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SYNTHESIS OF "CAPPED PORPHYRINS"+

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Abstract - The synthesis of "capped porphyrins" (10), (18), and (28), and their (chloro)iron(III), iron(II), cobalt(II), and zinc(II) complexes is reported. These complexes serve as models for the active site of the oxygen binding haemoproteins. In addition to reversible binding of dioxygen by each of the iron(II) porphyrin complexes, the 1-methylimidazole-("C_3-capped porphyrin") iron(II) complex (23) reacts reversibly with carbon monoxide, in solution at 25°C.

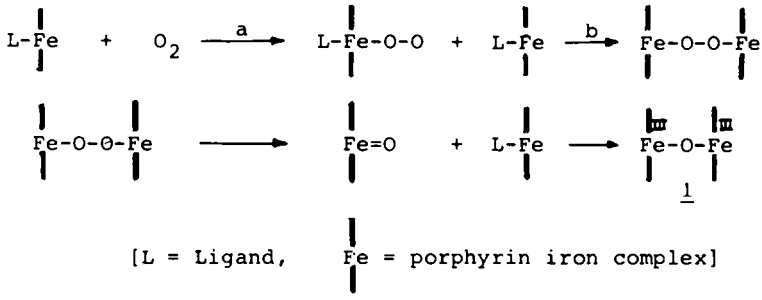
The development of a reversible oxygen-carrier based on a synthetic chelate molecule which could be suitably modified for testing *in vivo* and *in vitro* as a potential substitute for the haemoprotein systems, haemoglobin and myoglobin has been an important challenge in recent years.[1]

Haemoglobin and myoglobin bind oxygen reversibly in the lungs and muscle tissue respectively. The oxygen-binding site is an iron(II) protoporphyrin-IX complex (haem) held in an hydrophobic cleft in the protein with a covalent linkage between the iron(II) atom and the imidazole of the so-called proximal histidine residue of the globin. Dioxygen is reversibly bound at the sixth coordination site of the iron(II) atom which is within a sterically encumbered pocket open only for the binding of small molecules. Native haemoglobin and myoglobin are *ca* 10^8 times more stable towards autoxidation than the corresponding denatured haemoproteins or isolated haem.

The importance of the protein tertiary structure in preventing autoxidation has further emerged from studies on synthetic chelates designed to mimic the oxygen-carrying properties of the haemoproteins. Simple non-hindered iron(II) porphyrins are rapidly autoxidised, except at very low temperatures.[1]

Our studies on iron(II) octaazamacrocycles first showed that both the reversibility and stoichiometry of oxygen binding by an iron(II) complex in solution depended on the degree of ligand encumbrance.[2,3] It is now well established that the autoxidation mechanism for iron(II) porphyrin complexes involves an initial binding of dioxygen (scheme 1, step a) followed by a rapid bimolecular redox process (step b), which eventually

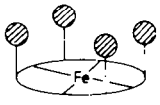
+We have adopted a trivial naming system in order to readily distinguish the "capped porphyrins":- "C_2-capped porphyrin" refers to compound (10), having two methylene groups in each rib of the capping structure, "C_3-capped porphyrin" refers to compound (18) which has three methylene groups in each rib, and "naphthyl-C_2-capped porphyrin" refers to compound (28) which has *meso*-naphthyl substituents and two methylene groups in each rib.



Scheme 1.

leads irreversibly to μ-oxo dimers (1).[1] An Fe-Fe distance of about 4.4Å is required for a 2:1 iron-dioxygen complex.[4]

Three different approaches have been developed in attempts to synthesize stable reversible-oxygen carriers based on the porphyrin nucleus and in which protection of the dioxygen-binding site is provided by steric hindrance above the porphyrin plane; the "picket-fence" model (2),[5] the "capped" model (3),[6] and the "strapped" model (4).[7]



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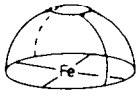

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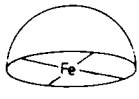

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So far however only the iron(II) complexes of the "picket-fence porphyrin" and the "capped porphyrins" have shown prolonged reversible-oxygenation behaviour at ambient temperature.[5,8]

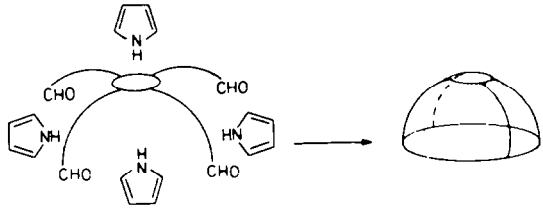
The "capped" model (3) was designed to provide a cavity for dioxygen binding in analogy to the natural systems and to prevent apical base binding on both faces of a metallated derivative since a 2:1 haemachrome complex $Fe^{II}(por)(B)_2$ is insensitive to oxygen.

The ability of the ligand structure to control the equilibrium and kinetic properties of chelates is becoming evident. Our initial synthesis of "capped porphyrin" has been extended to provide variation within the porphyrin ligand. Recent studies have shown that the 1-methyl-imidazole-("C_2-capped porphyrin") iron(II) complex (15) and the 1-methylimidazole-("C_3-capped porphyrin") iron(II) complex (23) have oxygen affinities similar to the T- and the R-state of haemoglobin respectively.[9,10]

In this paper we report our synthesis of "capped porphyrins", in full and also report some preliminary results of studies of carbon monoxide binding to their iron(II) complexes. The synthesis of "strapped metalloporphyrins" is reported in the accompanying paper.[11]

Synthesis of "Capped Porphyrins"

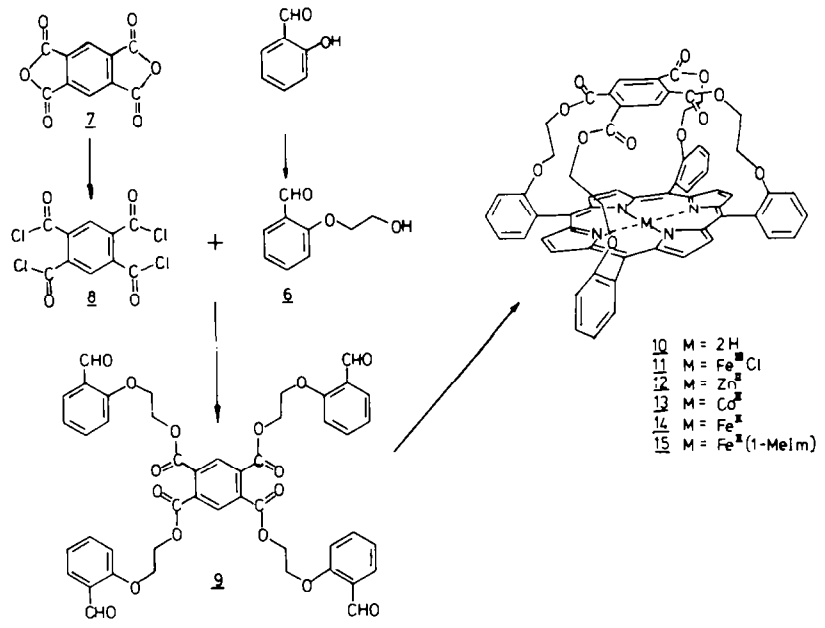
Previously we showed that a suitable tetraaldehyde (5) could be condensed with four equivalents of pyrrole to provide in one step a "capped porphyrin" which is necessarily a single meso-tetrasubstituted porphyrin isomer, scheme 2.



5 3

Scheme 2.

Variation within the tetraaldehyde allows for different cap sizes and for the synthesis of functionalized "capped porphyrins".[12] Since our initial report,[6] the reaction sequence to "C_2-capped porphyrin" (10) has been studied in depth and the overall yields have been improved markedly. The synthesis of porphyrin (10) is outlined in scheme 3.



Scheme 3.

Alkylation of the sodium salt of salicylaldehyde with 2-chloroethanol in boiling water for 16 hours afforded 2-(2-hydroxyethoxy)benzaldehyde(6) in 70% yield. The isolation of aldehyde (6) was carried out as far as possible at room temperature since hemiacetal and acetal impurities were obtained at higher temperatures under neutral conditions.

Acylation of four equivalents of (6) with pyromellitoyl chloride (8) in THF/triethylamine gave the required tetraaldehyde (9), which could be isolated by chromatography over silica in 72% yield. For large scale operations the tetraaldehyde (9) was conveniently crystallized directly from the reaction product in up to 42% yield (generally 25-30%), when aqueous acetonitrile was used as crystallization solvent.

The most significant increase in yield in our sequence resulted from the use of high dilution conditions for the condensation of pyrrole and tetraaldehyde (9) which enabled the capped porphyrin (10) to be isolated in good yield without chromatography. Under these conditions the competing linear polymerization reaction is minimized. These conditions with only minor variations were found to be suitable for the synthesis of other capped porphyrins in good yields.

Isolation of the "capped porphyrin" (10) was achieved by filtration and evaporation of the reaction solvent which yielded a crude product. Activated charcoal treatment of a chloroform solution of neutralized, dried reaction product removed polymeric and other polar impurities, and the porphyrin was isolated as glistening purple crystals.

The effect of the reaction conditions was investigated in order to optimize the yield of porphyrin. The results of this study are as follows.

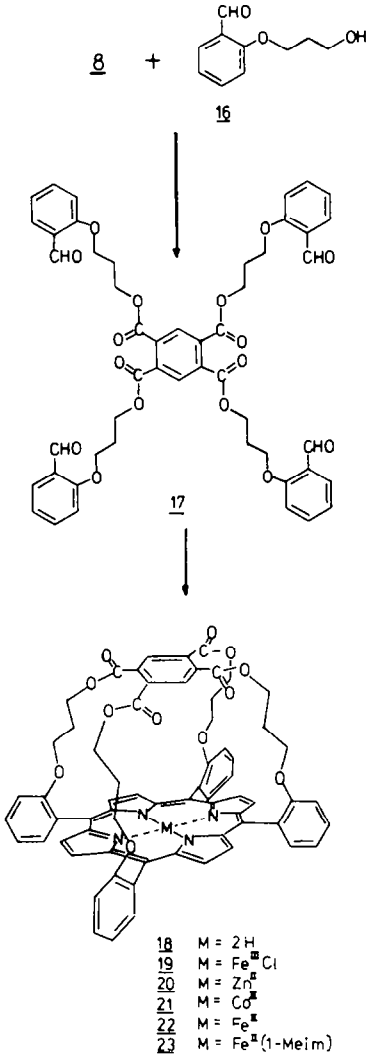
At a concentration of less than 2.3 x 10^{-3}M in (9) and a threefold excess of pyrrole the reaction afforded the porphyrin in 21-28%. The optimal reaction time appears to be about 1.5 hours since longer reactions gave appreciably more polymeric by-product from which isolation of porphyrin was difficult. At higher concentrations of (9) the yield of porphyrin was considerably lower and required chromatographic separation from considerable amounts of black polymer. Use of commercial-grade propionic acid without prior purification also resulted in lowered yields of porphyrin.

In all reactions the "C_2-capped porphyrin" (10) obtained was contaminated with trace amounts of the corresponding chlorin (λ_{max} 655 nm). Treatment of the crude porphyrin with DDQ gave analytically pure porphyrin with very high recovery.

A single-crystal X-ray structure of the "C_2-capped-porphyrin" (10) has recently been

determined,[13] and the spectroscopic properties of the "capped porphyrins" are discussed collectively below.

A similar reaction sequence starting from 2-(3-hydroxypropoxy)benzaldehyde (16) yielded the corresponding homologous or "C_3-capped porphyrin" (18) in which there is an extra methylene group in each rib of the capping structure, scheme 4.

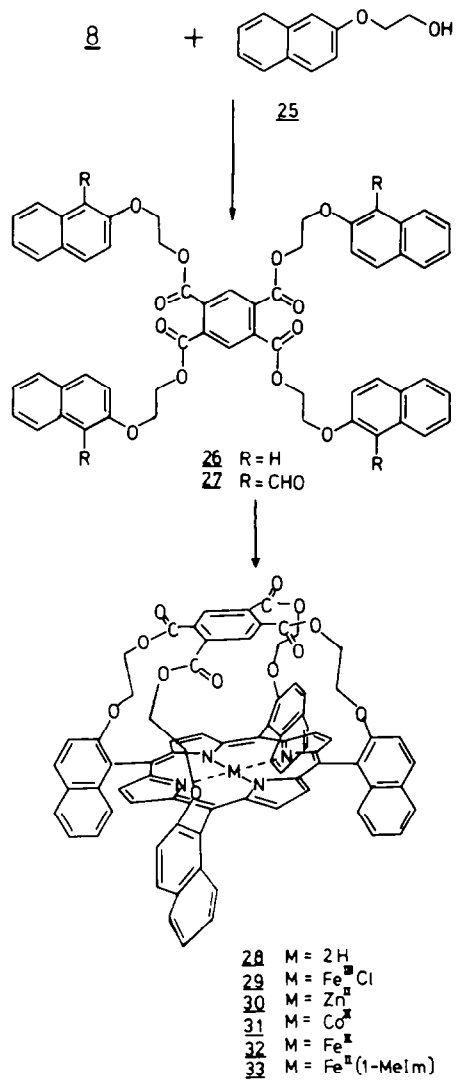


Scheme 4.

The starting benzaldehyde (16) was prepared from bromopropanol and the sodium salt of salicylaldehyde in 76% yield. The required tetraaldehyde (17) was obtained in 41% yield by reaction between the aldehyde (16) and the acid chloride (8).

Condensation of tetraaldehyde (17) and pyrrole, and charcoal and DDQ treatment of the product gave "C_3-capped porphyrin" (18) in 5% yield. The lower yield in this porphyrin-forming condensation than in the "C_2-capped porphyrin" cases is probably a consequence of the extra entropy factors required to form the larger cap. The synthesis of porphyrins with even larger capping structures by direct tetraaldehyde and pyrrole condensation might therefore be limited.

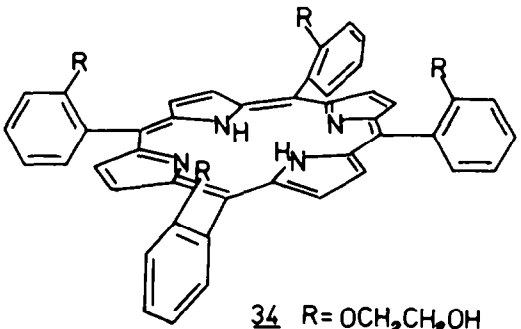
In an attempt to provide steric hindrance on both faces of the porphyrin to preclude the close approach necessary for formation of μ-oxo dimer, the corresponding "naphthyl-C_2-capped porphyrin" (28) was prepared, scheme 5. Thus alkylation of the



Scheme 5.

sodium salt of 2-naphthol (24) with ethylene oxide in a sealed bomb at temperatures up to 200°C afforded 2-(2-hydroxyethoxy)naphthalene (25) in 84% yield. Acylation of (25) with pyromellitoyl chloride (8) and formylation of the resultant tetraester (26) by the Vilsmeier procedure gave the naphthyltetra-aldehyde (27) in good overall yield. Condensation of (27) and pyrrole under high dilution conditions as before gave the "naphthyl-C_2-capped porphyrin" (28) in 13.6% yield. This porphyrin possesses a "picket-fence" type of open hindrance on the lower face to allow for apical base binding to the metallated derivatives, the capping structure being designed to prevent apical base binding on the upper face.

An alternative approach to the synthesis of "C_2-capped porphyrin" (10) involving formation of the cap at a stage later than the porphyrin-forming condensation was found to involve difficult separation of mixtures and the yield of (10) was low making this approach less useful. Thus the mixture of the four atropisomers (αααα, αααβ, αβαβ, ααββ)[14] of meso-tetra-(2-(2-hydroxyethoxy) phenyl)porphine (34), obtained in low yield by condensation of (9) and pyrrole, was acylated with pyromellitoyl chloride (8) in boiling phenol. The "capped porphyrin" (10) was isolated in 15% yield from the remaining



34 R= OCH_2CH_2OH
35 R= H

very polar polymeric material. The αααα-atropisomer of (34) was also obtained by cleavage of (10) with sodium ethoxide in ethanol at 0°C, and it was found to isomerize into a mixture of the four atropisomers very rapidly at ca 50°C. Since this temperature is well below that required for the capping reaction there was no advantage in using pure αααα-atropisomer as starting material.

Attempts to condense (34) with tetramethyl pyromellitate, using a catalytic amount of potassium t-butoxide, at temperatures up to 220°C gave only starting material. At higher temperatures extensive decomposition occurred. No reaction occurred between (34) and either (8) or tetramethyl pyro-mellitate in sulpholane heated at reflux. Attempts to extend this latter approach to other "capped porphyrins" by variation of the acylating agent were not promising.

The synthesis of other more-highly functionalized "capped porphyrins" in our laboratories has therefore followed our successful tetraaldehyde route outlined in scheme 2.

Each of the free-base "capped porphyrins" (10), (18) and (28) gave the correct molecular ion on field desorption mass spectral analysis. This technique is an extremely powerful one in porphyrin chemistry since most porphyrins desorb at approximately the same emitter currents and as little at 0.5% impurity is readily detected as only molecular ions are observed except for metalloporphyrins with weakly bonded apical ligands.[15] Demonstrated homogenity of samples by chromatographic analysis was thus confirmed by field desorption mass spectrometry.

The visible absorption spectrum of the porphyrins (10), (18) and (28) is very similar to that of meso-tetraphenylporphine (35). This suggests that in the free-base systems very little strain is introduced into the porphyrin ring by the capping structure. The meso-substituents do not contribute significantly to the porphyrin chromophore since steric interactions with the β-pyrrolic protons of the porphyrin ring result in the meso-phenyl substituents being essentially orthogonal to the plane of the porphyrin and thus deconjugated.[16]

The ^1H n.m.r. spectra of the "capped porphyrins" determined at 300 MHz are shown in figure 1. The spectra show C_{2v} symmetry

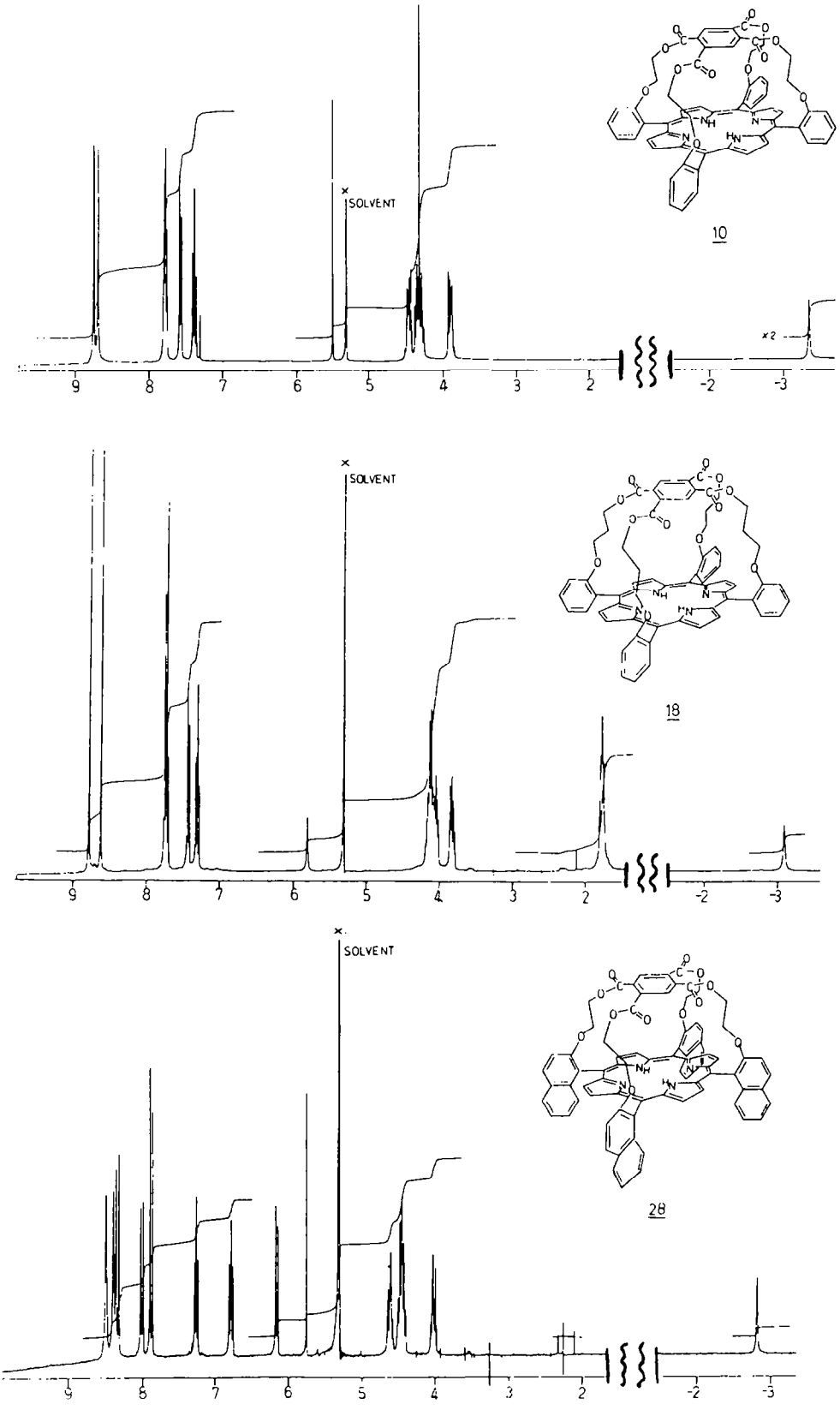


Figure 1. 300 MHz ^{1}H n.m.r. spectra of the "capped porphyrins" (10), (18) and (28).

for each of the porphyrins. The two protons of the "capping" benzene ring are shifted upfield (relative to the chemical shift of the protons in the corresponding tetraaldehyde) by the diamagnetic anisotropy of the suspended porphyrin. The chemical shift of these protons provide an indication of the distance between the plane of the "capping" benzene ring and the plane of the porphyrin ring. Variable temperature studies have shown that the spectra are deceptively simple and that the average separation of these planes varies with temperature, particularly in the case of "C_3-capped" porphyrin (18), and to a lesser extent in "C_2-capped" porphyrin (10), while the "naphthyl-C_2-capped" porphyrin (28) is essentially rigid. This degree of flexibility may have an important influence on oxygen and carbon monoxide affinities in the corresponding metalloporphyrins. The results of this work will be presented in a separate publication.[17]

Synthesis of "capped metalloporphyrins"

Reaction of "C_2-capped" porphyrin (10), with anhydrous ferrous chloride in THF heated at reflux for 18 hours under nitrogen gave chloro("C_2-capped porphyrin")iron(III) (11). Purification by chromatography on alumina converted (11) into ferric μ-oxo dimer, $(Por)Fe^{III}$-O-$Fe^{III}(Por)$ by facile ligand exchange. The dimer was reconverted to (11) quantitatively by treatment with hydrogen chloride in chloroform. The pure crystalline metalloporphyrin was obtained in 95% overall yield from (10). Similar treatment of "C_3-capped porphyrin" (18) gave the corresponding (chloro)iron(III) complex (19) in high overall yield.

Zinc(II) and cobalt(II) "capped porphyrin" complexes were obtained by standard reactions. Treatment of (10) with anhydrous zinc chloride in boiling DMF for 3 hours or with anhydrous zinc acetate in boiling chloroform-methanol solution for 20 minutes gave the zinc(II) complex (12) in quantitative yield. Similarly, reaction of (10) with cobaltous acetate gave the cobalt(II) complex (13). Zinc(II) "C_3-capped porphyrin" (20) and cobalt(II) "C_3-capped porphyrin" (21) were obtained in the same way.

Metallation of "naphthyl-C_2-capped porphyrin" (28) with anhydrous ferrous chloride was somewhat slower than the meso-phenyl-"capped porphyrins" (10) and (18). Complete metallation required heating for 4-6 days. This could be attributed to either extra steric hindrance in the vicinity of the metallation site compared with (10) and (18) or a greater impediment to distortion of the porphyrin structure to accommodate the metal ion which is too large to fit inside the porphyrin core and hence lies out of the plane of the porphyrin.[18] The (chloro)iron (III) complex (29) was recovered unchanged from chromatography on alumina. Ligand exchange and μ-oxo dimer formation is evidently impeded by the "picket-fence" hindrance on the open face of the porphyrin. Metallation of (28) with zinc acetate and cobaltous acetate gave (30) and (31) respectively.

Conversion of the five co-ordinate (chloro)iron(III) porphyrins into the iron(II) porphyrins was brought about by a number of reductants under an argon atmosphere. Successful reductions were carried out with sodium dithionite, chromous acetoacetate, sodium borohydride, ethanethiol and α-toluenethiol. Oxygenation studies and base equilibria studies on iron(II) "C_2-capped porphyrin" (14) and iron(II) "C_3-capped porphyrin" (22) have been described previously.[9,10,19,20] Similar studies on iron(II) "naphthyl-C_2-capped porphyrin" (32) will be reported separately.

Carbon Monoxide binding to Five-Coordinate Complexes

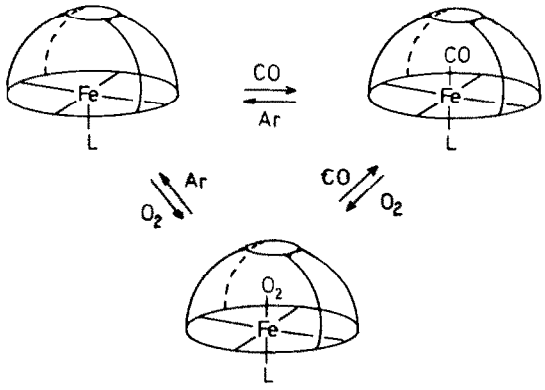
The haemoproteins haemoglobin and myoglobin have a much lower affinity for carbon monoxide than simple 1-methyl-imidazole(porphyrin)iron(II) complexes. This has been interpreted as being due to distortion and bending of the linear Fe-CO group by steric interactions with bulky amino acids near the binding site, thereby lowering the strength of the Fe-C bond.[21]

Since the oxygen affinities of the corresponding "capped porphyrin" systems are considerably lower than for the simple porphyrin systems and rather similar to those of the haemoproteins, we have investigated the ligation of carbon monoxide to iron(II) "capped porphyrin" in order to see if a similar correlation exists.

Exposure of a benzene solution of (14), containing 5% 1-methylimidazole to carbon monoxide at 25°C resulted in the irreversible formation of the carbon monoxide adduct, carbonyl(1-methylimidazole) ("C_2-capped porphyrin")iron(II) λ_{max} 426, 544, 581(sh) nm. The adduct was stable to freeze-thawing and attempted displacement of the carbon monoxide with dioxygen and with argon. Under identical conditions the same behaviour was observed for the iron (II) "naphthyl-C_2-capped" porphyrin system (32).

Figure 2. Visible spectrum of 1-methylimidazole-("C_3-capped porphyrin")iron(II) (24):
[————] under argon
[•— • —•] under carbon monoxide
[— — —] under argon after two carbonylation-decarbonylation cycles.

By contrast, a similar solution of iron(II) "C_3-capped porphyrin" (22) binds carbon monoxide reversibly at 25°C over several exchanges with dioxygen, or through the five-coordinate species (23) by freeze-thawing or flushing the system with argon, figure 2. This behaviour is summarised in scheme 6.



Scheme 6.

The visible spectrum of this carbon monoxide adduct λ_{max} 426, 545, 582(sh) nm is virtually identical with those of the carbon monoxide adducts of the other "capped porphyrin" systems, obtained irreversibly as described above, supporting the conclusion that the same six-coordination sphere is involved for each case.

Since 1-methylimidazole("C_3-capped" porphyrin)iron(II) (24) has 10^2 times lower affinity for oxygen ($P^{\frac{1}{2}}_{O_2}$ 120-180 Torr, 0°C in toluene) than the other "capped" porphyrin complexes (15) and (33) and about 10^4 times loweraffinity for oxygen than simple uncapped porphyrin systems it is clear that similar factors are influencing the carbon monoxide and dioxygen ligation properties of the complex. Results from H^1 NMR studies in progress suggest that the main factor may be steric interactions with the capping structure. Hence the distal groups in the haemoproteins may be playing an important role, not only in limiting carbon monoxide binding, but also in controlling dioxygen affinity.[17]

Studies involving the synthesis of more highly functionalized porphyrins, and pentadentate porphyrins are continuing in our laboratories, as is the synthesis of reversible oxygen-carriers based on other biological systems.

Acknowledgements We thank the National Science Foundation, the National Institutes of Health and the SRC for financial support and equipment. We wish also to thank Dr R.T. Aplin for mass spectral data.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus or a Kofler Micro Hot Stage block. Microanalyses were performed by Robertson Laboratory, Florham Park, New Jersey.

Infrared spectra were recorded on a Perkin-Elmer Model 700 Infrared Spectrophotometer and were calibrated against polystyrene. Ultraviolet and visible spectra were recorded on a Coleman Hitachi 124 Double Beam Spectrophotometer or on a Cary Model 14 Spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian Associates T-60 Spectrometer, on a Hitachi Perkin-Elmer R-22 spectrometer, or on a Bruker WH-300 spectrometer with an Oxford Instruments magnet. Field desorption mass spectra were obtained on a V.G. Micromass ZAB-2F; (7kV acc. voltage; emitter: + 3kV and 20-30 mA).

Silica gel for column chromatography was Merck Silica gel 60, No.7734. Alumina for chromatography was ICN aluminium oxide Woelm neutral, No.02087.

Solvents were purified by standard procedures. Solvents used in conjunction with air-sensitive compounds were deoxygenated either by freezing in liquid nitrogen, evacuating to less than 0.05 torr, sealing the vessel, and thawing (repeated over at least three freeze-pump-thaw cycles) or by refluxing for at least 10 min with a stream of argon being passed through the liquid, and then allowing the solvent to cool to room temperature while still being purged with argon.

Oxygen sensitive compounds were synthesized and manipulated using standard vacuum line techniques.[22] All glassware and connecting tubing used in the manipulation of oxygen sensitive compounds were carefully dried and made oxygen-free by placing the apparatus under an argon atmosphere, sealing the apparatus to argon, evacuating to less than 0.05 torr, and reopening the apparatus to argon (over three argon/vacuum cycles). Any trace of oxygen was removed from cylinder argon by passing it through a column (25 x 650 mm) of reduced BASF R3-11 catalyst at 150°C.

Pyromellitoyl chloride (8)

1,2,4,5-Benzenetetracarboxylic anhydride (7) (352.1 g) and phosphorus pentachloride (704.1 g) were melted together at 190° in a flask with a reflux condenser. The solution was then heated at 155° for 3 h, allowed to cool, and distilled first at atmospheric pressure to remove phosphorus oxychloride (b.p. 106°) and then at reduced pressure. The fraction b.p. 147-155°/0.65 mm Hg (471.7 g) was collected and redistilled to give a colourless fraction b.p. 125-133°/0.13 mm Hg which crystallized on standing to give (8) (436.4 g, 82.4%), m.p. 64° (lit.[23] 64°). IR: ν_{max} (nujol) (cm^{-1}); 1770. NMR: δ ($CDCl_3$): 8.32(s).

2-(2-Hydroxyethoxy)benzaldehyde (6)

Salicylaldehyde (1000.4 g) was added dropwise over 3½ h to a vigorously stirred solution of sodium hydroxide (328 g) in water (6000 ml). 2-Chloroethanol (644 g) was added dropwise over 1½ h and the solution was heated at 98° for 16 h. The solution was cooled and maintained at about 10° while sodium hydroxide was added until the solution was strongly alkaline (pH 10). The reaction mixture was extracted with methylene chloride (4 x 2000 ml). The combined extracts were washed with brine (3 x 1200 ml) dried ($MgSO_4$) filtered and evaporated to dryness at less than 35°. The resultant pale oil crystallized on drying under high vacuum to give the ether (6) as a colourless solid (930 g, 70% yield). Recrystallizations from dichloromethane/40-60° petrol after treatment with charcoal gave needles m.p. 46-46.5°. (Found: C, 64.79; H, 6.03. Calcd for $C_9H_{10}O_3$; C, 65.05; H, 6.07%). IR: ν_{max} (film) (cm^{-1}): 3400, 1680, 1600. MS: m/e 166(M+). NMR: δ($CDCl_3$): 3.86(br S, 1H, OH), 4.02 (m, 2H), 4.16(m, 2H), 6.95(d, J 8 Hz, 1H, H_3), 7.00 (t, J 9Hz, 1H, H_5), 7.52(dt J2 and 8 Hz, 1H, H_4). 7.78(dd, J 2 and 8 Hz, 1H, H_6), 10.38(s, 1H, CHO).

1,2,4,5-Tetrakis[2-(2-formylphenoxy)ethyl)] benzenetetracarboxylate (9)

A solution of pyromellitoyl chloride (8) (82 g) in dry THF (250 ml) was added over 3 h to a stirred solution of 2-(2-hydroxyethoxy) benzaldehyde (6) (166 g) and dry triethylamine (101 g) in dry THF (2000 ml), maintained at -20 ±5°. After the addition, the mixture was stirred for a further 1 h and allowed to warm up to ambient temperature overnight. Triethylamine hydrochloride was filtered off and washed with THF (200 ml). The combined filtrate and washings were evaporated (<35°) to a brown gum. The gum was dissolved in chloroform (1000 ml) and the organic phase washed successively with brine (3 x 500 ml) and water (1 x 500 ml), dried ($MgSO_4$), filtered and evaporated to dryness. The resultant oil was dissolved in acetonitrile (500 ml) and water (90 ml) was added dropwise to the stirred solution over 45 min. Further water (125 ml) was added to the stirred solution at ambient temperature from a constant addition funnel over 48 h. The solid was collected, washed with water (1500 ml) and dried over calcium sulphate at high vacuum to give the tetraaldehyde (9) as a colourless solid (88.2 g, 42%), m.p. 110-114°. Recrystallization from ethanol gave colourless crystals, m.p. 113-114°. (Found: C, 65.42; H, 4.70. Clcd for $C_{46}H_{38}O_{16}$ C, 65.25; H, 4.53%). IR: ν_{max} ($CHCl_3$) (cm^{-1}): 1735, 1690, 1600. MS: (FD) (m/e): 846(M^+). NMR: δ ($CDCl_3$): 4.39(m, 8H), 4.74(m, 8H), 7.05(m, 8H), 7.3-7.9 (m, 8H), 8.03 (s, 2H, H_3,H_6), 10.47 (s, 4H, CHO).

Preparation of "C_2-capped porphyrin" (10)

A 12L, three necked flask fitted with a mechanical stirrer, condenser, dropping funnel, and gas inlet tube was charged with propionic acid (9375 ml, redistilled from p-toluenesulphonic acid and then from potassium permanganate). A stream of air was blown through the vigorously stirred acid, which was heated to reflux. Redistilled pyrrole (13.5 g) was added to the solution. A solution of the tetraaldehyde (9) (20.0 g) in warm redistilled propionic acid (625 ml) was added over 10 min and when approximately half of the tetraaldehyde solution had been added further redistilled pyrrole (13.5 g) was added to the solution. The solution was heated at reflux for 1.5 h allowed to cool to 70° and filtered. The polymeric residues were washed with hot chloroform (2000 ml). The propionic acid filtrate was evaporated to dryness to leave a black solid with a purple sheen. The solid was dissolved in the chloroform washings and treated with saturated sodium bicarbonate solution (500 ml). The chloroform was removed by a rotary evaporator, the aqueous mixture filtered and the purple precipitate washed with water (3000 ml) until the washings were neutral. The solid was dried on the filter and then extracted with hot chloroform (2500 ml). The chloroform solution was heated at reflux with activated carbon (150 g) for 1 h, filtered and then treated twice more with activated carbon (50 g) in the same way. Evaporation of the final deep-red filtrate gave the "C_2-capped porphyrin" (10), slightly contaminated with the corresponding chlorin, as a lustrous purple solid (6.75 g, 28%); m.p. >260°. VIS: λ_{max} ($CHCl_3$) (nm): 422, 517, 548, 591, 647, 655(chlorin).

Chlorin-free "C_2-capped porphyrin" (10)

To a solution of "C_2-capped porphyrin" (8.84 g) in dry methylene chloride (3000 ml) was added a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (10.0 g) in dry benzene (1000 ml). The mixture was heated at reflux for 4 h and evaporated to dryness. The resultant dark solid was chromatographed over neutral alumina with chloroform. The fast-moving dark-red band afforded chlorin-free "C_2-capped porphyrin" as a purple solid (7.88 g, 89%). Recrystallization from methylene chloride/methanol gave lustrous purple needles; m.p. >300°. (Found: C, 71.8; H, 4.25; N, 5.4. Calcd for $C_{62}H_{44}N_4O_{12}$: C, 71.5; H, 4.45; N, 5.6%). M.W:(osmometric): 985. M.S: (FD) (m/e): 1036.2860; $C_{62}H_{44}N_4O_{12}$ requires 1036.2950. IR: ν_{max} (nujol) (cm^{-1}): 3320, 1725(br). VIS: λ_{max} (log ε) ($CHCl_3$) (nm): 405(sh) (4.73), 422 (5.48), 517 (4.20), 548 (3.62), 591 (3.70), 647 (3.32) NMR: δ (CD_2Cl_2): - 3.35 (br s, 2H, NH), 3.86 (m, 4H) 4.30 (m, 8H), 4.46 (m, 4H), 5.49 (s, 2H, capping benzene), 7.37 (dt, J 1.3 and 7.4 Hz, 4H), 7.56 (dd, J 8.8 and 1.3 Hz, 4H), 7.78 (m, 8H), 8.68 (s, 4H, pyrrolic CH), 8.74 (s, 4H, pyrrolic CH).

2-(3-Hydroxypropoxy)benzaldehyde (16)

Salicylaldehyde (91.5 g) was added dropwise (mechanical stirring) to a solution of sodium hydroxide (30 g) in water (1200 ml). 3-Bromopropanol (84 g) was added to the solution dropwise and the mixture was heated on a steambath for 12 h and allowed to cool overnight. The solution was made strongly alkaline (pH 10) by the addition of sodium hydroxide and extracted with chloroform (4 x 200 ml). The combined organic phase was washed with brine (3 x 200 ml), dried ($MgSO_4$), filtered and evaporated to yield 2-(3-hydroxypropoxy)benzaldehyde (16) as an oil, (82 g, 76% after removal of residual solvent at high vacuum). Distillation gave a clear liquid b.p. 120-122° at 1.8 x 10^{-3} mm Hg. (Found: C, 66.60; H, 6.62. Calcd for $C_{10}H_{12}O_3$; C, 66.65; H, 6.71%). MS: (m/e): 180; $C_{10}H_{12}O_3$ requires 180. IR: ν_{max} (film) (cm^{-1}): 3400, 1680. NMR: δ ($CDCl_3$): 2.1 (qnt, J 7 Hz, 2H) 3.9 (m, 2H), 4.3 (t_1 J 7 Hz, 2H), 6.9-7.7 (m, 4H), 10.4 (s, 1H, CHO).

1,2,4,5-Tetrakis[3-(2-formylphenoxy)propyl] benzenetetracarboxylate (17)

Pyromellitoyl chloride (8) (32.8 g) in dry THF (50 ml) was added dropwise to a mechanically stirred solution of (16) (70 g) and triethylamine (40.4 g) in dry THF (1450 ml), maintained at 0°. After the addition was complete the solution was kept at 0° for ½ h, allowed to warm to room temperature and stirred overnight.

Triethylamine hydrochloride was filtered off and the filtrate evaporated to dryness. The residue was dissolved in chloroform and the organic phase washed with 5% sodium bicarbonate solution, water, dried ($MgSO_4$), filtered and evaporated to dryness to yield a viscous oil. The oil was chromatographed over silica (500 g), eluting with dichloromethane-diethyl ether (9:1). The fast-moving band gave the tetraaldehyde (17) on work-up as a low melting solid (42 g, 41%). IR: ν_{max} (KBr disc) (cm^{-1}): 1730, 1685, 1600. MS: (FD) (m/e): 902(M^+). NMR: δ ($CDCl_3$): 2.3(qnt, J 7 Hz, 8H, $CH_2CH_2CH_2$) 4.2(t, 8H), 4.55(t, 8H), 7.5(m,16H), 8.0(s, 2H, capping benzene), 10.4 (s, 4H, CHO).

Preparation of "C_3-capped porphyrin" (18)

The condensation of the tetraaldehyde (17) and pyrrole in the same way as for the "C_2-capped porphyrin" (10) case above but on half the scale, and treatment of the isolated product with DDQ gave the "C_3-capped porphyrin" (18). Recrystallization from chloroform/methanol gave lustrous purple crystals (500 mg, 5% yield); m.p. >300°, IR: ν_{max} (nujol) (cm^{-1}): 3320, 1723 br; (CCl_4) (cm^{-1}): 3320, 1720. MS: (FD) (m/e): 1092(M^+). VIS λ_{max} (log ε) ($CHCl_3$) (nm): 405(sh) (4.49), 425(5.15), 485(sh) (3.32), 518(3.87), 551 (3.45), 595(3.46), 652(3.16). NMR: δ (CD_2Cl_2): -3.11 (br s, 2H, NH), 1.76(m, 8H, $CH_2CH_2CH_2$);3.82(m,4H), 4.09(m, 12H), 5.80(s, 2H, capping benzene), 7.29(dt, J 1 and 7.5 Hz, 4H), 7.42(br d,J 7.9 Hz 4H), 7.71(m, 8H), 8.61 (s, 4H, pyrrolic NH), 8.77(s, 4H, pyrollic NH).

2-(2-Hydroxyethoxy)naphthalene (25)

In a 3l autoclave was placed 2-naphthol (86.4 g), water (600 ml), sodium hydroxide (24.0 g) and THF (100 ml). The mixture was cooled in an acetone/dry ice bath and ethylene oxide (44.0 g) added. The autoclave was quickly sealed and with rocking heated at 200°C for 1½ h, allowed to cool to 60°C over 5½ h, and allowed to cool to ambient temperature overnight. The mixture was transferred to a round bottomed flask and THF distilled off at reduced pressure. The precipitate was collected, dissolved in chloroform (2500 ml) and the organic phase washed with aqueous sodium hydroxide (1M, 2 x 500 ml), water (3 x 1000 ml), dried ($MgSO_4$), filtered and evaporated to dryness, and the residue dried at high vacuum to yield (25) as a cream-coloured solid (95.0 g, 84%). Recrystallizations from chloroform/40-60° petrol after treatment with charcoal gave plates m.p. 73.5-74.5°. (Found: C, 76.46; H, 6.29. Calcd for $C_{12}H_{12}O_2$; C, 76.57; H, 6.43%) MS: (m/e): 188: $C_{12}H_{12}O_2$ requires 188. NMR: δ ($CDCl_3$): 2.56(br s, 1H, OH), 4.04 (m, 4H, CH_2CH_2), 6.9-7.7 (m, 7H).

1,2,4,5-Tetrakis[2-(2-naphthalenyloxy)ethyl] benzenetetracarboxylate (26)

To a stirred solution of the foregoing alcohol (25) (94.0 g) and triethylamine (50.5 g) in dry THF (1250 ml) kept at -20° was added, dropwise over 45 min a solution of pyromellitoylchloride (41.0 g) in dry THF (300 ml). The mixture was stirred for 1 h and then allowed to warm to room temperature overnight. Triethylamine hydrochloride was filtered off and washed with THF (200 ml). The filtrate and washings were evaporated to dryness. The resultant solid was taken up in chloroform (2000 ml) and the organic phase washed with brine (2 x 1000 ml), dried ($MgSO_4$), filtered and evaporated to dryness to yield the tetraester (26) as a pale yellow solid after extended drying in a vacuum (116 g,99%), m.p. 151-154°. Recrystallization from chloroform/methanol gave pale yellow crystals, m.p. 158-159°. IR: ν_{max} (KBr) (cm^{-1}): 1720, 1625, 1600, 1260. NMR: δ ($CDCl_3$): 4.25(m, 8H), 4.65 (m, 8H), 6.9-7.7 (m, 28H), 8.03(s, 2H, H_3 and H_6).

1,2,4,5-Tetrakis[2-(1-formyl-2-naphthalenyloxy) ethyl]benzenetetracarboxylate (27)

To a stirred mixture of phosphorus oxychloride (218 g) and N-methylformanilide (186. 3 g) under dry argon was added the tetraester (26)(112 g). The mixture was heated at 90° for 15 min, chlorobenzene (50 ml) was added and heating continued for a further 5 h. The mixture was poured into cold water (1500 ml) with stirring and the dark oil triturated to induce crystallization. The aqueous solution was decanted and the solid rubbed with further portions of cold water (2 x 2000 ml) and with acetone (3 x 500 ml) until washings were colourless. The solid was collected and dried under high vacuum to give the tetraaldehyde (27) as a cream-coloured solid (74.8 g, 60%), m.p. 191-192°. Recrystallization from glacial acetic acid did not raise the m.p. IR: ν_{max} (KBr) (cm^{-1}): 1730, 1668, 1620, 1595, 1270, 1245. MS: (FD) m/e: 1046(M^+). NMR: δ (d_6DMSO): 4.65 (m, 8H), 4.76(m, 8H), 7.51(ddd,J 1, 7, and 9 Hz, 4H), 7.57(d, J 9 Hz, 4H), 7.63(ddd, J 1, 7 and 9 Hz, 4H), 7.95(br d, J 9 Hz, 4H), 8.18(s, 2H), 8.25(d, J 9 Hz, 4H), 9.12(br, d, J 9 Hz, 4H), 10.81(s, 4H, CHO).

"Naphthyl-C_2-capped porphyrin" (28)

The condensation of the tetraaldehyde (27) and pyrrole in the same way as for the "C_2-capped porphyrin" (10) gave "naphthyl-C_2-capped porphyrin" (28) as a purple solid (3.22 g, 13.6%), m.p. >300°. Treatment with DDQ as above gave chlorin-free porphyrin as lustrous purple prisms (2.95 g) m.p. >300° (benzene/methanol). IR: λ_{max} ($CHCl_3$) (cm^{-1}): 1735 (sh), 1730. MS: (FD) (m/e): 1236; $C_{78}H_{52}O_{12}N_4$ requires 1236. VIS: λ_{max} (log ε) ($CHCl_3$) (nm): 405(sh) (4.84), 426(5.60), 485(sh) (3.68), 516(4.41), 547(3.66), 592 (3.88), 646(3.21). NMR: δ ($CDCl_3$): -2.67 (br s, 2H, pyrrolic NH), 4.0(m, 4H), 4.2-4.7 (m, 12H), 5.78(s, 2H), 6.23(d, J 9 Hz, 4H), 6.78(t J 9 Hz 4H), 7.18(t J 9 Hz,4H), 7.64 (d, J 9 Hz, 4H), 7.82(d, J 9 Hz, 4H), 8.10 (d, J 9 Hz, 4H), 8.25(s, 4H, pyrrolic CH), 8.45(s, 4H, pyrrolic CH).

Alternate route to "C_2-capped porphyrin" (10)

meso-Tetra (2-(2-propionoxyethoxy)phenyl) porphine (36)

A solution of 2-(hydroxyethoxy)benzaldehyde (6) (25 g) and pyrrole (10.1 g) in propionic acid (250 ml) was heated at reflux for ½ h, and evaporated to a tarry oil. The oil was dissolved in chloroform (500 ml) and the organic phase washed successively with 5% sodium bicarbonate solution (100 ml) and water, dried and evaporated to dryness. The resultant oil was chromatographed over silica gel with dichloromethane/diethyl ether. The red bandsgave a mixture of the tetraester, triester, diester, monoester, and tetra-alcohol atropisomers as a red-black oil (7.6 g, ca 20%). The title compound was isolated as a mixture of atropisomers following treatment of the porphyrin mixture with DDQ and chromatography over alumina with chloroform. The fast moving red band gave (36) as an oil (0.27 g, 0.7%). IR: ν_{max} (film) (cm^{-1}): 3330, 1725, 1595, 1585. NMR:δ ($CDCl_3$): 1.30(br, m 12H), 3.0(br m, 8H), 3.70(br m, 8H), 3.9(br m, 8H), 7.1-8.1(m, 16H), 8.7(s, 8H).

meso-Tetra-(2-(2-hydroxyethoxy)phenyl)porphine (34)

a) A solution of the porphyrin ester (36) (550 mg), and sodium hydroxide (1.0 g) in ethanol (100 ml) was heated at reflux for 1 h, and evaporated to dryness. The resultant green residue was partitioned between water (200 ml) and chloroform (500 ml). The organic layer was washed with water (2 x 300 ml), dried and evaporated to dryness to yield the title compound as a mixture of atropisomers as a black oil with a mauve sheen (430 mg, 99%). IR: ν_{max} (film) (cm^{-1}): 3400, 3330, 1595, 1585.

b) C_2-capped porphyrin (20 mg) was added to degassed dry ethanol (5 ml). To the stirred suspension under argon was added sodium (2 mg). Dry THF was added and the green solution stirred at 0°C for ½ h, evaporated to dryness and the residue partitioned between water

(20 ml) and dichloromethane (15 ml). The purple-brown organic layer was washed with water (2 x 10 ml), dried over Na_2SO_4 and evaporated to dryness at < 25° to yield αααα-(34) as a light-sensitive purple solid (15.5 mg, 94%), m.p. >300°. IR: ν_{max} (film) (cm^{-1}) 3400, 3300, 1595, 1585. NMR: δ($CDCl_3$): -1.6 (br s, 2H), 1.33(br s, 4H), 2.93(m, 8H), 3.75 (br m, 8H), 7.0-8.1(m, 16H), 8.75(s, 8H).

"C_2-capped porphyrin" (10)

The tetrahydroxyporphyrin (34) (100 mg) was dissolved in molten phenol (20 ml) and pyromellitoyl chloride (500 mg) was added. The solution was heated at reflux for 1.5 h, and the green mixture was taken up in chloroform. The chloroform solution was washed successively with 1N sodium hydroxide solution until the washings were basic, water, dried (Na_2SO_4) and evaporated to leave a brown residue. Chromatography of the solid over alumina with 3% methanol/dichloromethane and evaporation of the red band gave the "C_2-capped" porphyrin (10) (20.3 mg, 16%) m.p. >300° which had identical IR spectrum and chromatographic behaviour as authentic material from the preferred route above.

Synthesis of "Capped Metalloporphyrins"

Chloro("C_2-capped porphyrin")iron(III) (11)

A solution of anhydrous ferrous chloride (1.60 g) and "C_2-capped porphyrin" (10) (1.00 g) in dry THF (1000 ml) was heated at reflux for 15 h under dry argon. The solution was evaporated to dryness at 25° and the resultant solid extracted with chloroform (300 ml). The organic phase was washed with dil aqueous HCl (5 x 100 ml), and evaporated to dryness. The crude iron(III) complex was chromatographed over neutral alumina (Woelm, activity I, 165 g) using chloroform as eluant. The fast-moving main band was collected, λ_{max} 542, 580(sh) nm., and treated with anhydrous HCl gas for 3 min followed by argon, to remove residual HCl. The solution was evaporated and the resultant solid dried at high vacuum to give (11) as a mauve solid, (1.085 gm 99%), m.p. >300°. The compound was recrystallized from benzene/chloroform. μ 5.98 BM.[24] IR: ν_{max} (CS_2) (cm^{-1}): 1735. MS (FD) (m/e): 1125/1127 (M^+), 1090($M-Cl^+$). VIS: λ_{max} ($CHCl_3$) (nm): 383, 420, 513, 585.

Chloro("C_3-capped porphyrin")iron(III) (19)

Prepared in the same way as (11) above. Recrystallization (benzene/chloroform) gave (19) as purple-black crystals, m.p. >300°. IR: ν_{max} ($CHCl_3$) (cm^{-1}): 1715. MS: (FD) (m/e): 1181/1183(M^+) 1146($M-Cl^+$). VIS: λ_{max} ($CHCl_3$) (nm): 385, 425, 515, 585.

Chloro("naphthyl-C_2-capped porphyrin")iron(III) (29)

Prepared in the same way as (11) above, except that the reaction solution was heated for 6 days. Recrystallization (hexane/chloroform) gave (29) as purple-black crystals, m.p. >300°. IR: ν_{max} ($CHCl_3$) (cm^{-1}): 1735. MS: (FD) (m/e): 1325/1327 (M^+), VIS: λ_{max} ($CHCl_3$) (nm): 425, 514, 585, 659.

("C_2-capped porphyrin")zinc(II) (12)

a) Anhydrous zinc chloride (2.8 g) was added to a boiling solution of "C_2-capped porphyrin" (10) (1.1 g) in dry DMF (400 ml) and the solution heated at reflux for 3 h. The cooled solution was poured into cold water (1400 ml) and the suspension stirred for 30 min. The mauve solid was collected by filtration, dried and extracted with dichloromethane. The organic solution was dried (Na_2SO_4) and evaporated to yield (12) as a mauve-purple solid (1.15 g, 98%). Recrystallization from methanol/dichloromethane gave (12) as a purple solid, m.p. >300°. IR: ν_{max} (CCl_4) (cm^{-1}): 1738, 1725. MS: (FD) (m/e): 1100/1098 [$M(^{66}Zn)^+$,-$M(^{64}Zn)^+$]. VIS: λ_{max} (log ε) ($CHCl_3$) (nm): 403(sh) (4.49), 422(5.57), 510(3.53), 548 (4.31), 582(3.49). NMR: δ (CD_2Cl_2): 3.8-4.5 (m, 16H), 5.50(s, 2H, capping benzene), 7.1-8.0 (m, 16H), 8.82(s, 4H), 8.83(s, 4H).

b) As for the following compound (20) but with only 20 min reflux.

("C_3-capped porphyrin")zinc(II) (20)

A solution of anhydrous zinc acetate (110 mg) in dry methanol (4 ml) was added to a boiling solution of "C_3-capped porphyrin" (18), (60 mg) in boiling chloroform (20 ml). The solution was heated at reflux for 1 h, evaporated to dryness and the resultant solid extracted with dichloromethane. The organic solution was evaporated and the resultant solid was recrystallized from hexane/dichloromethane to give (20) as a pink solid (59 mg, 93%), m.p. >300°. IR: ν_{max} (CS_2) (cm^{-1}): 1750(br), 1730. MS: (FD) (m/e): 1154/1156 (M^+). VIS: λ_{max} (log ε) ($CHCl_3$) (nm): 404(sh) (4.52), 426(5.60), 518(3.50), 555(4.26), 594(3.70). NMR: δ ($CDCl_3$): 1.75(br t, 8H), 3.5-4.1 (m, 16H), 6.38(s, 2H, capping benzene), 7.1-8.0(m, 16H), 8.68(s, 4H), 8.78(s, 4H).

(Naphthyl-C_2-capped porphyrin)zinc(II) (30)

Prepared in the same way as (20) above, except that the reaction time was 15 min. Recrystallization from methanol/dichloromethane gave (30) as purple microcrystals (85%) m.p. >300°. (Found: C, 72.17; H, 3.99; N, 4.29. Calcd for $C_{78}H_{50}N_4O_{16}Zn$: C, 72.07; H, 3.88; N, 4.31%). MS: (FD) (m/e): 1298/1300 (M^+). VIS: λ_{max} (log ε) ($CHCl_3$) (nm): 404(sh) (4.56), 424(5.56), 507(3.62), 547 (4.41), 582(sh) (3.53). δ NMR: ($CDCl_3$): 3.85-4.8(m, 16H), 5.78(s, 2H, capping benzene), 6.12(d, J 8 Hz,4H), 6.69(br t, J 7 Hz, 4H), 7.19(br t, J 7 Hz, 4H), 7.73(d, J 7 Hz, 4H), 7.88(d, J 8 Hz, 8H), 8.18(d, J 8 Hz, 4H), 8.40(s, 4H), 8.48(s, 4H).

("C_2-capped porphyrin")cobalt(II) 13)

Cobaltous acetate tetrahydrate (250 mg) was added to a boiling solution of "C_2-capped porphyrin" (10) (200 mg) in chloroform (50 ml) and acetic acid (50 ml) and the solution heated a further 3½ h. The solution was allowed to cool and then washed with water (3 x 100 ml), dried (Na_2SO_4) and evaporated

to dryness. The resultant orange-red solid was recrystallized from hexane/dichloromethane to give (13) as a salmon-red solid (190 mg, 90%), m.p. >300°. (Found:C, 67.87; H, 4.10; N, 4.95. Calcd for $C_{62}H_{42}N_4O_{12}Co$; C, 68.04; H, 3.87, N, 5.12%). IR: ν_{max} ($CHCl_3$) (cm^{-1}): 1735(sh), 1730. MS: (FD) (m/e): 1093 (M^+). VIS: λ_{max} (log ε) ($CHCl_3$) (nm): 412(5.28), 528(4.05), 557(sh) 3.57).

("C_3-capped porphyrin")cobalt(II) (21)

Prepared in the same way as (13). Compound (21) was obtained as purple-red needles (from hexane/dichloromethane) in 87% yield, m.p. >300°. IR: ν_{max} ($CHCl_3$) (cm^{-1}): 1720(br). MS: (FD) (m/e): 1149 (M^+). VIS: λ_{max} (log ε) ($CHCl_3$) (nm): 416(5.14), 537 (4.06), 565(sh) 3.71).

("Naphthyl-C_2-capped porphyrin")cobalt(II) 31

By the same method as above, compound (31) was obtained in quantitative yield as a brick-red solid (from hexane/dichloromethane), m.p. >300°. IR: ν_{max} ($CHCl_3$) (cm^{-1}): 1735(sh), 1730. MS: (FD) (m/e): 1293(M^+). VIS: λ_{max} (log ε) ($CHCl_3$) nm: 416(5.38), 530(4.26), 560(sh) (4.00).

Iron(II) porphyrin complexes

The following reduction is typical of the general method which we used.

("C_2-capped porphyrin")iron(II) (14)

The (chloro)iron(III) complex (11) (500 mg) was mixed with excess chromous acetoacetate in a Schlenk apparatus under argon, and to the mixture was added dry degassed benzene (40 ml). The mixture was heated at 90° to complete dissolution and cooled immediately to room temperature. Dry, degassed methanol (90 ml) was added under argon to the clear red benzene solution. The mixture was allowed to stand at room temperature overnight and the solid collected by filtration under argon. The ferrous complex (14) was obtained as a microcrystalline brown-red solid and was dried under high vacuum for 8 h (383 mg, 79%). μ 4.10 BM^{24}. VIS: λ_{max} (degassed benzene) (nm): 420, 447, 537; (degassed benzene containing 5% 1-methylimidazole) 535, 565.

Carbon Monoxide Binding Studies

Carbon monoxide binding studies were carried out by the same method as has been described for oxygenation studies of synthetic porphyrin complexes.[5,8,9,10]

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