I. INTRODUCTION

Nature has found a prominent place for porphyrins and related macrocycles such as chlorins, bacteriochlorins, and corphins (Figure 1), particularly in their metallated forms. Iron protoporphyrin IX is the prosthetic group of heme proteins that serve diversified biological roles (Figure 2) including oxygen and electron transport and storage (hemoglobin and myoglobin), electron transfer (cytochromes), and biocatalysis (catalase, peroxidase, lignin peroxidase, cytochrome P450). The non metallated ("free base") porphyrins are generally present in organisms as precursors of metalloporphyrins and are accumulated and/or excreted in certain physiological disorders such as porphyrias [1]. The preferential localization of certain porphyrins in tumor cells, coupled with the ability of porphyrins to act as photosensitizers in the production of highly reactive singlet oxygen (which in turn exerts a cytotoxic action), has been used extensively in the novel treatment of malignant tissues and pathogens, a technique referred to as photodynamic therapy (PDT) [2,3].

Catalytic activity of heme enzymes is known to be controlled by changes associated with the macrocycle and by modifications of the protein matrix, which in addition to providing a suitable environment for substrate binding may also provide axial ligands to the metal center. As such, synthetic metalloporphyrins have been used extensively as biomimetic agents and thereby in
Figure 1  Tetrapyrrolic macrocycles and their numbering systems.

Figure 2  Biological roles of selected heme proteins.
attempts to understand the complex biological processes involved in enzymatic reactions. Furthermore such studies help in the design and development of protein-free in vitro catalysts which could be used to catalyze chemical reactions of industrial importance. In this context, cytochrome P450, the enzyme responsible for catalyzing the hydroxylation of nonpolar substrates (including drugs and pollutants) to yield partially water-soluble products, is probably the enzyme that has received the most attention of both chemists and biochemists [4]. Because of its role in dioxygen activation, understanding and successfully mimicking the catalytic cycle of cytochrome P450 has become extremely important in providing new and less expensive routes to hydroxylation of alkanes and epoxidation of olefins, both of which are industrially important reactions. Another enzyme that has received much attention, especially recently, is lignin peroxidase [5], produced by the lignolytic fungus *Phanerochaete chrysosporium*, which is responsible for the degradation of the biopolymer lignin. This is primarily due to the requirement for an environmentally acceptable delignification process as a substitute for the chlorine-based bleaching currently used in the pulp and paper industry.

With the increase in interest in porphyrins and metalloporphyrins from chemists of diverse backgrounds the necessity to access variously substituted porphyrins has been greater than in the past. Apart from the simplest symmetric porphyrins, most useful derivatives either are not commercially available or are priced beyond reach of an average researcher. In this chapter we will review the currently available major synthetic routes to porphyrins and suggest approaches to the construction of the macrocycle based on the substituents required at the periphery. It is appropriate that some of the salient features of porphyrins and metalloporphyrins be discussed first.

II. STRUCTURE AND PROPERTIES OF PORPHYRINS AND METALLOPORPHYRINS

The porphyrin nucleus (Figure 1) is a cyclic tetapyrrolic system consisting of a 20-carbon skeleton, the four pyrroles being linked by single carbon atom bridges. The nomenclature commonly used in porphyrin chemistry [6] was developed by Hans Fischer and is based on the numbering system shown in Figure 1A, where the pyrrolic (β) positions are numbered from 1 to 8 and the bridging (meso) positions named α, β, γ, and δ. Fischer nomenclature involves a large number of trivial names based on the substituents, which, however, do not convey any structural information. In addition, it involves a “type-isomer” system to distinguish between the different positional isomers. The inability of the Fischer system to name the large number of synthetic and newly isolated porphyrins led to the adoption of a systematic nomenclature based on the 1–24 numbering system (Figure 1B), developed by a
The porphyrin macrocycle contains a total of 22 \( \pi \) electrons with 18 \( \pi \) electrons in direct conjugation, conforming to Hückel's \( 4n + 2 \) rule for aromaticity. The two peripheral double bonds \( \Delta^7 \) and \( \Delta^{17} \) of rings B and D, respectively (Figure 1B) are cross-conjugated and can therefore be reduced while retaining the aromaticity of the molecule. As such, chlorin (the parent macrocycle of a variety of chlorophylls) with one peripheral double bond reduced and bacteriochlorin with both double bonds reduced still retain the aromaticity of the macrocycle. Of the 12 peripheral positions available for substitution, the reactivity of the eight pyrrolic positions (\( \beta \)) differ from that of the four bridging (meso) positions. It is also important to note that although porphyrins react primarily by substitution (electrophilic or radical) due to the aromatic nature of the macrocycle, the \( \Delta^7 \) and \( \Delta^{17} \) double bonds, which are not part of the direct conjugation, are known to react differently under certain reaction conditions [8].

Porphyrins exhibit characteristic absorption properties in the UV-visible region. The metal-free, their diprotonated forms, as well as metallated porphyrins have an intense absorption near 400 nm (\( \epsilon \approx 10^5 \)), referred to as the Soret band, which is characteristic of the macrocyclic system. In addition, the metal-free systems exhibit four less intense bands designated IV, III, II, and I, between 450 and 700 nm. The intensity and the exact positions of these bands are dependent on the solvent as well as the concentration. More importantly, correlations have been shown to exist between the relative intensities of the four bands and the nature and positions of the porphyrin side chains [9].

Four basic types of spectra have been observed based on the relative intensities of the four visible bands (Figure 3). Gouterman [9] proposed an interpretation of these spectral differences based on the perturbations of the \( \pi \)-electron levels by the electronic nature of the peripheral substituents.

### A. Etio Type

This type of spectrum is characterized by a IV > III > II > I order of intensity. Porphyrins in which six or more \( \beta \) positions have alkyl substituents with the other two being unsubstituted will exhibit an etio-type spectrum irrespective of the relative orientations of the substituents. In addition to etioporphyrin isomers (from which the name is derived), most naturally occurring porphyrins such as copro-, uro-, hemato-, proto-, and deuteroporphyrins exhibit this type of spectrum.
B. Rhodo Type

One strongly electron-withdrawing group (e.g., formyl, acetyl, or carboxyl) conjugated with the porphyrin ring causes a change in the intensity pattern $(III > IV > II > I)$ resulting in the rhodo-type spectrum (named after rhodoporphyrin). In addition, this produces a bathochromic shift of all bands in the spectrum. The rhodofying effect of one electron-withdrawing group is canceled by the presence of a similar group on an adjacent pyrrolic group, resulting in an etio-type spectrum. However, the effect on the red shift of absorption maxima is additive. We have shown that a rhodofying effect is also produced when the macrocycle is distorted by short-strap bridging, even without the introduction of any electron-withdrawing groups [10].

C. Oxorhodo Type

This spectral pattern, in which the intensities of the absorption maxima follow the order $III > II > IV > I$, is characteristic of porphyrins having
two electron-withdrawing groups on diagonally opposite pyrrole rings. This can be viewed as a further enhancement of the rhodofying effect.

D. Phyllo Type

This spectral pattern (IV > II > III > I) named after phylloporphyrin is distinguished from the etio type by less intense bands III and I. Two substitution patterns on the periphery are known to produce the phyllo-type spectrum: (a) a single meso-alkyl substitution and (b) four or more unsubstituted β positions.

As shown in Figure 4a, porphin (the unsubstituted parent porphyrin) exhibits a phyllotype spectrum [490, 520, 560, 568(sh), 614; Soret: 394 nm] while β-octaethylporphyrin (OEPPH₄) exhibits a typical etio-type spectrum (Figure 4b; 498, 534, 566, 620; Soret: 400 nm). However, most of the synthetic porphyrins, particularly those used in catalytic studies, exhibit spectral patterns that are different from any of the four types given above. The unsubstituted meso-tetraphenylporphyrin (TPPH₂) shows a modified etio-type four-band spectrum (Figure 4c; 514, 550, 588, 644; Soret: 418 nm) with an intense band IV. Tetraphenylporphyrins carrying ortho substituents on the phenyl groups show a significant reduction in the intensities of bands III and I relative to the corresponding para-substituted systems [11,12]. This is particularly so for the ortho-halogen (F, Cl, Br)-substituted porphyrins in which relative band intensities change to IV > II > III > I. This may be attributed to the restricted rotation of the phenyl groups resulting from steric interaction of the ortho-halogen substituent and the β-pyrrole hydrogen. meso-Tetrakis(pentafluorophenyl)porphyrin (TPFPFPH₂) with limited rotation exhibits a spectrum (506, 582; Soret: 412 nm) in which bands III (536 sh) and I (636 wk) are suppressed, while both meso-tetrakis(2,6-dichlorophenyl)porphyrin (TDCPPHP₂; 512, 588; Soret: 418 nm) and meso-tetrakis(penta-chlorophenyl)porphyrin (TPCPPH₂; 514, 590; Soret: 420 nm), whose bulky ortho-chloro substituents prevent free rotation of the phenyl groups, exhibit essentially two-band (corresponding to bands IV and II) spectra.

At low pH, the inner nitrogens of porphyrins are protonated to produce dicationic species whose visible spectra differ from those of the corresponding free base. As shown in Figure 4a, protonation changes the phyllo-type four-band spectrum of porphin to a single strong absorption at 544 nm with shoulders at 516 and 570 nm while the etio-type four-band spectrum of octaethylporphyrin changes to a two-band spectrum (548 and 590 nm) with a shoulder at 568 nm (Figure 4b). In acid, unsubstituted tetraphenylporphyrin shows a single broad band at 654 nm with a shoulder at 600 nm (Figure 4c) while the benzene ring-substituted tetraphenylporphyrins show a red shift
Figure 4  Absorption spectra of selected porphyrins: (a) porphine; (b) octaethylporphyrin; (c) tetraphenylporphyrin. ———, free base; ----, protonated dication.
of the two-band spectra [e.g., 576 and 624 nm for both meso-tetrakis(2,6-dichlorophenyl)porphyrin and meso-tetrakis(pentafluorophenyl)porphyrin].

The porphyrin dianion, formed by the removal of the inner NH protons, acts as a tetradeutate ligand capable of binding a wide variety of metal ions. Divalent metals such as Zn$^{2+}$, Mg$^{2+}$, Cu$^{2+}$, Fe$^{2+}$, Co$^{2+}$, and Ni$^{2+}$ form electrically neutral complexes which may either have a square-planar or octahedral geometry depending on the presence of axial ligation. Trivalent metals such as Fe$^{3+}$ and Mn$^{3+}$ carry anionic axial ligands to form electrically neutral pentacoordinate square-pyramidal complexes or hexacoordinate complexes with a neutral sixth ligand. Metallation leads to a simplification of the visible

Figure 5 Absorption spectra of meso-tetrakis(pentafluorophenyl)porphyrinatoiron(III): (a) chloride; (b) hydroxide; (c) $\mu$-oxo dimer.
region of the absorption spectrum while retaining the Soret absorption near 400 nm, primarily due to the change in the conjugated ring symmetry. For octaethylporphyrin and other porphyrins exhibiting etio-type spectra, coordination of a divalent metal results in two bands designated $\beta$ and $\alpha$ (between 500 and 600 nm), whose peak positions and relative intensities depend on the metal as well as the nature of the porphyrin ligand (e.g., OEP-Cu: 524, 560; Soret: 398 nm). In the tetraphenylporphyrin series, the visible region consists essentially of a single strong band with two shoulders [TPPCu: 502(sh), 538, 572(sh); Soret: 414 nm]. In the case of metalloporphyrins of trivalent metal ions, the UV-visible spectrum is significantly changed by the nature of the axial anionic ligand. *meso*-Tetrakis(pentafluorophenyl)porphyrinatoiron(III), (TPFPFeX; Figure 5a) shows a characteristic split Soret (350 and 410 nm) with two weak bands at 502 and 628 nm when the axial ligand $X = \text{Cl}^-$. When $X = \text{OH}^-$ (Figure 5b), a strong Soret band is observed at 406 nm with a weak band at 563 nm [13]. When steric factors permit, as in the case of TPFPPFeX, Fe(III)porphyrins are capable of forming oxo-bridged dimers (μ-oxo) whose UV-visible spectrum (e.g., Figure 5c) differs from that of the hydroxo complex in that the Soret and the $\beta$ bands are blue-shifted. Chromatographic purification of the hemin (following metal insertion) generally leads to the exchange of the axial ligand but the hemin can be regenerated by treating the resulting hydroxide (or the μ-oxo dimer) with hydrochloric acid.

Changes in the conjugation path affect the optical spectra of the porphyrin macrocycle significantly. Reduction of the one peripheral double bond, although not affecting the aromaticity of the molecule, produces a visible spectrum characterized by an intense long-wavelength absorption at $\lambda = 650-680$ nm (chlorins) while reduction of both $\Delta^6$ and $\Delta^7$ double bonds produces a strong absorption at $\lambda \sim 740$ nm (bacteriochlorins).

III. SYNTHESIS OF PORPHYRINS

A. Construction of the Macrocycle

Since the landmark synthesis of protohemin (iron protoporphyrin IX) by Hans Fischer in 1929 (which earned him the Nobel Prize), significant progress has been made in the field of porphyrin synthesis [14,15] especially through the efforts of A. W. Johnson, G. W. Kenner, S. F. MacDonald, and R. B. Woodward. During the first half of the 20th century, synthesis of porphyrins, like other areas of organic synthesis, was driven by the requirement for the establishment of structures of natural products. Each synthesis was based on the availability of structurally similar starting materials and the possibility of the introduction and modification of substituents by known chemical reactions. Since the mid-1960s, a new and more systematic approach to syn-
thesis has been adopted that focuses on the structural features of the target molecule rather than those of the starting material. Popularly known as retrosynthetic analysis, this approach transforms a synthetic target, in a stepwise manner, into progressively simpler systems that eventually lead to a readily available starting material [16]. The necessity to synthesize variously substituted porphyrins via multistep syntheses has resulted in proper planning by retrosynthetic analysis.

B. Symmetry and Substitution of the Target Molecule

The substitution pattern on the 12 peripheral positions of the target porphyrin molecule should form the basis of the synthetic strategy employed. Several elegant synthetic methods are available for the construction of the porphyrin macrocycle and a retrosynthetic analysis of the target system will narrow down the choices available even though certain routes are more convenient and/or produce higher yields than others. It is important to realize at the very outset that while certain substituents can be introduced after macrocyclization, others have to be already present in the pyrrolic precursor fragments.

The three most important factors to be taken into account in designing the synthesis are (a) the nature of the substituent; carbon- or heteroatom-bonded group, (b) the position of the substituent; \( \beta \) or meso, and (c) the overall symmetry of the molecule. Although most heteroatom substituents such as halogens, nitro, and sulfonic acid groups can be readily introduced onto the preformed porphyrin macrocycle because of the electrophilic (or radical) nature of their activity, carbon-bonded substituents such as alkyl and aryl as well as their derivatives usually need to be incorporated before or during macrocyclization. Furthermore, if such a substituent is required on a \( \beta \) position, that group or an interconvertible functional group has to be incorporated onto the pyrrole subunit during its synthesis from acyclic precursors. The most important factor, however, is the overall symmetry of the macrocycle. Symmetrically placed peripheral substituents in the target molecule allow a synthetic chemist to use a simple one- or two-step method for the construction of the macrocycle while highly unsymmetric systems such as those found in nature require multistep manipulations that require the skills of an experienced porphyrin chemist.

C. Retrosynthetic Analysis

Based on the currently available routes for the construction of the porphyrin macrocycle, retrosynthetic analysis of the target porphyrin would lead to several simple pyrrolic systems (Scheme 1). The choice of the route explored would depend on the nature and position of the substituent as well as how
that group would affect the reactivity of the pyrrolic precursor. This is particularly important in the case of electron-withdrawing β substituents since such groups reduce the electron density of the pyrrole, thereby affecting the electrophilic reactivity at the α position. The following skeletal disconnections lead to several simple synthetic precursors for porphyrins.

**Type 1 (Scheme 1a):** This approach disconnects the macrocycle into four pyrrole units and the meso carbons in a single step. This is possible only in highly symmetric porphyrins where the meso substituents as well as the β substituents are identical. In the synthetic direction, the most suitable functional group for the meso carbon is the aldehyde group with the substituent R attached to it. The pyrrole should be unsubstituted at the α position while the β positions may either be unsubstituted or may carry substituents that do not affect its reactivity. Although it is possible to prepare porphyrins having either different R groups or two different β substituents on each pyrrole, such approaches lead to a mixture of porphyrin products and/or isomers that will require tedious separation procedures.

**Type 2 (Scheme 1b):** This approach differs from type 1 in that the meso carbon is already attached to the 2 position of the pyrrole, which in turn carries the R group. In the synthetic direction this involves a self-condensation of a 2-substituted pyrrole via a pyrryl carbocation that undergoes a head-to-tail coupling of four units to give the porphyrin.

**Type 3 (Scheme 1c):** This disconnection leads to two identical dipyrrolic units and two meso carbons carrying substituent (R) groups. The dipyrrolic system is a 5,5'-unsubstituted dipyrromethane which can be coupled
with an appropriate aldehyde. This approach can be used where the target molecule carries different $\beta$ substituents (symmetrically placed) and different meso groups in the opposite positions.

Type 4 (Scheme 1d): This approach leads to dipyrrolic starting materials either directly by a simultaneous two-carbon disconnection or via linear tetrapyrroles by two one-carbon disconnections. This is undoubtedly the best method if the target molecule is unsymmetrically substituted. The linear tetrapyrroles can be built in a stepwise manner starting from monopyrroles that carry the required $\beta$ substituents and cyclized in the final step to give the porphyrin.

D. Synthetic Precursors

The above-mentioned disconnections lead to three types of pyrrolic precursors to porphyrins: monopyrroles, dipyrrolic systems, and linear tetrapyrroles. In order to transform these intermediates to porphyrins, they should be appropriately substituted at the $\alpha$ positions and the $\beta$ substituents should be so positioned that the reactivity of the fragment is not affected. The common precursors one encounters during porphyrin synthesis are given in Figure 6.

1. Dipyrrromethanes

Dipyrrromethanes contain two pyrrolic units linked by a methylene ($\text{CH}_2$) bridge (Figure 6a). They resemble monopyrroles in their reactivity especially in that the $\alpha$ position is more reactive than the $\beta$ position. They are prepared from monopyrroles by acid-catalyzed coupling methods but may undergo rearrangement to give isomeric mixtures under certain acidic conditions. In the coupling of dipyrrromethanes to yield porphyrins, the meso carbons are introduced as formyl groups, either directly linked to it (Scheme 1b) or coupled as an aldehyde (Scheme 1c).

2. Dipyrrromethenes

Dipyrrromethenes contain two pyrrolic units linked by a methine (CH) bridge and hence are oxidized forms of dipyrrromethanes. They are more stable in their protonated form. Figure 6b gives the four common dipyrrromethene pairs that are used for coupling where the meso carbons are provided by methyl or bromomethyl groups. A dipyrrrole of lesser importance is dipyrrroketone where two pyrroles are linked by a carbonyl group.

3. Linear Tetrapyrroles

The nomenclature of linear tetrapyrroles is related to that of bile pigments hence the prefix "bila") and the numbering is in accordance with the IUPAC
**Figure 6** Common pyrrolic precursors to porphyrins: (a) dipyrrromethanes; (b) dipyrrromethenes; (c) linear tetrapyrroles.
recommendations [7]. The stability of the tetrapyrrole increases with the introduction of unsaturation at the bridging carbons 5, 10, and 15 (a, b, c; Figure 6c) but the stability of saturated systems can be increased by the introduction of electron-withdrawing substituents. Bilenes b and biladienes a,c are the most commonly used linear tetrapyrroles in porphyrin synthesis.

IV. GENERAL SYNTHETIC METHODS

As stated earlier, the best approach to the synthesis of a desired porphyrin system is to analyze the target molecule retrosynthetically based on the symmetry of the system and the type and relative position of the substituents. This will lead to the most suitable precursors which can be used according to the established synthetic procedures. The synthetic methods currently available are grouped according to the precursors used.

A. Cocondensation of a Pyrrole and an Aldehyde

One of the most commonly used methods for the synthesis of porphyrins has been the reaction of pyrrole (or a 3,4-disubstituted pyrrole) with an aliphatic or aromatic aldehyde. This method, which produces meso-tetrasubstituted porphyrins, has limited synthetic value due to the symmetric nature of the porphyrin produced and the restrictions on the type (and position) of the substituent that can be introduced. However, due to the ease of carrying out the reaction, this method has been used extensively to prepare symmetric porphyrins, especially for catalytic studies.

+meso+Tetrasubstituted porphyrins (4; +A = H; Scheme 2) were first prepared in 1936 by Rothmund who heated pyrrole (1; +A = H) and an aldehyde (2) in pyridine in a sealed tube at 150°C for 24 h [17]. This reaction, which was later extended to include more than 25 aliphatic and aromatic aldehydes [18,19], had earlier been used to prepare the unsubstituted system porphin (4; +A = R = H) in 0.012% yield by reacting pyrrole and formaldehyde in methanol and pyridine [20]. The yields of porphyrins from this reaction were in general less than 3% and the product was contaminated with the corresponding chlorin, the 2,3-dihydroporphyrin. Ball et al. [21] obtained improved yields for TPPH₂ by adding zinc acetate to the reaction mixture, a modification that was later used by Badger et al. [11] to prepare several ortho-substituted tetrphenylporphyrins. However, the major drawbacks in this synthetic procedure continued to be the low yields and the difficulty of introducing sensitive substituents (using the appropriate benzaldehydes) due to the severe reaction conditions employed.

A major improvement in this area of cocondensation of pyrrole and aldehydes came from the work of Adler, Longo, and coworkers [22,23] when they showed that the yields of porphyrins can be greatly increased by carrying
out the reaction in acidic media, open to air. In refluxing propionic acid, this condensation gave yields of greater than 20%, where the product crystallized out on cooling, thus simplifying the purification procedure. Although higher yields (30–40%) were obtained by using acetic acid as the solvent, the product did not crystallize out due to the higher pKₐ of acetic acid, making the isolation and purification more difficult. As in the Rothmund synthesis, the isolated porphyrin was contaminated by the corresponding chlorin, which is indicated by the presence of a strong band ~ 650 nm in the absorption spectrum. Although this can be separated from the porphyrin by chromatography, significant loss of material occurs due to adsorption. The recommended method of purification is to treat the porphyrin/chlorin mixture with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in order to oxidize the chlorin to the porphyrin [24]. The progress of the reaction can be monitored by the disappearance of the band near 650 nm and subsequent chromatography on alumina removes the oxidant to yield a 95% recovery of the pure material. Several ortho-, meta-, and para-phenyl-substituted porphyrins have been prepared using this method [12].

Another general synthetic method for meso-tetraphenylporphyrins was developed recently by Lindsey et al. [25]. This takes into account the fact that under equilibrium conditions, the acid catalyzed condensation proceeds via the porphyrinogen 3. The intermediacy of the porphyrinogen in the Adler-Longo synthesis had been shown by Dolphin [26], who was able to isolate
$\beta$-octamethyl-meso-tetraphenylporphyrinogen (3; $A = \text{CH}_3$; $R = \text{C}_8\text{H}_8$) when 3,4-dimethylpyrrole was reacted with benzaldehyde under mild conditions (acetic acid, 50°C, 5 min). The porphyrin was obtained by treating it with an oxidizing agent (6 equivalents of iodine) since the oxidation of this sterically crowded porphyrinogen in air was slow. The Lindsey modification [25] is a two-step one-pot procedure where pyrrole and the aldehyde are initially condensed with a trace of acid catalysis under anaerobic conditions to produce the porphyrinogen, which is oxidized to the porphyrin by subsequently added oxidant. Extensive reaction optimization studies have shown that maximum yields of the porphyrin (30-40%) are obtained when equimolar concentrations ($10^{-2}$ M) of pyrrole and aldehyde are condensed in the presence of boron trifluoride etherate ($10^{-3}$ M). The reaction is generally carried out in a chlorocarbon solvent at ambient temperature for 1 h before the oxidant ($p$-chloranil or DDQ) is added. In most instances, evaporation of the solvent followed by flash chromatography affords the pure porphyrin.

Rothmund, Alder-Longo, and Lindsey methods (and modifications thereof) have all been used for the synthesis of meso-tetraphenylporphyrins with a wide variety of substituents on the phenyl groups. These include several biomimetic systems for heme oxygenation [27] as well as catalytic oxygen activation [28,29]. It is possible to prepare porphyrins carrying different groups at the meso positions by using mixed aldehydes in the cocondensation with pyrrole. However, this results in the formation of isomeric mixtures which have to be separated in order to obtain the desired porphyrin. The mild reaction conditions of the Lindsey method allow porphyrins to be prepared in good yields from sensitive aldehydes, but the optimum reaction concentration of $10^{-2}$ M poses a problem for any large-scale synthesis. The Adler-Longo method can therefore be considered complementary to the Lindsey method since it is amenable to scale-up for the synthesis of porphyrins in multigram quantities. However, the reaction of ortho-disubstituted benzaldehydes under the Adler-Longo conditions to produce the corresponding sterically hindered porphyrins has not met with much success. ortho-Disubstituted phenylporphyrins have been used extensively as catalysts since the bulky ortho substituents resist inactive $\mu$-oxo dimer formation and oxidative destruction during catalysis (Section VI). Although Longo et al. [30] reported the synthesis of both TPFPPH$_2$ (Adler-Longo conditions; 18% spectrophotometric yield, 11% crude product yield) and TPCPPH$_2$ (monochloroacetic acid/benzene; 7% spectrophotometric yield), no yields have been reported for the pure product. Furthermore, strong absorption bands (659 and 663 nm, respectively) are reported for the two compounds indicating that the porphyrin is contaminated with the corresponding chlorin. Kim et al. [12] have reported the synthesis of TDCPPH$_2$ in 0.7% yield by refluxing
a mixture of 2,6-dichlorobenzaldehyde and pyrrole in benzene in the presence of acetic acid. The yields have been improved using a modified Rothmund procedure (refluxing collidine instead of pyridinesealed tube) whereby the zinc complexes TPCPPZn and TDCPPZn have been synthesized in 4-10% yield [31,32]. The zinc complexes are demetallated with acid and treated with DDQ to obtain the pure porphyrin. However, under Lindsey conditions TDCPPH$_2$ and TPFPPH$_2$ have been synthesized in 40-50% yield [33]. This method allows the synthesis of the free base porphyrin directly with no necessity for removal of chlorin.

$\textit{meso}$-Tetramesitylporphyrin [TMPH$_2$, 4; $A=H$; $R=(C_6H_5(CH_3))_3$] is another sterically hindered porphyrin that has been used extensively for catalytic studies. Mesitaldehyde (2,4,6-trimethylbenzaldehyde) does not give the porphyrin product under either Adler-Longo or original Lindsey conditions, but has been converted to TMPH$_2$ in 4.5% yield under modified Rothmund conditions [34,35]. By a modification of the original Lindsey procedure (using ethanol for cocatalysis) it has been shown [36,37] that TMPH$_2$ can be synthesized in up to 29% yield under mild reaction conditions. Lindsey has extended this work to show that cocatalysis gives improved yields with 2-alkyl-, 2-alkoxy-, 2,6-dialkoxybenzaldehydes (in addition to 2,4,6-trialkylbenzaldehyde) but $\textit{ortho}$-halogen-substituted benzaldehydes (e.g., 2,6-dichloro-, 2,6-difluoro-, and pentafluorobenzaldehydes) show no increase in yields [33].

$\beta$-Octasubstituted $\textit{meso}$-tetraphenylporphyrins have also been synthesized by cocondensation of the 3,4-disubstituted pyrrole and the appropriate benzaldehyde. Dolphin [26] prepared $\beta$-octamethyl-$\textit{meso}$-tetraphenylporphyrin (4, $A=CH_3$; $R=C_6H_5$) in 43% yield by reacting 3,4-dimethylpyrrole with benzaldehyde in refluxing acetic acid, whereas Evans and Smith [38] prepared the analogous octaethyl-$\textit{meso}$-tetraphenylporphyrin in 10% yield starting from 3,4-diethylypyrrole. Using 3,4-diphenylpyrrole and benzaldehyde, Medforth and Smith [39] prepared dodecaphenylporphyrin (4; $A=R=C_6H_5$) in 5.7% yield under Lindsey conditions, whereas Takeda et al. [40] recently obtained a 55% yield of this porphyrin under modified Adler-Longo conditions (refluxing in acetic acid for 20 h followed by oxidation with DDQ).

A useful extension of the acid-catalyzed cocondensations of pyroles and aldehydes is the method developed by Cheng and LeGoff [41] to synthesize meso-unsubstituted $\beta$-substituted porphyrins. The reactions were carried out by refluxing ethanolic solutions of 3,4-disubstituted pyroles with excess of formaldehyde in the presence of hydrochloric or hydrobromic acids. After several hours of reflux, the reaction mixtures were allowed to stand exposed to air to complete oxidation. Several meso-unsubstituted porphyrins carrying the same alkyl group or different substituents (alkyl/acetyl,
alkyl/ester, and phenyl/ester) in the two $\beta$ positions of each pyrrole have been prepared in 64–96% yield. When the two $\beta$ substituents are different, isomeric mixtures are produced as expected. Changing the solvent (to methanol or tetrahydrofuran) or the aldehyde (to aliphatic or aromatic aldehydes) resulted in little or no porphyrin formation. Treibs and Haberle [42] obtained 77% $\beta$-octamethylporphyrin from the reaction of 3,4-dimethylpyrrole with formaldehyde in acetic acid and pyridine (Cheng and LeGoff report a 76% yield), while under similar reaction conditions 3,4-diphenylpyrrole gave $\beta$-octaphenylporphyrin (OPPH$_2$; 4, $A = C_6H_5$; $R = H$) in 26% yield [43]. Recently, Takeda and coworkers [44] prepared OPPH$_2$ in 72% yield by condensing 3,4-diphenylpyrrole with formaldehyde in ethanol/aq. HBr [cf. 41] and oxidizing the initially formed porphyrinogen with DDQ.

**B. Self-Condensation of 2-Substituted Pyrroles**

As shown in Scheme 3, this method uses the head-to-tail condensation of a monopyrrole 5 under acid conditions. The efficiency of this condensation reaction depends on the generation, stability and reactivity of the pyrryl-2-carbocation 6, produced by the removal of the leaving group (L) of the monopyrrole 5. The 5 position of the pyrrole should be unsubstituted or should carry a carboxyl group ($X = H$ or $CO_2H$), which would undergo facile elimination (decarboxylation) under the reaction conditions. As is not the case in the cocondensation described earlier, the nature of this reaction allows the $\beta$ substituents of the pyrrole to be different ($A \neq B$) and yet yield a single porphyrin product, although under certain acid concentrations the linear polypyrrolic intermediates are known to undergo fragmentation/recombination at the bridging carbons leading to isomer formation. Nature has chosen this method to construct the common tetrapyrrolic macrocycle uroporphyrinogen using the monopyrrole porphobilinogen (5, $A = CH_2CO_2H$; $B = CH_2CH_2CO_2H$; $R = H$; $X = H$; $L = NH_2$).

Siedel and Winkler [45] prepared several $\beta$-substituted porphyrins by heating 5-carboxy-3,4-dialkyl-2-hydroxymethylpyrroles either dry or in sol-
ution; the 3,4-dimethylpyrrole analog (5; A = B = CH₃; R = H; X = CO₂H; L = OH) produced a 46% yield of octamethylporphyrin (OMP) on heating at 160–170°C. However, if one or both β positions were unsubstituted, no porphyrin product was obtained. Octamethylporphyrin has also been prepared (as the copper complex) by reacting 2-aminomethyl-5-carboxy-3,4-dimethylpyrrole (5; A = B = CH₃; R = H; X = CO₂H; L = NH₂) with copper(II) acetate in refluxing methanol [46]. A template effect by the metal has been suggested because only traces of porphyrin were produced in the absence of metal. However, octaethylporphyrin (OEP), one of the most widely used porphyrin model systems, has also been made by a similar head-to-tail condensation, without any added metal salts. The precursor pyrrole used is 5-carboxy-3,4-diethyl-2-N,N-dimethylaminomethylpyrrole [5; A = B = CH₃; R = H; X = CO₂H; L = N(CH₃)₂]. This is refluxed in near-neutral aqueous solution to give initially the porphyrinogen, which is oxidized to the porphyrin in air [47,48]. The precursor pyroles for these syntheses are prepared from 3,4-dialkyl-5-methylpyrrole-2-carboxylates, which in turn are obtained from acyclic precursors by standard Knorr reactions [49]. A recent report describes the synthesis of several 2-(substituted methyl) pyroles and their transformations to porphyrins under near-neutral or basic conditions [50].

Porphyrins carrying β-fluoro substituents have also been synthesized by the cyclocondensation of the appropriately substituted pyroles. 2,7,12,17-Tetrakis(trifluoromethyl)-3,8,13,18-tetraethylporphyrin (7, A = C₆H₅; B = CF₃) has been prepared in 12% yield (as its copper complex) by refluxing 2-acetoxyethyl-5-carboxy-3-ethyl-4-trifluoromethylpyrrole (5; A = C₆H₅; B = CF₃; R = H; X = CO₂H; L = OOCCH₃) in acetic acid in the presence of copper acetate used as a template [51]. Once again, the starting pyrrole has been prepared via a modified Knorr reaction [52]. The analogous 2-hydroxymethylpyrrole (5; A = C₆H₅; B = CF₃; R = H; X = CO₂H; L = OH), however, has been converted to the same porphyrin product in 30% yield by a room temperature reaction in ethanol catalyzed by hydrobromic acid without added metal salts [53]. β-Fluoro-substituted 2-hydroxymethylpyrrole (5, A = CH₃; B = F; R = H; X = CO₂H; L = OH) has also been converted to the corresponding porphyrin, 2,7,12,17-tetrafluoro-3,8,13,18-tetramethylporphyrin by refluxing in acetic acid in the presence of potassium ferricyanide although in low 2% yield [54]. In the latter two cases, the starting pyrroles carrying the appropriate β substituents were prepared by special reactions.

Another porphyrin synthesis that involves a self-condensation of a 2-hydroxymethylpyrrole uses as the starting material 3,4-disubstituted pyrrole-2-carboxylate esters. The ester at the 2 position is reduced in situ with lithium aluminum hydride to give the corresponding 2-hydroxymethylpyrrole pre-
cursor (5, R = X = H; L = OH), which is cyclocondensed in dichloromethane (without isolation) using *p*-toluenesulfonic acid as catalyst [55]. This method has been used to synthesize, in good yields, a series of porphyrins carrying a variety of β substituents including alkyl groups, substituted (2-, 3-, 4- as well as 2,6 and 2,4,6-) phenyl groups and ester groups. It has been shown that the ester group in the α position of the starting pyrrole is selectively reduced by lithium aluminum hydride leaving any ester groups at the β position unaffected [56]. The appropriately β-substituted 5-unsubstituted pyrrole-2-carboxylate esters required for this synthesis are prepared by the reaction of nitroolefins or β-acetoxynitro compounds with α-isocyanates in the presence of an organic base [57].

Self-condensation of β-unsubstituted 2-hydroxymethylpyrrole (5, A = B = R = X = H; L = OH) has been used to prepare porphin itself. Krol [58] obtained yields of up to 5% by treating dilute solutions of the above pyrrole with potassium persulfate in glacial acetic acid at 60°C. Longo et al. [59] reported yields as high as 18% for this synthesis by carrying out the cyclocondensation in dilute ethylbenzene solutions at 100°C over a period of 11 days. Yalman [60] emphasized the importance of the metal template effect in his reported synthesis of copper porphin (1-20% yield) by adding a precooled solution of 2-hydroxymethylpyrrole in ether/dimethylformamide/acetic acid to a preheated (145°C) mixture of excess copper acetate and dimethylformamide.

Recently, a new synthesis was been reported [61] for the meso-tetra-substituted porphyrins via the self-condensation of β-unsubstituted 2-hydroxymethylpyrroles 5 (A = B = H; X = CO₂H; L' = OH) where the R group is alkyl or aryl. The reactions have been carried out in refluxing propionic acid with yields ranging from 9% to 34%. Addition of zinc acetate to the reaction mixture improves the yield by 30-200%, which once again suggests a template effect of the metal. The R group was introduced into the pyrrole precursor via a Vilsmeier-type acylation followed by reduction with lithium aluminum hydride.

**C. Direct Coupling of Dipyrrolic Intermediates**

This method, commonly referred to as the “2 + 2 synthesis,” has been used extensively in porphyrin synthesis due to the variety of unsymmetric β-substituent patterns that can be accessed. It is important to note that only one of the two components needs to be symmetric to ensure a single porphyrin product. Dipyrrromethanes and dipyrrromethenes are the widely used intermediates in the 2 + 2 syntheses and must carry suitable functional groups at the α positions in order to couple to each other. These can be prepared starting from monopyrroles, which are easily obtained by the classical Knorr reactions followed by functional group modifications [49].
SYNTHETIC ASPECTS OF Porphyrin CHEMISTRY

1. Porphyrins from Dipyrromethenes

The 2 + 2 synthesis using dipyrromethenes as intermediates formed the backbone of Fischer’s classical porphyrin syntheses [62]. The coupling reaction involved the fusion, in succinic acid, of one of four pairs of dipyrromethene intermediates shown in Figure 6b. The yields were generally low since the sensitive β substituents did not survive the harsh reaction conditions. Self-condensation of dipyrromethenes has been used in the synthesis of porphyrins under milder reaction conditions [63]. The appropriately substituted 5'-bromo-5-methyl dipyrromethenes (111) in refluxing formic acid (one equivalent of added bromine) produced etioporphyrin I and coproporphyrin I in up to 60% yield. This synthesis can be generalized to prepare porphyrins of C2 symmetry using the more readily available 5'-carboxy-5-methyl dipyrromethene, which is brominatively decarboxylated under the reaction conditions. It has also been shown that the dipyrromethene pair IV (Figure 6b) can be used to synthesize porphyrins under similar reaction conditions [64].

2. Porphyrins from Dipyrromethanes

MacDonald [65] developed an alternative 2 + 2 synthesis that uses dipyrromethanes, a procedure later modified by Kenner [66]. This method (Scheme 4) involves the condensation of 5,5'-diformyldipyrromethanes (8) with 5,5'-diumunsubstituted dipyrromethanes (9) under mild acid catalysis. The intermediate porphodimethene (11) is rapidly oxidized to the porphyrin in air. Under the same conditions, 5'-unsubstituted 5-formyldipyrromethanes (10) can undergo self-condensation to give porphyrins 12a or 12b of twofold axial symmetry [67]. This method has been used successfully in the synthesis of highly deformed porphyrins [68], hindered capped porphyrins [69], and functionalized capped porphyrins [70]. Ogoshi and coworkers recently developed a modified 2 + 2 coupling of dipyrromethanes where instead of the 5,5'-diformyldipyrromethane (8), a 5,5'-bis(hydroxybenzyl)dipyrromethane was coupled with a 5,5'-diumunsubstituted dipyrromethene (9) to give unsymmetric 5,15-diphenylporphyrins [71].

A useful extension of this 2 + 2 coupling was reported by Ogoshi et al. [72] who cocondensed β-alkyl-5,5'-unsubstituted dipyrromethanes (13) and aromatic aldehydes (14) to prepare 5,15-diaryl-β-octaalkyporphyrins (16) according to Scheme 5. By carrying out the reactions in refluxing propionic acid in the presence of zinc acetate, several porphyrins with substituted phenyl groups in the meso positions were obtained (as the zinc complex) in 15-25% yield, while the reaction in benzene with catalytic quantities of trifluoroacetic acid gave higher (30-40%) yields of the desired porphyrins after air oxidation. As in the acid-catalyzed cocondensation of pyrrole and benzaldehydes, this reaction was shown by Gunter and Mander [73] to proceed via a porphyrinogen intermediate (15). In the reaction of β-tetramethylid-
i) HI in CH$_3$CO$_2$H, then CH$_3$CO$_2$Na and O$_2$
ii) TsOH in CH$_3$OH/CH$_2$Cl$_2$, then CH$_3$CO$_2$Na and O$_2$

**Scheme 4**
pyrromethane (13, \(A = B = \text{CH}_3\)) with ortho-nitrobenzaldehyde carried out in methanol with catalytic amounts of \(p\)-toluenesulfonic acid, they isolated the porphyrinogen in >60% yield and subsequently oxidized it quantitatively to the porphyrin using a quinone oxidant.

Several useful modifications of this synthesis have been reported, primarily to improve yields and increase the stability of the sensitive substituents. Manka and Lawrence [74] reported the synthesis of a series of \(\beta\)-unsubstituted 5,15-dialkylporphyrins (73–92% yield) by carrying out the cocondensation of 3,3',4,4'-unsubstituted dipyrromethane (13; \(A = B = \text{H}\)) and substituted benzaldehydes in dichloromethane at room temperature in the presence of catalytic amounts of trifluoroacetic acid, the intermediate being oxidized with \(p\)-chloranil. Maruyama and coworkers used milder conditions (trichloroacetic acid/acetonitrile) to prepare a series of 5,15-dialkylporphyrins (52–87% yield) carrying acid-labile substituents on the phenyl groups [75]. This system appears to be attractive for model building purposes, i.e., for sterically hindered porphyrins [76], strapped porphyrins, and face-to-face dimers [77]; for porphyrin oligomers for photosynthetic charge separation studies [78]; as well as for carotenoid-linked porphyrins used in intramolecular energy transfer studies [79].

D. Cyclization of Linear Tetrapyroles

The need to synthesize porphyrins with totally unsymmetric \(\beta\) substitution led to the development of procedures involving the coupling of individual pyrroles in an unambiguous manner to give a linear tetrapyrole, which is cyclized in the final step to give the desired porphyrin. Of the four types of linear tetrapyroles shown in Figure 6c, bilenes b and biladienes ac are the most commonly used precursors to porphyrins [80].

1. Porphyrins from Bilenes b

Bilenes b (19) are prepared [80,81] (Scheme 6) by the acid-catalyzed decarboxylative coupling of 5-carboxydipyrromethane (17) with a 5-formyldipyrromethane (18). The most commonly prepared bilene is the 1,19-dimethyl derivative 19, which is readily cyclized to the copper complex of the porphyrin (20) using cupric salts. The free base porphyrin (21) is obtained by the removal of copper with strong acids.

2. Porphyrins from Biladienes ac

Biladienes ac are usually prepared and handled in their protonated form, commonly as the crystalline dihydrobromides. Their inherent stability makes them the most commonly used linear tetrapyrole in porphyrin synthesis. Biladienes ac (24) were originally prepared by Johnson and Kay [82] by the
Scheme 6

Scheme 7

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acid-catalyzed condensation of two equivalents of 2-formyl-5-methylpyrrole (23) with a dipyrromethene-5,5'-dicarboxylic acid (22) or, alternatively, of 5-unsubstituted 2-methylpyrrole (26) with 5,5'-diformalidipyrromethane (25) (Scheme 7). Cyclization of the biladiene was effected with cupric salts to give the porphyrin copper complex in 20-30% yield.

The symmetry imposed on this system, i.e., the terminal rings having a symmetric arrangement of substituents, has since been removed by a completely stepwise approach. Differentially protected benzyl tert-butylpyrromethene-5,5'-dicarboxylates can be selectively decarboxylated (by hydrogenolysis or acid cleavage) and coupled with a 2-formylpyrrole to give initially a tripyrrin. Removal of the remaining ester allows the coupling of a different formylpyrrole to give the biladiene ac whose β-substituent arrangement can be totally unsymmetric [83-85].

Johnson and coworkers [86] developed a regioselective synthesis of octaalkylporphyrins using 1-bromo-19-methylbiladienes ac as the tetrapyrrolic precursor. As shown in Scheme 8, the biladiene is prepared from dipyrromethenes rather than dipyrromethanes. A 5'-bromo-5-bromomethyl-dipyrromethene 29 is reacted with a 5'-unsubstituted 5-methyleneipyrromethene 28 in the presence of tin(IV) chloride to give the tin complex of the biladiene, which on treatment with methanolic hydrobromic acid produces the required biladiene 30 (as its dihydrobromide salt), in 80-95% yield. This is cyclized to the porphyrin either in refluxing o-dichlorobenzene (15 min) [86] or by allowing a solution in dimethylsulfoxide/pyridine to stand at room tempera-
ture for several days in the dark [87]. The yields reported for the cyclization step vary from 30% to 78%. Although this two-step procedure is by far the mildest for the synthesis of unsymmetric porphyrins in high yield, it was not exploited to the fullest extent for some time due to the limited accessibility of the obligatory dipyrromethene components 28 and 29. Significant improvements and modifications of some of the existing methodology for the synthesis of these dipyrromethenes (hence the biladienes and porphyrins) have been developed, the details of which were reviewed recently [88]. This two-step procedure has been employed to synthesize several porphyrins in high yield; these include unsymmetric porphyrins, e.g., etioporphyrin III [89], singly and doubly linked porphyrin dimers [90,91], β-unsubstituted porphyrins [92] as well as porphyrins with sensitive functional groups, e.g., mono- and divinylporphyrins [92,93] and uroporphyrins I and III [94].

V. METALLATIONS AND DEMETALLATIONS OF PORPHYRINS

The tetradeutate anionic porphyrinate ligand generated by the loss of the two inner NH protons is very versatile in its coordination chemistry, and almost all metals and some metalloids have been combined with it. Five essential stages can be identified in the synthesis of a metalloporphyrin [95]:

A. Protonation-Deprotonation Equilibria

\[ \text{H}_4\text{P}^{2+} \rightleftharpoons \text{H}_3\text{P}^+ \rightleftharpoons \text{H}_2\text{P} \rightleftharpoons \text{HP}^- \rightleftharpoons \text{P}^{2-} \]

Deprotonation of the free base porphyrin \( \text{H}_2\text{P} \) occurs so as to produce the dianion \( \text{P}^{2-} \) which coordinates to the metal ion. The presence of strong acids therefore retards metallation reactions and any reagent (or solvent) that absorbs the protons generated (decreases the acidity or buffers the system) will favor it.

B. Release of Metal Ion from the “Metal Carrier”

The metal carrier dissociates in the reaction medium producing a coordinatively unsaturated species which can combine with the dianion \( \text{P}^{2-} \). The choice of the carrier depends on its activity, its availability and its solubility in the solvent used to dissolve the porphyrin.

C. Formation of the MN₄ System

The initial metallation reaction involves the coordination of the four pyrrole nitrogen atoms to the metal. For divalent metal ions which prefer square-planar arrangements (e.g., Ni, Cu), this produces a stable metalloporphyrin complex.


**D. Charge Neutralization**

For metal ions with a charge greater than $2^+$, the above step produces a charged metalloporphylin. In order to attain electroneutrality, axial coordinadination is built up with anionic ligands. For $\text{Fe}^{3+}$ and $\text{Cl}^-$, the square-pyramidal PFeCl$_4$ that is formed has the metal center coordinatively saturated, thus producing a stable metalloporphylin complex. It is important to note that chromatographic purification using added polar solvents (e.g., methanol) generally results in axial ligand exchange which can be distinguished by absorption spectroscopy (see Section II). Treatment with dilute aqueous hydrochloric acid usually regenerates the chloride form.

**E. Completion of the Coordination Sphere**

For metal ions that prefer octahedral geometry, the coordination sphere is completed by further complexation with neutral donor ligands such as water, pyridine, etc.

As discussed in Section II, metal insertion leads to a change in the absorption spectrum, particularly in the 500-700 nm region. Absorption spectroscopy can therefore be used to monitor metal insertion reactions. Buchler [95] discussed in detail the different metallating systems classified by solvent as well as the metal carrier. No single metal insertion procedure is applicable to all metals or porphyrins and special precaution should be taken with porphyrins carrying sensitive functional groups. Metallation is best carried out in solutions as concentrated as possible since dilute solutions tend to slow the bimolecular reaction significantly. This would result in longer reaction times, which for high-boiling solvent systems could lead to decomposition of starting material or product. For the catalytically useful metals such as iron and manganese, insertion is carried out with the M(II) salts, but subsequent autoxidation under aerobic conditions produces the stable higher oxidation states M(III). Some common metallating methods are briefly discussed below [95,96].

**F. Chloroform/Methanol Method**

A refluxing concentrated chloroform solution of the porphyrin is treated with a saturated solution of the metal(II) acetate and the insertion is followed by absorption spectroscopy. Upon completion, the reaction mixture is concentrated and diluted with methanol to yield the metalloporphylin in near-quantitative yield. For acid-sensitive systems (e.g., zinc), it is recommended that some sodium acetate be added to buffer the medium. This method has been used to introduce divalent metal ions such as Zn(II), Co(II), Cu(II), and Ni(II), the last of which requires longer reaction times.
Another organic solvent that we have found useful, particularly for the insertion of iron to \( \beta \)-alkylporphyrins, is tetrahydrofuran (THF) because of the good solubility properties of porphyrins in this solvent. Furthermore, both chloroform and THF are low-boiling solvents which reduce the thermal decomposition of sensitive substituents.

G. Acetic Acid/Acetate Method [97–99]

The metal salt, usually the acetate, is heated with the porphyrin in acetic acid at 100°C. The product is crystallized either directly by cooling or by the addition of water or methanol. This method is applicable to the synthesis of metalloporphyrins of most divalent metal ions; Mn(II) and Fe(II) are autoxidized to the more stable high oxidation state. Once again, the use of sodium acetate is recommended for the synthesis of acid-sensitive systems.

H. Dimethylformamide Method [100]

Adler et al. showed that several metals can be conveniently introduced into porphyrins by refluxing a metal salt (usually metal chlorides) in dimethylformamide (DMF). DMF is a uniformly good solvent for both porphyrins and metal salts. The HCl produced in the reaction escapes at the reflux temperature of the solvent. This is the method of choice for phenyl- and/or pyrrole-substituted meso-tetraphenylporphyrins primarily due to their insolubility in low-boiling solvents and also due to their higher thermal stability. The product is crystallized directly by dilution with water or with dilute HCl (3–6 N) to dissolve the excess metal salts in the reaction mixture.

A major disadvantage of this solvent is that at reflux it decomposes into dimethylamine which, though neutralizing the HCl produced in the reaction, can lead to complicating side reactions, if long reaction times are required. This is particularly so in the case of highly electron-deficient halogenated porphyrin systems where dimethylamine may act as a nucleophile leading either to halogen substitution [101] or to porphyrin destruction. We have observed that \( \beta \)-octachloro-meso-tetrakis(4-sulfonatophenyl)porphyrin undergoes rapid decomposition if iron insertion is attempted in DMF [102]. This is probably due to the lack of steric protection at the meso positions (ortho-phenyl positions being unsubstituted), allowing attack by a nucleophile leading to ring opening.

I. Pyridine Method [103]

This is a useful method for metalloporphyrins labile toward acetic acid since pyridine is a good solvent for porphyrins as well as metal salts. The metalloporphyrins are usually isolated as the pyridinates. Pyridine forms complexes with metals of high charge and consequently retards the metallation process.
J. Metal Carbonyl Method [104,105]

This method has been proven to be especially useful for the preparation of metalloporphyrins of groups VI–VIII metals. The metal carbonyl or the carbonyl chloride is heated with the porphyrin in an inert solvent such as benzene, toluene, or decalin.

K. Acetylacetonate Method [106,107]

Metal acetylacetonates make very useful “carriers” due to their ready availability, solubility in organic solvents, and the low $pK_a$ of the acid liberated during the reaction. With metal ions of high charge and small size, a weakly acidic solvent (e.g., phenol) is required to liberate the active metallating species. This method has been used with metals of groups IIIa and IIIb.

The process of demetallation is favored by the presence of acid since protonation of the free base, once formed, drives the equilibrium in the forward direction. Metalloporphyrin stability is often defined in terms of the degree of resistance to the displacement of the metal atom by acid. Several stability classes have been identified based on complete demetallation in (a) acetic acid, (b) aqueous HCl-dichloromethane, and (c) sulfuric acid. While some divalent metals (e.g., zinc) are readily removed by trifluoroacetic acid in dichloromethane, others (e.g., Cu) require 15–25% sulfuric in trifluoroacetic acid or sometimes even stronger conditions.

In order to remove iron from porphyrins, the stable ferric state is best reduced to the ferrous state. Several reagents can be used for this purpose [96] and the choice is usually based on the sensitivity of the substituents. Reduction is commonly carried out by a saturated solution of ferrous sulfate whereas demetallation is effected by hydrochloric acid or gaseous HCl [108].

VI. BIOMIMETIC METALLOPORPHYRIN CATALYSTS

During the 1970s and early 1980s, the synthesis of biomimetic metalloporphyrins was directed towards generating systems that could mimic the reversible binding of dioxygen to the Fe(II) center of hemoglobin and myoglobin [27]. The primary structural requirement therefore was the presence of steric protection to prevent a second Fe(II) system from approaching and reacting to produce an oxidized $\mu$-oxo Fe(III) species. However, since the late 1970s when much of the attention was diverted to understanding the mechanism of action of hemoprotein catalysts, the structural requirements for the metalloporphyrin models also changed. Although cytochrome P450 continues to be the focus of attention in biomimetic studies, lignin peroxidase has also been studied extensively since its discovery in 1984. In order
to design efficient model catalysts, it is necessary to understand as best as possible the mechanism by which the enzyme functions.

A. Catalytic Cycle of Lignin Peroxidase

Lignin peroxidase is an extracellular enzyme that catalyzes oxidations in lignin-related aromatic molecules. Much of the attention that this enzyme has received recently is not only due to its oxidative depolymerization of lignin but to its ability to degrade a variety of environmental pollutants including polycyclic aromatic hydrocarbons [109,110], dibenzo-p-dioxins [110], and chlorinated phenols [111]. The catalytic cycle of lignin peroxidase (Figure 7) is initiated by a two-electron oxidation of the Fe(III) state of the resting enzyme, by hydrogen peroxide. The active high-valent iron-oxo species (compound I) so produced initiates lignin degradation by one-electron oxidations of methoxylated aromatic substructures of lignin, forming cation-radical species. These undergo bond cleavage and further nonenzymatic reactions with water and/or oxygen leading to lignin degradation. The enzyme reverts to its resting Fe(III) state via compound II, which is a one-electron oxidized form.

B. Catalytic Cycle of Cytochrome P450

Cytochrome P450 catalyzes the insertion of one oxygen atom from dioxygen into the substrate, the other being lost as water; hence its designation as a monooxygenase. Hydroxylation of alkanes and epoxidation of alkenes

\[ \text{Fe(IV)Por}^+ \longrightarrow \text{Fe(III)Por} \quad \text{RESTING ENZYME} \]

\[ \text{H}_2\text{O} \rightarrow \text{H}_2\text{O}_2 \]

\[ \text{Fe(III)Por} \leftrightarrow \text{Fe(IV)Por} \quad \text{COMPOUND I} \]

\[ \text{lignin} \rightarrow \text{lignin}_{\text{ox}} \]

\[ \text{O} \]

\[ \text{Fe(IV)Por} \rightarrow \text{Fe(IV)Por}^+ \quad \text{COMPONENT II} \]

\[ \text{Figure 7} \quad \text{Proposed catalytic cycle of lignin peroxidase.} \]
are the two most important reactions catalyzed by this enzyme. As shown in Figure 8, the resting enzyme Fe(III) undergoes a one-electron reduction to the Fe(II) state, which binds dioxygen. Following another one-electron reduction, the rate-limiting enzymatic step, and subsequent protonation of the terminal oxygen atom, a heterolytic cleavage of the O-O bond leads to the active oxygen complex, which is believed to be a high-valent iron-oxo complex [4], the other oxygen atom being released as water. Transfer of the oxygen atom to the substrate results in C-H bond hydroxylation or alkene epoxidation regenerates the resting Fe(III) state of the enzyme.

C. Design of Biomimetic Metalloporphyrin Catalysts

The postulation of a high-valent iron-oxo system as the active species in the proposed catalytic cycles of both lignin peroxidase and cytochrome P450 have resulted in similar structural requirements for the synthetic metalloporphyrin systems used in biomimetic studies. Understanding its nature, stability, and reactivity is important in the design and synthesis of a suitable catalyst. The properties of compounds I of peroxidases are consistent with an oxoiron(IV)porphyrin π-cation radical [112,113] while a similar structure has been postulated for cytochrome P450 as well [4]. However, an oxoiron(IV) species with a protein-centered radical (compound I of cytochrome c peroxidase) [114] has not been ruled out.

It has been shown that the oxidation of simple metalloporphyrins can give rise to similar highly oxidized species corresponding to the catalytic intermediate. Using TMPFeCl and m-chloroperbenzoic acid, Groves et al.
prepared and characterized the oxoiron(IV)porphyrin intermediate \( [\text{FeIV} = \text{O(TMP)}] \) which has since been studied extensively. More recently, similar species have been generated and spectroscopically characterized for two other iron porphyrins, TDCPPFeCl and meso-tetrakis(2,4,6-trimethoxyphenyl)porphyrinatoiron(III) \[116\]. However, unlike in the enzyme system where the active species is bound to the protein moiety and hence protected, in homogeneous reaction media this highly reactive intermediate of simple metalloporphyrins is capable of self-destruction. In order to minimize such loss of activity, catalyst design has been directed primarily to increasing the electron deficiency, while providing steric bulk around the metalloporphyrin system. This has been shown to improve catalyst stability by resisting oxidative destruction.

It is important to note, however, that the generation of an active oxoiron(IV) species from the resting Fe(III) state of the two enzymes differ, lignin peroxidase using hydrogen peroxide (a two-electron oxidant) directly, while cytochrome P450 uses molecular oxygen and two reducing equivalents provided by NADPH. Thus, mimicking the lignin peroxidase system involves the direct use of a metalloporphyrin catalyst in the presence of hydrogen peroxide or a similar single-atom oxygen transfer reagent. However, the catalytic cycle of cytochrome P450 is very difficult to mimic using simple metalloporphyrin systems with molecular oxygen and a reducing agent. Several model systems using Mn(III)porphyrins as catalysts have been reported \[117\], but with low rates and yields. Groves et al. \[118\] were the first to demonstrate that a system consisting of TPPFeCl as the catalyst and iodosylbenzene as an oxygen atom donor was able to perform the reactions catalyzed by cytochrome P450, suggesting the generation of the high-valent intermediate. It is this shunting that has been studied extensively for epoxidation of alkenes, hydroxylation of alkanes, as well as the oxidation of other organic substrates, although various combinations of metalloporphyrins and single-atom donor reagents (AO in Figure 8) have been used \[119\].

**D. Synthesis of Electron-Deficient Porphyrins**

Due to the ease of synthesis, the metalloporphyrin catalysts used in biomimetic studies have been of the meso-tetraphenylporphyrin type. Since Groves et al. demonstrated that a high-valent oxoiron porphyrin system could be observed with the TMPFe system \[115\], it was realized that bulky ortho substituents on the phenyl groups could be important in preventing oxidative self-destruction of the catalyst. By using TPFPPFe, Chang and Ebina \[120\] showed that electron deficiency can enhance the stability of the catalyst and also increase reactivity to the substrate by generating a more electrophilic oxoiron intermediate. Traylor et al. \[31\] showed that TDCPPFeCl is a very efficient catalyst since both electron deficiency and steric bulk are
incorporated into the molecule with ortho-chloro groups. In order to adapt this catalyst for use in aqueous media as a model for lignin peroxidase, Dolphin et al. [121] prepared a water-soluble form by introducing sulfonic acid groups to the phenyl moieties, which also helped in increasing the electron deficiency of the catalyst. The synthetic methods available for TMPFe, TPFPPFe, and TDCPPFe catalysts have already been discussed in Section IV.A. Sulfonation of TDCPPH₂ has been carried out using fuming sulfuric acid at 165°C for 7 h. Due to the directing influence of the ortho-chloro groups, sulfonation takes place at the meta (3-) positions of the phenyl groups.

The development of the next generation of catalysts saw the introduction of more electron-withdrawing substituents into the catalyst molecule. Considering the electrophilic and radical nature of reactivity of the porphyrin macrocycle, β-perhalogenation was the method of choice for creating greater electron deficiency in the system. Chlorination of TDCPP has been achieved by reacting its iron complex (31, M = FeCl, X = H), with chlorine gas at 140°C in the presence of anhydrous ferric chloride [122]. The 24-nm red shift of the Soret band indicates the completion of the reaction (20-30 min) and the purified β-octachloroporphyrinatoiron (32, M = FeCl) has been isolated in >85% yield. The zinc complex (31; M = Zn, X = H) has also

![Scheme 9](image)
been chlorinated with N-chlorosuccinimide [123] in refluxing chlorocarbon solvents to give the analogous zinc complex (32; M = Zn) in 78% yield, but had required extended reaction times (22 h). Perchlorination of TPFPP (34) has been achieved [123, 124] via both methods while the truly perchloroporphyrin 37 has been prepared by the chlorination of TPCPPFe (36, M = FeCl) using the Cl₂/FeCl₃ procedure [122]. Chlorination of TMP'Zn (38, M = Zn, X = H) by N-chlorosuccinimide, in refluxing methanol, produced 39 (M = Zn, X = Y = Cl) in which one meta position of each phenyl ring is chlorinated in addition to the eight pyrrolic positions [125]. Demetallation with trifluoroacetic acid produced the free base porphyrin in 45–60% overall yield. Chlorination of unsubstituted TPPFe (40, M = FeCl, X = H)
could not be achieved using the Cl\textsubscript{2}/FeCl\textsubscript{3} system due to destruction of the macrocycle, while attempted chlorination of TPPFe, TPPZn, or TPPCu with \textit{N}-chlorosuccinimide produced the desired \(\beta\)-octachlorinated porphyrin \((41, \text{M} = \text{FeCl, Zn, or Cu})\) in low yield. However, TPPNi reacted with \textit{N}-chlorosuccinimide at 140°C to give \(41 (\text{M} = \text{Ni})\) in 75% yield which was readily demetallated and converted to the ferric complex in \(>75\%\) overall yield [122]. This confirms the observation that the centrally coordinated metal exerts a directive influence on peripheral substitution [126]. Heating the Ni complex of \(41 (\text{M} = \text{Ni})\) in concentrated sulfuric acid for 5 h followed by stirring at room temperature for a further 12 h produced, after iron insertion, the sulfonated hemin \(42 (\text{M} = \text{FeCl})\), while the sulfonation of \(32\) to give \(33\)
required the use of fuming sulfuric acid [121,122]. These compounds have been used as models for lignin peroxidase.

Perbromination of the porphyrin periphery has also been achieved with either bromine or N-bromosuccinimide. Octabromination of TDCPPZn (31, M = Zn, X = H) was first reported in refluxing carbon tetrachloride (1 g/100 ml) using 10 equivalents of N-bromosuccinimide to give the desired product 31 (M = Zn, X = Br) in 71% yield [127]. However, low solubility of the starting material in this solvent leads to extended reaction times resulting in partial demetallation and incomplete bromination. The use of chloroform or tetrachloroethene as the solvent has been recommended in order to improve the yields [123]. TMP, as its zinc complex (38, M = Zn,
X = H), has also been octabrominated using 10 equivalents of \( N \)-bromosuccinimide in refluxing methanol solution [125]. The product 38 (\( M = \text{Zn}, \ X = \text{Br} \)) has been isolated in 50-65% yield. TPFPP, as its zinc complex (34, \( M = \text{Zn} \)), has been brominated with \( N \)-bromosuccinimide in refluxing chloroform/tetrachloroethane (1:1) over a period of 48 h while trifluoroacetic acid was slowly added [128]. The octabrominated product (35, \( M = \text{Zn} \)) has been isolated in 70% yield after zinc reinsertion and purification. The chloroiron complex 34 (\( M = \text{FeCl} \)), however, has been brominated with a 6 M solution of bromine [129], in dry degassed carbon tetrachloride by refluxing for 18 h, to give a 74% yield of 35 (\( M = \text{FeCl} \)). Unsubstituted TPP, as its copper complex (40, \( M = \text{Cu}, \ X = \text{H} \)), has been octabrominated [130], by stirring a solution in chloroform/carbon tetrachloride (1:1) with liquid bromine at room temperature (4 h) followed by the addition of pyridine and further stirring (12 h). The product 40 (\( M = \text{Cu}, \ X = \text{Br} \)), isolated in 75% yield, was demetallated with perchloric acid.
The effect of halogen substitution of the porphyrin ligand on the metal center has been demonstrated by cyclic voltammetry of the chloroiron(III) complexes [131]. In general, electron-withdrawing chloro substituents produce anodic shifts of reduction potentials, but the effect was shown to be more pronounced for pyrrolic substitution. This reflects the ease of reduction of the metal center of \( \beta \)-halogenated porphyrins. While the positive shift of \( E_{\text{red}}^{\text{Fe}^3+/\text{Fe}^2+} \) for \( 31 (M = \text{Fe}, X = \text{H}) \) compared to \( 40 (M = \text{Fe}, X = \text{H}) \) was marginal, the corresponding shifts for \( 32 (M = \text{Fe}) \) compared with \( 31 (M = \text{Fe}, X = \text{H}) \) as well as that for \( 41 (M = \text{Fe}) \) compared to \( 40 (M = \text{Fe}, X = \text{H}) \) were approximately 0.4 V. Perchlorination of TPPFeCl \( (40, X = \text{H}) \) to TCPPFeCl \( (37) \) produced a shift of 0.64 V.

The X-ray crystallographic structures of \( \beta \)-octabromo-TMPNi \( (38, M = \text{Ni}, X = \text{Br}) \), TPFPPNi \( (35, M = \text{Ni}, X = \text{Br}) \), as well as octachloro-TPFPPPCu \( (35, M = \text{Cu}, X = \text{Cl}) \) exhibit saddle-shape conformations, created by the buckling of the macrocycle [128,132]. This distortion from planarity minimizes the nonbonded interaction between \( \beta \)-halogen atoms and the \( \text{ortho} \)-phenyl substituents.

E. Synthetic Metalloporphyrins for Commercial Applications

It is not the objective of this chapter to review the catalytic studies carried out with the different metalloporphyrin model systems prepared to date, since that aspect will be discussed in several chapters of this volume (for a recent review, see Ref. 119). However, it should be noted that some of the metalloporphyrin systems developed for biomimetic studies have shown considerable promise in commercial applications.

The water-soluble (sulfonated) polychlorinated metalloporphyrins prepared by Dolphin and coworkers as models for lignin peroxidase have also been examined for their ability to bleach kraft pulp [122,133]. This possible commercial application is particularly important due to the necessity to limit the current use of chlorine in pulp bleaching. \( \text{meso-Tetrakis}(2,6\text{-dichloro-3-sulfonatophenyl})-\beta\text{-octachloroporphyrinatoiron(III)} \) \( [33, M = \text{FeCl}] \), in the presence of \( \text{tert}-\text{butylhydroperoxide} \), has been shown to effect greater than 45% delignification of pulp when incubated for 18 h at 60°C in pH = 4.8 buffer. A second possible application that has been investigated is the decolorization of highly colored effluent from bleach plants, which is an environmental problem. Once again, the above catalyst/oxidant combination was capable of decolorizing (greater than 50%) undiluted effluent in less than 13 min under appropriate conditions. Further studies are underway to determine the optimal reaction conditions as well as the use of cheaper oxidants.
The hydroxylation of light alkanes to alcohols is an important reaction in the commercial production of fuel additives and other oxygenated chemicals. However, the major problem with biomimetic systems is that the use of single-atom oxygen transfer reagents to generate the active intermediate would not necessarily be economically viable. The work of Ellis and Lyons [132,134] is therefore unique in that oxidations of light alkanes to alcohols are carried out using activated metalloporphyrins and molecular oxygen rather than single-atom donor reagents. With β-octachloro- and β-octa-bromo-meso-tetrakis(pentafluorophenyl)porphyrinatoiron(III) as catalysts, it has been possible to oxidize isobutane with air even at room temperature to give tert-butyl alcohol in >90% selectivity with >13,000 turnovers. The fact that catalysis is effected without the use of an added coreductant suggests that the mechanism is different from that proposed for cytochrome P450 itself. According to a postulated mechanism, the electron deficiency in the porphyrin ligand facilitates the reduction of the metal center to the Fe(II) state, which binds dioxygen and subsequently produces the catalytically active oxoiron(IV) species by homolytic cleavage of the μ-peroxo dimer. The Fe(II) state and the oxoiron(IV) state are thought to be in equilibrium with a μ-oxo dimer species, the position of this equilibrium being dependent on steric and electronic factors. Although no crystallographic data are yet available for the catalytically active hemins, it is likely that the enhanced catalytic activity observed in β-halogenated systems is related to the saddle shape of the ligand (observed for Ni and Cu complexes [132]), which restricts its ability to form stable μ-oxo dimer species. According to this mechanism, the catalyst essentially serves as a dioxygenase rather than a monooxygenase (cytochrome P450) since both atoms of molecular oxygen are transferred to the substrate via the oxoiron(IV) intermediate.

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