

Chapter 1

General Introduction

Porphyrins are planar aromatic macrocycles and ubiquitous in nature [1]. Their monometallic complexes are involved in many key processes of life, such as: respiration and photosynthesis [2–4]. Since their discovery, these exceptional systems stimulated enormous interest. Their isolation and subsequent total synthesis shed light on their constitution and function and in turn this research was rewarded with several nobel prizes [5]. With the synthetic procedures in hand, a range of synthetic modifications [6] were made viable utilizing the attachment of various backbone residues, replacement of subheterocyclic units and the expansion of the core structure. The latter opens a completely new subfield of porphyrinoids: the class of expanded porphyrins [7–11]. These higher analogs of porphyrins are excellent candidates to study fundamental questions of aromaticity [12, 13] and with their larger cavities they provide ligand scaffolds capable of supporting late transition metal or even bimetallic complexes [14–16]. Sessler, Osuka, Kim, Latos-Grazynski, Chandrashekar and Vogel pioneered the field, which has developed rapidly within the last 40 years.

In the present work, a novel expanded porphyrin system with biomimetic elements is introduced: the Siamese-twin porphyrin [17]. Inspired by the mechanisms of cytochrome P450 and the bimetallic active center of methane monooxygenase [3, 4], it was designed to combine their motifs and to yield fascinating redox properties.

1.1 Porphyrins

After the short introduction, the porphyrinic macrocycle is now described in more detail (Fig. 1.1). Pyrrole, as the basic unit of porphyrins, is an aromatic five-membered nitrogen heterocycle and belongs to the group of azoles [18, 19]. Due to its six π -electrons distributed over five atoms, pyrroles are π -excessive and therefore good π -donors. Its new nomenclature of arabic numbers is not consistently used. Particularly, in porphyrin chemistry, the old greek letters are common, because they retain its validation when pyrrole is part of the porphyrinic scaffold.

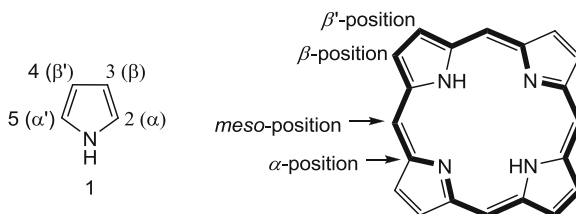
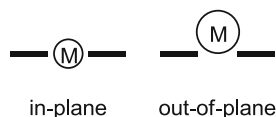


Fig. 1.1 *Left:* Pyrrole labeled according to the old (Greek letters) and new (Arabic numbers) nomenclature; *Right:* Chemical structure of the porphyrin system with labeling and the highlighted 18 π -electrons counting conjugation pathway (Sect. 1.2.1)

Fig. 1.2 Different possibilities of metal complexation by porphyrin ring systems depending on the metal ion size



Porphyrin consists of all together four pyrrole units that are linked between their α -positions via methine bridges, also denoted as *meso* carbon atoms. Porphyrins are planar and have an extended π -system, in which only 18 out of 24 π -electrons contribute to the delocalized “conjugation pathway” which is highlighted in Fig. 1.1. Due to their delocalized system, the highest occupied molecular orbital (HOMO)–lowest unoccupied molecular orbital (LUMO) gap shrinks and light absorption is seen in the visible region, which explains their intense colors. Porphyrins show characteristic absorption at around 400 nm with an extinction coefficient of around $10^5 \text{ M}^{-1}\text{cm}^{-1}$, the so called Soret-band [20, 21].

In its twice deprotonated form, porphyrins are tetradentate chelating ligands offering a rigid, square planar cavity (radius of 0.6 – 0.7 Å) [2]. Only with metal ions of distinct size in-plane coordination modes can be formed (Fig. 1.2) [22, 23]. With larger metal ions complexes can only be formed adopting an out-of-plane coordination mode. A change of the metal oxidation or spin state can introduce a geometry flip due to the change of the metal ion’s size.

1.1.1 Natural Porphyrins

The most famous natural porphyrins are heme and chlorophyll (Fig. 1.3). The first is an iron porphyrin complex, which is part of many active sites of different proteins, such as hemoglobin and cytochrome P450. Chlorophyll is a magnesium porphyrin complex which is indispensable for photosynthesis [3]. In photosynthesis light energy is converted to chemical energy stored as glucose (Scheme 1.1).

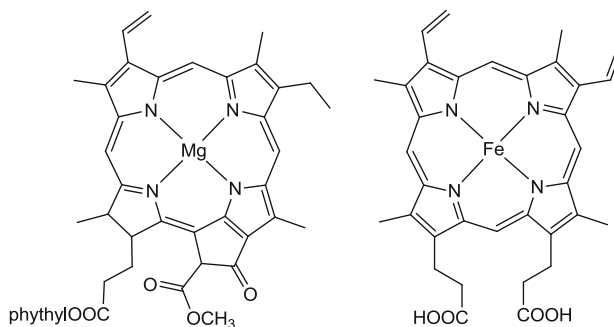
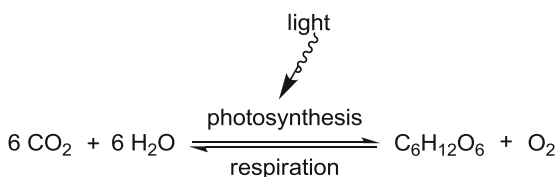


Fig. 1.3 Chlorophyll *b* (left) and the heme-*b* unit (right) [4]

Scheme 1.1 Connection of photosynthesis and respiration. In photosynthesis light energy is stored in form of glucose ($\text{C}_6\text{H}_{12}\text{O}_6$). Heterotrophs consume this energy via respiration



Chlorophyll

Chlorophyll consists of a chlorine ring, which is a β, β' -hydrated porphyrin although the aromatic 18 π -electron conjugation pathway is preserved (Fig. 1.3, left) [2, 24]. The aliphatic phytyl side chain can be understood as an anchor to connect the system to the hydrophobe thylakoid membrane within the chloroplasts, the location of photosynthesis. The magnesium ion bound by the chlorine scaffold fits perfectly in the porphyrinic cavity, is redox inactive and favors an octahedral coordination sphere. Hence, additional axial binding results in a neat arrangement of the chlorophylls, which is crucial for their activity in light-harvesting. Therefore, the carbonyl groups of chlorophyll act as lone-pair donors and rigidify the array additionally. Besides chlorophyll, also diverse carotenoids, phycoerythrins and phycocyanins are among the antenna pigments, which belong to the light-harvesting complex to cover almost the whole spectrum of light. The green color of chloroplasts appears from the left-over wavelengths, that were not absorbed. The energy absorbed by the antenna pigments is funneled to the reactive center, the photosystem, which again consist of two chlorophylls. These get oxidized and become cationic π -radicals (Fig. 1.4) which is the initial step needed for chemical energy storage—the charge separation. Thus, porphyrins are redox-active, which can be denoted as non-innocent behavior.

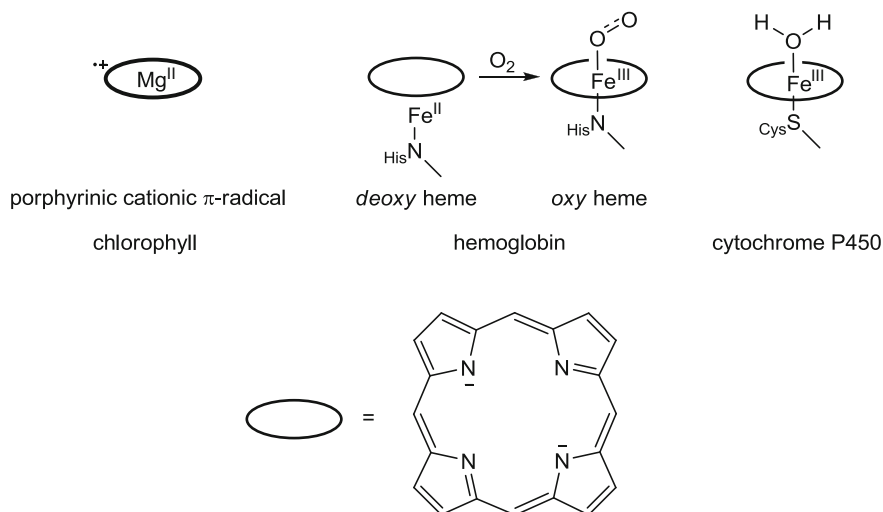


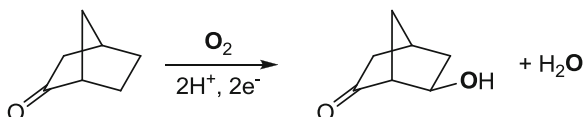
Fig. 1.4 Relevant intermediate of chlorophyll after light excitation (porphyrinic cationic π -radical), the transformation of the heme-*b* unit in hemoglobin from its *deoxy* to its *oxy* form and the resting state of the heme-unit in cytochrome P450

Hemoglobin

Respiration describes the reverse reaction of photosynthesis, in which oxygen and the stored chemical energy is consumed e.g. by vertebrates, which thus are heterotrophs (Scheme 1.1). The consumption of oxygen takes place in muscle tissue, and therefore the oxygen transport within the body has to be regulated. Hemoglobin is an oxygen carrier, found in blood of vertebrates as well as in some bacteria and plants [4]. Hemoglobin is not only responsible for the supply of O_2 to the tissue but also for the removal of the produced CO_2 . If hemoglobin contains O_2 , the prefix *oxy* is commonly used. When O_2 is not bound the prefix *deoxy* is used. Depending on the creature, hemoglobin can be found as monomers, dimers, tetramers or higher weight assemblies concerning their quaternary structure [24]. Binding of O_2 to one subunit positively affects the affinity of the remaining subunits toward oxygen—a phenomenon known as cooperativity [25–27]. Due to this mechanism, the solubility of O_2 in blood is increased 30-fold compared to its solubility in plain water [2].

In its *deoxy* form hemoglobin carries high spin Fe^{II} , which is relatively large (ionic radius; 0.78 Å) and is coordinated in an out-of-plane mode with an axial histidine ligand (Fig. 1.4) [4]. Upon binding of O_2 , a redox reaction takes place in which high spin Fe^{II} gets oxidized to low spin Fe^{III} while dioxygen is bound as O_2^- , a superoxide [28]. The change in oxidation state and in turn the switch between high spin and low spin results in a size change of the ion. Low spin Fe^{II} (ionic radius: 0.55 Å) is much smaller and flips right into the cavity

Fig. 1.5 Campher oxidation catalyzed by cytochrome P450_{cam} [4]



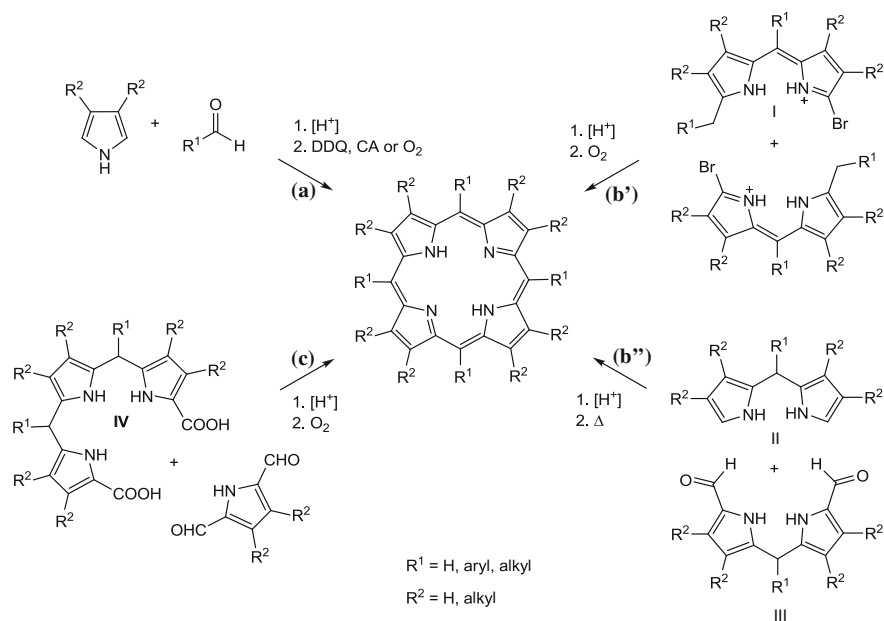
simultaneously pulling its axial bound histidine ligand toward the center of the cavity. This accounts for a structural change that affects the remaining subunits (cooperativity) [29]. Hence, hemoglobin demonstrates descriptively the different coordination modes of porphyrins depending on the size of the metal ion.

Cytochromes

Cytochromes also consist of a heme unit. Among the class of cytochromes, some are responsible for electron transport, while cytochrome c oxidase and cytochrome P450 catalyze redox reactions [2]. Their different reactivity arises mainly from their protein surrounding which determines the occupation of the axial heme positions. While in cytochromes functioning as electron carriers both axial positions are permanently occupied and no substrate binding is allowed, in cytochrome c oxidase and cytochrome P450 only one permanent axial ligand is provided by the protein scaffold. Cytochrome c oxidase is part of the complicated respiratory chain and catalyzes the final reduction step of dioxygen, also referred to as dioxygen activation. Here, dioxygen is converted to two water molecules.

The active center of cytochrome P450 consists of a heme-*b* unit (Fig. 1.3), exactly as in hemoglobin but carries an axial cysteine instead of a histidine ligand. Cytochrome P450 is a monooxygenase and mediates oxidation of small organic molecules with dioxygen. This gets reduced, whereupon one oxygen atom gets inserted into the substrate and simultaneously the second becomes a water molecule (Fig. 1.5 and Sect. 1.4). All P450-enzymes are metabolizing endogeneous substrates via oxidation and regulate the decontamination of xenobiotics [2]. Cytochrome P450 is able to catalyze the hydroxylation of saturated carbon-hydrogen bonds (Fig. 1.5), the epoxidation of double bonds, the oxidation of heteroatoms and dealkylation reactions and the oxidations of aromatics [30]. Its high reactivity but low substrate specificity requires a tight activity control. In the resting state, the two axial positions are generally blocked with a proximal cysteine ligand and a labile-bound water molecule (Fig. 1.4).

Porphyrins and their complexes are colorful and inevitably needed for life and thus are described as “Pigments of Life” [31]. Because their discovery as well as their functional and structural determination marked cornerstones, several nobel prizes were awarded, e.g. to Willstätter (constitution elucidation of chlorophyll), Fischer (total synthesis of heme), Woodward (total synthesis of chlorophyll), etc. [5, 32].



Scheme 1.2 Different strategies for porphyrin syntheses: **a** Rothemund synthesis, **b'** Fischer synthesis, **b''** [2 + 2] Macdonald synthesis and **c** [3 + 1] Macdonald synthesis. For **b'** and **c**, R^1 for the fusion points in the synthesized porphyrin corresponds to a hydrogen atom [9]

1.1.2 Synthetic Porphyrins

The first synthetic approaches towards porphyrins started in the 1930s. Fischer and Rothemund almost simultaneously reported on the synthesis of a porphyrin [33–35]. Overall, three fundamental synthetic routes toward porphyrins have been developed, in which a cyclization step to build the not yet oxidized macrocyclic arrangement (porphyrinogen) is always followed by the oxidation of the ring (Scheme 1.2) [6]:

- (a) The most popular way is the acid-catalyzed Rothemund synthesis where the pyrrole building block attacks the desired aldehyde's carbon atom. An equimolar ratio of the two is needed to yield the porphyrinogen. Subsequent oxidation with air or with commonly used proton coupled oxidants such as chloranil (CA) or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), gives the desired highly symmetric (D_{4h}) porphyrin. Eventually, the reaction conditions were slightly modified by Lindsey toward milder conditions so that porphyrins carrying functional groups were accessible [36].
- (b) The [2 + 2] self-condensation of two dipyrromethenes **I** in e.g. boiling formic acid (Fischer route; Scheme 1.2, (b')) is limited to centrosymmetrically substituted porphyrins due to scrambling effects. The use of acid sensitive

dipyrromethanes **II** was not successful until Macdonald (Scheme 1.2, (b'')) discovered that α -formylated dipyrromethanes **III** readily undergo a [2 + 2] condensation reaction with an α -dicarboxylic or α -unsubstituted moiety in good yields [37], but still the same symmetry restrictions are apparent as in Fischer's route.

- (c) Macdonalds approach was expanded to the so called [3 + 1] strategy. Here, the ability to selectively functionalize a porphyrin in one unit is given. Demanding is hence the synthesis of the tripyrrolic building block **IV**. The tripyrrane **IV** usually carries two carboxylic acid substituents in its α -positions and is then condensed with a monopyrrolic diformylated precursor [9].

Each method has its advantages and depending on the desired symmetry and later application, a suitable synthetic approach can be chosen. A general drawback in porphyrin synthesis is the low yields obtained in the cyclization reaction [6], which also explains the demand for improved synthetic strategies. Due to the manifold synthetic strategies, a variety of synthetic porphyrins were prepared (Fig. 1.6). Tetraphenylporphyrin (TPP) is a *meso*-modified system, while octaethylporphyrin (OEP) is modified in its β -positions. Further porphyrins with extended π -systems such as **V** were synthetically made viable [38].

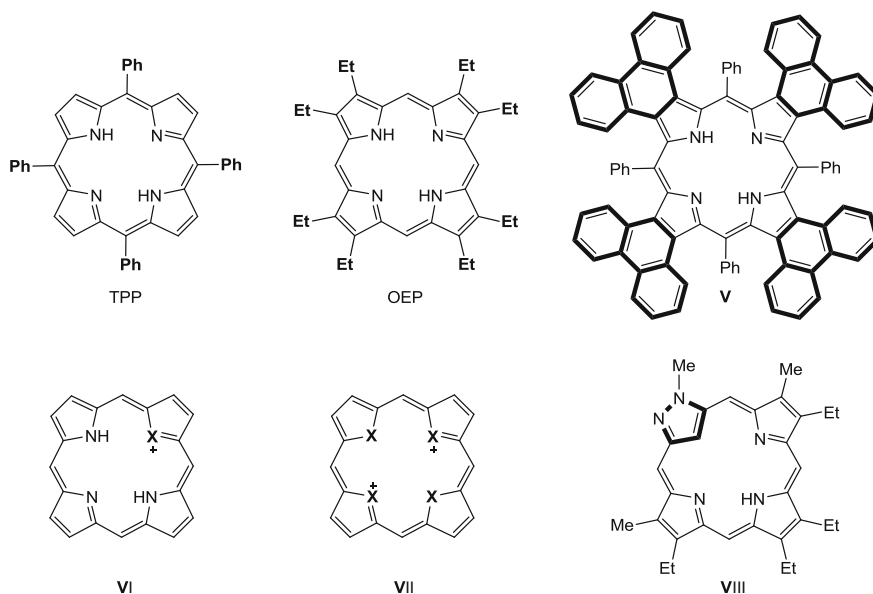
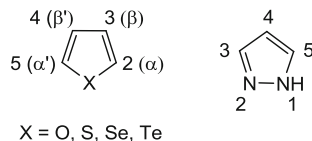


Fig. 1.6 Different porphyrin modifications: Variations of the substitution pattern: tetraphenylporphyrin (TPP), octaethylporphyrin (OEP), tetraphenyltetraphenanthroporphyrin **V**, and core-modified porphyrins (*meso* and β -residues are omitted for clarity) with one **VI** ($X = S, O, Se$ or Te) or four heteroatoms **VII** ($X = S, O$ or Se), and the first porphyrin incorporating a pyrazole unit **VIII**. Modifications are highlighted in bold. [38–44, 46]

Fig. 1.7 Furan (X = O), thiophene (X = S), selenophene (X = Se), tellurophene (X = Te) and 1*H*-pyrazole (*right*)



Apart from modifications in the substitution pattern Latos-grazynski and Vogel contributed pioneering work to the field of core-modified porphyrins, where pyrrole was (partially) substituted by furan (X = O), thiophene (X = S), selenophene (X = Se) or tellurophene (X = Te) (Fig. 1.6) [39–44]. These are all pyrrole analogous, five-membered heterocycles incorporating another heteroatom than nitrogen (Fig. 1.7) [19]. In contrast, pyrazole is a diazole. Its five-membered heterocycle carries two adjacent nitrogen atoms. The second nitrogen atom is slightly basic and pyrazole's reactivity resembles the one of pyrrole [45]. Lash et al. were the first realizing the synthesis of a pyrrole/pyrazole based porphyrin framework **VIII** [46]. With this enormous library of porphyrin systems, syntheses of manifold main group and transition metal complexes could be realized [22].

Porphyrin Assemblies

The expansion of the π -system is interesting due to the smaller HOMO–LUMO gap and hence a red-shifted Soret band. Expanded π -systems may furthermore serve as functional dyes, as ligands for a variety of metal complexes (Sect. 1.2.2) or to mimic photosynthesis. The expansion itself can be addressed differently, e.g. the substitution pattern can be modified as in **V** or the core structure can be expanded as in the expanded porphyrins (Sect. 1.2). The third method is discussed in this chapter: the assembly of several porphyrin units via covalent and non-covalent linkage, which then become supramolecular systems [47].

The first covalently linked porphyrin **IX** was published in 1972 and was named a doubleporphyrin (Fig. 1.8) [48]. Since then various systems, e.g. **X**, were built where up to five porphyrins were covalently linked [49, 50]. Only conjugated linkers were chosen to guarantee a complete conjugation and thus a smaller HOMO-LUMO gap leading to a red-shifted absorption.

Using the axial vacant positions, further cross-linking between different porphyrin complexes was achieved [51]. Therefore backbone substituents are modified in this way such that σ -donor atoms were incorporated, which then induce the axial binding (Fig. 1.8, **XI**). For axially linked supramolecular systems zinc often is the preferred metal. Zinc is similar to magnesium, the bound metal in chlorophyll, as it has a closed shell. Thus, zinc is redox-inert and its *d*-orbital splitting is not affected by ligand field stabilizing energy. These macromolecular porphyrin arrays are self-assembling systems and their ability to biomimic the convoluted process of photosynthesis is under investigation [52, 53].

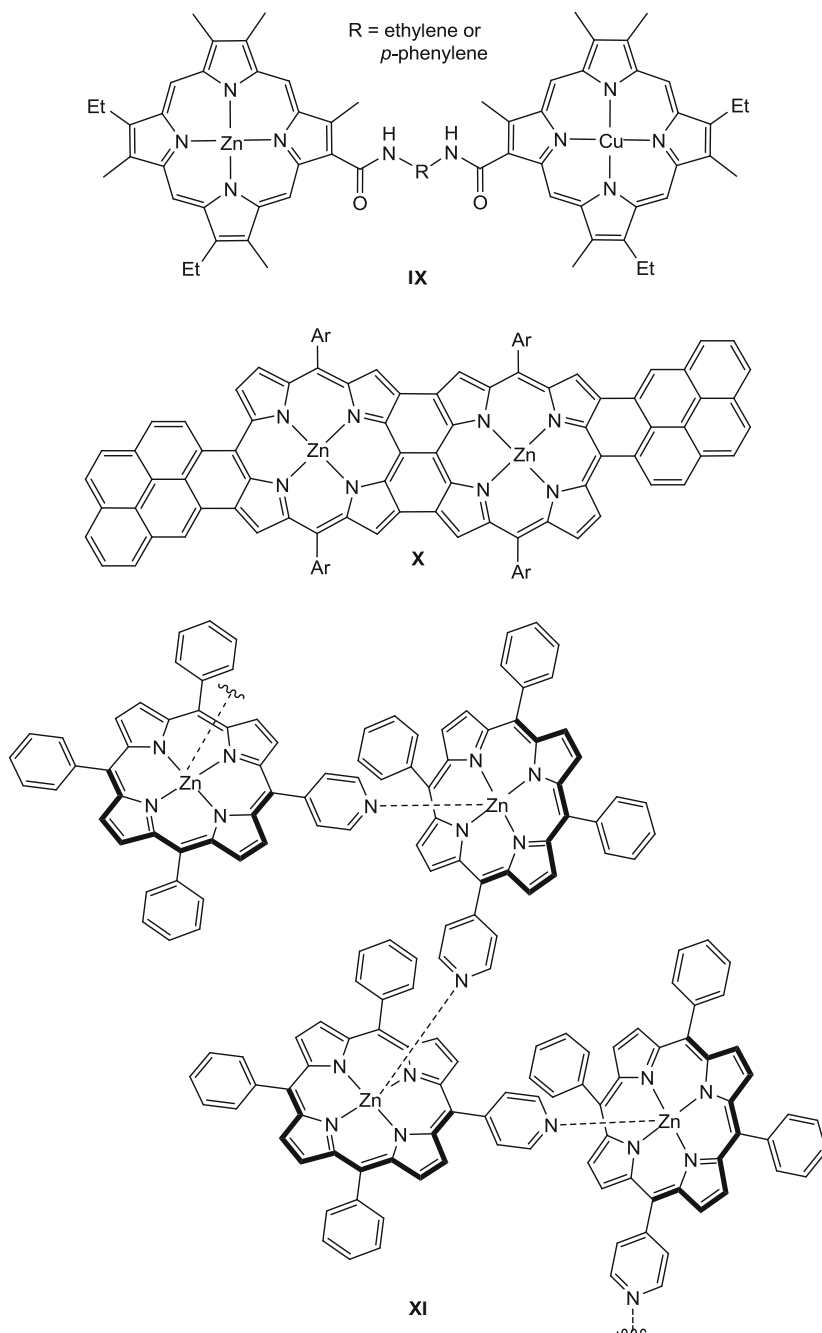


Fig. 1.8 Macromolecular assemblies of porphyrins linked via different units [48, 50, 51]

1.2 Expanded Porphyrins

Besides linking different porphyrin units, an enlargement of the π -system can also be realized by expanding the core itself, in the so called expanded porphyrins. Expanded porphyrins are artificial analogs of porphyrins, which consist of minimal 17 atoms within the internal ring [9]. The resulting cavity is larger than that of porphyrins, thus complexes with later transition metals and even bimetallic complexes can be formed [14, 15]. The cavity and π -system size can be tailored varying the amount, type or the connectivity of the heterocyclic subunits. Woodward discovered the first expanded porphyrin, sapphyrin **XII**, serendipitously in 1966 (Fig. 1.9) [54, 55]. Since then the field exploded and a multitude of different expanded porphyrins are currently available. Expanded porphyrins are named after their core-size: five-pyrrolic systems are called pentaphyrins **XII**, six-pyrrolic systems hexaphyrins **XIII**, seven-pyrrolic systems heptaphyrins **XIV**, eight-pyrrolic systems octaphyrins **XV**, and so on (Fig. 1.9). The largest expanded porphyrin synthesized is composed of 18 pyrrolic units and is referred to as octadecaphyrin [56]. In addition to different core sizes due to a varying amount of

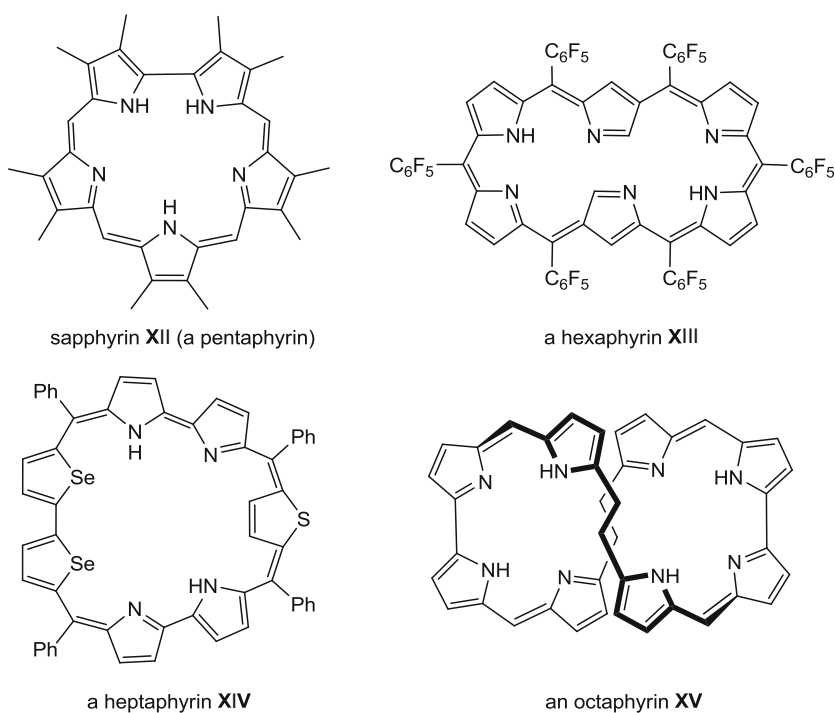


Fig. 1.9 Structural diversity in expanded porphyrins. β -ethyl groups in **XV** are omitted for reasons of clarity [11, 63–65, 101]

pyrrolic units, the linkage between them can either be direct, via a methine bridge or a longer alkyl chain (Fig. 1.9). This is usually indicated in parentheses which follow the name, where the number represents the amount of carbon atoms between each heterocyclic unit [19]. The different numbers are separated via a dot, which marks the heterocyclic unit. The number of π -electrons within the conjugation pathway is prefixed in square brackets, which completes the name to [57–59] hexaphyrin(1.1.1.1.1.1) for the **XIII**-core.

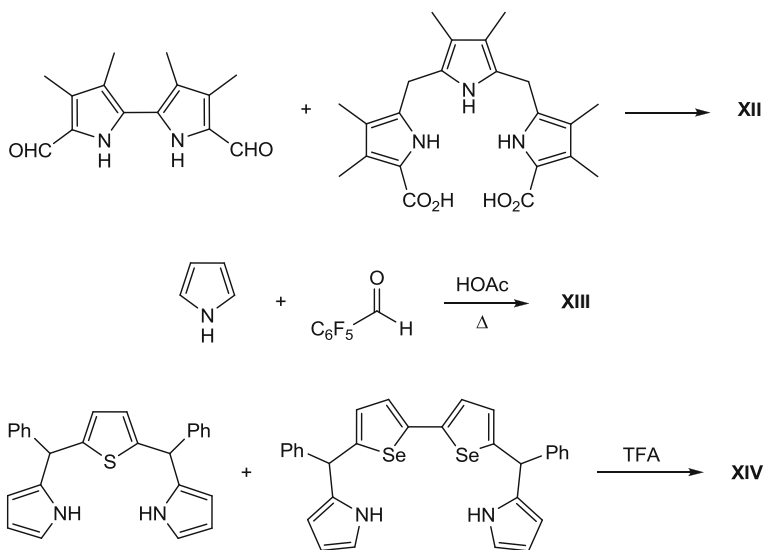
Except all-aza expanded porphyrins (only pyrrole) also core-modified expanded porphyrins are present as in porphyrins, e.g. **XIV**. Expanded porphyrins can exhibit *normal* conformations when all heteroatoms point inward, such as **XII** and **XV**. When heteroatoms point to the outside as the one thiophene unit in **XIV**, it is called *inverted*. In structure **XIII**, two pyrrole units are incorporated into the macrocycle via an α,β -connection, which is referred to as *N-confused*. All mentioned factors, plus the substitution pattern in β - and *meso*-positions, affect the actual geometry. Pentaphyrins and hexaphyrins are mainly planar, except when extremely bulky substituents are involved which force the system into a ruffled or twisted conformation. As octaphyrins, most heptaphyrins exhibit a figure-eight structure [7]. However, a universal structure cannot be derived, because solvent, temperature, protonation, oxidation and metal complexation immensely influence the geometry [60–62].

For the syntheses of expanded porphyrins mono-, bi-, tri- and tetra-pyrrolic fragments are basic building blocks. Depending on the desired connectivity, namely the number of heterocycles, methine bridges and the substitution pattern, appropriate building blocks have to be chosen. Three general synthetic strategies are applied for the syntheses of expanded porphyrins: Macdonald-type condensations, Rothemund condensations or oxidative coupling reactions.

The synthesis of sapphyrin **XII** follows a Macdonald-type [3 + 2] condensation [11] while in the synthesis of hexaphyrin **XIII** pyrrole and an aldehyde are condensed according to the Rothemund approach with low yields of 15 % [63] (Scheme 1.3). Heptaphyrin **XIV** can be synthesized following the oxidative coupling of unformulated tripyrranes and tetrapyrroles, in which distinct pyrrole units were replaced via thiophene and selenophene [64]. Octaphyrin **XV** was synthesized using a Macdonald-type [2 + 2 + 2 + 2] condensation [65].

1.2.1 Aromaticity in Large Systems

Aromaticity describes the delocalization of π -electrons and stabilizes the system [66]. It is solely observed when distinct conditions are met: only systems which are planar and cyclic, have conjugated double bonds and obey Hückel's rule ($4n + 2$ π -electrons) are considered aromatic according to Hückel while $4n$ π -electrons are considered antiaromatic. The classic Hückel's aromaticity concept is derived from small molecules of only one sort of atoms. Heilbronner evolved a different concept of aromaticity which is named Möbius aromaticity due to the Möbius stripe [67].



Scheme 1.3 Varieties in the syntheses of expanded porphyrins: Macdonald-type approach toward sapphyrin **XII**, Rothemund-type approach toward hexaphyrin **XIII** and oxidative coupling reaction toward **XIV** [11, 63, 64]

A Möbius stripe is best constructed by taking a stripe of paper, twist it by 180° and join the ends. Heilbronner proposed that $4n$ π -electronic Möbius stripes are aromatic while $4n + 2$ π -electrons are antiaromatic [68].

Expanded porphyrins are extremely large systems and ideal partners to highlight the rules of aromaticity [12]. Especially hexaphyrin systems are suitable examples due to the easy two electron switch of [26] to [28] hexaphyrin (Fig. 1.10) [69, 70]. The conjugation pathway, which was already mentioned earlier in this work (Sect. 1.1), was defined by the annulene model dating back to the 1960s, which is a useful tool for aromaticity in molecules larger than benzene [71]. A conjugation pathway is present within the π -system when the following criteria are met:

- Passes through all subunits and encompasses the macrocycle.
- Can be represented by two resonance structures.
- Does not involve charge separation.

In general, the aromatic character cannot be quantified using a single criterion. Structural evidence for aromaticity is found by the observation of equal bond lengths along the conjugation pathway due to delocalized single and double bonds. Theoretical studies usually further fortify the assignment revealing the energy stabilization gained by aromaticity.

In nuclear magnetic resonance (NMR) experiments diatropic ring currents dramatically influence the chemical shifts of the inner and outer protons

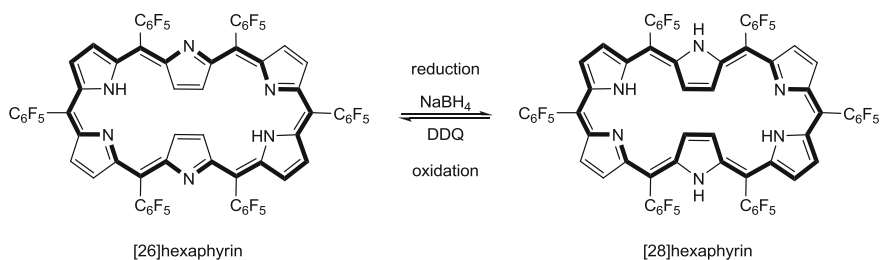
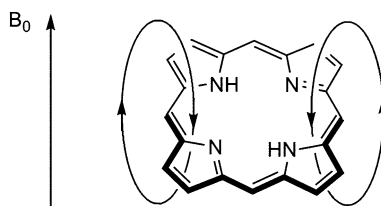


Fig. 1.10 Reversible interconversion of [26] and [28] hexaphyrin. The conjugation pathway is highlighted in *bold* [69, 70]

Fig. 1.11 Diatropic ring current induced in aromatic compounds as porphyrin in the presence of an external magnetic field (B_0)



(Fig. 1.11). Inner protons are shifted to high-field while outer protons are low-field shifted [72]. In porphyrinic systems this is evidenced by the observation of small or negative chemical shifts for the inner protons and extremely positive values for the outer protons/substituents [8]. Antiaromatic systems have paratropic ring currents and all mentioned effects are reversed. On top, ^1H chemical shifts are remarkably sensitive to structural changes and a perfect indicator for acid–base chemistry.

1.2.2 Complexes of Expanded Porphyrins

Many mono- and bi-metallic complexes have already been synthesized with expanded porphyrins as ligands. The cavity of sapphyrin seems large enough to form actinoid complexes, e.g. upon reaction with dioxouranium(IV) chloride in methanol the uranyl complex is built (Fig. 1.12). Simultaneously a nucleophilic attack of methanolate in a *meso* position occurs annihilating the aromaticity, which has been proven by normal chemical shifts in the NMR spectrum and thus an absence of any aromatic ring current [73]. Furthermore, sapphyrin can form homo- and hetero-bimetallic complexes with rhodium and iridium [74].

With [57–59] hexaphyrin some homo- and hetero-bimetallic complexes were synthesized by Osuka et al. (Fig. 1.13). These complexes exhibit *normal* (XVI) and *inverted* conformations (XVII–XIX). The reaction with copper(II) chloride and sodium acetate yielded the dicopper complex XVI. Comparable to the uranyl-sapphyrin complex one *meso* position got oxidized. This oxygen atom is involved

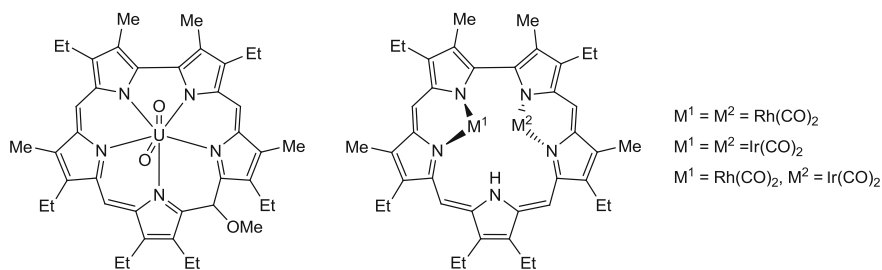


Fig. 1.12 Mono- and bi-metallic complexes of sapphyrin [73, 74]

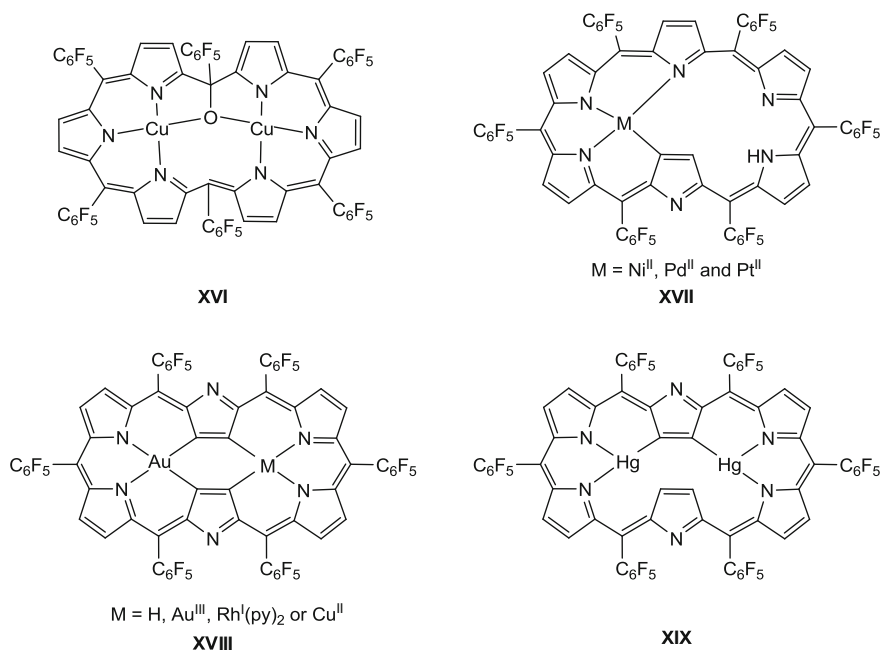


Fig. 1.13 Mono and bimetallic complexes of [26] hexaphyrin [75, 77, 78, 102]

in the square planar complexation. The molecule exhibits a gable structure and is non-planar. Thus, in some cases metal complexation comes along with yet not understood ligand reactions [75]. [26] hexaphyrin reacted with group 10 metal(II) acetates to primarily form mononuclear complexes (**XVII**).

In the monogold, digold and the hetero-bimetallic gold/copper, gold/silver and gold/rhodium complexes (**XVIII**), [26] hexaphyrin carries two inverted pyrrole units, offering two square planar N_2C_2 donor sets for complexation. The digold complex is nearly planar. Rhodium captured two additional pyridine residues to complete its desired octahedral coordination sphere [76, 77]. In the homobimetallic

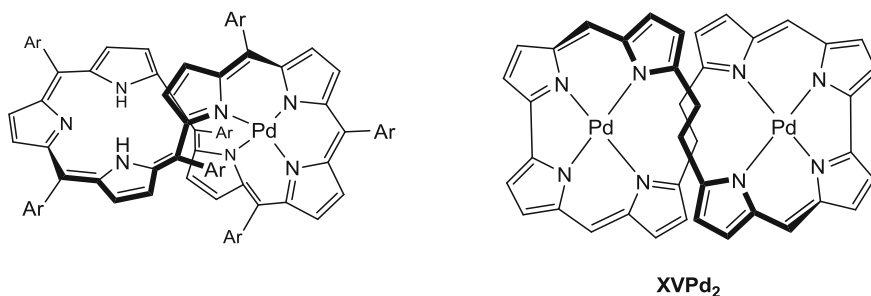


Fig. 1.14 Exemplarily chosen metal complexes of hepta- and octa-pyrin [79, 80]

mercury complex (**XIX**), mercury is bound only via an N_2C donor set leaving one vacant side [78]. For all metalation products summarized in Fig. 1.13, the same [26] hexapyrin as starting material was used, consequently distortion and inversion is solely originated from complexation (Fig. 1.13).

Additionally, metal complexes of heptapyrins and octapyrins were reported (Fig. 1.14). Under the retention of the organic scaffold of heptapyrin, only monometallic complexes were feasible [79]. With **XV**, the dipalladium complex was published [80]. Both chosen metal complexes depicted in Fig. 1.14 exhibit a figure-eight structure.

1.2.3 Applications

Expanded porphyrins are useful materials to back up the concept of aromaticity and prepare late transition metal or bimetallic complexes (Sects. 1.2.1 and 1.2.2). Even though expanded porphyrins are non-natural products, some are biologically compatible. Since low energy radiation is sufficient for excitation of expanded porphyrins and due to their observed red-shift they can be directly addressed in body's tissue while radiation does not excite biologically relevant porphyrins. This is used in photodynamic therapy (PDT) of tumors [16, 81, 82] and magnetic resonance imaging (MRI). In general terms, PDT uses a tumor localizing light-absorbing dye which upon radiation gets excited to its triplet state and converts triplet oxygen to singlet oxygen. That is cell toxic and initiates the destruction of unwanted tissue, such as carcinomas [83].

Further expanded porphyrins were proven useful for anion recognition with sapphyrin as the pioneer [84, 85]. Here, it was found that in its protonated form, sapphyrins are capable of binding halide and phosphate anions. However, other expanded porphyrins in their protonated and their neutral form showed affinity toward anions.

Many expanded porphyrins possess pronounced non-linear optical (NLO) properties [86, 87], which are desirable properties for use in optoelectronics [88].

Expanded porphyrins have greater thermal stability compared to typical organic chromophores, their extended π -conjugated macrocyclic ring gives large NLO effects and chemical modification of their backbone results in subtle variation in their physical properties.

1.3 Oxidoreductase Enzymes

As was already mentioned in [Sect. 1.1.1](#), porphyrin-containing enzymes play an important role in nature. It was shortly discussed that in respiration glucose gets oxidized using dioxygen and the chemically stored energy is released. Because oxidation in general is an energy releasing process and energy is needed for life, oxidation of small organic molecules is an attractive reaction. Dioxygen, with a percentage of 21 % in air, is always present and thus an interesting and cheap source for oxidation reactions.

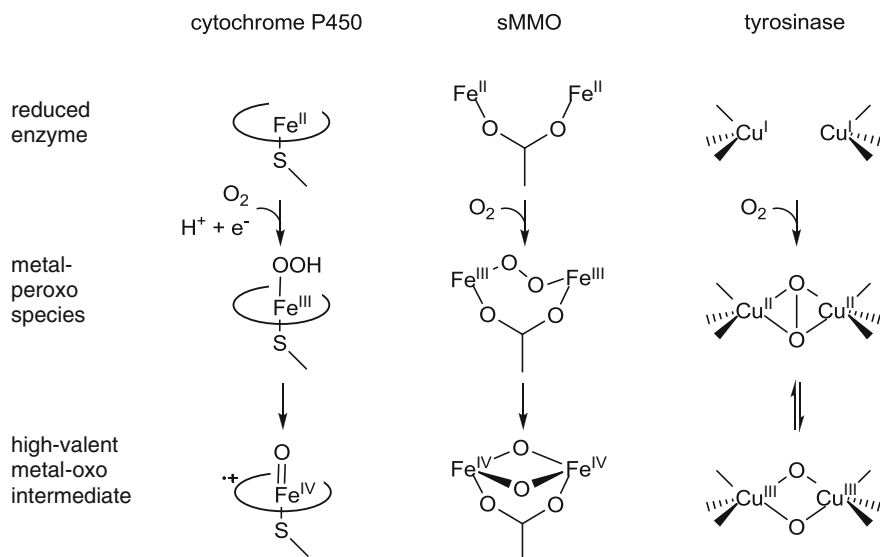
The consumption of the ambient dioxygen is not as simple as one may assume. Dioxygen is a triplet molecule while most organic molecules, so is glucose, are singlets and thus direct oxidation is usually spin-forbidden [4]. The dioxygen activation results in a redox-state change from 0 to -2 per oxygen atom, which is a four electron consuming process that rarely occurs in one concerted step in non-catalyzed reactions. Enzymes with their often paramagnetic metal based active centers help to overcome the spin-forbiddance and the difficulties of a four electron reduction process.

The final step of oxygen activation in the respiratory chain is catalyzed by the porphyrin-based enzyme cytochrome c oxidase. In oxidase enzymes the two oxygen atoms become water molecules. In contrast, cytochrome P450 is a monooxygenase, where one out of the two oxygen atoms is transferred to the organic substrate [2]. The residual oxygen atom becomes a water molecule. In dioxygenases, both oxygen atoms are transferred to the organic substrate.

1.3.1 Monooxygenases

Cytochrome P450 has a mononuclear heme-*b* core with Fe^{II} bound in its resting state. Upon reaction with dioxygen, two out of four electrons are provided by the redox state change from Fe^{II} to the high-valent Fe^{IV} , which is formed as an intermediate. The oxidation of the porphyrin system toward the cationic π -radical further contributes one electron, while the fourth electron has to be delivered from an electron transferring reagent (Scheme 1.4).

Besides the porphyrin-based monometallic active center in cytochrome P450, two monooxygenase enzymes with bimetallic active centers need to be mentioned, the soluble methane monooxygenase (sMMO) and tyrosinase. While sMMO is an iron based enzyme, tyrosinase has a dinuclear copper center [2]. The two iron



Scheme 1.4 Comparison of the key steps of the three introduced monooxygenases: cytochrome P450, sMMO and tyrosinase. The high-valent dicopper species was only observed in model complexes [2, 90–92]

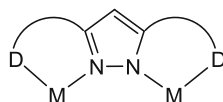
metals in sMMO are bridged via a carboxylate ligand [89]. The four electrons are here simply provided by a redox-state change from Fe^{II} to Fe^{IV} for both metal ions. In tyrosinase, first a two electron reduction of dioxygen to peroxide occurs which then reacts with the substrate. The exact mechanism has not yet been resolved [90–92]. Besides its monooxygenase activity, tyrosinase can also act as a dioxygenase.

In summary, among others, nature uses two different principles to provide the overall four electrons for dioxygen activation in monooxygenase enzymes: Either one metal center and the redox-active porphyrin ligand are involved or a binuclear center, in which the latter bares the advantage that no additional electron sources are required. In a schematic drawing the three different presented monooxygenases and their key steps in oxygen activation are compiled (Scheme 1.4). In all key steps, high-valent metal species are formed.

1.4 Pyrazole: A Common Motif in Dinuclear Complexes

Bioinorganic chemistry tries to learn from nature by understanding it. In a simple approach, the active centers of metalloenzymes are tried to be modeled in their first coordination sphere with low molecular weight complexes [93, 94]. For mimicking dinuclear centers pyrazoles were shown to be a good replacement for

Fig. 1.15 Typical pyrazolate based bimetallic complex motif, *D* donor atom



the often observed carboxylate bridge. In its deprotonated form, pyrazolate is singly negatively charged and additional to its σ -donor function offers an enhanced π -donor function. Furthermore, side arms in its 3 and 5 position with donor atoms (*D*) can easily be attached and thus the coordination motif individually tailored. Diverse dinuclear complexes can be designed exhibiting the motif depicted in Fig. 1.15 [95]. By changing the lengths of the side arms, the metal–metal separation can be tuned within the range observed for carboxylate bridged systems.

Pyrazolate bridges in dinuclear complexes mediate cooperative effects due to its conjugated nature. The phenomena of cooperativity was introduced in hemoglobin, in which the binding of dioxygen to one subunit enhanced the affinity of the remaining subunits toward dioxygen. On a lower molecular level as in dinuclear pyrazolate-bridged complexes, magnetic exchange interactions are observed such that the spin orientation of the first metal ion influences the spin orientation of the second metal ion. Synergistic electronic effects enhance the reducing power in dinuclear systems [96, 97]. Using dinuclear complexes as catalysts, cooperativity is noticeable in the sense that the substrate can be preorganized on one metal center while the actual transformation takes place at the second.

Besides pyrazole-based complexes of the motif depicted in Fig. 1.15, several macrocyclic pyrazol-based ligands and dinuclear complexes of these were isolated [95]. Brooker et al. prepared a bimetallic macrocyclic pyrazolate-based dicopper complex **XX**, in which extra Schiff-base nitrogen atoms are provided [98]. Navarro and co-workers published the first pyrazole based cryptand-type ligand **XXI** in 1995 along with di- and tetra-nuclear silver(I), copper(II) and zinc(II) complexes [99]. Katsiaouni from our group synthesized macrocyclic pyrazole-based Schiff-base ligands **XXII** with a cavity too small to built dinuclear complexes (Fig. 1.16) but represent the first examples of pyrrole/pyrazole hybrid macrocycles to date [100].

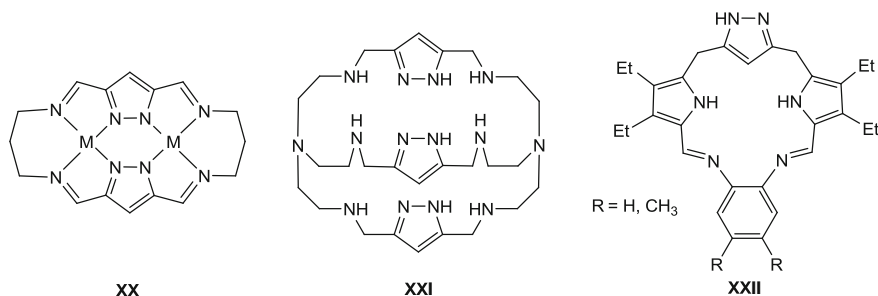


Fig. 1.16 Examples of non-aromatic macrocyclic 3,5-functionalized pyrazolate-based ligands [98–100]

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Blusch, L.K.

2013, XVIII, 158 p. 142 illus., 48 illus. in color.,

Hardcover

ISBN: 978-3-319-01673-3