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Free-Base and Metal Complexes of 5,10,15,20-Tetrakis(N-Methyl Pyridinium L)Porphyrin: Catalytic and Therapeutic Properties

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http://dx.doi.org/10.5772/intechopen.68225

Abstract

Porphyrins are tetrapyrrole macrocycles that can coordinate transition metal ions such as iron, cobalt and magnesium and are able to perform a diversity of functions and applications. In biological systems, these molecules are associated with proteins involved in photosynthesis, cell respiration, cell death, antioxidant defence, among others. The stability and versatile applications of porphyrins inspired the synthesis of derivatives including 5,10,15,20-tetrakis(N-methyl pyridinium-4-yl)porphyrin (TMPyP) that is the object of the present chapter. In synthetic porphyrins such as TMPyP, the catalytic and photochemical properties can be achieved by the coordination with a diversity of central metal ions. In photodynamic therapy (PDT), TMPyP and other porphyrins act as photosensitizers. The photochemical properties of TMPyP and other porphyrins are also useful for the fabrication of solar cells. The catalytic properties require the presence of a central metal. The MnTMPyP have antioxidant activity that is influenced the capacity of membrane binding, substituents, and meso substituents. Manipulation of the interfacial confinement properties is one of the newest application areas of porphyrins. The association of porphyrins with different surfaces modulates the electronic and physicochemical properties of these molecules. All of these properties are the object of experimental and theoretical studies discussed in the present chapter.

Keywords: porphyrins, TMPyP, antioxidant activity, photodynamic therapy



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1. Introduction

Porphyrins constitute a group of aromatic organic molecules, composed of four pyrrole rings linked by methene (=CH-) bridges (5, 10, 15 and 20), that are the *meso*-carbon atoms/positions [1]. Free base porphyrins are able to complex with metal ions such as iron, zinc, copper and others at themacrocycle center to form metalloporphyrins. Therefore, the properties of a porphyrin can be modulated by the inserting or changing the central metal and appending different substituents at the *peripheral* (β -positions (2, 3, 7, 8, 12, 13,17 and 18)) and *meso* positions (**Figure 1**). Furthermore, the activity of a metalloporphyrin frequently involves redox cycling of the central metal. When peripheral and meso substituents are exclusively hydrogen atoms, and two of the four macrocycle nitrogen atoms are protonated, this molecule is known as a free-base porphine. When different organic groups are appended at the *peripheral* or *meso* positions, these compounds are known as porphyrins [2]. The manipulation of different substituents and central metal provides a wide diversity of biochemical functions for porphyrins.

In biological systems, the porphyrins are associated with proteins involved in important cellular processes such as photosynthesis, molecular oxygen transport, cell respiration, cell death, the combat of the oxidative stress, biological synthesis, fat acid oxidation and others [1, 3–5]. The iron protoporphyrin IX (known as heme group) is the biological metalloporphyrin present in almost all biological processes. Heme is the prosthetic group of myoglobin, hemoglobin and a diversity of enzymes such as peroxidases, cytochromes, NO* synthase and others. Besides iron ion, other metals are found in biological porphyrins, the magnesium ion in chlorophyll, and the cobalt ion in vitamin B 12 [6]. Biological and synthetic porphyrins and metalloporphyrins have been extensively investigated and applied in medicine, chemistry, sensing and other technological devices due to their catalytic, photochemical and photophysical properties [6, 7]. In biological systems, free-base porphyrins are largely used as photosensitizer (PS) in photodynamic therapy (PDT) [2, 5, 8, 9]. Otherwise, metalloporphyrins have been used for mimicking the function of hemeproteins such as cytochrome P-450 in oxidative catalysis and superoxide dismutase SOD against oxidative stress. Porphyrins are also used as building blocks and in transport chains of molecular devices [4, 9–11].

Porphyrins are versatile catalytic and therapeutic agents. The properties of porphyrins can be modulated by changing the central metal, substituents at the *peripheral* and *meso* positions and the microenvironment. Different microenvironments respond for the diversity of functions of heme group in the hemeproteins: oxygen transport, electron transport, hydroxylation, peroxide cleavage and others. The versatility of functions can also be achieved for synthetic porphyrins by manipulating their structures and microenvironments. One example of interchangeable functions of porphyrins is the substitution of the central metal in TMPyP (5,10,15,20-tetrakis(N-methyl pyridinium L)porphyrin). MnTMPyP exhibits antioxidant function, and it has been attributed to the superoxide dismutase (SOD)-like and

Free-Base and Metal Complexes of 5,10,15,20-Tetrakis(N-Methyl Pyridinium L)Porphyrin... 3 http://dx.doi.org/10.5772/intechopen.68225



Figure 1. Free-base porphine with peripheral and meso positions.

glutathione peroxidase (GPx)-mimetic capacities [12, 13], while FeTMPyP exhibits pro-oxidant activity that responds to the toxicological effects of these compounds [14]. The prooxidant activity of FeTMPyP has been attributed to the generation of free radicals due to the homolytic cleavage of peroxides. The introduction and modification of substituents in a metalloporphyrin changes the redox potential and the solubility. In this regard, TMPyP and TPPS4 are examples of synthetic porphyrins made water soluble by the meso substitution of pyridine and sulfonate groups, respectively. Depending on the meso substituent, there is the possibility of a refined modulation of the porphyrin activity by isomerization. Previous studies comparing SOD activity of ortho, meta and para isomers of MnTMPyP (Figure 2) showed that the former exhibits the most effective SOD-like activity due to an appropriate combination of redox potential and electrostatic facilitation [15-18]. Para MnTMPyP exhibits a lower redox potential value that disfavors SOD activity [19]. However, the association of para MnTMPyP to negatively charged membranes (phosphatidylcholine (PC)/phosphatidylserine (PS)) modulates its redox potential toward a more efficient SOD activity [20]. Thus, the study of Araujo-Chaves et al. [13] is an example of the modulation of a porphyrin activity by the microenvironment. The different activities of TMPyP and other porphyrins are described herein.



2. Biological applications of porphyrins

2.1. Porphyrins in photodynamic therapy (PDT)

2.1.1. A brief historical of PDT

The term PDT – photodynamic therapy – is recent. However, the heliotherapy – the therapeutic exposure to sunlight—was already used more than 4000 years ago by Egyptians, Greeks, and Indians as a treatment for several skin disorders, like psoriasis, vitiligo, cancer and even psychosis [21–29]. Heliotherapy, recently known as phototherapy, employs either UV and visible light with/without an exogenous photosensitizer. The photosensitizer is a molecule which when exposed to light absorbs determined wavelength becomes electronically excited and starts photochemical reactions that can produce a desirable beneficial effect, as in the case of vitamin D synthesis or damage and death, as in the case of tumor and infections treatment [2, 30]. Phototherapy without an exogenous photosensitizer is used in dermatology to treat vitiligo, eczema, neonatal jaundice and vitamin D deficiency, and even some cancer types [30–33]. During 18th and 19th centuries, phototherapy without exogenous photosensitizer was used in France in the treatment of many diseases, including tuberculosis, rheumatism, edema, rickets and paralysis [28, 34]. When an exogenous photosensitizer is used in tandem with the sunlight, this therapy is called photochemotherapy. An example of the exogenous photosensitizer is the psoralen series (Figure 3). These molecules are used as active treatments of HIV-associated dermatoses, seborrheic dermatitis, mycosis fungoids, prurigo, palmar and plantar pustulosis, among other diseases [30, 35]. The use of psoralens and ultraviolet light— UV (300-400 nm) was used by ancient Egyptians to treat vitiligo in the past and has been accepted for the treatment of psoriasis (PUVA) and in immunotherapy throughout the world [22, 27, 30, 35, 36].

Photodynamic therapy (PDT) is a non-invasive treatment method that uses light, photosensitizer and molecular oxygen for the treatments of cancer, inflammation, immunological Free-Base and Metal Complexes of 5,10,15,20-Tetrakis(N-Methyl Pyridinium L)Porphyrin... 5 http://dx.doi.org/10.5772/intechopen.68225



Figure 3. Psoralen series.

diseases and bacterial infections [8, 37–41]. In ancient times, phototherapy was used based on the observation of positive results without a mechanistic knowledge. People using and advocating phototherapy did know the key role of the photosensitizer in this type of treatment. In that times, the photosensitizer role was played by an endogenous biomolecule absorbing sunlight. The domain of the PDT mechanism initiated with the isolation of hematoporphyrin (Hp) (**Figure 4**) [28, 42]. From dried blood cells by Scherer in 1841 followed by the discovery of its fluorescence properties in 1871 [43]. In 1911 and 1913, the side effects of sun exposure after the administration of hematoporphyrin were described by Hausmann and Friedrich Meyer-Bertz. The latter scientist tested on himself the effect of Hp and sun and provided the first scientific communication of human photosensitization [44]. Besides, the powerful cytotoxic effect of phototherapy, another significant finding favoring the consolidation of this type of treatment, was the report of Auler and Banzer showing the affinity of Hp for cancer cells in 1942 [45]. In the following, several other studies led to the development of new range of porphyrinic photosensitizers [28, 43, 46–51].

2.1.2. The PDT mechanism

The Jablonski diagram [52], first proposed by Professor Alexander Jablonski in 1935, has been used to describe the photodynamic processes of photosensitizer molecules used in PDT. The PDT principles are based on the presence of an endogenous or exogenous photosensitizer in the target tissue that can absorb red light to be promoted to a long-lived electronic excited state. In the electronic excited state, the photosensitizer triggers photooxidative events directly or more commonly via energy transfer to molecular oxygen. The quantum yield triplet state generation depends on the molecular structure, and the energy transfer to molecular oxygen competes with other deactivating routes for the excited state [25].

According to **Figure 5**, Jablonski diagram shows that the ground state photosensitizer (S_0) can absorb a photon and be converted to the short-lived excited singlet state (S_p) at different

Figure 4. Hematoporphyrin.

vibrational sublevels (S_n'). The S_n state, if n > 1 can lose energy *via* internal conversion (IC) to populate the first excited single state (S_1). In the first singlet excited state, the photosensitizer can return to the ground state via fluorescence and thermal irradiation. Also, the S_1 state of the photosensitizer can undergo intersystem crossing by spin inversion and populate the lowerenergy first excited triplet state (T_1), a long-lived state [2, 30, 37, 49]. At this point, two different reaction processes involving molecular oxygen can occur Type I or Type II processes. In the first process, Type I, the photosensitizer in a triplet excited state is reduced with organic substrates by electron exchange. The reduced photosensitizer can react with molecular oxygen ($^{3}O_2$) to produce reactive oxygen species (ROS) such superoxide anion (O_2^{-}), hydroxyl radical (OH⁻) and hydrogen peroxide (H_2O_2) [30, 37, 53]. In the second process, Type II, the triplet excited state photosensitizer transfers energy to molecular oxygen, resulting in a long-lived and highly reactive species, the singlet oxygen ($^{1}O_2$) [37, 49, 54]. Types I and II mechanisms occur concomitantly. However, Type II is the dominant process during PDT [30, 37]. Free-Base and Metal Complexes of 5,10,15,20-Tetrakis(N-Methyl Pyridinium L)Porphyrin... 7 http://dx.doi.org/10.5772/intechopen.68225

Figure 5. Energy levels of Jablonski diagram for a typical type II photosensitizer and oxygen.

In PDT, singlet oxygen is the principal reactive species. However, as well as others ROS, singlet oxygen has the capacity of damage limited due to its short lifetime (~100 ns in lipid regions of membranes and 250 ns in the cytoplasm) [30, 49, 55], and a diffusion range of approximately 45 nm in the cellular medium [28, 56–58]. The PDT has amino acid residues in proteins, unsaturated lipids, and DNA as the targets for oxidation leading to cell damage [59–61].

2.1.3. Porphyrin as photosensitizers

An ideal photosensitizer needs to have the following characteristics: (1) chemical purity; (2) high yield of singlet oxygen production; (3) high absorption coefficient in the red region of the visible spectrum (680–800 nm). Wavelengths longer than 900 nm should be avoided due to their insufficient energy to excite a dye photosensitizer to the triplet state; (4) efficient accumulation in tumor tissue associated with a rapid clearance in healthy organs; (5) low toxicity in the dark extensive to their metabolites; and (6) small aggregation [8, 30, 49, 62–64].

Porphyrins satisfy most of the desirable properties of photosensitizers, such as high efficiency of singlet oxygen generation, absorption of the higher wavelengths of the electromagnetic spectrum and a relatively higher affinity for malignant cells. Porphyrins have 18π electrons on the aromatic macrocycle that responds for the "*Soret*" band, with a strong absorption band around 400 nm, and Q bands in the 500–700 nm range that constitute the therapeutic window for this photosensitizer (**Figure 6**) [10, 65]. The absorption spectrum of the porphyrins is influenced by ligands and the central metal [66–68].

Figure 6. Porphyrin absorption spectrum. a = Soret band; b = Q band.

In the early twentieth century, data of literature described experiments that demonstrated the potential role of Hp in the detection and treatment of cancers; however, one of the major drawbacks was the large doses required to achieve consistent photosensitizer uptake in tumors, which led to inappropriate phototoxicity [45, 69–71]. In 1955, Schwartz et al. [72] demonstrated Hp to be impure and attributed selective fluorescence of malignant tissue after in vivo administration of Hp to a mixture of porphyrins with different properties. Subsequent studies led to the development of a derivative of hematoporphyrin (HpD) by the treatment of crude Hp with acetic and sulfuric acids, which enhanced tumor accumulation. The ability to accumulate selectively in neoplastic tissue using lower doses of HpD than Hp was reported by Lipson and coworkers [73–77]. In 1972, Diamond et al. demonstrated the destructive potential of HpD irradiated with white light on glioma in rats [78]. Six years later, Dougherty et al. reported the partial and complete response of many tumors, including malignant melanomas and carcinomas of the colon, breast, and prostate, treated by photodynamic therapy using HpD as a photosensitizer [79]. In the following, HpD compounds were purified, many of the less active monomers were removed, and the most efficient HpD derivatives were used to produce Photofrin (Figure 7).

For a complete study of different porphyrinic photosensitizers [80–109], it is recommended the reviews Josefsen et al. [2], Connor et al. [25], Pushpan et al. [28], and Ethirajan et al. [49]

Among a diversity of porphyrinic photosensitizers, *meso*-tetraphenylporphyrin (TPP) and TMPyP are readily synthesized and metallized, and several derivatives have been studied as a photosensitizer for PDT. The photochemical efficiency of anionic 5,10,15,20-*meso*-tetra(4-sulfonatophenyl)porphyrin (H_2 TPPS₄) (**Figure 8A**) was compared with *meso*-tetraphenyl porphyrins with a lower number of sulfonate groups [99, 100] and

Free-Base and Metal Complexes of 5,10,15,20-Tetrakis(N-Methyl Pyridinium L)Porphyrin... 9 http://dx.doi.org/10.5772/intechopen.68225

Figure 7. Photofrin.

with 5,10,15,20-tetrakis(4-sulfonatophenyl-21,23-dichalcogenaporphyrin [110] (**Figure 8B**). These studies showed that H_2 TPPS₄ is less efficient in PDT than *meso*-tetraphenyl porphyrins with a lower number of sulfonate groups. Also, the replacement of nitrogen atoms of the macrocycle by chalcogens S and Se increased the photodynamic efficiency of the porphyrin in vitro and in vivo studies. Particularly in vivo, these chalcogen derivatives exhibited lower toxicity, morbidity and side effects post administration in animal models.

Regarding TMPyP, the focus of the present study, its efficiency as a photosensitizer is related to its topology. A study comparing photodamage in a mitochondrial membrane model modulated by the topology of TPPS4 and 5,10,15,20-tetrakis(N-methyl pyridinium L)porphyrin (TMPyP) [8] shows that in L- α -phosphatidylcholine/cardiolipin (PC/CL)liposomes (mitochondrial membrane model) both porphyrin can damage the membrane *via* the Type II mechanism. However, the injuries on the lipid membranes promoted by TMPyP were greater than the damages promoted by TPPS4 due to the affinity between TMPyP and this biological

Figure 8. TPP-based photosensitizers. (A) Tetrasulfonated *meso*-tetraphenyl porphyrin; (B) *meso*-tetrakis(4-sulfona tophenyl)-21,23-dichalcogenaporphyrin.

structure [111, 112] that in turn influences the photosensitizer and the generation of longlived singlet oxygen. In cells, the positively charged TMPyP accumulates in the nucleus and mitochondria and could attack DNA, mitochondrial DNA and cardiolipin. The association of TMPyP with the inner mitochondrial membranes due to the affinity to cardiolipin favors the generation of singlet oxygen in situ with a high efficiency since its concentration is higher in the hydrophobic core of the lipid bilayers. Metalloporphyrins have also been studied as potential sensitizers for PDT. However, the results were less promising than those obtained with the free-base species [113, 114].

2.2. Porphyrins in chemical therapy

The synthetic analogs of porphyrins are widely used in therapy of diseases connected to oxidative stress processes. A quantitative structure-activity relationship (QSAR) studies have been performed to identify the optimal active molecule within a series of analog structure characteristics to diversify the biological action of the compound. The QSAR studies can correlate the physicochemical characteristics that affect the compound's activity in biological systems. These studies assumed that the binding affinity of the compound to the target receptor could determinate the biological activity [115]. The biological effects of two meso-tetrakis porphyrins, TPPS4 (anionic) and TMPyP (cationic) demonstrated that the cationic porphyrin has affinity to the inner mitochondrial membrane [99]. Therefore, in mitochondria, Mn³⁺TMPyP has been used as an antioxidant against superoxide ions. The replacement of manganese by an iron ion in TMPyP makes this porphyrin a prooxidant agent [116]. Au-porphyrins have been reported as excellent antiproliferative agents, showing cytotoxic effects on cancer cells. Regarding to the mimetic SOD activity of porphyrins, the correlation between the metal-centered reduction potential and the catalytic rate constant for the O₂^{•-} dismutation was found for Fe and Mn porphyrins. The structure-activity relationships have been established over the years by the rate-limiting step of metal reduction of this class of compounds [117]. Modulation of SOD activity has been achieved by decreasing the electron density of the groups at the meso and β -pyrrile positions, thus increasing the Mn³⁺/Mn²⁺ potential and facilitating its reduction [118–120]. Either the mimetic SOD activity can occur when the O_2 is directed to the catalytic site by the metal-centered positive charges via electrostatic facilitation [118, 119]. The manganese (III) 5,10,15,20-tetrakis(N-ethylpyridinium-2-yl) porphyrin (Mn³⁺TE-2-PyP⁵⁺, $E_{1/2}$ = +228 mV vs NHE, \log_{kcat} = 7.76) and manganese (III) 5,10,15,20-tetrakis(N-n-hexylpyridinium-2-yl) porphyrin (MnTnHex-2-PyP⁵⁺, $E_{1/2}$ = +314 mV vs NHE, log _{kcat} = 7.48), alkylated manganese (III) 5,10,15,20-tetrakis(2-pyridyl)porphyrin (MnT-2-Pyp⁺), combined the thermodynamic and electrostatic optimizations and yielded compounds because they exhibit the E₁₄ close to the reduction potential of the SOD enzyme and are excellent mimetics of the SOD activity $(E_{\frac{1}{12}} \approx +300 \text{ mV } vs \text{ NHE}, \text{ kcat} \approx 2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1})$ [19, 117–122]. Recently, it has been reported that the para isomer ($E_{1/2}$ = +60 mV vs NHE) of Mn³⁺TMPyP is less efficient as a SOD mimic relative than the *ortho* isomer (E_{14} = +260 mV *vs* NHE) [12, 19, 123, 124].

In a cell redox balance, the association of Mn³⁺TMPyP to membrane lipid bilayers can be intrinsically related to the redox potential of the Mn²⁺/Mn³⁺ couple. In homogeneous systems, Batinić-Haberle et al. [19] had reported the effect of Mn³⁺TMPyP in a CL-containing inner

mitochondrial membrane under pH 11 to 7.8 conditions. The potential values of Mn^{2+}/Mn^{3+} redox process were found to be $E_{1/2}$ =94 mV for *ortho* $Mn^{3+}TMPyP$ and $E_{1/2}$ = 42 and 50 mV, respectively, for *meta* and *para* isomers. However, in a heterogeneous system, Araujo-Chaves et al. [20] have reported that the *para* isomer has the redox potential increased by the association with the negatively charged interface of lipid bilayers. Interestingly, the association of *para* $Mn^{3+}TMPyP$ to PC/PS liposomes at physiological pH exhibited a redox potential of +110 mV *vs* NHE. The shift of the $Mn^{2+}/Mn^{3+}E_{1/2}$ value to a more positive value favors the SOD and peroxidase activities. Theoretical calculations corroborated with these results.

3. Technological applications

Porphyrins free base are extensively applied in solar cells and sensor due to their photophysical characteristics. The intense absorption bands covering a significant range of the visible region of the electromagnetic spectrum and due to the relatively low cost of these compounds as compared with inorganic semiconductors make these molecules appropriate for application in solar cells. These characteristics experimentally observed are consistent with the results obtained by density functional theory (DFT). Therefore, DFT/time-dependent (TD)DFT calculation is a useful strategy for the molecular design of porphyrins with the more appropriate characteristics for application is dye-sensitizer solar cells (DSSCs) [125–129]. As an example, Santhanamoorthi et al. [129] have presented the theoretical study of newly designed porphyrin dyes (1-5) for DSSC applications. In this study, the authors calculated seven different structures of porphyrins and found the best characteristics for use in solar cells for two calculated molecules that were named Dyes 2 and 4. Dyes 2 and 4 presented smaller HOMO-LUMO energy gaps and absorption in Q band significantly stronger. Equally, DFT/TDDFT can be used for conceiving porphyrin derivatives for a diversity of technological applications. Theoretical calculations allow the prediction of the best characteristics for porphyrins to be used in technological applications and optimize the subsequent efforts for the synthesis.

3.1. Porphyrins in solar cells

Solar energy is an important source of energy ($\sim 3 \times 10^{24}$ J year⁻¹) that sustains the life on the Earth [130–132], and it can be an alternative to using fossil fuels due to be a clean, inexhaustible and sustainable source of energy [133–139]. The utilization of solar energy as solar fuel or electricity is fundamental for the maintenance of development and live on Earth and has attracted the attention of various members of the scientific community.

O'Regan and Grätzel [140] have discussed dye-sensitized solar cells (DSSC), a viable and promising technology which have low-cost production and high power conversion efficiency [141–148]. To build an efficient system of the solar cell is necessary [149–152] three components: (1) dye (light-absorber); (2) a hole transport agent; and (3) an electron-transport agent. **Figure 9** shows the schematic representation of components and representative operational principles of DSSC.

Figure 9. Schematic representation of components and representative operational principles of DSSC.

A typical DSSC device consists of a dye-sensitizer photoanode (TiO_{2'} anode) and a platinum counter electrode (Pt-coated, cathode) sandwiching an electrolyte that contains a redox mediator (iodine-based or cobalt complexes, redox mediator). Upon light illumination, the photoexcited dye in the LUMO level of sensitizer injects an electron into a conduction band (CB) of TiO_{2'}, and then, the resultant oxidized dye is reduced by I⁻ species (or Co²⁺ complex). The injected electrons move through an external circuit to the platinized counter electrode. Finally, the I⁻ species (or Co²⁺ complex) is regenerated to produce the I₃⁻ species (or Co³⁺ complex) at the surface of the platinized counter electrode, and the circuit is completed [133]. The efficiency of conversion of light to electric power (η) increases when a light-absorbing the dye, and therefore, the choice of a suitable dye is essential to a high η [127, 144, 153–156].

Despite to the intense absorption band, typical porphyrins have poor light-harvesting ability in the Q bands, being necessary the introduction of a push-pull structure [157–160] and the elongation of porphyrin π -conjugated system into *meso* or β -positions to improve the light-harvesting property of porphyrins [158].

Porphyrin also can be used as a dye in thin layers on the porous TiO₂ film. However, this system results in weak absorption of irradiated light, being essential the development of a way to strongly absorb the light in the dye layer. Gold layer can have been used in these systems due

to its surface plasmon resonance (SPR) that offers an enhanced optical field with increased short-circuit current, which can be corroborated by theoretical calculations [161].

3.2. Porphyrins in catalysis and sensing

The application of metalloporphyrins in bioinorganic chemistry has attracted interest in catalytic reactions. Synthetic metalloporphyrins are mimetic models inspired two heme proteins: cytochrome P450 (biosynthesis and degradation of biomolecules) and peroxidases as lignin peroxidases (degrades the lignin-cell wall). In 1970, Groves et al. [162] designed the firstgeneration of metalloporphyrin chlorine (5,10,15,10-tetraphenyl-porphyrinato)iron(III), or [Fe³⁺TPPCl], activated by iodosylbenzene (PhIO) revealed a catalytic activity in the epoxidation of alkenes and the hydroxylation of alkanes. About 30 years ago, Traylor and Tsuchyia [163] presented the first synthesis of porphyrins with more stability and more efficient catalytic activity due to the introduction of electronegativity and/or bulky auxiliaries groups such as halogen, nitro or sulfonate at the *meso* and/or β-pyrrolic positions, to obtain the second and third generation of porphyrin catalysts. Lately, the metal complexes like meso-tetrakis(penta fluorophenyl)porphyrin H₂(TPFPP) represent alternative possibilities to structural modification of porphyrins by nucleophilic substitution of its fluorine atoms [164, 165]. The second generation of porphyrins, especially the manganese (II) and iron(III) porphyrins is the most important representatives as catalysts in the epoxidation of alkenes (cyclohexane, adamantane, or n-hexane). In this case, during the epoxidation reactions, Mn and Fe ions can accept active species from different substrates and oxygen atom donors that result in metal-oxo species formation. In some conditions, the catalytic efficiency of iron(III) porphyrins can be limited due to the presence of some by-products resulted from the epoxidation of alkenes, for example to the allylic oxidation reactions. In anadamant oxidation reaction, the catalytic reaction of manganese porphyrins (MnPor) derived from 5,10,15,20-tetrakis(4-methoxyphenyl)porphyrin had an increased product yield of 1-adamantanol than those obtained with [Fe3+TPPCl] catalyst [166]. The MnPors can exhibit different behaviors regarding the electron-withdrawing substituents in the macrocycle structure. Doro et al. [167] revealed that MnPors had lower catalysis efficient than the second generation of catalyst [Mn³⁺PFTDCPP]Cl due the high-valence active species caused by the electronegativity of the substituents (fluoro and chlorine) at the meso-aryl positions of the macrocycle in [Mn³⁺PFTDCPP]Cl. Consistently with this observation, Rayati et al. [168] made a comparative catalytic study of two partially brominated MnPs, namely [Mn³⁺Br₄TPP]Cl and [Mn³⁺Br₄T₄(-OME)PP]Cl revealing that the electron-deficient Mnps were a better catalyst than electron-rich MnPs. Lately, new materials of metalloporphyrin catalysts supported on mesoporous silica have shown a high efficiency of stability and reaction conditions. Poltowicz et al. [169] have studied the supported MnTMPyP catalysts on aluminated MCM-41 and SBA-15 mesoporous to investigate the oxidation of cyclooctane with molecular oxygen (as air) without the use of sacrificial co-reductant. Due to the existence diffusion limitations within the pore inner space, the supported MnTMPyP had increased the catalysis activity in the SBA-15 mesoporous because it exhibits increased-size pore. The catalytic activity of porphyrins, including TMPyP, allows the use of these compounds in sensing. Porphyrins can form complexes with almost all metals, and consequently, a broad diversity of catalytic properties can be achieved. The central metal in porphyrins determines the affinity for additional ligands. In general, the complex of Cu²⁺ and Ni²⁺ has low affinity for additional ligands. The Mg³⁺, Cd²⁺ and Zn²⁺ porphyrins form pentacoordinate complexes with square-pyramidal structure. The metalloporphyrins with (Fe²⁺, Co²⁺, Mn²⁺) in the central position produce distorted octahedral structure with two axial ligands. Metallo *meso* tetrakis porphyrins have been extensively used in the voltammetric determination of oxygen, NO, sugars, organohalides, DNA, alcohols, dopamine and others. Therefore, due to their switchable structures and a diversity of catalytic properties, porphyrins are widely used in analytical chemistry. A diversity of porphyrins can be applied biosensors and as stationary phases in HPLC.

Acknowledgements

We are grateful to FAPESP (2015/17688-0; 2016/15465-7) for the financial support.

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