Studies on the Synthesis of Oxygen Carriers

by

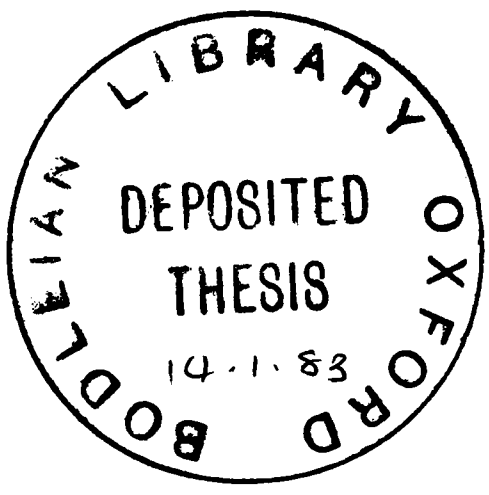
Simon Roger Hall

Christ Church, Oxford

1982

A thesis submitted in partial fulfillment

of the requirements for the degree of D.Phil.



To my parents

ACKNOWLEDGEMENTS

I would like to thank Professor J.E. Baldwin, F.R.S., for his supervision of this work and for financial support in the later stages.

I also wish to acknowledge the financial support of the S.E.R.C.

I am greatly indebted to all the people who helped me in the performance of this work, particularly: Drs M.J. Crossley and I.J. Dagley, without whom this project would have been impossible to complete; Dr. P. Perlmutter who read the manuscript; Dr. J. Murphy along with Neil Stephenson who proof-read the typed copy; and all the people who ran p.m.r. spectra for me (particularly Les Field).

To mention all the people who helped with this work is impossible in such a limited space and my thanks go to all those in the Dyson-Perrins Laboratory.

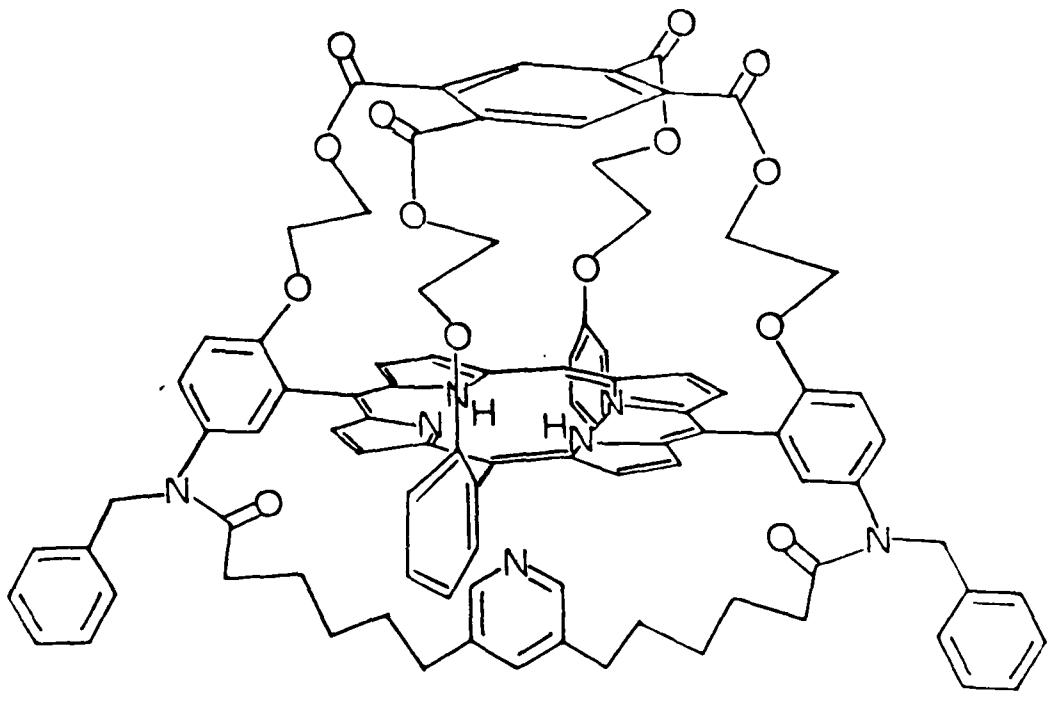
Finally my thanks go to Heather Holloway who typed this thesis quickly and accurately.

ABSTRACT

To mimic the properties of haemoglobin (Hb) and myoglobin (Mb) it has been found necessary to synthesise a five-coordinate ferrous porphyrin with a protecting structure over the sixth coordination site at iron.

This thesis describes approaches to the synthesis of such a compound where the protecting structure is the "capped" moiety[30] and where the base which occupies the fifth coordination site is held in position by two covalent linkages to the porphyrin.

The preparation of the target molecule involved the synthesis of a new "capped" porphyrin and a series of difunctionalised pyridines. These were then successfully coupled under high dilution conditions to give the "capped/strapped" porphyrin (60). Metallation and reduction completed the synthesis.



(60)

The behaviour of the ferrous complex in the presence of dioxygen was investigated. High stability toward irreversible

oxidation was found. In the presence of oxygen the ferrous complex had a half-life in excess of 40h at room temperature.

CONTENTS

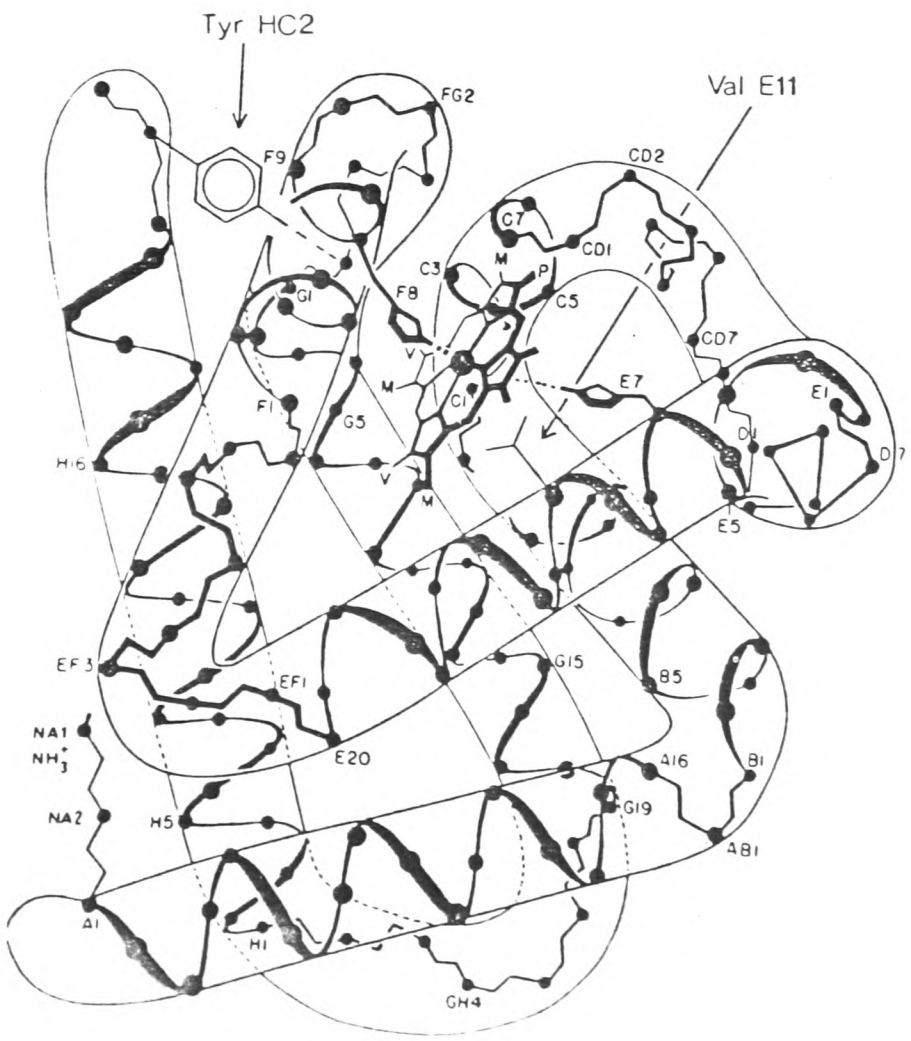
Page No.

INTRODUCTION

1. Haemoglobin and Myoglobin

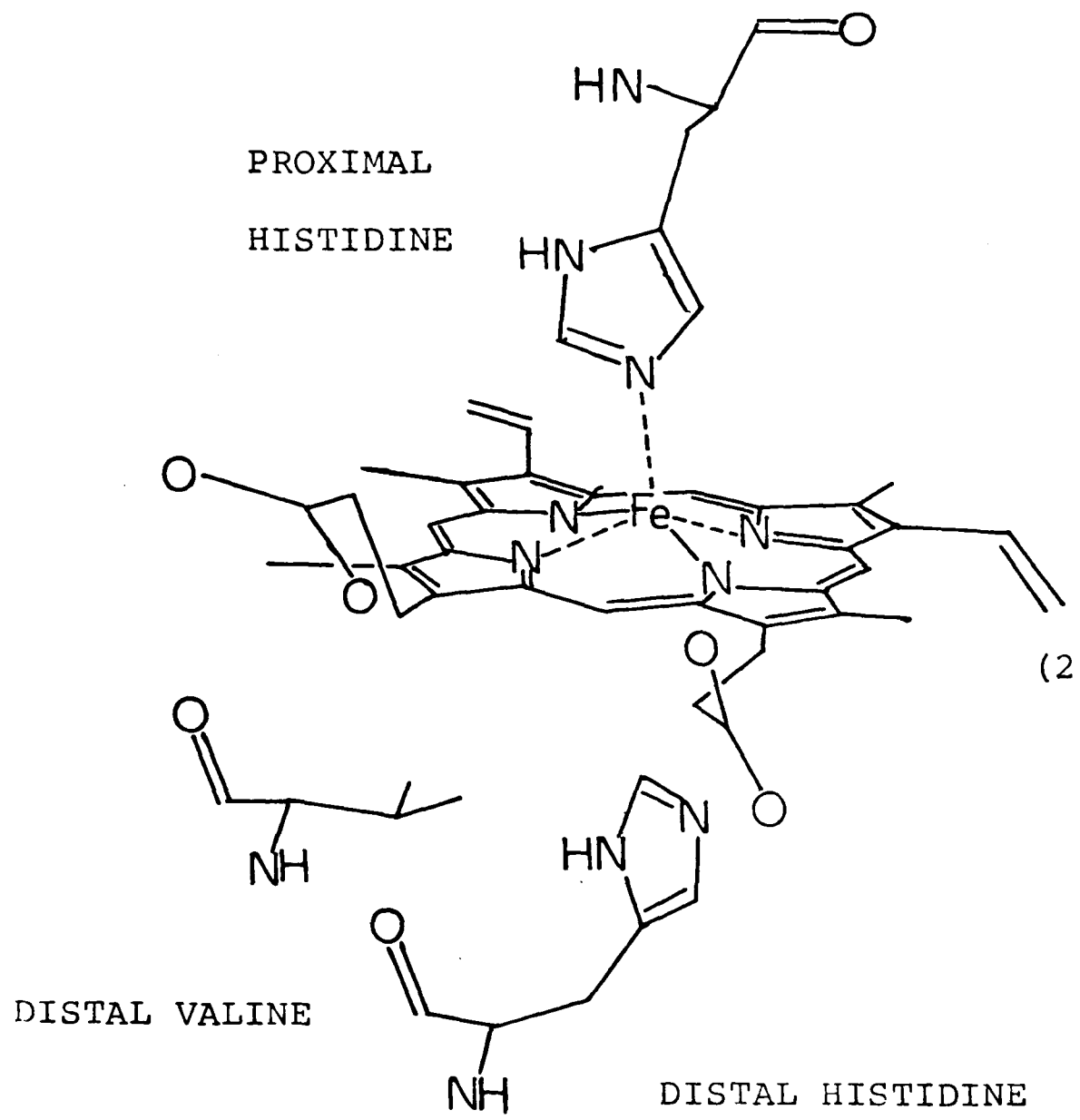
One of the major functions of the human blood stream is the transport of molecular oxygen (dioxygen). This is achieved by the metallo-protein haemoglobin (Hb)[1] which is situated in the red blood cell (erythrocyte).[1d] Hb (molecular weight 64,000) consists of four loosely connected sub-units, each of which can bind one molecule of dioxygen. The interaction between sub-units controls the dioxygen binding properties of Hb - the phenomenon known as cooperativity.[1]

A related metallo-protein, myoglobin (Mb)[1], which acts as a store of dioxygen, is situated in muscle tissue. Mb is monomeric (molecular weight 13,500) and can bind only one equivalent of dioxygen. Its structure is closely related to that of a sub-unit of Hb (1).



(1)

The binding site for oxygen is shown in more detail below



Iron in the ferrous state is coordinated to proto-porphyrin IX (2). This complex, "haem", is held in a hydrophobic cleft of the globin by a coordinate bond from the "proximal" histidine as well as several weaker interactions with the enfolding protein. Oxygen and other small ligands bind to the iron atom on the "distal" side of the ferrous porphyrin to give an octahedral complex.

The "distal" histidine is able to form a hydrogen bond

with suitable molecules co-ordinated to haem. This has recently been established for oxymyoglobin.[2] Results with model compounds (see later under simple ferrous porphyrins and oxygen) suggest that this effect may also promote proton catalysed autoxidation. The "distal" histidine also exerts a considerable steric influence and is thought to be largely responsible for the ability of dioxygen to displace bound carbon monoxide.[3] In simple porphyrins this does not occur and the effect is attributed to the "distal" histidine enforcing a bent Fe-C-O geometry rather than the energetically more favourable linear geometry.

Both Mb and Hb are prone to irreversible oxidation. The oxidation product of Hb, methaemoglobin is present in up to 3% *in vivo*. The concentration of oxidised product is held at this low level by an array of reductase enzymes present in the red-blood cell.

2. The Behaviour of Simple Ferrous Complexes with Dioxygen

The iron protoporphyrin IX moiety can be removed from Hb as its ferric derivative or ferrous carbonyl complex. Even in the presence of an exogenous base (to mimic proximal co-ordination), ferrous protoporphyrin IX and other simple porphyrins are rapidly and irreversibly oxidised on exposure to oxygen.[5] This irreversible oxidation of ferrous to ferric states is not confined to ferrous porphyrins and occurs in solution with virtually all ferrous complexes in the presence of oxygen.

The oxidation process can be inhibited by high-dilution,[6]

high oxygen pressure[7] and low temperature.[8] Below -50°C the reaction is slow enough to permit spectroscopic studies.

The most stable environment for reversible dioxygen binding is an aprotic one.[8d] Even the N<u>H</u> proton of imidazole can catalyse oxidation.[8c] Studies on Hb suggest[9] a correlation between the extent of hydrogen bonding from the distal histidine to bound dioxygen and the relative susceptibility of each sub-unit towards irreversible oxidation.

Despite the above, Hb and Mb are still 10^8 times more stable towards oxidation than simple ferrous porphyrins.

Recent studies[10] at very low temperature have shown that the aprotic pathway for oxidation of ferrous porphyrins is that shown in scheme 1.

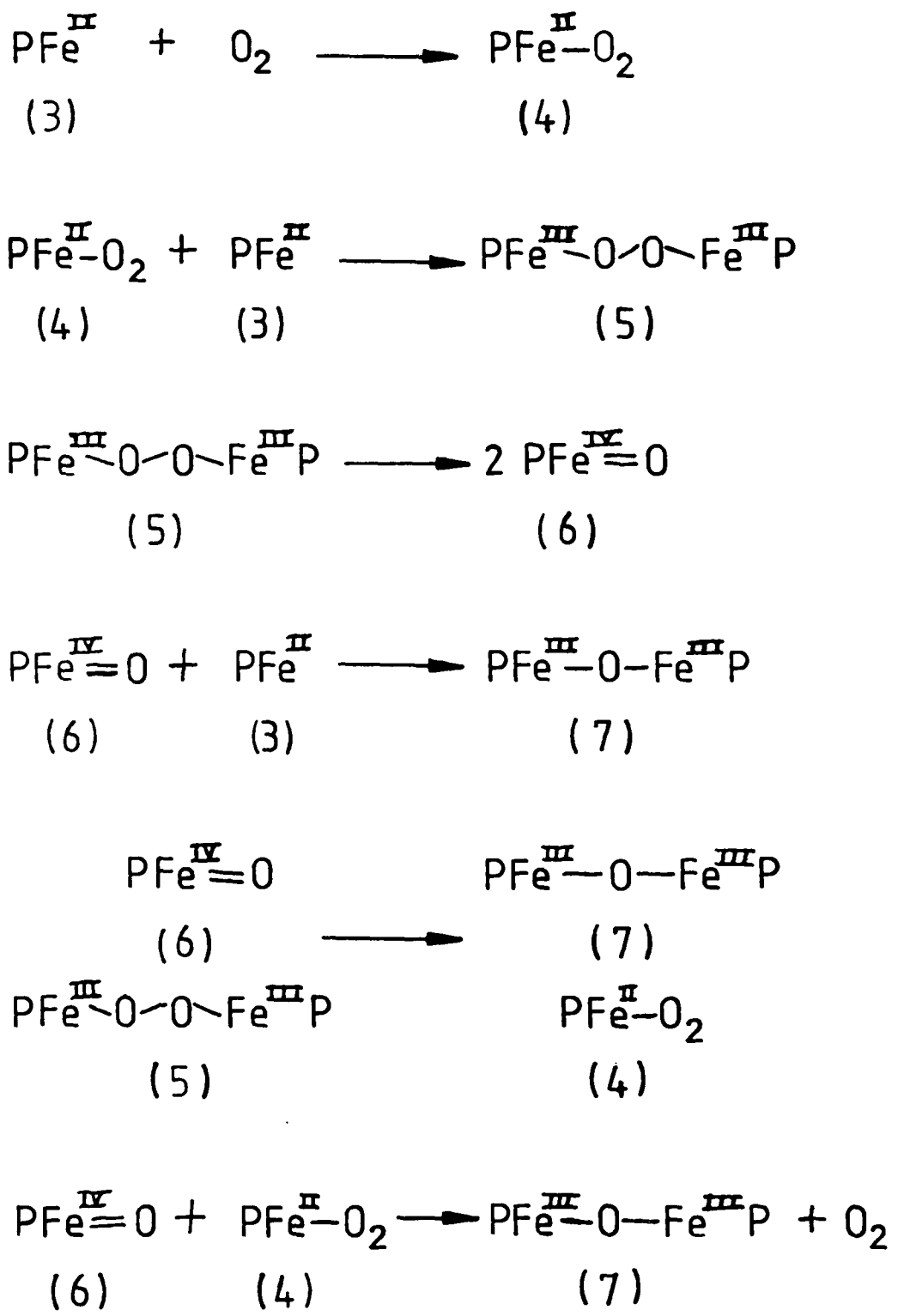
The final product of oxidation seen is the μ-oxo dimer (7). When base is present, as in the natural situation, the relative stability of the intermediates changes. One major effect is that in the presence of base, reversible oxygen binding to iron is observed whereas, in the absence of base, the ferrous oxygen complex (4) rapidly reacts to form μ-peroxo dimer (5) and is not observed even at -80°C.

When a proton source is present a different mechanism of oxidation is believed to operate,[11] (scheme 2). If water is the nucleophile the product is the ferric hydroxide or "met" form.

Another problem encountered with the simple ferrous porphyrin complex is associated with the need for an exogenous base to mimic proximal co-ordination. If too little base is used then, as mentioned above, rapid decomposition of the ferrous oxygen complex results even at low temperature.[10]

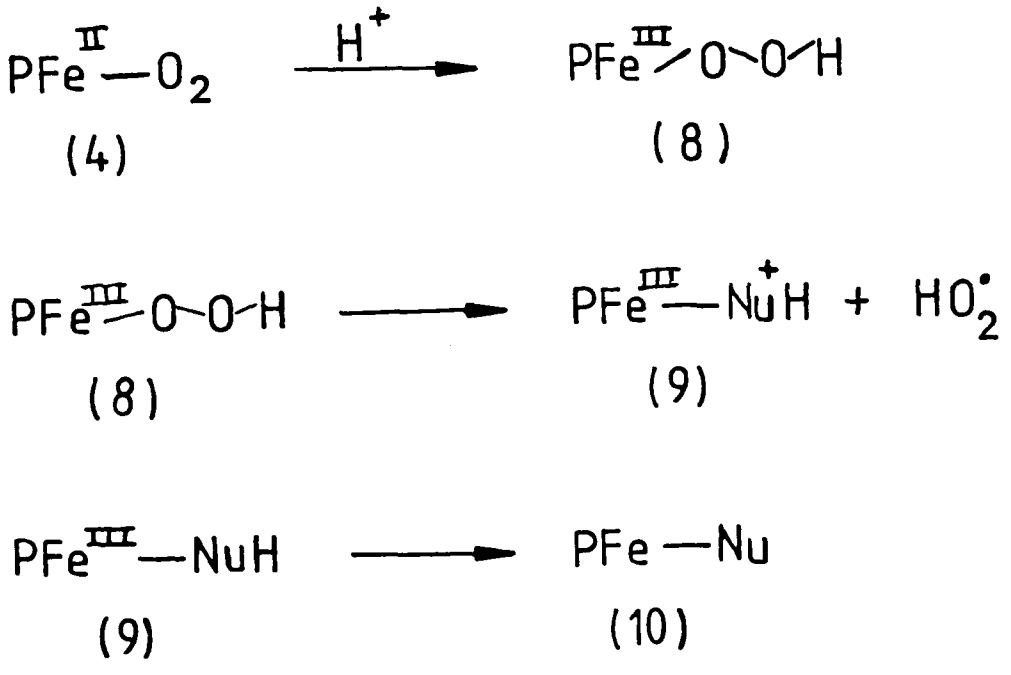
Scheme 1

The Autoxidation of Ferrous Porphyrins in an Aprotic Solvent[10]



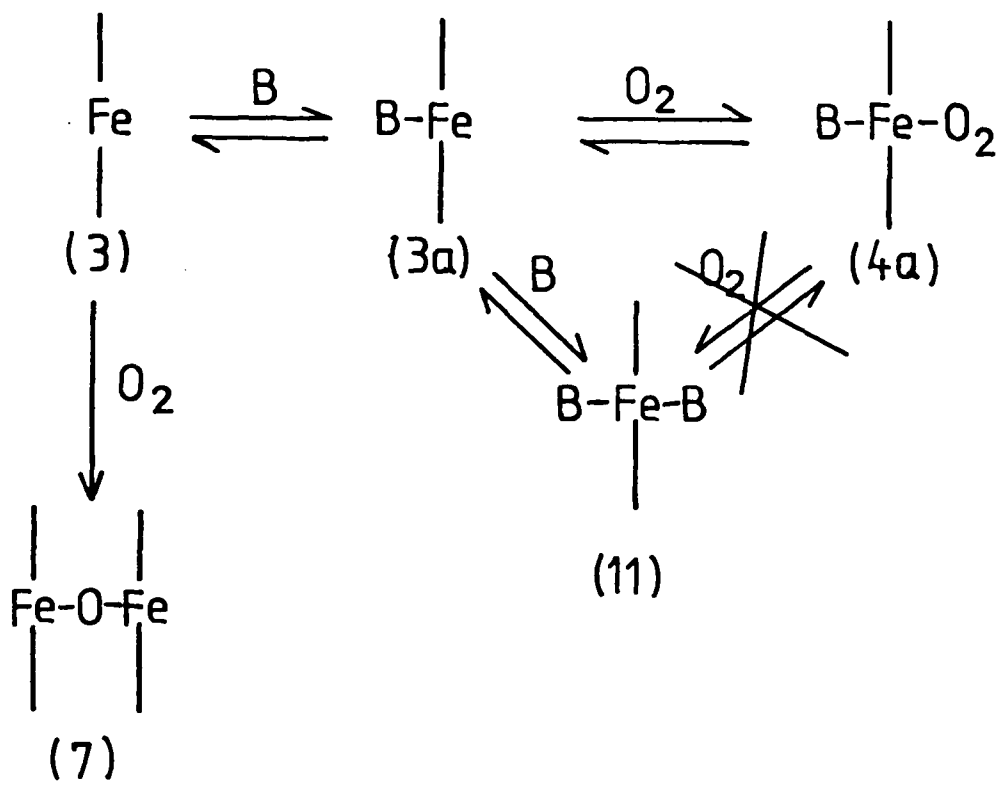
Scheme 2

The Autoxidation of Ferrous Porphyrins in the Presence of Protons[11]



If too much base is used then oxygen insensitive six-co-ordinate iron haemochromes (11) are formed.[12]

Scheme 3



3.1 The Study of Synthetic Analogues of Hb and Mb

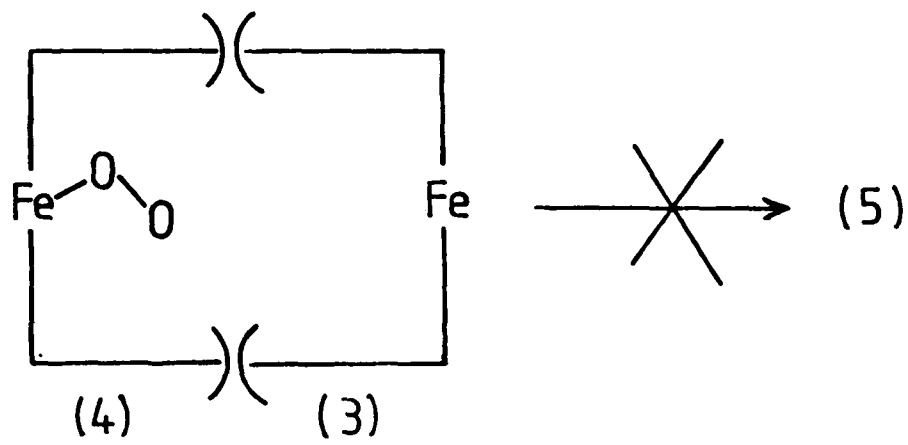
Given the vast difference in stability between Hb, Mb, and simple ferrous complexes towards oxidation, the enfolding globin protein must play a crucial role.

The study of simpler structural analogues of Hb and Mb was originally undertaken to elucidate the mechanism of stabilisation of the ferrous state and the factors controlling oxygen and carbon monoxide affinity.

A considerable amount of research has been conducted into the carriage of molecular oxygen by metal complexes and the work in this field has already been extensively reviewed[13,14,15,16] This introduction will concentrate on the synthesis of ferrous macrocyclic complexes and their reactions with oxygen.

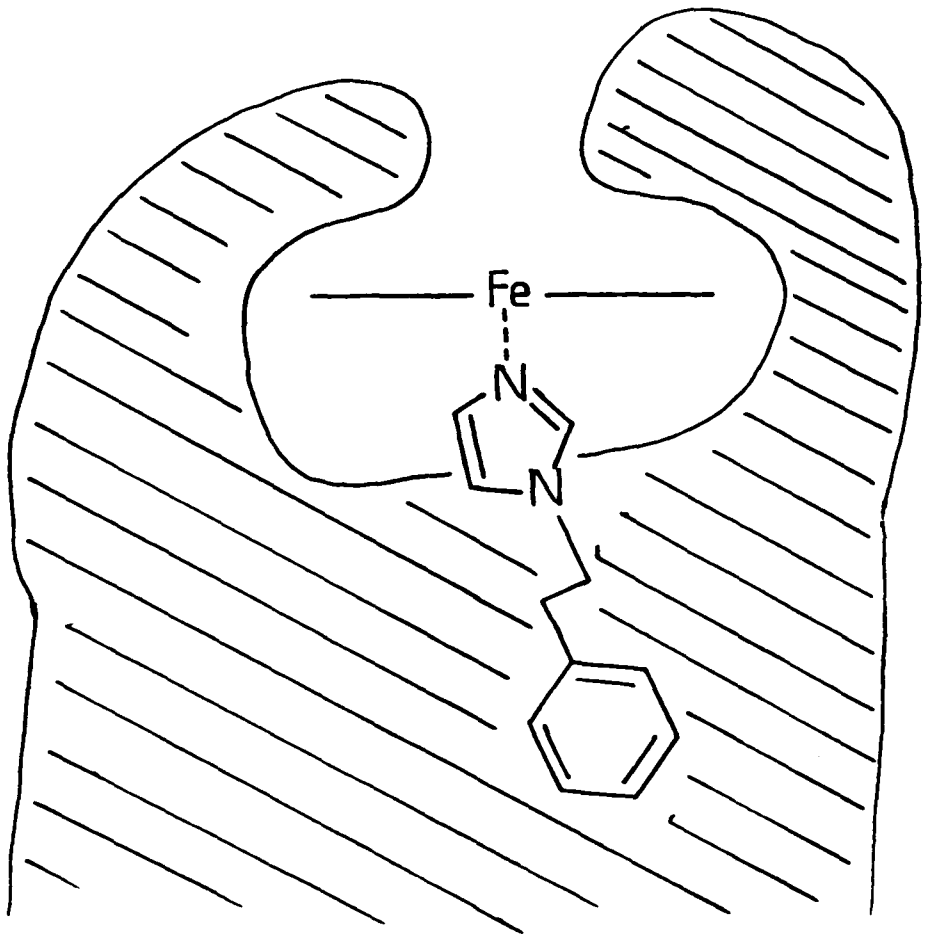
3.2 The Concept of Steric Protection

The first step on the oxidation pathway of a ferrous complex in an aprotic solvent is a bimolecular process between a ferrous porphyrin and an oxygenated ferrous porphyrin. Besides the aforementioned techniques of low temperature, high oxygen tension, or high dilution, it should be possible to mimic the globin protein and encase the ferrous complex in a protective hydrophobic pocket to prevent μ-peroxo dimer (5) formation.



Even before the final proof[10], the initial bimolecular step had been postulated[6] and working on the above hypothesis a ferrous porphyrin with a base was embedded in a polymeric matrix (12)[17].

This arrangement was found to reversibly bind molecular oxygen.

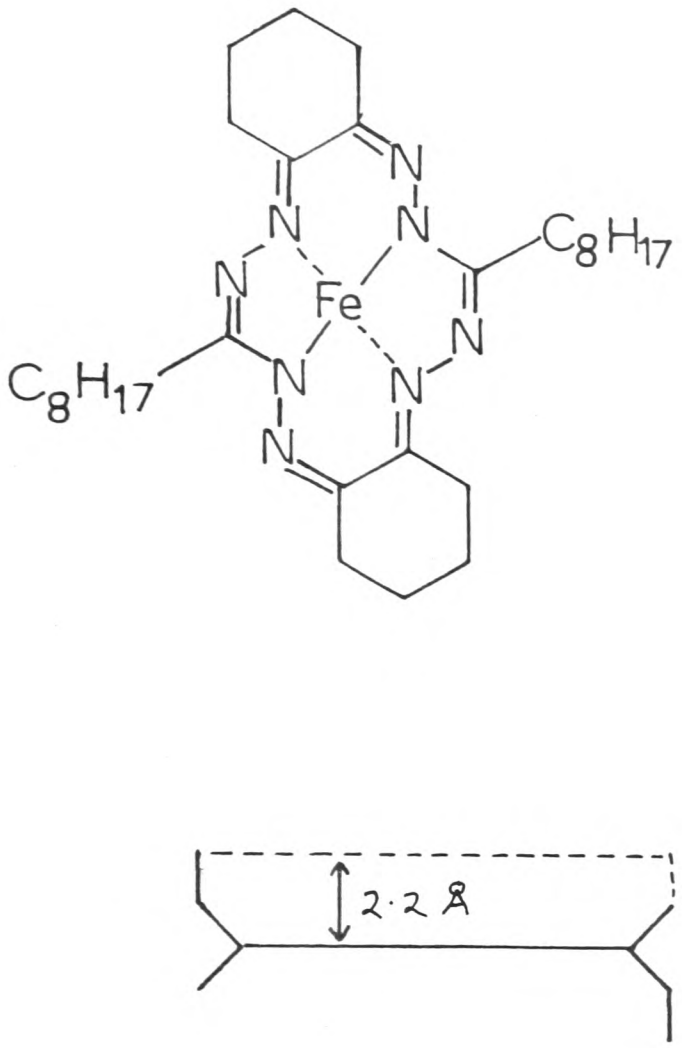


(12)

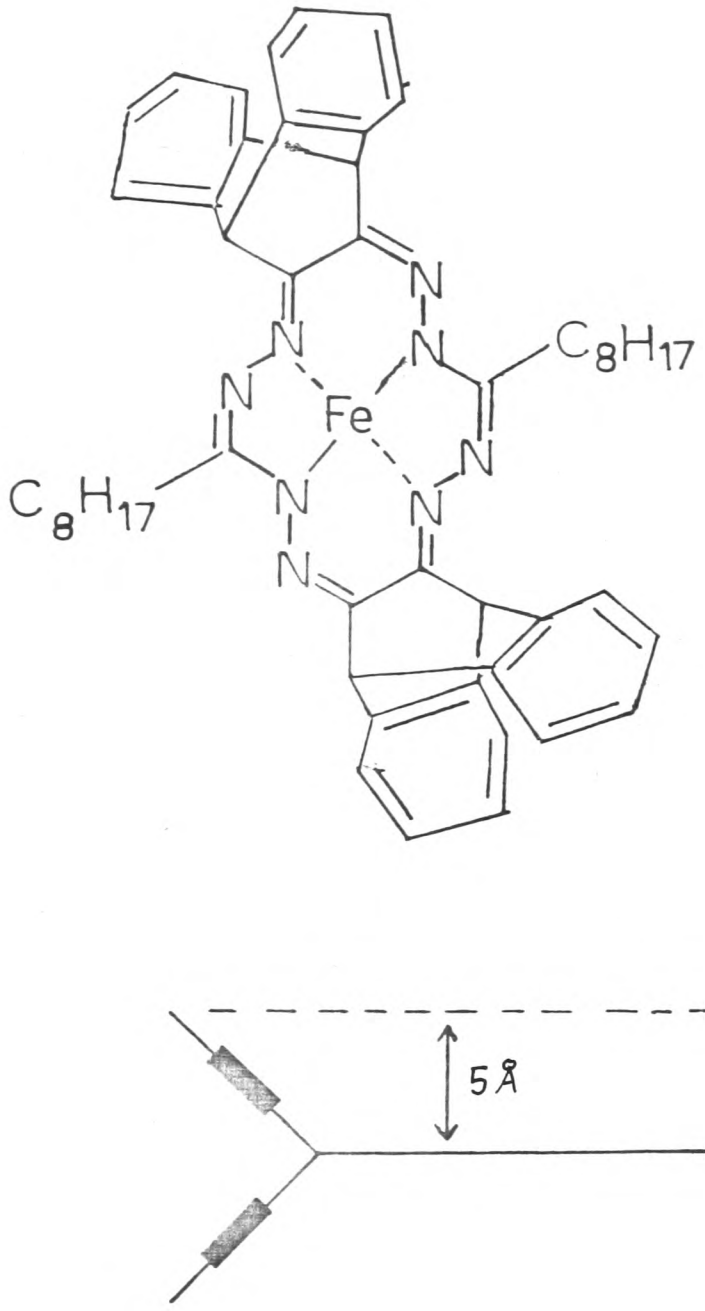
The other approach to reversible dioxygen binding was the synthesis of discrete monomolecular "protected" ferrous complexes.

3.3 Protected Non-Porphyrin Macrocycles

Baldwin's group[18] synthesised the buttressed macrocyclic complexes (13) and (14).



(13)



(14)

At room temperature in the presence of dioxygen both of these complexes rapidly irreversibly oxidised. At -80°C (13) was still found to react irreversibly with dioxygen, but (14) now exhibited reversible behaviour with dioxygen. This difference in behaviour was due to the larger buttresses in (14) inhibiting close approach of two ferrous ions.

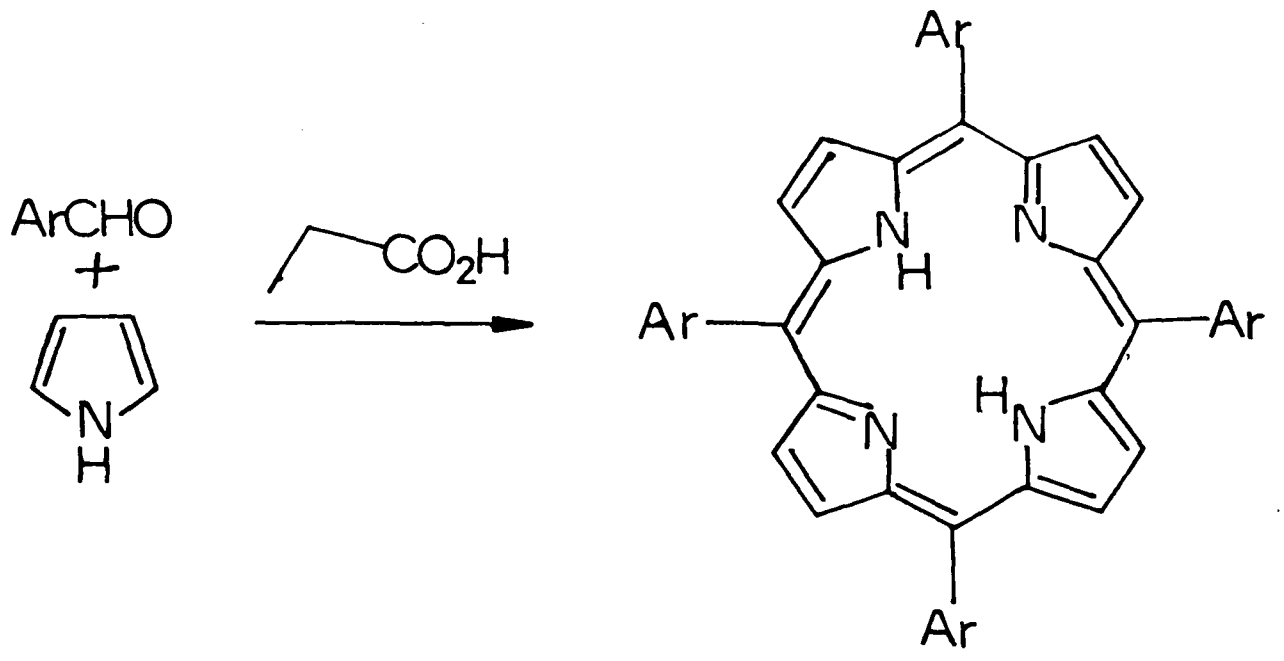
Further studies have been pursued on non-porphyrin macrocyclic complexes notably by Busch and co-workers[19], but none of

the ferrous systems so far examined binds oxygen reversibly at room temperature.

3.4 The Synthesis and Properties of Protected Ferrous Porphyrins

The interest in porphyrin-containing natural products has led to many synthetic routes to the porphyrin ring system and the development of synthetic methods compatible with porphyrins[20,21]. As well as this, numerous syntheses of unnatural porphyrins have been reported. One reaction that deserves special mention is the Rothemund reaction[22] of aromatic aldehydes with pyrrole in refluxing propanoic acid producing tetraaryl-porphyrins (15).

Scheme 4



(15)

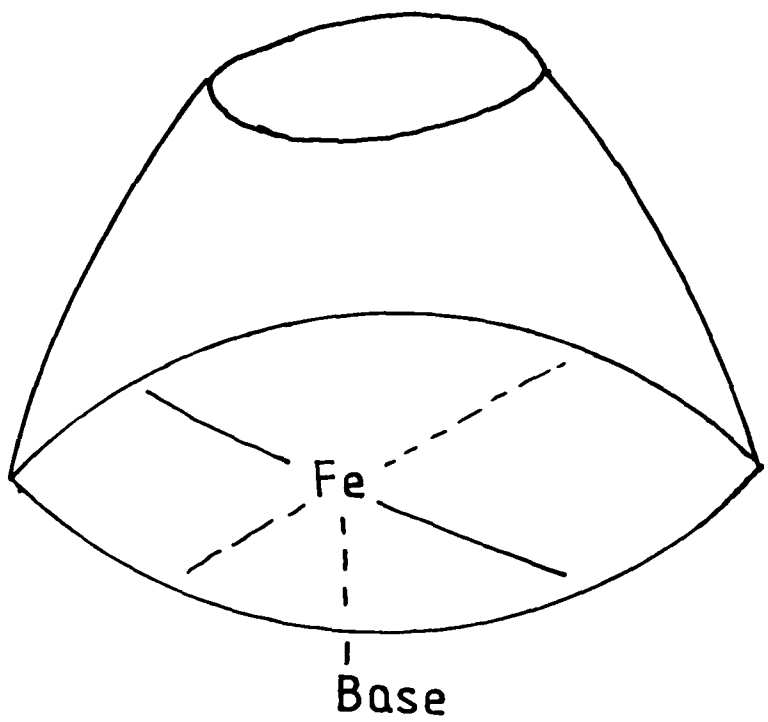
The approaches to oxygen transport at room temperature using porphyrins have involved the synthesis of ferrous complexes protected on one face, to prevent oxidative

dimerisation or haemochrome formation, leaving the other face unencumbered to permit co-ordination of one molecule of nitrogenous base.

The different approaches will now be considered in order of increasing protection offered to one face of the porphyrin.

3.4.1 Strapped Porphyrin Systems

The "strap" concept involves connection of a protective chain across one face of the ferrous complex.



The precise nature of the strapping structure has ranged from alkyl chains[23,24], naphthyl[23] and anthracenyl[25,26] linkages to a crown ether[27]. Crown ether protection gave the best result with a half life of approximately 1h for the oxygenated ferrous complex in solution, in the presence of an exogenous base, at 25°C. The above systems will only fully reversibly oxygenate at low temperatures and in many cases ferrous haemochrome formation

occurs with excess base, demonstrating complete lack of protection of the porphyrin.

From studies of molecular models, and the generally low yields encountered on high-dilution strap formation it seems probable that attempts to prepare more tightly strapped systems would not be fruitful. Large reductions in yield would be likely on closure at high dilution of more highly strained ring systems.

One successful synthesis of a tight cavity by Traylor and co-workers[25], utilised a subsequent Diels-Alder addition to a loose anthracene strap. Unfortunately this yielded a cavity so tight that not even carbon monoxide would bind to the iron.

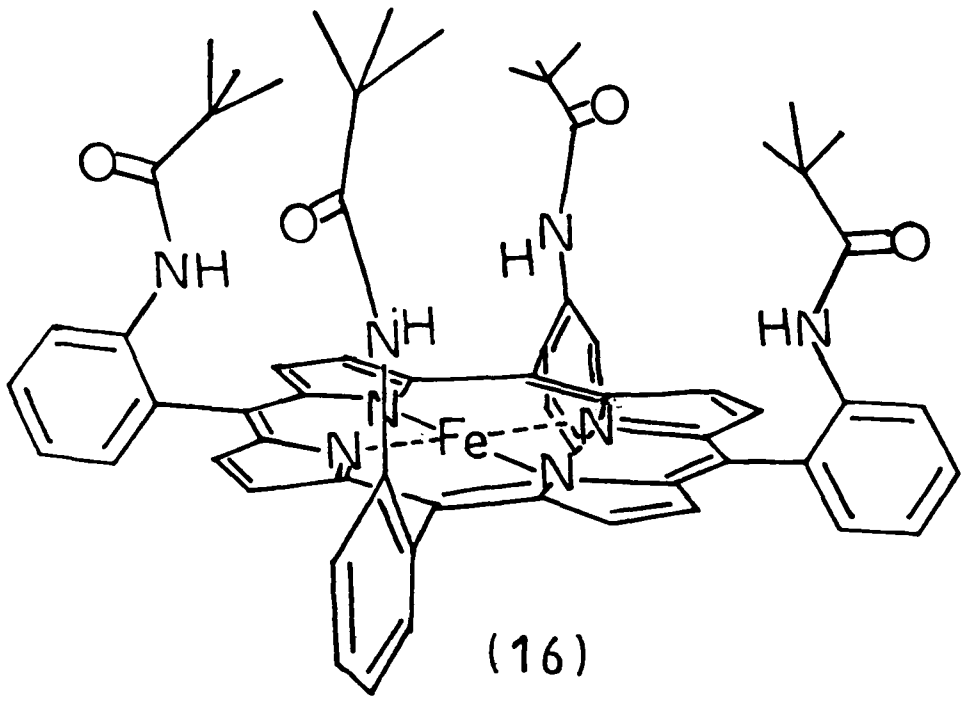
The results with strapped systems suggested that better protection might be gained with structures emanating from more than two points on the porphyrin periphery.

3.4.2 The Picket-Fence and Related Approaches

Collman and co-workers[28] acylated the αααα-atrop-isomer of meso-tetra (o-amino) phenyl porphyrin with pivaloyl chloride, and metallated the product, yielding the ferrous picket-fence porphyrin (16).

In the presence of N-methyl imidazole, this complex reversibly oxygenates in an aprotic solvent at room temperature. The half life in the presence of oxygen is 2 months.

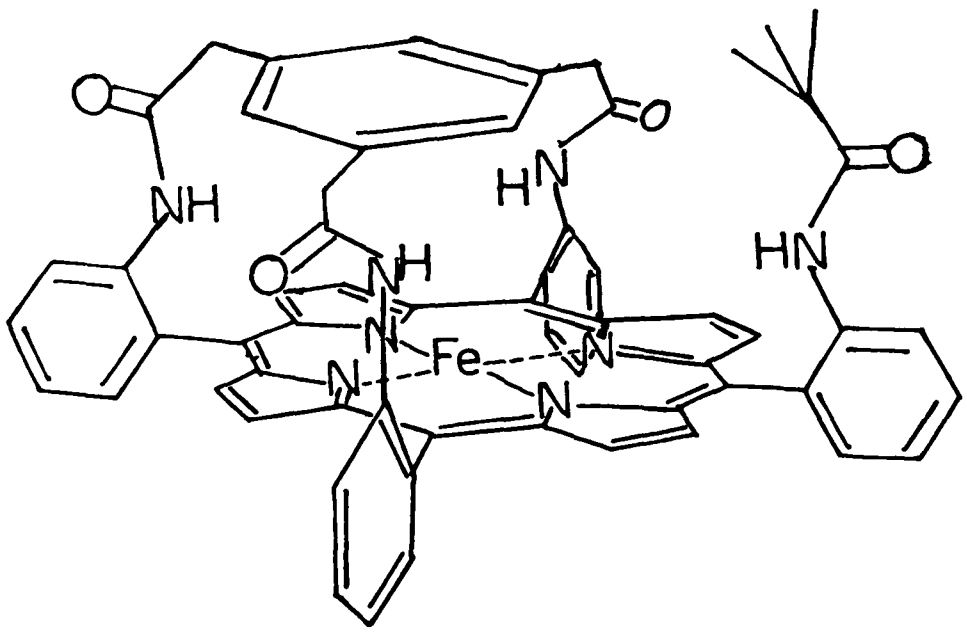
The protecting structure is not quite bulky enough to prevent formation of a haemochrome in excess base. However di-oxygen is able to displace the nitrogenous ligand that is weakly co-ordinated to the protected face. It so happens that this effect of haemochrome formation in fact confers an extra



(16)

stability on the ferrous picket-fence system in solution by dramatically reducing the concentration of free four coordinate iron (see later under "capped porphyrin").

A related complex synthesised by the same group, using a variant of the procedure for picket-fence porphyrin is the ferrous "pocket" porphyrin (17)[29].



(17)

Besides oxygenating reversibly (cf capped porphyrin) this complex demonstrates reduced affinity for carbon monoxide over oxygen compared to that of (16). This is explained by increased steric effects leading to a non-linear geometry and weaker Fe to CO bonding in (17) but not in (16).

3.4.4 The Capped Porphyrin

The capped porphyrin structure (23), (24) was obtained[30] by the condensation of a suitable tetra-aromatic aldehyde with pyrrole at high dilution in refluxing propanoic acid. The synthesis is outlined in Scheme 5.

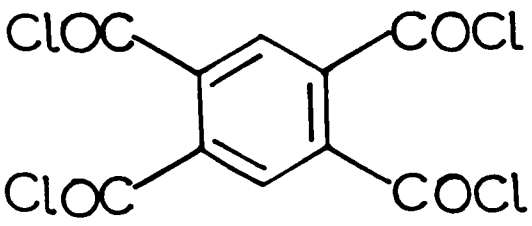
The ferrous complexes reversibly oxygenate at room temperature in the presence of a large excess of base. The capping structure in (23) completely prevents haemochrome formation while the homologous structure (24) permits formation of only a very weak six - coordinate ferrous complex.[31]

The half-life of these complexes in oxygen is extremely dependent on the concentration of exogenous nitrogen base due to the equilibrium between stable five - coordinate iron and oxidatively unstable four - coordinate iron. For the picket-fence system in solution the formation of a haemochrome biases the equilibria away from four - coordinate iron resulting in an apparently more stable complex.

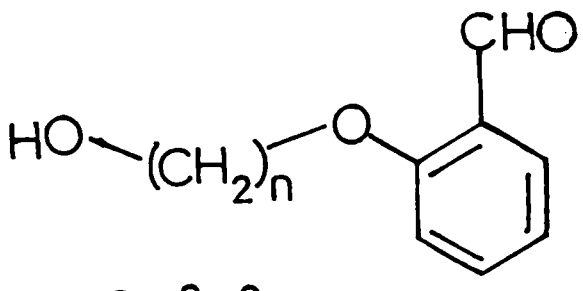
In an attempt to prevent the dimerisation via the "uncapped" face the so-called ferrous naphthyl-capped porphyrin (25) was synthesised.[30]

Although the exact products have not been clearly characterised, the ferrous complex irreversibly oxidises faster than the ordinary ferrous capped system. This is thought to be

Scheme 5

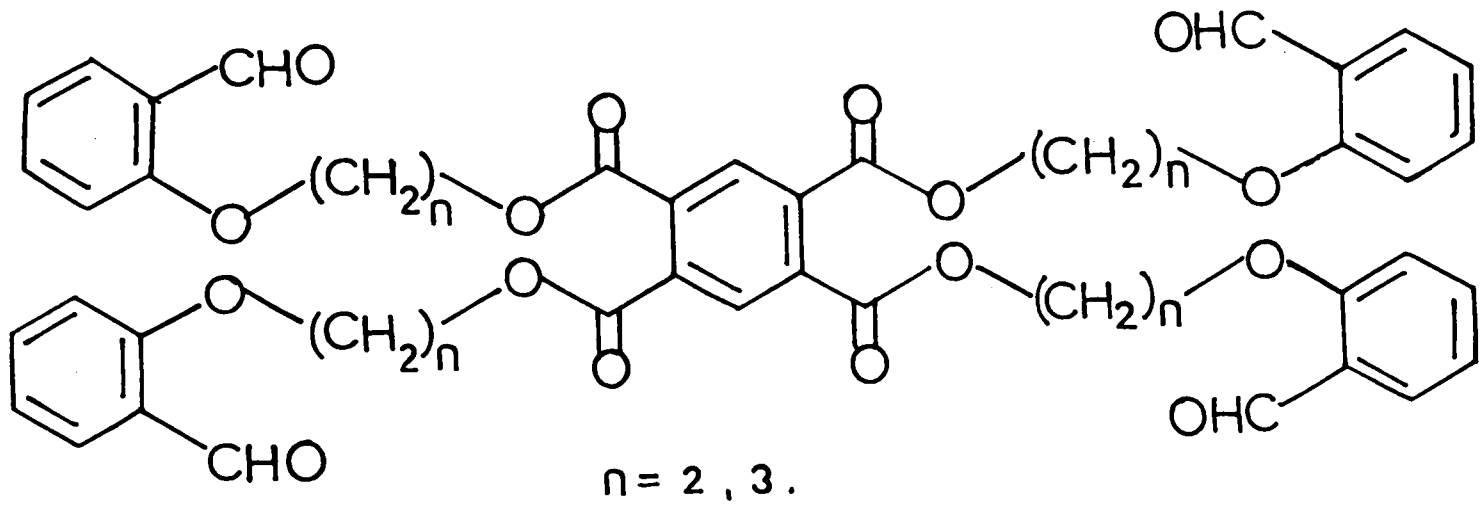


(18)



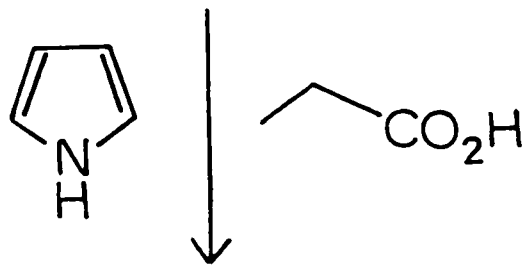
n= 2 , 3.

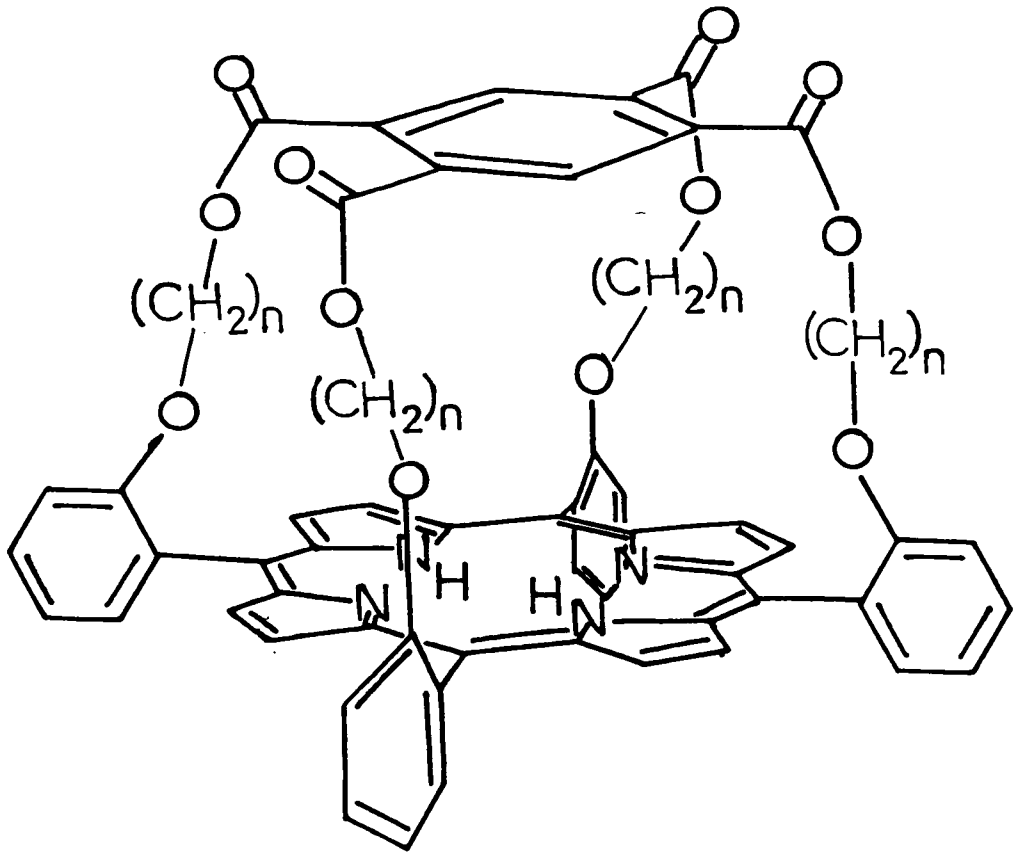
(19),(20).



n= 2 , 3.

(21),(22)

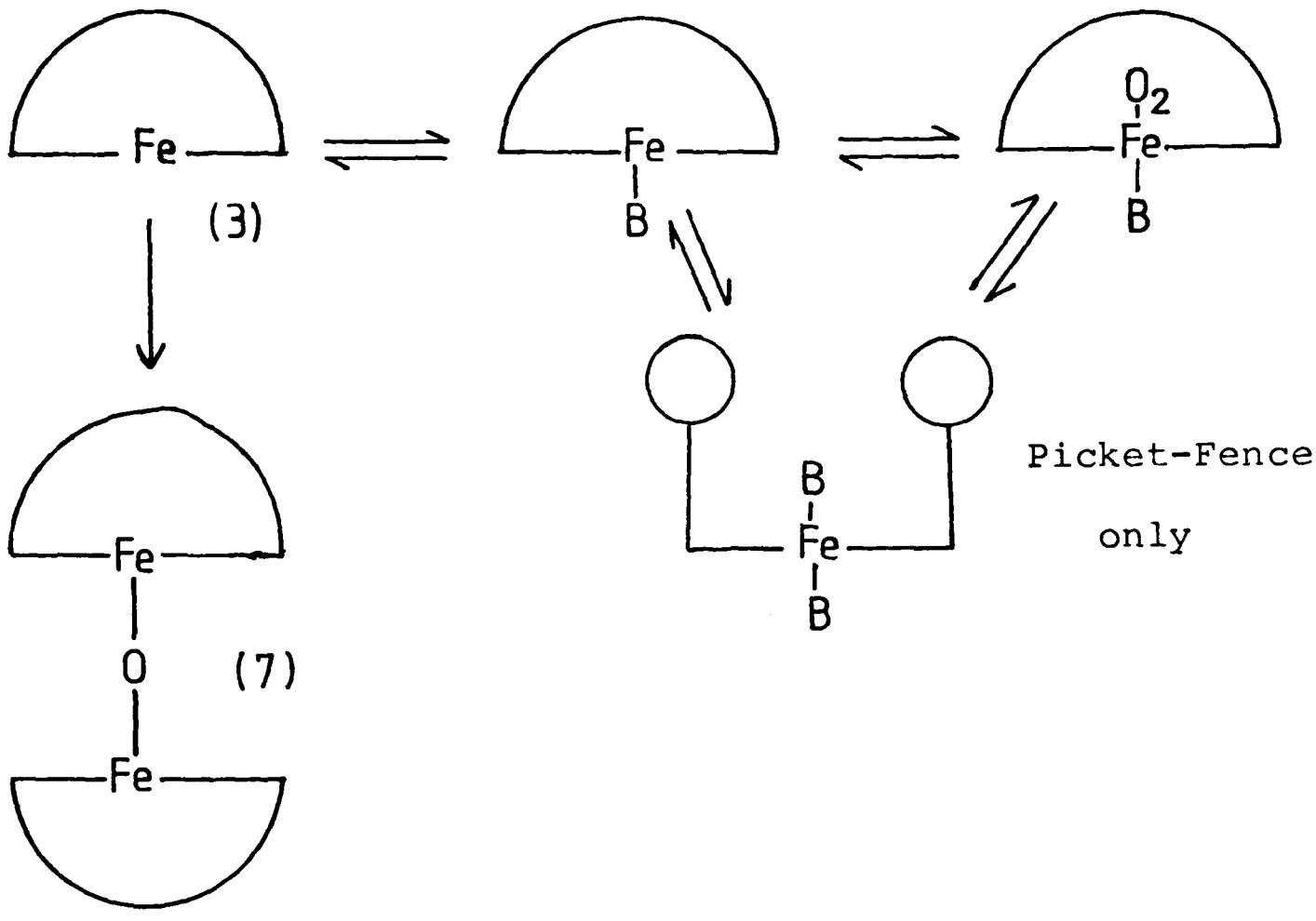


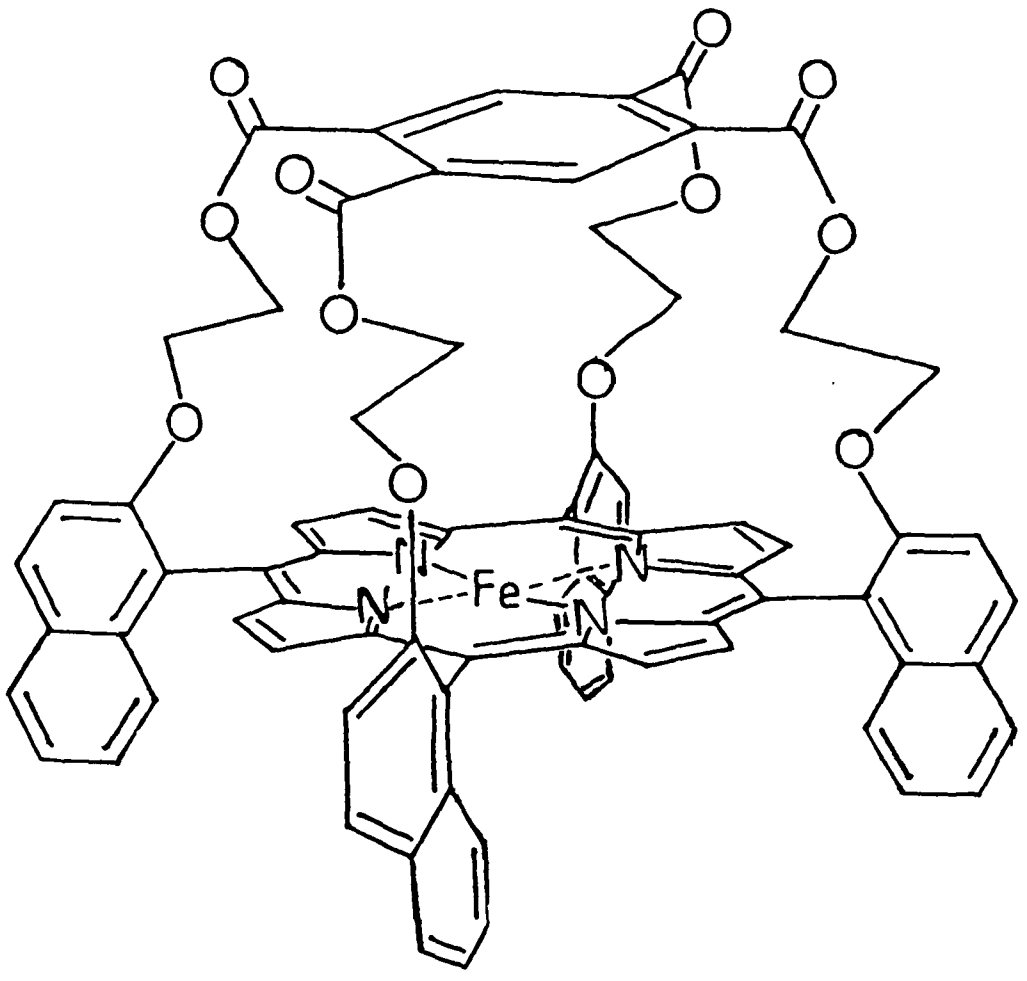


n= 2 , 3.

(23), (24).

Scheme 6





(25)

due to unfavourable interactions between proximal base and naphthalene rings favouring reactive four- coordinate iron.

3.5 Enforcement of Five Coordinate Iron by Chelation of the Proximal Base

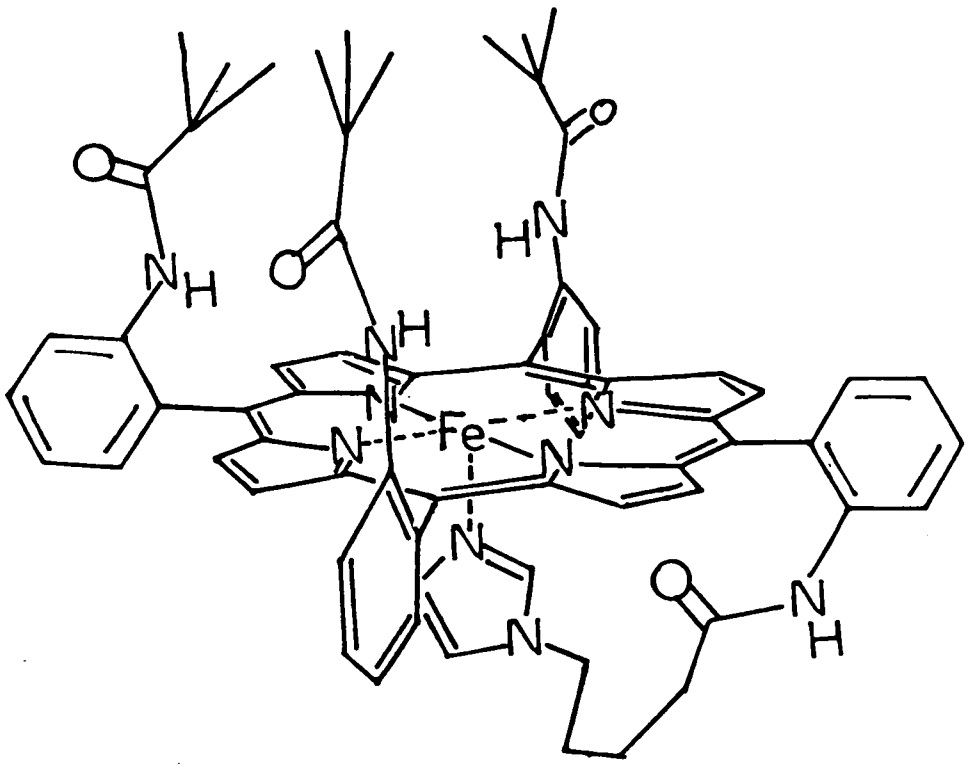
As discussed above, even the highly hindered oxygen transport models (the picket-fence and capped systems) irreversibly oxidise to the ferric state. This oxidation takes place *via* the unprotected face of the porphyrin when the exogenous base is not coordinated.

To avoid such losses it became apparent that the preparation of iron complexes containing a covalently attached base was required. Such compounds would then serve as truly monomolecular oxygen carriers.

3.5.1 Attachment of Base by a Chain

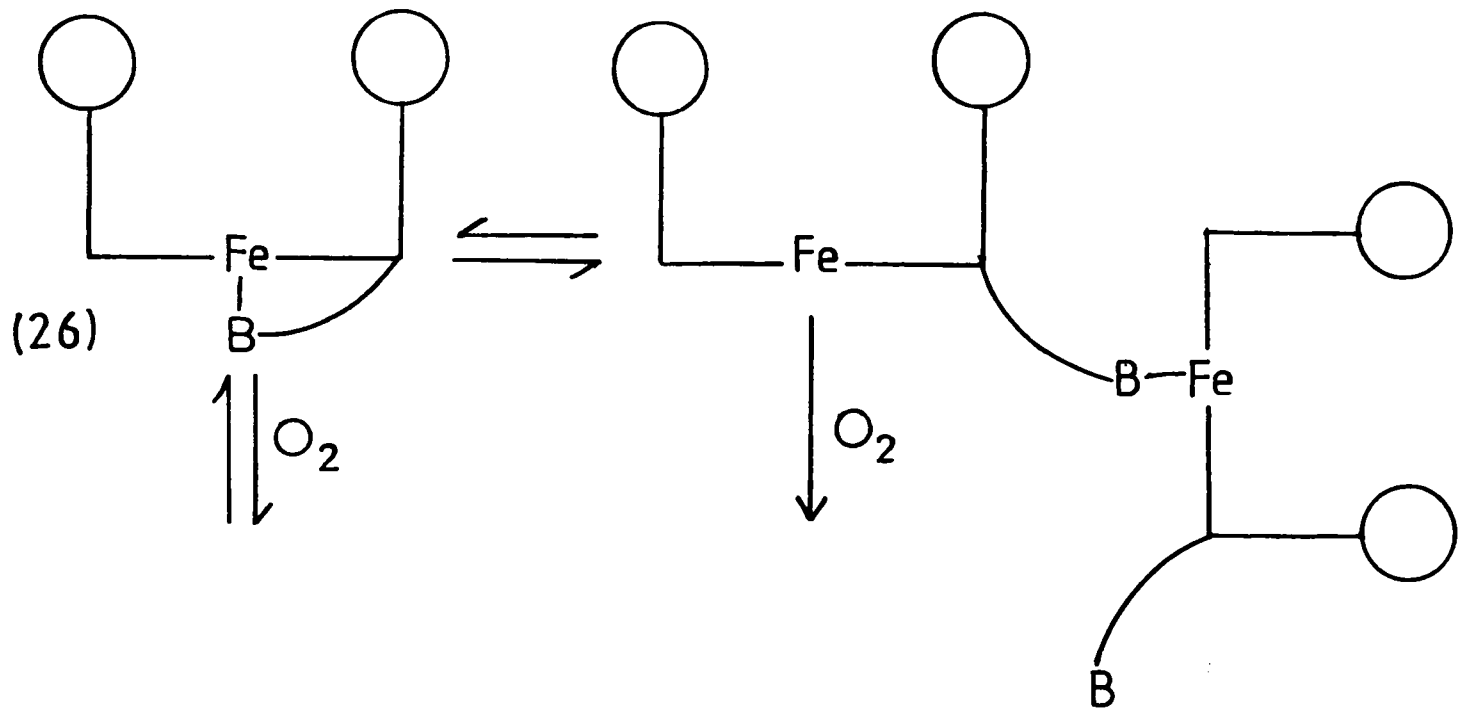
Using another variation on the picket-fence synthesis to attach one arm containing an alkylated imidazole, Collman and co-workers produced the "tail-base" porphyrin (26)[32].

This system has a half-life of 33h in toluene under an atmosphere of oxygen at 25°C.[14] At high dilution it was shown to exist predominantly in the monomolecular five-coordinate form. However the observed half-life is lower than that of the simple picket-fence complex (16) with an exogenous base. This is due to the tail not *rigorously* enforcing five coordinate iron. Indeed recent ligation studies of metallo-porphyrins have shown that an exogenous base can out-compete a similar base attached by a chain.[33]



(26)

Scheme 7

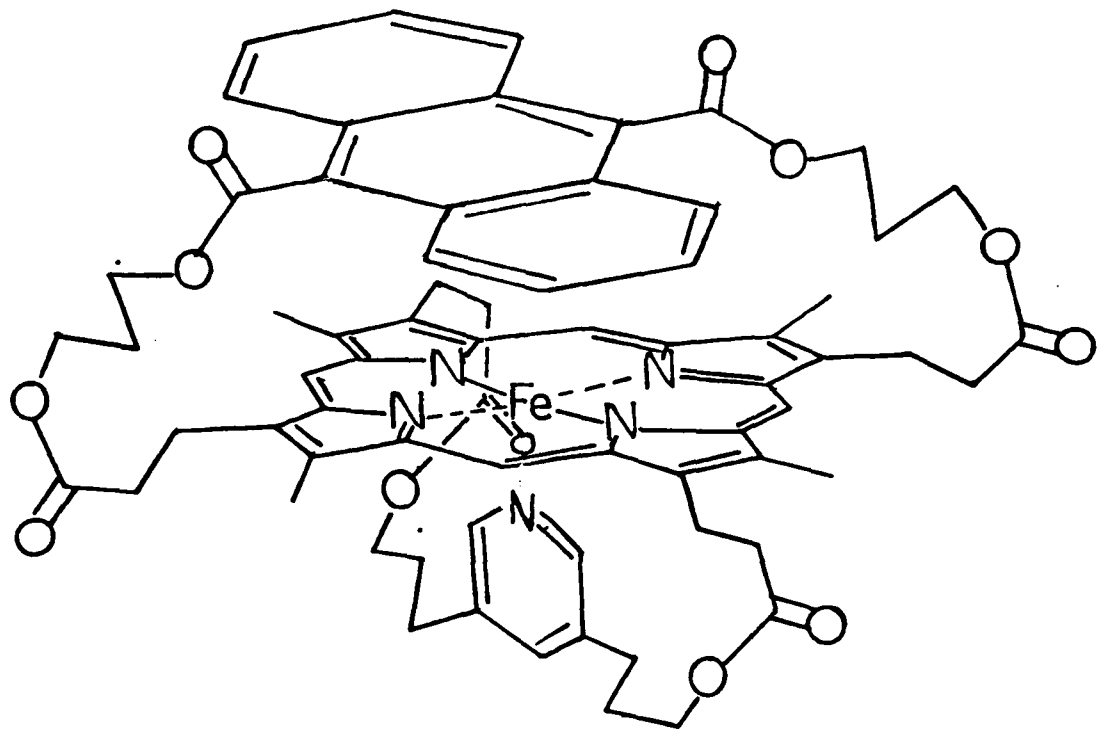


3.5.2 Attachment of Base by a Strap or Constrained Chain

To reinforce five- coordination at iron the base chain must either be made more rigid or be attached to more than one point on the porphyrin.

Using the capped porphyrin system attempts were made to extend a rigid chain from a β position but these were unsuccessful.[34,35]

Following the alternative strategy of attachment of base chain at more than one point on the porphyrin, Battersby and co-workers synthesised the doubly-strapped system (27).[26]



(27)

Despite the inefficiency of the anthracene bridging structure this complex exhibits a half-life of 15 min in dichloromethane at room temperature in the presence of oxygen.

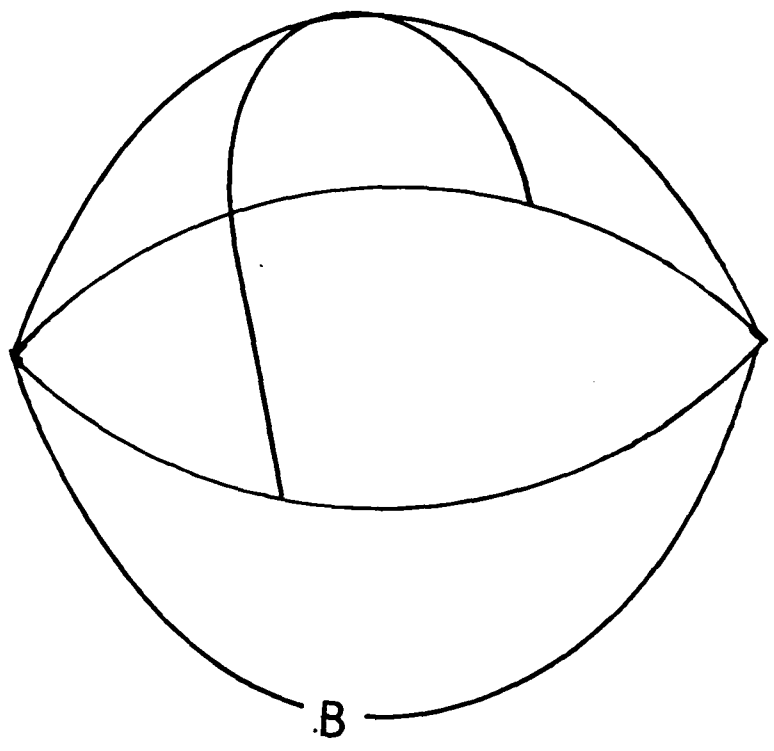
One other interesting observation on (27) is its reduced affinity for carbon monoxide relative to oxygen. This may be due to π-π interactions between the anthracene bridge and the porphyrin.

3.6 Pentadentate Ligands Based on the Capped Porphyrin System

The capped porphyrin system is the most protected ferrous porphyrin synthesised to date. If a base were attached to this system an improved oxygen carrier might be produced.

Following the lack of success in the synthesis of a rigid chain attached to β-functionalised capped porphyrins,[32] attention turned towards the attachment of a base *via* a strap.

The ideal places for attachment of a strap are the *meso*-aryl rings in this system. The synthesis undertaken was the production of a difunctionalised C_2-capped porphyrin and a strap containing a nitrogenous ligand. These two molecules could then be coupled at high-dilution to give convergent synthesis of a strapped/capped porphyrin (28).



(28)

Approaches to the synthesis of such a molecule will be the subject of this thesis.

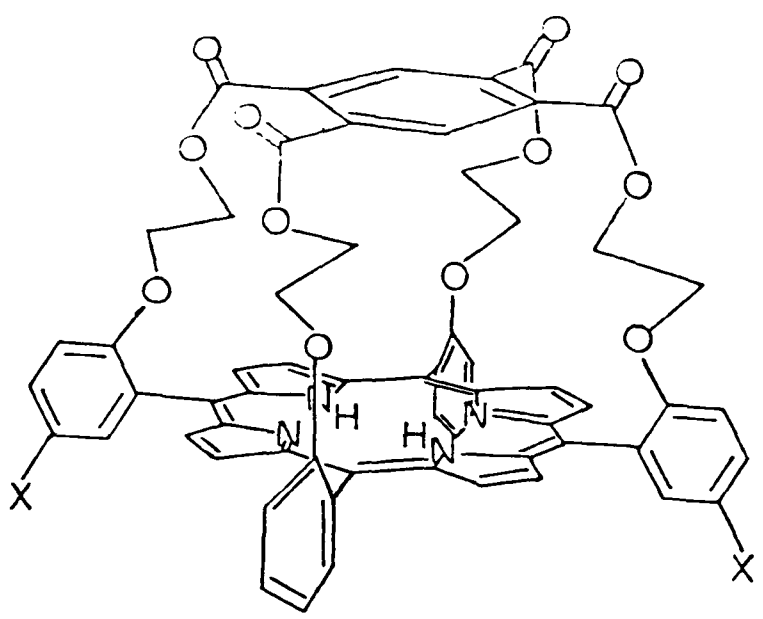
RESULTS AND DISCUSSION

As outlined in the Introduction, the aim of this work was the convergent synthesis of a strapped/capped ferrous porphyrin containing a heterocyclic base in the strap.

1.1 The Capped Porphyrin Component

The ideal points for attachment of a strap to a capped porphyrin are diametrically opposed meso phenyl rings.

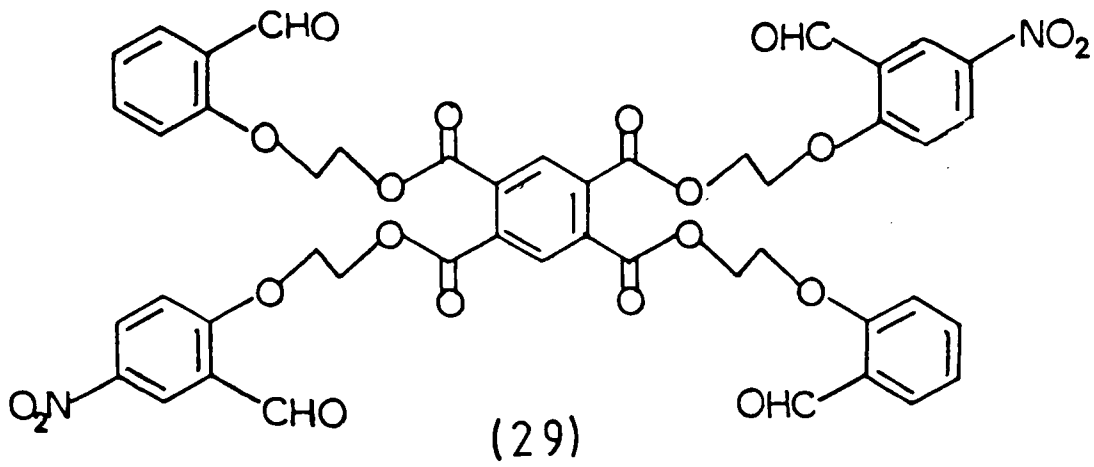
Examination of molecular models indicated that the optimum points of attachment of the strap were at the meta positions (with respect to the phenyl carbon attached to one of the meso positions). Such meta substituents would then point in the correct direction for ring formation. Furthermore, they are situated in a relatively accessible environment. It was thought that placing the point of strap attachment ortho or para to the porphyrin would lead to steric and directional problems respectively on attempted ring formation.



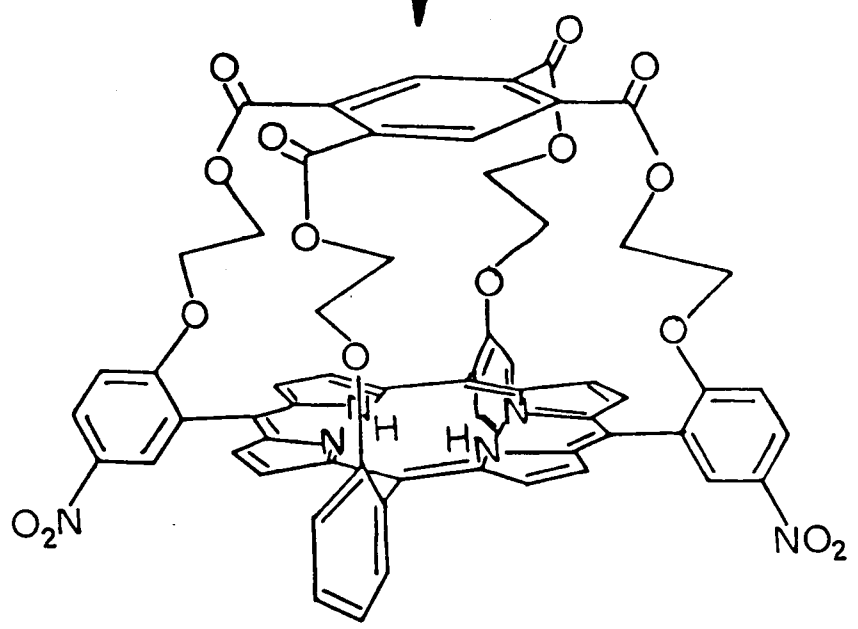
The choice of the reactive group 'X' on the porphyrin was the amino-group, which can be introduced conveniently in a latent form as the nitro group. Furthermore, methodology compatible with the capped porphyrin system had already been developed to reduce a nitro-group to an amine[34]. Hence, the strategy adopted (based on the original capped porphyrin synthesis) was the production of an appropriately functionalised tetraaldehyde (29), followed by condensation with pyrrole to produce bis-nitro-C_2-capped porphyrin (30)†, and reduction of (30) to the required bis-amino-C_2-capped porphyrin (31). This synthesis was carried out originally by Crossley on a small scale.[36] The following section describes efforts to improve this and carry it out on a large scale.

† A trivial system of nomenclature has been adopted for the capped porphyrin systems to be described. Bis-X-C_2-capped porphyrin (abbreviated to C_2-cap) refers to a compound such as (30) or (31) having the substituents X emanating from two diametrically opposed meso phenyl rings and two methylene groups in each rib of the capping structure.

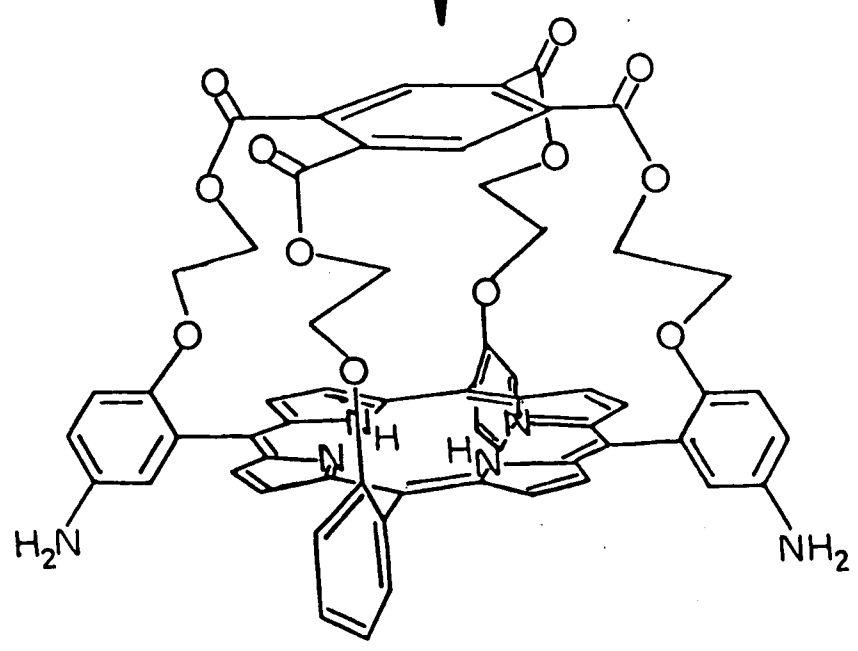
Scheme 8



(29)



(30)



(31)

1.2 The Synthesis of "Dinitrotetraaldehyde" (29)

The synthesis of dinitrotetraaldehyde (29), containing the required centre of symmetry is outlined in Scheme 8.

Condensation of hydroxyaldehyde (19)[30] with pyromellitic dianhydride (32) in pyridine at reflux overnight gave a mixture of the desired centrosymmetric diacid-diester (33) and the mirror symmetric isomer (34).

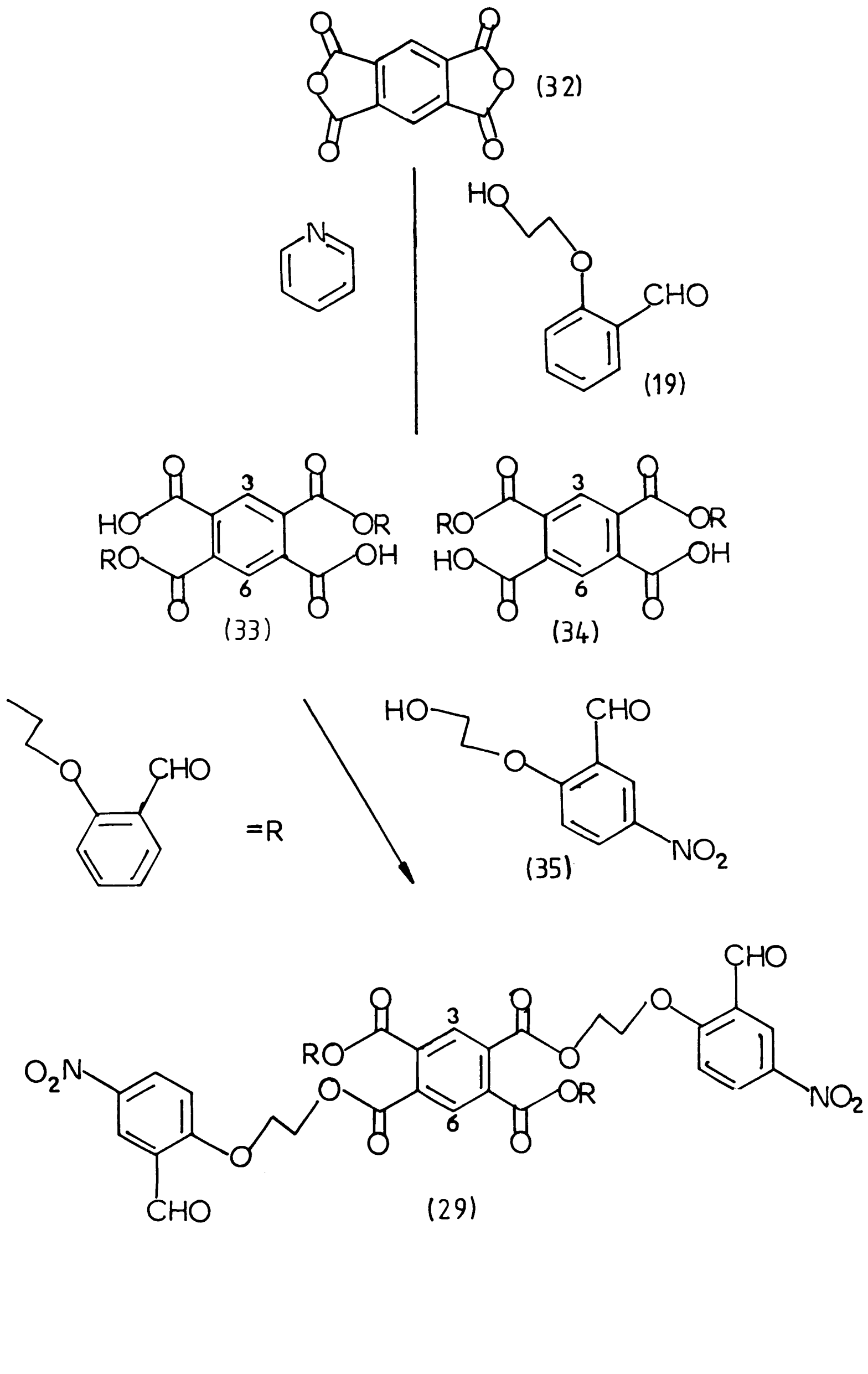
A model reaction, using neat methanol instead of hydroxyaldehyde (19) and pyridine, gave a 50-50 mixture of centrosymmetric diacid-diester (33, R=Me) and mirror symmetric isomer (34, R=Me).[37] In the p.m.r. spectrum of the former, the aromatic protons resonated as a singlet δ8.03 whereas in the latter the aromatic protons were non-equivalent and appeared as two signals δ8.13 (H_3) and δ7.95 (H_6). On examining the p.m.r. spectrum of the crude reaction product of (32) and (19) related resonances could be seen.

Crystallisation from glacial acetic acid gave the pure centrosymmetric isomer (33). The protons on the central aromatic ring resonated as a sharp singlet δ7.98 with the aldehydic protons appearing as a sharp singlet δ10.40. The yield of this reaction was variable (between 15 and 30%) but the procedure could be easily performed on a large scale.

The reaction of diacid-diester (33) with the nitrohydroxyaldehyde (35)[36,38] proved to be difficult. Production of a diacid chloride from (33) failed presumably due to prior reaction of the aromatic aldehyde groups.[37]

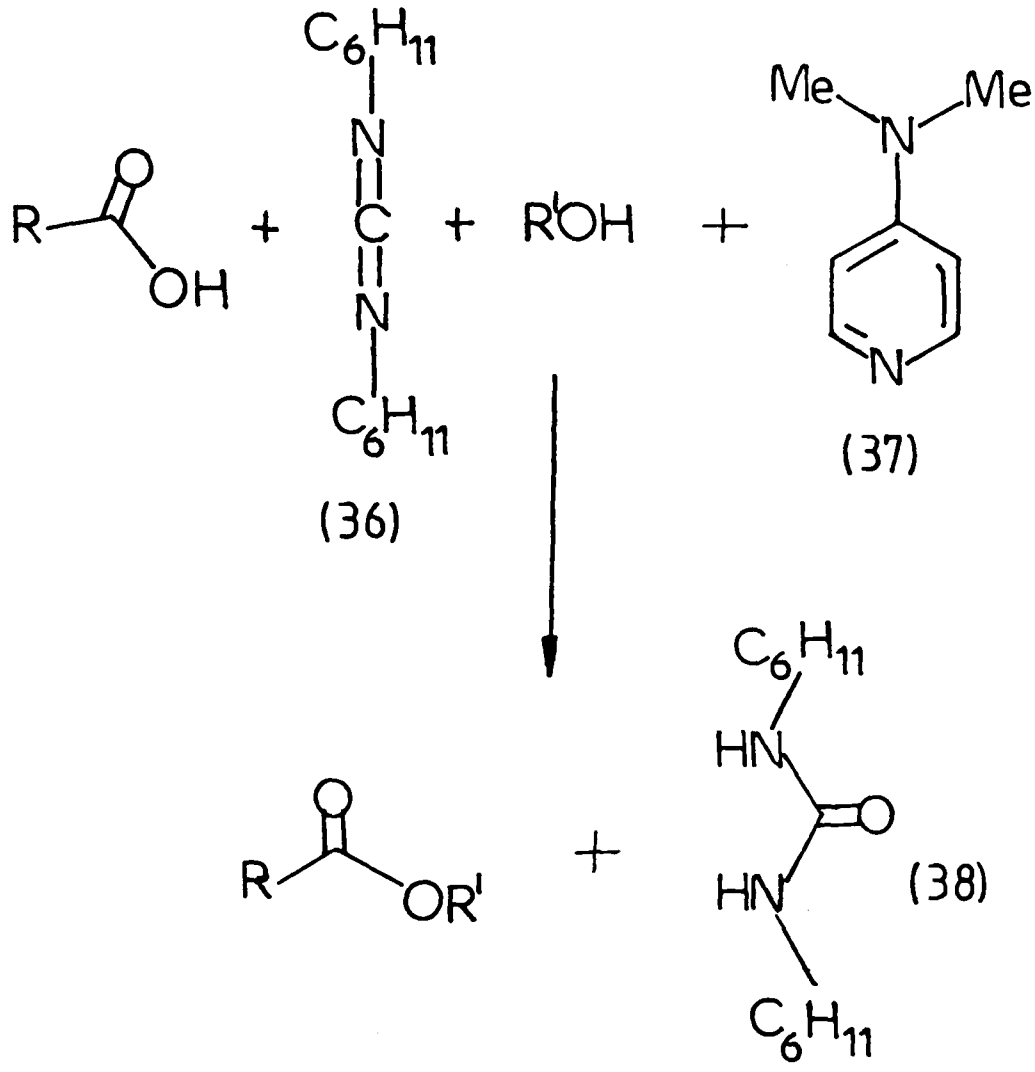
The reaction of (33) and 1,1'-carbonyl diimidazole[39] or 2-mercaptopyridine/triphenylphosphine[40] gave very insoluble derivatives that would not react with nitrohydroxyaldehyde (35)[36,38].

Scheme 9


(32)
N
HO
CHO
(19)
HO
RO
OR
OH
3
6
(33)
RO
HO
OR
OH
3
6
(34)
CHO
O
=R
HO
CHO
O
NO2
(35)
O2N
CHO
RO
OR
3
6
CHO
O
NO2
(29)

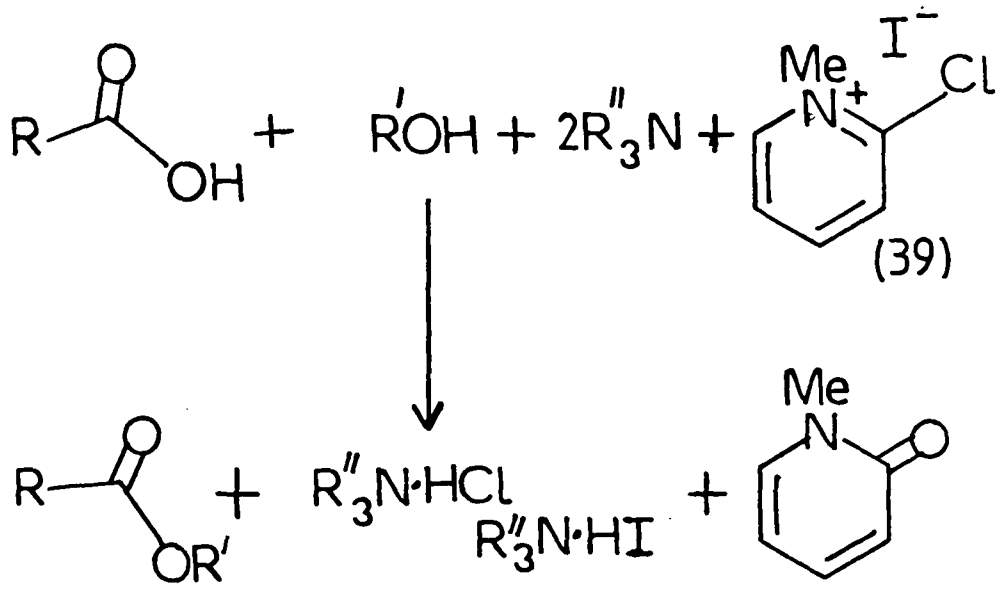
The only two methods found to produce the desired dinitrotetraaldehyde (29) were the use of N,N'-dicyclohexyl-carbodiimide (DCCI)(36)/4-N,N-dimethylaminopyridine (37)[41] and 1-methyl-2-chloropyridinium iodide (39)/trialkylamine,[42] (schemes 10 and 11)

Scheme 10



The use of DCCI/DMAP by Crossley[36] gave the desired dinitrotetraaldehyde (29) in only 31% highest isolated yield. The compound showed the expected infrared absorptions at 1720 cm^{-1} and 1690 cm^{-1} for the ester and aldehyde carbonyls respectively. Its p.m.r. spectrum contained a singlet at δ8.09 for the protons on the central aromatic ring and another singlet for all the aldehyde protons at δ10.28.

Scheme 11



The low yield was shown to be due to an isolation problem by: (i) the recovery of N,N'-dicyclohexylurea (38) (co-product) in high yield and, (ii) the fact that the same procedure had been used to synthesise the known tetraaldehyde (21)[30] from (33) and (19) in 60% yield after chromatography.[36] The major problem appeared to be associated with solubility. When pure, dinitrotetraaldehyde (29) would only dissolve in cold DMF or DMSO or in refluxing acetic acid, propanoic acid or acetonitrile. However if substantial amounts of N-acylurea by-product were present, the compound (29) was solubilised into other solvents such as dichloromethane and only slowly crystallised out, pure, in low yield. Chromatography could not be used because as soon as the tetraaldehyde (29) separated from the by-products of reaction it precipitated onto the adsorbent.

Another problem associated with the DCCI reaction was its unreliability. The major advantage of this procedure was that the product obtained was generally >90% pure, and required no chromatography.

To avoid formation of the N-acyl urea by-product an attempt was made to prepare an O-alkylisourea[43] from DCCI and nitro-hydroxyaldehyde (35). However no clearly defined product was obtained and this approach was abandoned.

Condensation of diacid-diester (33) and nitrohydroxy-aldehyde (35) using 1-methyl-2-chloro-pyridinium iodide (39) and triethylamine at 60°C,[42] gave dinitrotetraaldehyde (29) in an optimum yield of 27%.

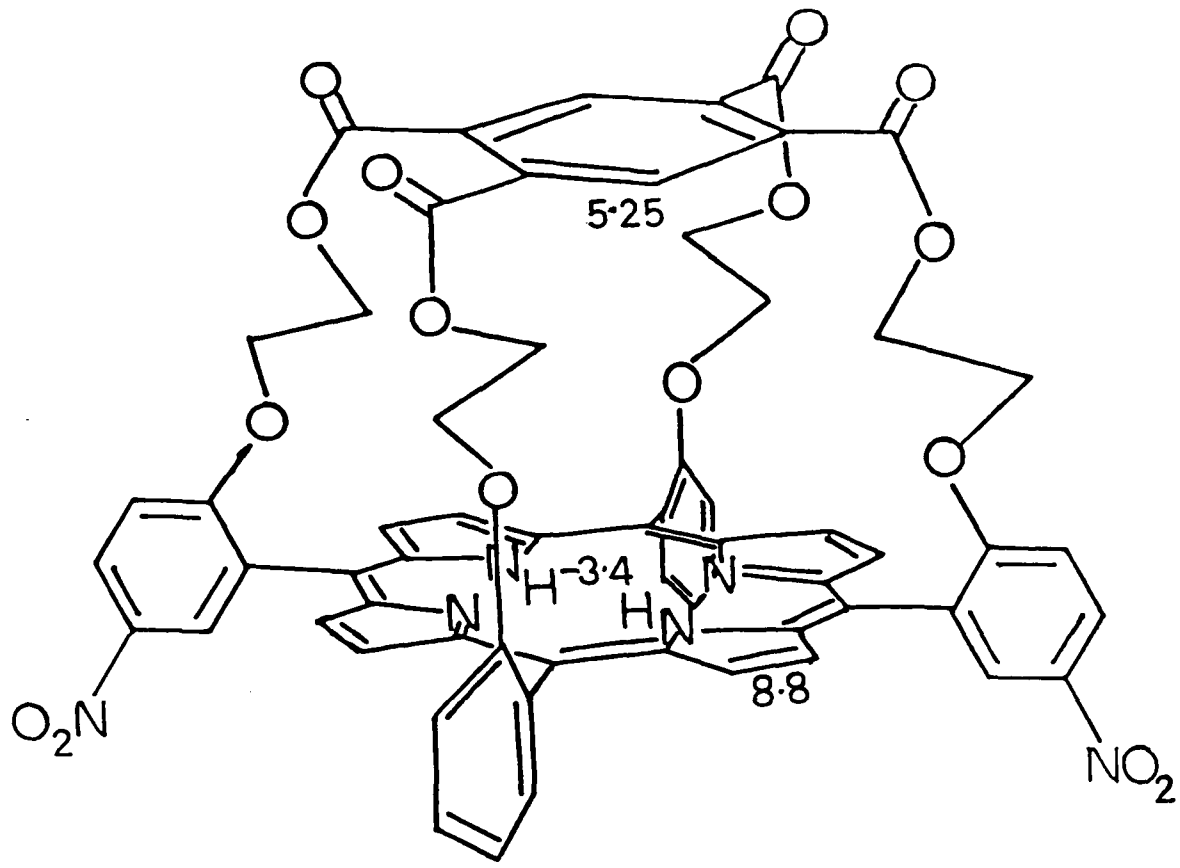
It was found that the DCCI/DMAP route was more convenient for large scale production of dinitrotetraaldehyde (29).

1.3 The Formation and Properties of Bis-Nitro-C_2-Capped Porphyrin (30)

Condensation of dinitrotetraaldehyde (29) with pyrrole in refluxing propanoic acid at high-dilution[30] gave bis-nitro-C_2-capped porphyrin (30)[36,38]. This compound exhibited the characteristic visible spectrum associated with the capped porphyrin system: λ_{max} 422 (Soret), 516(I), 545(II), 589(III), 643(IV) nm; ε, I>III>II>IV. Detailed investigation of this reaction was carried out by Dagley[38] resulting in optimum yields of 4-7%.

Of particular interest were the p.m.r. data at 300 MHz and the chirality of the molecule.

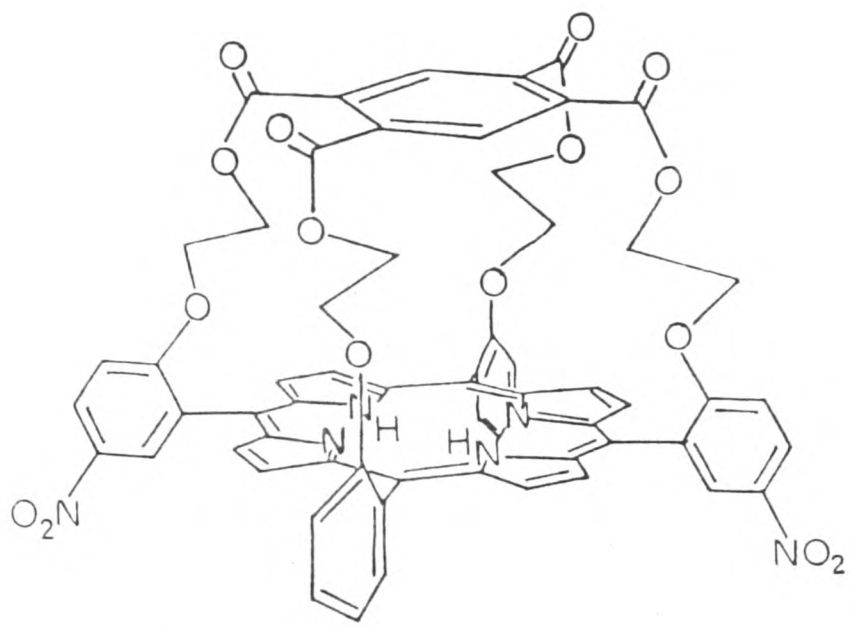
The p.m.r. spectra, at 300 MHz, of this series of bis-substituted capped porphyrins showed certain general features

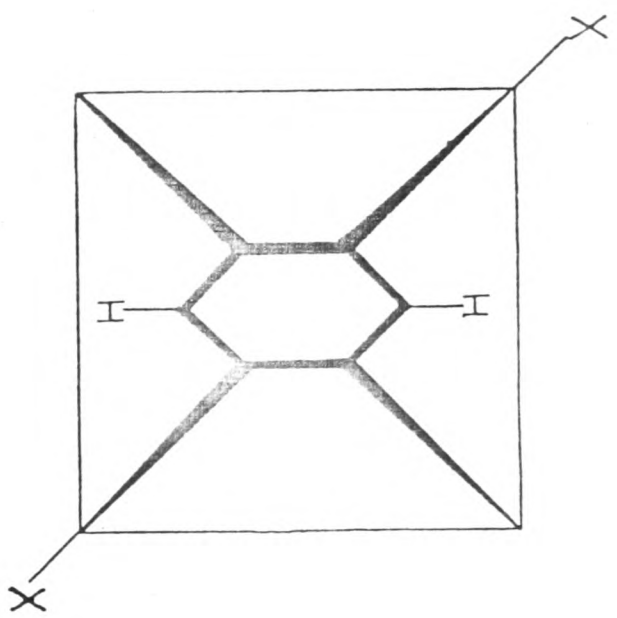


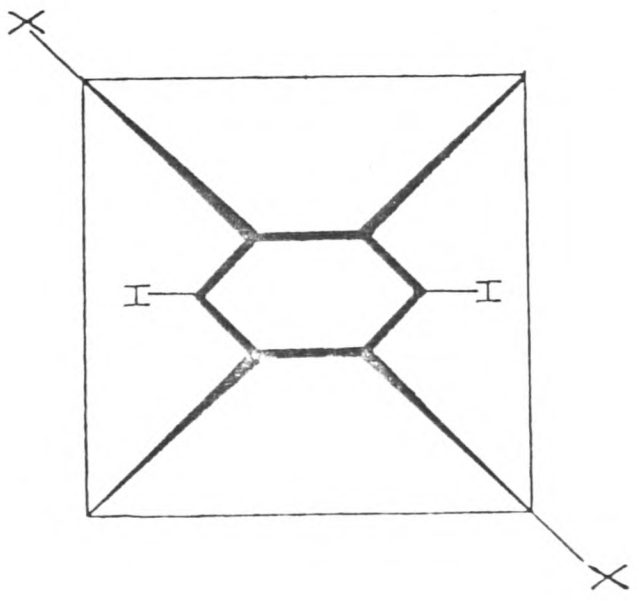
(30)

exemplified by (30). The protons on the central capping ring resonated as a sharp singlet at δ5.25, shifted 2.8 ppm upfield from the position of the equivalent resonance in tetraaldehyde precursor. This is due to the diamagnetic anisotropy of the aromatic porphyrin ring. Correspondingly shifted, by 11.5 ppm to δ-3.4, were the NH protons in the centre of the porphyrin The β-pyrrolic resonances, shifted slightly downfield, appeared as four discrete doublets δ~8.8 (J4.5 Hz). In the series of capped porphyrins discussed in this thesis, all of the above signals plus the other aromatic resonances were found to be highly dependent on the symmetry, the conformation and the substitution of any capped porphyrin produced.

If a mono-, tri- or centro-symmetrically di- substituted tetraaldehyde is condensed with pyrrole, a racemic mixture of chiral capped porphyrins results. For the series of bis-substituted capped porphyrins this is best demonstrated symbolically below.


O2N
NO2
H
N
N


X
I
I
X


X
I
I
X

As will be seen later, this property led to important effects in the p.m.r. spectra of groups attached to the chiral capped porphyrin system.

1.4 The Reduction of Bis-Nitro-C_2-Capped Porphyrin (30)

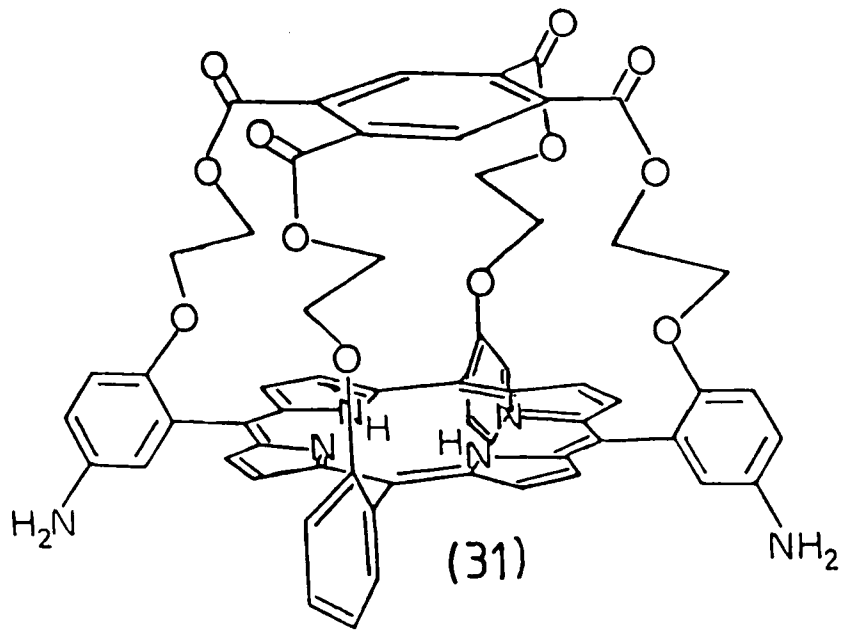
The reduction of bis-nitro-C_2-cap (30) was effected using 10% palladium on carbon/sodium borohydride/methanol as described before.[34] The product formed by this procedure was homogenous by t.l.c. and gave the correct mass spectrum for the bis-amine (31); m/z 1066.[36]

Re-examination of this reaction using 300 MHz F.T. p.m.r. showed that unless the methanol used was absolutely dry three products were formed. From the p.m.r. data of the mixture it is proposed that the by-products formed were chlorins (by reduction of the porphyrin ring) and decapped porphyrins (by cleavage of the capping ester groups).

The method by which the full result of this reaction was determined, illustrates the vital role played by high field p.m.r. spectroscopy. Throughout this work, this spectroscopic tool was of great importance in investigating the outcome of small scale reactions carried out on these high molecular weight porphyrins.

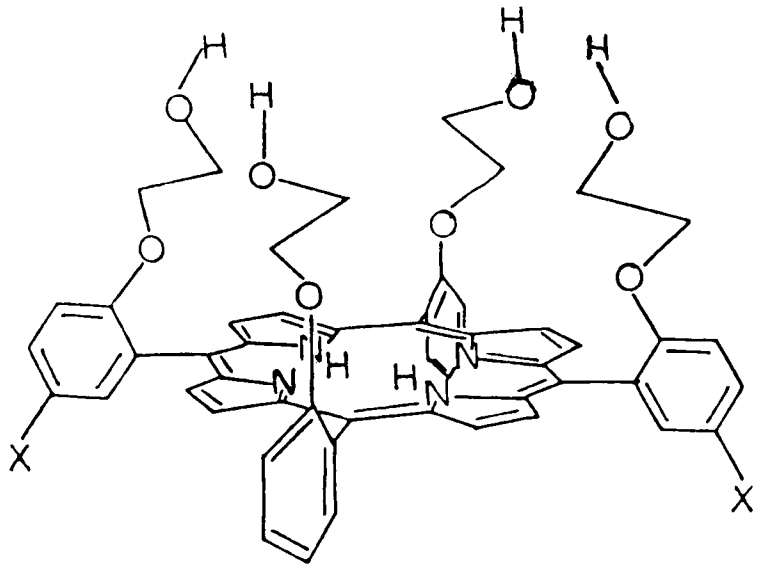
Following the outcome of the reduction above, other procedures were tried. Catalytic reduction by molecular hydrogen preferentially gave chlorin unless done in acetic acid as solvent.[38] Attempted catalytic transfer of hydrogen from 1,3-cyclohexadiene or cyclohexene also failed.

Returning to the original conditions, it was found that controlled addition of the borohydride reducing agent to the



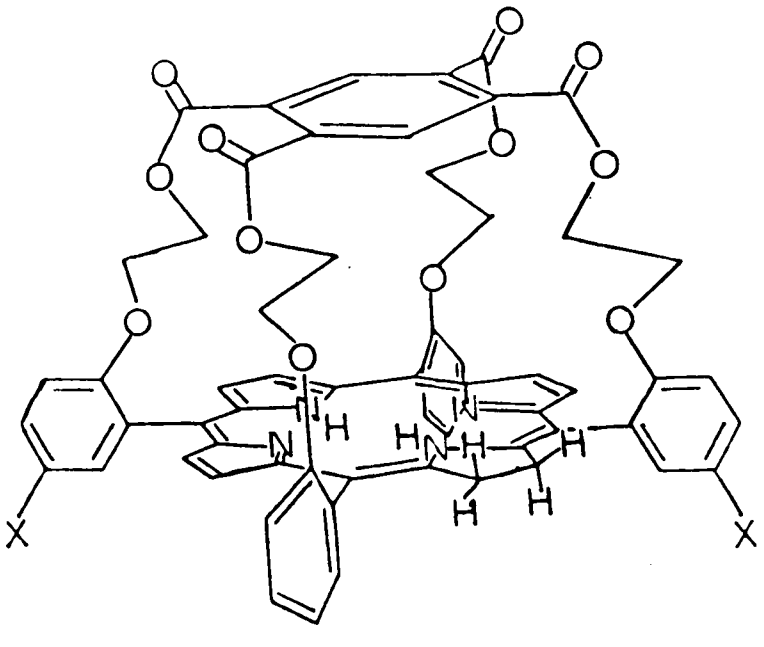
(31)

	cap	NH
δ	5.25	δ-3.4
	singlet	



DECAPPED

	cap	NH
		δ -2.5



CHLORIN

	cap	NH
δ	5.8, 5.9	δ-1.8, -1.9
	doublets	

dichloromethane/methanol solution of porphyrin (30) gave satisfactory results. Subsequent substitution of dry 2-propanol for dry methanol gave a reactive system that reproducibly gave smooth reduction of bis-nitro-C_2-cap (30). The presence of a trace water was not a problem, in fact super-drying the 2-propanol appeared to slow down excessively the reduction process.

The p.m.r. spectrum of the crude porphyrin product from above showed the purity of bis-amino-C_2-cap (31) to be >95%. The protons on the cap appeared as a sharp singlet δ5.25, the pyrrolic N<u>H</u> as a broad singlet δ-3.4 and the β-pyrrolic protons as four doublets δ≈8.7 (J4·5 Hz) [<u>cf</u> bis-nitro-C_2-cap (30)]. All other data collected were in complete accord with structure (31).

One property of importance associated with (31) is combined light and oxygen sensitivity. It is well known[44] that the porphyrin nucleus can sensitise the formation of $^1\Delta O_2$ from $^3\Sigma O_2$ by visible light, which then reacts with electron rich groupings such as sulphides, electron rich aromatic rings and amines. Taking account of this reactivity bis-amine (31) was protected from light and oxygen, especially when in solution.

2. <u>The Strap Requirements for a Pentadentate Ligand Based on the Capped Porphyrin System</u>

Various nitrogen bases have been used to mimic the proximal base in oxygen transport models, usually imidazoles or pyridines.

For the synthesis of a strapped/capped porphyrin, the use of imidazole derivatives would have the disadvantages of lack of

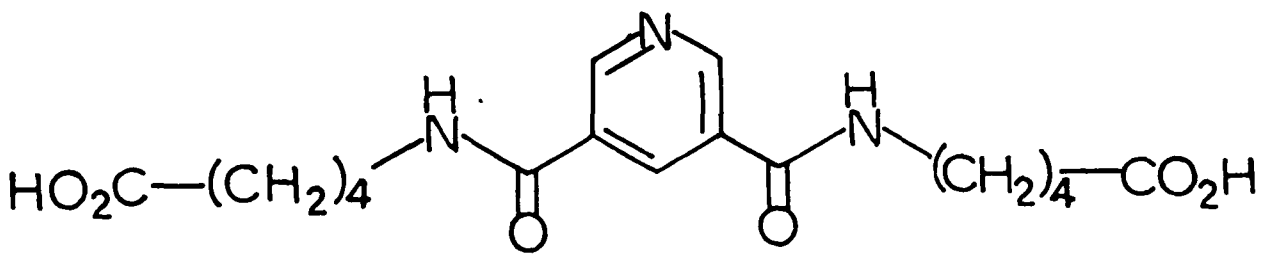
availability and a high susceptibility to oxidation by singlet oxygen.[45,32]

Although not as efficient a base as imidazole, the pyridine nucleus has the advantages of much better stability to oxidation and better availability of suitable derivatives. For the synthesis of a strapped/capped porphyrin it was decided to use a strap containing a 3,5 disubstituted pyridine (2,6-disubstitution would hinder co-ordination of pyridine to iron).

To complete the convergent synthesis of the strapped/capped porphyrin the final step envisaged was high dilution coupling between the strap and the bis-amino-C_2-cap (31). Two approaches were undertaken: (a) The formation of amide bonds between an activated bis-acid and bis-amine (31) (or its alkylated derivatives) and (b) condensation of a bis-aldehyde with bis-amine (31).

3. The Synthesis of a Bis-Amide/Bis-Acid Strap and its Reaction with Bis-Amino-C_2-Cap (31)

In the course of earlier work towards a doubly strapped porphyrin, the strap (40) had been synthesised.[46]



(40)

The earlier work involved attempted coupling of (40) to a bis-amine and relatively stable activated acid derivatives had been chosen (azide or succinimidooxy ester). For the reaction of strap (40) and bis-amine (30) it was decided to pre-form a solution of acid chloride (41) and use the syringe pump addition method successfully employed by Chang.[27]

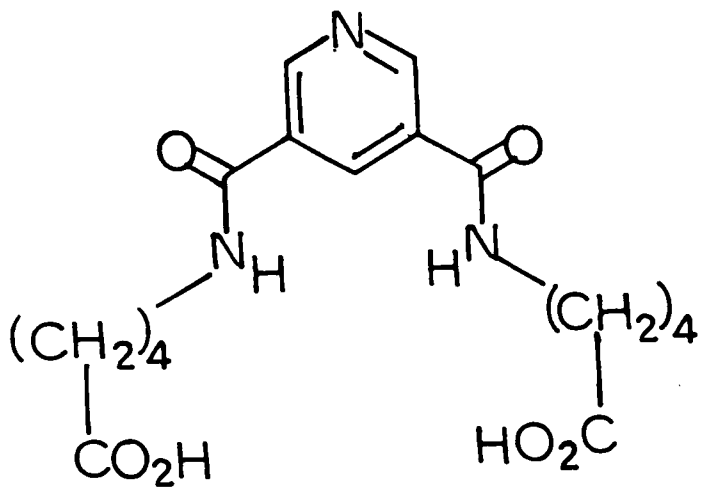
Formation of acid chloride (41) was carried out using thionyl chloride at room temperature with dry DMF as both solvent and catalyst.[47] Reaction with p-anisidine [DMAP (36) as base catalyst] gave the known bis-anilide (42)[46] in up to 75% yield. In the p.m.r. spectrum of this compound, the resonances for the chain protons appeared at δ1.56, 2.24 and 3.2, while those of the pyridine came at δ8.50 (γ-PyH) and δ8.98 (α-PyH). The anilide NH protons appeared as a broad singlet δ9.60.

High dilution coupling of bis acid chloride (41) with bis-amino-C_2-cap (31) gave one major porphyrin containing fraction. This product would only dissolve in DMF, DMSO or a mixture of chlorinated solvent and methanol.

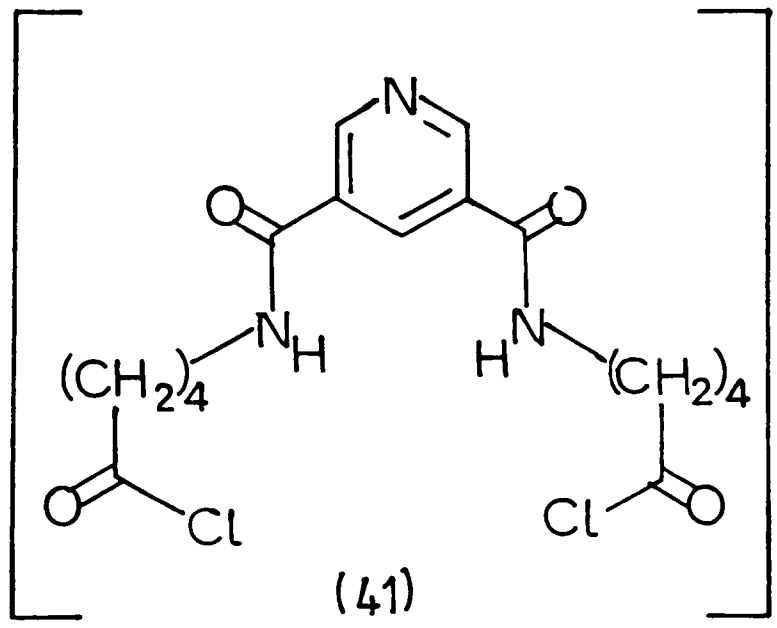
P.m.r. examination of all porphyrins produced indicated that the major fraction was the only one containing an adduct of (31) and (41) in a 1:1 ratio. The p.m.r. spectrum of the compound showed the expected resonances for the pyrrolic NH at δ-3.4 and the capping ring at δ5.25. The resonance for the anilide NH came at δ10.05 and the strap resonances occurred at approximately the same chemical shifts as in the open-chain bis-anilide (42).

The p.m.r. spectrum of the compound was broad and this, along with the lack of diamagnetic shielding of the strapping

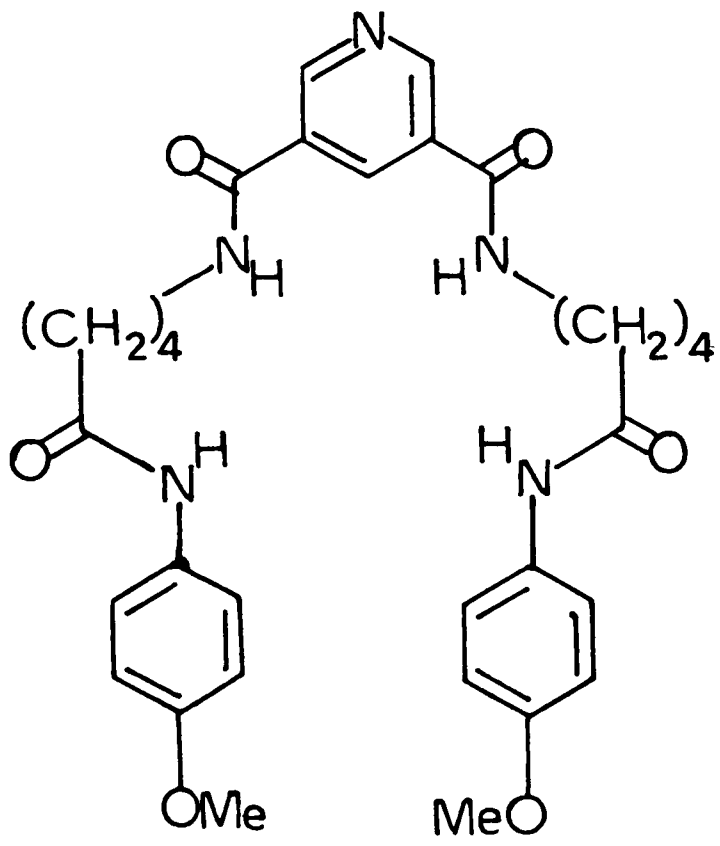
Scheme 12



(40)



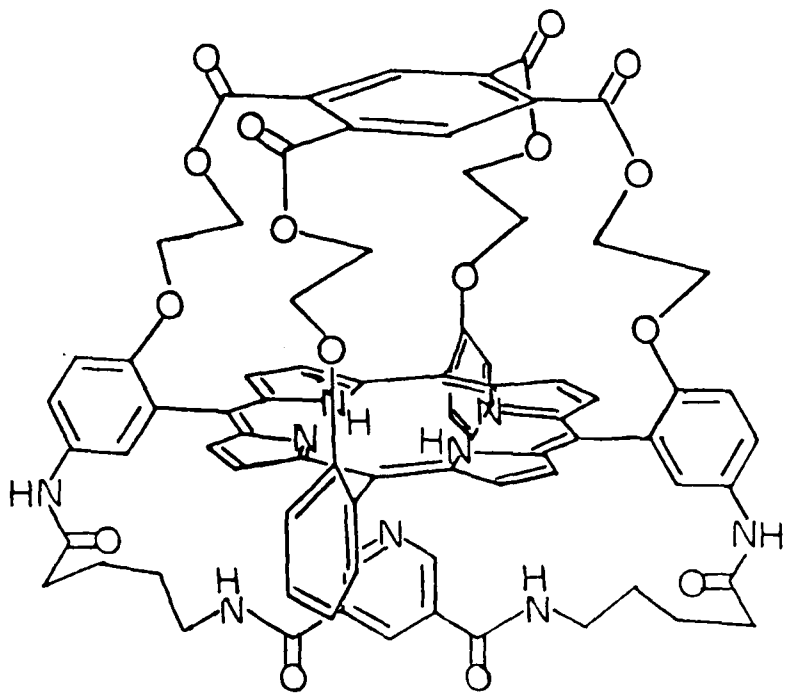
(41)



(42)

, (38).

chain protons suggested the formation of higher molecular weight products rather than the desired porphyrin (43), ($\underline{m/z}$ 1395).

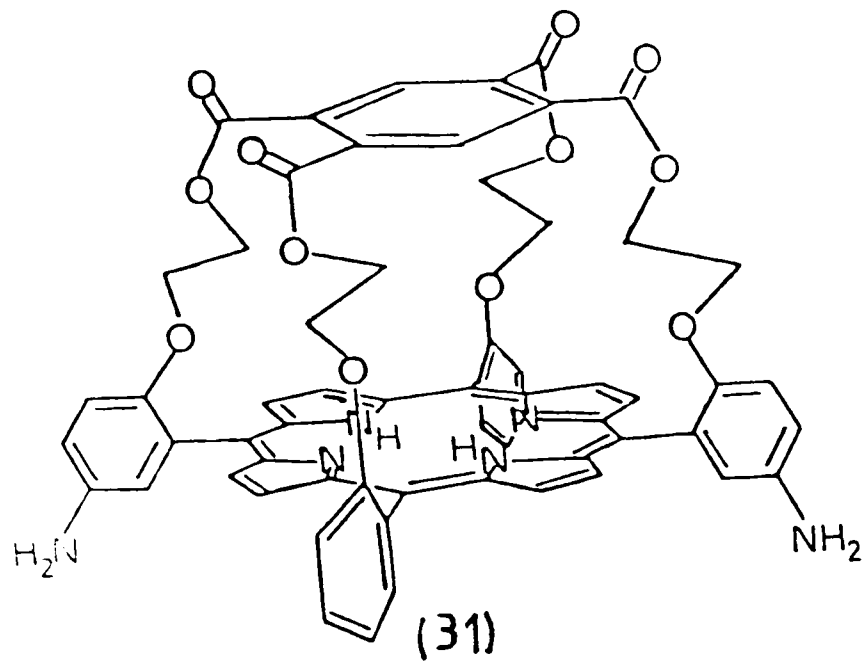


(43)

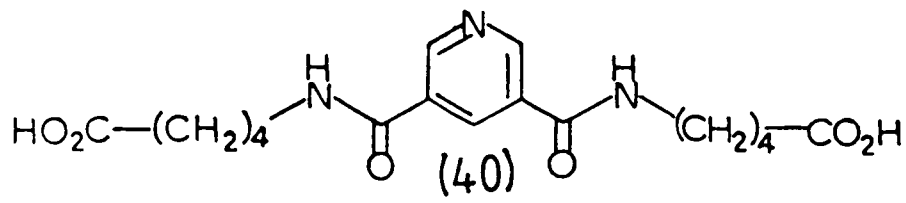
Field desorption mass-spectrometry only gave weak ions in the region $\underline{m/z}$ 1400.[48] Ultracentrifugal analysis[49] suggested one compound molecular weight 4057, but this technique is prone to large error when compounds of low molecular weight and unusual molecular shape are involved. Osmotic pressure measurement[50] suggested an apparent molecular weight in DMF solution of 6306.

The first clear indication of discrete molecular weights came from ^{252}Californium mass spectrometry[51], which gave clear ion clusters at 2792 and 4212 a.u. but nothing at 1396 a.u., showing the reaction product to be a mixture of cyclic oligomers of (43), scheme 12.

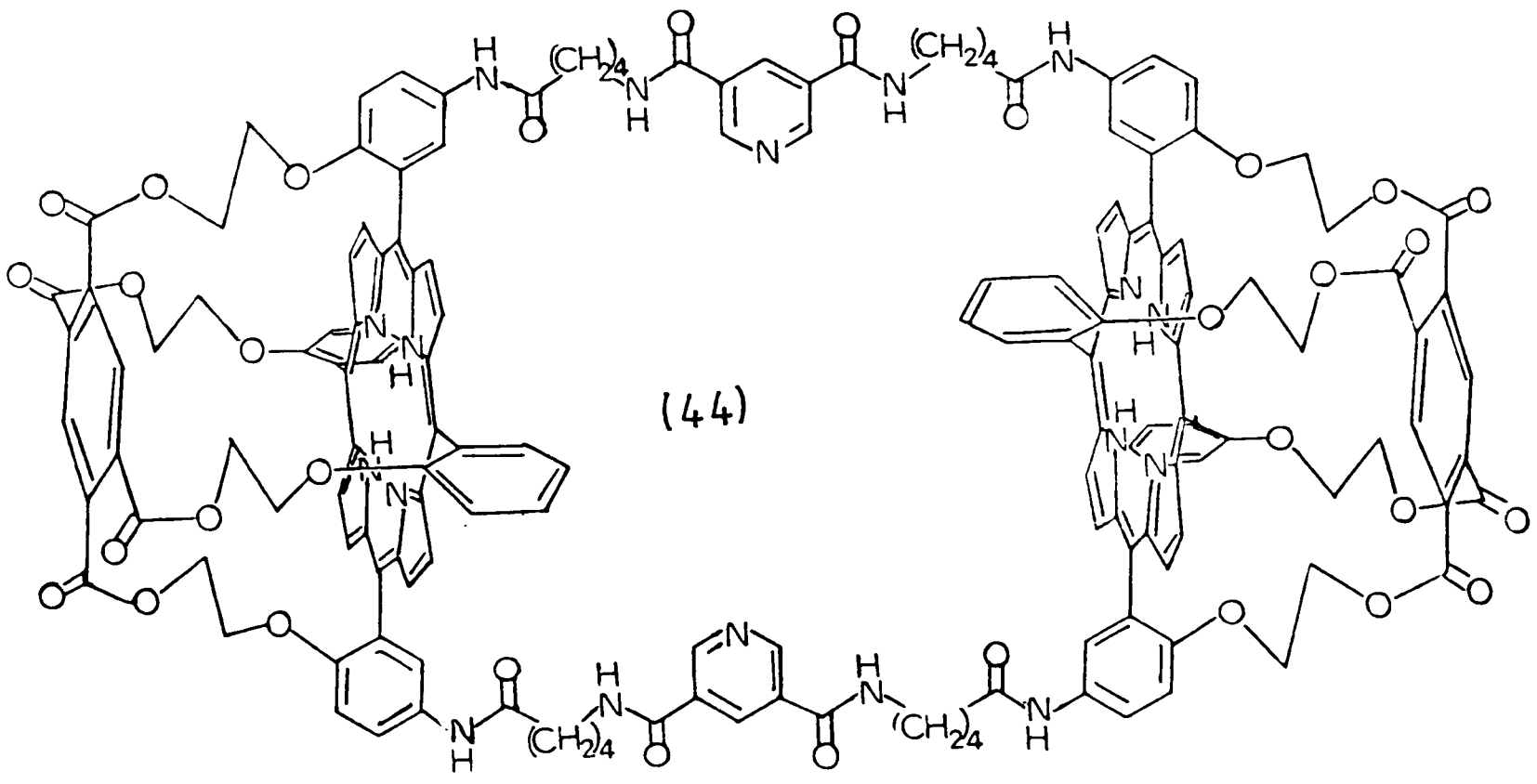
Scheme 13



(31)



(40)

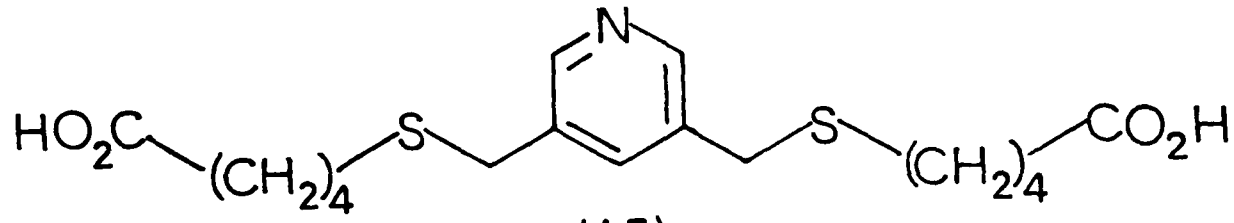


(44)

The conclusion reached above has been further confirmed by Xenon fast atom bombardment[52] which gave a clear ion for (44) and its protonated equivalent.

The result of the high-dilution reaction indicates that, in solution, the acid chloride (41) adopts a conformation that makes it too short to span the face of bis-amino-C_2-capped porphyrin (31).

The main sources of conformational rigidity in solution for (41) are the amide linkages next to pyridine. To avoid this, and possibly solubility problems as well, the sulphide containing strap (45) was synthesised and reacted in a similar way with bis-amino-C_2-cap (31).[38]



(45)

The adduct formed between (45) and bis-amine (31) was only soluble in the same solvents as the product between (41) and (31).[38] The p.m.r. spectrum of the product was again badly resolved and mass data were again hard to obtain. However, this time ^{252}Cf mass spectrometry[51] suggested the formation of a variety of products around the correct molecular weight for a 1:1 cyclo-adduct of (45) and (31).

4. Approaches to a Strap/Cap via Formation of a Tertiary Amide

One obvious impediment encountered in the formation of a secondary amide at a capped porphyrin (see above) was the low solubility of the products, which precluded the use of chromatography.

To avoid this solubility problem a strapped/capped porphyrin containing tertiary amide linkages was proposed. This approach was pioneered by Dagley[38] and the aim here was to improve this route and investigate further.

4.1 The Benzylation of Bis-Amino-C_2-Capped Porphyrin (31)

Condensation of benzaldehyde with bis-amino-C_2-capped porphyrin (31) by methods already developed (see Section 5) and reduction of the imine *in situ* gave a high yield of the bis-benzylamine (46).

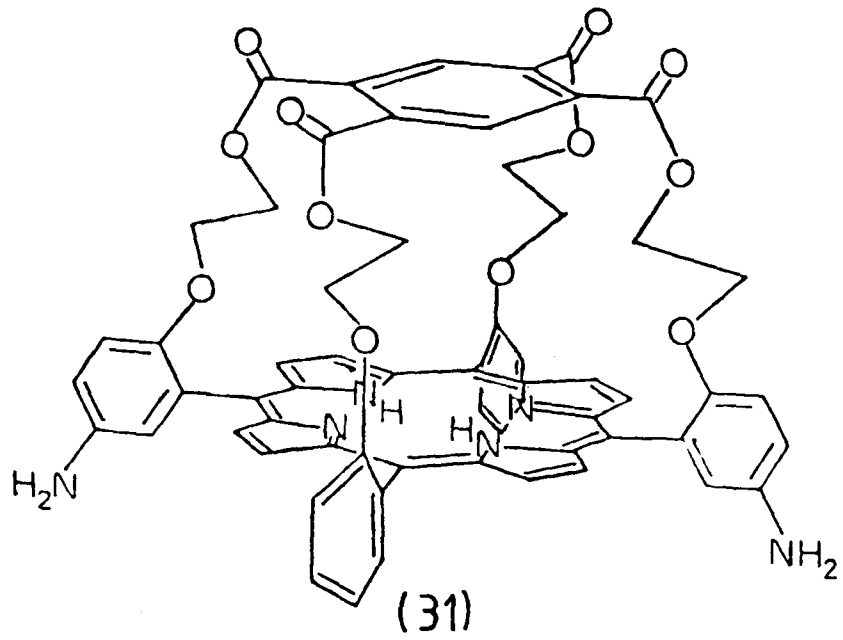
The spectral data of (46), especially its p.m.r. spectrum, were completely consistent with the proposed structure.

4.2 Some Reactions Between Bis-Benzylamino-C_2-Cap (46) and Bis-Acids[38]

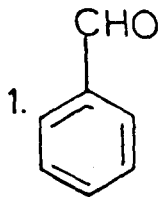
Dagley[38] investigated the reaction between the "sulphide strap" (45) and bis-benzylamine (46).

The method of activation of the acid (45) was changed to the powerful method of pyridinium salts[42] after the discovery through model reactions that the strap (45) was decomposing on formation of the corresponding acid chloride. This method of activation of the acid functionality was adopted for all further reactions of other straps.

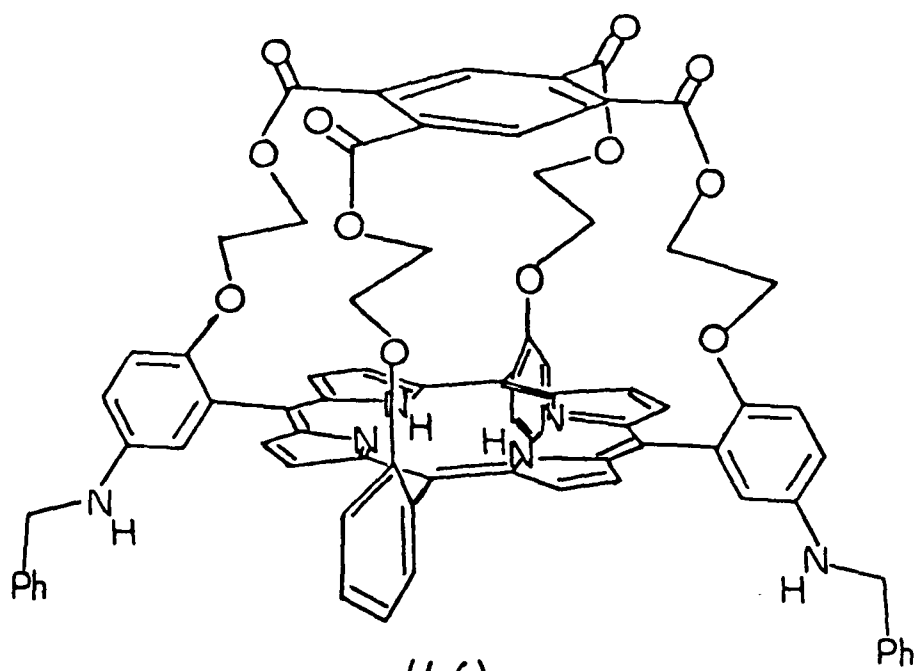
Scheme 14



(31)

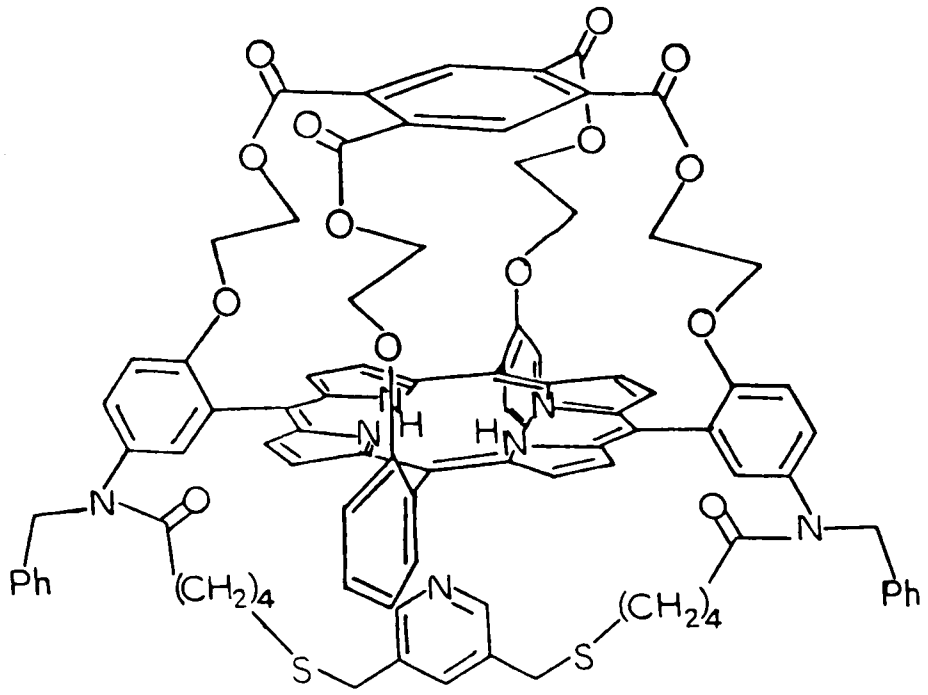
1. 
, THF, TsOH, Sieves.

2. $NaCNBH_3$, NH_4OAc, MeOH , HOAc.



(46)

Reaction of sulphide strap (45) and bis-benzylamine (46) at high dilution gave a variety of products of vastly improved solubility compared to those of the corresponding secondary amide. Chromatography <u>in the dark</u> eventually gave the pure strapped/capped system (47), which was found to be very light/oxygen sensitive. It appeared that the free base porphyrin was sensitising the formation of singlet oxygen which then oxidised the sulphide.



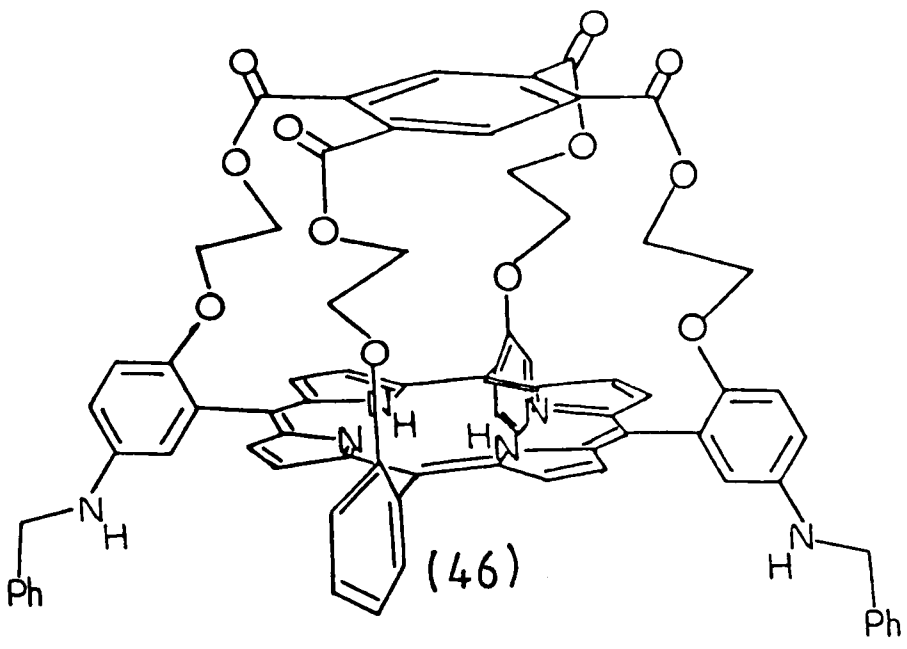
(47)

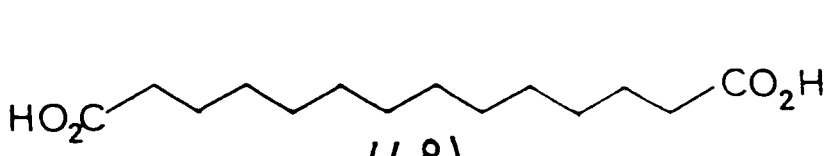
To avoid this problem, straps containing only a methylene chain between the pyridine ring and acid functionality were examined.

A model study using 1,12-dodecanedicarboxylic acid (48) at high dilution gave the stable system (49) in 34% yield. Besides the correct molecular weight, the compound (49) exhibited the usual p.m.r. spectrum for a bis-substituted-C_2-capped

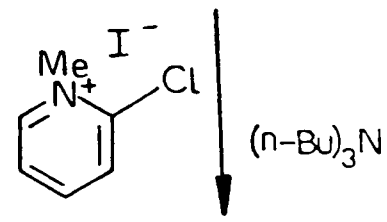
porphyrin plus a series of diamagnetically shifted signals for the methylene chain strung underneath the porphyrin.

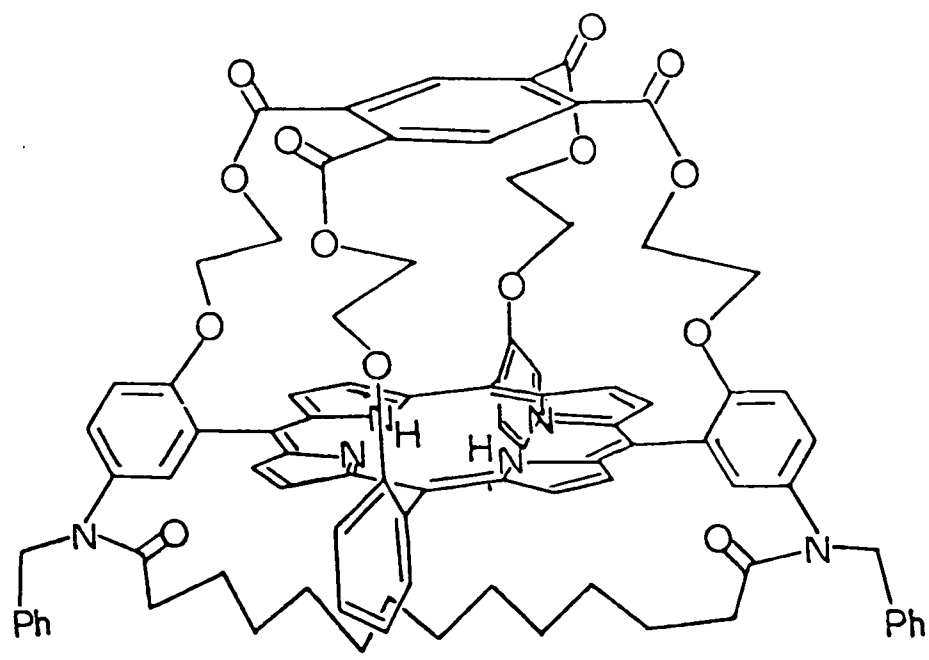
Scheme 15





(48)





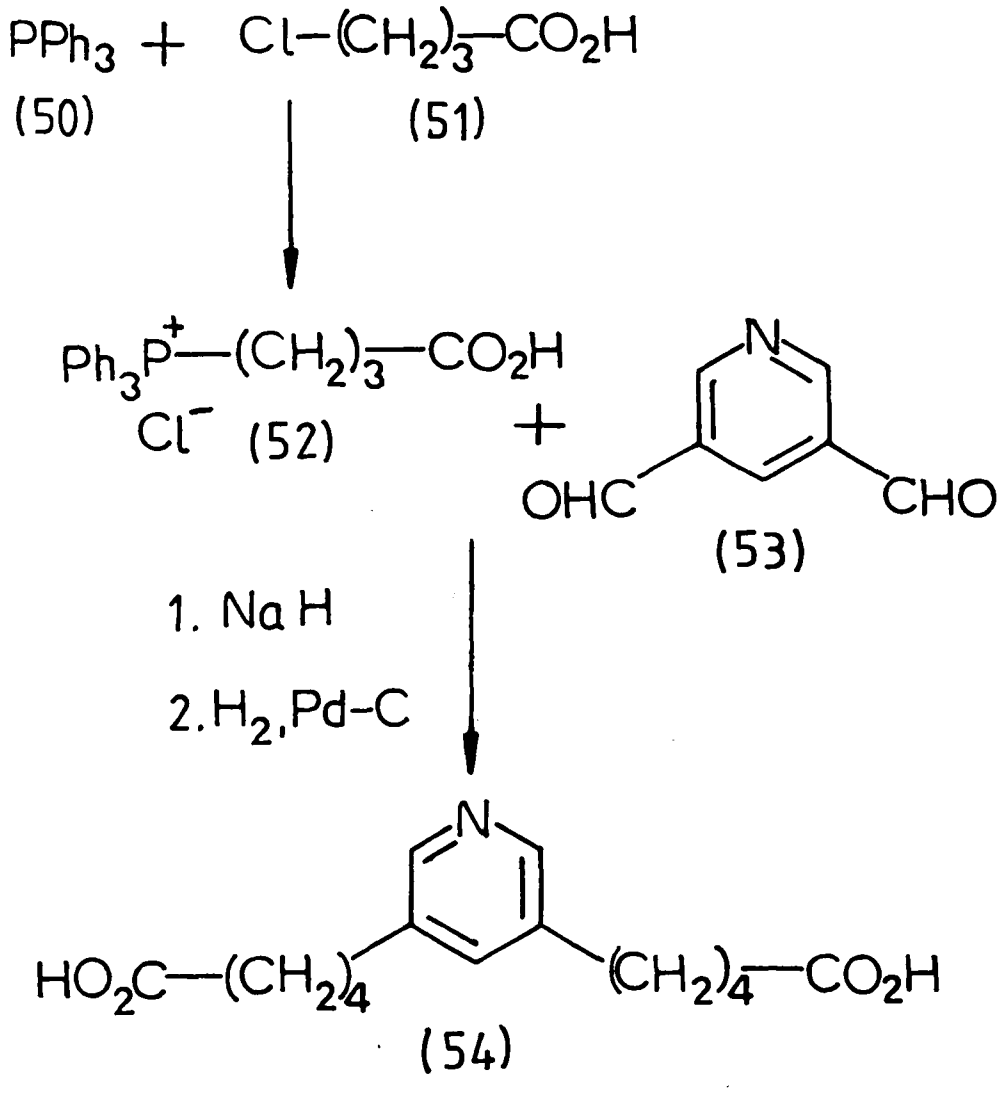
(49)

4.3 The Synthesis of 3,5-Bis (4-Carboxybutyl) Pyridine and its Reaction with Bis-Benzylamino-C_2-Capped Porphyrin (46)

From the model study above it was concluded that a strap, containing four methylene units between the pyridine nucleus and each acid functionality, should give a reasonable yield of a strapped capped porphyrin.[38] The strap was chosen to be tight so that the chelating of pyridine to ferrous porphyrin would be as effective as possible.

The synthesis of the desired strap is outlined below.

Scheme 16



Reaction of triphenylphosphine (50) with 4-chlorobutyric acid (51) gave the phosphonium salt (52)[53] in 67% yield after

crystallisation from acetonitrile/chloroform/ether. Crystallisation by the literature method[53] produced problems due to the easy formation of the ethyl ester of (52). Reaction of the ylid derived from (52) with pyridine-3,5-dicarboxaldehyde,[54] and reduction of the crude product gave 3,5-bis (4-carboxybutyl) pyridine (54) (otherwise known as the "C_4-strap") in yields up to 40%. The original Wittig procedure developed[38,55] using THF/DMSO as solvent proved unreliable in this case and more satisfactory results were obtained using DMF/DMSO as solvent.

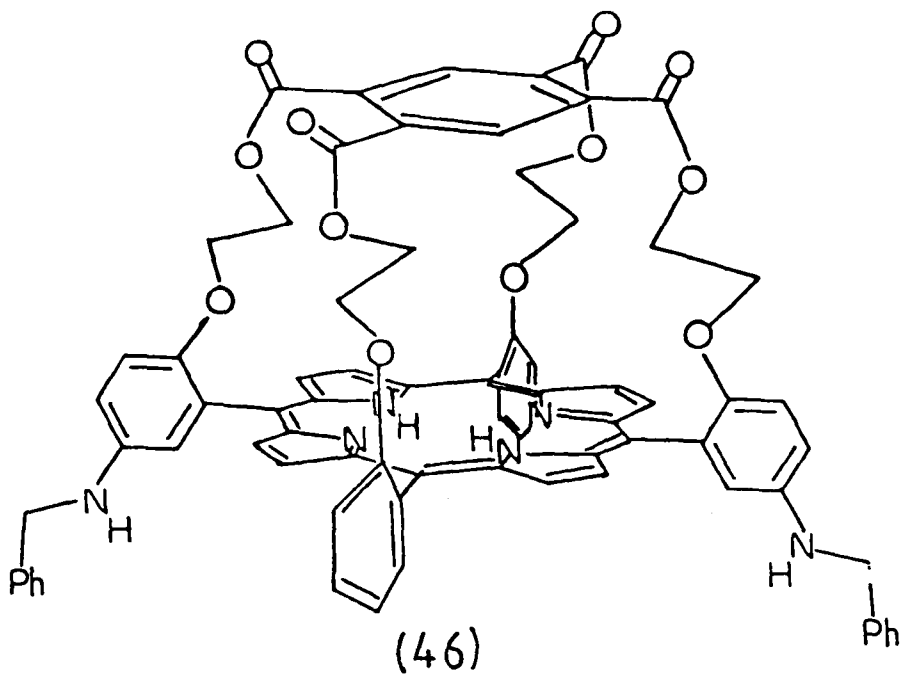
The strap (54) showed the expected infrared absorption at 1725 cm^{-1} for the carboxylic acid group plus a pH dependent p.m.r. spectrum. The pyridine signals appeared at δ8.22 (α-Py$\underline{\underline{H}}$) and 7.59 ($\gamma$-Py$\underline{\underline{H}}$), the former being best resolved at high pH. This compound exhibited three sets of methylene resonances. The group next to pyridine resonated at δ2.67, the group next to the acid at δ2.33, and the two central methylenes at δ1.67.

High dilution reaction of C_4-strap (54) and bis-benzylamino-C_2-cap (46) using the pyridinium salt (39)[42] gave a complex mixture of products.

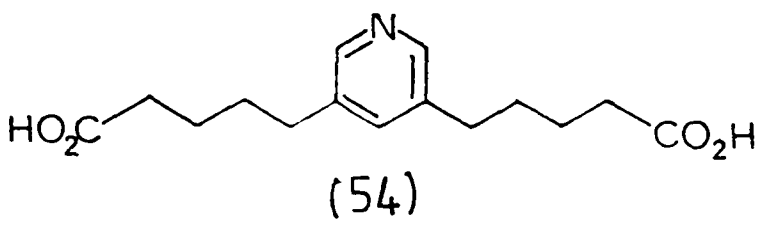
By comparison with Dagley's product[38] and numerous chromatographic separations, a 5.1% yield of pure C_4-strapped/C_2-capped porphyrin (55) was obtained.

The C_4-strapped/C_2-capped porphyrin gave the expected molecular ion at $\underline{m/z}$ 1489. The p.m.r. spectrum, besides exhibiting the usual features for the bis-substituted capped system (see diagram), showed a set of diastereotopic resonances for the benzylic protons and the methylene protons indicating connection to a chiral centre. Furthermore, the strap protons (including

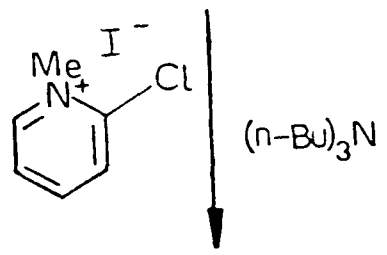
Scheme 17

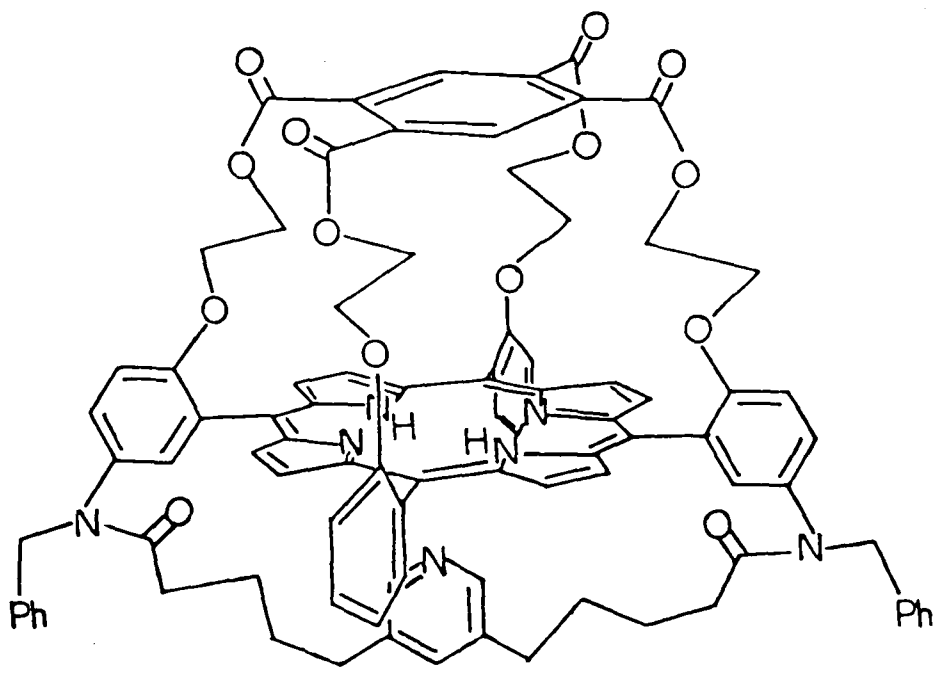


(46)

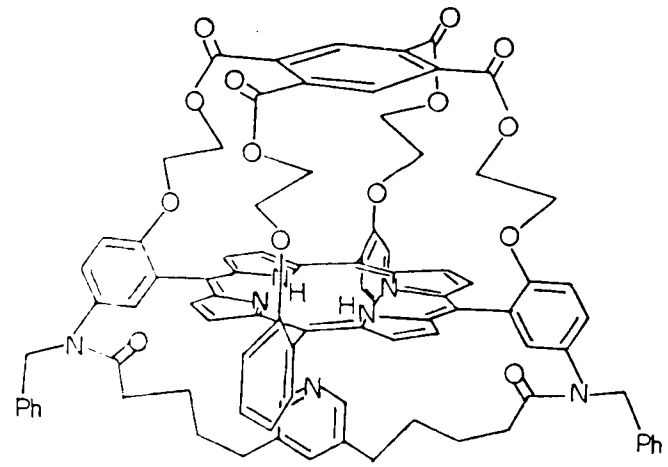


(54)





(55)



(55)

the pyridine) were diamagnetically shifted, the methylenes appearing at δ0.5, 0.9, 1.2 and 2.2, indicating that the strap was strung across the face of the porphyrin. The resonances due to pyridine were not easily seen in the p.m.r. spectrum when the solvent used was deuteriochloroform. Changing the solvent to deuterated dichloromethane revealed the α-protons at δ6.73, while it is suspected that the γ proton [by analogy with C_5 strap/C_2 cap (60)] lies in the region δ3.7-4.7.

The precise assignment of the various proton signals in this compound was performed by the use of 2-dimensional p.m.r. spectroscopy.[56] This technique proved to be markedly superior to the previous method of double irradiations for assigning the resonances in the p.m.r. of (55) (see Appendix 1).

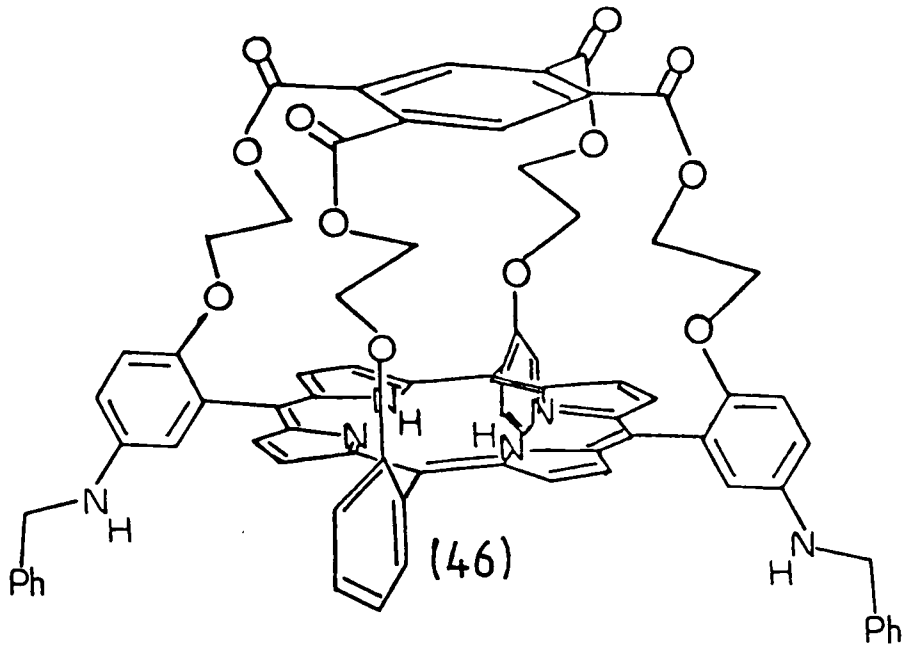
The free base porphyrin (55) was metallated using ferrous chloride in THF at reflux for 48h.[38] The resulting ferric complex was converted into the ferric chloride·hydrochloride.

4.4 Further Investigation of Strap Requirements

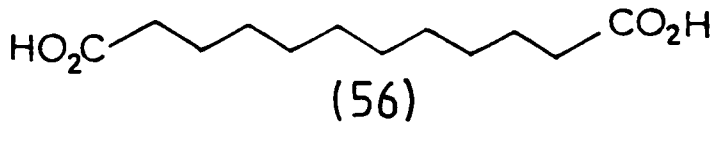
The low yields obtained on coupling C_4-strap (54) to bis-benzylamine (46) suggested that the strap (54) was too short for efficient ring formation, perhaps due in part to the rigidity of the pyridine nucleus. To confirm that this was the case, the high dilution reaction between activated 1,10-decanedicarboxylic acid (56) and bis-benzylamino-C_2-cap (46) was carried out.

Only one product from this reaction showed properties consistent with the desired adduct (57) [$^m/_z$ 1440 (M^+) and diamagnetically shifted resonances in the p.m.r. spectrum].

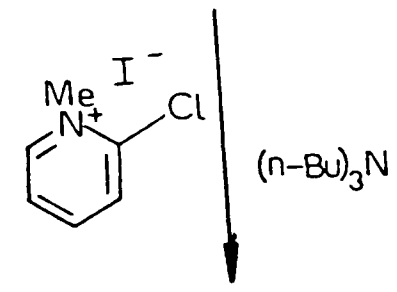
Scheme 18

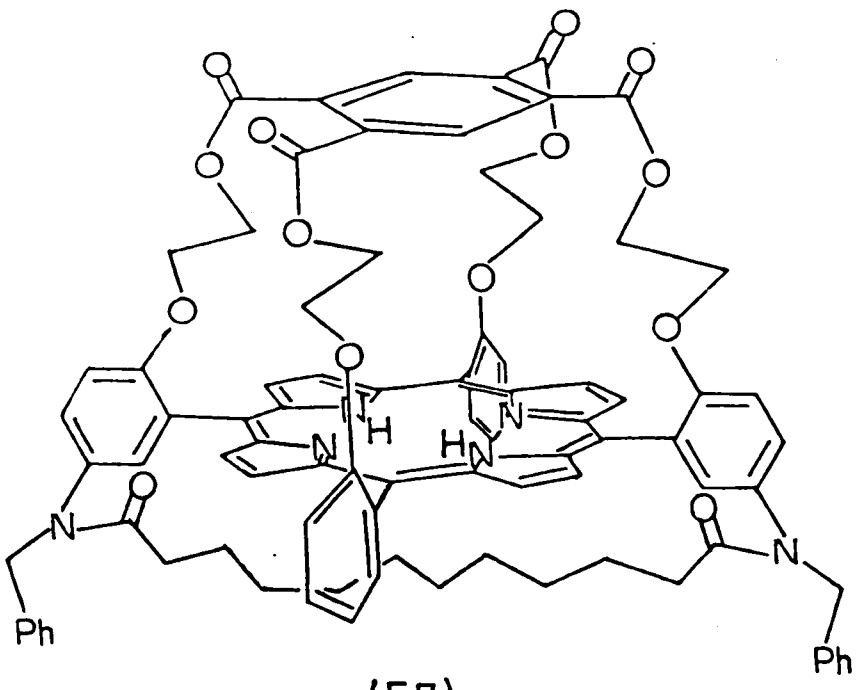


(46)



(56)





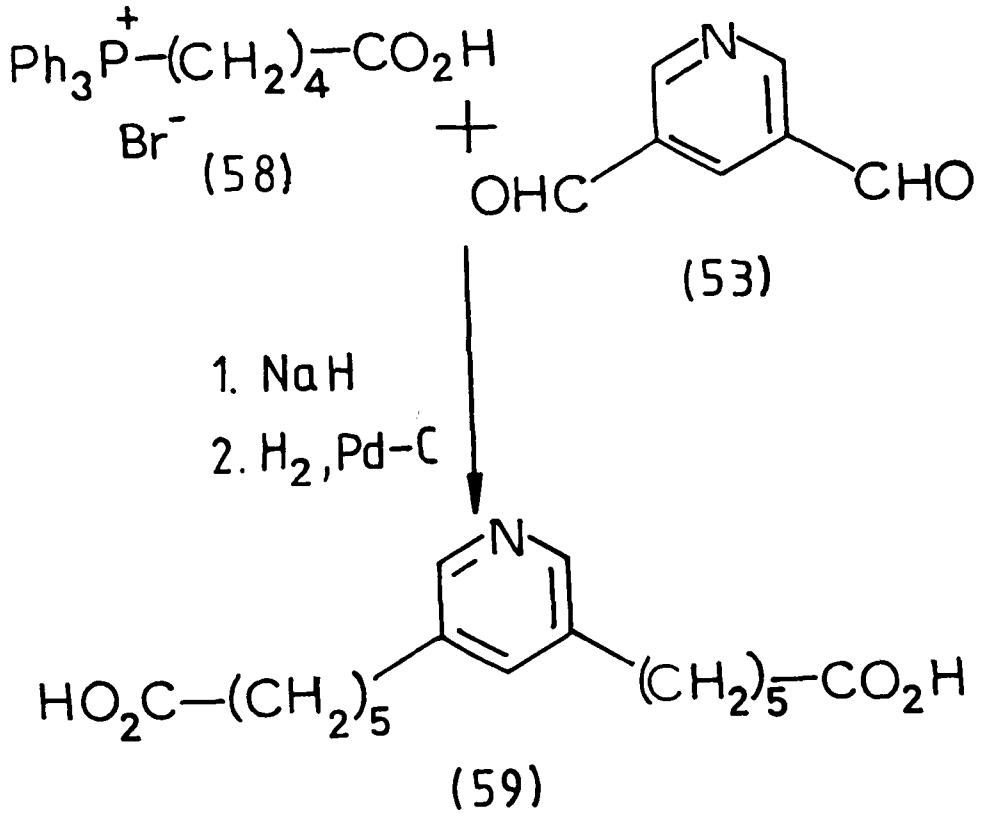
(57)

The crude yield of this product was only 16% *cf.* C_{12} analogue (49) yield 34% . This result suggested that strap size was indeed the reason for the low yield for production of C_4-strapped/C_2-capped porphyrin (55).

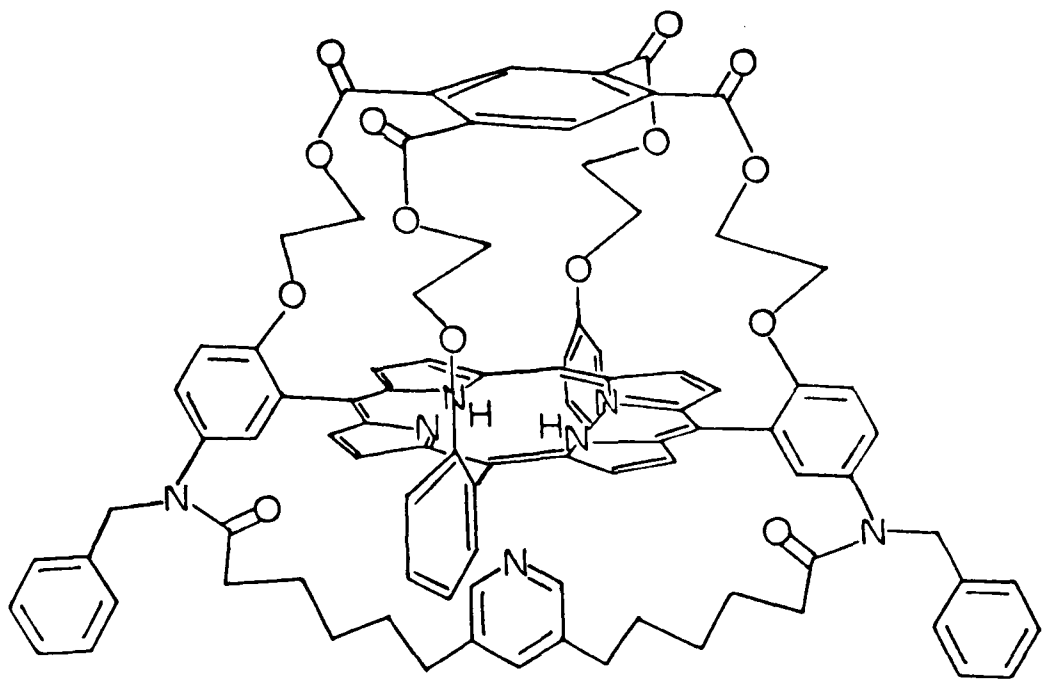
4.5 The Synthesis of 3,5-Bis (5-Carboxypentyl) Pyridine and its Reaction with Bis-Benzylamino-C_2-Cap (46)

To produce a higher yielding synthesis of a strapped/capped porphyrin a longer pyridine-containing strap was synthesised.

Scheme 19



Application of the same general procedure as used in the synthesis of C_4-strap (54) on the phosphonium salt (58) gave 3,5-bis (5-carboxypentyl) pyridine (59) (the "C_5-strap") in 35% yield. The p.m.r. spectrum of this compound showed the pyridine resonances at δ8.20 (α) and δ7.57 (γ). The methylene protons next to pyridine and acid groups resonated as expected at δ2.66 and δ2.29 respectively with the central methylenes appearing at δ1.65 (8H) and δ1.39 (4H). The infrared spectrum was extremely broad even when the compound was analytically pure, but all the other data were in accord with structure (59).



(60)

High-dilution coupling of C_5-strap (59) and bis-benzylamino-C_2-cap (46) gave a 25% yield of the desired C_5-strapped/C_2-capped porphyrin (60).

This compound had the expected p.m.r. spectrum in deuteriochloroform with slight upfield shifts for the strapping methylene resonances. Changing the p.m.r. solvent to deuterated dichloromethane caused the pyridine resonances to appear clearly at δ7.75 (αPyH, diamagnetic shift 0.5 ppm) and δ4.7 (γ-PyH, diamagnetic shift 2.8 ppm).

One difference in the p.m.r. spectrum of C_5-strap/C_2-cap (60) compared to that of C_4-strap/C_2-cap (55) was that the methylene and benzylic resonances appeared as broad signals. This broadening also occurred to a lesser extent in the rest of the spectrum and indicated the slightly more flexible nature of the ligand produced.

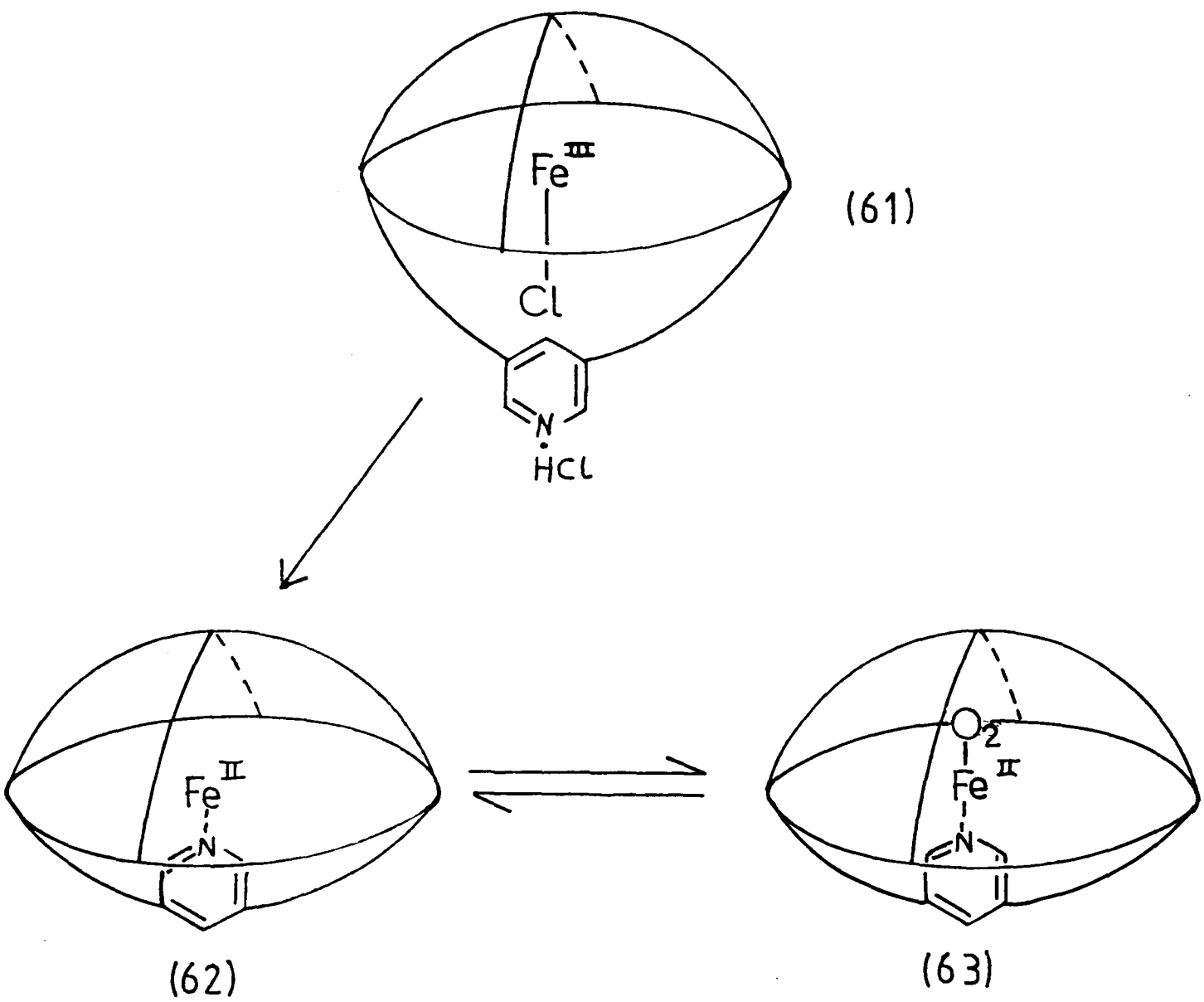
Treatment of the porphyrin (60) with ferrous chloride in THF at reflux, followed by t.l.c. and gaseous hydrogen chloride treatment gave the ferric derivative (61) as the chloride·hydrochloride, m/z 1571 $(M-HCl_2)^+$.

Reduction of the Ferric Complex of C_5-Strap/C_2-Cap and Subsequent Behaviour with Oxygen

Reduction of a toluene solution of ferric complex (61) as the chloride·hydrochloride (λ_{max} 510 nm) with aqueous alkaline dithionite solution gave the ferrous complex (62) (λ_{max} 537-8 nm). The spectra of this compound and subsequent compounds were compared with those of simple ferrous C_2-capped porphyrin systems in pyridine.[30]

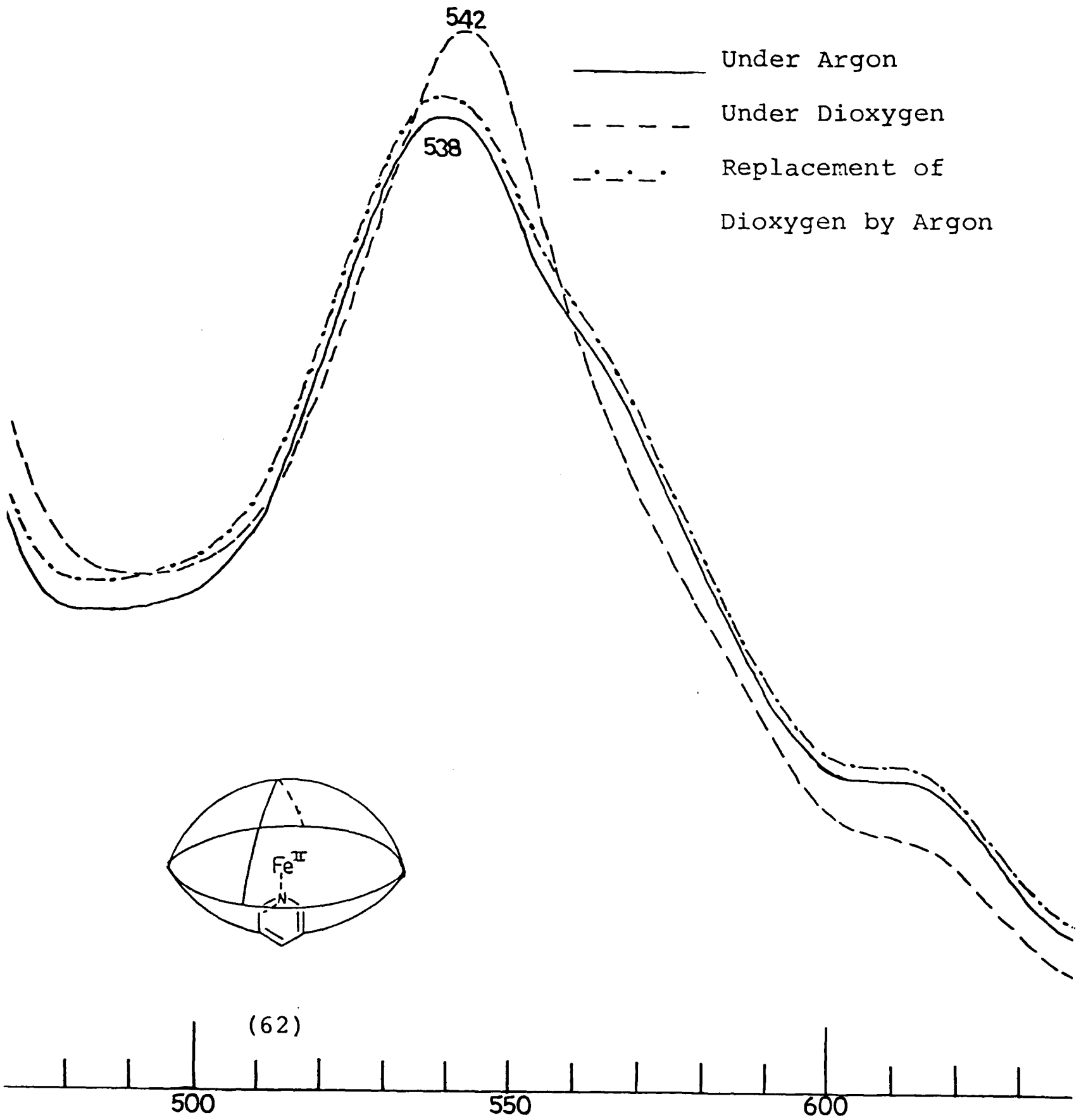
Exposing a solution of (62) to air did not result in any appreciable change. However if (62) was exposed to pure oxygen then a reversible change occurred to give a new species (λ_{max} 542 nm) proposed to be the ferrous·oxygen complex (63).

Scheme 20



(see attached spectra).

An attempt was made to observe this oxygenation behaviour using p.m.r. spectroscopy. The free ferrous complex (62) gave a complicated broadened p.m.r. spectrum, as expected for a paramagnetic metalloporphyrin. Upon addition of oxygen certain small changes were observed but the expected diamagnetic spectrum, for a low spin ferrous porphyrin, was not obtained. This problem was probably due to the poor oxygen affinity of (62) at room temperature preventing complete formation of oxy-complex (63). Fast exchange of oxygen between ferrous centres would then account for the observation of a broadened spectrum.


542
538
Under Argon
Under Dioxygen
Replacement of
Dioxygen by Argon
Fe II
N
(62)
500
550
600

A similar spectral change was observed in dichloromethane as solvent, although the wavelength shift on oxygenation was not so great [(62) λ_{max} 538 nm; (63) λ_{max} 540 nm].

Having established the presence of a reversible reaction with oxygen, qualitative studies were undertaken into the stability of the ferrous complex (62).

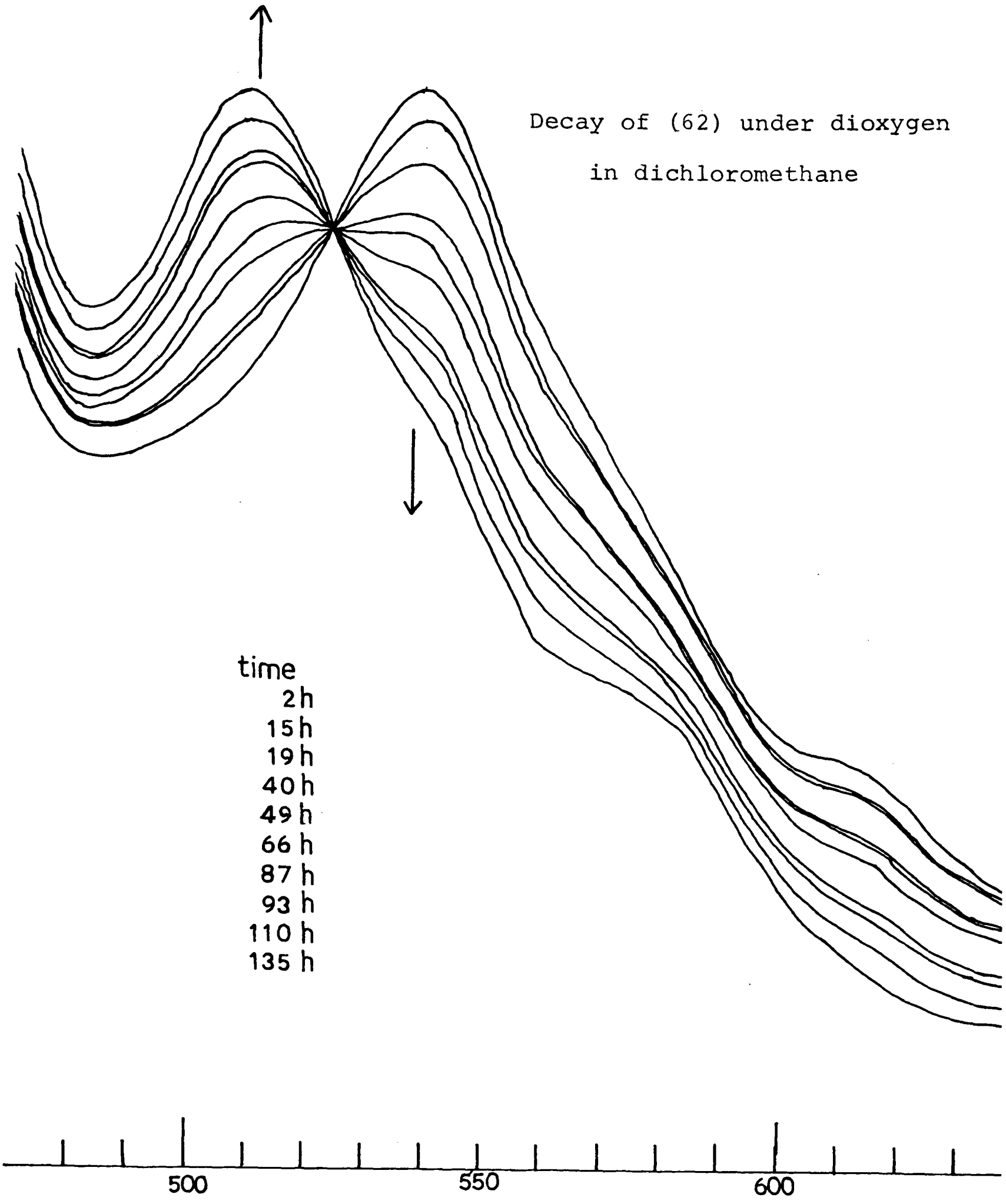
Shaking a toluene solution of (62) with portions of aqueous sodium bicarbonate solution in air gave an organic solution that still clearly showed the presence of a ferrous complex λ_{max} 538 nm. The spectrum was broad but demonstrated a clear stability for (62) even in the presence of a proton source.

The stability of (62) was investigated under oxygen in two dry solvents, dichloromethane and toluene.

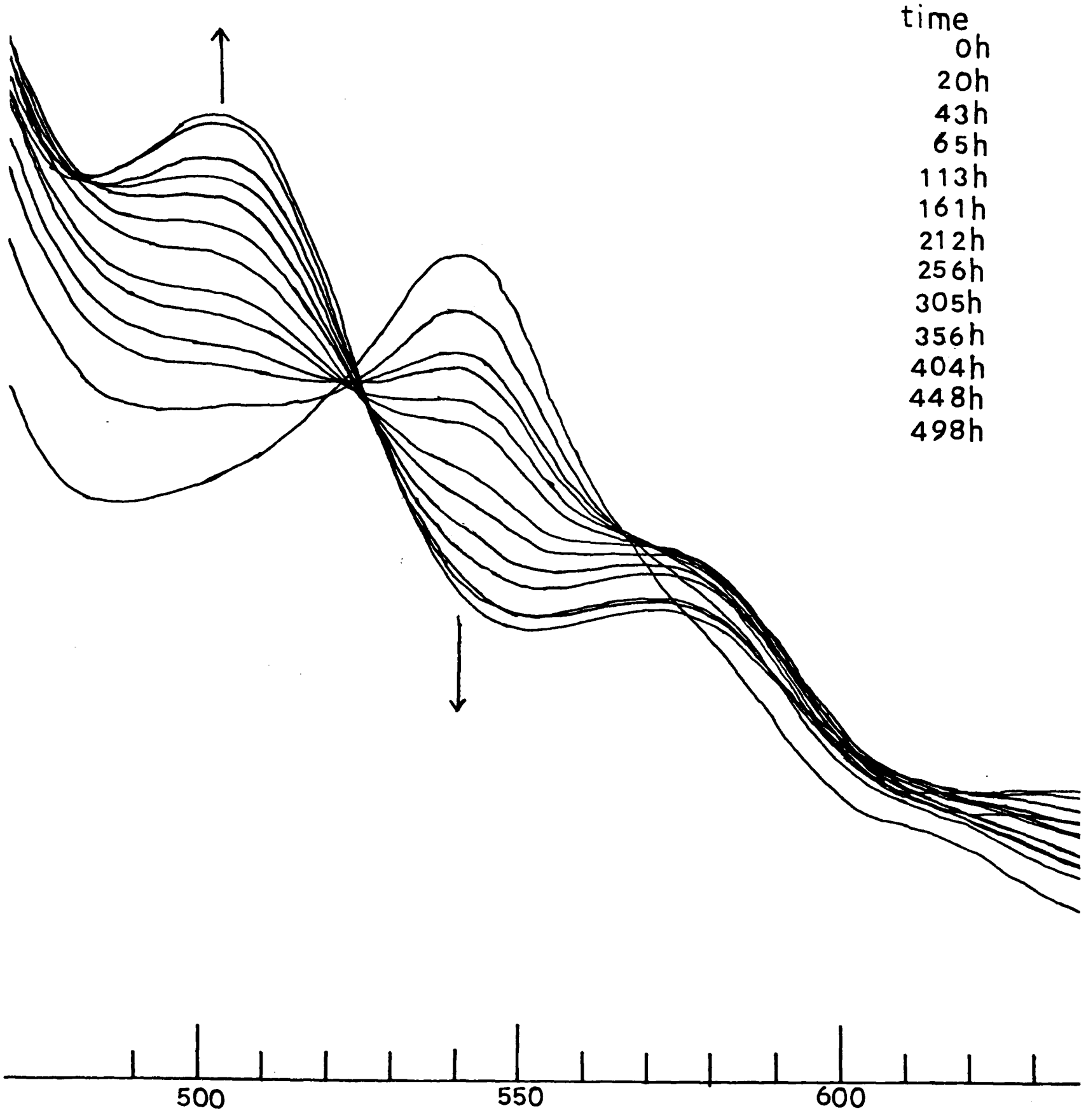
In dichloromethane, problems were encountered with solvent loss but clean conversion of the ferrous oxygen complex to a new product (λ_{max} 510 nm) was seen (see diagram) with a half life greater than 40h at room temperature. The end product could be re-reduced to the ferrous complex (62) which in turn reversibly bound oxygen. It is known that ferrous porphyrins will react with dichloromethane to give the ferric-chloro species[8c] and it is thought that this process occurred here on a longer time scale.

In toluene the oxidation of ferrous·oxygen complex (63) appeared to be slower, half life in excess of 100h, and appeared to take place <u>via</u> a more complex process to give a final product λ_{max} 504 and 570 nm. Bubbling argon through the solution did not regenerate ferrous complex (62), but subjecting the product to aqueous alkaline dithionite regenerated (62).

The re-reduction with dithionite suggested that the product


Decay of (62) under dioxygen
in dichloromethane
time
2h
15h
19h
40h
49h
66h
87h
93h
110h
135h
500
550
600

Decay of (62) under dioxygen in toluene



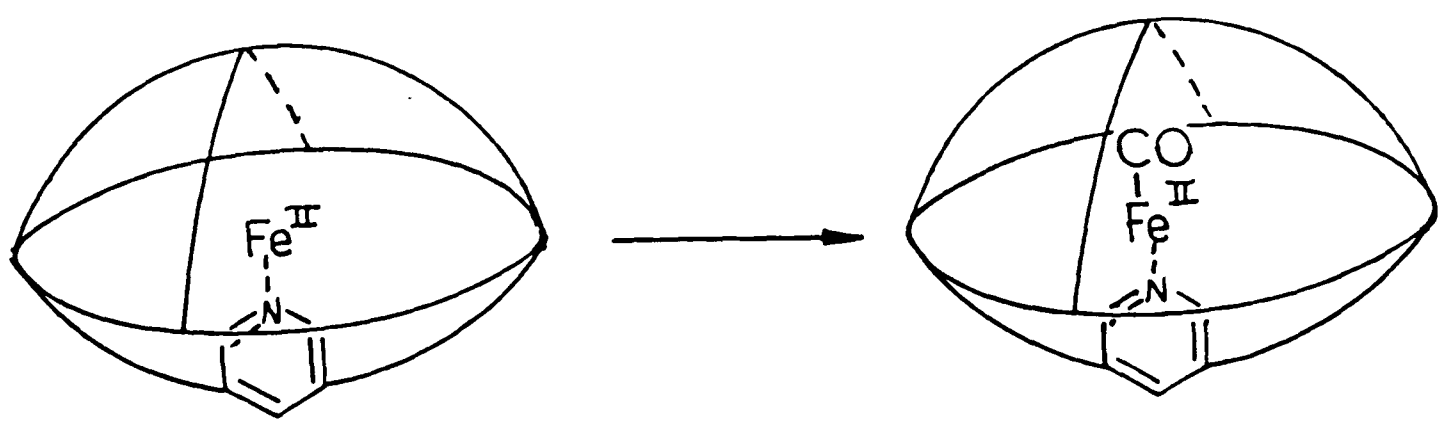
of oxidation in toluene was not μ-oxo dimer. Further investigation will be necessary to identify the final product(s).

The above results confirm that the ferrous complex (62) under oxygen is exceptionally stable. The conclusion drawn is that the chelation of a heterocyclic base by a strap to the capped porphyrin system produces a more stable monomolecular oxygen carrier, than a ferrous capped porphyrin in pyridine solution.

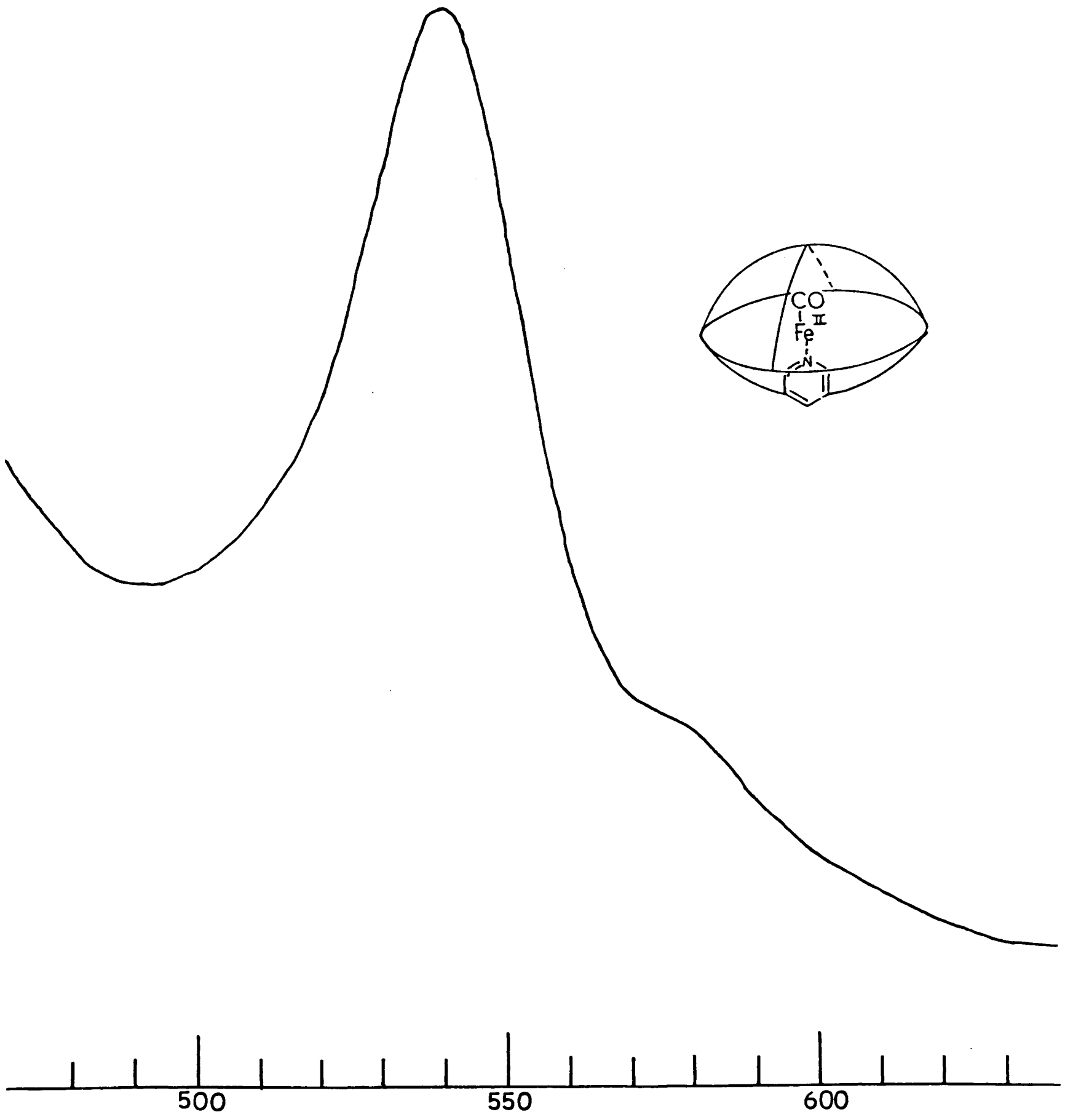
The Behaviour of Ferrous C_5-Strapped/C_2-Capped Porphyrin (62) with Carbon Monoxide

Dissolution of ferrous complex (62) in dry toluene, under carbon monoxide, gave a bright red solution of the carbonyl complex (64). Bubbling argon or oxygen through the solution,as expected with this type of complex, did not remove the carbon monoxide.[30] Interestingly in this case the visible spectrum of the carbonyl complex (64) showed λ_{max} 540 and 580 (shoulder) nm, rather than the expected spectrum for a ferrous capped porphyrin carbonyl complex[30]; λ_{max} 545 and 580 (shoulder) nm.

Scheme 21



(62) (64)


CO
II
Fe
N
500
550
600

To confirm the identity of (64) a p.m.r. study was carried out. On the addition of carbon monoxide, the broadened spectrum of a ferrous high spin complex was replaced by the diamagnetic spectrum of an octahedral ferrous low spin complex. The capping protons appeared as a singlet at δ6.53 with the β-pyrrolic protons appearing as the expected four doublets (J = 4.5Hz) at δ8.50, 8.52, 8.61 and 8.64. Of especial interest were the positions of the pyridine protons. These signals could be seen and their connection established by double irradiation experiments. The α protons were shifted upfield by 6.7 ppm and the γ-protons shifted upfield by 2.7 ppm relative to the open chain C_5-bis-acid (59). The relative diamagnetic shifts indicated that in the carbonyl complex (64) the pyridine ligand is co-ordinated to iron. Furthermore the good resolution of the spectrum obtained suggested that the pyridine was totally bound to iron, illustrating that the strap was rigorously enforcing co-ordination of pyridine to iron.

5.1 Approaches to a Strapped/Capped Porphyrin Based on Condensation of a Bis-Aldehyde with Bis-Amino-C_2-Capped Porphyrin (31)

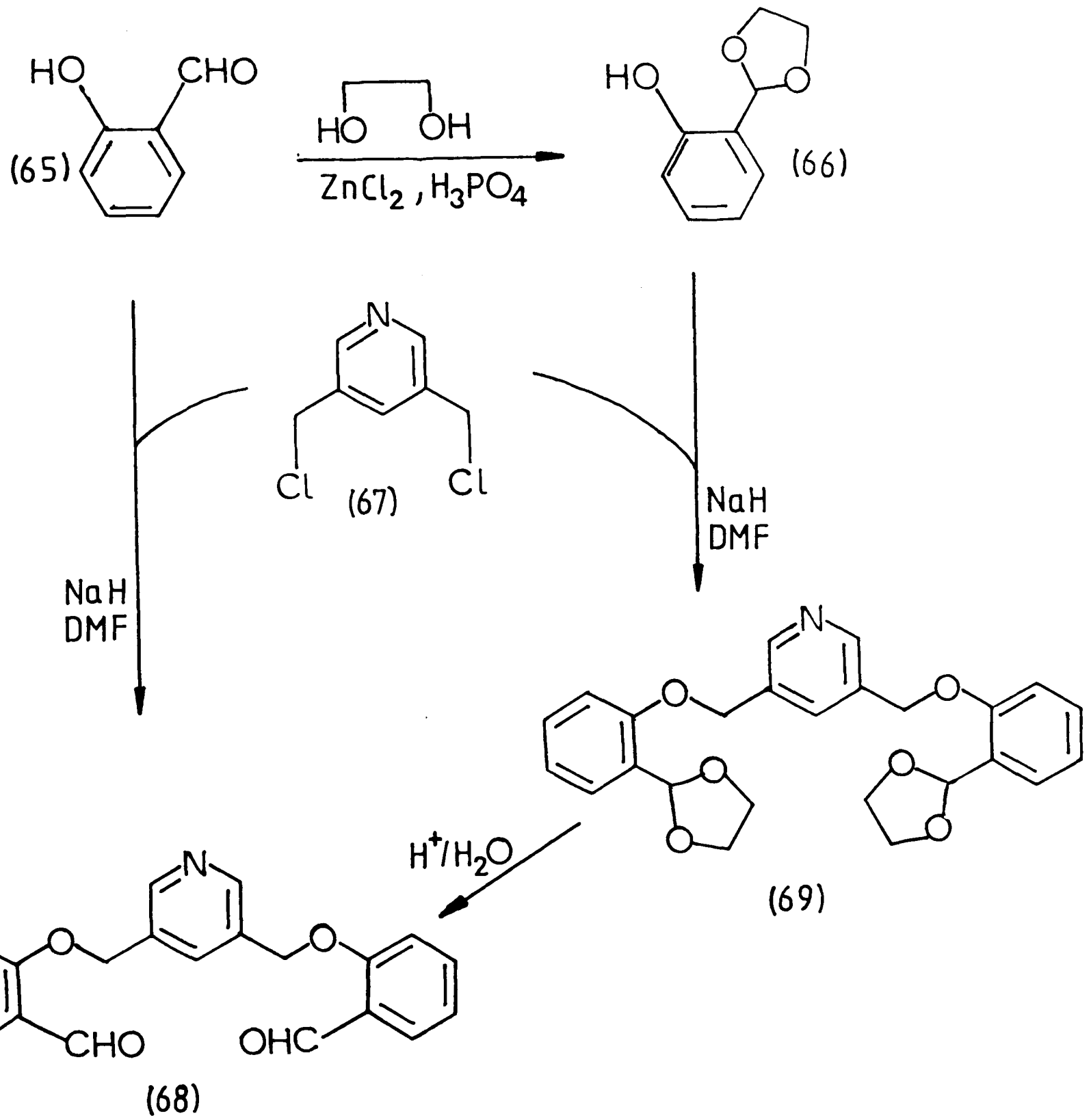
Following the failure of the reaction between bis-amide/bis-acid strap (40) and bis-amine (31), condensation between an aldehyde and amine (31) was examined. Considering the possible instability of a cyclic bis-imine the formation of a di-aryl-imine and its reduction in situ was investigated.

Successful condensation of 2-methoxybenzaldehyde with (31) indicated that the approach was worth further study.

5.2 The Construction of a Pyridine-Containing Bis-Aldehyde and its Reaction with Amines

Examination of models indicated that the strap (68) should fit across the face of bis-amino-C_2-capped porphyrin (31). The synthesis is outlined in Scheme 21.

Scheme 22



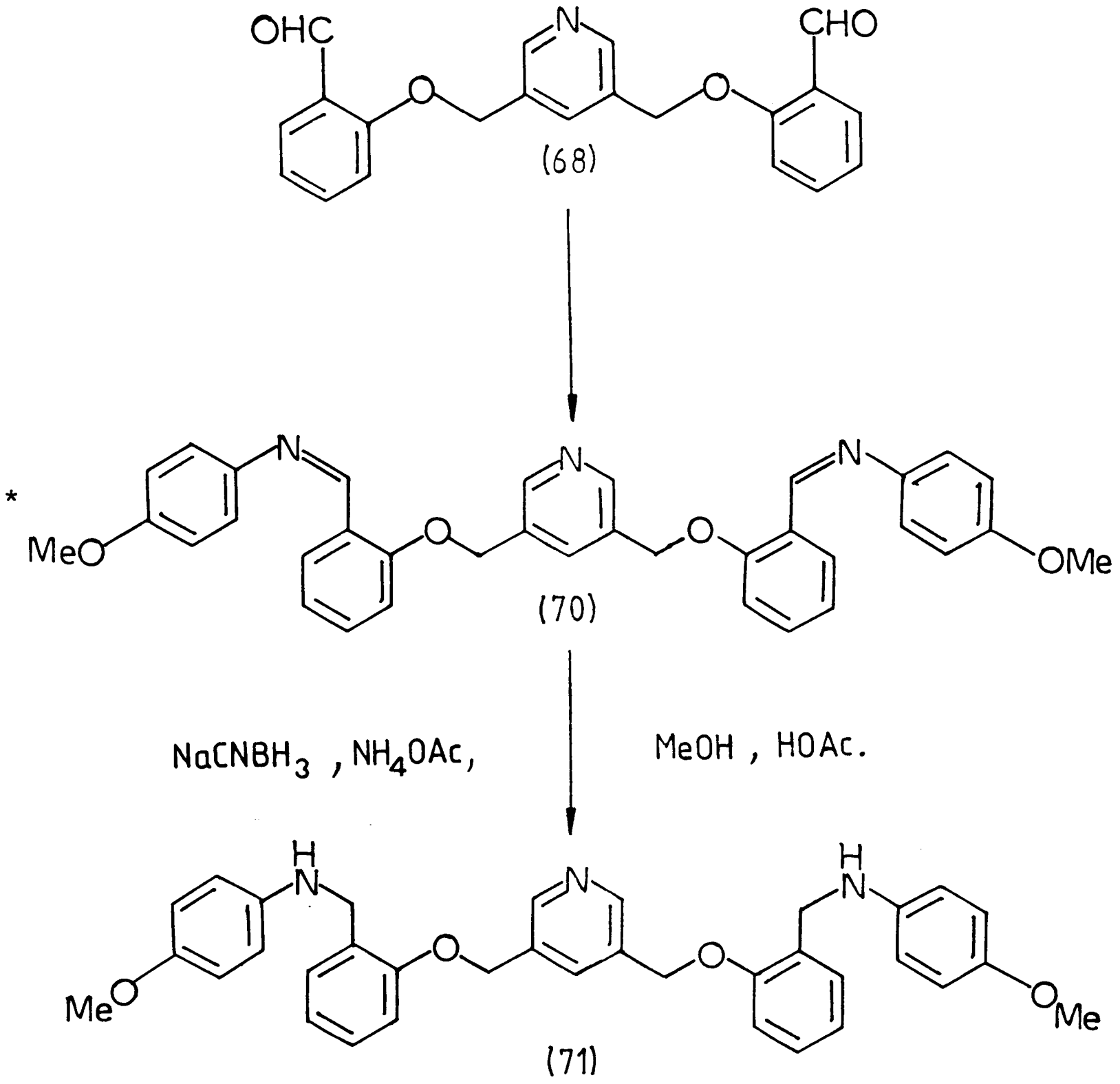
Direct alkylation of salicylaldehyde (65) with 3,5-bis (chloromethyl)pyridine (67)[54] gave the desired bis-aldehyde (68) in low yield. The infrared of this compound showed the expected absorption at 1690 cm^{-1} for the aldehyde group. The p.m.r. spectrum besides the signal for the aldehyde protons at δ10.49, also showed the appropriate signals for the pyridine ring at δ8.72 (α-PyH) and 7.94 (γ-PyH). The synthesis of bis-aldehyde (68) *via* the readily available salicylaldehyde acetal[57] gave better yields.

A model reaction of (68) with *p*-anisidine gave the stable yellow imine (70). The infrared of this compound showed a rather weak absorption at 1620 cm^{-1}, but the p.m.r. spectrum showed a very sharp singlet for the imine proton. Reduction of the imine was achieved using sodium cyanoborohydride[58] with acetic acid and ammonium acetate. The product amine (71) formed, gave the correct mass spectrum ($^{m}/z$ 561, M^{+}) and the benzylic methylene was clearly seen at δ4.31.

The reduction could be carried out *in situ* on a preformed solution of bis-imine (70) to give 75% from aldehyde (68) of the bis-amine (71), which was a moderately air sensitive compound.

Application of this latter procedure at high dilution on bis-aldehyde (68) and bis-amino-C_2-capped porphyrin (31) gave a complex mixture of products. The amines that were produced were both light and air sensitive. Acylation of the products was employed to give more stable derivatives, but again a homogeneous sample of porphyrin was not obtained.

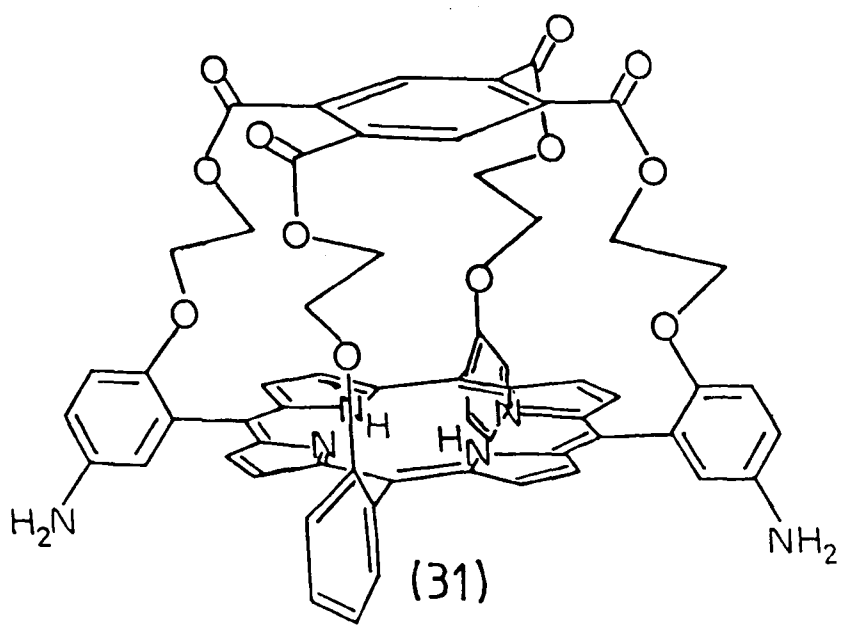
Scheme 23



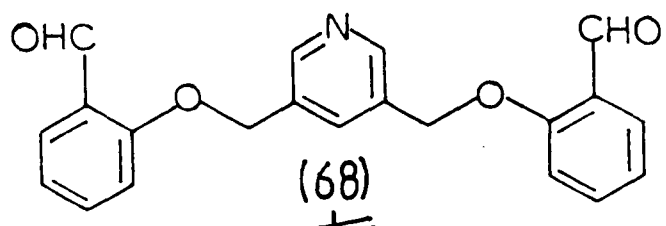
* The stereochemistry drawn here is not implied for the product (70).

The concurrent formation of bis-benzylamino-C_2-capped porphyrin (46) by the same <u>in situ</u> procedure, and the <u>in situ</u> studies on the open chain analogue (71), suggested that strap size might have been the problem. If the imine formed is strained, it will be very reactive[59] and the large number of products formed suggested that this was the case.

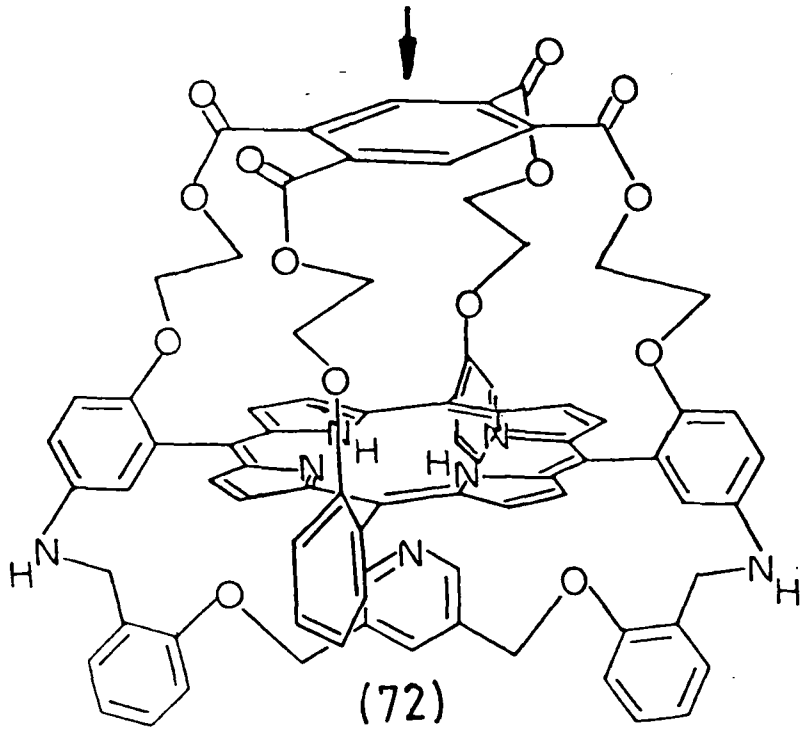
Scheme 24



(31)



(68)



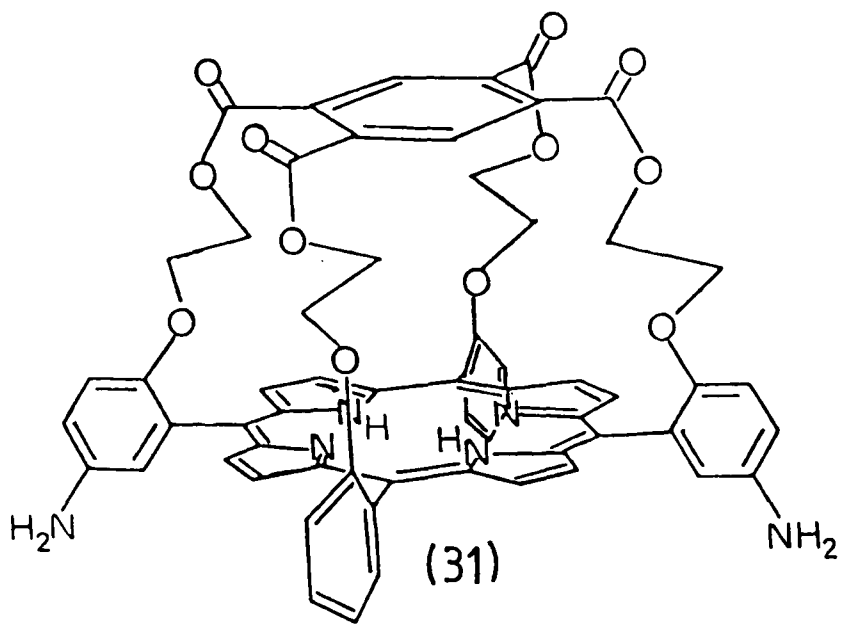
(72)

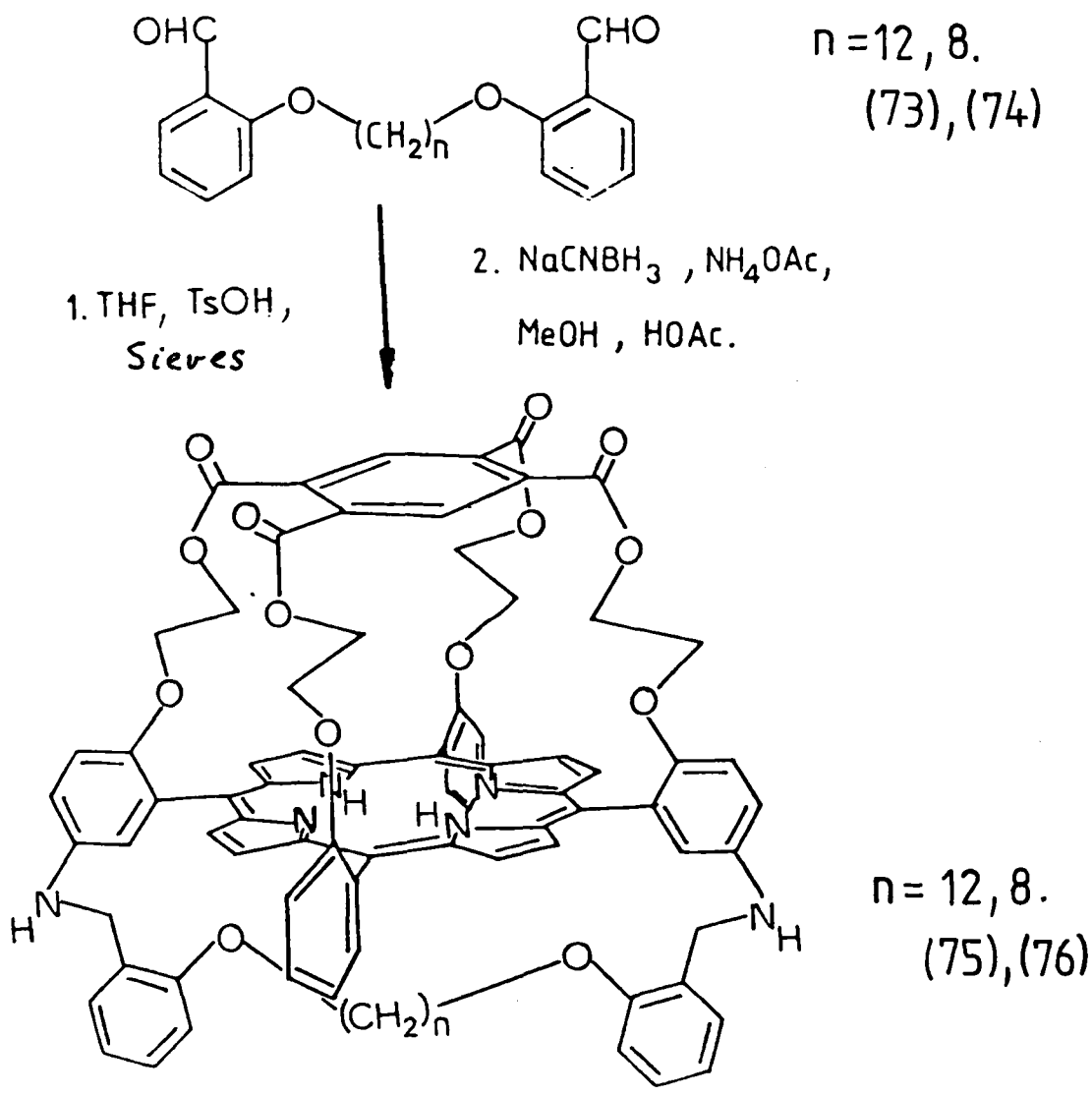
5.3 The Reaction of 2,2′-(Alkylidenedioxy) Bis-Benzaldehydes with Bis-Amino-C_2-Capped Porphyrin (31)

To test the above hypothesis the reaction of bis-salicylaldehyde units, connected by a methylene chain of varying length, with bis-amino-C_2-capped porphyrin was investigated.

2,2'(1,12-Dodecylidenedioxy) bis-benzaldehyde (73) had already been prepared in the course of the synthesis of strapped porphyrins.[28] This bis-aldehyde showed the expected infrared absorption at 1690 cm^{-1} for the aldehyde carbonyl. In the p.m.r. spectrum of this compound, the resonances for the

Scheme 25





methylene next to oxygen appeared at δ4.1 with the rest of the methylene protons resonating in the region δ1.3-2.1.

Reaction of (73) with bis-amino-C_2-capped porphyrin (30) at high dilution gave three products plus baseline by t.l.c.

The major product (30%) was the desired bis-amine (75), $\underline{m/z}$ 1444. The p.m.r. spectrum of the product was as expected with a series of diamagnetically shifted resonances for the methylene chain strung underneath the porphyrin.

The other two clear products of reaction were also shown to be 1:1 cyclo-adducts but of a more complex nature. Mass spectral analysis indicated molecular weights around 1450 a.u. and the products were shown to be <u>not</u> due to oxidation. The conclusion was that in this case some other process hindered clean reduction of the cyclic bis-imine.

Following the success of the above condensation, a tighter strap, based on molecular models, was designed. The approach used was the construction of a chain such that <u>no</u> change in conformation of the "capping structure" occurred.

As a result 2,2′ (1,8-octylidenedioxy) bis-benzaldehyde (74) was chosen as the optimum sized bis-aldehyde. The bis-aldehyde (74) was synthesised by alkylation of salicylaldehyde with 1,8-dibromooctane (yield not optimised) and exhibited the usual aldehyde infrared absorption at 1690 cm^{-1}.

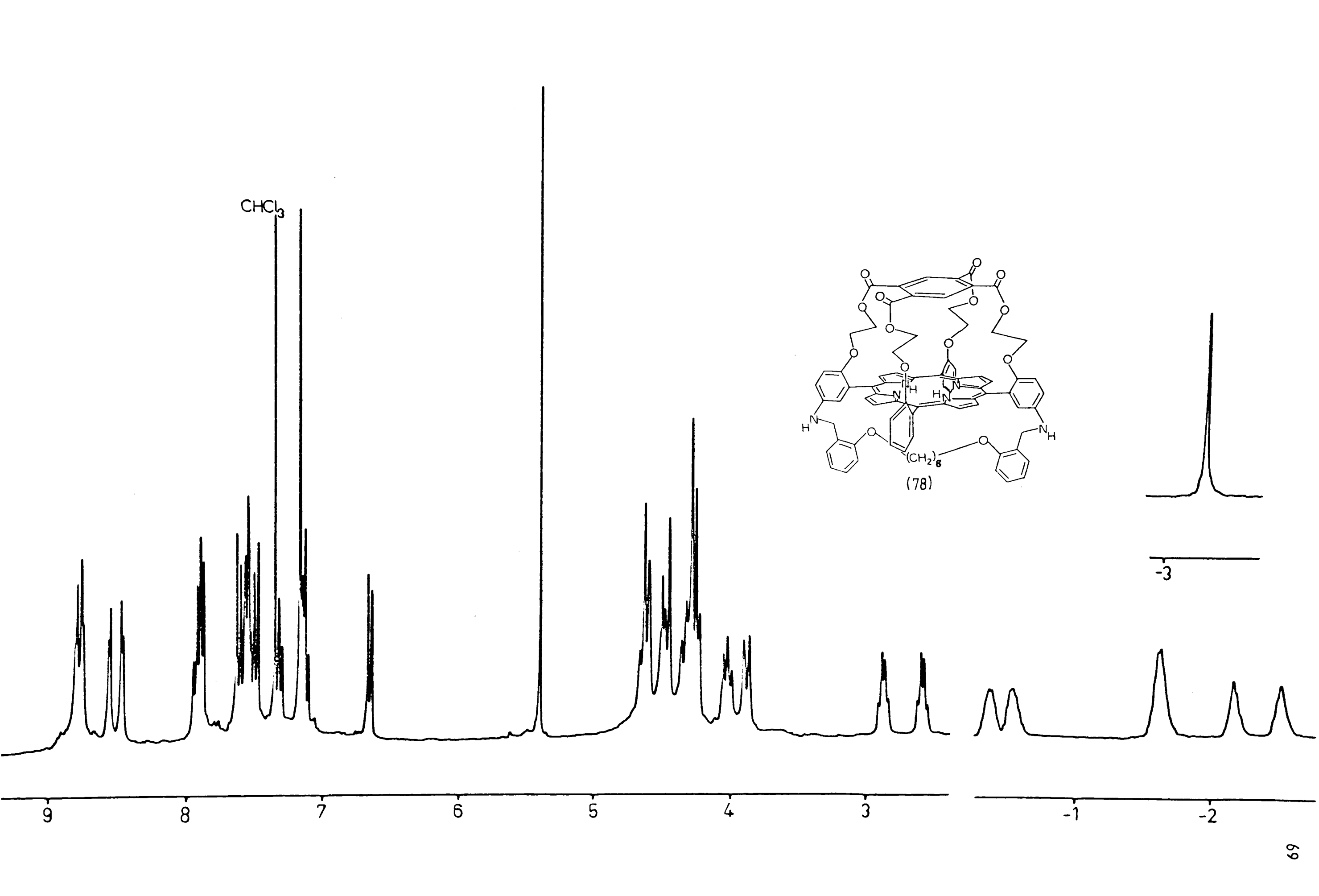
In the p.m.r. spectrum the protons for the methylene next to oxygen appeared at δ4.08 with the rest of the methylene resonances appearing at δ1.4-1.9, (<u>cf</u> C_{12} analogue).

Condensation of bis-aldehyde (74) with bis-amine (31) and reduction <u>in situ</u> gave the desired strapped/capped system (76) in 64% yield. In this case the reduction was left for a

shorter time than in the formation of (75) but studies on production of bis-benzylamine (46) suggested that this did not matter.

The p.m.r. spectrum of the C_8-strapped/capped system (76) showed all the usual features plus a series of highly diamagnetically shifted, diastereotopic, resonances for the strapping methylene chain, (see diagram). The diamagnetic shift was up to 4 ppm and in this case sequential irradiation was used to show that the diamagnetic shift was clearly related to the location of each methylene over the porphyrin.[60]

The results with simple alkylidene-bis-benzaldehydes suggest that formation of a strapped/capped porphyrin is indeed possible *via* cyclic bis-imine formation and that the yields may be very high.


CHCl3
9
8
7
6
5
4
3
-1
-2
-3
(78)

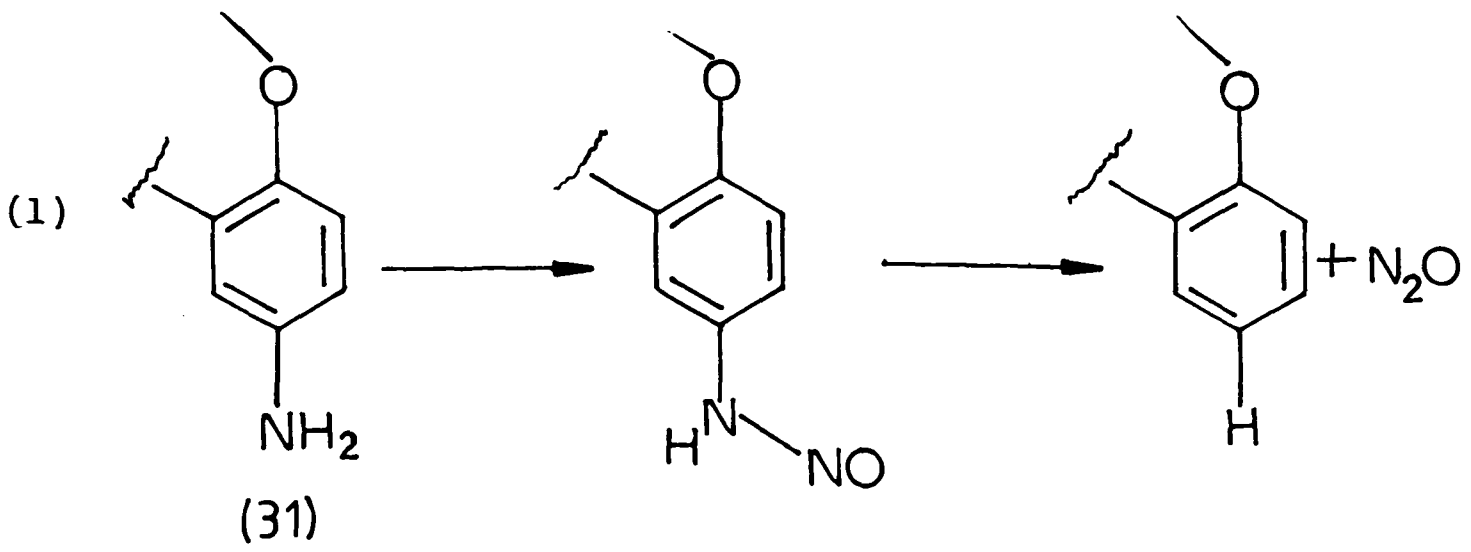
The Nitrosation of Bis-Amino-C_2-Capped Porphyrin (31)

To investigate alternative methods for formation of strap linkages on a capped porphyrin, diazotisation was attempted. This route was chosen to avoid the initial need for a complete synthesis of a new bis-substituted-C_2-capped porphyrin.

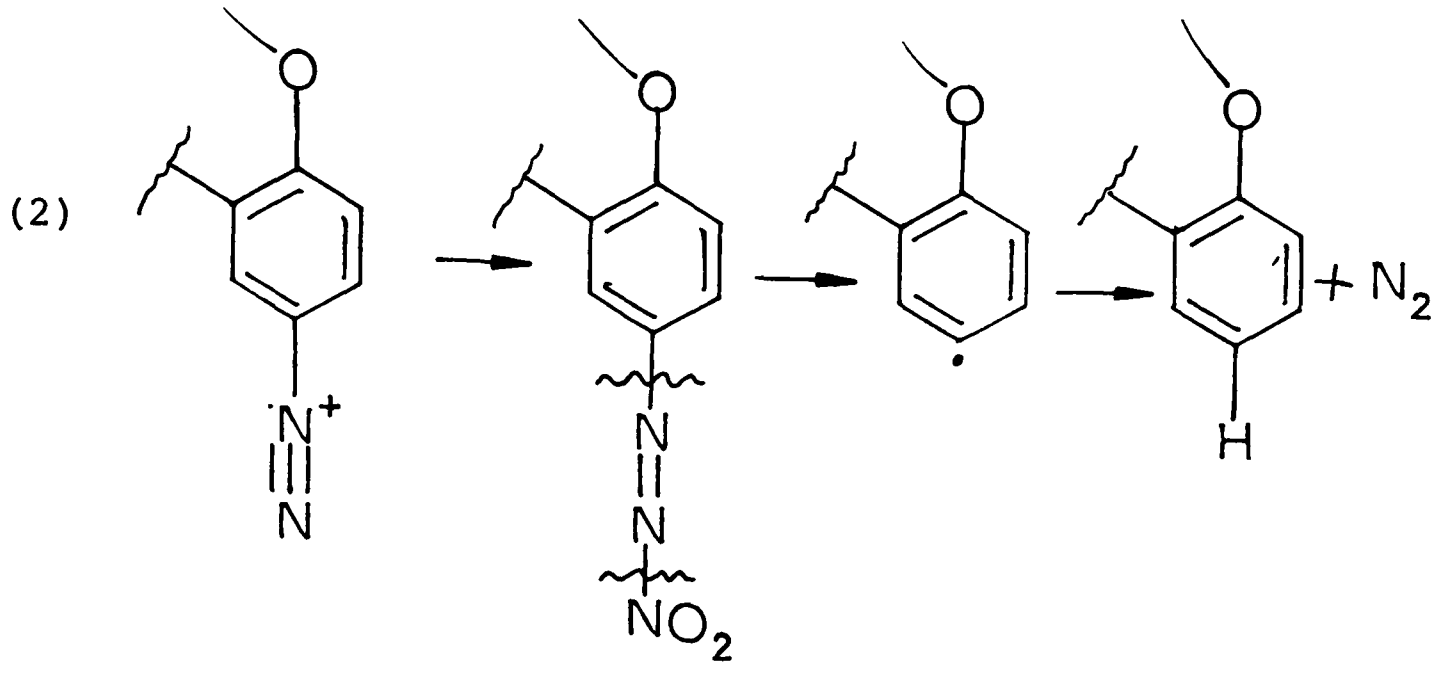
Treatment of the bis-amine (31) with an excess of sodium nitrite in acetic acid gave a fast reaction. The purified product was shown to be C_2-capped porphyrin (23) (identical by t.l.c., m/z, and p.m.r. with an authentic sample). The yield was 55% and mass spectrometry did show a trace of mono acetate, mono deaminated, porphyrin.

The yield of C_2-capped porphyrin (23) seemed to be proportional to the amount of nitrite used. Two possible mechanisms are:

Scheme 26



Scheme 27



To accomplish deamination <u>via</u> the diazonium salt in (2) some other hydrogen source may participate. In this case the amino groups or the porphyrin N<u>H</u> protons may serve this function.

CONCLUSIONS

The original hypothesis, concerning the way in which the ferrous protoporphyrin IX prosthetic group (2) is stabilised towards oxidation in Hb and Mb, has been further substantiated by the properties of the ferrous strapped/capped porphyrin (62).

The results with various "straps" have now defined the "strap size" required to extend across the face of the porphyrin ring in (31) and (46). The studies described can now be extended to the construction of a whole range of strapped/capped porphyrins and should shed further light on the phenomenon of oxygen transport *in vivo*.

EXPERIMENTAL

Melting points (m.p.) were performed on a Kofler hot-stage apparatus, or a Büchi 660 apparatus, and are uncorrected.

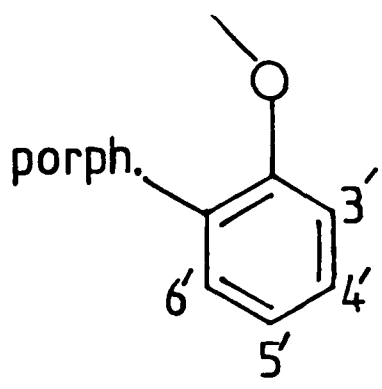
Microanalyses were performed by Dr. F.B. Strauss of the Dyson-Perrins Laboratory.

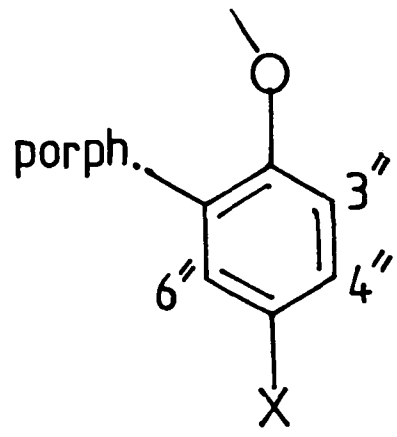
Electronic spectra were measured on a Perkin-Elmer 555 UV-VIS spectrophotometer (characterisation) and a Unicam SP 800A spectrophotometer (routine).

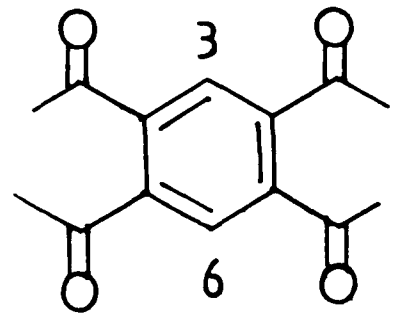
Infrared spectra were recorded on either a Perkin-Elmer 521, a Perkin-Elmer 297, or a Perkin-Elmer 257 spectrophotometer.

Proton nuclear magnetic resonance (p.m.r.) spectra were recorded at 300 MHz using a Bruker WH 300 instrument, and referenced with respect to residual undeuterated solvent. Non-porphyrin routine spectra were recorded at 60 MHz, using Hitachi Perkin-Elmer R24A spectrometers, and referenced with respect to internal or external tetramethylsilane (TMS).

The following diagrams contain the numbering system used for porphyrin spectra.







Mass spectra performed in the Dyson-Perrins Laboratory were recorded on either a VG-ZAB-1F or a VG-16F instrument. The ionisation modes are denoted by the following abbreviations: EI - electron impact; CI - chemical ionisation; FD - field desorption; IBEI - in beam electron impact; DCI - desorption, chemical ionisation.

Preparative and analytical thin layer chromatography (t.l.c.) were carried out on the appropriate layers prepared by Mr. R. Prior of the Dyson-Perrins Laboratory.

Molecular sieves were activated by heating to 200°C in a vacuum (ca. 10mm) for >12h.

Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone ketyl under an inert atmosphere.

N,N-Dimethylformamide (DMF), dimethylsulphoxide (DMSO), tri(n-butyl)amine, and dichloromethane were first distilled from calcium hydride and then further dried by sequential exposure to sieves.

Methanol was dried by treatment with magnesium followed by distillation. Super-dry methanol was obtained by distillation onto freshly activated 3A sieves.

2-Propanol for reduction of bis-amino-C_2-capped porphyrin (31) was dried by treatment with magnesium followed by distillation under argon.

Thionyl chloride was purified by treatment with triphenylphosphite followed by careful distillation.

Organic solutions from aqueous extractions were dried before evaporation using anhydrous sodium sulphate, unless otherwise indicated.

Evaporations were performed *in vacuo* using a Büchi Rotavapor, unless otherwise stated.

Diacid-Diester[36] (33)

Pyromellitic dianhydride (32) (89.95g, 0.4 mol) and 2-(2-hydroxyethoxy)benzaldehyde (19) (132.8g, 0.41 mol) were mixed in pyridine (300 ml) and the mixture heated at reflux for 6h. After cooling the pyridine was evaporated under high vacuum and the resulting brown oil dissolved in acetone (ca. 1 l). Seed crystals of the desired centrosymmetric diacid-diester[36] were added, followed by diethyl ether (300 ml), and the solution placed in a refrigerator at 2°C overnight. The resulting slurry was filtered and the residue washed well with ether. The air dried solid was boiled in chloroform (1l) and allowed to cool. The solution was filtered and the filtrate evaporated to give a solid which was heated at 50°C under high vacuum for 12h. The p.m.r. spectrum of the solid showed it to be ~70% the desired centrosymmetric isomer (33). The solid was recrystallised from glacial acetic acid to give the 1,4 diacid-2,5 diester (33) after high vacuum (12h at 70°C) as a colourless solid (32g, 15%), m.p. 188-191°. δ(d^6DMSO) 4.57, 4.67 (m, 8H, $-CH_2-$), 6.93-7.77 (m, 8H, ArH), 7.98 (s, 2H, H_3, H_6 on central ring), 10.40 (s, 2H, -CHO), identical with authentic material.[36]

Formation of Dinitrotetraaldehyde (29) Using D.C.C.I. (36)[41]

Diacid-diester (33) (11g, 0.02 mol), nitrohydroxyaldehyde[36,38] (35) (10g, 0.047 mol), and 4-N,N-dimethylaminopyridine (37) (750 mg, 0.061 mol) were placed in a dry 250 ml three-necked flask, under argon, fitted with a mechanical stirrer. Dry DMF (20 ml) was added, with vigorous stirring. Omission of stirring led to the formation of a solid mass which was impossible to stir. To this vigorously stirred slurry was added a solution of

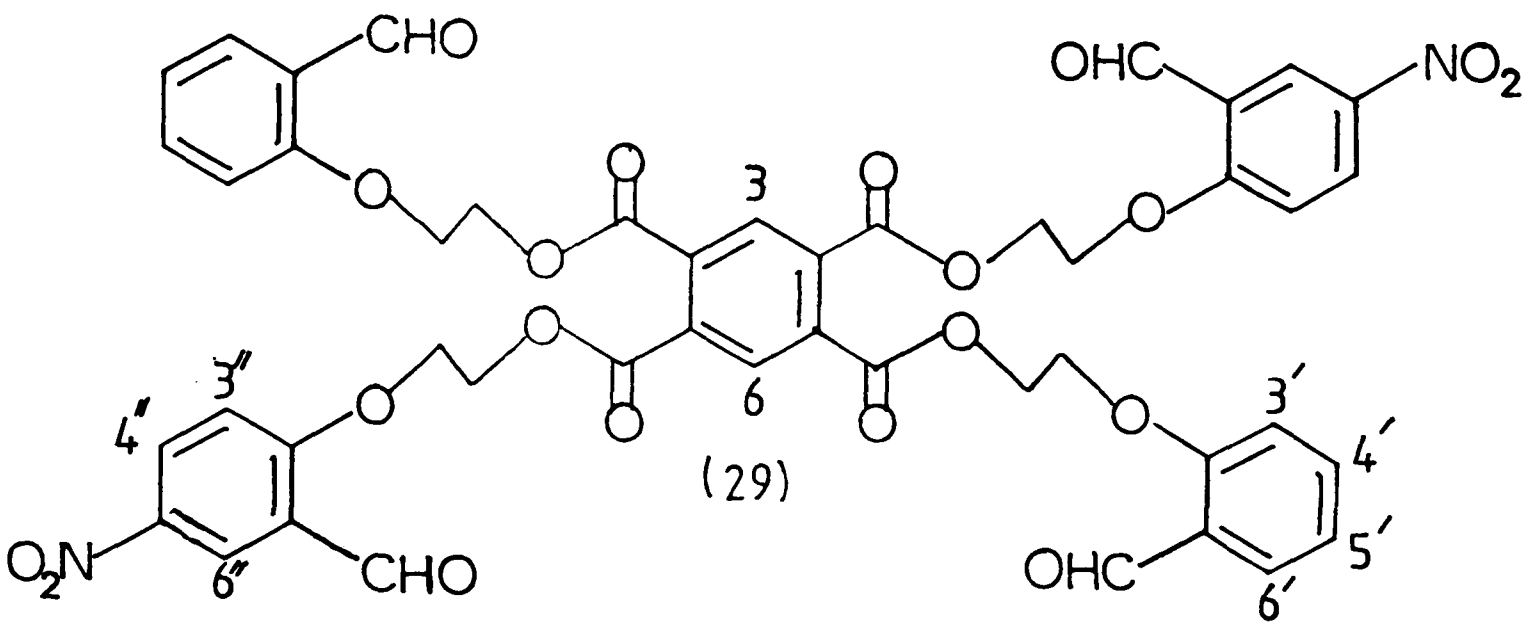
N,N'-dicyclohexylcarbodiimide (D.C.C.I.) (36) (9.2g, 0.044 mol) in dry D.M.F. (5 ml) over a period of 30 min. The DCCI was washed in with more dry DMF (2 ml) and the slurry stirred for a further 16.5h, before being taken from under the inert atmosphere and filtered.

The residue was washed with DMF (10 ml), followed by dichloromethane (50 ml). This left N,N'-dicyclohexylurea (38) (D.C.U.) as a white solid (6.94g, 70%) identical, by infra-red, to an authentic sample. The filtrate was diluted to 80 ml with dichloromethane and the solution washed successively with, 5% hydrochloric acid solution (2 x 150 ml), water (150 ml), 3% aq. sodium bicarbonate solution (2 x 150 ml), and finally water (3 x 150 ml). If necessary sodium chloride was added to clear any emulsion that formed during the last three water washes. After each of the above washes the aqueous and organic layers were filtered to remove further DCU (0.78g, 7.8%). If the above work-up took less than 1h to perform, all the DCU was not removed and, if the work-up took more than 1.5h, tetraaldehyde product was lost.

The organic layer was dried ($MgSO_4$, 2 min), filtered, evaporated *in vacuo* to *ca.* 20 ml, and set aside for crystallisation to occur. By repeated filtration of crystals, re-evaporation to lower volume, and leaving, the dinitrotetraaldehyde (29) was obtained as a white solid (5.59g, 30%). When the liquors were treated with dichloromethane/diethyl ether at boiling point, followed by *slow* evaporation further tetraaldehyde (29) was obtained (0.78g, 4%). M.p. of the above product was 158-162^{o}C; (>95% pure by p.m.r.).

The dinitrotetraaldehyde could be recrystallised from glacial acetic acid or with more difficulty, from acetonitrile.

Two recrystallisations from acetic acid gave the dinitrotetraaldehyde (29) as a white microcrystalline solid m.p. 164.5-167°C which was dried over KOH pellets (36h, 0.1mm). Found: C, 57.84; H, 4.33; N, 2.82. $C_{46}H_{36}N_2O_{20}\cdot C_2H_4O_2$ requires C, 57.84; H, 4.04; N, 2.81%. δ(d^6-DMSO) 4.34-4.88 (m, 16H, $-C\underline{H}_2-$), 7.01 (dJ 7.5Hz, 2H, $H_{3'}$), 7.19 (dJ 8.9 Hz, 2H, $H_{5'}$), 7.44 (dJ 9.3 Hz, 2H, $H_{3''}$), 7.56-7.62 (m, 4H, $H_{4'}$ and $H_{6'}$), 8.09 (s, 2H, H_3 and H_6), 8.31 (dJ 3Hz, 2H, $H_{6''}$), 8.43 (ddJ 9.3 Hz and 2.9 Hz, 2H, $H_{4''}$), 10.28 (s, 4H, $-C\underline{H}O$).



(29)

ν_{max} (nujol) 1730, 1680, 1610, 1600, 1530, 1490, 1460, 1380 and 1350 cm^{-1}.

Attempted O-Alkyl Isourea Formation With the Nitrohydroxy-aldehyde (35)

A mixture of N,N'-dicyclohexylcarbodiimide (36) (200 mg), nitrohydroxyaldehyde (35) (200 mg) and a trace of cupric

chloride (anhydrous) was heated to 50°C and dry DMF (50 µl) added. Thin layer chromatography on silica HF_{254} using dichloromethane/diethyl ether (1:1) indicated the concurrent formation of 4 different products which were not pursued further.

Formation of Dinitrotetraaldehyde (29) Using the Pyridinium Salt Method[42]

1-Methyl-2-chloropyridinium iodide (39) was prepared, by the method of Mukaiyama,[42] as yellow crystals. The compound was kept refrigerated and under desiccation.

Diacid-diester (33) (220 mg, 0.4 mmol), nitrohydroxy-aldehyde (35) (200 mg, 0.95 mmol) and 1-methyl-2-chloropyridinium iodide (39) (250 mg, 1.03 mmol) were placed in a flask under argon. Dry DMF (3 ml) was added with the resultant dissolution of all except the pyridinium salt. On the addition of dry triethylamine (0.5 ml, 3.4 mmol) the salt dissolved and the solution changed colour from orange, through green, to brown. The solution was then heated at 60°C for 24h. After cooling water (15 ml) was added. The water layer was decanted and the residual oil triturated with dichloromethane to give, on standing for 15 min, a solid. The solid was collected by filtration and washed repeatedly first with water and then dichloromethane. Drying gave the dinitrotetraaldehyde (29) as an off-white solid (101 mg, 26.9%). ν_{max} (nujol) was identical to that of authentic tetraaldehyde. It was also homogeneous by t.l.c. (dichloromethane/diethyl ether (1:1) on silica HF_{254} (Rf ≈0.4).

Selective Reduction of Bis-nitro-C_2-Capped Porphyrin (30) to the Diamine (31)

(All of these reactions were protected from light).

(a) Methanol/Palladium-Carbon With Careful Addition of Sodium Borohydride

Bis-nitro-C_2-capped porphyrin (30) (5 mg, 0.0047 mmol) and 10% palladium on carbon (5 mg) were placed in a flask under argon purge. Dry dichloromethane (2 ml), and dry methanol (1.4 ml) were added. The solution was purged with argon for 10 min. The gas flow was then turned down and sodium borohydride added in small portions. After each addition of borohydride the reaction was monitored by t.l.c. on silica GF_{254} using toluene/ethyl acetate (6:4) as eluant. At the end of the reaction ca. 5 mg of borohydride had been added in seven lots over 50 min.

The suspension was filtered through a celite pad under argon pressure and the solvent removed. The resultant brown solid was triturated with dichloromethane and filtered, again through a celite pad under argon pressure, before evaporation. Redissolution in dichloromethane and filtration through cotton wool left, after evaporation, the diamine (31) as a purple iridescent solid (5 mg). Its p.m.r. spectrum showed only one "capping" proton at δ5.4 and one pyrrolic NH proton at δ-3.4. λ_{max} ($CHCl_3$) 422 (A rel=100), 484 (Sh, 15), 517 (82), 547 (19), 594 (21), and 653 (0.8) nm.

(b) 2-Propanol/Palladium-Carbon/Sodium Borohydride

Bis-nitro-C_2-capped porphyrin (30) 25 mg, 0.023 mmol) and 10% palladium on carbon (25 mg) were placed in a flask under

argon purge. Dry dichloromethane and dry 2-propanol (7 ml, distilled from magnesium only, see Discussion) were added. The mixture was purged for 15 min with argon. Sodium borohydride (25 mg, 0.68 mmol) was added and the reaction stirred vigorously under a gentle flow of argon. The reaction was monitored by t.l.c. as in (a). After 55 min, further sodium borohydride (10 mg, 0.27 mmol) was added to ensure completion of reaction. After a total of 85 min the mixture was filtered through a pad of celite, under argon, and the solvent removed. The solid produced was triturated with dichloromethane and filtered through celite under argon pressure. The red solution was evaporated. The resultant solid was dissolved in dichloromethane and filtered through cotton wool. This gave 29.1 mg of solid. The compound after passage through Sephadex LH-20-100 in chloroform and evaporation was used directly in further reactions.

The bis-amino-C_2-capped porphyrin (31) was purified by chromatography on silica G using ethyl acetate/toluene (1:1) as eluant. The major band was extracted from the silica with dichloromethane (or chloroform)/methanol (10:1). The product after evaporation was applied to a Sephadex LH-20-100 column in chloroform. Elution, filtration, and evaporation gave the diamine (31) (17.2 mg, 74%) as a purple iridescent solid. The diamine (31) could also be chromatographed on alumina using toluene/2-propanol (95:5) as eluant. The compound was crystallised from benzene/methanol in the dark using red light illumination to give a pure sample (see spectrum 1).
$\delta(CDCl_3)$ -3.4 (broad s, 2H, $N\underline{H}$), 3.6 (broad s, 4H, $-N\underline{H}_2$), 3.80-4.55 (m, 16H, $-O-C\underline{H}_2-$), 5.42 (s, 2H, cap), 6.95 (dJ2.5Hz, 2H, H_6"), 7.00 (ddJ7.5 and 2.9Hz, 2H, H_4"), 7.3-7.38 (m, 4H, H_3")

and H_5'), 7.49 (dJ8.1Hz, 2H, H_3,), 7.7 (d and t superimposed, 4H, H_4, and H_6,) 8.68, 8.76, 8.81, 8.85 (four dJ4.8Hz, 8H, β-pyrrolic H). m/z (FD) Found 1066·3184 calculated for $C_{62}H_{46}O_{12}N_6$ 1066.3173. λ_{max} (CH_2Cl_2, $\log_{10}\varepsilon$); 404 (shoulder, 4.90), 421 (5.51), 483 (3.48), 515 (4.24), 548 (3.68), 591 (3.74), and 646 (3.38) nm. λ_{max} (CH_2Cl_2) 1732 (CO_2-), 1500, and 1280 cm^{-1}.

Formation of N,N'-Bis (4-Chlorocarbonylbutyl)pyridine-3,5-dicarboxamide (41) and its Reaction in situ with 4-Methoxyaniline

Bis (4-carboxybutyl)pyridine-3,5-dicarboxamide[46] (40) (50 mg, 0.14 mmol) was dissolved in dry DMF (1 ml) under argon and cooled to 0°C in an ice-bath. Thionyl chloride (purified, 22 µl, 0.30 mmol) was added by syringe and the solution allowed to warm to room temperature over 20 min.

p-Anisidine (41 mg, 0.33 mmol) and 4-N,N-dimethylamino-pyridine (37) (67 mg, 0.55 mmol) were added, as solids, into the colourless acid chloride solution. After 10 min a precipitate appeared and the resultant mixture was stirred overnight. Distilled water (20 ml) was added and after 1h the precipitate formed was filtered, washed with dichloromethane (ca. 10 ml), collected, and dried at 50°C under high vacuum. This gave N,N'-bis[4-(p-anisidinocarbonyl)butyl]-3,5-pyridinedicarboxamide[46] (42), as a white solid, (58.5 mg, 74%), δ(d^6-DMSO) identical with that of authentic bis-anilide.[46]

High Dilution Reaction Between N,N'-Bis(4-Chlorocarbonylbutyl)-Pyridine-3,5-Dicarboxamide (41) and Bis-Amino-C_2-Capped Porphyrin (31)

Solution A - Bis-amino-C_2-capped porphyrin (31) (100 mg, 0.09 mmol)

was dissolved in super-dry dichloromethane (20 ml) under argon.

Solution B - N,N'-Bis(4-chlorocarbonylbutyl)pyridine-3,5-dicarboxamide (41) was produced *in situ* from N,N'-bis(4-carboxybutyl)pyridine-3,5-dicarboxamide (40) (53.5 mg, 0.15 mmol), dry DMF (1.3 ml) and thionyl chloride (24 µl) under argon. The solution of acid chloride produced was diluted (after 20 minutes) with super-dry dichloromethane (25 ml), and a 20 ml aliquot withdrawn for the high dilution reaction.

Solutions A and B were driven, over 3h, into super-dry dichloromethane (40 ml), containing 4-N,N-dimethylaminopyridine (37) (80 mg, 0.66 mmol) under argon, in the dark, using a syringe pump. The addition was performed at room temperature. T.l.c. after 4h showed virtually complete consumption of diamine (31).

The reaction was left overnight and then poured onto 3% aq.sodium bicarbonate solution. The resulting slurry was filtered and the precipitate collected. This was washed with both dichloromethane and distilled water. The residue was then collected by dissolution through the filter in DMF to leave behind a small amount of an intractable solid. Evaporation gave a purple iridescent solid which was purified by boiling in turn with chloroform, diethyl ether, and methanol followed by filtration. This gave a purple shiny solid (62 mg, 47.4%) after drying at high vacuum. δ(d^6-DMSO) -3.4 (pyrrolic N$\underline{\underline{H}}$), 1.6 ($CH_2$-C$\underline{\underline{H}}_2$-C$\underline{\underline{H}}_2$-$CH_2$), 2.2 (-C$\underline{\underline{H}}_2$-CO), 3.2 (-C$\underline{\underline{H}}_2$-NH), 3.8-4.6 (-O-C$\underline{\underline{H}}_2$), 5.4 (cap), 7.3-8.2 (Ar$\underline{\underline{H}}$), 8.5-8.9 (β-pyrrolic, Py-CON$\underline{\underline{H}}$, and γ-Py$\underline{\underline{H}}$), 9.0 (α-Py$\underline{\underline{H}}$), 10.05 (CON$\underline{\underline{H}}$Ar). $\underline{m/z}$ (refer to Discussion), (FD)[48] 1395 (v. weak); (fast atom bombardment)[52] 2790 (strong); (^{252}Cf desorption)[51] 2794.1 ± 0.5 a.u.,

4192.3 ± 1 a.u.; (different sample preparation - ^{252}Cf) 2816.7 ± 0.5 a.u., 4212.3 ± 1 a.u. also 3232 and 3204 weak; (^{252}Cf negative ion spectrum) 2792.1 ± 0.5 a.u. Osmotic pressure molecular weight (ΔT method)[50] weight found 6306 (4-4.5 units) (C_2 capped porphyrin M.Wt=1036 standard). Ultracentrifuge,[49] one compound M.Wt = 3985 a.u. (bis-nitro-C_2-capped porphyrin, M. Wt = 1126, standard). λ_{max} (DMF, $\log_{10}\varepsilon$) 419 (5.31), 513 (4.04), 544 (3.61), 589 (3.58), and 646 (3.30) nm.

The filtrate from the high-dilution reaction contained only a very small amount of porphyrin in the dichloromethane layer. This layer was separated, dried, and evaporated. The product was t.l.c.'d and examined by p.m.r., see Discussion for details.

Bis-Benzylamino-C_2-Capped Porphyrin (46)

Bis-amino-C_2-capped porphyrin (31) (150 mg, 0.14 mmol) and a quantity of freshly activated 3A molecular sieves were placed in a flask under argon in the dark. Dry THF (15 ml) and distilled benzaldehyde (34 µl, 0.33 mmol) were added, followed by a small amount of 4-toluenesulphonic acid monohydrate. The mixture was stirred for 2h. T.l.c. on silica G using toluene/ethyl acetate (1:1) showed virtually complete consumption of the primary amine. After 4h, sodium cyanoborohydride (66 mg, 1.05 mmol), ammonium acetate (360 mg, 4.68 mmol), distilled methanol (1.5 ml) and glacial acetic acid (0.5 ml) were added. The mixture was left overnight. The sieves were filtered off, washing well with dichloromethane/methanol, to remove any last traces of adhering porphyrin, and

the solvent removed. The resultant purple solid was partitioned between 3% aq. sodium bicarbonate solution and dichloromethane. The organic layer containing the porphyrin was dried and evaporated. The compound was purified by chromatography on silica G (three 20 x 20 x 0.1 cm) plates using toluene/ethyl acetate (1:1) to elute and dichloromethane/methanol (9:1) to extract the major band (R£ 0.7). Evaporation, filtration in dichloromethane, and re-evaporation gave bis-benzylamino-C_2-capped porphyrin (46) as a purple solid (134.7 mg, 76%) which was used without further purification in the high dilution coupling reactions.

A sample of the above product was subjected to preparative chromatography, in the dark on alumina plates (20 x 20 x 0.1 cm, 10 mg per plate), using toluene/2-propanol (95:2) as eluent and dichloromethane/methanol (9:1) to extract the major band. The product was crystallised from distilled benzene/distilled methanol in the dark, using red light illumination to give a purple solid. $\underline{m/z}$ (FD) found 1246·4119. $C_{76}H_{58}O_{12}N_6$ expects 1246·4112. $\delta(CDCl_3)$-3·32 (br s, 2H, pyrrolic N$\underline{H}$), 3.8-4.6 (m, 22H, -C$\underline{H}_2$-O, Ar-C$\underline{H}_2$-N$\underline{H}$-), 5.40 (s, 2H, cap), 6.97 (dJ3Hz, 2H, $H_{6''}$), 7.05 (ddJ8.8 and 3Hz, 2H, $H_{4''}$), 7.25-7.39 (m, Ph$\underline{H}$ and C$\underline{H}Cl_3$), 7.42 (tJ7.4Hz, 2H, $H_{5'}$), 7.46 (dJ8.5Hz, 2H, $H_{3''}$), 7.54 (dJ8.4Hz, 2H, $H_{3'}$), 7.77-7.82 (m, 4H, H_4, and $H_{6'}$), 8.66, 8.74, 8.79, 8.85 (four dJ4.7Hz, 8H, β-pyrrolic $\underline{H}$). λ_{max} (CH_2Cl_2, $\log_{10}\varepsilon$) 421 (5.41), 480 (Sh, 3.55), 516 (4.25), 548 (3.72), 591 (3.75), and 648 (3.47) nm. ν_{max} (CH_2Cl_2) 1735 cm^{-1}.

Pyridine-3,5-dicarboxaldehyde (53)

This was prepared by the method of Sondheimer[54] in 49.6% yield or by the method of Perlmutter.[61]

3-Carboxypropyltriphenylphosphonium Bromide (52)

Triphenylphosphine (50) (26.2 g, 0.1 mol) and 4-chlorobutanoic acid (51) (12.2g, 0.1 mol) were fused at 140°C for 20h.[53] After allowing to cool, the solid mass was triturated with diethyl ether and filtered. The compound was then dissolved in the minimum amount of boiling acetonitrile/chloroform, filtered, and diethyl ether added to excess. The desired phosphonium salt (52) precipitated as colourless needles. (23.7g, 67.9%) m.p. 232-238°C, lit.[53], 234-240°C. $\delta(CD_3OD)$ 1.88 (sxt J5.5Hz, 2H, $-CH_2-C\underline{H}_2-CH_2$), 2.58 (ddJ5.5 and 1Hz, 2H, $-C\underline{H}_2-CO$), 3.45 (m, 2H, $-C\underline{H}_2-P^+$), 7.8 (m, 15H, Ar$\underline{H}$). ν_{max} (nujol), 2800 (broad), 1710, and 1440 cm^{-1}. (KBr) 1760 and 1710 cm^{-1}.

Before use in the next reaction the compound was dried over phosphorous pentoxide under vacuum.

When the preparation of the above compound was attempted using recrystallisation from ethanol/diethyl ether[53] esterification occurred. Crystallisation of the product from dichloromethane/diethyl ether gave the ethyl ester of 3-carboxytriphenylphosphonium bromide as a colourless solid m.p. 185-187°C. $\delta(CDCl_3)$ 1.25 (t, 3H, $-C\underline{H}_3$), 1.9 ($CH_2-C\underline{H}_2-CH_2+H_2O$), 2.9 (t, 2H, $-C\underline{H}_2-CO$), 4.1 (q and m, 4H, $-C\underline{H}_2-CH_3$ and $C\underline{H}_2-P^+$), 7.6-7.95 (m, 15H, Ar$\underline{H}$). m/z (FD) 377 $(M-Br)^+$. ν_{max} ($CHCl_3$) 2910 and 1725 cm^{-1}.

3,5-Bis(4-Carboxybutyl)pyridine (54)

Sodium hydride (50% dispersion in oil, 345 mg, 7.2 mmol) was placed in a flask under argon (vac./purge x2). Pyridine-3,5-

dicarboxaldehyde (53) (200 mg, 1.5 mmol) and acid phosphonium salt (52) (1.2g, 3.12 mmol) were placed under argon (vac./purge x2) and slurried in a mixture of dry degassed DMF (20 ml) and dry degassed DMSO (11ml). The slurry was transferred onto the dispersion of sodium hydride, by cannula, and washed in with further dry DMSO (5 ml). After 15 min at room temperature the reaction was heated at 50°C, for 28h, under argon. The reaction colour changed from yellow through deep orange-red to dark brown. The solvent was removed in vacuo, after addition of water, and the light yellow residue was triturated with water (50 ml). Filtration gave, as residue, triphenyl-phosphine oxide (851 mg, 98%, after drying) m.p. 151-154°C, lit., 156-157°C.[62] The filtrate, at pH 13, was washed with methylene chloride (3 x 50 ml) and the aqueous layer adjusted to pH<1 with concentrated hydrochloric acid. The pH<1 solution was washed with ethyl acetate (2 x 100 ml) and the pH adjusted to 4.0-4.8. A white cloudy precipitate appeared and was extracted with ethyl acetate (7 x 50 ml). After drying and evaporation, this gave a yellow oily solid (278 mg).

The yellow oily solid was placed under argon (vac./purge) and 10% palladium on carbon (140 mg) was added, followed by distilled, purged, ethanol (30 ml). The mixture was placed under hydrogen and stirred. Further portions of catalyst were added at intervals until hydrogenation was complete. The slurry was filtered through celite, washing well with more ethanol. Removal of the solvent gave an oil which solidified overnight in the freezer. This solid was dissolved in ethyl acetate/ methanol (2:1, 10 ml) and excess petrol (40-60°C) was added. Leaving in the fridge, then freezer, gave 3,5-bis(4-carboxybutyl)-pyridine (54) as off-white hygroscopic needles (166.2 mg, 40.2%).

After passage down an ion-exchange column (Dowex AG-IX8-400) and recrystallisation from ethyl acetate, with the addition of charcoal, the bis acid (54) was obtained as colourless needles m.p. 128-131°C. Found: C, 64.40; H, 7.51; N, 4.98. $C_{15}H_{21}NO_4$ requires C, 64.49; H, 7.58; N, 5.01%. $\delta(CD_3OD)$ 1.67 (m, 8H, $-CH_2-C\underline{H}_2-CH_2$), 2.33 (t, 4H, $-C\underline{H}_2-CO$), 2.67 (t, 4H, $-C\underline{H}_2-Py$), 7.59 (1H, γ-Py$\underline{H}$), 8.22 (2H, α-Py$\underline{H}$); the p.m.r. was found to be pH dependent with the signal for the α-pyridine protons sharpest at high pH. ν_{max} (nujol) 3100 (v. broad), 1727 (CO_2H), 1670, 1595, 1460, 1405, 1377, 1227, and 1173 cm^{-1}; (KBr) 3100, 1726, 1675, 1590, 1460, 1400, 1360, 1223 and 1170 cm^{-1}. m/z (EI) 279 (M^+, 10%), 206 (100); (ammonia CI) 280 [$(M+H)^+$, 100%], 206 (45).

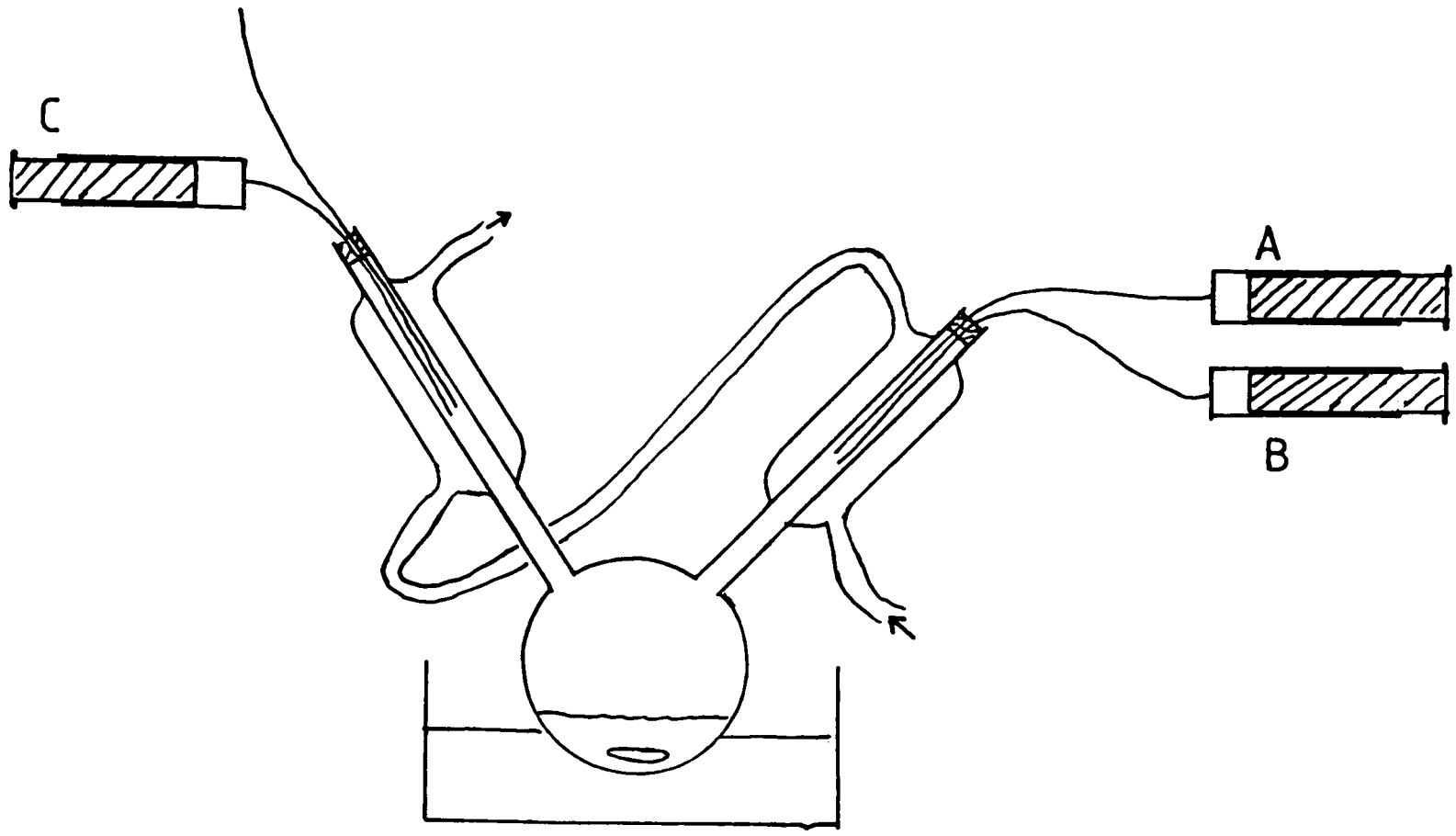
Reaction of Bis-Benzylamino-C_2-Capped Porphyrin (46) With 3,5-Bis(4-Carboxybutyl)Pyridine (54) Using 1-Methyl,2-Chloro-Pyridinium Iodide (39), Under High-Dilution Conditions

Solution A: Bis-benzylamino-C_2-capped porphyrin (46) (124 mg, 0.1 mmol) was dissolved in super-dry dichloromethane (40 ml), under argon, and dry tri-(n-butyl)amine (125 µl, 0.53 mmol) was added.

Solution B: 3,5-Bis(4-carboxybutyl)pyridine (54) (28 mg, 0.101 mmol) was dissolved in dry DMF (2ml), under argon and super-dry dichloromethane (38 ml) was added.

Solution C: 1-methyl,2-chloropyridinium iodide (39)(64 mg, 0.25 mmol) was dissolved in dry DMF (6 ml) under argon.

Solutions A, B and C were driven over 5h, into super-dry dichloromethane (40 ml) heated at reflux under argon, in the dark (see diagram over).



The reaction was heated at reflux overnight and allowed to cool. The solvent was removed *in vacuo* and the resulting solid partitioned between dichloromethane (50 ml) and 3% aq. sodium bicarbonate solution (50 ml). The porphyrin containing organic layer was separated, washed with distilled water (50 ml x 2), dried, and the solvent removed *in vacuo*. (The sodium sulphate drying agent was washed with ethyl acetate to recover all porphyrin possible).

The crude solid product was purified by preparative t.l.c. on silica G (three 20 x 20 x 0.1 cm) plates using dichloromethane/methanol (95:5) as eluant, (one double development). The band corresponding to the desired C_2-cap/C_4-strap (*55*) (by comparison with an authentic sample[38]) was extracted using dichloromethane/methanol (9:1). The porphyrin was re-chromatographed on silica G to give a product that still contained impurities (p.m.r.). Flash chromatography[63] did not remove the impurities.

Separation of the minor impurity was achieved using silica blend 41 plates (two 20 x 20 x 0.1 cm) using ethyl acetate/ethanol (9:1) as eluant, and dichloromethane/methanol (9:1) to extract the major band. This gave the C_2-capped and C_4-strapped porphyrin (55) (8.9 mg, 5.1%), clean by p.m.r. spectroscopy, identical with that produced by Dagley.[38] m/z (DCI) 1489 $(M+H)^+$. λ_{max} (CH_2Cl_2, $\log_{10}\varepsilon$) 353 (shoulder, 4.23), 370 (4.30), 421 (5.58), 483 (shoulder, 4.09), 515 (4.24), 548 (3.68), 591 (3.73), and 647 (3.31) nm. ν_{max} ($CHCl_3$) 1732 (broad) (CO_2^-), 1645 (broad) CON, and 1495 cm^{-1}. δ($CDCl_3$) -3.4 (broad s, 2H, NH), 0.5 (diastereotopic m, 4H, $-CH_2-CH_2-Py$), 0.92 (diastereotopic m, 4H, $-CH_2-Py$), 1.25 (quintet, 4H, $-CH_2-CH_2-CO$), 2.25 (t, 4H, $-CH-CO$), 3.70-4.75 (m, 17H, $O-CH-CH-O$ and γ-PyH), 5.12 (diastereotopic AB, 4H, $-CH_2-Ph$), 5.31 (s, 2H, cap), 6.87 (dJ2Hz, 2H, $H_{6''}$), 7.23-7.35 (m, $H_{3'}$, Ph H and $CHCl_3$), 7.39 (tdJ8 and 1Hz, 2H, $H_{5'}$), 7.50 (ddJ8 and 1Hz, 2H, $H_{6'}$), 7.53 (ddJ8 and 2Hz, 2H, $H_{4''}$), 7.65 (dJ8.8Hz, 2H, $H_{3''}$), 7.79 (tdJ8 and 1Hz, 2H, $H_{4'}$), 8.45, 8.49, 8.61, 8.66, (four dJ4.5Hz, β-pyrrolic H). The aromatic resonances were assigned precisely using 2-dimensional p.m.r. spectroscopy (see Appendix 1 and Discussion). δ(CD_2Cl_2) similar to above except 5.1 (singlet, 4H, CH_2-Ph), 6.73 (broad s, 2H, αPy-H).

Reaction Between Bis-Benzylamino-C_2-Capped Porphyrin (46) and 1,10 Decanedicarboxylic Acid (56) Using 1-Methyl 2-Chloro-pyridinium Iodide (39) Under High Dilution Conditions

Solution A: Bis-benzylamino-C_2-capped porphyrin (46) (20 mg, 0.016 mmol) was dissolved in super-dry dichloromethane (10 ml), under argon, and dry tri-(n-butyl)amine (26 µl, 0.11 mmol) was

added.

Solution B: 1,10-Decanedicarboxylic acid (56), (3.7 mg, 0.016 mmol) was dissolved in dry DMF (1 ml), under argon, and super-dry dichloromethane (9 ml) was added.

Solution C: 1-Methyl 2-chloropyridinium iodide (39) (12.5 mg, 0.049 mmol) was dissolved in dry DMF (2 ml) under argon.

Solutions A, B and C were driven into super-dry dichloromethane (20 ml) at reflux as before, over 4h, under argon, in the dark. The reaction was left at reflux overnight, cooled and then the solvent was removed in vacuo. The residue was partitioned between 3% aq. sodium bicarbonate solution and dichloromethane. The organic layer was dried, evaporated, and the residue was purified by preparative t.l.c. on silica G (two 20 x 20 x 0.1 cm) plates, eluted with toluene/ethyl acetate (1:1). Each of the various products (including base-line) separated was extracted with dichloromethane/methanol (9:1) and examined by p.m.r. spectroscopy. The band at Rf = 0.9 was unreacted bis-benzylamine (46) (1.7 mg, 7%). The band at Rf. 0.7 (3.8 mg, 16% crude) was the only one to give upfield shifted resonances of the strapping chain in p.m.r. $\delta(CDCl_3)$ -3.44, -1.25, -0.88, and -0.13. The sample was still impure. m/z (FD) 1440 (M^+).

3,5-Bis(5-Carboxypentyl)pyridine (59)

3,5-Pyridinedicarboxaldehyde (53) (500 mg, 3.7 mmol) and 4-carboxybutyltriphenylphosphonium bromide (58) (3.5 g, 7.9 mmol) were dissolved in a mixture of dry degassed DMSO (25 ml) and dry degassed DMF (20 ml). This solution was transferred onto sodium hydride (50% dispersion in oil, 775 mg, 16.1 mmol),

under argon, using a cannula. The aldehyde and phosphonium salt were washed in with further dry DMSO (15 ml) and dry DMF (10 ml). The reaction turned from yellow through orange-red to brown on heating to 60°C for 48h.

The reaction was allowed to cool and, after quenching the reaction with water, the solvent was removed. Heat was employed in conjunction with high vacuum to remove last traces of DMSO. The solid left, was triturated with water (~150 ml) and filtered to give, as residue, triphenylphosphine oxide (2g, 91%). The filtrate pH>10 was washed with dichloromethane (3 x 150 ml) and the pH adjusted to <1.0 with concentrated hydrochloric acid. The acid solution was washed with ethyl acetate (2 x 150 ml). The pH of the aqueous layer was then adjusted to the range 4.0 to 4.8 and exhaustive extraction carried out with ethyl acetate (6 x 150 ml) varying the pH in the above range. The combined ethyl acetate extracts were dried and the solvent removed in vacuo to give an oil (540 mg).

The oil was dissolved in a suspension of 10% palladium/carbon (290 mg) in distilled degassed ethanol (60 ml) and put under an atmosphere of hydrogen. Hydrogenation was carried out over 24h, uptake being 60 ml. The crude mixture was passed down celite and the solvent removed in vacuo to give a brown oil. The oil was extracted with boiling ethyl acetate (~100 ml) and the ethyl acetate solution boiled down till cloudy. An oil separated which crystallised overnight in the fridge. The solid was collected, and after drying (359 mg, 31.5%) was used as such in high dilution reactions. A portion of the product was applied to a column of Dowex anion exchange resin (1 x 8 - 400) in methanol and washed with distilled water (100 ml). Elution with glacial acetic acid gave an almost colourless oil which was

crystallised from freshly distilled ethyl acetate (charcoal) to give bis-3,5-(5-carboxypentyl)pyridine (59) as a colourless amorphous solid m.p. 89.5-94°C. Found: C, 66.05; H, 8.34; N, 4.96. $C_{17}H_{25}NO_4$ requires: C, 66.42; H, 8.20; N, 4.56%. δ(CD_3OD) 1.39 (m, 4H, γ-CH_2), 1.65 (m, 8H, δ-CH_2 and β-CH_2), 2.29 (mtJ6.5Hz, 4H, CH_2-CO), 2.66 (mtJ6.5Hz, 4H, CH_2-Py), 7.57 (m, 1H, γ-Py H), 8.20 (m, 2H, α-PyH). m/z (EI) 307 (M^+, 15%), 220 (100%); ammonia (CI) 308 [$(M+H)^+$, 100%], 220 (50%). ν_{max} (nujol) 2400-3300 (v. broad), 1720 (broad); (KBr) 2500-3400, (v. broad), 1730 (broad) cm^{-1}.

Reaction of Bis-Benzylamino-C_2-Capped Porphyrin (46) and 3,5-Bis-(5 carboxypentyl)Pyridine (59) Using 1-Methyl-2-Chloropyridinium Iodide (39)

Solution A: Bis-benzylamino-C_2-capped porphyrin (46) (101 mg, 0.081 mmol) and dry tri-(n-butyl)amine (117 µl) were dissolved in dry dichloromethane (20 ml) under argon.

Solution B: 3,5-Bis(5-carboxypentyl)pyridine (59) (26 mg, 0.085 mmol) was dissolved in dry DMF (5 ml) and dry dichloromethane (15 ml) was added under argon.

Solution C: 1-Methyl-2-chloropyridinium iodide (39) (63 mg, 0.25 mmol) was dissolved in dry DMF (7 ml) under argon.

Solutions A, B and C were driven into dry dichloromethane (80 ml), at reflux, over 5h under argon in the dark. The mixture was left at reflux overnight and the solvent then removed in vacuo.

The resulting solid was partitioned between dichloromethane (50 ml) and 3% aq. sodium bicarbonate solution (50 ml). The organic layer was separated and the aqueous phase extracted

twice more with dichloromethane (20 ml). The combined organic extracts were dried and evaporated *in vacuo*.

Preparative t.l.c. was carried out on silica G (four plates, 20 x 20 x 0.1 cm) using ethyl acetate/ethanol (9:1) to elute and dichloromethane/methanol (9:1) to extract the band Rf 0.6. This product still contained tri-(*n*-butyl)amine and was precipitated from distilled dichloromethane with petrol. This gave the C_5-strapped/C_2-capped porphyrin (60) as a purple solid (31 mg, 25%) with only trace impurities left by p.m.r. *m/z* (IBEI) 1517/8 (M^+), 1473/4, 1446/7, 1273, 1246/7, 1229, 1203, 1185. ν_{max} ($CHCl_3$) 1735 ($-CO_2-$), 1645 broad (CON<), and 1495 cm^{-1}. λ_{max} (CH_2Cl_2, $\log_{10}\varepsilon$) 370 (4.32), 419 (5.56), 483 (3.48), 514 (4.24), 546 (3.68), 590 (3.73), and 646 (3.36) nm. $\delta(CDCl_3)$ -3.4 (br s, 2H, NH), 0.6 (broad, 4H, strap), 0.89 (broad, 4H, strap), 1.37 (broad, 4H, strap), 1.68 (broad, 4H, strap), 2.33 (broad, 4H, $-CH_2-CO$), 3.80-4.68 (m, 17H, $-O-CH_2-CH_2-O$ and γPy-H), 5.0 (broad, 4H, $-CH_2-Ph$), 5.38 (sharp s, 2H, cap), 6.89 (dJ2.5Hz, 2H, $H_{6"}$), 7.10-7.57 (m, $H_{3"}$, $H_{4"}$, $H_{3'}$, $H_{5'}$, PhH and $CHCl_3$), 7.63 (dJ8.5Hz, 2H, $H_{6'}$), 7.76 (broad t, 2H, $H_{4'}$), 7.89 (dJ2Hz, 2H, α-PyH), 8.39, 8.49, 8.64, 8.72 (four dJ4.5Hz, 8H, βpyrrolicH). $\delta(CD_2Cl_2)$ similar except 7.75 (d, 2H, α-PyH) and δ4.7 (broad, 1H, γ-PyH) (signals connected by irradiation). $\delta(d^8$ toluene) same as in $CDCl_3$ except 5.63 (sharp s, 2H, cap), 6.9-7.13 (m, ArylH plus toluene), 7.18 (ddJ8 and 2.5Hz, 2H), 7.25 (dJ2.5Hz, 2H, $H_{6"}$), 7.36 (ddJ7.5 and 1.5 Hz, 2H0, 7.46 (d and t superimposed J8Hz, 4H, $H_{4'}$, $H_{6'}$), 7.82 (dJ1.5Hz, α-PyH), 8.44, 8.50, 8.70, 8.71 (four dJ4.5Hz, 8H, β-pyrrolic H).

C_5-Strapped/C_2-Capped Porphyrin Ferric Chloro Complex·Hydrochloride (61)

C_5-strapped/C_2-capped porphyrin (60) (16.1 mg, 0.011 mmol) and ferrous chloride (200 mg, 1.732 mmol) were placed under argon. Dry degassed THF (15 ml) was added and the mixture heated at reflux for 64h. After cooling and removal of solvent, the residue was partitioned between dichloromethane (ca. 15 ml) and 5% aq. hydrochloric acid solution (ca. 15 ml). The organic layer was separated, dried (calcium chloride), and evaporated. The yellow residue was subjected to preparative t.l.c. on four silica G plates (20 x 20 x 0.1 cm) with kieselguhr strip using ethyl acetate/ethanol (9:1) to elute and dichloromethane/methanol (9:1) to extract the major band (Rf 0.2). The residue, after filtration, evaporation of solvent, and filtration in dichloromethane, was re-evaporated to give 12.9 mg (74%) of the desired C_5-strap/C_2-cap ferric complex. The compound was crystallised from distilled chloroform and distilled hexane, then treated in distilled chloroform with gaseous hydrogen chloride to give the ferric chloride·hydrochloride (61). m/z (IBEI) 1569 9% (calculated percentage = 5.6), 1570 9% (6.2), 1571 94% (95.3), 1572 100% (100), 1573 50% (55.6), 1574 19% (21.5), 1575 6% (6.4). λ_{max} ($CHCl_3$, $\log_{10}\varepsilon$), 380 (3.72), 424 (4.00), 512 (3.1), 585 (2.54), 656 (2.48) and 684 (2.47) nm. λ_{max} (toluene) 509, 582, 652 and 680 nm.

Ferrous C_5-Strapped/C_2-Capped Porphyrin (62)

Ferric chloro complex · hydrochloride (61), as a suspension in toluene, was treated with degassed 3% aq. sodium bicarbonate solution containing 0.1M aq. sodium dithionite. The two phase

system was stirred vigorously, and a colour change from brown-yellow to claret red was observed. The porphyrin gradually dissolved in the toluene layer. After 1h the toluene layer was separated by syringe and the red solution examined spectroscopically. λ_{max} (toluene), 436, 537, 565 (shoulder), 610 (shoulder) and 650 (shoulder) nm (See Discussion). λ_{max} (CH_2Cl_2) 538, 560 (shoulder), and 610 nm.

For anhydrous conditions the aqueous layer after reduction was frozen (dry ice/acetone) and the toluene layer removed by syringe under argon. The toluene was evaporated using high vacuum to give the solid ferrous complex (62).

Behaviour of Ferrous C_5-Strapped/C_2-Capped Porphyrin (62) With Air and Oxygen in the Presence of Water

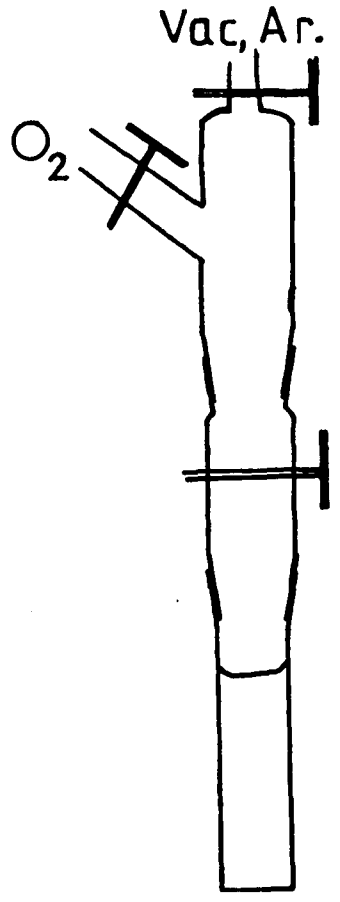
Exposure of a wet solution of ferrous complex (62) to the atmosphere gave no change in the visible spectrum. Bubbling air through the solution resulted in a slight change in the spectrum to λ_{max} 538.5, 610 (shoulder), and 650 (shoulder). This solution was shaken with two portions of 3% aqueous sodium bicarbonate solution in the air, the organic layer separated and re-examined; λ_{max} was 538.5 nm as before but the spectrum was broader and wavelength maximum less well defined [1] (see diagram). This solution after 17h exposure to wet air [2] still showed a slight maximum at λ_{max} 538 nm.

Bubbling oxygen through a fresh solution of ferrous complex (62) in wet toluene resulted in a change of spectrum to λ_{max} 542, 610 (shoulder), and 650 (shoulder) nm. Bubbling argon through then reverted the spectrum to that of deoxy complex (62).

Behaviour of Ferrous C_5-Strapped/C_2-Capped Porphyrin (62) With Oxygen

A dry toluene solution of ferrous complex (62) was exposed to dry oxygen by freeze thaw to give a new species λ_{max} (toluene) 436, 542, 610 (shoulder) and 650 (slight shoulder) nm (see diagram in Discussion). In dichloromethane a similar change occurred on exposure to oxygen. λ_{max} (CH_2Cl_2) 540 and 610 (shoulder) nm. In both solvents replacement of oxygen by argon restored the spectrum of ferrous complex (62).

For the observation of the behaviour of the ferrous complex under oxygen over a period of time the following apparatus was used.



In dry dichloromethane a change was observed from the spectrum for oxygen complex (63) to a spectrum λ_{max} (CH_2Cl_2) 509, 540 (shoulder), and 580 nm at room temperature. Correcting for solvent loss, tracings were taken of the spectral changes (see Discussion) to give a good isosbestic point. A qualitative estimate of half-life was >40h, taken from the decrease in absorbance at 540 nm and increase in absorbance at 510 nm.

The product was treated with 3% aq. sodium bicarbonate solution containing 0.1M aq. sodium dithionite to give a species λ_{max} (toluene) 538, 562 (slight shoulder), and 610 (shoulder) nm. On the addition of oxygen a spectral change occurred to λ_{max} 542 and 610 (shoulder) nm. Bubbling argon through the solution then regenerated the spectrum before, with λ_{max} 538 nm.

When left in dry toluene under oxygen a sample of the oxy-complex (62) decayed to a new species λ_{max} (toluene) 504, 570, and 620 (slight shoulder) nm. The half-life, based on loss of absorbance at 540 nm (to constant spectrum), was estimated at >100h.

Treatment of the above solution with 3% aq. sodium bicarbonate solution containing 0.1M aq. sodium dithionite regenerated ferrous complex (62) λ_{max} (wet toluene) 538, 562 (slight shoulder), 610 (shoulder) and 650 (shoulder) nm. This sample also bound oxygen reversibly.

Carbonyl Complex of Ferrous C_5-Strapped/C_2-Capped Porphyrin (64)

Some ferrous C_5-strapped/C_2-capped porphyrin (62) was allowed to decay under oxygen in toluene and then re-reduced to

the ferrous state, using 0.1M aq. sodium dithionite, in 3% aq. sodium bicarbonate solution. The aqueous layer was frozen, the toluene layer separated, and the solvent removed. The solid ferrous porphyrin (62) was dissolved in d^8-toluene under carbon monoxide to give a deep red solution. δ(d^8-toluene) 0-2 impurity + strap, 1.5 (dJ1.8Hz, 2Py-H), 2.5 (diastereotopic m, 4H, CH_2-CO), 3.5-4.0 (m, 16H, -O-CH_2-CH_2-O), 4.83 (broad t, 1H, γPy-H), 5.25 (AB diastereotopic, 4H, -CH_2-Ph), 6.53 (s, 2H, cap) 6.78-7.2 (m, ArH plus toluene), 7.24 (m, 6H, ArH), 7.40 (m, 6H, ArH), 7.68 (ddJ7.5 and 2.5Hz, 2H), 7.83 (dJ2.5Hz), 2H, $H_{6''}$), 8.50, 8.52, 8.61, 8.64 (four dJ4.5Hz, 8H, βpyrrolic H). λ_{max} (toluene) 422, 540, 580 (shoulder), and 650 nm (see diagram in Discussion). ν_{max} 2930, 2005 (C≡O), 1740 (CO_2-), 1735 (CO_2-), 1650, and 1495 cm^{-1}.

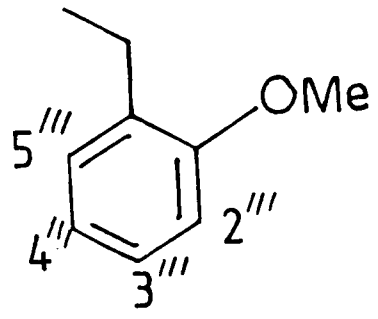
Bubbling argon or oxygen through a solution of the carbonyl complex (64) did not produce any spectral change.

Condensation of Bis-amino-C_2-Capped Porphyrin (31) and 2-Methoxybenzaldehyde

Bis-amino-C_2-capped porphyrin (10 mg, 0.01 mmol) and 2-methoxybenzaldehyde (6 mg, 0.04 mmol) were heated in refluxing benzene (15 ml) with a trace of 4-toluenesulphonic acid under nitrogen. Water was removed using a calcium chloride filled Dean-Stark trap. After 3h the reaction was allowed to cool. T.l.c. on silica G using ethyl acetate/toluene (4:6) showed the presence of two reaction products. Reflux was continued for 3h but no further reaction appeared to occur by t.l.c.

The solvent was removed and the residue dissolved in dry

THF (10 ml). Sodium borohydride (10 mg, 0.27 mmol) was added but after 1h no observable change in t.l.c. could be seen. The solvent was removed in vacuo and the solid subjected to preparative t.l.c. on silica G using toluene/ethyl acetate (1:1) to elute and dichloromethane/ethyl acetate (1:1) to extract the porphyrin products. The band at highest Rf (≃0.5) was passed down a column (20 x 2 cm) of Sephadex LH-20-100 in chloroform, and filtered to give, after evaporation, a purple solid (5.8 mg). $\delta(CDCl_3)$ -3.33 (br s, NH), 3.73 (s, O-CH_3), 3.6-4.7 (m, O-CH_2 and CH_2-NH-), 5.40 (s, cap), 6.83 (d, $H_{2'''}$), 6.95 (t, $H_{4'''}$), 7.01 (d, $H_{6''}$), 7.10 (d, $H_{4''}$), 7.18-7.50 (m, ArH plus $CHCl_3$), 7.57 (d, $H_{3'}$), 7.77 (m, $H_{4'}$ and $H_{6'}$), 8.67, 8.75, 8.78, 8.86 (four d, β-pyrrolic H).



ν_{max} ($CHCl_3$) 1720 cm^{-1}. m/z (FD) 1302-1306.

3,5-Bis(chloromethyl)pyridine (67)

This compound was prepared according to the method of Sondheimer[54]. The product was not crystallised before use, m.p. 80-84°C lit.,[54] 84-86°C. $\delta(CDCl_3)$ 4.58 (s, 4H, $-CH_2$), 7.73 (t, 1H, γ-PyH), 8.51 (d, 2H, α-PyH).

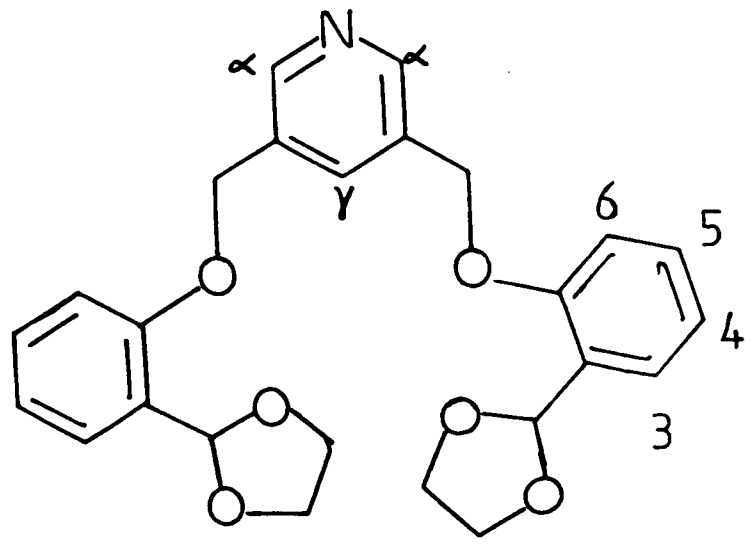
2-(2-Hydroxyphenyl)1,3-Dioxolan (66)

This was prepared by the method of Dyer[57] in 37.5%. $\delta(CDCl_3)$ 4.00 (s, 4H, $-C\underline{H}_2-$) 5.86 (s, 1H, $ArC\underline{H}O_2$), 6.67-7.49 (m, 4H, Aryl$\underline{H}$), 7.67 (broad s, 1H, exchanges D_2O, $-O\underline{H}$).

3,5-Bis[2-(1,3 Dioxolanyl)phenoxymethyl]pyridine (69)

To sodium hydride (60 mg, 1.3 mmol, 50% dispersion in oil) suspended in dry DMF (3 ml) under nitrogen, was added 2-(2-hydroxyphenyl)1,3-dioxolan (66) (175 mg, 1.05 mmol). The mixture was then left overnight. 3,5-Bischloromethylpyridine (67) (100 mg, 0.56 mmol) was added and the brown mixture heated on an oil bath at between 50 and 70°C for 22h. The solvent was removed in vacuo and the residue partitioned between 1M aq. sodium hydroxide solution (100 ml) and dichloromethane (200 ml). The organic layer was washed with more aq. sodium hydroxide (100 ml) and water (100 ml, pH = 7). Drying and removal of solvent gave a yellow oil which was washed with petroleum ether (40-60°C, 2 x 50 ml) before being placed under high vacuum. The resulting oil was then extracted with boiling diethyl ether (100 ml) and the solution boiled down to 10 ml. Petroleum ether (30-40°C) was added at boiling point until the solution was just cloudy and the crystallising mixture placed in the fridge. This gave colourless crystals of the desired bis-acetal (69) (144.4 mg, 58%), m.p. 64-68°C. This product could be further crystallised from diethyl ether/petrol (30-40°C) to give colourless needles m.p. 68-69°C. Found: C, 69.23; H, 5.86; N, 3.33. $C_{25}H_{25}O_6N$ requires C, 68.95; H, 5.79; N, 3.22%. $\delta(CDCl_3)$ 4.0 (m, 8H, $O-C\underline{H}_2-C\underline{H}_2-O$), 5.18 (s, 4H, $-C\underline{H}_2-Py$), 6.21 (s, 2H, $ArC\underline{H}O_2$), 6.96 (dJ8.4Hz, 2H, H_6), 7.03

(tJ7.5Hz, 2H, H_4), 7.33 (t J7.7 and 1.8Hz, 2H, H_5), 7.58 (ddJ1.8 and 7.7Hz, 2H, H_3), 7.91 (broad s, 1H, γ-PyH), 8.69 (dJ1.5Hz, 2H, α-PyH).



m/z (field ionization) 435 $(M)^+$; 436 $(M+H)^+$; (EI) 435 (7%), 390 (25), 269 (50), 198 (25), 164 (100), 106 (50), 105 (40), 73 (80).

Bis 3,5-(2-Formylphenoxymethyl)Pyridine (68)

(a) Bis-acetal (69) (50 mg, 0.11 mmol) was dissolved in dichloromethane (ca. 2ml) and distilled water (ca. 2 ml) added. Concentrated hydrochloric acid was added to pH 1.0-1.5 and the mixture magnetically stirred for 2.75h. The pH was adjusted to 7.5-8.5 by the addition of 3% aqueous sodium bicarbonate solution and more dichloromethane was added. The organic layer was separated, the aqueous layer extracted with further dichloromethane (50 ml), and the combined organic fractions dried and evaporated.

The white solid produced was crystallised from dichloromethane/diethyl ether to give colourless needles (35 mg, 87.8%), m.p. 146.5-149°C. Found: C, 72.46; H, 4.78; N, 3.92. $C_{21}H_{17}O_4N$ requires C, 72.61; H, 4.93; N, 4.03%. ν_{max} ($CHCl_3$)

1690, 1600 (sharp), 1485, 1460 and 1290 cm^{-1}. $\delta(CDCl_3)$ 5.26 (s, 4H, $-C\underline{H}_2-$), 7.05-7.12 (dJ7.5Hz, 2H, H_6, tJ7.5Hz, 2H, H_4) 7.54-7.60 (tdJ7.5 and 2Hz, 2H, H_5), 7.88 (ddJ8.0 and 2Hz, 2H, H_3), 7.94 (broad s, 1H, γ-Py$\underline{H}$), 8.72 (broad signal, 2H, α-Py$\underline{H}$), 10.49 (dJ0.7Hz, 2H, -C$\underline{H}$O). m/z (field ionisation) 347 $(M)^+$, 348 $(M+H)^+$; (EI) 347 (M^+, 0.5%), 329 (0.75), 225 (100), 198 (50), 106 (95), 105 (55), 78 (45).

(b) The bisacetal (170 mg, 0.39 mmol) was dissolved in the minimum volume of distilled THF and 5% aq. hydrochloric acid (ca. 3ml) was added. The suspension was stirred for 3h and 3% aq. sodium bicarbonate solution was added to pH >7.5. Dichloromethane (50 ml) was added, the mixture shaken well, and the organic layer separated. The aqueous layer was treated again with dichloromethane, the combined organic fraction dried, and the solvent removed to give an off-white solid. The solid was crystallised from dichloromethane/diethyl ether to give the bis-aldehyde (68) (127.3 mg, 94%) m.p. 146-148.5°C.

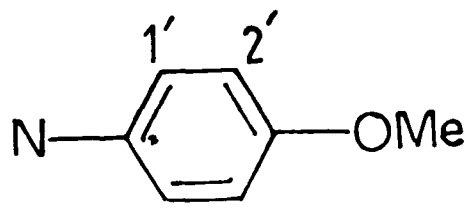
(c) To a stirred suspension of sodium hydride (50% dispersion in oil, 68 mg, 1.48 mmol) in dry DMF (3 ml), under nitrogen, was added salicylaldehyde (143 mg, 1.17 mmol). After evolution of gas ceased, 3,5-bis(chloromethyl)pyridine (100 mg, 0.56 mmol) was added, and the reaction stirred for 20h at 60-80°C. The mixture was first cooled and then partitioned between 1M aq. sodium hydroxide solution (100 ml) and dichloromethane (100 ml). The organic layer was separated, washed again with 1M aq. sodium hydroxide (100 ml) and then with water (100 ml). After drying the solvent was removed in vacuo (high vacuum to remove traces of DMF) to leave a brown solid. The solid was purified

by chromatography on basic alumina (2 cm x 13 cm), being applied in dichloromethane, and eluted with an increasing percentage of diethyl ether in dichloromethane to a maximum of 50% ether. The white solid eluted was crystallised from dichloromethane/diethyl ether to give the bis-aldehyde (68) as off-white needles (46.2 mg, 23.4%) m.p. 146-148^{o}C.

Formation of the Imine Between 4-Methoxyaniline and 3,5-Bis (2-Formylphenoxymethyl)Pyridine (68)

Bis-aldehyde (68) (80 mg, 0.23 mmol) and 4-methoxyaniline were added to dry acetonitrile under nitrogen. 4-Toluene-sulphonic acid (10 mg) was added and the yellow solution heated at reflux over 3A sieves (soxhlet), for 36h. After cooling, dry triethylamine was added and the solvent removed to leave a yellow oil. The oil was dissolved in dichloromethane (50 ml), washed with 1M aqueous sodium hydroxide solution (50 ml), dried (K_2CO_3), and the solvent removed to leave a yellow oil 142.6 mg, ν_{max} ($CHCl_3$) 1610, 1600 cm^{-1}, which was reduced to the amine.

A portion of the oil was dissolved in dichloromethane and petroleum ether (40-60^{o}C) added to excess. The oily solid precipitated was extracted with boiling diethyl ether and, at boiling point, petroleum ether (30-40^{o}C) was added. On cooling in the fridge, the imine (70) crystallised as a light yellow solid m.p. 94.5-98.5^{o}C. δ($CDCl_3$) 3.8 (s, 6H, -OC$\underline{H}_3$) 5.21 (s, 4H, Py-C$\underline{H}_2$-O) 6.87 (part of AA'BB' system, 4H, $H_{2'}$) 7.00 (dJ8.1Hz,



H_6) 7.1 (tJ7.3Hz, 2H, H_4) 7.19 (part of AA'BB' system, 4H, H_1,) 7.41 (J7.8 and 1.9Hz, 2H, H_5) 7.89 (t, 1H, γ-PyH) 8.16 (ddJ7.7 and 1.8 Hz, 2H, H_3) 8.71 (dJ1.8 Hz, 2H, α-PyH) 8.92 (s, 2H, -CH=N) m/z (EI) 557 (M^+, 10%), 452 (10), 330 (95), 227 (70), 123 (100).

Reduction of the Imine (70) to the Bis-Amine (71)

Crude imine (70) (39 mg) was dissolved in dry THF (2 ml) under nitrogen. Dry methanol (1 ml), sodium cyanoborohydride (10 mg, 0.16 mmol), ammonium acetate (20 mg, 0.26 mmol) and glacial acetic acid (0.3 ml) were added, in that order. The solution was left for 2.5h, then poured onto 3% aqueous sodium bicarbonate solution (50 ml) and the amine extracted with dichloromethane (2 x 20 ml). The organic solution was dried (K_2CO_3) and evaporated to give a brown oil. Preparative t.l.c. was conducted on alumina using dichloromethane/diethyl ether (100:6) to elute and (45:5) to extract the bis-amine. Evaporation gave the desired bis-amine as an oil (21 mg, 59% from bis aldehyde) which tended to discolour rapidly. This oil was dissolved in a small volume of dichloromethane and petroleum ether (30-40°C) added carefully. The coloured material deposited first as an oil, and the colourless liquors were decanted. The liquors were then treated carefully with more petroleum ether, and the amine (71) was deposited, as a white solid; m.p. 101·5-104°C. Found C, 74.92; H, 6.27; N, 7.15. $C_{35}H_{35}N_3O_4$ requires C, 74.84; H, 6.28; N, 7.48%. m/z (FD) 561 $(M)^+$. δ($CDCl_3$) 3.70 (s, 6H, $-OCH_3$) 4.31 (s, 4H, $ArCH_2$-NH) 5.10 (s, 4H, Py-CH_2-O) 6.57 (part of AA'BB' system, 4H, H_2,) 6.73 (part of AA'BB' system, 4H, H_1,) 6.92-6.99 (t and d, 4H, H_5, H_3) 7.26 (tdJ7.7 and 1.5Hz, 2H, H_4) 7.34 (dJ7.4Hz, 2H, H_6) 7.86 (broad, 1H, γ-PyH) 8.65 (dJ1.8Hz, 2H, α-PyH).

Reaction of 3,5-Bis(2-Formylphenoxymethyl)Pyridine With 4-Methoxyaniline and Reduction in Situ

3,5-Bis(2-formylphenoxymethyl)pyridine (68) (20 mg, 0.058 mmol) and 4-methoxyaniline (15 mg, 0.122 mmol) were placed in a flask under argon and dry THF (65 ml) added. A trace 4-toluenesulphonic acid monohydrate was added followed, after 18h, by a quantity of freshly activated 3A sieves.

After 24h, sodium cyanoborohydride (21 mg, 0.33 mmol), dry methanol (5 ml), ammonium acetate (120 mg) and glacial acetic acid (0.6 ml) were added, and the mixture left for 4.5h. The mixture was filtered, evaporated to dryness and partitioned between dichloromethane and 3% aq. sodium bicarbonate solution. The organic layer was separated, dried (K_2CO_3) and evaporated to leave a brown oil, shown by p.m.r. spectroscopy to be essentially all bis-amine (71). Increasing the reduction time (to 16h) did not alter the product yield.

The oil was purified by preparative t.l.c. on alumina using dichloromethane/diethyl ether (100:6) to elute and dichloromethane/diethyl ether (100:5) to extract the major band. Evaporation, filtration in dichloromethane, and re-evaporation gave the bis-amine (71) as a colourless oil (24.4 mg, 75.5%).

Reaction Between Bis-Amino-C_2-Capped Porphyrin (31) and Bis-3,5-(2-Formylphenoxymethyl)Pyridine (68) under high dilution conditions followed by Reduction in Situ

Dry THF (25 ml) and a quantity of freshly activated 3A sieves were placed under argon, in the dark. Bis-amino-C_2-capped porphyrin (31) (30 mg, 0.028 mmol) in dry THF (10 ml)

and bis-aldehyde (68) (9.8 mg, 0.028 mmol) in dry THF (10 ml) were added over 2.5h. T.l.c. on silica G using toluene/ethyl acetate (6:4) or on alumina using diethyl ether/dichloromethane (5:50) showed only bis aldehyde and diamine. A trace of 4-toluenesulphonic acid monohydrate was added and the mixture stirred for 2.5h. On quenching an aliquot with 3% aq. sodium bicarbonate solution, t.l.c. showed virtually complete consumption of diamine (31) and bis-aldehyde (68).

The reaction mixture was treated with dry methanol (2 ml), sodium cyanoborohydride (10 mg, 0.16 mmol), ammonium acetate (60 mg, 0.78 mmol) and acetic acid (0.3 ml). It was then stirred for 1h, when further cyanoborohydride (10 mg) was added. After 0.5h, the mixture was poured onto 3% aq. sodium bicarbonate solution (100 ml). The organic layer was separated (ca. 100 ml), washed with distilled water (100 ml), dried and the solvent removed in vacuo. No insoluble porphyrin residues were seen. The product was subjected to preparative t.l.c. on alumina F_{254} using 1-propanol/dichloromethane (1:50) to elute and dichloromethane/methanol (95:5) to extract the major band (circa eleven minor bands were seen). On evaporation this gave a purple solid (26 mg) which was dissolved in chloroform and passed down a column (20 x 2 cm) of Sephadex 2H-20-100 in chloroform. m/z (FD) 1381-1383, 1393, 1401.

If allowed to stand in dichloromethane or chloroform the porphyrin became gradually insoluble, treatment with DMF and evaporation restored solubility.

Acylation of the Product From Reaction of Diamine (31) With Bis-Aldehyde (68)

The porphyrin was suspended in acetic anhydride (2 ml), dry triethylamine (2 ml) and a trace of N,N-4-dimethylaminopyridine (38). After 3h at room temperature the solvent was removed. The solid was partitioned between 3% aq. sodium bicarbonate solution and dichloromethane. After 1.5h the organic layer was separated, dried and evaporated in vacuo. The residue was purified by preparative t.l.c. on alumina using dichloromethane/1-propanol (50:1.5) to elute and dichloromethane/methanol (10:1) to extract the major band which, after evaporation, was passed down a column (20 x 2 cm) of Sephadex LH-20-100 in chloroform. The above complete chromatography procedure was repeated to give a porphyrin ($^{m}/_{z}$, (FD) 1465) that was still impure by p.m.r. spectroscopic analysis.

The product was subjected to preparative t.l.c. on silica impregnated with 0.1M sodium hydroxide solution using chloroform/methanol (100:5) to elute and collect the one band that migrated. On evaporation and filtration in dichloromethane this gave a porphyrin (3 mg, 7%) still impure by p.m.r. spectroscopic analysis.

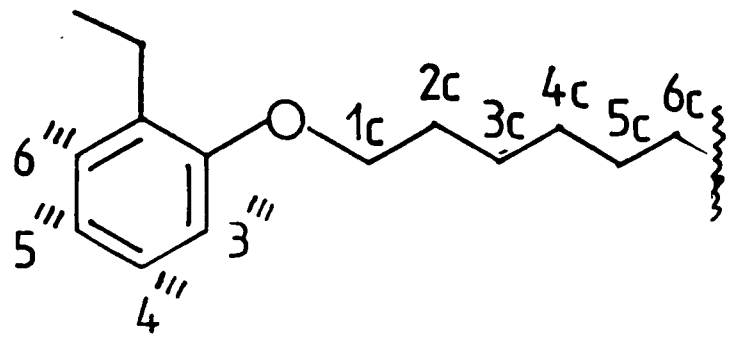
Reaction of Bis-amino-C_2-Capped Porphyrin (31) With 2,2'(1,12-Dodecylidenedioxy)Bis-Benzaldehyde (73)

Bis-amino-C_2-capped porphyrin (31) (29 mg, 0.027 mmol) and 2,2'(1,12-dodecylidenedioxy)bis-benzaldehyde (73) (11.6 mg, 0.028 mmol) were dissolved in dry THF (70 ml) in the dark under argon. A trace of 4-toluenesulphonic acid monohydrate was added followed after 1.5h by a quantity of freshly activated 3A sieves.

After a further 1.5h, t.l.c. showed one product on silica G using toluene/ethyl acetate (1;1) as eluant.

Sodium cyanoborohydride (20 mg, 0.318 mmol, dry methanol (4½ ml), ammonium acetate (100 mg), and glacial acetic acid (0.4 ml) were added. The mixture was allowed to stand overnight, then was filtered and evaporated. The residue was partitioned between dichloromethane and 3% aq. sodium bicarbonate solution. The organic layer was separated, dried, and evaporated. The solid was subjected to preparative t.l.c. on silica G (three 20 x 20 x 0.1 cm) plates using toluene/ethyl acetate (1;1) to elute and chloroform/methanol (9:1) to extract the three major bands at Rf 0.2, 0.55, and 0.75. The p.m.r. spectra of the bands at Rf 0.2 and 0.55 contained upfield shifts of the 1,12 dodecylidene chain but were otherwise complex.

The band at Rf 0.75 (12.3 mg, 31%) was the desired product (75). m/z (FD) 1444 $(M)^+$. $\delta(CDCl_3)$ -3.37 (broad s, 2H, pyrrolic NH), -0.59 (broad m, 4H, H_{6c}), -0.48 (broad m, 4H, H_{5c}), -0.18 (m, 4H, H_{4c}), 0.27 (m, 4H, H_{3c}), 0.91 (m, 4H, H_{2c}), 3.44 (m, 4H, H_{1c}), 3.25-4.36 (m, 22H, O-CH_2-CH_2-O, ArNHCH_2Ar'), 5.39 (s, 2H, H_3, H_6), 6.70 (dJ8Hz, 2H, H_3''), 6.95 (dJ3Hz, 2H, H_6''), 7.00 (tJ6.6Hz, 2H, H_5'''), 7.14 (ddJ8.5 and 3Hz, 2H, H_4''), 7.23 (tdJ8.1 and 2Hz, 2H, H_4'''), 7.37-7.48 (m, 6H, H_5', H_3'', H_6'''), 7.54 (dJ8Hz, 2H, H_3'), 7.80 (d and t, 4H, H_4', H_6'), 8.58, 8.66, 8.69, 8.77 (four dJ4.8Hz, 8H, βpyrrolic H).



λ_{max} ($CHCl_3$, $\log_{10}\varepsilon$) 348 (shoulder) (4.34), 368 Sh (4.40), 423 (5.47), 483 Sh (3.51), 517 (4.21), 548 (3.73), 591 (3.74), and 651 (3.52) nm. ν_{max} ($CHCl_3$) 2925 (medium), 1725 (broad strong), 1600 (med), 1490 (strong), 1280 and 1240 cm^{-1}.

2,2'-(1,8-Octylidenedioxy)Bis-Benzaldehyde (74)

Salicylaldehyde (65) (11g, 0.09 mol) and 1,8-dibromo-octane (5g, 0.02 mol) were added directly to distilled water (100 ml). Sodium hydroxide (3.7g, 0.09 mol) in water (20 ml) was added over 15 min to the vigorously mechanically stirred mixture. The reaction was heated at reflux for 36h and allowed to cool. Ethyl acetate (ca. 150 ml) was then added. The organic layer was separated and washed with portions of 1M aq. sodium hydroxide solution (70 ml) until the base layer was colourless. After a wash with distilled water and drying, the solvent was removed to give an oil, shown by p.m.r. spectroscopic analysis, to be a mixture of phenyl ether (t, δ4.1) and bromide (t, δ3.4). The oil was subjected to flash chromatography[63] on silica using dichloromethane and then dichloromethane/diethyl ether (95:5) to elute. The purest fractions from this were passed down another flash silica column using only dichloromethane to elute. The fractions containing a compound, Rf 0.5 on silica $HF_{254/366}$ eluted with dichloromethane, gave, on removal of trace solvents at high vacuum, 2,2'-(1,8-octylidenedioxy)bis-benzaldehyde (74) as a yellow crystalline solid (1.5g, 21.7%). A portion of this solid was crystallised from diethyl ether/petroleum ether (30-40°C) as colourless needles m.p. 59-62°C. Found: C, 74.49; H, 7.24. $C_{22}H_{26}O_4$ requires C, 74.55; H, 7.24%. δ($CDCl_3$) 1.43 (m, 4H, chain, H_4,H_5), 1.54 (m, 4H,

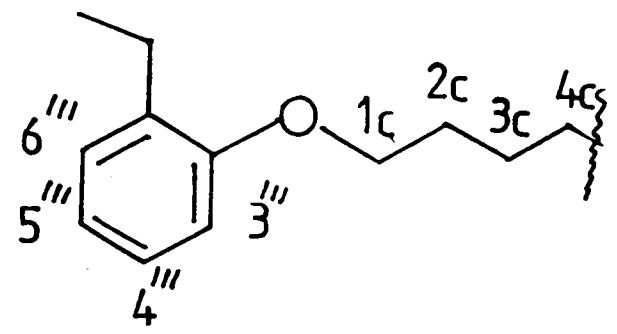
chain, H_3, H_6), 1.87 (quint J6.2Hz, 4H, chain H_2, H_7), 4.08 (tJ6.2Hz, 4H, $-C\underline{\underline{H}}_2-O$), 7.0 (m, 4H, $H_{3'}$, $H_{5'}$), 7.53 (tdJ7.5 + 2Hz, 2H, $H_{4'}$), 7.83 (ddJ7.5 and 2Hz, 2H, $H_{6'}$), 10.52 (s, 2H, $-C\underline{\underline{H}}O$). ν_{max} ($CHCl_3$) 2940, 1685, 1490, 1460, 1405, 1390, 1290, and 1245 cm^{-1}. m/z (EI) 355 (20%, M^+), 121 (55), 69 (100); (methane CI) 355 (55%), 354 (25), 233 (15), 121 (80), 77 (30), 69 (100).

Reaction of Bis-Amino-C_2-Capped Porphyrin (31) With 2,2'-(1,8-Octylidenedioxy)bis-benzaldehyde (74)

Bis-amino-C_2-capped porphyrin (31) (20 mg, 0.019 mmol) and 2,2'-(1,8-octylidenedioxy)bis-benzaldehyde (6.7 mg, 0.019 mmol) were dissolved in dry THF (30 ml), under argon, in the dark. A quantity of freshly activated 3A sieves was added, followed by a trace of 4-toluenesulphonic acid monohydrate. T.l.c. after 4h on silica G eluting with toluene/ethyl acetate (1:1) showed conversion of the diamine (31) to a single product.

Sodium cyanoborohydride (10 mg, 0.16 mmol), dry methanol (2 ml), ammonium acetate (40 mg) and glacial acetic acid (0.2 ml) were added. The mixture was left for 3h, filtered and evaporated. The residue after evaporation was partitioned between dichloromethane and 3% aq. sodium bicarbonate solution. The organic layer was dried and evaporated. The residue was subjected to preparative t.l.c. on silica G using toluene/ethyl acetate (1:1) to elute, and chloroform/methanol (10:1) to extract the one major band. This gave, after filtration in dichloromethane and evaporation, the desired strapped/capped porphyrin (76) as a purple solid (16.8 mg, 64%). m/z (FD) 1389·5157 $(M+H)^+$ $C_{84}H_{73}O_{14}N_6$ expects 1389·5179. $\delta(CDCl_3)$ -3.38

(broad s, 2H, pyrrolic NH), -2.6 (m, 2H, H_{4c}), -2.27 (m, 2H, H_{4c}), -1.73 (m, 4H, H_{3c}), -0.63 (m, 2H, H_{2c}), -0.47 (m, 2H, H_{2c}), 2.49 (m, 2H, H_{1c}), 2.76 (m, 2H, H_{1c}), 3.77-4.57 (m, 22H, -O-CH_2-CH_2-O, and ArCH_2NHAr'), 5.33 (s, 2H, cap), 6.57 (dJ7.7Hz, 2H, $H_{3'''}$), 7.0-7.13 (m, 6H, $H_{6''}$, $H_{5'''}$, $H_{4''}$), 7.24 (tdJ8 and 2Hz, 2H, $H_{4'''}$), 7.41 (dJ8.5Hz, 2H, $H_{6'''}$), 7.45-7.52 (m, 4H, $H_{5'}$, $H_{3''}$), 7.54 (dJ8Hz, 2H, $H_{3'}$), 7.85 (d and t, 4H, $H_{4'}$, $H_{6'}$), 8.39, 8.47, 8.67, 8.70 (four dJ4.8Hz, 8H, β-pyrrolic H).



λ_{max} ($CHCl_3$, $\log_{10}\varepsilon$) 349 (shoulder) (4.26), 354 Sh (4.32), 4.23 (5.40), 482 Sh (3.60), 517 (4.15), 548 (3.67), 591 (3.68) and 648 (3.36) nm. ν_{max} ($CHCl_3$) 2915, 1727, 1610, 1500, 1490, 1440, 1280 and 1240 cm^{-1}.

Reaction of Bis-Amino-C_2-Capped Porphyrin (31) With Nitrous Acid

Bis-amino-C_2-capped porphyrin (10 mg, 9×10^{-6} mol) was dissolved in glacial acetic acid (4 ml) and distilled water (2 ml) added. The green solution was cooled to $0^{o}C$ and sodium nitrite (3.5 mg, 0.051 mmol) added. After 2h, t.l.c. of an aliquot, (quenched with saturated aq. sodium bicarbonate solution) showed consumption of diamine and production of a higher Rf product on silica G eluted with toluene/ethyl acetate

(1:1). The solvent was removed from the reaction and, after high vacuum treatment, the solid was dissolved in dry dichloromethane (4 ml). Acetic anhydride (1 ml), triethylamine (½ ml) and a trace of 4-N,N-dimethylaminopyridine were added, under argon. After 4h the solvent was removed and the resultant purple solid partitioned between dichloromethane and 3% aq. sodium bicarbonate solution. The organic layer was dried and evaporated. The solid was subjected to preparative t.l.c. on silica G using toluene/ethyl acetate (6:4) to elute and chloroform/methanol (10:1) to extract the major band; (5.4 mg, 55%) C_2-capped porphyrin (23), identical by p.m.r., $^m/z$ and t.l.c. with an authentic sample. $\underline{^m/z}$ did show a trace of mono acetate $\underline{^m/z}$ 1094. A quantity of baseline material was also extracted but did not give any good p.m.r. or mass spectral data.

Repetition of the above procedure using sodium nitrite (1.5 mg, 2.2×10^{-6} mol, 150 µl of 10 mg/ml solution in water) and stirring for 1.5h gave 2.1 mg, 22.6% of C_2-cap (23) plus baseline and other dichloromethane insoluble residues.

REFERENCES

1. (a) M.F. Perutz, Brit. Med. Bull., 1976, 32, 193; (b) R.E. Dickerson and I. Geis, "The Structure and Action of Proteins", Harper and Row, New York, 1969; (c) E. Antonini and M. Bruniori, "Haemoglobin and Myoglobin in Their Reactions with Ligands", Elsevier, Amsterdam, 1971; (d) D.M. Surgenov, "The Red Blood Cell", 2nd Ed., Academic Press, New York, 1974.

2. S.E.V. Phillips and B.P. Schoenborn, Nature, 1981, 292, 81.

3. J.M. Baldwin, J. Mol. Biol., 1980, 136, 103.

4. D. Shemin and D. Rittenberg, J. Biol. Chem., 1945, 159, 567; 1946, 166, 627.

5. A.H. Corwin and Z. Reyes, J. Am. Chem. Soc., 1956, 78, 2437.

6. (a) I.A. Cohen and W.S. Caughey, Biochemistry, 1968, 7, 636; (b) G.S. Hammond and C-H. S. Wu, Adv. Chem. Ser., 1968, 77, 186.

7. C.K. Chang, D. Powell and T.G. Traylor, Croat. Chem. Acta. 1977, 49, 295.

8. (a) D.L. Anderson, C.J. Weschler, and F. Basolo, J. Am. Chem. Soc., 1974, 96, 5599; (b) G.C. Wagner and R.J. Kassner, J.Am. Chem. Soc., 1974, 96, 5593; (c) J. Almog, J.E. Baldwin, R.L. Dyer, J. Huff, and C.J. Wilkerson, J. Am. Chem. Soc., 1974, 96, 5600; (d) W.S. Brinigar, C.K. Chang, J. Geibel, and T.G. Traylor, J. Am. Chem. Soc., 1974, 96, 5597.

9. B. Shaanan, Nature, 1982, 296, 683.

10. D-H. Chin, G.N. LaMar and A.L. Balch, J. Am. Chem. Soc., 1980, 102, 4344.

11. Y. Satoh and K. Shikama, J. Biol. Chem., 1981, 256, 10277.

12. A.H. Corwin and J.G. Erdman, J. Am. Chem. Soc., 1946, 68, 2473.

13. R.D. Jones, D.A. Somerville, and F. Basolo, Chem. Rev., 1979, 79, 139.

14. J.P. Collman in "Metal Ion Activation of Dioxygen", ed. T.G. Spiro, Wiley-Interscience, New York, 1980, Vol. II.

15. T.G. Traylor, Acc. Chem. Res., 1981, 14, 102.

16. B.R. James in "The Porphyrins" ed. D. Dolphin, Academic Press, London, 1978, Vol. IV.

17. J.H. Wang, Acc. Chem. Res., 1970, 3, 90.

18. J.E. Baldwin and J. Huff, J. Am. Chem. Soc., 1973, 95, 5757.

19. D.H. Busch, L.L. Zimmer, J.J. Grzybowski, D.J. Olszanski, S.C. Jackels, R.C. Callahan and G.C. Christoph, Proc. Natl. Acad. Sci. USA, 1981, 78, 5919 and references therein.

20. K.M. Smith in "Porphyrins and Metallo-porphyrins", ed. K.M. Smith, Elsevier, Amsterdam, 1975.

21. "The Porphyrins", ed. D. Dolphin, Academic Press, London, 1978, Vols I and II.

22. P. Rothemund, J. Am. Chem. Soc., 1935, 57, 2010.

23. J.E. Baldwin, M.J. Crossley, T. Klose, E.A. O'Rear III, and M.K. Peters, Tetrahedron, 1982, 38, 27.

24. A.R. Battersby, D.G. Buckley, S.G. Hartley, and M.D. Turnbull, J. Chem. Soc., Chem. Commun., 1976, 879; A.R. Battersby, S.G. Hartley, and M.D. Turnbull, Tetrahedron Lett., 1978, 34, 3169.

25. T.G. Traylor, D. Campbell, and S. Tsuchiya, J. Am. Chem. Soc., 1979, 101, 4748.

26. A.R. Battersby, and A.D. Hamilton, J. Chem. Soc., Chem. Commun., 1980, 117.

27. C.K. Chang, J. Am. Chem. Soc., 1977, 99, 2819.

28. J.P. Collman, R.R. Gagne, C.A. Reed, T.R. Halbert, G. Lang, and W.T. Robinson, J. Am. Chem. Soc., 1975, 97, 1427.

29. J.P. Collman, J.I. Brauman, T.J. Collins, B. Iverson, J.L. Sessler, J. Am. Chem. Soc., 1981, 103, 2450.

30. J. Almog, J.E. Baldwin, M.J. Crossley, J.F. DeBernardis, R.L. Dyer, J.R. Huff, and M.K. Peters, Tetrahedron, 1981, 37, 3589.

31. J.R. Budge, P.E. Ellis Jr., R.D. Jones, J.E. Linard, F. Basolo, J.E. Baldwin, and R.L. Dyer, J. Am. Chem. Soc., 1979, 101, 4790.

32. J.P. Collman, J.I. Brauman, K.M. Doxsee, and T.R. Halbert, Proc. Natl. Acad. Sci. USA, 1978, 75, 564; J.P. Collman, J.I. Brauman, K.M. Doxsee, T.R. Halbert, E. Bunnenberg, R.E. Linder, G.N. LaMar, J. DelGaudio, G. Lang and K. Spartelian, J. Am. Chem. Soc., 1980, 102, 4182.

33. F.M. Walker and M. Benson, J. Am. Chem. Soc., 1980, 102, 5530.

34. J.E. Baldwin, M.J. Crossley, J.F. DeBernardis, Tetrahedron, 1982, 38, 685.

35. J.E. Baldwin, M.J. Crossley, J.F. DeBernadis, and M.I. Vallejo, unpublished data.

36. J.E. Baldwin and M.J. Crossley, unpublished data.

37. J.E. Baldwin and T. Klose, unpublished data.

38. J.E. Baldwin and I.J. Dagley, unpublished data.

39. H.A. Staab and A. Mannschreck, Chem. Ber., 1962, 95, 1284.

40. E.J. Corey and K.C. Nicolaou, J. Am. Chem. Soc., 1974, 96, 5614.

41. B. Neises and W. Steglich, Angew. Chemie Int. Ed. Engl., 1978, 17, 523.

42. K. Saigo, M. Usui, K. Kikuchi, E. Shimada and T. Mukaiyama, Bull. Chem. Soc. Jpn., 1977, 50, 1863.

43. E. Schmidt, E. Däbritz, K. Thulke, and E. Grassman, Annalen, 1965, 685, 161.

44. (a) "Singlet Oxygen", ed. H.H. Wasserman and R.W. Murray, Academic Press, New York, 1979; (b) A.A. Gorman and M.A.J. Rogers, Chem. Soc. Rev., 1981, 10, 205.

45. (a) M.L. Kaplan, Chemtech., 1971, 621; (b) M. Tomita, M. Irie, and T. Ukita, Biochemistry, 1969, 8, 5149.

46. S.R. Hall, Part II Thesis, Christ Church, Oxford, 1979.

47. H.H. Bosshard, R. Mory, M. Schmid, and Hch. Zollinger, Helv. Chim. Acta, 1959, 42, 1653.

48. Performed by R.T. Aplin, Dyson-Perrins Laboratory, University of Oxford; and A. Dell, Dept. Biochemistry, Imperial College of Science and Technology, London.

49. Performed under the supervision of I.O. Walker, Dept. of Biochemistry, Oxford.

50. Performed by J.G. Jones, University of Coleraine, Northern Ireland.

51. Performed by R.D. MacFarlane, Texas A. and M. University, Texas, U.S.A.

52. Performed by V.G. Limited, Manchester.

53. D.B. Denney and L.C. Smith, J. Org. Chem., 1962, 27, 3404.

54. P.J. Beeby and F. Sondheimer, J. Am. Chem. Soc., 1972, 94, 2128.

55. H.S. Corey Jr., J.R.D. McCormick, and W.E. Swenson, J. Am. Chem. Soc., 1964, 86, 1884.

56. (a) Performed by W.E. Hull, Bruker Spectrospin Ltd., Karlsruhe, West Germany; (b) A. Bax and R. Freeman, J. Magn. Res., 1981, 44, 542.

57. J.E. Baldwin and R.L. Dyer, unpublished data.

58. R.F. Borch, M.D. Bernstein and H.D. Durst, J. Am. Chem. Soc., 1971, 93, 2897.

59. (a) D.A. Hall, King's College, London, private communication; (b) D.H. Cook and D.E. Fenton, Inorg. Chim. Acta, 1977, 25, L95.

60. Performed by L.D. Field, Dyson-Perrins Laboratory, University of Oxford.

61. J.E. Baldwin and P. Perlmutter, unpublished data.

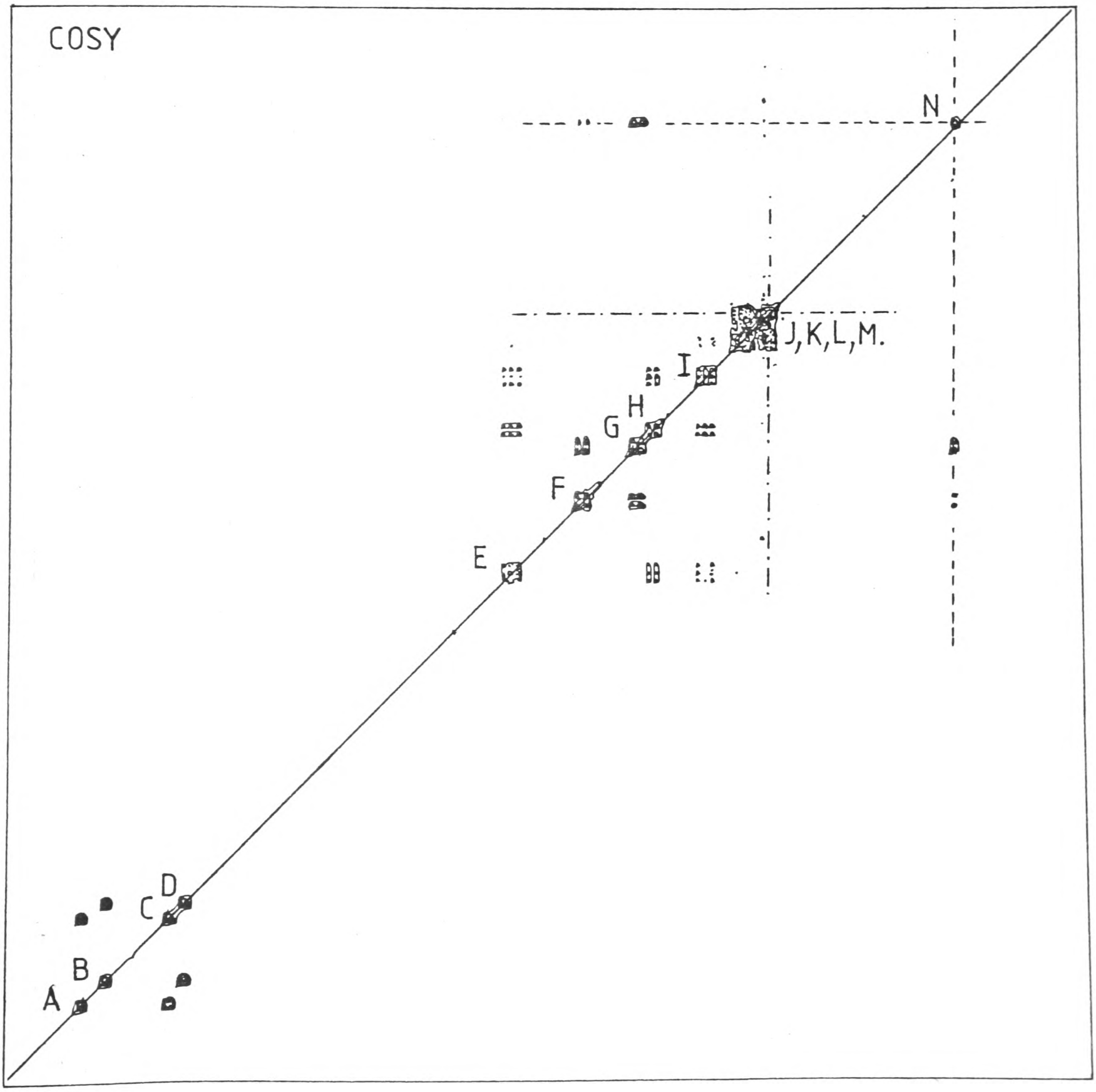
62. Beilstein, "Organische Chemie", 1st ed., p.783, Vol. XVI.

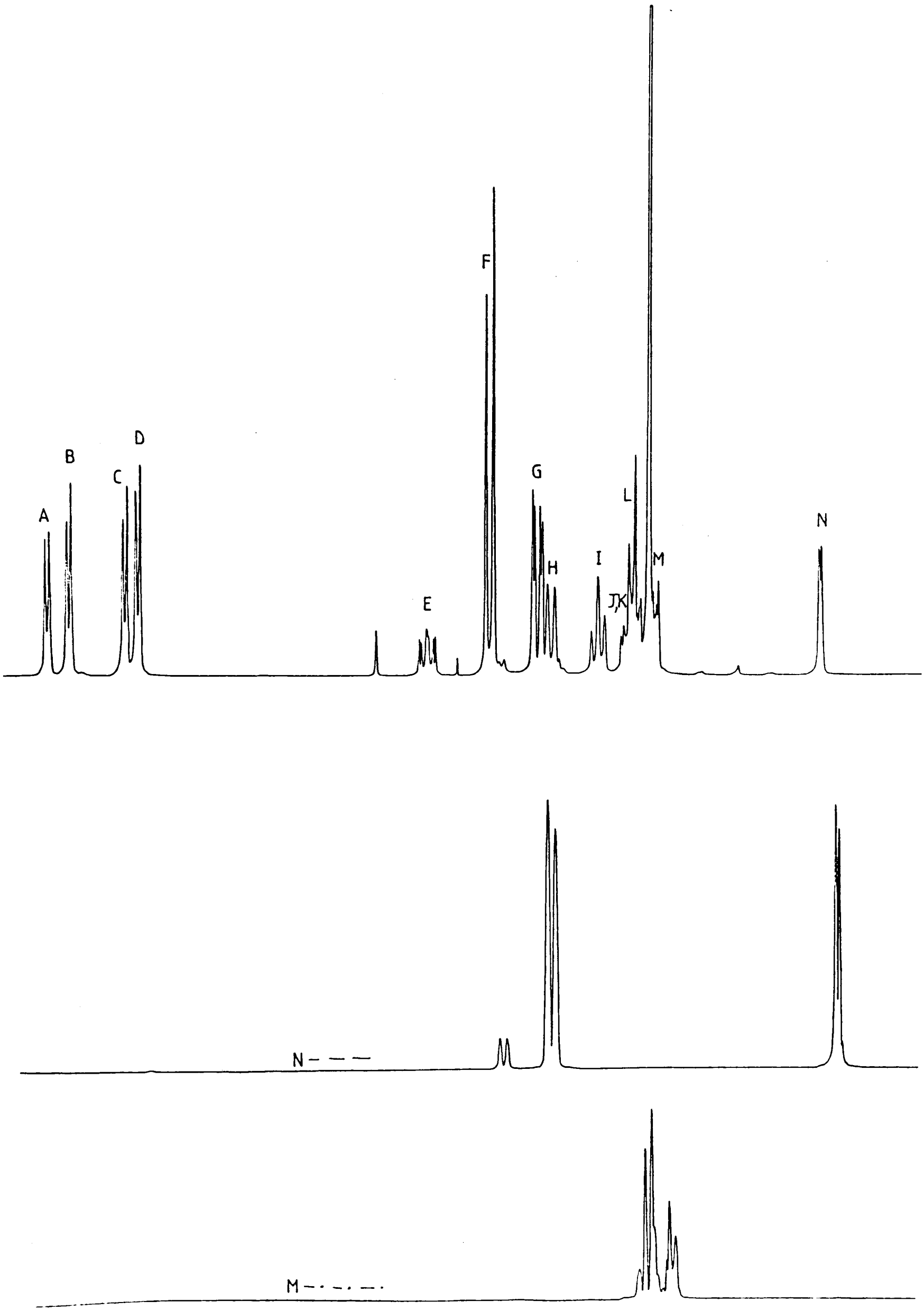
63. W.C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 1978, 43, 2923.

APPENDIX 1

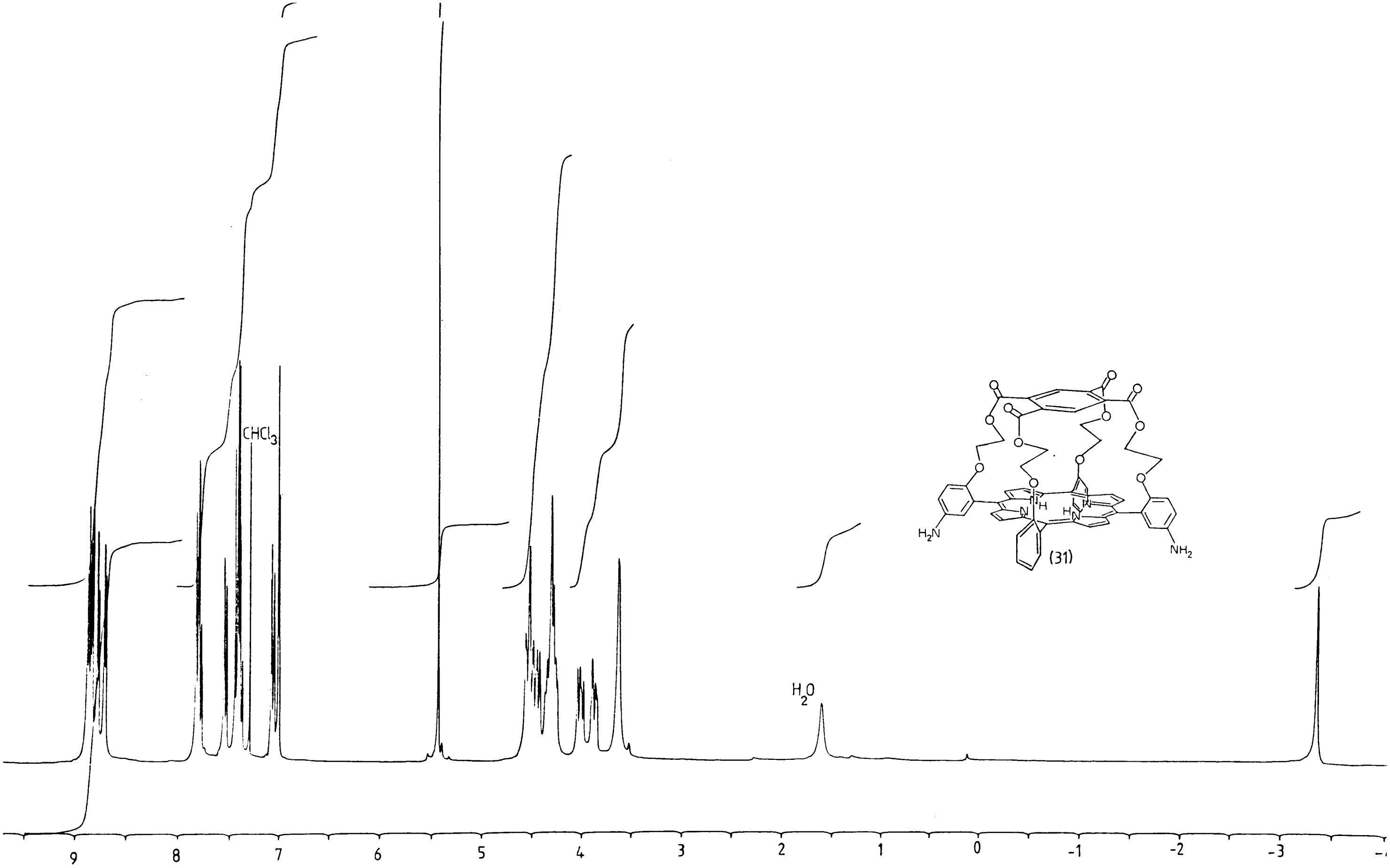
2-Dimensional p.m.r. Spectroscopy of C_5-Strapped/C_2-Capped Porphyrin (60) at 500 MHz

This procedure was applied to the aromatic region using the COSY program.[56]

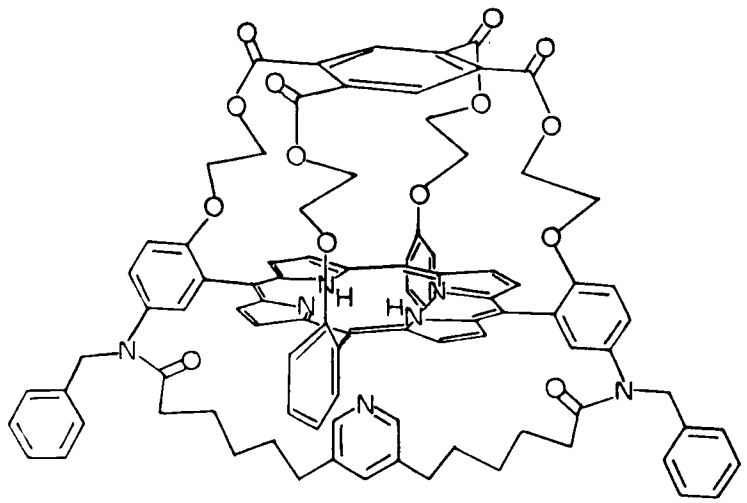



A
B
C
D
E
F
G
H
I
J,K
L
M
N
N
M

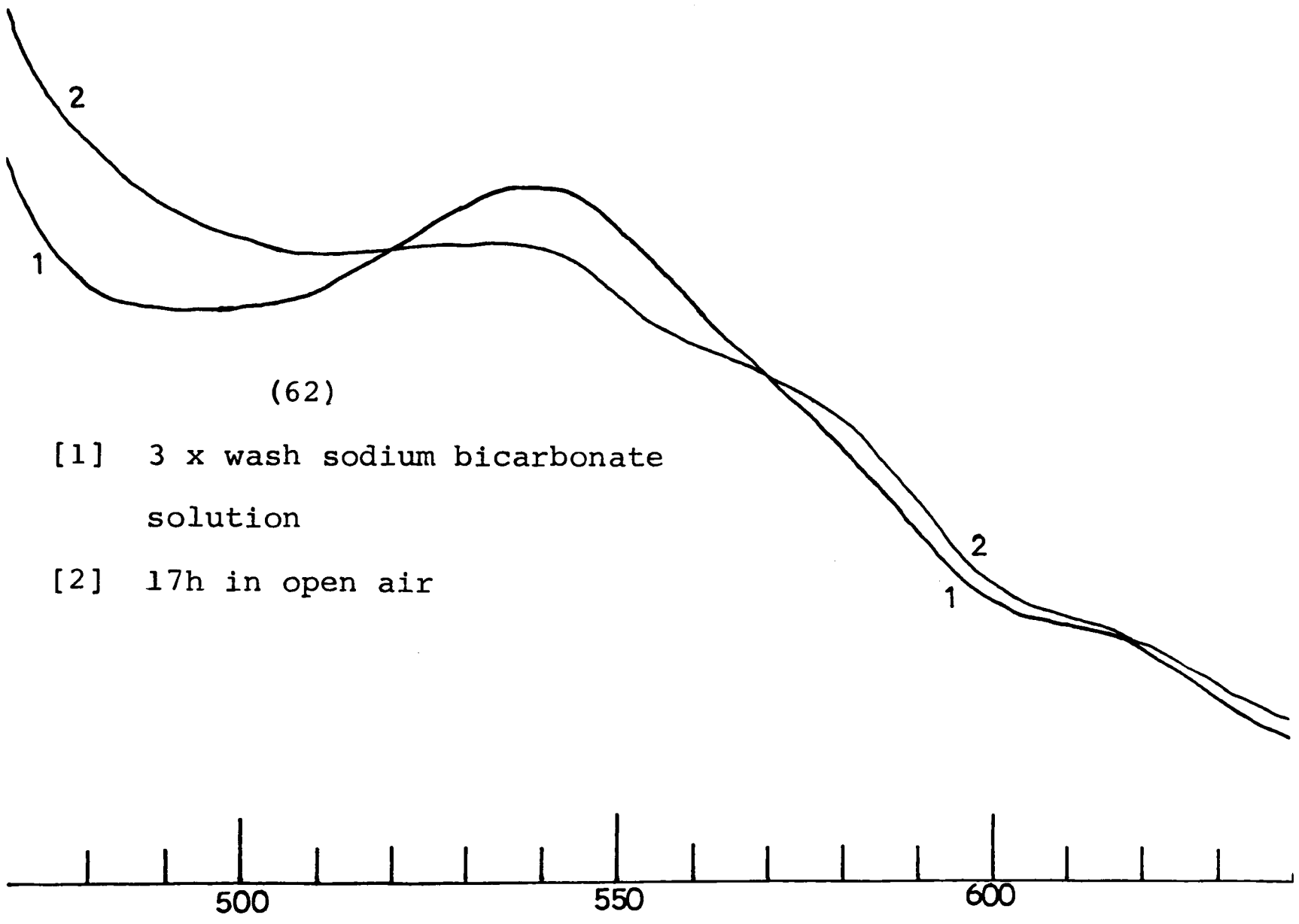
APPENDIX 2



(31)



(60)



(62)

[1] 3 x wash sodium bicarbonate solution

[2] 17h in open air