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Electron transfer in natural and unnatural flavoporphyrins

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Abstract

The development of chemical models for enzymes and their chemical and physical studies constitutes an important area of research from a scientific as well as an industrial point of view. Covalently linked flavin and porphyrin (flavoporphyrins) have attracted attention due to their applications as chemical models for flavoproteins and related enzymes. In this review, the literature has been surveyed to provide a comprehensive coverage of the synthetic methodology and characterization techniques of various types of synthetic flavoporphyrins.

1. Introduction

Electron and energy transfer are fundamental processes in biology, chemistry, and material sciences [1–5]. Electron transfer reactions are ubiquitous in nature [4–7]. The proteins involved in such reactions catalyze the oxidation of a substrate molecule with the concomitant reduction of a cosubstrate or cofactor. The mechanism of a redox reaction catalyzed by a protein may be a single-electron transfer, two-electron transfer or may involve atom and/or ion transfer. The mechanism of electron transfer by a protein, particularly the metalloproteins, has been the focus of much research [8–19]. In general, such electron transfer proteins consist of one or more polypeptides folded around one or more redox-active prosthetic groups. The selection of distance between donor and acceptor group, free energy and reorganization

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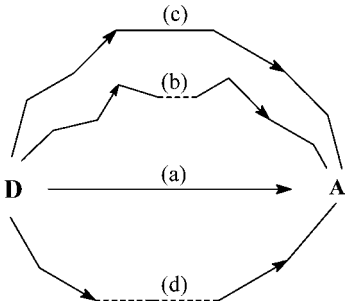


Fig. 1. (a) Direct electron transfer through space; (b) electron tunneling through a covalent, σ-bonded pathway with one through-space jump (dashed line); (c) electron tunneling through a σ-bonded pathway alone; and (d) through a covalent (line) and hydrogen-bonded (dashed line) pathway.

energy are sufficient to define rate and directional specificity of biological electron transfer, meeting physiological requirements in diverse systems [5]. A schematic diagram showing various types of pathways for electron transfer in biological systems from a donor (D) to an acceptor (A) is shown in Fig. 1 [4].

Various topics involving electron transfer including the overall structure of electron transferring components [20–23], the protein disposition within complex structures [24–27] and the relationship between electron transfer and energy transduction [28–31] have already been reviewed. This review is focused on the electron transfer in natural and synthetic flavoporphyrins (flavin and porphyrin either covalently or non-covalently attached). This review will also discuss detailed synthetic methodology and characterization techniques of various types of synthetic flavoporphyrins.

2. Electron transfer in flavocytochromes and related enzymes

Nature selects from a library of redox active cofactors and places them within a protein matrix to help essential functions such as substrate binding, electron transfer, energy conversion, and chemical catalysis. The protein environment adjusts the chemical and physical properties of the cofactors to perform the desired function.

Flavoproteins and related enzymes are a class of redox enzyme containing flavin (isoalloxazine) (Fig. 2) and porphyrin derivatives [natural pigment containing a fundamental skeleton of four pyrrole nuclei united through the α-positions by four methine groups to form a macrocyclic structure (porphyrin is designated porphine in Chemical Abstracts indexes)] (Fig. 3) either covalently or non-covalently attached as prosthetic group. In almost all the cases, the transfer of electrons takes place from NAD(P)H to FAD (flavin adenine dinucleotide) and then to a separate electron acceptor which can be situated on the same or a different polypeptide chain. Also, the orientation of the flavin and its distance from the heme–iron is an important factor in determining the rate of electron transfer. A brief description of the selected enzymes containing flavin and porphyrin as their cofactors has been given under different subheadings.

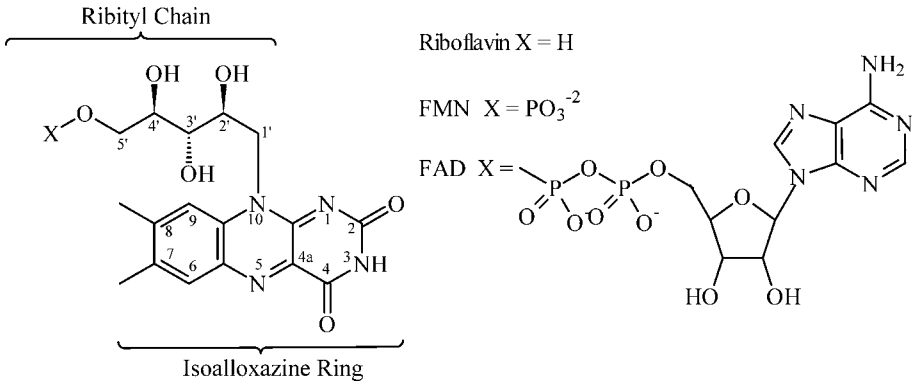


Fig. 2. Molecular structures of flavin chromophores.

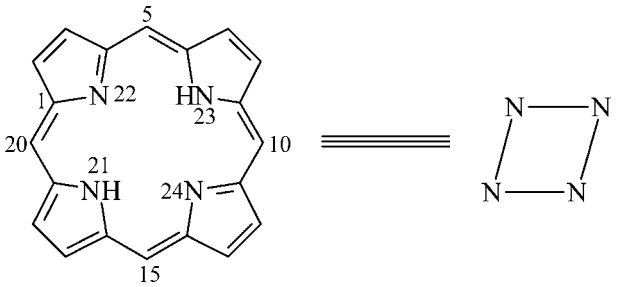


Fig. 3. Free base porphyrin nucleus.

2.1. NADPH–cytochrome P450 oxidoreductase (CPR) (EC 1.6.2.4)

NADPH–cytochrome P450 oxidoreductase (CPR) is a 78,225-Da flavoprotein containing 1 mol each of FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide) [32]. This protein is bound to the endoplasmic reticulum [33,34] and nuclear envelop [35] of a variety of cell types and is responsible for the transfer of reducing equivalents to the cytochrome P450 [36,37] as well as other microsomal enzyme systems including heme oxygenase [38] and the fatty acid desaturation [39] and elongation systems [40].

Electron transfer in this enzyme system occurs as shown in Fig. 4 [41–48]. It has been established that NADPH is the electron donor and the microsomal flavoprotein (NADPH-dependent cytochrome P450 reductase) or mitochondrial system consisting of a flavoprotein and a protein containing a Fe–S cluster is the electron carrier from NADPH to the hemoprotein (cytochrome P450). The closest distance between the FMN of CPR and the heme of cytochrome *c* is less than 9 Å.

NADPH → NADPH-dependent Cyt P450 reductase → Cytochrome P450

Fig. 4.

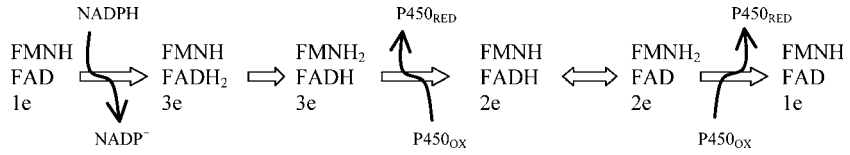


Fig. 5.

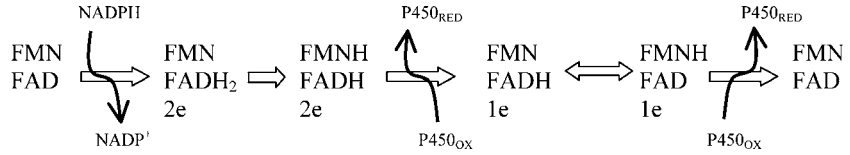


Fig. 6.

Under physiological conditions the enzyme is proposed to cycle between the 1- and 3-electron reduced states (Fig. 5) but the redox cycle of the reductase from *Bacillus megaterium* P450BM3 and housefly cycle between the fully oxidized enzyme and the 2-electron reduced form (Fig. 6) [49,50]. A noticeable difference between these two enzymes is the redox state of the FMN cofactor during catalysis. The fully reduced flavin ($FMNH_2$) is the electron donor to P450 (or other electron acceptor protein) with the mammalian enzyme, whereas with the P450BM3 reductase, the one-electron reduced semi-quinone (FMNH) is the donor. These differences are related to the flavin midpoint potentials of these enzymes. The redox midpoint potentials for CPR is −110 mV (FMN/FMNH), −270 mV ($FMNH/FMNH_2$), −290 mV (FAD/FADH), and −365 mV ($FADH/FADH_2$) [44,45].

2.2. Flavocytochrome b_2 (EC 1.1.2.3)

Flavocytochrome b_2 is a flavin and heme containing 57.5 kDa enzyme which catalyzes the transfer of electron from L-lactate to cytochrome *c* [51]. The enzyme is a homotetramer located in the mitochondrial inter-membrane space and contains two noncovalently bound cofactors FMN and heme per subunit [52–55]. Each subunit is composed of two distinct domains: an N-terminal, heme-containing cytochrome domain and a C-terminal, FMN containing flavodehydrogenase domain [56]. The shortest distance between the flavin and the heme groups is ~9.7 Å. The arrangement of the flavin and heme group in one of the two crystallographically distinguishable subunits is shown in Fig. 7.

The flow of electrons through flavocytochrome b_2 follows the path: L-lactate → FMN → b_2-heme → cytochrome *c*. This process involves two intra-molecular electron transfer steps [57], one from fully reduced flavin to b_2-heme and the other from flavin semiquinone to b_2-heme. This occurs because the flavin group has three oxidation states available to it and hence has the ability to act as a one- and two-electron redox center. The first flavin to heme electron transfer is reversible with the forward and reverse rate constant of 1500 and 270 s^{-1}, respectively [58].

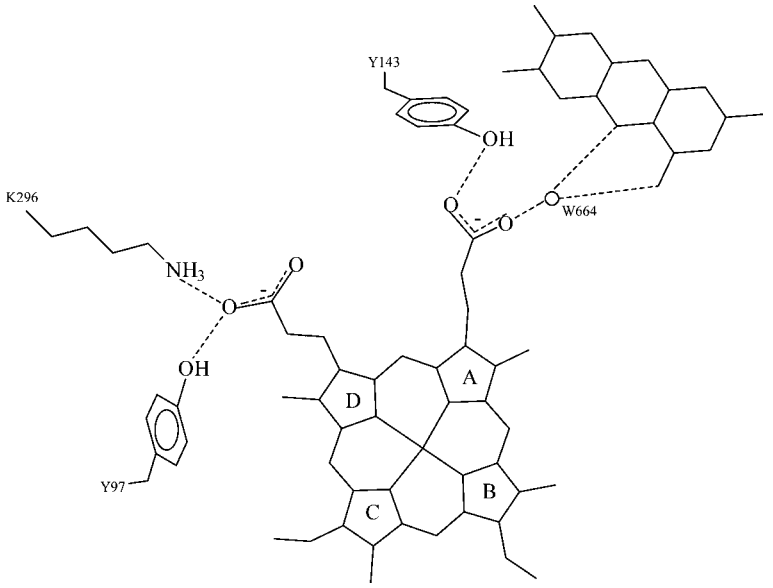


Fig. 7. Tyr-143 is hydrogen-bonding to one of the heme propionates. The shortest distance between the heme and flavin rings is 9.7 Å (from flavin C-2A to flavin N-5). W664 is a water molecule.

2.3. Flavocytochrome c_3 (Fcc_3) (EC 1.3.99.1)

Flavocytochrome c_3 (Fcc_3) is a tetraheme redox enzyme of the type called fumarate reductase (reduces fumarate to succinate) from the bacterium *Shewanella frigidimarina* [17,59]. It consists of a single polypeptide chain of 571 amino acids (63.8 kDa) which form two domains: an N-terminal cytochrome domain containing four c-type heme binding motifs and a flavin domain which binds FAD non-covalently [60] (Fig. 8). The hemes seem to form a wire to deliver electrons to FAD in the active site of the molecule. The longest edge-to-edge distance between the adjacent cofactors is <9 Å which help the faster electron transfer [61].

2.4. Flavocytochrome P450BM3 (EC.1.14.14.1)

Flavocytochrome P450BM3 is a 119 kDa, self-sufficient NADPH-dependent fatty acid monooxygenase from *Bacillus megaterium* consisting of a heme and FMN/FAD containing reductase domains linked together on a single polypeptide [62–68]. The structural organization and amino acid sequence are similar to the Class II (microsomal) P450 system in which P450s receive electrons directly from membrane bound FAD and FMN containing reductase [68,69].

The flow of electrons in this system follows the path: NADPH → FAD → FMN → heme. The fusion of the P450 to its diflavin P450 reductase makes this enzyme a very efficient electron transport system and hence the highest monooxygenase activity of all the P450s yet characterized [70,71]. The flavin and heme

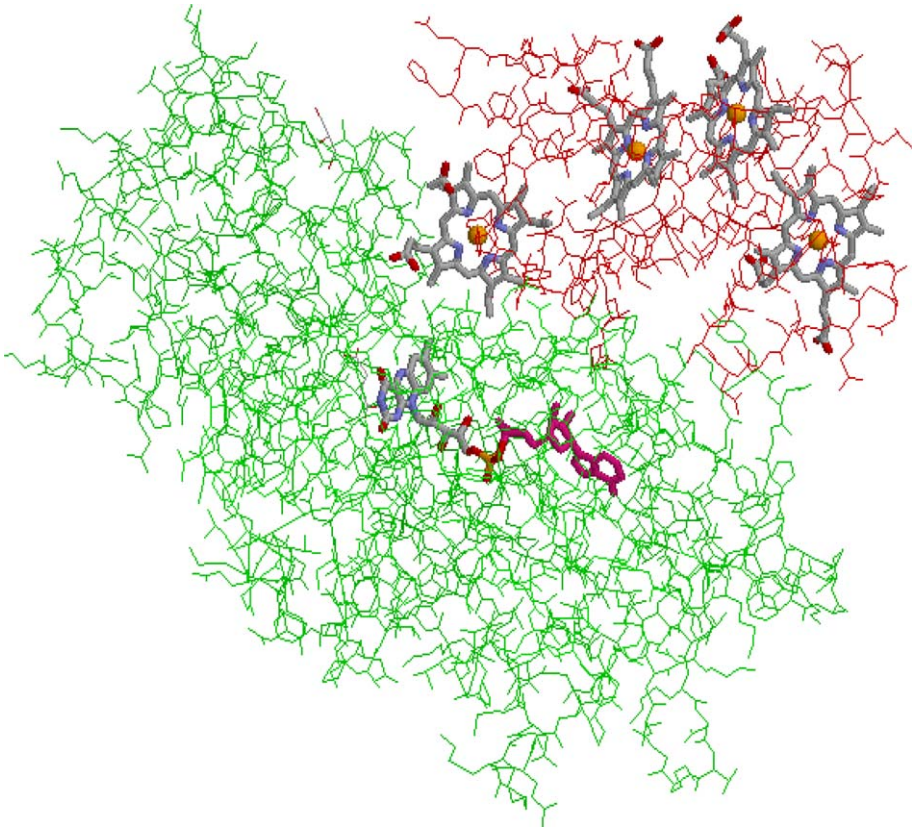


Fig. 8. Flavocytochrome c_3.

planes of this enzyme are nearly perpendicular where the 7-methyl group of the FMN is 18.4 Å away from the heme–iron. The FAD and FMN cofactors are positioned such that the distance between their respective flavin ring systems is <4 Å [66]. Similarly, the NADPH-binding site is close to the FAD binding site and is poised to effect hydride transfer [66]. The proximity of the flavin ring of the FMN and indole ring of the Trp-574 with their conjugated π-orbitals to the heme binding peptide implicates the latter as the through-bond electron-transfer pathway from the flavin to the heme [66].

2.5. Nitrate reductase (NR) (EC 1.6.6.x)

NR is a soluble, multi-center redox enzyme that catalyzes the two-electron reduction of nitrate to nitrite using pyridine nucleotide as the electron donor [72–76]. There are three related forms of NR: NADH NR (EC 1.6.6.1), NAD(P)H NR (EC 1.6.6.2), and NADPH NR (EC 1.6.6.3). NR is a homodimer with each subunit composed of a ~100 kDa polypeptide and three cofactors FAD, iron–heme

(heme–Fe), and molybdenum (Mo)-pterin in 1:1:1 ratio [77]. NR shuttles electrons from NADH to nitrate via these cofactors. The enzyme has a redox couple between FAD and heme–Fe (cytochrome *b*) and is highly homologous with cytochrome b_5 reductase. The sequences of NR have been found to contain one conserved cysteine (Cys) residue that is located in the cytochrome *b* fragment of the enzyme [78]. This Cys residue is essential for the efficient catalytic transfer of electrons from the NAD(P)H to FAD [79].

2.6. NADPH–sulfite reductase (EC 1.8.1.2)

NADPH–sulfite reductase from *Escherichia coli* or *Salmonella typhimurium* is a 780 kDa multimeric and soluble hemoflavoprotein containing 4 FMN, 4 FAD, 20–21 atoms of iron, 14–15 labile sulfides, and 3–4 molecules of a novel type of heme (octacarboxylic iron–tetrahydroporphyrin or siroheme) per enzyme molecule in eight α-subunits (SiR-FP) and four β-subunits (SiR-HP) [80–83]. The octamer is a flavoprotein (SiR-FP; $M_r = 528,000$) and the tetramer is a hemoprotein (SiR-HP; $M_r = 252,000$) [83].

The enzyme catalyzes the stoichiometric conversion of sulfite to sulfide at the expense of three NADPH molecules. The flow of electrons from NADPH to sulfite follows the pathway: NADPH → FAD → FMN → heme → sulfite [81]. FAD is the entry port for the electron from NADPH while FMN serves as a mediator for the rapid transfer of these electrons to hemoprotein component where sulfite is reduced. Electrons can also be transferred from the FMN site to non-physiological acceptors such as cytochrome *c* or ferricyanide or directly from the FAD to 3-acetylpyridine adenine dinucleotide phosphate or free exogenous flavins [84].

2.7. Nitric-oxide synthase (NOS) (EC 1.14.13.39)

NOSs are hemoproteins with a cytochrome P450-like active site that catalyze the oxidation of L-arginine to nitric oxide and citrulline at the expense of NADPH and molecular oxygen [85–89]. NOSs incorporate several domains in a single polypeptide: (i) the P450 type iron-protoporphyrin IX heme domain that binds a tetrahydrobiopterin cofactor and is the site of oxidation of L-arginine to nitric oxide and citrulline, (ii) a P450-reductase domain that has a binding site for FMN and NADPH and is responsible for providing electrons to the heme domain, and (iii) a connecting peptide between the heme and flavin domains. The electron transfer takes place from NADPH through FAD and FMN cofactors to the heme and the tetrahydrobiopterin cofactors [89]. A schematic view of NOS showing the interaction of the flavin reductase and oxidative heme domain is presented in Fig. 9. NOS and CPR are the only two mammalian enzymes known to contain both FAD and FMN along with heme. The distance between the flavin radical and the active-site heme is found to be at least 15 Å [86]. This distance is too great to allow direct transfer of electron between the flavin and heme centers and suggest the participation of other protein components.

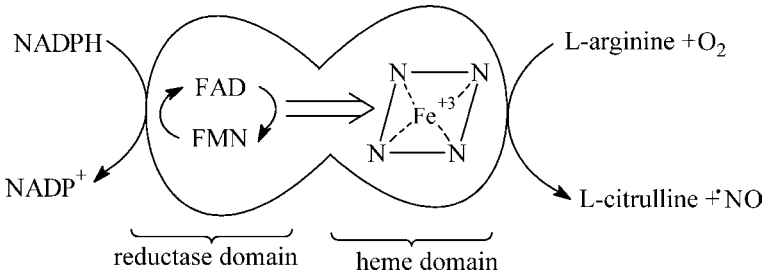


Fig. 9. Schematic view of NOS.

3. Mechanism of O_2 activation

Electron transfer controls the O_2 activation by monooxygenases that transfer an oxygen atom from dioxygen to various organic substrates [90–108]. Various chemical models of heme-containing monooxygenase cytochrome P450 have been studied in recent years to understand the molecular mechanism of O_2 activation [109–116]. Cytochrome P450s metabolize up to 200,000 compounds and catalyze about 60 types of chemical reactions, including hydroxylations, N-, O- or S-demethylation, dealkylation, and epoxidation reactions, to name a few [117].

The detailed studies uncovered a major problem involving the useless reductive decomposition pathway of the metal oxene $[P \cdot M(IV)^{+\cdot}O]$ (Fig. 10). The possible solution includes: (i) transfer of an electron to $P \cdot M(III)$ quite rapidly to give a high turnover frequency while (ii) a further electron must be transferred to $P \cdot M(IV)^{+\cdot}O$

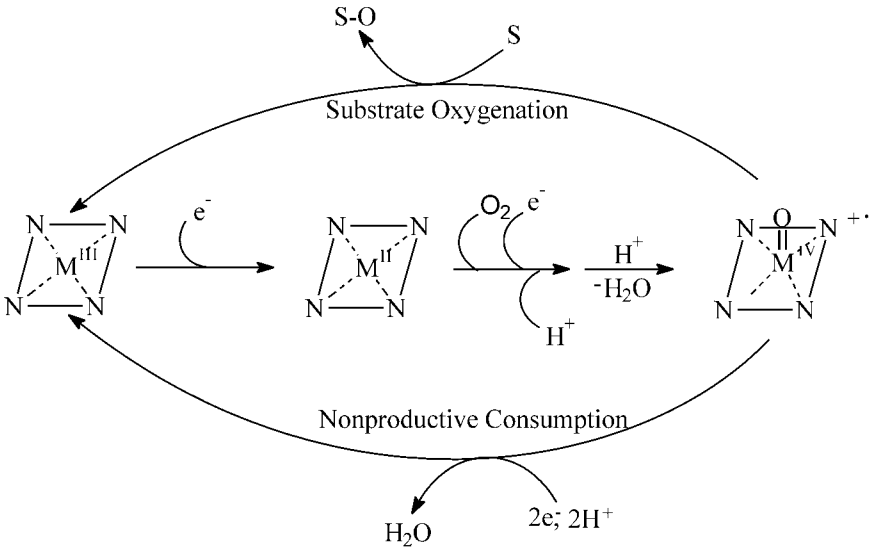


Fig. 10. Schematic view of oxygenation.

extremely slowly to prevent the futile oxene consumption. The enzymatic mechanism of electron transfer control depends upon the structure and molecular organization of the enzyme system. The flavin moiety in the reductase accelerates one electron transfer from the NAD(P)H bound to the reductase to the porphyrinatoiron(III) in the P450 active site via a temporary association with P450-reductase [118]. Thus, the overall rate determining production of $P \cdot Fe(II)$ may be very much accelerated. Whenever a substrate is bound to the P450 binding site, the resting $P \cdot Fe(III)$ low spin state may be converted to the high spin state, allowing electron transfer. Oxygen binding to $P \cdot Fe(II)$ is reasonably fast and a subsequent one electron transfer to $P \cdot Fe(II) \cdot O_2$ must be fast, since the total molecular system still has one nearly free electron $(NAD(P) \cdot Fl)^-$. The two protons required for the O–O cleavage, are supplied from either bound water or from the residues on the enzyme.

The beauty of this system is that now there are no more available electrons, since NAD(P)H is converted to NAD(P) after two-electron transfer. Hence, the flavin moiety in the P450 enzyme system acts as a switch between one and two electron transfer.

Since most of the enzymes are membrane bound and are difficult to isolate in large quantity for chemical synthesis and industrial applications, the development of chemical models for these monooxygenases and their reactions constitutes an important area from scientific as well as industrial point of view. This review strives to provide a comprehensive coverage of the synthetic methods and flavoporphyrin characterization.

4. Chemical modifications of flavocytochromes for triggering catalytic functions

The synthesis of protein structures, that assemble working arrays of cofactors and reproduce native-like function, are important in determining how natural proteins function. These semi-synthetic structures, sometimes called as molecular maquettes, have been quite informative for the elucidation of the molecular mechanism of cofactors and hence, the proteins during various metabolic processes.

The cytochrome P450 shows monooxygenase activity only within a complex with flavoprotein reductase. The flavin nucleotides (FMN and FAD) represent electron carriers that reduce the heme–iron of cytochrome P450 (Fig. 10). The introduction of flavin derivatives into cytochrome P450 converts the latter into a self-competent enzyme that does not require the involvement of partner proteins for the biological activity. To understand the role of the reductase, a semi-synthetic flavohemoglobin has been synthesized by the attachment of activated flavin derivatives to the β-subunit of hemoglobin in a 2:1 ratio [119–122]. The covalent binding of flavin to hemoglobin makes it possible to conduct the monooxygenase reactions in the absence of reductase which confirmed the role of flavin in the mechanism of reductase.

Hemoglobin catalyzes a wide variety of monooxygenase reactions in a typical P450 like electron-transport system consisting of oxygen, NADPH and NADPH–cytochrome P450 reductase [120,122]. The replacement of reductase by a flavin moiety covalently attached to hemoglobin in the vicinity of the heme is called

flavohemoglobin. The resulting molecule serves as a hydroxylase for aniline without requiring the P450 reductase. The rates of the catalytic reactions of aniline hydroxylation in the presence of flavohemoglobin and the microsomal monoxygenase system are comparable [121]. The aniline hydroxylase activity of semi-synthetic flavohemoglobin is better when compared with hemoglobin and the hemoglobin-reductase system [120].

Some of the other selected examples include the catalytic activity of covalent complexes "cytochrome P450-flavin adenine dinucleotide" (FAD) and "cytochrome P450-flavin mononucleotide" (FMN) [123]. The N-demethylation and aniline hydroxylation with the complex in which cytochrome P450 is covalently bound to FMN (1:3) is more active than the cytochrome P450–FAD complex [46]. Similarly, the covalent binding of flavodoxin to ferredoxin–$NADP^+$ reductase (1:1) gave an artificial enzyme that catalyzes the reduction of cytochrome *c* with high efficiency [124]. The transfer of electrons in this system follows the same scheme as in CPR (Fig. 4) [NADPH → FAD (from ferredoxin–$NADP^+$ reductase) → FMN (flavodoxin) cytochrome *c*].

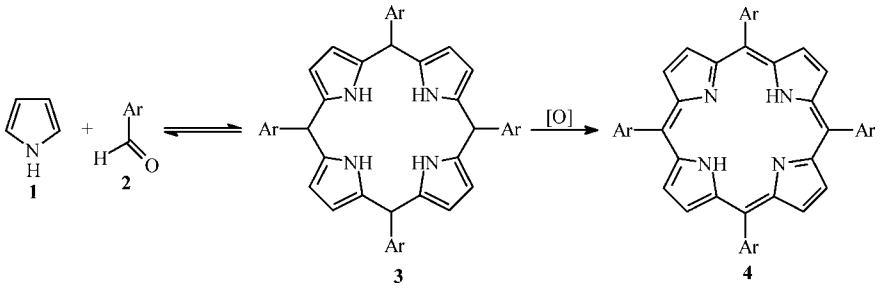
All of the aforementioned systems exhibit the key properties of their natural counterparts with respect to the physical and chemical charcteristics of the cofactors and display new and novel catalytic functions. Hence, the covalently flavin-linked porphyrin molecular conjugates (flavoporphyrins) are important in understanding the electron transfer mechanism during O_2 activation and hence, their catalytic functions by heme-containing monooxygenases.

5. Synthesis of covalently linked flavin and porphyrin (flavoporphyrins)

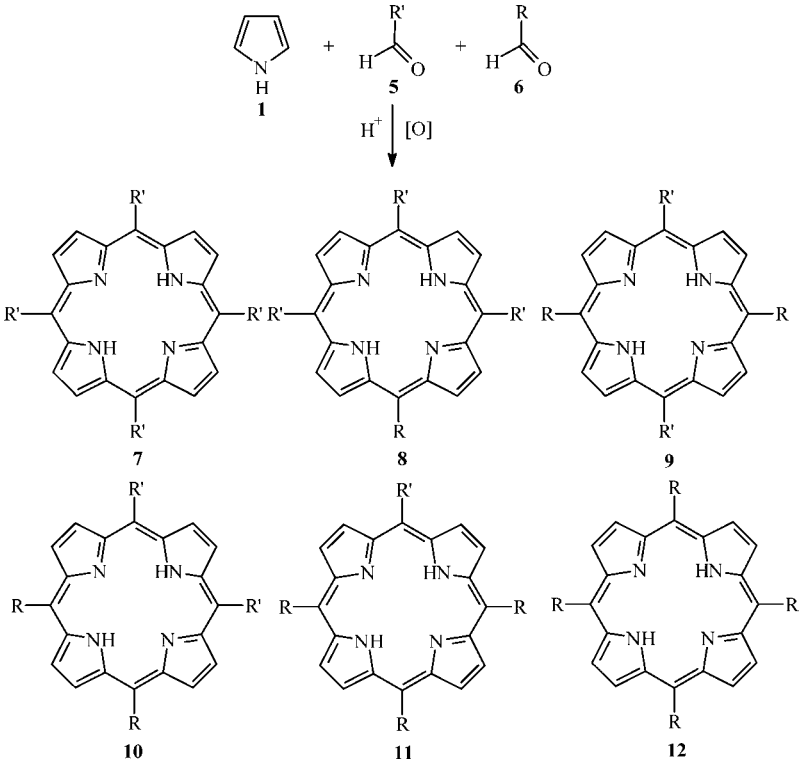
The driving force for the design of a flavoporphyrin results from the requirements for specific properties or functionality. Hence, a chemist will choose not only a particular porphyrin unit but also the type of linkage between units that will provide the desired properties and be easily incorporated into the synthetic design. Therefore, any synthetic strategy must take into account the flavin and porphyrin functionalization as well as the linkage between them.

5.1. Synthesis of symmetrical and unsymmetrical porphyrins

There is much literature concerning the synthesis of porphyrins [125–132]. The reaction of pyrrole (**1**) with a suitable aldehyde (**2**) under acidic conditions, followed by oxidation of the resulting porphyrinogen (**3**), developed by Rothemund and Menotti [133] and Lindsey et al. [134], is an important method for the synthesis of symmetrical synthetic 5,10,15,20-tetraarylporphyrins (TAPs, **4**) (Scheme 1). Various workers have modified this procedure to give a maximum of 50% yield for TAPs [135–137]. The Rothemund or Lindsey method has also been employed to synthesize unsymmetrical substituted porphyrins via mixed aldehyde condensations (Scheme 2) [130,138,139]. The reaction of pyrrole (**1**) with two different aldehydes (**5** and **6**) gives a mixture of six porphyrins (**7–12**) that can be separated by column chromatography. There are two disadvantages: the yields are lower by virtue of the statistical outcome



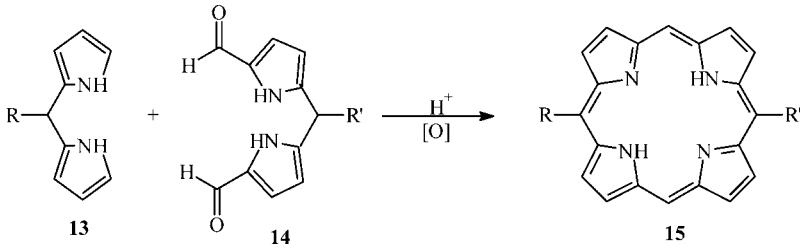
Scheme 1. Condensation of pyrrole and arylaldehydes to afford TAPs.



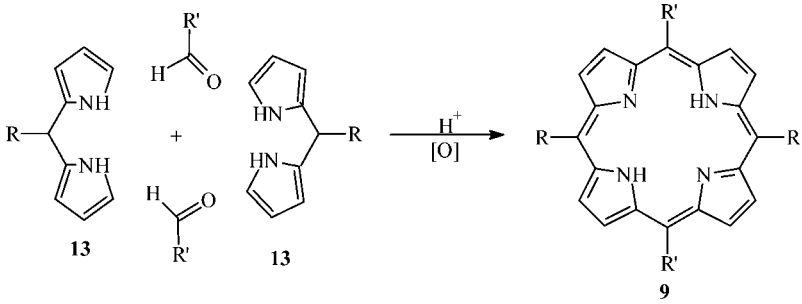
Scheme 2. Mixed aldehyde condensation to afford mixture of porphyrins.

of the reaction and the separation procedures can be troublesome, particularly if the reactions are carried out on a large scale [140,141].

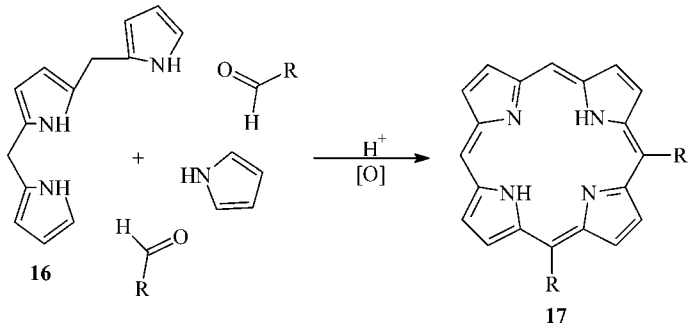
Alternative approaches for synthesizing substituted porphyrins have been devised in which dipyrrolic starting materials (**13** and **14**) are combined to form tetrapyrroles. Dipyrromethenes, dipyrryl ketones and dipyrrylmethanes have been used in these "2 + 2" synthetic methodologies (Scheme 3) [142–144]. The condensation was



Scheme 3. "2 + 2" condensation of dipyrrylmethanes to afford porphyrin.



Scheme 4. "2 + 2" condensation of α-free dipyrrylmethanes to afford porphyrin.



Scheme 5. "3 + 1" condensation of tripyrrolic compound to afford porphyrin.

catalyzed by acid to afford the porphyrinogen that was further oxidized by exposure to air to give the desired porphyrin (**15**) in 20–30% yields [143,144]. Alternative "2 + 2" methods involve the acid-catalyzed condensation of α-free dipyrrylmethanes (**13**) with aldehydes to form porphyrinogens, which are further chemically oxidized to give porphyrins (**9**) in 14–48% yields (Scheme 4) [145].

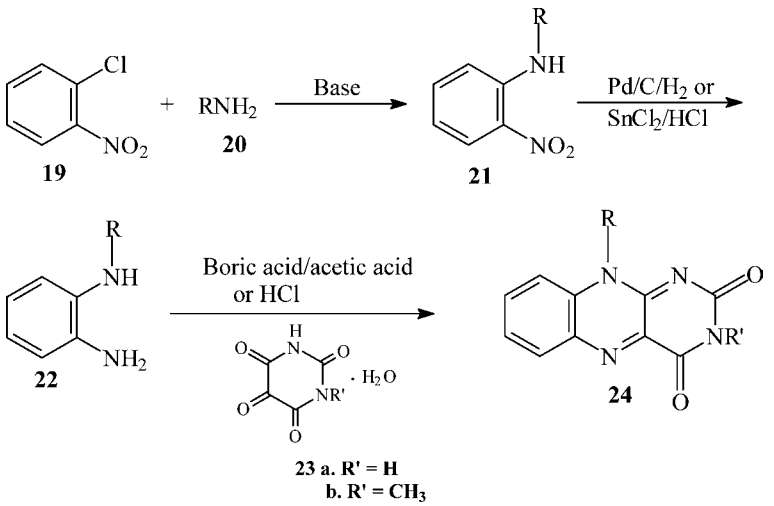
In a variation to the "2 + 2" method, "3 + 1" synthetic methodologies have been developed in which tripyrrolic species (**16**) are condensed with 2,5-diformylpyrroles (**18**) [146] or a pyrrole with two aldehydes [147] to afford porphyrins (**17**) (Scheme 5).

5.2. Synthesis of flavins

The different synthetic routes for flavins involve the condensation of 2-arylazo compound with barbituric acid [148–151], aniline with violuric acid [152] and 4-halouracil [153], quinoxaline with guanidine [154,155], and *ortho*-benzoquinone with diaminopyrimidine [156]. The acid-catalyzed cyclocondensation of 2-substituted aminoaniline (**22**) with alloxane monohydrate or its derivatives (**23**) is an important and most used method to synthesize flavins (**24**) (Scheme 6, Table 1) [157–167]. Several linked coenzymes containing the flavin moiety have been synthesized to investigate flavin–flavin [168–172], flavin–nicotinamide [173,174], flavin–thizolium [175,176] redox interactions. A functional group, attached at the positions N-3, N-10, C-6 or C-8 of the flavin ring systems has been used to covalently link the two moieties.

5.3. Synthesis of flavoporphyrins

The flavoporphyrins have been broadly classified on the basis of functional groups, such as amide, ester, amine and arene, forming a covalent bond between flavin and porphyrin.



Scheme 6.

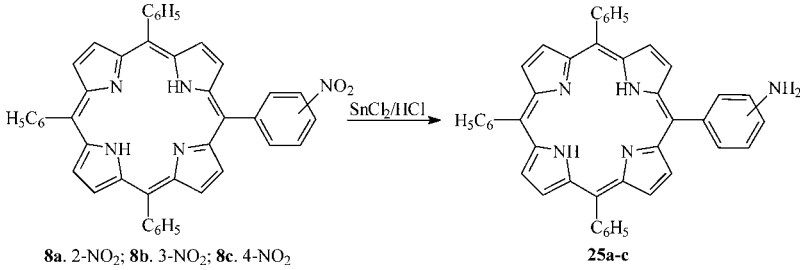
Table 1
Flavins synthesized by the cyclocondensation of 2-substituted aminoaniline with alloxane monohydrate

Entry	Flavins	R	R′
24a	10-Methylflavin	CH_3	H
24b	10-(Alkyl ester)flavin	$(CH_2)_nCOOEt$	H
24c	10-Phenylflavin	C_6H_5	H
24d	10-Benzylflavin	$CH_2C_6H_5$	H
24e	10-Aldehydeflavin	$(CH_2)_nCHO$	H

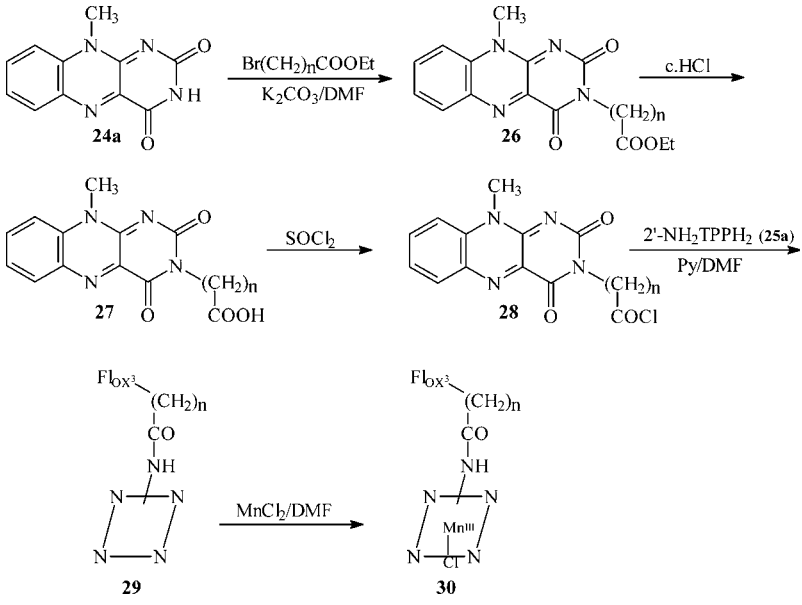
6. Flavoporphyrins attached via amide linker

Linkers containing an amide moiety have been used extensively for the formation of diporphyrin arrays [177–180] and also sometimes porphyrins in conjugation with other moieties [181–185] due to the ease of formation of amide bond. The synthesis of flavoporphyrins via amide linkage requires a porphyrin with amino group and a flavin with acid group or vice versa. The synthetic route to flavoporphyrins via amide linkage is shown in Schemes 8–11 [186,187].

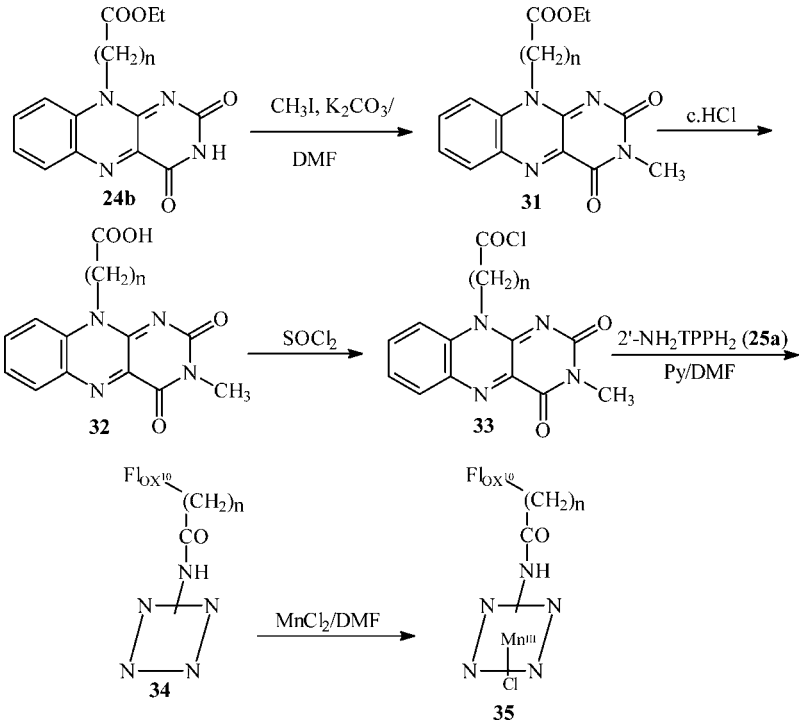
The cyclocondensation of pyrrole (**1**) with benzaldehyde [$R' = C_6H_5$] (**5**) and 2-nitrobenzaldehyde [$R = 2\text{-}NO_2C_6H_4$] (**6a**) in refluxing propionic acid gives a mixture of six isomers (**7,8a–12a**) (Scheme 2) [138,139]. The desired 5-(2′-nitrophenyl)-10,15,20-triphenylporphyrin [2′-NO_2TPPH_2, Table 2] (**8a**) was separated from this mixture by column chromatography over silica gel. The reduction of **8a** with $SnCl_2$/HCl [188]



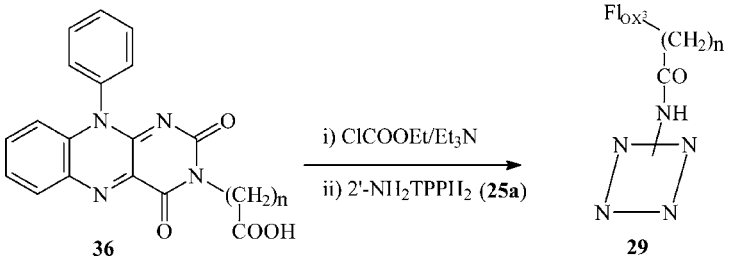
Scheme 7.



Scheme 8.



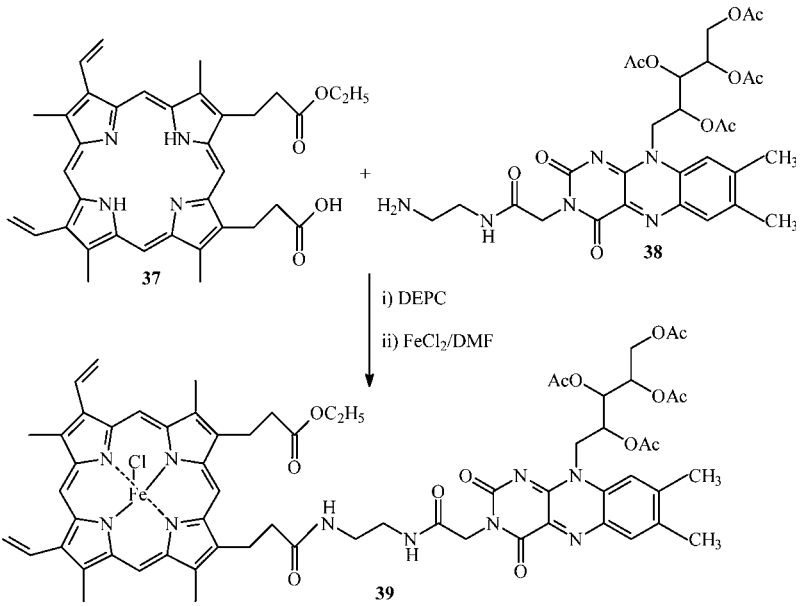
Scheme 9.



Scheme 10.

gave the required 5-(2′-aminophenyl)-10,15,20-triphenylporphyrin [2′-NH_2TPPH_2, Table 2] (**25a**) in 70–75% yields (Scheme 7) [189].

The flavin carboxylic acid **27** was obtained as shown in Scheme 8. The reaction of 10-methylflavin (**24a**, Table 1) with haloester and potassium carbonate in dry DMF gave the N^3-alkylated flavin (**26**). The alkylation occurred readily, giving the ester flavin **26** in good yield [186]. The hydrolysis of the ester flavin **26** was done in conc. HCl due to the instability of flavins in the alkaline media [190–195]. The condensation of acid flavin **27** with 2′-NH_2TPPH_2 (**25a**) using dicyclohexylcarbodiimide, carbonyldiimidazolide and diphenylphosphoryl azide as condensing agent was not



Scheme 11.

Table 2
Porphyrins synthesized by the cyclocondensation of pyrrole with substituted benzaldehydes

Entry	Porphyrins	R′	R
8a	2′-NO_2TPPH_2	C_6H_5	2-$NO_2C_6H_4$
8b	3′-NO_2TPPH_2	C_6H_5	3-$NO_2C_6H_4$
8c	4′-NO_2TPPH_2	C_6H_5	4-$NO_2C_6H_4$
8d	2′-OHTPPH_2	C_6H_5	2-OHC_6H_4
8e	3′-OHTPPH_2	C_6H_5	3-OHC_6H_4
8f	4′-OHTPPH_2	C_6H_5	4-OHC_6H_4
25a	2′-NH_2TPPH_2	C_6H_5	2-$NH_2C_6H_4$
25b	3′-NH_2TPPH_2	C_6H_5	3-$NH_2C_6H_4$
25c	4′-NH_2TPPH_2	C_6H_5	4-$NH_2C_6H_4$

successful, probably as a result of steric hindrance of the 2′-amino group. To overcome this problem, **27** was further reacted with thionyl chloride to give flavin acid chloride **28**, which was then coupled with **25a** in pyridine/DMF to give flavoporphyrin **29** in greater than 60% yield (Scheme 8) [186].

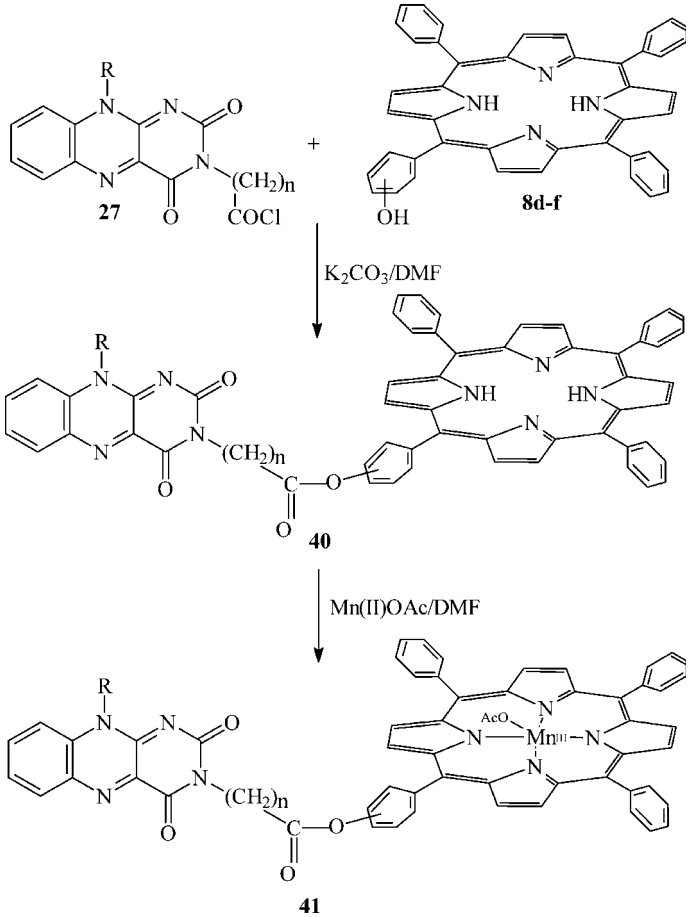
Similarly, the reaction of flavin **32** with **25a** in the presence of pyridine/DMF gave the flavoporphyrin **34** in greater than 65% yields (Scheme 9) [186]. The flavin **32** has been synthesized from 2-chloronitrobenzene (**19**) and amino ester (Schemes 6 and 9). The coupling of **32** with amino porphyrins has also been achieved in 41% yield by a mixed anhydride method using ethyl chloroformate (Scheme 10) [196]. The flavin **36** has been synthesized from 10-phenylflavin (**24 c**) following Scheme 8. The manganese

(III) insertion was carried out with $Mn(OAc)_2$ in DMF at 130 °C and the products were purified by column chromatography on alumina [186].

A riboflavin-appended myoglobin was successfully synthesized by the reconstitution of a chemically modified heme with apomyoglobin [187]. Protoporphyrin IX monoethylester **37** was condensed with a tetra-*O*-acetylriboflavin derivative **38** in the presence of diethylcyanophosphate (DEPC), followed by complexation of iron ($FeCl_2$/DMF under N_2 atmosphere) to give metallated flavoporphyrin **39** (Scheme 11) [197].

7. Flavoporphyrins attached via esters linker

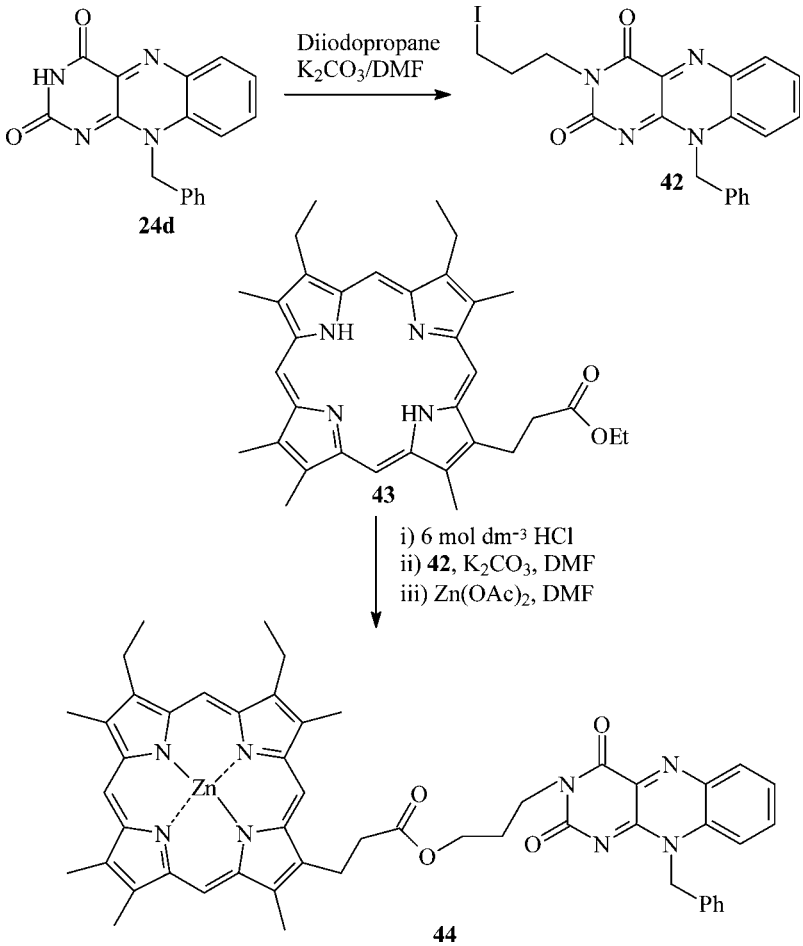
Ester bonds have been used in a number of porphyrin assemblies such as diporphyrins, triporphyrins, etc, and other biologically important heterocyclic compounds



Scheme 12.

[198–202]. These linkages are synthetically facile, which compensates somewhat for the generally low yields. The flavoporphyrins having ester linkage **40a–c** were synthesized in 25–37% yields by the condensation of the flavin acid chloride (**27**) with 5-[hydroxyphenyl]-10,15,20-triphenylporphyrins (**8d–f**, Table 2) (Scheme 12) [203,204]. The required porphyrins **8d–f** were synthesized from the cyclocondensation of corresponding hydroxybenzaldehyde (**6d–f**) and pyrrole (**1**) (Scheme 2) [138,139].

Another flavoporphyrin having an ester linkage **44** was synthesized as shown in Scheme 13 [205]. The reaction of 10-benzylflavin (**24d**) with diiodopropane in the presence of potassium carbonate in DMF gave 10-benzyl-3-(3′-iodopropyl)flavin (**42**). Further, the reaction of ester porphyrin **43** with HCl gave the hydrolyzed acid porphyrin which on treatment with **42** in the presence of potassium carbonate in DMF gave the flavoporphyrin, which was metallated by zinc acetate in DMF to give metalloflavoporphyrin **44** [205].



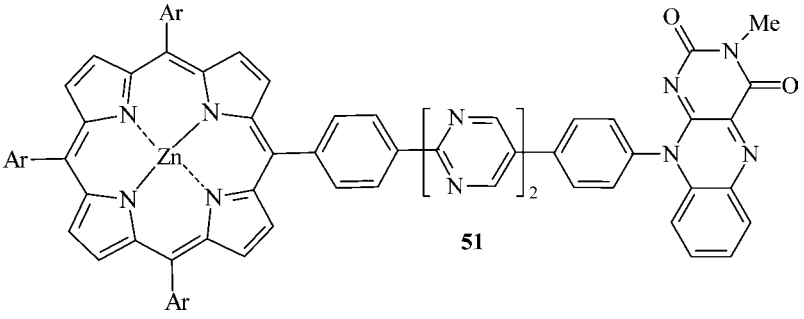
Scheme 13.

8. Flavoporphyrins attached via amine linker

The process of reductive alkylation has been used to generate an amine linkage. This process involves the treatment of ammonia or primary or secondary amines with an aldehyde or ketone under reducing conditions [206,207]. The flavoporphyrin **45** was synthesized by the reductive alkylation of aminoporphyrins **25** with flavin having aldehyde group at N-10 position **24e** in the presence of sodium cyanoborohydride in trifluoroacetic acid (Scheme 14) [118].

9. Flavoporphyrins attached via arene linker

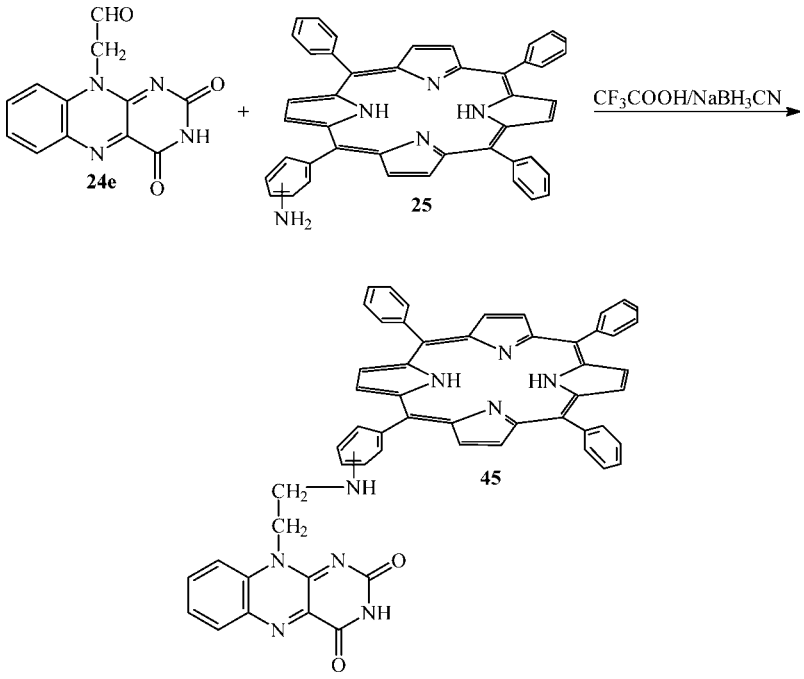
The flavoporphyrins **50** and **51** were synthesized according to the Scheme 15 [208]. The synthesis of pyrimidines from amidines and vinamidinium salts is an excellent method for the preparation of rigid rods of the oligophenyl type [209–211]. This method has a number of advantages. Amidines and vinamidinium salts are readily available with virtually no limitations regarding possible substituents [209–213]. Pyrimidine rings can be added step-by-step to get a homologous series of donor/acceptor systems with a controlled spacer length. This method also avoids the use of metal catalysts and so the insertion of metal ions into the porphyrin ring can be avoided [208]. The flavoporphyrin **49** was obtained from the persilylated porphyrinyl amidine **47** and the flavinyl-vinamidinium salt **48**.



51

The required cyanoporphyrin **46** was prepared from 4-cyanobenzaldehyde, 4-*tert*-butylbenzaldehyde and pyrrole (**1**) using Alder's method [214]. The product was separated from the porphyrin mixture by chromatography on silica gel. Conversion of the cyano into the amidine group by the Pinner synthesis [215] was not possible because of the low solubility of **46** in alcohol. However, **46** could be converted into **47** with lithium bis(trimethylsilyl)amide/chlorotrimethylsilane [209–211,216,217], **47** was further condensed with **48** in a one-pot reaction to afford **49** in 28% yield. The insertion of zinc by standard methods [218] yielded **50** in 71% yield (Scheme 15).

The synthesis of the flavin **48** started from 4-chloro-1-methyluracil (**52**) [219] (Scheme 16). Its reaction with 4-aminophenylacetic acid ester (**53**) in *N*,*N*-dimethylaniline and acetic acid gave **54** in 83% yield [208]. The flavin **55** was formed from **54**



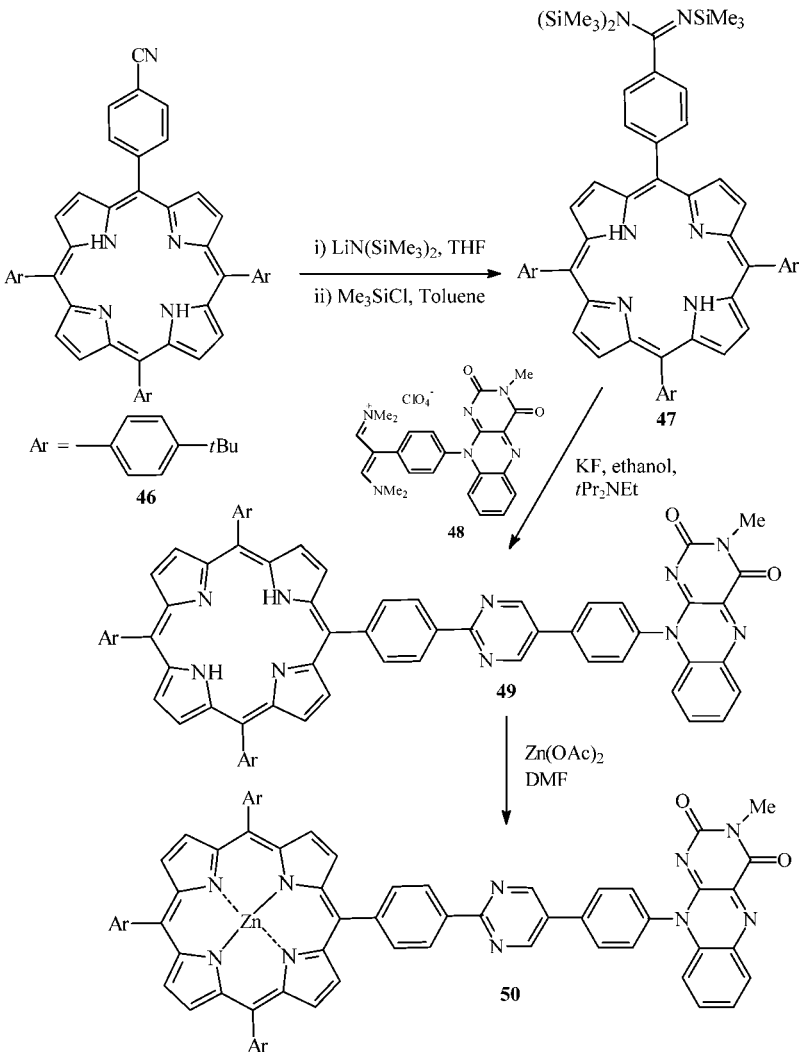
Scheme 14.

with nitrosobenzene in a mixture of acetic acid and acetic anhydride. Hydrolysis of **55** with HCl gave rise to acid flavin **56**. Finally, the flavinyl-vinamidinium salt **48** was obtained in 92% by the Vilsmeier–Haack–Arnold reaction [220,221] from flavin **56** with *N*,*N*-dimethylformamide and phosphoryl chloride.

10. UV–Visible and fluorescence spectroscopy in the spectroscopic characterization of flavoporphyrins

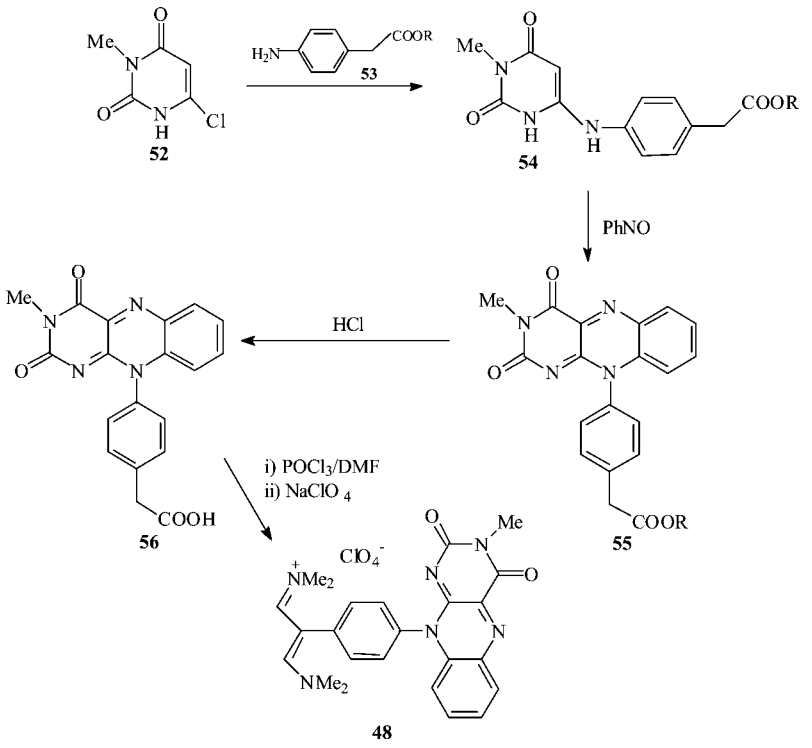
The free base porphyrin exhibit four bands (Q_{Y01}, Q_{Yoo}, Q_{X01}, Q_{X00}) in the 500–700 nm wavelength range and intense Soret band absorption around 420 nm [222]. The flavin exhibits three absorption bands in the range of 270–280, 310–325, and 450–460 nm [223]. The absorption bands at 310–325 and 450–460 nm are sensitive to solvent polarity and micro-environments [224,225]. The UV–Visible spectra of the flavoporphyrins are very similar to that of $TPPH_2$ (**7**) except for a band at 280 nm and a shoulder at 460 nm, which originates from the flavin moiety [186].

The shape of the Soret and visible bands are noticeably broadened. This broadening of the absorption bands of flavoporphyrins is due to close proximity of the two chromophores. The manganese (III) complexes of the flavoporphyrins gave spectra similar to the corresponding Mn–TPP complex. The main contribution from the porphyrin sub-structure to the absorption spectra is easily recognizable. In case



Scheme 15.

of flavoporphyrins separated by an arene spacer (e.g., **50** and **51**), absorption in the far UV around 300 nm and a bathochromic shift of 2–5 nm and a slight broadening of the Soret band becomes significant [208]. The absorption due to the flavin moiety is well separated from the porphyrin Soret and Q bands. Consequently, the flavin moiety can be nearly selectively excited in the wavelength range between 450 and 475 nm. The excitation at 465 nm of the flavin subsystem is selectively excited to 78% in the solvent toluene, to 80% in THF and to 76% in DMF [208]. On the other hand, the porphyrin group is excited at 517 nm. Hence, the fluorescence spectra of flavoporphyrins are measured at two excitation wavelengths (517 and 465 nm)



Scheme 16.

Table 3
Absorption maxima for free base porphyrins and flavoporphyrins in $CHCl_3$

Entry	λ_{max} (nm)					
	UV	Soret	IV	III	II	I
o-NH_2TPPH_2 (**25a**)		418	512	548	588	643
$Fl_{ox}C_1TPPH_2$ (**29a**)	273	418	514	548	588	642
$Fl_{ox}C_2TPPH_2$ (**29b**)	272	417	514	548	587	643
$Fl_{ox}C_3TPPH_2$ (**29c**)	270	418	514	548	588	643
N^{10}-$Fl_{ox}C_2TPPH_2$ (**34a**)	280	419	515	550	589	642
N^{10}-$Fl_{ox}C_3TPPH_2$ (**34b**)	276	419	515	549	588	643
o-$OHTPPH_2$ (**8d**)		419	513	553	593	653
o-$Fl_{ox}TPPH_2$ (**40a**)	243	420	514	552	593	653
m-$OHTPPH_2$ (**8e**)		420	513	553	593	653
m-$Fl_{ox}TPPH_2$ (**40b**)	243	420	514	552	593	653
p-$OHTPPH_2$ (**8f**)		420	513	553	593	653
p-$Fl_{ox}TPPH_2$ (**40c**)	243	420	514	552	593	653
N^{10}-$Fl_{ox}TPPH_2$ (**49**)	264	420	514	550	592	648

[208]. Excitation of the flavoporphyrin at 517 nm results in the typical porphyrin emission spectrum showing maxima at 654 and 720 nm that correspond to the Q^*_{X00} and Q^*_{X01} vibrational bands. Excitation at 465 nm gives only a very low

emission in the wavelength range corresponding to the flavin group, but a strong fluorescence is also observed. The flavin-excited state is thus strongly quenched and relaxes predominantly to the porphyrin excited state. A complete list of absorption maxima of selected flavoporphyrins is listed in Table 3.

11. ^{1}H NMR spectroscopy of flavoporphyrins

In contrast to UV–Visible spectroscopy, ^{1}H NMR data provide information about the geometry of the flavoporphyrin. There is a significant upfield shift of the internal pyrrole NH and β-H signals by a shielding effect of the ring current of the closely linked flavin ring system (Table 4). Similarly, a pronounced upfield shift for the flavin N^{10}-methylene spacer protons, which results from the ring current effects of the porphyrin macrocycle, has been observed. Changes in the chemical shift caused by the diamagnetic anisotropy of the porphyrin ring systems are well known [226] where the magnitude of these changes depends directly on the distance from the ring center.

12. Electrochemistry of flavoporphyrins

Electrochemical investigations of flavoporphyrins have been carried out with cyclic voltammetry (CV) or differential-pulse polarography (DPP) in DMF and CH_3CN containing 0.1 M tetraethylammonium perchlorate. DPP of the flavoporphyrin free base, *meso*-[*o*-(10-methylflavin-3-acetamidophenyl]triphenyl porphyrin [$Fl_{ox}C_1TPPH_2$] (**29a**, $n = 1$) produced three reduction waves with half wave potentials of −0.73, −1.07, and −1.41 V [186]. The redox potentials of the flavin reference compound (3,10-dimethylflavin) have almost the same values (−0.74, −1.31 V). The redox potentials of $TPPH_2$ have been found to be −1.08 and −1.46 V [186]. These results suggest that the redox potential of flavoporphyrins free base at −0.73 V corresponds to the $Fl_{ox}/Fl^{\cdot -}$ couple and the second wave at −1.07 V to the ($TPPH_2/TPPH_2^{\cdot -}$) couple. The third wave at −1.41 V resulted from mixing of the two redox

Table 4
^{1}H NMR chemical shifts for the free base flavin-linked porphyrins in $CDCl_3$

	$\delta^a(\Delta\delta)^b$	
	Internal py NH	Py β-H
o-NH_2TPPH_2 (**25a**)	−2.75	8.82, 8.86
$Fl_{ox}C_1TPPH_2$ (**29a**)	−3.51 (0.76)	8.71, 8.77 (0.10)
$Fl_{ox}C_2TPPH_2$ (**29b**)	−3.82 (1.07)	8.71 (0.13)
$Fl_{ox}C_3TPPH_2$ (**29c**)	−4.32 (1.57)	8.42, 8.55 (0.38)
N^{10}-$Fl_{ox}C_2TPPH_2$ (**34a**)	−3.75 (1.00)	8.50, 8.62 (0.28)
N^{10}-$Fl_{ox}C_3TPPH_2$ (**34b**)	−4.41 (1.66)	8.36, 8.69 (0.33)

[a] δ values were expressed downfield of internal TMS.
[b] $\Delta\delta$ values were expressed as follows: $\Delta\delta = \delta(2'\text{-}NH_2TPPH_2) - \delta(Fl_{ox}TPPH_2)$.

reactions. This also suggests a negligible interaction between flavin and porphyrin free-base in DMF. However, DPP of **29a** in acetonitrile shows the redox potentials at −0.74, −1.11, −1.38, and −1.55 V. The redox potentials of the flavin reference compound (3,10-dimethylflavin) are −0.82 and −1.39 V which indicate a flavin–porphyrin interaction. In DMF, the interaction did not occur due to solvation of the two chromophores. However, the Mn(III)flavoporphyrin complex in DMF exhibited a strong flavin–manganese(III)porphyrin interaction. The introduction of Mn(III) into the flavoporphyrin leads to a redox wave of approximately −0.2 V vs SCE, which is typical for the Mn^{III}/Mn^{II} redox couple of $(TPP)Mn^{III}Cl$ [227]. The flavin-catalyzed 2e/1e electron-transfer reactions from dihydropyridines (PyH_2) to TPPMn(III)Cl have been studied kinetically in intermolecular systems ($PyH_2 + Fl_{ox}$ + TPPMn(III)Cl) as well as in intramolecular systems ($PyH_2 + Fl_{ox}C_n$TPPMn(III)Cl) in ethanol solution [186]. In intermolecular systems, the presence of flavin enhances the apparent rates of electron transfer significantly. The kinetic behavior of the intermolecular system is zero order with respect to the TPPMn(III)Cl concentration and first order with respect to the PyH_2 and Fl_{ox} concentrations, when PyH_2 is in excess and the Fl_{ox} is used in 0.25–1.5-fold to TPPMn(III)Cl. These observations show that the flavin acts as 2e/1e catalyst. In intramolecular systems, the kinetic behavior differs for the various $Fl_{ox}C_n$TPPMn(III)Cl systems. The $Fl_{ox}C_1$TPPMn(III)Cl shows first order, but $Fl_{ox}C_2$TPPMn(III)Cl and $Fl_{ox}C_3$TPPMn(III)Cl exhibit mixed order behavior. The rate constant of electron transfer are also affected by the methylene spacer length and linking positions [186].

Cyclic voltammetric studies on the flavoporphyrin **44** were performed in methylene chloride [208]. The result showed reversible waves with oxidation potentials at +0.82 and +1.15 V, relative to ferrocene as reference redox system. Both half-wave potentials are in good agreement with that of the first and second oxidation steps of the parent porphyrin **43** which showed two oxidation waves with half-wave potentials at +0.81 and 1.13 V under the same conditions [208]. The first and second reduction potentials appear at −0.74 and −1.29 V. The first one corresponds to the reduction of the flavin, that is, $Fl_{ox}/Fl^{\cdot -}$ (−0.73 V was found previously [186] and the second one to the first reduction potential of the porphyrin ($TPPH_2/TPPH_2^{-}$) [186].

13. Future projection of flavoporphyrins and related heterocycles

The electron transfer is an inseparable part of living system and so is the case with redox enzymes performing electron transfer. The understanding of the molecular mechanism of redox enzymes will remain the focus of research from both chemical and pharmacological perspectives. Hence, the physical and chemical properties, synthesis and characterizations of various cofactors and their modifications is going to be an essential part of future research. The mechanistic studies of the redox enzymes will help in understanding the unusual chemistry catalyzed by these enzymes and also shed light on their electron transfer reactions. The details of the mechanism will also provide the basis for the design of isoform-selective inhibitors of therapeutic significance.

The synthetic methodologies of flavoporphyrins still require many modifications to generate them in quantitative amounts with less environmental impact. The detailed application of flavoporphyrins in medicine still requires attention.

14. Conclusions

The synthesis, characterization, and electron transfer of different types of flavoporphyrins have been reviewed and classified on the basis of linking group. The condensation of flavin and porphyrin via amide linker has been used more extensively than other linkers. The methods reviewed allow the synthesis of nearly all types of flavin-linked porphyrins. The electrochemical studies suggest an interaction of the chromophores in redox reactions. The flavin-catalyzed 2e/1e electron transfer reactions between NADH model compounds and $TPPM^{III}Cl$ have been investigated in inter- as well as intramolecular systems. Electron transfer is strongly affected by the methylene spacer length and the position of the linker.

Acknowledgments

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