

Water-soluble porphyrins and their metal complexes

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Nowadays the chemistry of porphyrins and related compounds are one of the most interesting and promising subjects of supramolecular chemistry, because of their unique photoactive properties and the ability to electron transfer. The possibility of synthesis of porphyrin complexes with almost all metal ions and easy to modify the molecular structure of such obtained compounds give a chance of using the porphyrins in many different areas of life. In this paper we present the most significant problems concerning water-soluble porphyrins and their metal complexes, such as the molecular structures, different manners of synthesis, physicochemical properties, as well as the origin and classification of porphyrins and metalloporphyrins UV-VIS spectra. We also show the most interesting applications, including the role of porphyrins as molecular conductors and photosensitizers in photolysis of water and in photodynamic therapy of cancer (PDT).

1. INTRODUCTION

The rapidly growing development of contemporary civilisation is first of all based on introducing of new, better, more efficient and more complicated technologies. New technologies require new and more useful solutions. One of them is surely the application of light, conducting and easy to modify organic materials. The best candidates for this purpose seem to be porphyrins, the group of macrocyclic compounds (Figure 1), because of their photoactive properties and the ability to electron transfer. The unique spectroscopic, magnetic, luminescence properties, and what is the most important, the ability of porphyrins to photoconduction and photoemission have been being utilized in the nature for a long time. Natural porphyrins and their metal complexes, such

as chlorophyll, hemoglobin and cytochromes, as well as their derivatives, for example cobalamin and bilirubin, perform the pivotal biological functions in fauna and flora. The compounds mentioned above are responsible for photosynthesis, cell respiration, transport, accumulation and exchange of gases, processes of blood cells formation and pigmentation [1–3]. The porphyrins have become an indispensable component in the evolution of living organisms, due to many types of chemical reactions, characteristic of this group of compounds, such as: coordination, polymerization, aggregation, oxidation and reduction, catalysis, sorption and photochemical changes.

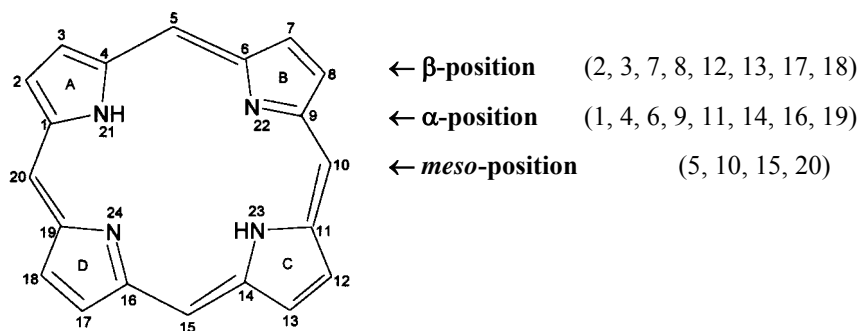


Fig. 1. The structure of porphyrin molecule

Following both the porphyrins properties mentioned above and variety of chemical reactions they are involved in, new kinds of macrocyclic compounds have been synthesized in order to their future potential applications. The research conducted for many years proved versatility of porphyrins applications, including often the different areas of life. These extraordinarily interesting compounds can act for example as catalysts of many chemical reactions, they also play the role of pigments and dyes, photoconductors and semiconductors, analytical reagents, as well as sensitizers in photodynamic therapy (PDT). In the future they will be probably used as active elements of biosensors, molecular switches, elements of selective electrodes, non-linear optical materials, parts of electrochromic displays [4] or special equipment cumulating solar and conventional energy, also in synthesis of new types of chemical structures – molecular wire, dendrimers [5] or porphyrins complexes with fullerenes.

The chemistry of porphyrins have been being developed for last decades very intensively. The great importance of this subject is testified by many publications, concerning synthesis, structure, properties and applications of these macrocyclic compounds and their derivatives [6–18]. In this paper we present a review of the most important topics connected with water-soluble porphyrins and their metal complexes.


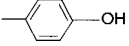
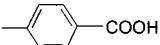
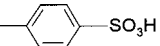
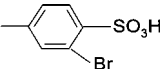
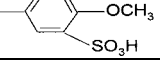
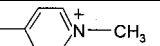
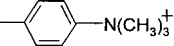
2. MOLECULAR STRUCTURE

The molecule of porphyrin occurs as the specific aromatic macrocycle. The macrocycle is consisted of four pyrrole rings joined by methine bridges and forms the coupled system of double bonds, including 18 delocalized π electrons ($4n+2$, where $n=4$). The pyrrole rings build up closed aromatic plane, playing the role of a nucleus of the compound. The flat porphyrin ring can be deformed in the process of metalation, where a metal ion replaces the hydrogen atoms in imide groups of pyrrole.

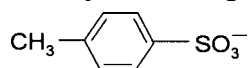
One can find many possible ways of atoms numeration in the porphyrin macrocycle. One of them is the numeration according to Bonnett (Figure 1), called the canonical form of the porphyrin. Another way of the numeration is based on the determination of substituents places by using the letters α , β and the prefix *meso*.

There are many parameters, according to which the porphyrin compounds can be classified. One of the most useful is their solubility in water, which implies the kind of interactions with the other molecules. Water is the most universal solvent and the environment for a lot of chemical reactions and physical processes, especially these occurring in living organisms. That is why the best solution is to obtain such systems, which are both water-soluble and do not lose their specific properties. The porphyrins are generally not soluble in water, but it can be changed by adding the adequate substituents. The substitution proceeds in β positions (at 2, 3, 7, 8, 12, 13, 17 and 18 carbon atoms) or *meso* positions (at 5, 10, 15 and 20 carbon atoms) and leads to generate the water-soluble compounds with all the aromatic properties of porphyrin ring. Depending on the type of substituents, the anionic porphyrins – slightly and well water-soluble, or the cationic porphyrins were obtained [19] (Table 1). To increase the stability of received molecules, the compounds, which are able to neutralise the anionic or cationic charge of the porphyrin systems are employed. The anionic porphyrins are usually obtained in the form of sodium salts, whereas the charge of the cationic porphyrins is neutralized by the negative *para*-methylsulfonate group. They are usually said to exist as the tosylate salts.

Tab. 1. The common cationic and anionic groups usually used for water solubilization of porphyrins

anionic porphyrins – slightly water-soluble	
<i>Meso</i> -tetrakis(3-bromophenyl)porphyrin	
<i>Meso</i> -tetrakis(4-hydroxyphenyl)porphyrin	
anionic porphyrins - water-soluble	
<i>Meso</i> -tetrakis(4-carboxyphenyl)porphyrin	
<i>Meso</i> -tetrakis(sulfophenyl)porphyrin	
<i>meso</i> -tetrakis(3-bromo-4-sulfophenyl)porphyrin	
<i>meso</i> -tetrakis(4-methoxy-3-sulfophenyl)porphyrin	
cationic porphyrins	
<i>meso</i> -tetrakis(N-methyl-4-pirydy)porphyrin	
<i>meso</i> -tetrakis[4-(trimethylamino)phenyl]porphyrin	

para-methylsulfoniam group



The cationic porphyrins seem to be more interesting object of study, especially because of their interactions with the double helix of DNA – these porphyrins cause the cleavage of the deoxyribonucleic chain, joining the chain in several manners. Such interactions could be the base for different kinds of therapies of many incurable up to now diseases. Although the anionic porphyrins are comparable in the structure, do not lead to similar effects [4].

The particular porphyrin systems show resembling scheme of structure, nevertheless they differ in some details:

- in the character of bridge groups between pyrrole units (it can be $-\text{CH}=\text{C}(\text{R})-$, $-\text{N}=\text{C}(\text{R})-$ and their combinations);
- in the type of substituents (it can be $-\text{H}$, $-\text{CH}_3$, $-\text{C}_2\text{H}_5$, $-\text{CH}=\text{CH}_2$, $-\text{CH}(\text{OH})\text{CH}_3$, $-\text{CHO}$, $-\text{COOH}$, $-\text{CH}_2\text{COOH}$, $-(\text{CH}_2)_2\text{COOH}$);
- in the possibility of hydrogenation of one or more double bonds in pyrrole rings and forming the new ring from the neighbouring substituents;

- in the type of metal or non-metal ions joined instead of hydrogen atoms in the imide groups of pyrrole units.

The four nitrogen atoms, situated symmetrically in the porphyrin ring, give a chance to obtain the metal chelate complexes. During forming of such compounds the porphyrin loses two protons from N–H bonds, what results in metal coordination by four equivalent nitrogen atoms [20]. The bonding force of the central ion is diversified and depends on the type of metal ion used for the reaction, as well as on the valence, the concentration and the carrier of metal ion.

The metal complexes of porphyrins show different structures (Figure 2). The type of coordination depends on the type of metal, its charge and the coordination number. The best known is the coordination, where the metal ions is situated centrally in the middle of the porphyrin plane, but there are also bi-, tri-, tetra- or hexadentate ligands, with metal ions outside the porphyrin plane [21].

There are many parameters, according to which the metal complexes of porphyrins can be classified. One of the most important is classification done by Büchler [22], taking into account the stoichiometry of N_4 plane. The ratio of metal atoms to porphyrin ligands implies generation of the various classes of metalloporphyrins:

- monometallic and mononuclear **MP**;
- “semimetallic” **M(P)₂** (half a metal atom per one porphyrin molecule) – “sandwich” complexes [23];
- bimetallic **M₂(P)** (two metal atoms per one porphyrin molecule);
- monometallic binuclear **[M(P)]₂** (two monometallic units connected by metal-metal bond or bridge ligand);
- polymetallic **M₃(P)**, **M₄(P)** (more than two metal atoms per one porphyrin molecule);
- polynuclear **M_x(P)_y** (in most cases they are coordination polymers of monometallic porphyrins).
- The others classifications of metalloporphyrins are based on axial stoichiometry (the type of axial ligands) and geometry of the porphyrin molecule [24].

Typical of macrocyclic porphyrin complexes is low rate of metalation and demetalation; a metal ion is both slowly inserted into the cavity of porphyrin and slowly removed outside in the reverse process. Such compounds show high thermodynamic stability – the formation constants for macrocyclic systems can be several orders of magnitude higher than the formation constants for non-macrocyclic ligands (“macrocyclic effect” [25]).

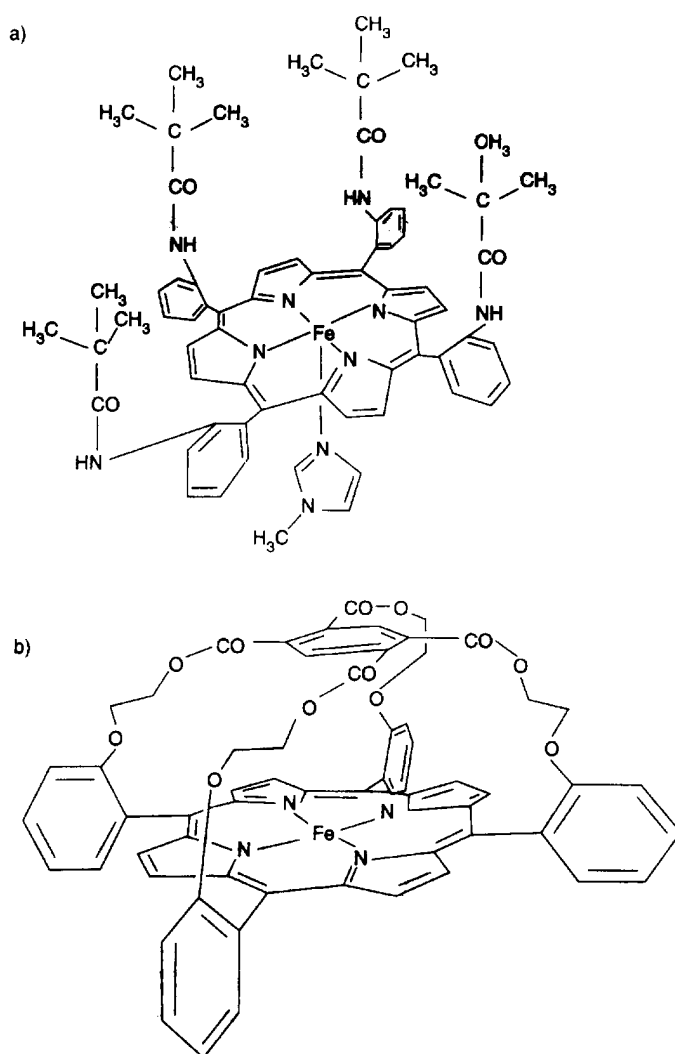


Fig. 2. The models of heme molecule: a. the „picket-fence” model; b. the „capped” model [116]

One of the most important properties of macrocyclic ligands is also their ability to complexing the metal ions, which are on the oxidation states unsuitable in standard conditions for generating stable complexes with other ligands. Such behaviour is first of all connected with the kinetic stability of macrocyclic complexes and their redox properties.

3. SYNTHESIS

The porphyrins are obtained in the reaction of pyrrole and suitable aldehydes, during long lasting multi-stage organic synthesis [6, 7, 26], at high temperature, usually with a catalyst and in propionic acid. The suitable and accurate method of synthesis needs a proper optimization, depending on the desirable reaction product. A large majority of the porphyrin compounds are obtained on the base of similar scheme, typical of organic synthesis. The differences are connected with generating of systems with different substituents. In this case two ways are possible: the synthesis of the porphyrin and then adding of substituents to the macrocycle or substitution of the suitable groups to aldehyde and then the reaction of such obtained configurations with pyrrole.

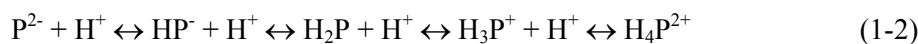
The synthesis of the metalloporphyrins can be even more complicated. Seemingly simple reaction of metalation could be written:



Many metal ions have the valence different than II or the coordination number different than 4 – in this case the structure of complex is more complicated, because of axial ligands, which must be joined to the porphyrin ring.

The five essential processes are involved in metalloporphyrin synthesis [22]; they can proceed simultaneously or in different combinations:

1. Protonation / deprotonation equilibria;



2. Deconvolution of the metal ion from the „metal carrier” (the most „popular” metal carriers are acetates);
3. Formation of the equatorial MN_4 plane – in this stage the intermediate complexes are generated between metal ions and strongly deformed porphyrin ring; this process is responsible for the reaction kinetics of metalloporphyrin formation;
4. Adjustment of the charge balance – leads to built up the axial coordination sphere;
5. Completing of the coordination sphere – by neutral donor molecules.

The traditional organic synthesis of the porphyrin complexes is based on the reaction of free-base porphyrin with the excess of metal salt in solvents with high boiling temperature [22]. This way leads to obtaining only a few grams of product. During metalation, acetic acid, propionic acid, pyridine and DMF are usually used as the solvents and simple salts (acetates, halides), organometallic compounds, carbonyls and alkoxides as the metal carriers. In the synthesis of porphyrin complexes with lanthanides and actinides the role of metal carriers

play acetylacetonates and the most common solvent is 1,2,4-trichlorobenzene. The porphyrins are generally soluble in organic solvents and the metal salts usually in water, what can be a problem for synthesis of metalloporphyrins, but is desirable during the separation of mixture after the reaction.

The radius of the porphyrin central cavity is constant (although it can change in a certain range because of the deformation of the porphyrin ring) and measures from 1.929 to 2.098 Å. Whereas the optimal radius of a metal ion taking part in metalation process should have from 0.60 to 0.69 Å. Not all of the metal ions can meet this condition; nevertheless, some of them are able to form complexes by fitting the porphyrin cavity – the porphyrin molecule undergoes the deformation and the lengths of bonds with nitrogen atoms are changed [27]. A good example for such situation can be the copper ions – the radius of Cu(II) is too short, while the radius of Cu(I) is too long for generate a porphyrin complex according to the condition mentioned above. However it is widely known that Cu(II) ions are able to form the compounds with porphyrins. If the metal ion does not fit the cavity, the “out-of-plane” complexes are created, where the metal ion is situated outside the macrocyclic plane. The polymer compounds with metal atoms between porphyrin rings are also possible.

There are several factors which can influence the rate of metalation processes. One of them is ability of porphyrin macrocycle to undergoing the deformation [28, 29]. Moreover, the higher is the metal ion charge in the metal carrier MX_mL_n , the slower is the rate of metalation, because of the electrostatic interactions: a high charge of metal ion inhibits the decomposition of metal carrier. This is the reason why the metalation rate for the ions with 2+ charge is higher, in comparison with the ions demonstrating the higher charges.

Till now the porphyrin compounds with all metal ions were synthesized. The next step is connected with synthesis of the porphyrin complexes with the central ions demonstrating unique oxidation numbers or complexes consisted of more than one porphyrin ring, for example “sandwich” or “shish kebab” porphyrins [4], where several macrocyclic rings are joined by metal ions. The mixed complexes, where the role of ligands play not only the porphyrins, but also the other macrocyclic compounds, as phthalocyanines, are known as well. The metalloporphyrins have typical properties of both porphyrins and metals, but they are more stable and more various from the point of view of three-dimensional systems. As the porphyrins, they can interact with DNA, although such processes are difficult to interpret, because of more elements involved in such relatively weak interactions.

a)

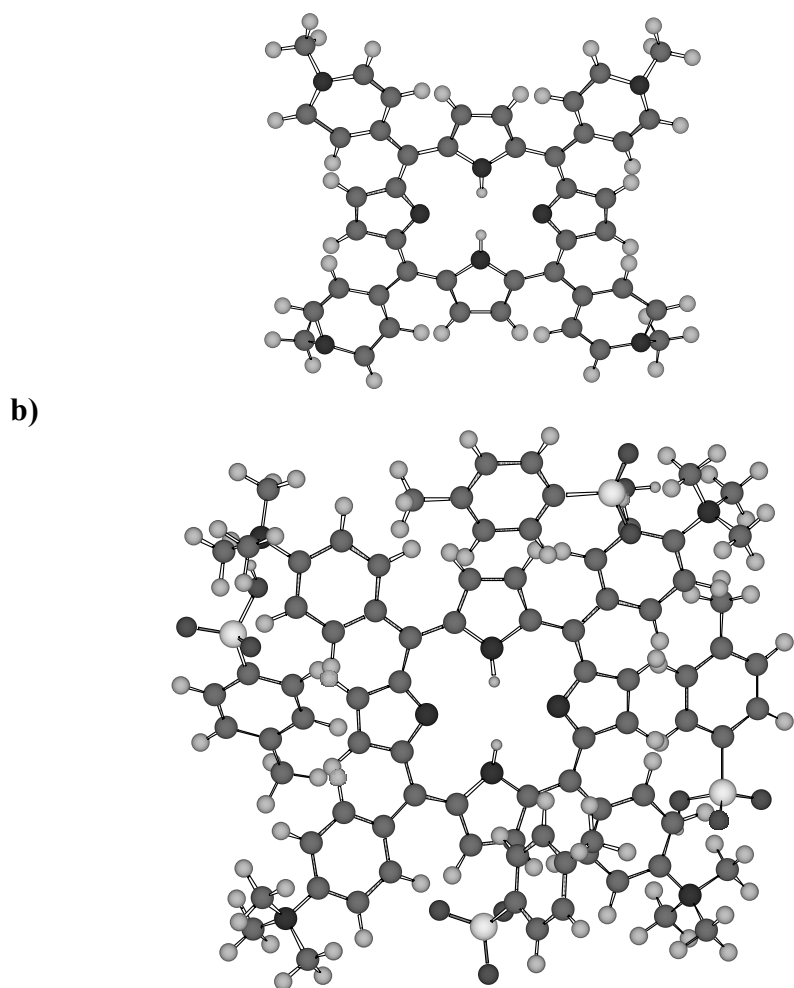


Fig. 3. The molecular structures of cationic porphyrins a. H₂TMePyP; b. H₂TTMePP

All general tendencies characterizing the porphyrin chemistry concern water-soluble porphyrins. These ligands form complexes not only with all metal ions, but also with boron, silicon and phosphorus [30]. First studies on the metal complexes with water-soluble cationic porphyrins, describing the Cu(II) and Zn(II) complexes with *meso*-tetrakis(1-methyl-4-pyridyl)porphyrin (H₂TMePyP) (Figure 3a), have been performed by Hambright and published in 1970 [31, 32]. Other examples of such compounds are complexes of *meso*-tetrakis(4-sulfonatophenyl)porphyrin (H₂TPSP) with Zn, Cd, Mn, Co, Ni, Cu, Pb [24], and *meso*-tetrakis[4-(trimethylamino)phenyl]porphyrin (H₂TTMePP) (Figure 3b), with Cd [33]. There appear to be also the porphyrin complexes with

lanthanides: H₂TTMePP gives the complex with Eu [34], H₂TPSP with Gd and Lu [35], H₂TMePyP with Sm [36], Eu, Lu [37, 38] and Pr [38]. About H₂TTMePP there are relatively little information, because this porphyrin was synthesized a few years ago [33, 39–41]. Extensive studies on water-soluble porphyrins and phthalocyanines have been also performed by Berezin [42].

All the compounds mentioned above are found to obtain by traditional organic synthesis. Whereas the chelate porphyrin complexes forming by simple mixing of metal and porphyrin solutions occur rarely [31, 43–45]. Nevertheless, they are compounds of a great interest because of application, among other things, in analytical chemistry – this fact is connected with high values of their molar absorbance coefficient, of the order of 10⁵-10⁶ M⁻¹ cm⁻¹ [46]. An example of application such complexes generated by simple mixing of solutions is determination in water the trace amounts of copper (10⁻⁸ M dm⁻³) by H₂TMePyP porphyrin [47].

Taking into account the synthesis of metalloporphyrins, the nine metalating systems can be distinguished (Table 2). This distinction were made either by the solvent or the metal carrier used during the metalation process [22]. The choice of suitable system depends on all the factors important for the synthesis of a specific metalloporphyrin.

The metalloporphyrins are separated from the reaction mixture by means of crystallization or adsorption chromatography; sometimes by sublimation [22]. However, the most complicated stage is purification of obtained complexes. For this purpose “flash chromatography”, high performance liquid chromatography (HPLC) [48], preparative thin-layer chromatography, capillary electrophoresis [49] and traditional electrophoresis [48] are used. The stationary phase is usually silica gel or alumina and the mobile phase – chloroform, toluene or dichloromethane. If the complex is able to be adsorb strongly, because of the presence of polar axial ligands, is necessary to add methanol or other polar solvent to eluent used during separation. Too acidic or too basic conditions can lead to degradation of obtained compounds. Besides, both the substrates and the products are dissolved in the same solvents; the differences in the solubility of porphyrins and the solubility of their complexes are rather slight. The non-stable complexes are purified by recrystallization. A big problem connected with purification of metalloporphyrins is uncontrolled exchange of the axial ligands during processes of chromatography or crystallization.

Tab. 2. Selected metalating systems serving to prepare metalloporphyrins, characterized either by the solvent or the metal carrier used (*italic*)

No.	Metalating system	Temp. [°C]	Scope of metals inserted
I	The acetate method <i>MX_mL_n' / HOAc</i>	100	Zn, Cu, Ni, Co, Fe, Mn, Ag, In, V, Hg, Tl, Sn, Pt, Rh, Ir
II	The pyridine method <i>MX_m / Py</i>	115 - 185	Mg, Ca, Sr, Ba, Zn, Cd, Hg, Si, Ge, Sn, Pb, Ag, Au, Tl, As, Sb, Bi,

			Sc, P
III	The acetylacetonate method $M(acac)_n$ / solvent	180 - 240	Mn, Fe, Co, Ni, Cu, Zn, Al., Sc, Ga, In, Cr, Mo, Ti, V, Zr, Hf, Eu, Pr, Yb, Y, Th
IV	The phenoxide method MX_m / $PhOH$	180 - 240	Ta, Mo, W, Re, Os
V	The benzonitrile method MCl_m / $PhCN$	191	Nb, Cr, Mo, W, Pd, Pt, Zr, In
VI	The dimethylformamide method MCl_m / DMF	153	Zn, Cu, Ni, Co, Fe, Mn, V, Hg, Cd, Pb, Sn, Mg, Ba, Ca, Pd, Ag, Rh, In, As, Sb, Tl, Bi, Cr
VII	The metal organyl method MR_m / solvent	25 - 200	Mg, Al., Ti
VIII	The metal carbonyl method $MX_m(CO)_n$ / solvent	80 - 200	Cr, Mo, Mn, Tc, Re, Fe, Ru, Co, Rh, Ir, Ni, Os
IX	The metal alkoxide method $M(OR)_n$ / solvent	35 - 80	Li, Na, K, Rb, Cs, Mg, Ca, Sr, Ba

4. UV-VIS SPECTRA

The UV-VIS spectra of porphyrins consist of two distinct bands, one appears in the near-ultraviolet and another one in the visible region, which is the reason of rich and often beautiful colours typical for porphyrins. Forming of porphyrins spectra is connected with π - π^* transition and is explained by the Gouterman theory [50].

The first, more intense absorption band, called Soret or B band, is situated between 390–420 nm, depending on whether the macrocycle is *meso*- or β -substituted. The second, much less intense absorption band, called Q band, is situated between 480–700 nm and divided in two or four components. The Soret band is created in the consequence of allowed electron transitions from $\mu = \pm 3$ (HOMO) to $\mu = \pm 5$ (LUMO), whereas the Q band is forming as the result of forbidden electron transitions from $\mu = \pm 4$ (HOMO) to $\mu = \pm 5$ (LUMO). The number and intensity of these bands and their components can indicate whether the porphyrin is substituted or not and give a proof for the presence of metal ion inside the plane of the porphyrin. These parameters are also the base for classification of porphyrin spectra. The ratio of Soret band and Q band intensities for one sample can equals even 50 : 1.

The classification of porphyrin spectra, according to Milgrom [4], relates to the number and relative intensity of Q bands – in the case of a free-base porphyrin is connected with the substituents on the *meso*- and β -position, whereas in the case of a metalloporphyrin, with the stability of the central metal cation.

The metal-free porphyrins have four Q bands, which are denoted in the direction of increasing wavelength as IV, III, II and I. When the relative intensities of these bands are in the sequence $IV > III > II > I$, then the spectrum is called *etio-type*. The name originates from the etioporphyrins, in which six or more β -positions are substituted with groups without π -electrons, for example with alkyl groups (Figure 4).

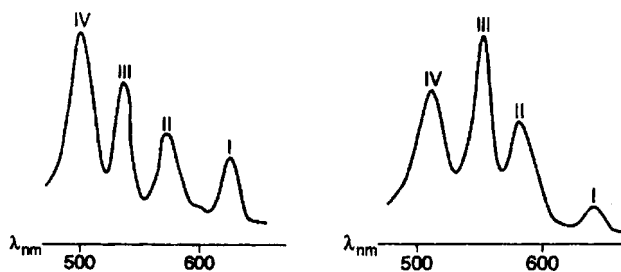


Fig. 4. The spectra of Q band for metal-free porphyrins of *etio*- and *rhodo*-type [4]

When the groups with π -electrons, as carbonyl groups, are directly substituted to β -positions, some differences in intensities of Q bands could be observed and in this case *rhodo-type* spectrum (after rhodoporphyrin) is created, with the sequence of relative intensities as $III > IV > II > I$. Such groups are able to shift the spectrum to longer wavelength. If two groups of this kind are situated on pyrrole unit of macrocycle next to each other, they can cancel each other out. But when these groups are on opposite pyrrole units, the effect of shifting is intensified and in the result an *oxo-rhodo-type* spectrum is obtained, with the sequence of relative intensities as $III > II > IV > I$. In the case when some of β -positions stay unsubstituted (usually no less than four), and also when *meso*-positions are occupied, the *phyllo-type* spectrum is forming, with the intensity ratio of the Q bands as $IV > II > III > I$ (Figure 5).

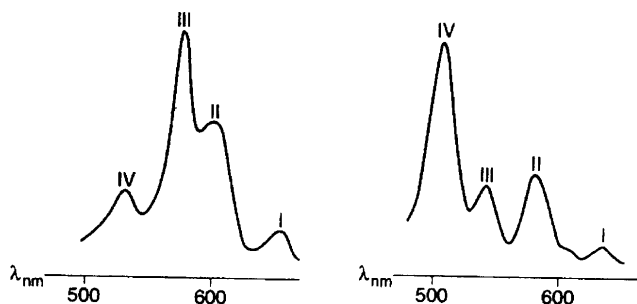


Fig. 5. The spectra of Q band for metal-free porphyrins of *oxo-rhodo*- and *phyllo*-type [4]

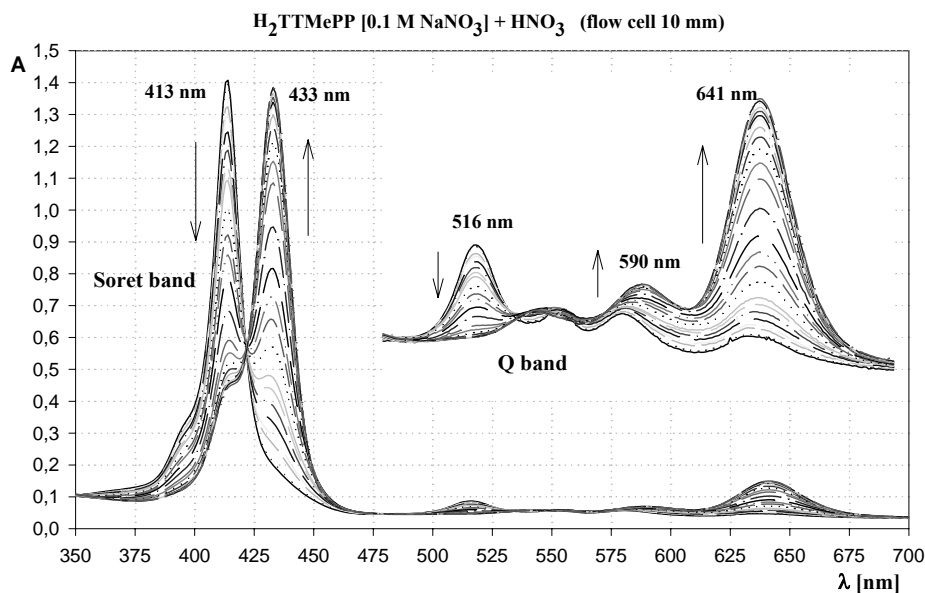


Fig. 6. Evolution of porphyrin spectrum during titration by HNO_3 in flow cell, at controlled pH values

Protonation of porphyrins with acid leads to attaching of two additional protons to the central nitrogen atoms. This change is the reason of creating only two Q bands, what has an influence on the colour of a porphyrin solution (Figure 6). The colour of the porphyrin solution with substituents in the β -positions changes from the red wine to magenta, whereas the colour of the porphyrin solution with substituents in the *meso*-positions changes to deep green, coinciding with a shift of the Soret band towards the longer wavelength, sometimes even by 40 nm, depending on the kind of *meso*-substituent. Such processes lead to the change of the porphyrin macrocycle conformation, and give not only the effect of a tilting of the pyrrole rings about their α -carbons, but also a rotation of the *meso*-substituent (for example aryl groups) into the plane defined by the α - and *meso*-carbon atoms of the porphyrin macrocycle (Figure 7).

The spectra of metalloporphyrins usually consist of two Q bands. Their relative intensities points at the level of a complex stability (Figure 8). The proof for the creating of metal complex of porphyrin can be also a decay of the fluorescence characteristic of a free-base porphyrin, because of a fulfilling of proper orbitals [22].

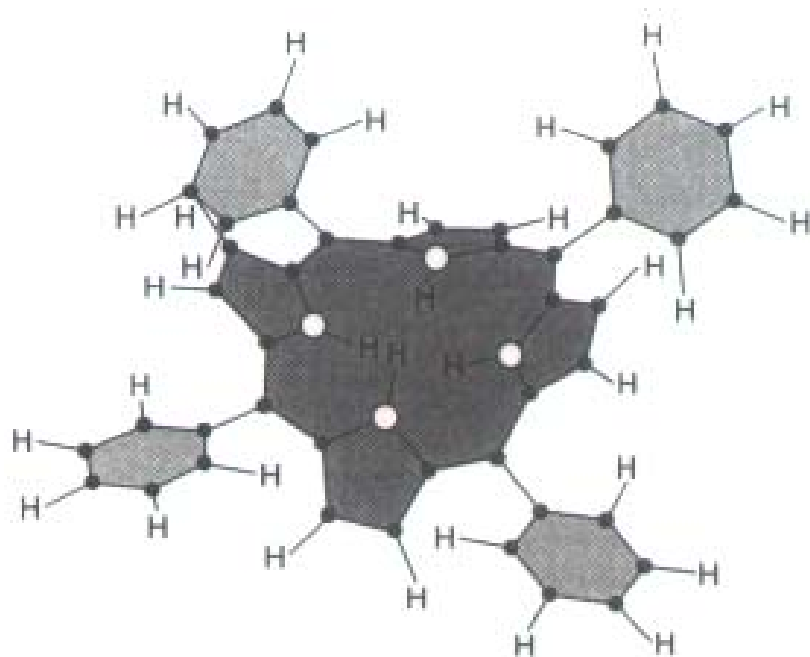


Fig. 7. The changes of conformation of porphyrin macrocycle skeleton (only for *meso*-substituted porphyrins) during dication formation. The pyrrole subunits “hinge” about carbon atoms 1, 4, 6, 9, 11, 14, 16 and 19 (two up and two down), while the *meso*-aryl units can rotate more into the mean porphyrin plane [117]

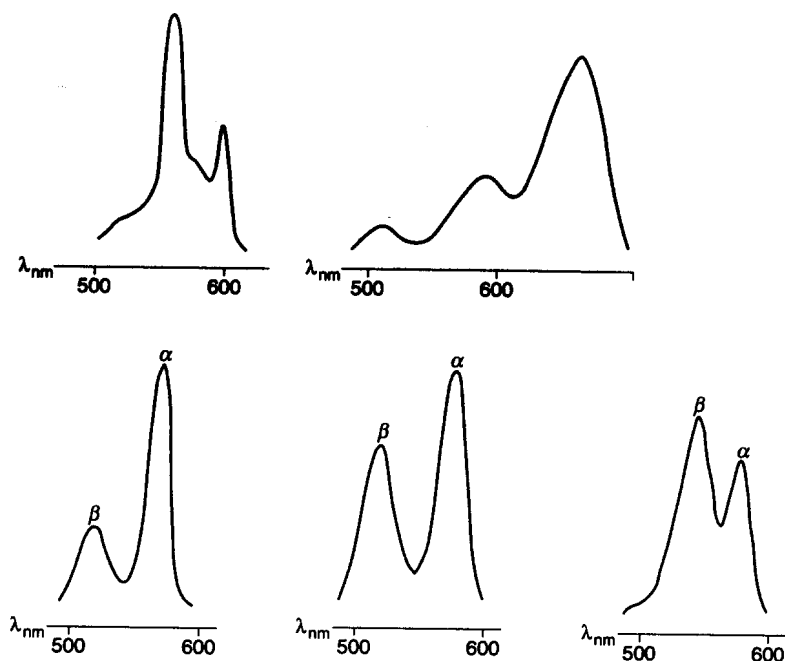


Fig. 8. The spectra of Q band for dication, monocation and some metal complexes. The smaller the ratio $\alpha : \beta$ of band intensities the less stable the metal complex [4]

The spectra of metalloporphyrins can be classified as “regular” or “irregular”, depending on whether the metal inside the porphyrin ring has an open or closed valence electron shell [51]. The “regular” spectra of metalloporphyrins are consisted of Soret band (390–425 nm, depending on the way of macrocycle substitution) and two Q bands, α and β . The α band is situated within the range 570–610 nm for the β -substituted complexes and within the range 590–630 nm for *meso*-substituted complexes. The position of α band is connected with the type of metal and their axial ligands.

The regular metalloporphyrin complexes have ability to fluorescence. The solid state complexes are usually purple, while in solution they have the red wine colour. Normal-type absorption spectra of regular porphyrins indicate of little or no interactions between the atomic metal orbitals and π -molecular porphyrins orbitals. That is the reason why absorption and emission spectra of regular metalloporphyrins depend on π -electrons of porphyrin.

In the case of “irregular” metalloporphyrins there are three main types of spectrum: normal-, hypso- and hyper-type. Normal-type spectra are characteristic of metals from d- or f-block, but the low energy of d- and f-electron metals does not let them interact meaningfully with the porphyrin π -electrons.

Hypso-type spectra are similar, but with the Soret and Q bands shifted hypsochromically towards the UV wavelengths. Such type of spectrum is presented by d-block elements with unfilled d-orbitals, that is metals belonging to groups 8–11. In this case d-electrons of a metal can complete the empty π^* -orbitals of porphyrins in charge transfer reaction, called metal-to-ring charge transfer, what is the cause of raising of their energy. This effect is in direct proportion with the atomic number of the transition metals. A good example of such compounds, demonstrating the hypso-type spectra, are porphyrin complexes with Cu(II) ions.

Hyper-type spectra are much more different than the spectra mentioned before and come additionally in two more types: p-type and d-type hyper spectra. The type of spectrum depends on whether the central cation belongs to 14 or 15 group of elements and is in an oxidation state two below the group number, as in the case of Sn(II), Pb(II) or Bi(III)); or is a transition metal in which the number of d-electrons is five or less – for such cations as Fe(III), Mn(III) and Mo(V)). The p-type hyper spectra are the consequence of charge transfer from the metal p-orbitals into the empty porphyrin π^* -orbitals. The d-type hyper spectra are of different origin: they occur during charge transfer from the filled porphyrin π -orbitals into the empty d-orbitals of transition metals. This process is called ring-to-metal charge transfer. Typical for hyper-type spectra is forming of additional absorption bands. They are hard to analyse, because their number changes depending on the metal and their position depends on axial ligands.

The theory of UV-VIS spectra of metal-free porphyrins and their metal complexes was studied extensively by Martin Gouterman. He developed the “four-orbital model”, taking into account the considerations concerning HOMOs and LUMOs porphyrin orbitals, as well as connected with this model the „free electron theory” (FET) and the „cyclic polyene theory” (CPT) [50].

5. PHYSICOCHEMICAL PROPERTIES

The porphyrins and their metal complexes are found to be the compounds with interesting physicochemical properties, which can be investigated by many analytical methods. The characteristics of these molecules includes the unique spectroscopic, luminescence (fluorescence and phosphorescence), magnetic (para- and diamagnetic) properties, as well as their thermal stability, photoconduction, photoemission and surface activity.

One of the most specific properties of porphyrins is their high molar absorbance coefficient, with order of magnitude equals 10^4 - 10^6 , which is the reason for common using of spectroscopic techniques in investigation of these class of compounds [23, 39, 52–55]. Such strong chromophore as a porphyrin is, causes the fact, that the absorption bands of metal ions are hard to observe

and that is why they can not interfere with the picture of porphyrins. The other techniques employing often in examination of the porphyrin systems are: nuclear magnetic resonance (NMR) [6, 23, 52, 53], circular magnetic dichroism [55, 56] or excitation and emission spectra [57]; and more rarely: electron paramagnetic resonance (EPR) [23, 58, 59], luminescence, elementary analysis, oxidation (chemical, electrochemical, photochemical), infra-red spectroscopy (IR) [23], mass spectroscopy (MS) [6, 23], thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), electron spectroscopy for chemical analysis (ESCA), flow dichroism (FD), Raman spectroscopy (RR) [23, 60, 61], thermogravimetry [29], electrochemical methods, X-ray analysis [6] and potentiometric methods [39]. All these techniques are the irreplaceable tools for precise studies on the porphyrin systems. The most popular subjects of interest connected with porphyrins and their metal complexes are first of all: the changes of substituents and axial ligands, processes of metalation, protonation, aggregation, dimerization, oxidation and reduction of the macrocycle and the stability of obtained complexes. Recently extensive studies are performed on the interdisciplinary aspects of the porphyrin chemistry, connected with their interactions with DNA and the role in photodynamic therapy of cancer (PDT).

The consecutive substantial property of investigated compounds is their stability. Some porphyrins and metalloporphyrins are unstable under atmospheric conditions (light, air, moisture). Contact with light can lead to photooxidation of the porphyrin – if this process is followed by fission of the macrocyclic ring, the complexes are more readily demetalated. The result of photooxidation is creating of many colour bands and spots during separation by column or thin-layer chromatography (the colours are changing predominantly from red to green or brown). The light sensitivity increases with the fluorescence activity of the porphyrin complexes and with their stability toward acids [29, 62].

The stability of metalloporphyrins depends also on electrostatic interactions, defined by the charge-to-radius ratio of a metal ion: a high charge, a high electronegativity and a small radius lead to increase of metalloporphyrin stability, but a low charge, a low electronegativity and a large radius cause the instability. Therefore the porphyrins with Sn(IV) and Sb(IV) are stable, whereas the porphyrins of alkali metals and the heavier alkaline earth metal ions have a tendency to be labile.

A high reactivity is characteristic of the water-soluble porphyrins, they undergo the reactions of coordination, polymerization, aggregation, oxidation and reduction, sorption and photoreactions. The different parts of the porphyrin ring can take part in the chemical reactions:

- two acidic centres N–H;
- two atoms =N– with free electron pairs;
- unsaturated ethylene bonds –CH=CH–;

- π -electron macrocycle $C_{12}H_4$.

First four centres are responsible for the acid-base properties of porphyrins and play the role of the chelate coordination centre. During formation of the metal complexes the porphyrin loses two protons from N–H bonds and is coordinated to the metal ions by four equivalent N atoms.

Adding of two or four more hydrogen atoms by the disruption of double bonds in the porphyrin ring leads to occurring of the hydroporphyrins (chlorins, bacteriochlorins and isobacteriochlorins), which have still the system of 18 π electrons and aromatic properties.

The oxidation or reduction of π -electron porphyrin ring give π -cations and π -anions. They are generated because of adding or abstraction of electron from the 18-electron system of the porphyrin aromatic macrocycle. The stable π -cation and π -anion radicals and electron transfer between them, as well as the electron transfer caused by the change of metal oxidation state in the macrocycle, play the most important role in working of chlorophyll, cytochromes and heme, helping them in the energy transport in different biological systems. A great variety of reaction centres and substituents leads to producing of many compounds with the characteristic porphyrin system.

Separate problem is the conception of the porphyrin ring aromaticity. The porphyrins are aromatic substances and undergo the electrophilic substitution reactions characteristic of these class of compounds, such as halogenation, sulphonation, nitration, acylation, formylation, deuteration and Friedel-Crafts reactions. The porphyrins differ from other aromatic molecules, as benzene for example, because there are two different sites on the macrocycle where the reactions of electrophilic substitution are possible [63] – the *meso*-position and the β -position; what is more, they proceed not in the same manner. The place of undergoing the reaction depends on the degree of electronegativity of the porphyrin. The process can be controlled by the choice of metal, which is coordinated to the nitrogen atoms of the macrocycle. The introduction of divalent central metal, as Cu(II) for example, leads to creating the electronegative porphyrins ligands. Such complexes, substituted on the carbons situated on the *meso*-positions, can be scheduled in regard to degree of their electronegativity in the following order: MgP > ZnP > CuP > NiP > PdP. However, on the other hand, metals in electrophilic oxidation states, such as Sn⁴⁺ and the free-base porphyrins have the tendency to deactivate the *meso*-carbons and prepare the β -positions to electrophilic attack. This problem can be wider explain on the grounds of canonical form of the porphyrin (Figure 1).

The aromaticity of porphyrins has been proved by NMR spectra, measurements of their heat of combustion and crystallographic parameters, which indicate the planar topology of the porphyrin macrocycle.

6. π -CATION CHEMISTRY

To explain better the porphyrin spectra appearing as a result of π - π^* transitions the theory of Gouterman is applied [50]. Starting point of this theory is a statement showing that the porphyrin ring is a coupled macrocycle meeting the Hückel aromaticity rule $4n+2$ [30, 64]. The porphyrin ring is therefore said to be a 16-membered cyclic polyene carrying 18 π electrons. In such case the ground state of the macrocycle is related to the completed orbitals with $\mu = 0, \pm 1, \dots, \pm 4$, while the population of the lowest excited orbitals corresponds to the transitions from $\mu = \pm 4$ to $\mu = \pm 5$.

The energetic levels resulting from the polyene model are disturbed by the nitrogen atoms of the porphyrin ring. The consequence of this disturbance are two the highest degenerate completed orbitals a_{1u} i a_{2u} and two the lowest degenerate uncompleted orbitals e_g . The porphyrin spectra are the result of electron transitions $a_{1u} \rightarrow e_g$ (Soret band) and $a_{2u} \rightarrow e_g$ (Q band); both of them are equally possible. The Soret band refers to allowed electron transitions from $\mu = \pm 3$ (HOMO) to $\mu = \pm 5$ (LUMO), whereas the Q band refers to forbidden electron transitions from $\mu = \pm 4$ (HOMO) to $\mu = \pm 5$ (LUMO) (Figure 9).

The oxidation reaction of the 18-electron porphyrin ring, consisting in the detachment of one electron from the HOMO orbital, leads to obtaining stable radicals named π -cations. The effect of π -cations, described firstly for Mg, Zn, Cu and Ni porphyrins, is widely explained in the publications of Dolphin and Fajer [65–68], as well as Mauzerall and Fuhrhop [69–71], which are now the base of π -cations chemistry. So far almost all known metal complexes with porphyrins have been obtained in the form of π -cations, although not always as the result of all possible oxidation methods – chemical, photochemical (radiolysis) and electrochemical. It is suggested that different methods of oxidation could give sometimes different products of such reactions.

The oxidation of porphyrin complexes to their π -cations can be additionally disturbed by the changes of the oxidation number of metal inside a complex, what is easy to observe for Fe and Co porphyrins. The processes of free-base porphyrins oxidation to their π -cation radicals, studied by Fajer, as well as the possibility to obtain such cations for metal complexes with chlorin, bacteriochlorin and isobacteriochlorin (the products of incomplete hydrogenation of the porphyrin ring) have played the important role in the understanding of the activity of chlorophyll and heme.

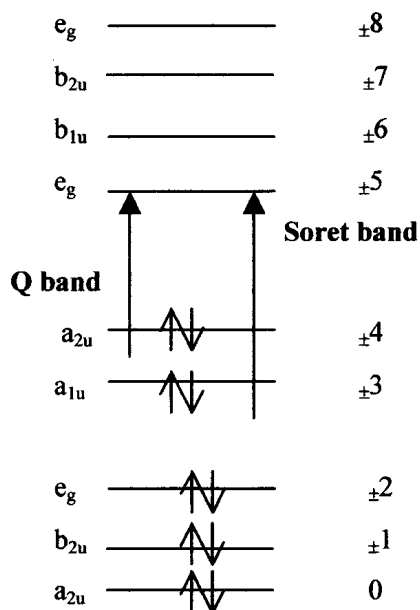


Fig. 9. The origin of π - π^* transition in porphyrins

The metalloporphyrins oxidation by the detachment of one electron from the 18-electron ring leads to serious changes of the absorption spectra. The electron transitions π - π^* , situated for oktaethylporphyrin complexes in the Q band, about 560 nm ($a_{2u} \rightarrow e_g$) and in the Soret band, about 410 nm ($a_{1u} \rightarrow e_g$), are replaced in the oxidation state by the series of overlaying bands. In the π -cation radicals forming by one-electron oxidation, unpaired electron can be localized either on a_{1u} orbital or on a_{2u} orbital. In the result the ground state for π -cation refers to $^2A_{1u}$ (in the case of phthalocyanines) or to $^2A_{2u}$ (in the case of metalloporphyrins). Till now the sequence of the highest orbitals (HOMO) completing, so the ground state of the π -cations of porphyrin complexes with metals, is not decided, because of their well-defined and not susceptible to disturbances symmetry. Some authors, on the base of obtained EPR spectra, believe in the presence of mixed orbitals, where the domination of the one of the possible configurations depend on the type of the axial ligands.

The Gouterman theory, known also as the “four-orbitals” theory, tries to explain the electron structure of the porphyrins and their absorption spectra, obtained as a result of π - π^* transitions. This theory is also the base for mathematical models, leading to estimation of frequencies and intensities of the porphyrin spectral bands.

7. APPLICATION AND THE ROLE IN THE NATURE

The natural porphyrins are compounds of the great importance for the nature. Such complexes as chlorophyll (magnesium porphyrin), heme (iron porphyrin), cytochromes (cobalt porphyrins), peroxidases or cobalamin (vitamin B₁₂) are responsible for the fundamental processes of living organisms, taking part in photosynthesis, cell respiration, fermentation, transport, accumulation and exchange of gases, processes of pigmentation and in this manner controlling the metabolism of the whole body. Abnormalities of the porphyrin functions can lead to such serious diseases as anemia, porphyria and cancer.

Studies on the structure and physicochemical properties of natural porphyrins were helpful in the synthesis of related macrocyclic systems. A great variety of such systems let them be utilized in different areas of industry and science. Nowadays porphyrins and their metal complexes are very important for the production of dyes and pigments, semiconductors and catalysts of many reactions. They also play the role of analytical reagents in spectrophotometric determination of metals (e.g. determination of Cu(II) using porphyrins in natural waters [47] and blood [43]), and take part in redox reactions [72, 73], in the photosterilization of water [74], or as the “electronic nose” – a specific sensor for volatile organic compounds [75–77].

The porphyrins appeared to be very useful in medicine, helping in the treatment of some bacterial infections [78, 79]; while the metalloporphyrins are used as a contrast in magnetic resonance procedure [80]. Recently the serious studies have been performed concerning the porphyrin ligands, which could behave as the model of hemoglobin able to completely reversible addition of oxygen [21]. Till now only the porphyrin complexes with Fe(II) are obtained, but Fe(II) undergoes the oxidation to Fe(III) and the oxygen is attached irreversibly. The completely reversible hemoglobin model will be formed possibly on the base of “picket-fence” porphyrins (Figure 2). Other group of porphyrin compounds looking promising for medicine, especially for photodynamic therapy of cancer, are also water-soluble glycosylated porphyrins.

Some of the porphyrins are able to interact with DNA, causing the block of adequate fragments and both chemical and photochemical cleavage of DNA molecule – because of this fact they can serve as the potential anti-virus agents. Particularly useful seem to be the cationic porphyrins, although they produce photochemically singlet oxygen, anyway, as the anionic porphyrin; nevertheless, the anionic porphyrins do not cause the cleavage of DNA helix. Very interesting compound is also the gadolinium complex with *meso*-tetrakis(1-methyl-4-pyridyl)porphyrin, which can be used as a special probe in DNA chain – this complex interacts stronger than a free-base porphyrin with DNA molecule [30, 81].

The compounds with molecules characterised by high anisotropic properties can serve as the liquid crystals [82]; they are suggested to be used in electrochromic displays, watches or calculators. Such properties, connected with the ability to changing the molecular orientation in the electric field, are typical also of the porphyrins [83, 84].

Very promising seem to be the porphyrin complexes with other compounds, such as cyclodextrins [85, 86] and fullerenes [87], as well as “expanded” porphyrins, for example texaphyrins [88–91], “porphyrin wheels” [92], sapphyrins, platyrins and others [93]. The studies on the porphyrin tend to synthesis of the multiple-plane systems – the example are the co-planar diporphyrins. Other direction of porphyrin modification is synthesis of the “crown” porphyrins, where the role of the “crown” plays the cryptate ring, able to attach two metal atoms. Such “cap” can be also form by pyridyl groups.

The porphyrins are also suitable elements of more complicated systems. One of them are dendrimeric structures, similar in some points to the neuronal net. Such compounds can take part in forming of the big agglomerates, which have probably the ability to maintain their properties in spite of the destroying of some parts of the molecule (like in the case of the neuronal net).

The role of porphyrins in the process of alternative energy production. For many years the subject of photolysis, in which pure hydrogen and oxygen can be received by using solar energy to photochemical splitting of water have been the great challenge for many scientists [4, 94]. The hydrogen obtained in the photolysis process could be used as friendly for the environment, clean burning fuel, delivering more energy than hydrocarbon fuels or coal [95, 96]. The product of hydrogen combustion is water, which can be also a source of hydrogen – in such case the renewable source of energy could be created.

The photolysis of water, known also as the photochemical reduction of water, is the conversion of solar energy to the chemical one in the result of photocatalytic splitting of water into O₂ and H₂.



The visible radiation is not absorb by water – and that is the reason why the sunlight can not be used directly to splitting of water. Therefore the adequate chemical system is necessary for the photolysis reaction, consisting of a photosensitizer (photocatalyst), an electron relay, a sacrificial electron donor, and a catalyst (colloidal platinum or platinum on SrTiO₃). The most important element of such constructed system is a correct photocatalyst, able to absorb the light in the right range of λ and use the obtained excess of energy as activation energy for the reaction.

Synthetic porphyrins could play an important role of photosensitizers in the process of solar energy conversion [95–97] – is widely known that chlorophyll has the same function during photosynthesis. The porphyrin compounds are the best candidates for being photocatalysts because they have good light-absorbing properties and favourable redox potentials for photochemical reduction of water. The processes of photoreduction [95, 96] and photooxidation [98] have been investigated experimentally, using water-soluble zinc porphyrins. It was also observed that these porphyrins exhibit a “photogalvanic effect” [99] – the light shone into the solution containing the dissolved porphyrins and two electrodes connected to a battery leads to the passing of a small current.

The photolysis process with porphyrins as the photosensitizers could be used not only for generating of the hypothetical “fuel of the future”, but also for simulation of natural photosynthetic processes.

Molecular conductors. The concept of electrical conductivity is usually associated with metals. However, during the late 1970s a new type of conducting material appeared, the so-called “molecular metal”, containing one or two metal atoms, covalently bound into an organometallic structure. In spite of many theories proving that organic materials should be insulators [100], the systems mentioned above are able to conduct the electric current. But there is one thing, which differs the new type of molecular conductors from metals and organic semiconductors – while the conductivity of metals tends to be isotropic (the same in all dimensions), the conductivity of conducting organic materials tends to be highly anisotropic, what means that it is connected with a preferred direction [101]. Unquestionable advantage of such materials is a fact, that their conductivity is a result of their inner structure and does not depend on the complicated technological processes – in the consequence the generating of molecular conductors is much more cheaper and easier.

One of the type of such conductors are the “charge-transfer” complexes. An example can be the “shish-kebab” conducting polymers, where porphyrins or phthalocyanines are assembled according to co-facial strategy. In such prepared metallomacrocyclic materials, electrical conductivity is at the right angle to the plane of the macrocycle. The synthesis of these conducting stacks in a controlled manner is a big problem. Unfortunately, the control will be necessary for constructing of micro- and nanoelectronic circuits, useful as “molecular wires”, transistors, diodes and organic “chips”, where the number of circuit elements will be counted even in billions. The best solution seems to be chemical synthesis of conducting molecules and their connections; for example, the porphyrins connected chemically together edge to edge can bring the molecular wires of a desired length [102].

Electrons are not the only charges that are conducted in such manner. There is also the possibility of photon conductivity thanks to the structure of the

porphyrin molecular wire, as well as proton conductivity by use of many proteins [103]. It is also suggested that protons could be conducted by the porphyrins specially substituted with groups allowing the macrocyclic subunits to generate intermolecular hydrogen bonding.

Photodynamic therapy of cancer. One of the most important and the most desirable application of the water-soluble porphyrins is photodynamic therapy (PDT) [4, 104–107]. Photodynamic therapy and diagnosis of cancer consist in intravenous injection of hematoporphyrin solution, which has the ability to accumulate in cancer tissue after 24 – 48 hours since the injection. The exposure of such tissue for the laser generated light around 630 nm leads to destruction of the tumour, but does not damage the healthy tissues. Whereas irradiation by the light with wavelengths 407 nm excites the red fluorescence of hematoporphyrin (690 nm) and allows to make the diagnosis of “sick” cells cumulated in the cancer tissues (Figure 10). It appeared that strong fluorescence is the most intensive on the periphery of tumour and its intensity depends on the thickness of the cancer tissue. It was also observed that other compounds are responsible for the destruction of cancer (the porphyrin aggregates) and others for fluorescence – the porphyrin monomers [108]. That is the reason why these two processes give the results not in the same time since the using of hematoporphyrin.

So far the mechanism of tumour destruction is not clear. One of the theories assumes that during irradiation of the tissue with a big amount of accumulated hematoporphyrin by krypton or neodymium laser, the excited hematoporphyrin can transmit energy to the molecular oxygen and in the consequence chemically active singlet oxygen is generated, able to destroy the cancer tissue. The second explanation is based on the presence of peroxide ion (which can be generated by electron transfer or hydroxyl radical forming). Both the mechanisms are possible and depend on the kind of substrate (the cancer tissue), chemical structure of the porphyrins and the degree of their aggregation.

First person trying to use the porphyrins for the fight against cancer was in 1913 Meyer-Betz who demonstrated the phototoxicity of these compounds by injecting himself the hematoporphyrin mixture. Then this problem was studied by Policard, Auler, Lipson and Diamond. Nowadays the photodynamic therapy is very popular subject of investigations all over the world. In Poland the studies of PDT are developed by Prof. A. Graczyk from WAT in Warsaw [107].

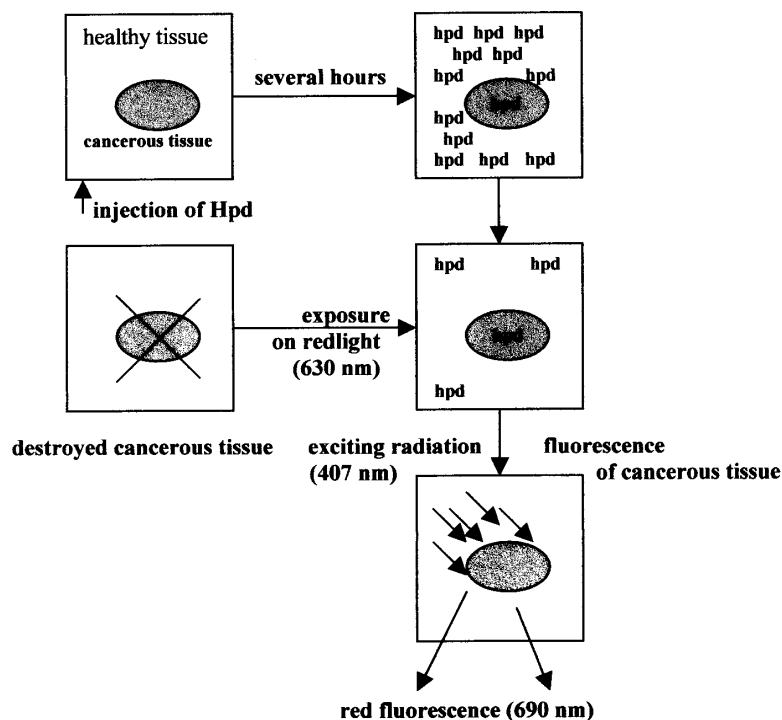


Fig. 10. The course of PDT therapy

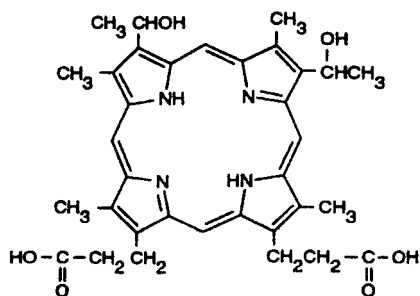


Fig. 11 The structure of hematoporphyrin molecule

At the beginning of photodynamic therapy only a hematoporphyrin – HpD played the role of photosensitizer (Figure 11). But this substance is not, however, the ideal agent for photodynamic treatment of cancer. Firstly, it is the mixture of compounds (20% of mono- and diacetates of hematoporphyrin, 3-5% of protoporphyrin, 20-30% of hydroxyethylvinyldeuteroporphyrin, and 50% of oligomers of the compounds mentioned above with undefined structure

[107]), some of which are PDT-inactive. Because of these obstacles it is difficult to obtain similar photodynamic properties from different HpD samples. It should be taken into account that this agent accumulates also, to a lesser extent, in non-cancer tissues, leading to photosensitivity of the patient even about 1 month after injection of HpD. However, the biggest disadvantage of HpD is its ability to absorb the light in the wrong region of the spectrum for PDT, what results in the little photodynamic effect. This photosensitizer is usually used for the treatment of skin, breasts, urinary bladder and eyes tumours; rarely for the cancer of lungs, oesophagus, stomach, brain, digestive system and genitals.

To choose the best PDT photosensitizer, the following rules have been established [4]:

1. A good PDT photosensitizer must be a pure compound, generated in a reproducible synthesis;
2. It should undergo the activation at wavelengths > 650 nm, to ensure the best absorption of red light, which penetrates the tissues, and so the sensitisation by an external light source;
3. It must be non-toxic and give no side-effects;
4. Its excited states (especially the triplet excited states) should be long-lived enough to enable it to photosensitise the singlet oxygen production (which is suggested to be the photoreagent responsible for the effect of photodynamic therapy);
5. It must localise specifically in the cancer tissues;
6. It should be removed quickly from the body after the process of PDT;
7. It must be soluble in the body's tissue fluids so that it could be injected and carried to the tumour site.

Making a choice of an ideal photosensitizer one should remember about the correct proportions between its hydrophobic and hydrophilic properties. Highly lipophilic agents are slightly water-soluble and undergo the aggregation processes more easily, while hydrophobic compounds are not good at penetrating into the cell membranes [109]. The ratio of these properties can be controlled by changing a hydrocarbon chain length – that is the reason why porphyrins with the spacer arm are so promising for the PDT therapy. It is very interesting that some of the PDT-inactive porphyrins, which are monomers, becoming more active after the dimerization process (like in the case of hematoporphyrin) [110].

Hematoporphyrins are the first-generation PDT agents. The most famous photosensitizer of this class is an agent based on the structure of hematoporphyrin, known commercially as the Photofrin® II (Quadra Logic Technologies, Inc, Vancouver, BC, Canada).

Second-generation PDT agents are defined as newer, more effective and easier to deliver compounds. The well-defined structures of these agents

facilitate the understanding of their toxic and enzymatic properties, the mechanisms of functioning and carrying them around the body, as well as their localisation in human tissues [107, 111–114]. The best known second-generation PDT agents are:

- *meso*-tetrakis(tetraphenyl)porphyrin derivatives (water-soluble sulfonyl and pyridyl porphyrins);
- uroporphyrin I;
- ZnTMePc (water-soluble zinc phthalocyanine with sulfonyl groups);
- H₂TPSP (water-soluble *meso*-tetrakis(sulfonatophenyl)porphyrin);
- AlPcS (water-soluble sulfonated complex of aluminium phthalocyanine);
- glycosylated porphyrins (water-soluble tetraphenylporphyrins with lactose and maltose);
- “expanded” porphyrins (purpurins, metallopurpurins, texaphyrins, metallotexaphyrins, platyrins, verdins, benzoporphyrins (Verteporphin®), as well as the modified chlorins, bacteriochlorins, naphthalocyanines, phthalocyanines and metallophthalocyanines).

All these agents and their metal complexes are able to interact easily with nucleic acids.

It was demonstrated that even the “ideal photosensitizer” does not always cause the proper effect. Red light can penetrate into the tissues for only 4–20 mm, depending on their blood supply. Therefore the light must be “delivered” into the internal organs – the good solution is the application of specially constructed light pipes, so-called optical fibres.

There are also trials of using porphyrins as skin cream, which contains δ -aminolevulinic acid derivatives (δ -ALA), acting as a prodrug. After 4 hours, the “saturated” skin tumour is irradiated by the laser light [112].

The PDT is said to be the universal and non-toxic therapy for internal organs. The only one side-effect is photosensitivity of skin during about 1 month after the operation. Photodynamic therapy could be used in the future not only for cancer treatment, but also for other diseases, for example atherosclerosis, autoimmune diseases, blood purging (deactivation of different kinds of viruses) [112], HIV-virus, psoriasis, restenosis and tapetoretinal degeneration [106].

The modification of PDT is recently developed “photodynamic antimicrobial chemotherapy” (PACT) [115]. Like photodynamic therapy, PACT takes advantage of photosensitizers and irradiation by visible or ultraviolet light, but it is applied rather for inactivation of viruses and bacteria (especially antibiotic-resistant ones), yeast and parasites. This therapy promotes the application of not only artificial photosensitizers (porphyrins and their derivatives), but also

natural compounds, such as psoralens and furanocoumarins, which are able to interact with deoxyribonucleic acid.

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