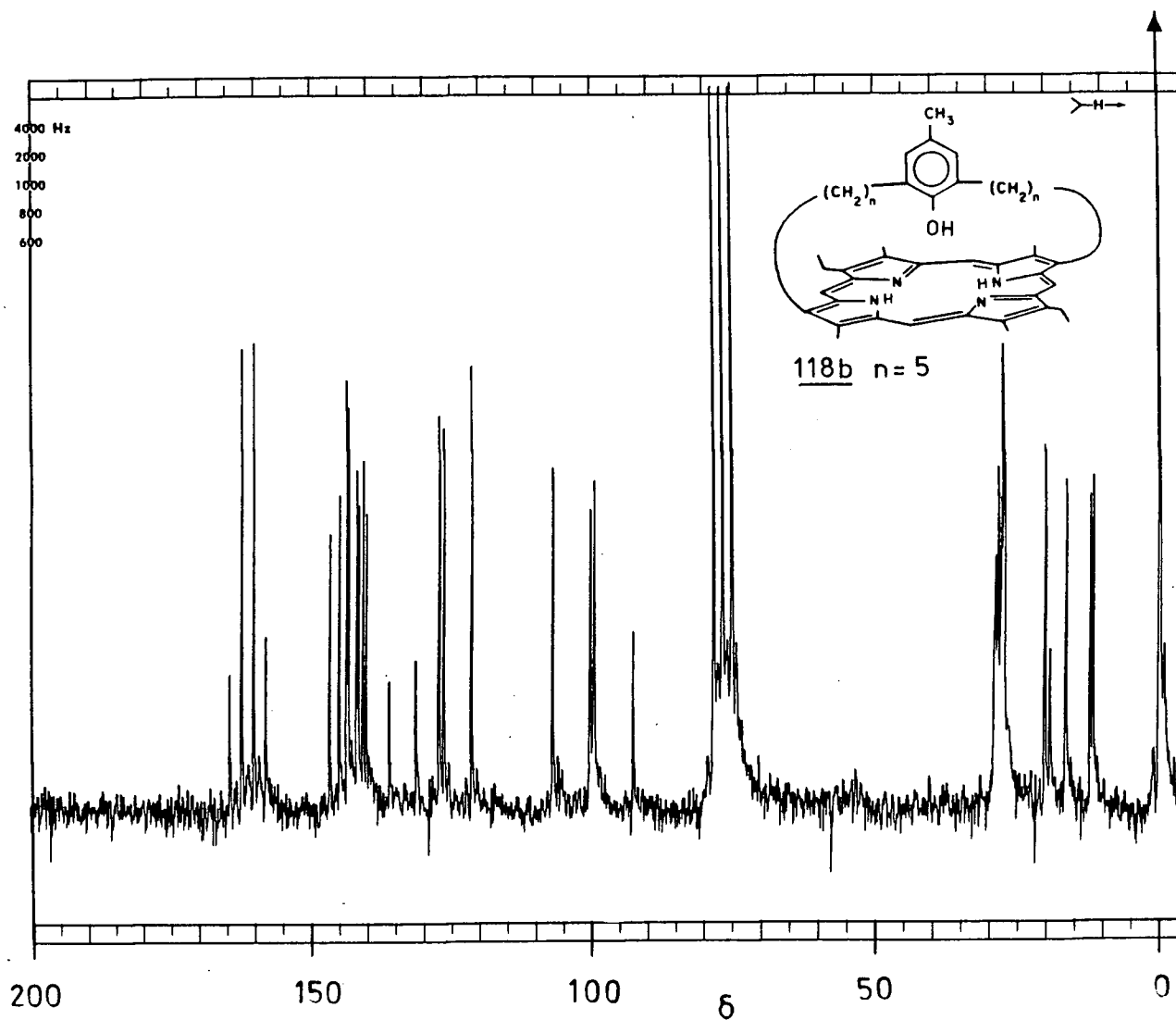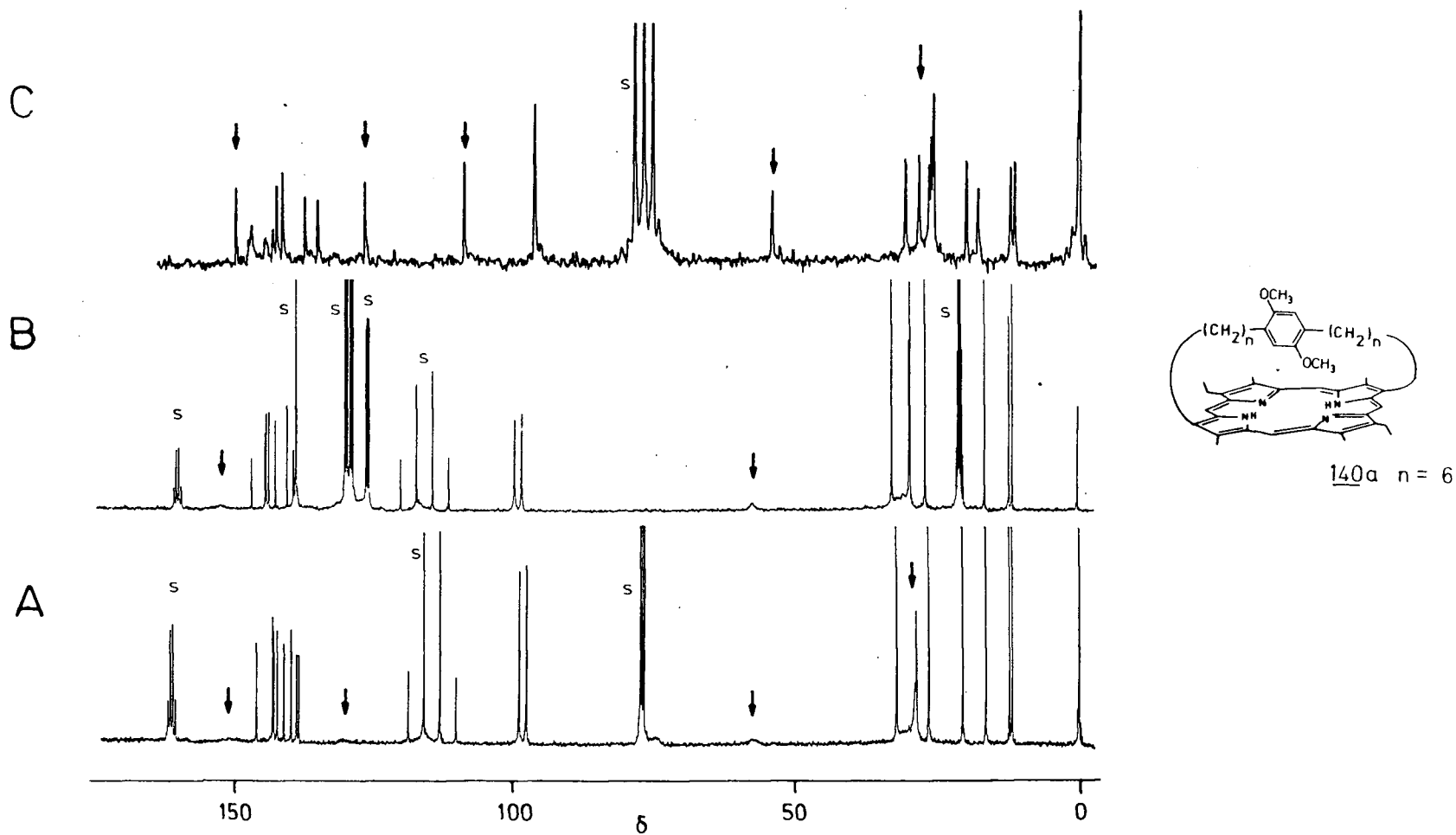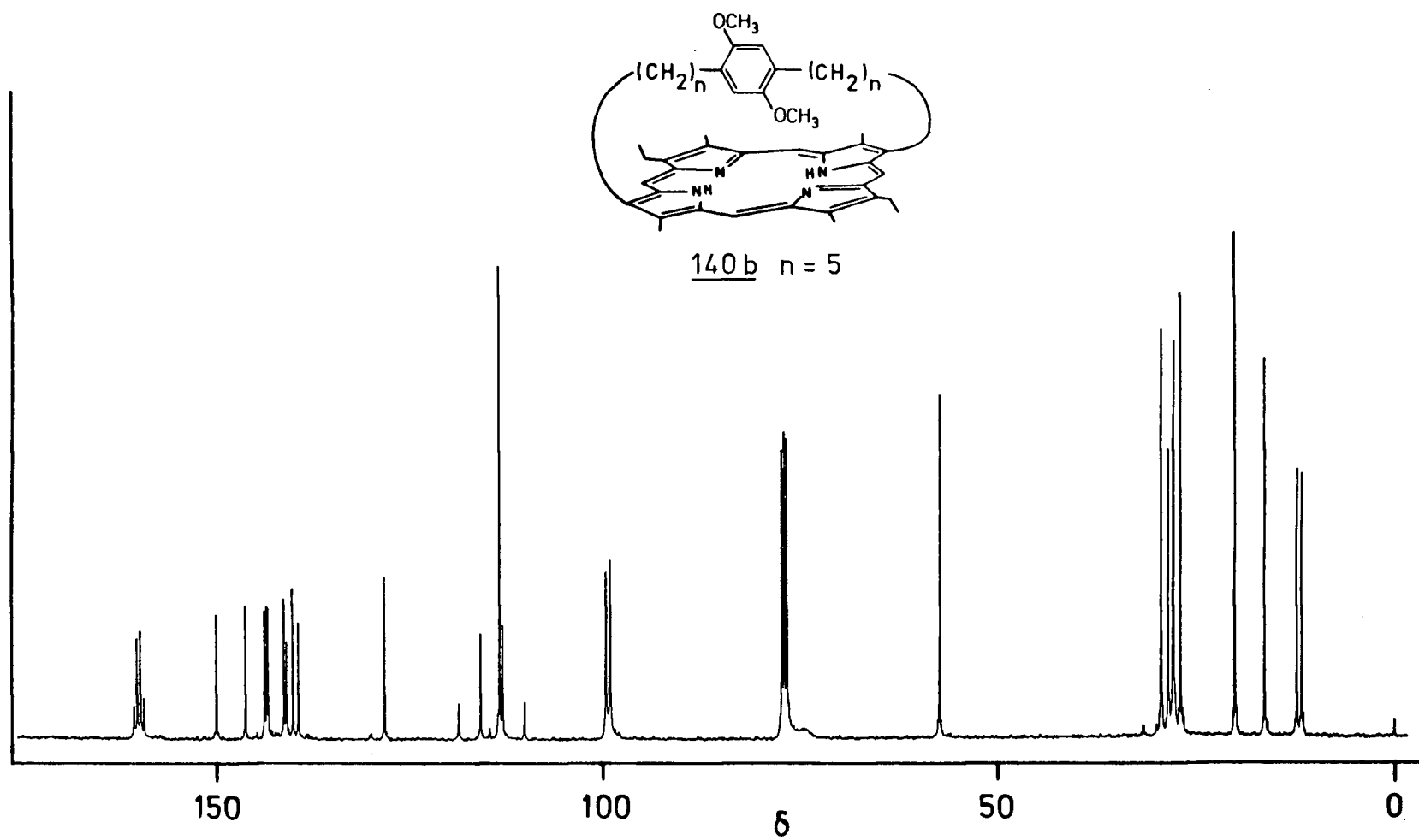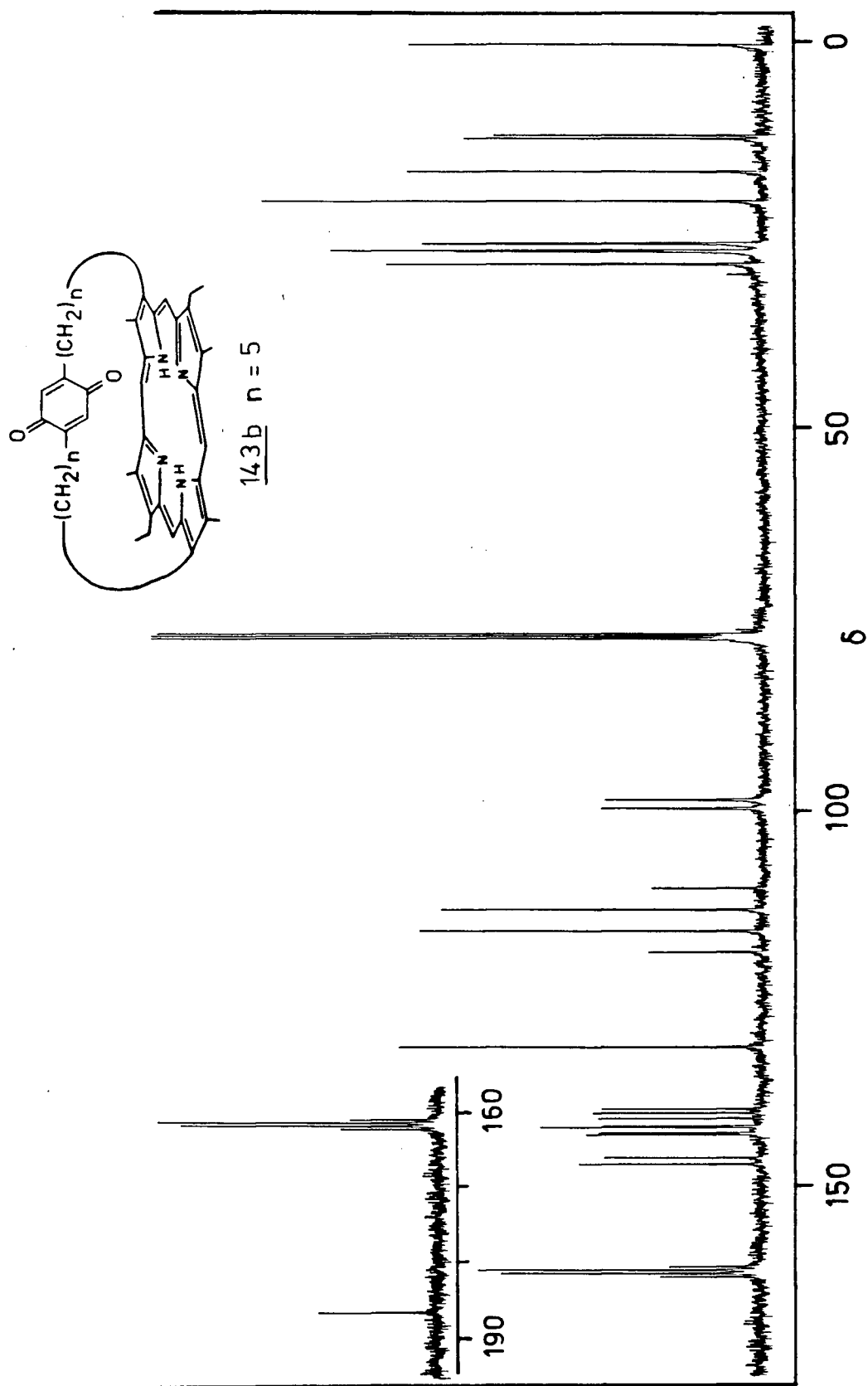Fig. 57: ^{13}C NMR Spectrum of 143b in 10% TFA-CDCl$_3$

4.3. ELECTRONIC ABSORPTION SPECTRA OF PORPHYRINS

The electron absorption spectrum of a porphyrin derivative is dominated by an intense band between 380 and 420 nm. This band, commonly called the Soret band, has a molar extinction coefficient from 2 to 4 x 10^5 $M^{-1}cm^{-1}$. For free base porphyrins four less intense bands, designated I-IV in order of increasing energy, are observed in the region 450-650 nm. Insertion of a metal or protonation of the nitrogens at the porphyrin core results in a similar change in the spectrum. Both metalloporphyrins and porphyrin dications still display an intense Soret band, but only two bands, α and β, are observed in the region 500-600 nm. This dramatic change is attributed to an increase in symmetry of the porphyrin.

For the free base porphyrins the pattern of intensities of bands I-IV may be correlated with the substitution pattern on the porphyrin periphery. Stern and coworkers[147] used the terms etio, rhodo, oxorhodo and phyllo to classify the intensity patterns shown in Scheme 97.

(i) Etio-type Spectra: The pattern IV > III > II > I is found in all porphyrins where at least six peripheral sites are substituted by alkyl groups and the remaining sites are unsubstituted.

(ii) Rhodo-type Spectra: Introduction of an electron-withdrawing group (e.g. carboxylic acid, aldehyde) results in an increase in intensity of band III relative to band IV, i.e., III > IV > II > I. This change is accompanied by a shift in absorption to longer wavelengths.

SCHEME 97

ETIO

RHODO
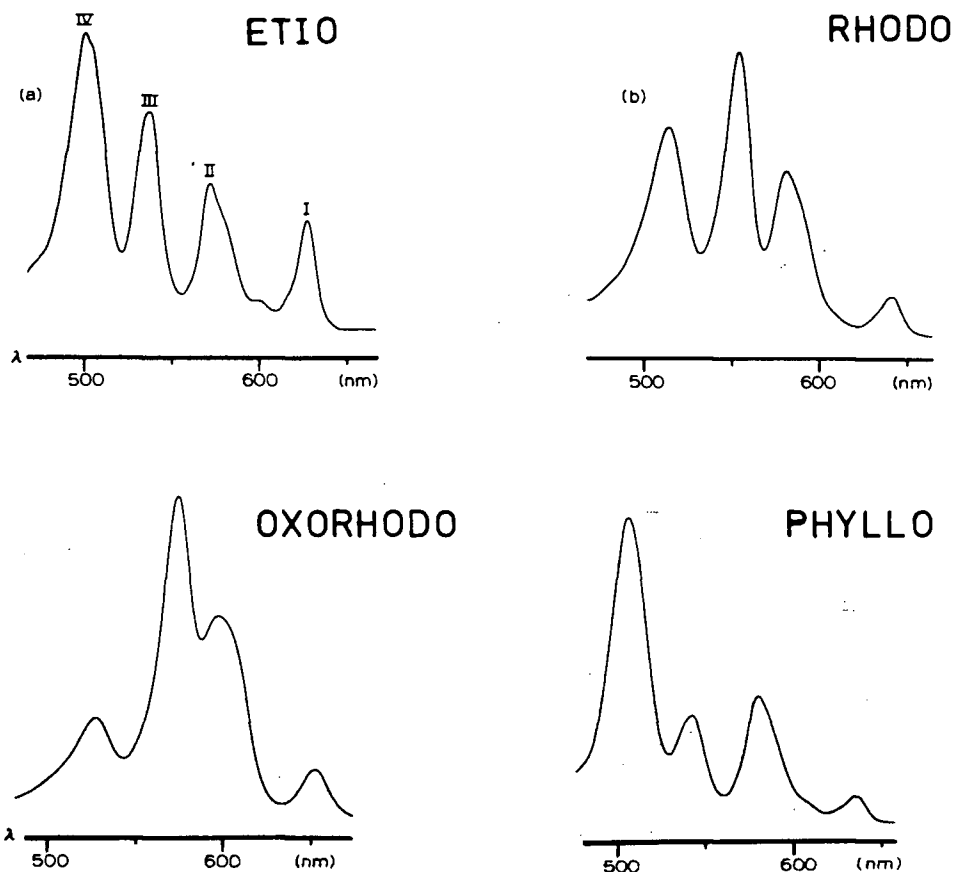
OXORHODO

PHYLLO

(iii) Oxorhodo-type Spectra: Two "rhodofying" groups on diagonally opposite pyrrole rings enhance each other's effect resulting in a pattern, III > II > IV > I.

(iv) Phyllo-type Spectra: The presence of four or more unsubstituted positions on the porphyrin may result in an intensity pattern, IV > II > III > I.

Since the strapped porphyrins have alkyl substituents at the eight

β-positions, one would expect them to show the typical etio-type spectrum with IV > III > II > I. This is indeed the case for those straps which incorporate a phenyl or quinone ring (Figs. 62-69). Even so, within each pair, comparison of the extinction coefficients (Table XI) shows a small decrease in intensity of band IV and increase in intensity of band III for the C_5 over the C_6 straps. As the strap length decreases this change becomes more dramatic. For C_5SC_5 87a and C_5-sulfoxide 88a the intensities of bands III and IV are approximately equal (Figs. 58, 60). Decreasing the strap length even further, C_4SC_4 87b displays a typical rhodo-type spectrum with III > IV > II > I (Fig. 59). On oxidation to the C_4-sulfoxide 88b the spectrum takes on oxorhodo-type features with III > II > IV > I (Fig. 61). These changes in intensities are accompanied by a shift to longer wavelength of the absorption maxima.

Similar behaviour is displayed by the protonated porphyrins. For the longer straps the spectra are similar with the lower energy α band about half as intense as the β-band. However as the strap becomes tighter there is an increase in intensity of the α relative to the β band; indeed for C_4-sulfoxide 88b α > β.

The "rhodofying" effect of the strap is obviously due to distortion of the porphyrin macrocycle as the strap becomes tighter. However why this effect should manifest itself in the same way as an electron withdrawing group is unclear.

TABLE XI: Comparison of Electronic Absorption Spectral Data of
Porphyrins (Free base in CH_2Cl_2)

PORPHYRIN		λ_{max} nm ($\log \varepsilon$)				
		Soret	Band IV	Band III	Band II	Band I
Etioporphyrin II[*]		396.5	497.0	530.0	565.7	619.7
		(5.23)	(4.16)	(4.02)	(3.84)	(3.72)
C_6-(OMe)$_2$	140a	397.2	496.6	530.0	565.6	620.0
		(5.19)	(4.14)	(3.99)	(3.80)	(3.72)
C_5-(OMe)$_2$	140b	398.4	498.4	532.4	567.2	621.8
		(5.19)	(4.10)	(4.01)	(3.80)	(3.68)
C_6-OCH$_3$	117a	398.2	497.2	530.6	567.2	620.6
		(5.21)	(4.13)	(3.99)	(3.82)	(3.70)
C_5-OCH$_3$	117b	397.2	497.8	533.6	567.2	620.8
		(5.18)	(4.07)	(3.98)	(3.78)	(3.63)
C_6-OH	118a	398.0	498.0	534.8	564.4	618.0
		(5.24)	(4.12)	(4.00)	(3.84)	(3.69)
C_5-OH	118b	397.2	499.2	535.2	563.6	617.6
		(5.25)	(4.10)	(4.01)	(3.84)	(3.59)
C_6-quinone	143a	397.2	497.2	530.4	567.2	621.6
		(5.21)	(4.08)	(3.94)	(3.79)	(3.63)
C_6-quinone	143b	396.8	498.0	534.8	567.2	620.8
		(5.21)	(4.07)	(3.98)	(3.82)	(3.58)
C_5-sulfide	87a	400.0	502.4	539.0	570.0	624.0
		(5.22)	(4.03)	(4.03)	(3.79)	(3.52)
C_5-sulfoxide	88a	399.6	502.4	539.2	568.0	621.6
		(5.20)	(4.01)	(4.03)	(3.82)	(3.49)
C_4-sulfide	87b	405.6	512.6	551.0	576.0	630.0
		(5.16)	(3.84)	(4.01)	(3.79)	(3.32)
C_4-sulfoxide	88b	404.4	513.2	551.6	573.6	627.2
		(5.24)	(3.89)	(4.09)	(3.89)	(3.35)

[*] Ref. 117

TABLE XII: Comparison of Electronic Absorption Spectra of Porphyrins
(Dication in CH_2Cl_2)

		λ_{max} nm (log ε)		
PORPHYRIN		Soret	β	α
Etioporphyrin II[*]		399.5 (5.58)	549.1 (4.25)	590.7 (3.90)
C_6-(OMe)$_2$	<u>140a</u>	403.6 (5.50)	546.6 (4.16)	592.4 (3.81)
C_5-(OMe)$_2$	<u>140b</u>	401.2 (5.65)	546.6 (4.18)	590.8 (3.75)
C_6-OCH$_3$	<u>117a</u>	400.0 (5.54)	546.0 (4.15)	590.0 (3.77)
C_5-OCH$_3$	<u>117b</u>	400.0 (5.47)	545.4 (4.15)	588.4 (3.74)
C_6-OH	<u>118a</u>	405.6 (5.55)	548.4 (4.18)	594.0 (3.88)
C_5-OH	<u>118b</u>	400.0 (5.58)	546.8 (4.21)	587.2 (3.65)
C_6-quinone	<u>143a</u>	401.2 (5.57)	546.0 (4.20)	591.2 (3.85)
C_5-quinone	<u>143b</u>	403.2 (5.60)	547.2 (4.21)	592.4 (3.82)
C_5-sulfide	<u>87a</u>	406.0 (5.49)	551.0 (4.13)	597.2 (3.82)
C_5-sulfoxide	<u>88a</u>	408.4 (5.52)	551.6 (4.14)	597.2 (3.87)
C_4-sulfide	<u>87b</u>	410.0 (5.32)	558.4 (3.97)	609.2 (3.88)
C_4-sulfoxide	<u>88b</u>	416.8 (5.43)	562.0 (4.02)	612.0 (4.04)

[*] Ref. 117

Fig. 58:   Electronic Absorption Spectra of 87a

Fig. 59: Electronic Absorption Spectra of 87b

Fig. 60:   Electronic Absorption Spectra of 88a

Fig. 61:   Electronic Absorption Spectra of 88b

Fig. 62:   Electronic Absorption Spectra of 117a

Fig. 63:   Electronic Absorption Spectra of 117b

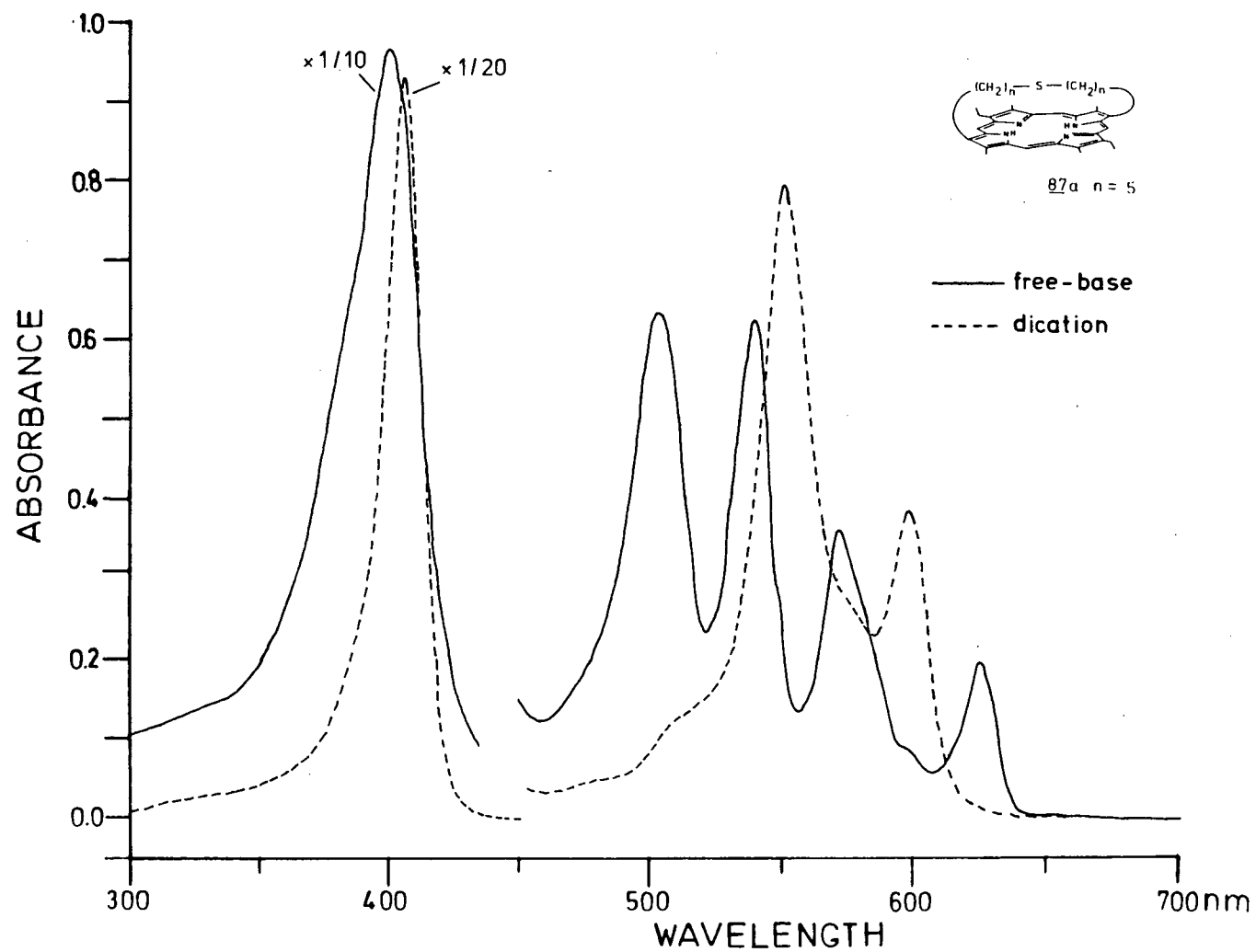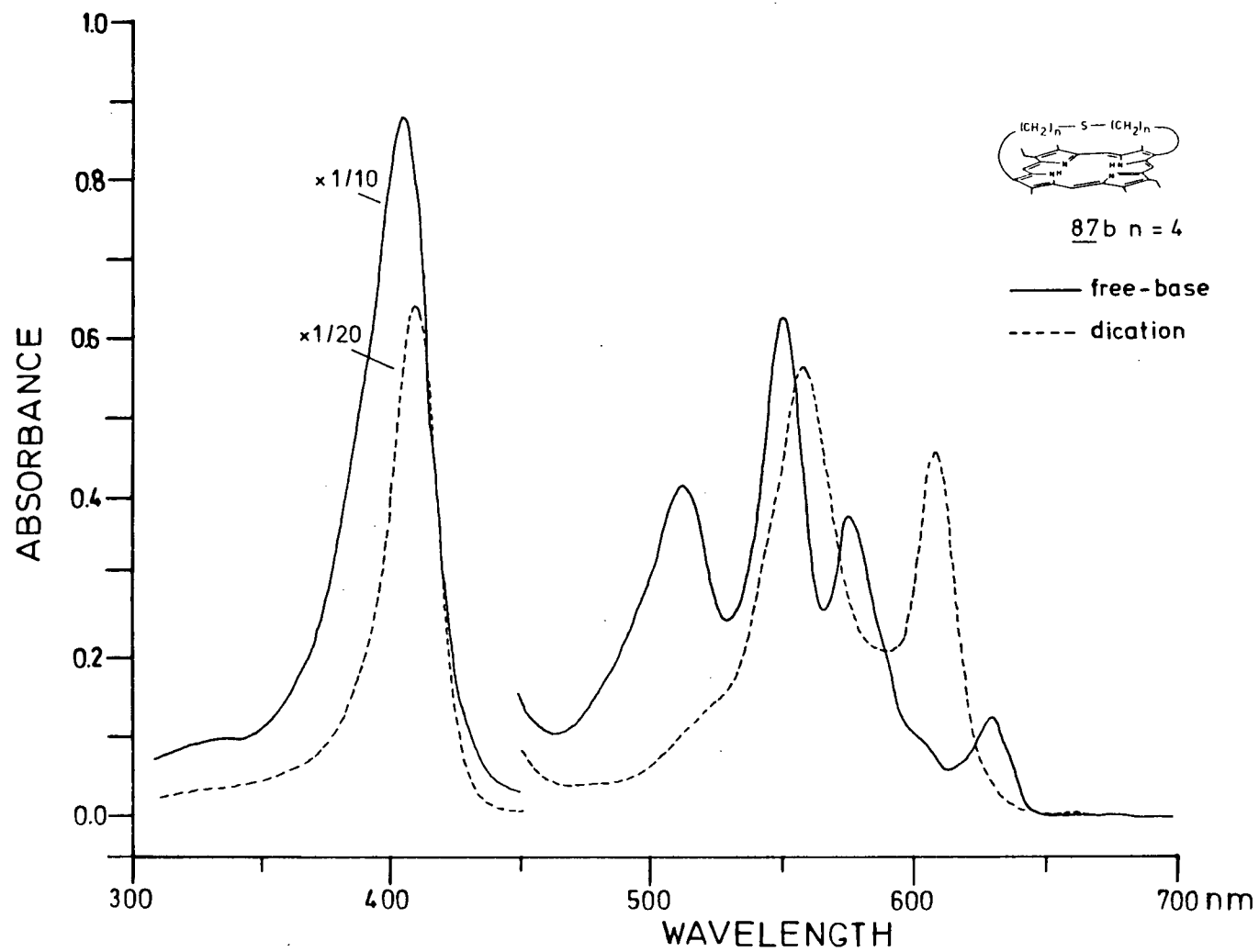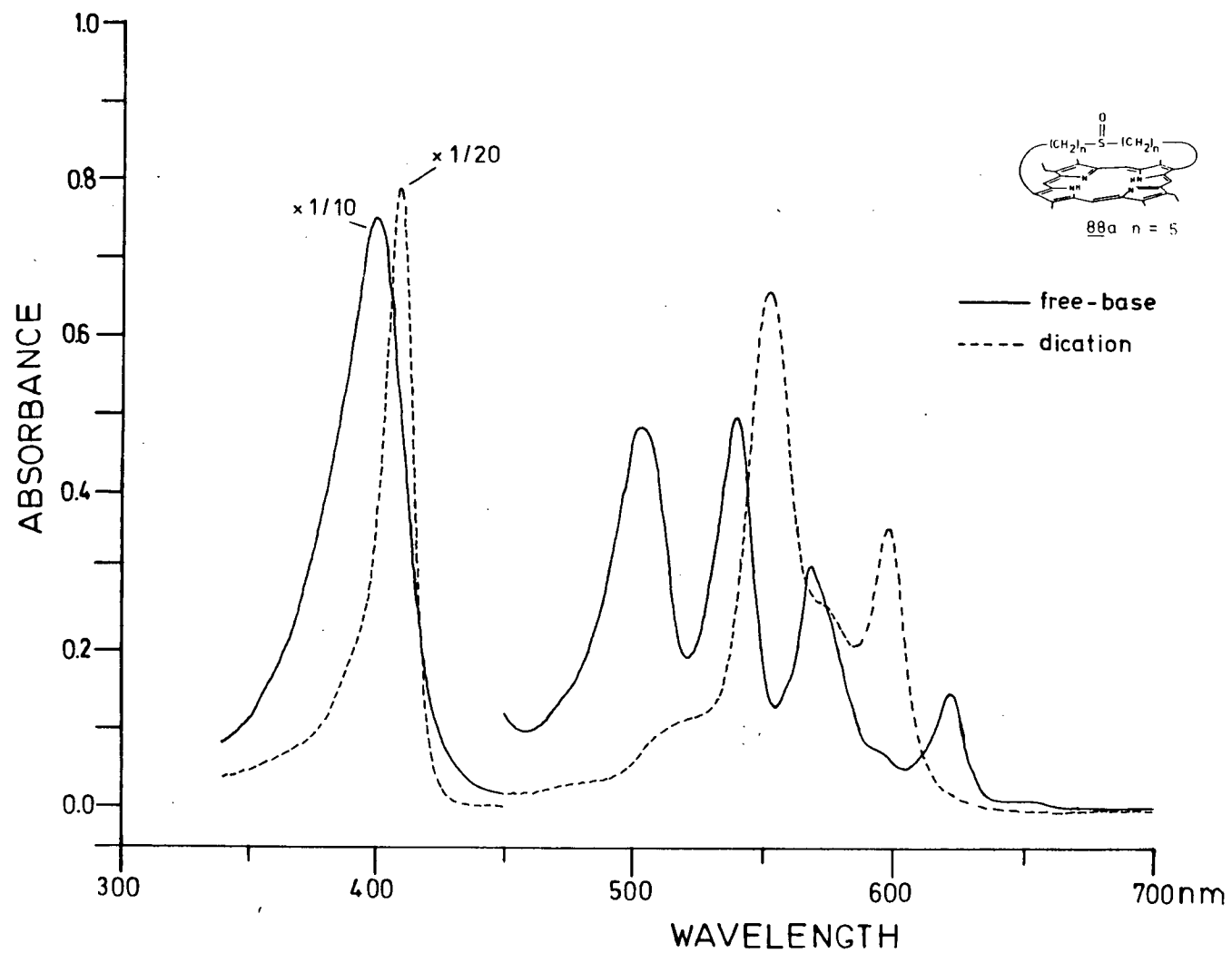Fig. 64:   Electronic Absorption Spectra of 118a

Fig. 65:   Electronic Absorption Spectra of 118b
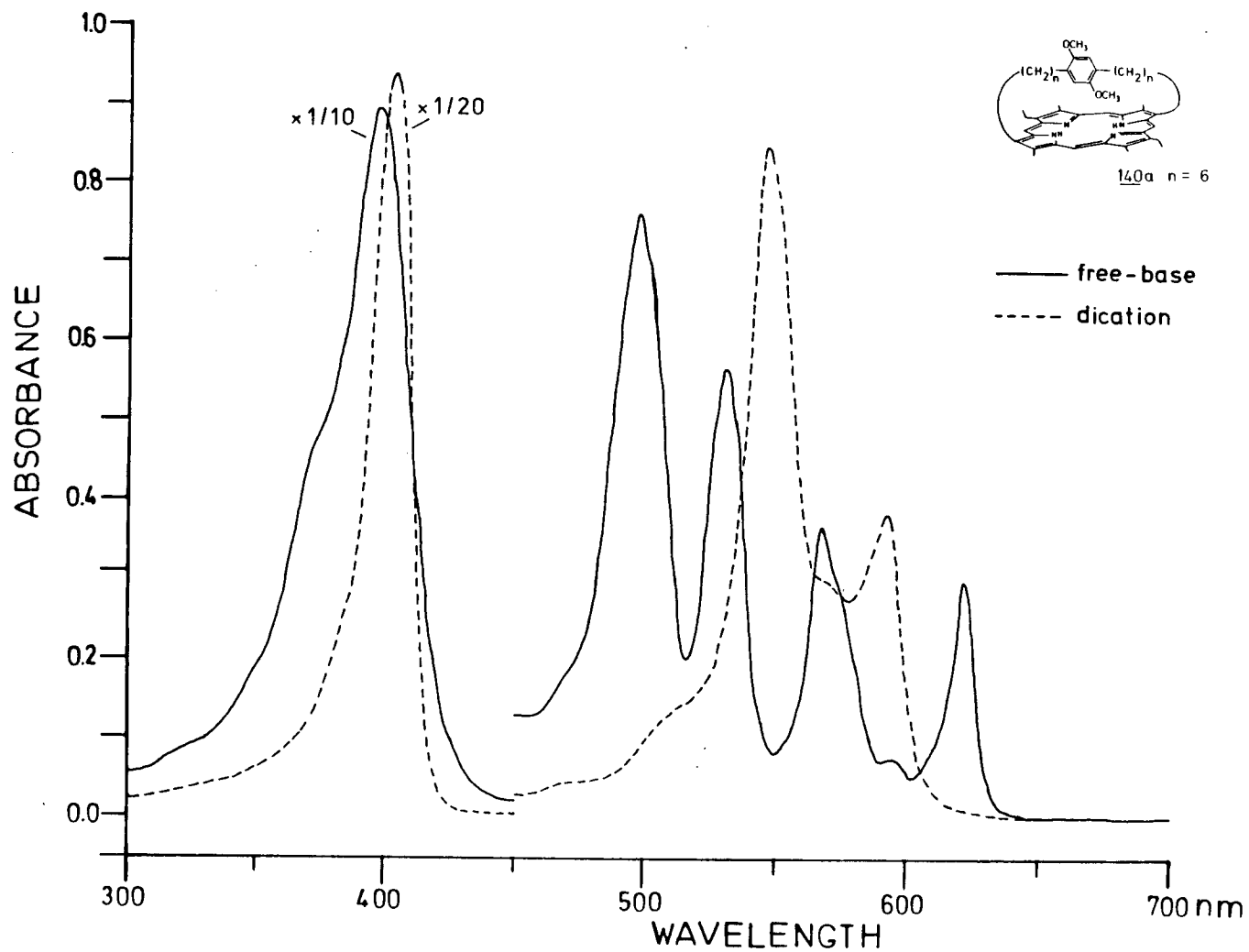
Fig. 66:   Electronic Absorption Spectra of 140a
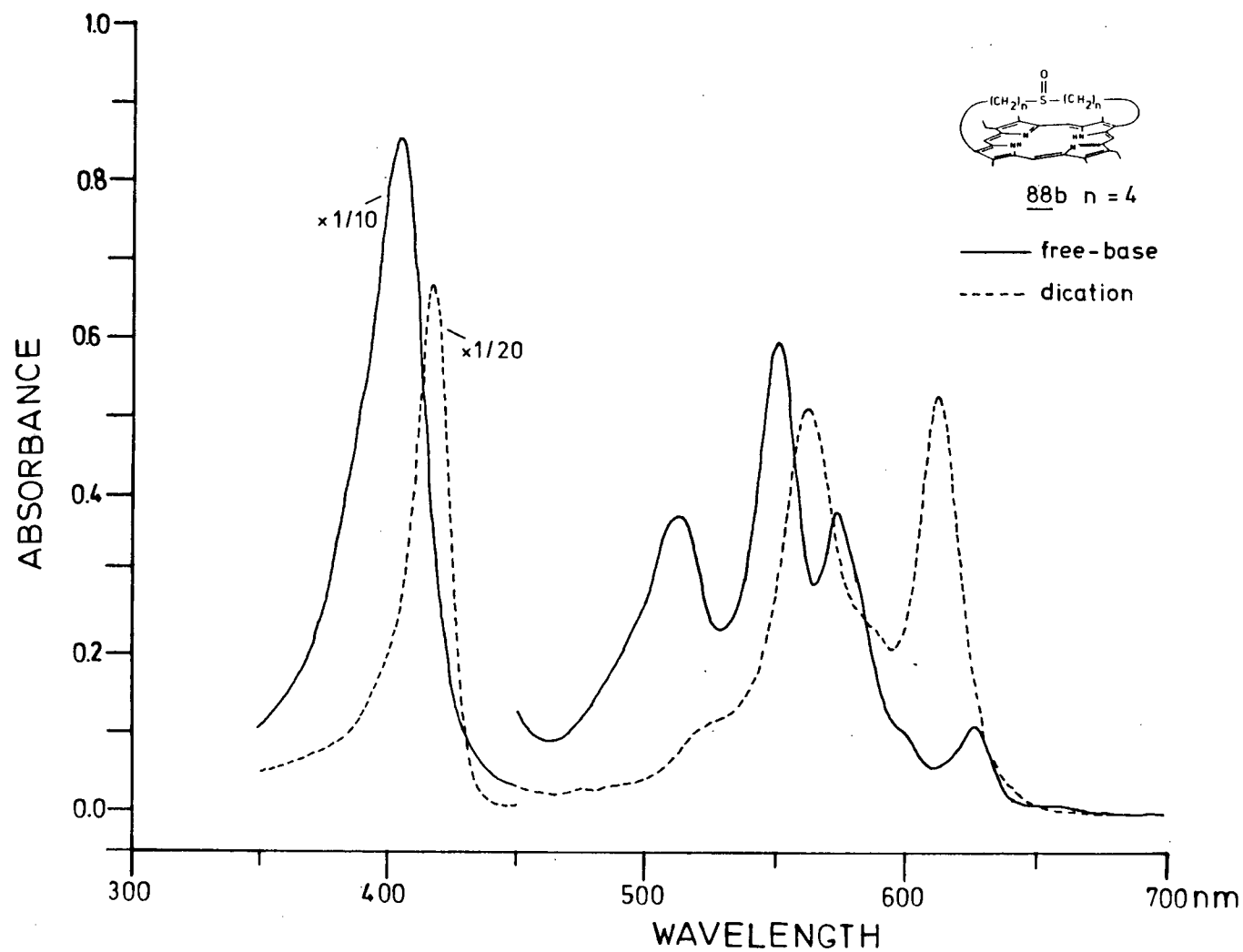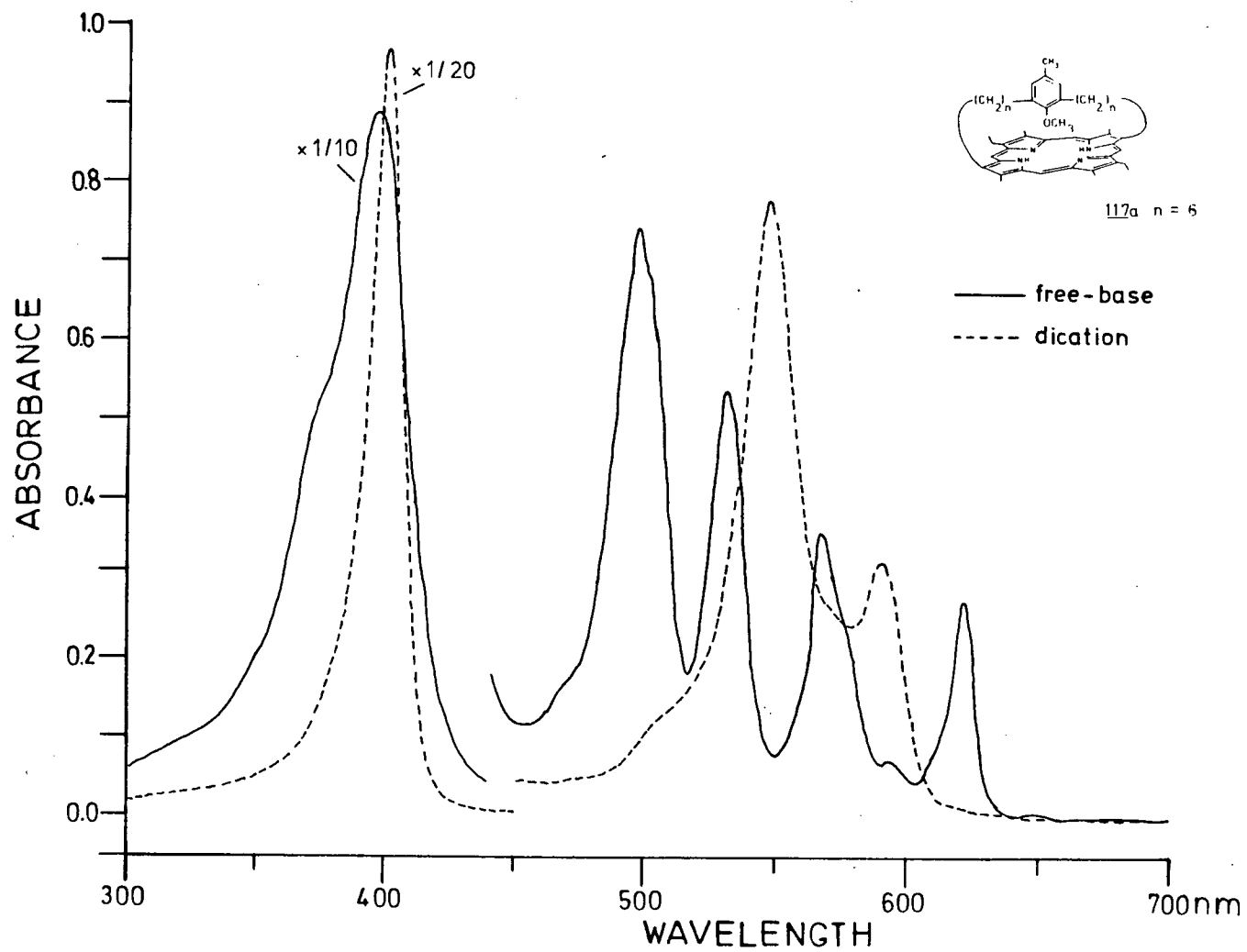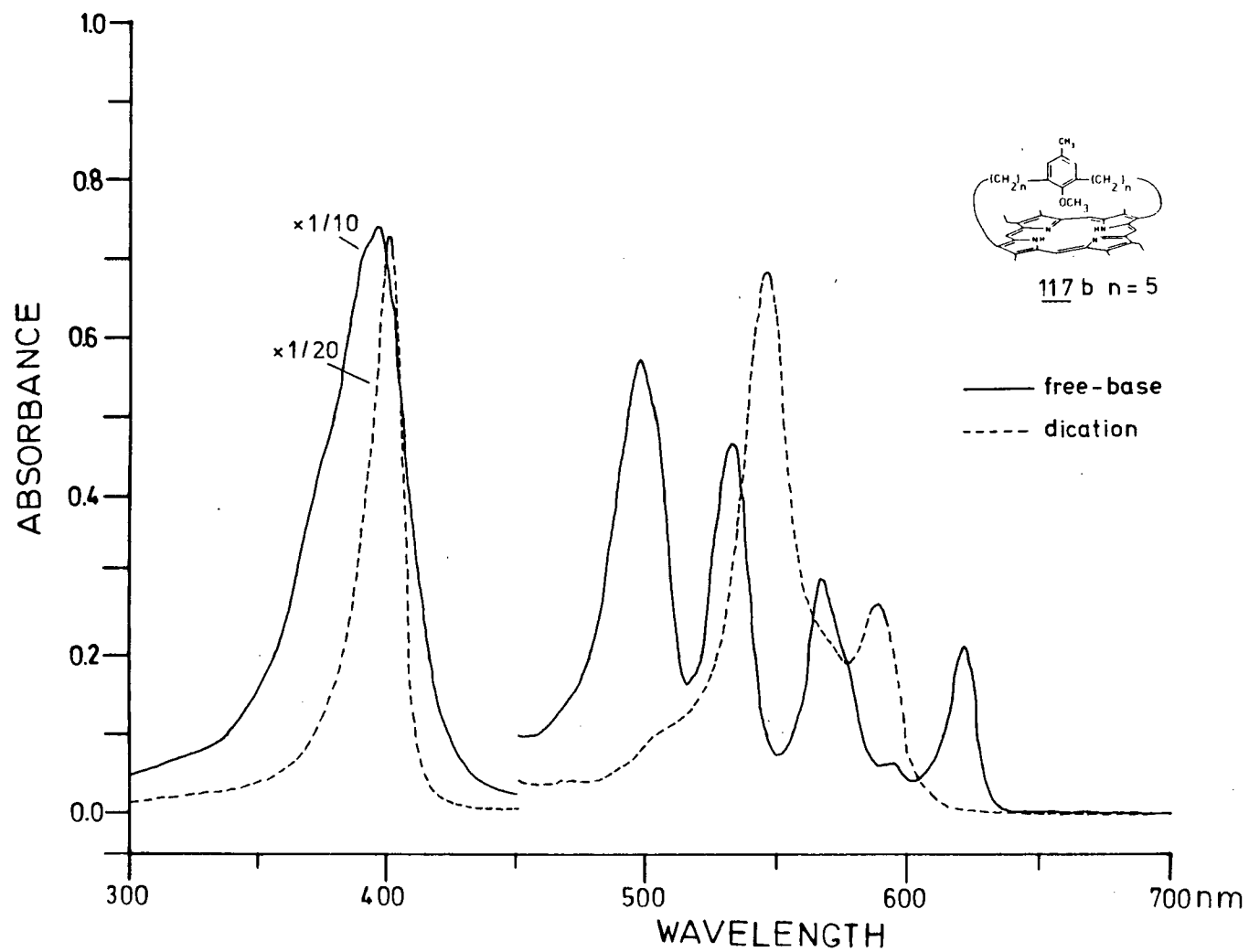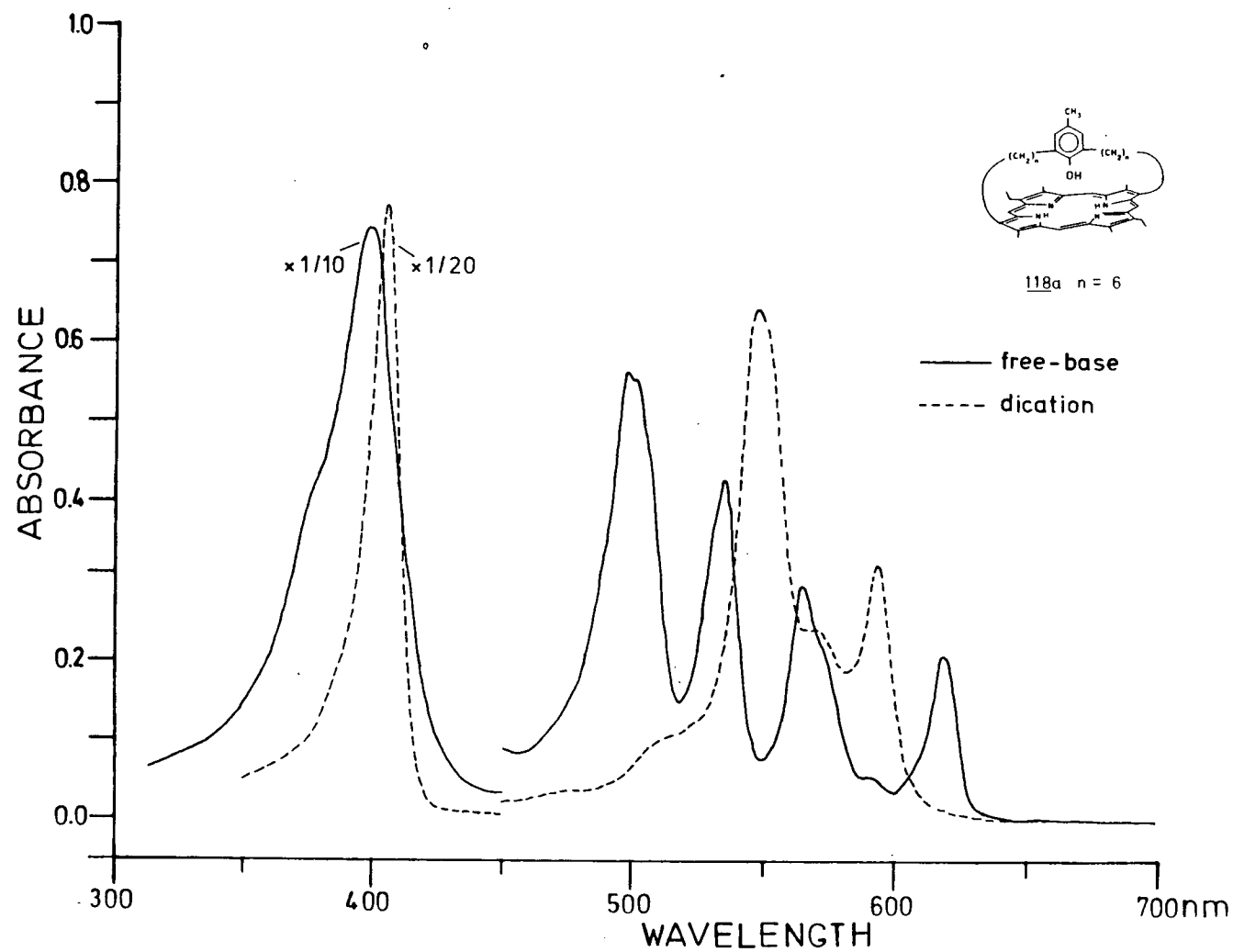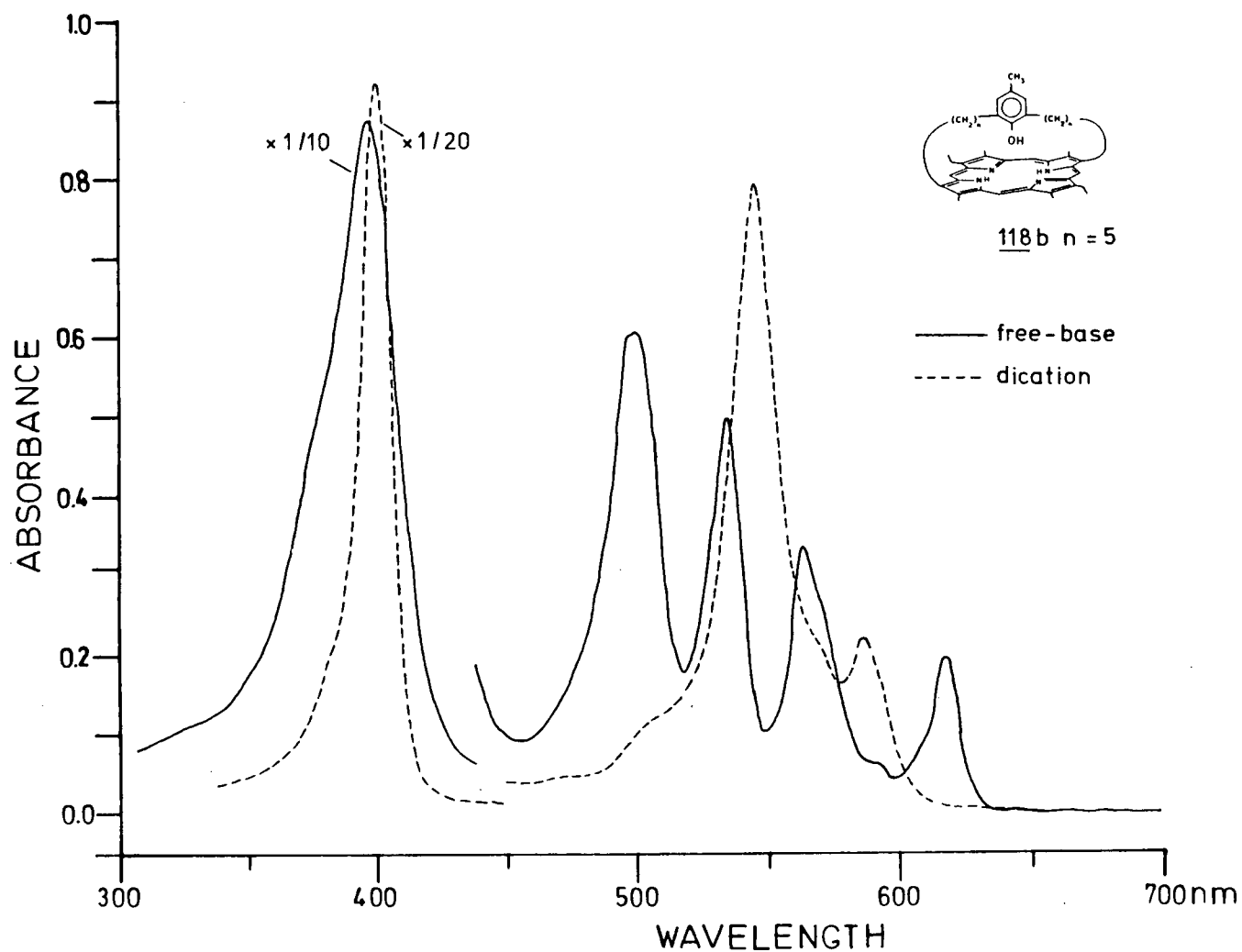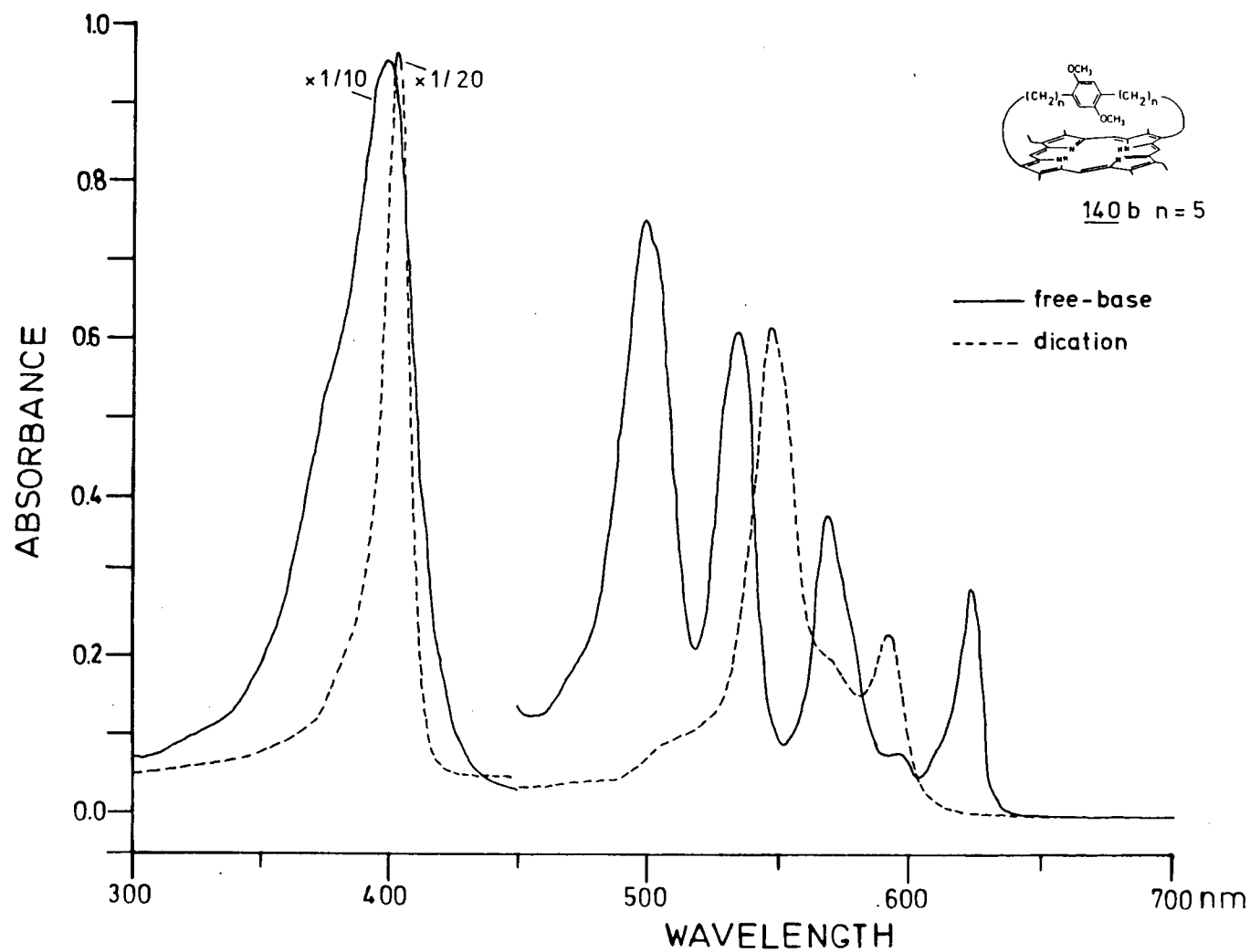
Fig. 67:   Electronic Absorption Spectra of 140b
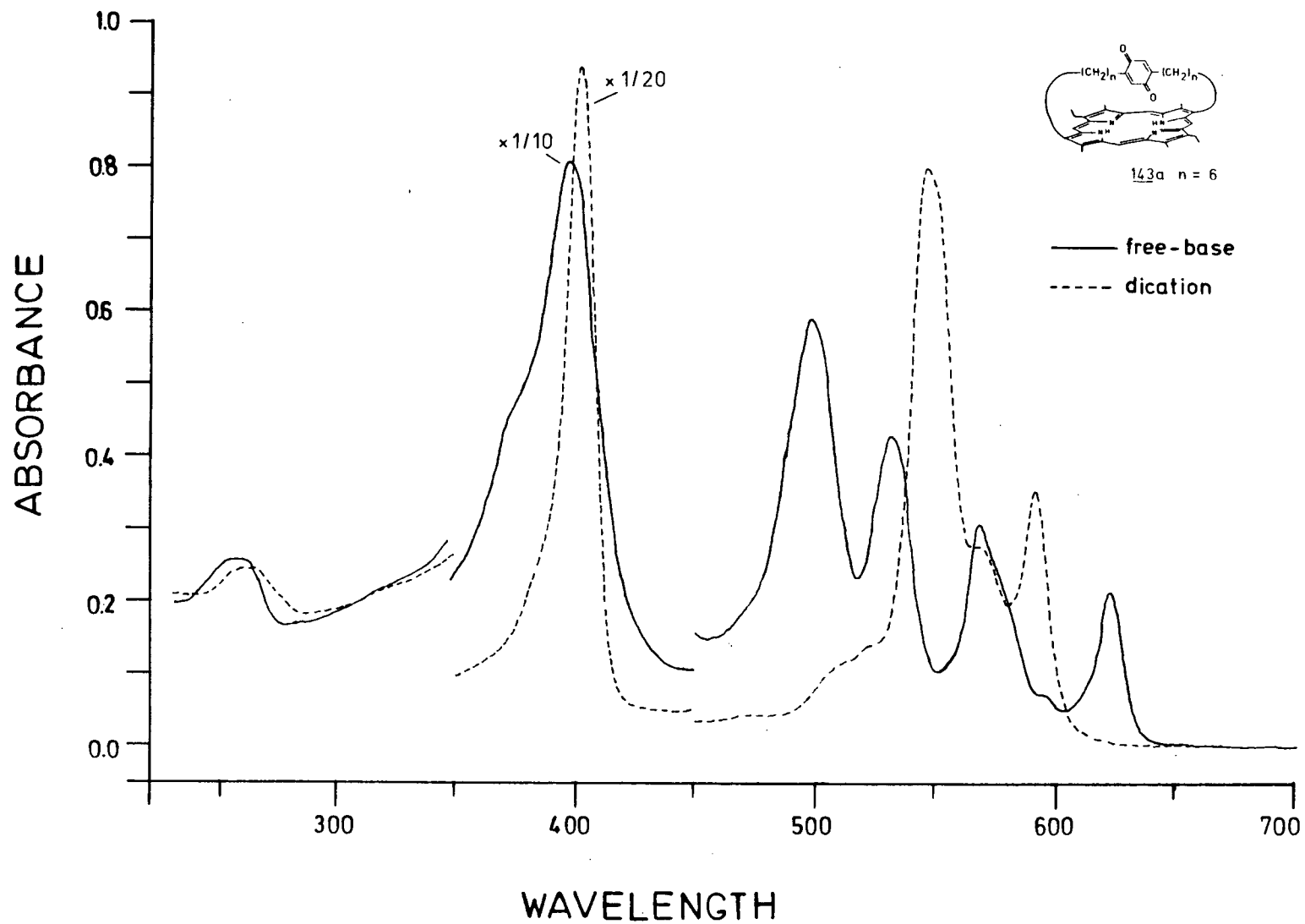
Fig. 68:   Electronic Absorption Spectra of 143a
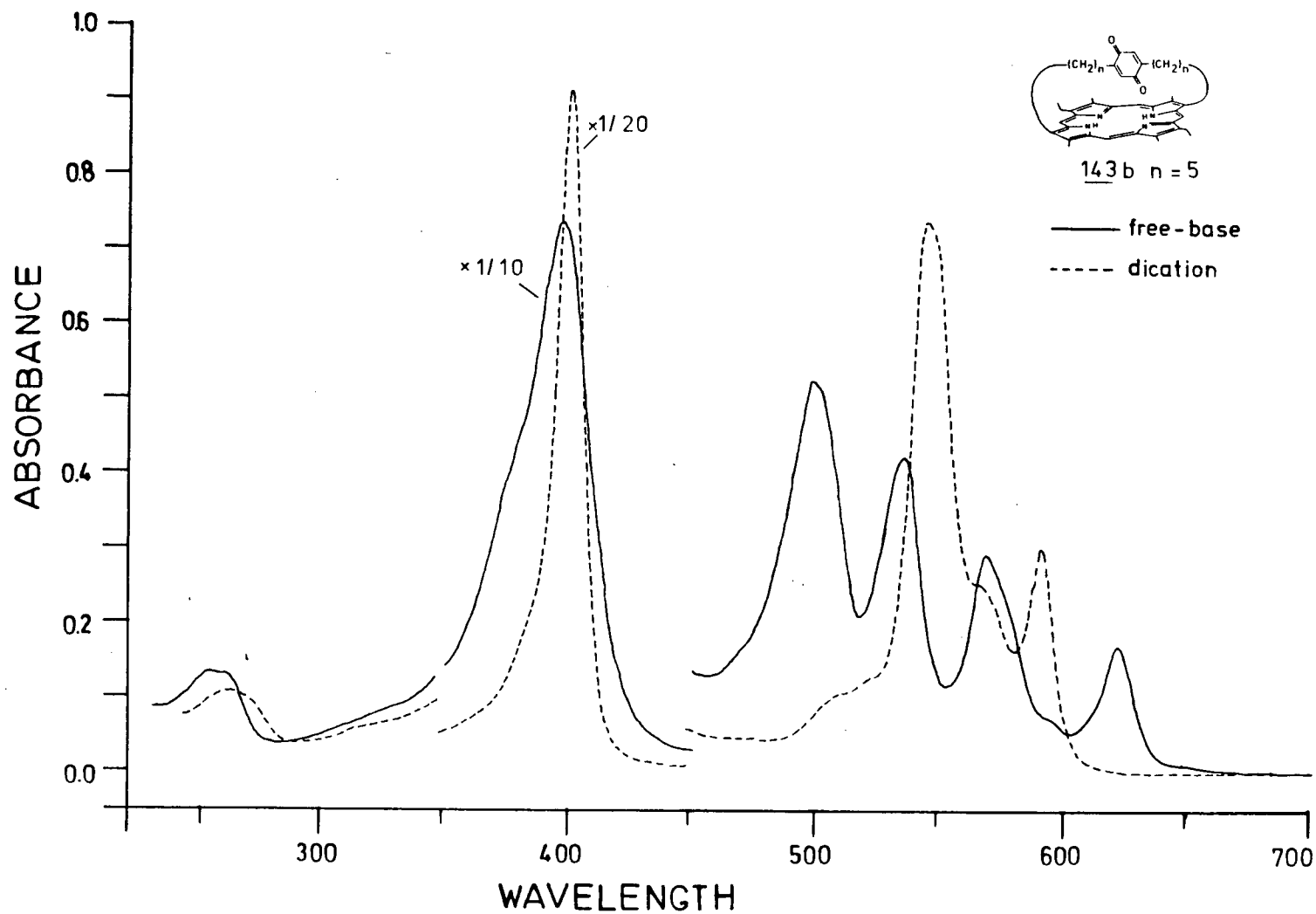
Fig. 69:   Electronic Absorption Spectra of 143b

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