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Bioinorganic Photochemistry: Frontiers and Mechanisms

Konrad Szaciłowski, Wojciech Macyk, Agnieszka Drzewiecka-Matuszek, Małgorzata Brindell, and Grażyna Stochel*

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1. Introduction

For more than 50 years bioinorganic chemistry has remained an expanding and exciting interdisciplinary field of science.[1−6] One of the rapidly growing and evolving new research areas is *bioinorganic photochemistry* (Figure 1), which connects inorganic photochemistry[7−23] with biological, medical, and environmental sciences.[24−50] The role of light and metal compounds in natural systems and the possibility of their application in artificial systems of medical or environmental importance are in the center of bioinorganic photochemistry interest.

From the earliest times man has been aware of the influence that solar radiation has on matter and the environment; however, it is mainly during the last century that a systematic understanding of photochemical and photophysical processes has been developed.[40,42,43] By definition, light is the narrow spectral region of electromagnetic radiation (Figure 2) perceived by human vision; however, it is very often extended to UV rays. The spectral range of sunlight reaching our planet has varied with time. Atmospheric dioxygen appeared via photosynthesis 2.7 billion years ago. Atomic oxygen produced by short-wavelength UV irradiation (<240 nm) reacted with molecular dioxygen to form an ozone layer

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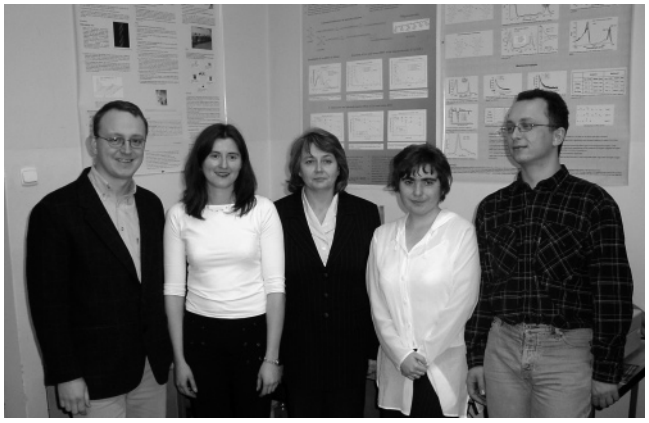

Konrad Szaciłowski (far right) was born in Kraków, Poland, in 1971. He graduated from Jagiellonian University (Kraków) in 1995 (M.Sc., in cooperation with Professor Horst Kisch, Erlangen, Germany) and 2000 (Ph.D.) under the guidance of Professor Zofia Stasicka. He studied homogeneous catalysis with Professor Karl Anker Jørgensen (Århus, Denmark) and the chemistry of molybdenum–sulfur clusters with Professor Michele Aresta (Bari, Italy). He spent 1 year with Professor John F. Endicott (Wayne State University, Detroit, MI) as a postdoctoral fellow working on the spectroscopy and magnetic properties of nickel complexes. Now he is a member of the Coordination Compounds and Bioinorganic Chemistry Group. His research interests are focused on several areas of coordination and bioinorganic chemistry: spectroscopy and photoreactivity of nitrosyl complexes, chemistry of metal compounds with antibacterial and antifungal properties, molecular switches, and logic gates. Recently he has also been involved in photoelectrochemical studies of nanocrystalline semiconductors.

Wojciech Macyk (far left), born in 1973 in Mielec, Poland, graduated from Jagiellonian University (Kraków) in 1997 under the supervision of Professor Zofia Stasicka. In the same year he started his Ph.D. studies at the University of Erlangen-Nürnberg, Germany, in the group of Professor Horst Kisch working on photosensitization of TiO_2 toward visible light. After finishing his Ph.D. degree in 2000, he spent 2 years as a postdoctoral fellow in the same group. He has received some prizes and fellowships, among which are the Albert Weller Prize, the Staedtler Prize, and a fellowship from the Foundation for Polish Science (FNP). In 2002 he joined the Coordination Compounds and Bioinorganic Chemistry Group, Faculty of Chemistry, Jagiellonian University. His research interests include heterogeneous photocatalysis (especially TiO_2 sensitization), photocatalytic water detoxification, and photoelectrochemical properties of nanocrystalline semiconductors.

Agnieszka Drzewiecka-Matuszek (second from right), born in Kraków, graduated from Jagiellonian University in Kraków with her M.Sc. degree in Chemistry, specialization biological chemistry, in 2000. During her studies she spent a few months in Professor Luis G. Arnaut's group at the University of Coimbra in Portugal exploring the photochemistry of new photosensitizers for photodynamic therapy. She is currently working toward her Ph.D. degree under the supervision of Professor Grażyna Stochel in the Coordination Compounds and Bioinorganic Chemistry Group at the Faculty of Chemistry of the Jagiellonian University. Her research interests include the development, photochemical studies, and biological testing of new photosensitizers containing metals designed for medical application.

Małgorzata Brindell (second from left) attended the Interdisciplinary Mathematical-Natural Science Studies and graduated with her M.Sc. degree in Chemistry from Jagiellonian University in 1999. She then received her Doctoral degree in 2004 for work on thermal and photochemical reactions of ruthenium and platinum complexes with oligonucleotides under the supervision of Professor Grażyna Stochel and in collaboration with Dr. Sofi Elmroth (Lund University, Sweden). In 2003 she spent a few months in Dr. Alison Rodger's group (Warwick University, U.K.), where she was engaged in the synthesis and study of metal complexes interacting with DNA. In 2004 she worked on the photochemistry of ruthenium complexes in Professor Orazio Traverso's laboratory (University of Ferrara, Italy). She is currently working as a Research Associate in the Coordination Compounds and Bioinorganic Chemistry Group, Faculty of Chemistry, Jagiellonian University. Her interests concern the anticancer activity of ruthenium complexes and application of light for activation of metallodrugs.

Grażyna Stochel (middle) is Professor of Inorganic Chemistry and Head of Coordination and Bioinorganic Chemistry Group at Jagiellonian University (Kraków, Poland). Since 1999 she has been Deputy Dean of the Faculty of Chemistry, Jagiellonian University, and a member of a few Senat's commissions. She received her Ph.D. (1983) and habilitation (1993) degrees in Chemistry from Jagiellonian University; in 1993 she became Associate Professor and in 2001 Full Professor in the Inorganic Department, Jagiellonian University. As an Alexander von Humboldt Fellow she spent 2 years with Professor Rudi van Eldik at the University of Frankfurt am Main (1987), Witten-Herdecke (1991), and Erlangen-Nürnberg (1998) studying the kinetics and mechanisms of inorganic and bioinorganic reactions with applications of high-pressure techniques. She also spent some time with Professor Arnd Vogler, University of Regensburg (1988), and Professor Orazio Traverso, University of Ferrara (1994/1995) working on the photochemistry and photophysics of coordination compounds. She is a member of several international and national scientific associations and committees, among them are the following: Inorganic Reaction Mechanisms Group of the Royal Chemical Society (1996 to present); European High-Pressure Research Group (1988 to present); International Committee of Symposia on Photochemistry and Photophysics of Coordination Compounds (ISPPCC, 1995–2007); Management Committee COST, Chemistry Action D10 "Innovative methods and techniques for chemical transformations" (1999–2002); Management Committee COST, Chemistry Action D30 "High-Pressure Tuning of Chemical and Biochemical Processes" (2003–2007); International Program Committee of Central European Conferences "Chemistry Toward Biology" (2001 to present), European Society for Photobiology, Scientific Council of the Institute of Catalysis and Surface Chemistry PAS and Polish Chemical Society. She has been awarded by the Polish Chemical Society (1997), Ministry of National Education and Science (1998, 2002), and Rector of the Jagiellonian University. She is the author or coauthor of ca. 100 publications and several reviews, coeditor of a special issue of *Coordination Chemistry Reviews* (1997), and editor of a few monographs. Her research interests are focused on the chemistry, photochemistry, and photophysics of coordination compounds, kinetics and reaction mechanisms, biomedical and bioinorganic chemistry of metal compounds and small molecules (NO, O_2), metal compounds in homogeneous and heterogeneous catalysis, and high-pressure chemistry and biochemistry.

shielding the earth's surface from the most harmful UV. Four hundred million years ago the concentration of ozone reached 10% of the present level and allowed living systems to evolve from aquatic to terrestrial life. Today this ozone layer, with a maximum concentration in the stratosphere at 25 km above sea level, absorbs all solar UV at wavelengths shorter than 290 nm. The radiation energy effective for photobiology lies between 300 and 900 nm. Practically all photobiological behavior of plants and animals—photosynthesis, phototropism, phototaxis, photoperiodism, and vision—utilize this range of radiation.[40,42,43,49]

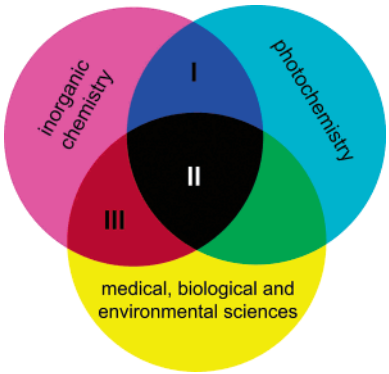

Figure 1. Bioinorganic photochemistry (II) as a part of bioinorganic chemistry (II + III) connects inorganic photochemistry (I + II) with biological, medical, and environmental sciences.

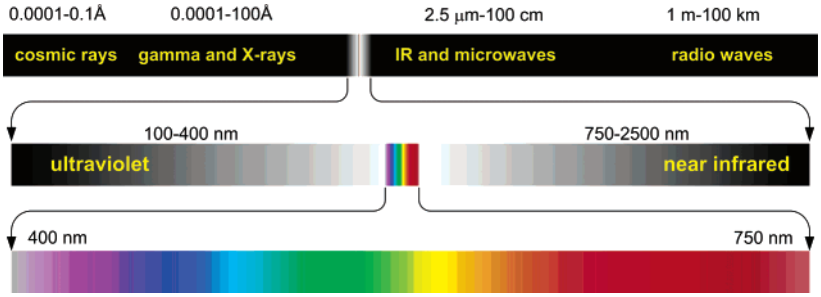

Figure 2. Spectrum of electromagnetic radiation.

Natural photobiochemical processes, as a result of evolution, follow essentially the biologically desirable pathways.[44] In contrast, adventitious photobiochemical processes are likely to follow a multiplicity of pathways and usually find a variety of targets.[44,45] Metal ions and compounds can be involved in both natural and adventitious processes. The mechanisms that underline both types of photoprocesses are highly complex, and their elucidation requires knowledge of the physics of light, the chemistry and structures of a photoacceptor molecule and its microenvironment, as well as physical and chemical processes leading to the final effect.

Light is composed of energy packets called photons that at the same time are energy quanta and bits of information. All phenomena related to the interaction between light and matter and the great number of photochemical and photophysical applications in science and technology can ultimately be traced back to these two aspects of light.[31] The results that can be obtained from the interaction of light with matter depend on the degree of the receiving matter organization. To be useful for solar energy harvesting, organic synthesis, pollutants degradation, therapeutic or diagnostic processes, and others, the systems activated by light must fulfill various requirements.[11,17,31,34,41,43] In this context, inorganic photochemistry has attracted much attention recently as it offers feasible solutions.[14,22−41] There are numerous systems containing various metal ions and compounds which are flexible enough to drive their photochemistry or photophysics toward desired actions. Knowledge of the behavior of such systems is useful for a better understanding of the natural phenomena and designing various molecular devices of medical, biochemical, or environmental importance. Metal complexes exhibit a high level of organization, and therefore, they are quite useful as components of molecular level photochemical devices. Moreover, a variety of transition-metal-based supramolecular systems or heterogeneous nanoassemblies supplemented with transition-metal compounds can be carefully designed to perform desired functionalities such as energy conversion, molecular sensing, labeling, switching, catalysis, etc.[11,14,17,33]

Photochemical processes induced by sunlight or artificial light sources are often damaging to biological systems, especially when suitable photoprotective mechanisms are absent or insufficient. Typical examples are represented by photocarcinogenesis and the photoinduced generation of pollutants. In many cases there is a possibility to take advantage of the damaging action of light in order to obtain beneficial

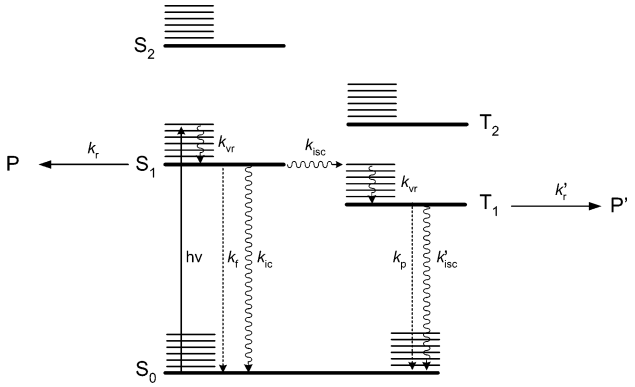

Figure 3. Jabłoński diagram.

effects. Achieving this goal requires again a detailed knowledge of the mechanisms involved in given photoprocesses, so that their progress can be strictly controlled and their intermediates and ultimate actions directed toward defined targets.

Some specific aspects of light and metal compound interactions in bioscience and biotechnology have been reviewed recently.[24−32,37−39,41,46−48] The aim of this review is to give a brief overview of various frontiers in *bioinorganic photochemistry* underlying mechanisms involved in the studied or applied systems.

2. Inorganic Photochemistry: From Transition-Metal Complexes to Supramolecular Systems and Nanoassemblies

Photochemistry is the chemistry of excited electronic states. The change in electron distribution due to photon absorption can cause substantial modifications in the chemical and physical properties of a molecule. Among these properties the energy, molecular geometries, polarizabilities, dipole and magnetic moments, and related redox and acid-based properties can change on passing to excited states. Fundamental properties of a photochemical process can be discussed according to Figure 3. In a molecule in condensed phase photon absorption ($h\nu$) is followed by a rapid vibrational relaxation (vr) which, in less than a picosecond, causes the molecule to reach an equilibrium geometric configuration corresponding to its electronic excited state (S_1). In every excited state there is a competition between physical, radiative (f = fluorescence, p = phosphorescence), nonradiative (ic = internal conversion, isc = intersystem crossing), and chemical reaction r modes of deactivation. For example, the number of molecules in the S_1 state,

which gives rise to the reactions (thus forming product P) is proportional to $k_r/(k_r + k_f + k_{ic} + k_{isc})$. This represents the quantum yield (Φ) of the reaction itself

$$\Phi = \frac{\text{molecules undergoing the processes}}{\text{photons absorbed by the molecules}}$$

The chemical reactions which give rise to products P and P′ can arise from all excited states. However, most photochemical reactions take place from the lowest energy excited states (S_1, T_1) because lifetimes of molecules at these states are longer as compared to those of higher energy. Intermolecular energy exchange from one species to another, leading to excitation of a species other than the absorbing one (sensitization), can be used to promote chemical change that may not be possible through direct absorption. The different route to excitation may lead to a population of excited states that is inaccessible by direct absorption. Thus, unsensitized and sensitized photochemistry may be quite different.

During the past decades inorganic photochemistry, which extends from simple Werner transition-metal complexes through supramolecular and multimetallic systems to homogeneous and heterogeneous nanoassemblies, has attracted increasing interest in various fields of science and technology including bioscience and biotechnology.[7−48]

One of the tremendous advantages of photochemical activation of transition-metal complexes is generation of electronic excited states under very moderate reaction conditions. These states are ca. 100 kJ mol^{-1} higher in energy than the activation energy of the usual chemical reactions of metal complexes.[16] Transition-metal complexes distinguish themselves from organic compounds both by the number of accessible electronic excited states and their spin multiplicity. Consequently, depending on the wavelength (energy) of irradiation, optical excitation leads to various electronic excited states of different reactivity. In some favorable instances this behavior allows tuning of photochemical reactivity and switching between various pathways such as electron transfer (preferably due to the population of diverse charge transfer states; CT), dissociation/substitution/rearrangement reactions (caused by excited ligand-field states; LF), and ligand-centered reactivity due to the population of intraligand states (IL). The great variety of available electronic excited states may be used for photogeneration of coordinatively unsaturated species, transition-metal compounds with changed formal oxidation number as well as free ligands and ligand redox product formation. Such species generated photochemically not only can take part in stoichiometric processes but open new pathways into both light-induced catalytic reactions and chain processes.[16,22] Two limiting cases of photocatalysis, photoinduced catalytic and photoassisted reactions, can be distinguished. Photoinduced catalysis is the photogeneration of a catalyst that subsequently promotes a catalyzed reaction. Photoassisted reactions include interactions between electronic excited states or short-lived intermediates and substrate molecules leading to product formation under the concomitant regeneration of the starting complex in its electronic ground state. The activation of transition-metal complexes by visible and UV light provides definite advantages when compared to the usual thermal activation. Catalysts are formed photochemically within one reaction step and are usually generated with high selectivity. Moreover, their constitution may frequently be identified very easily. The strategic synthetic design of transition-metal complexes or organometallic compounds as well as the choice of the irradiation wavelength (ligand field, charge transfer, and intraligand excitation) allows modeling of photoinduced catalytic or photoassisted reactions. Photocatalytic reactions can be carried out at ambient temperature and pressure. However, photochemical side reactions, fast back electron transfer, and recombination may considerably limit the efficiency of photocatalytic reactions. The photochemical decomposition of the catalyst may further lead to fast termination of photocatalytic cycles. To utilize the broad-band solar energy spectrum it is necessary to involve some spectral sensitization.[16,22]

Supramolecular systems are constituted of a number of discrete molecular components with definite individual properties held together by various interactions. In natural systems the molecular components are very often assembled by intermolecular forces (hydrogen bonds, donor−acceptor interactions, van der Waals forces, etc.), whereas in artificial systems covalent or coordination bonds are used to achieve a better control of the supramolecular structure.[21,31,51] Supramolecular systems began the concept of molecular devices, assemblies of molecular components designed to achieve specific functions, such as photoinduced electron and energy transfer in solar energy conversion, electron collection, photosensitization, antenna effect, photoswitching of electric signals, light-energy conversion, photoinduced structural changes in switch on/off applications (photoisomerizable systems, molecular wires, and sensors).[11,17,22,31,33,51] The development of supramolecular chemistry has allowed construction of structurally organized and functionally integrated chemical systems capable of elaborating the energy and information input photons to perform complex functions. During the past decade research on transition-metal supramolecular systems has experienced extraordinary progress. In terms of bonding strength, the moderate coordination bonds between transition metals and ligands are between strong covalent bonding in carbon-based systems and weak interactions in biological systems. Some advantages of employing transition metals to build supramolecular systems include the following: (i) involvement of d orbitals which offer more bonding modes and geometric symmetries than simple organic molecules; (ii) a range of electronic and steric properties which can be fine-tuned by employing various ancillary ligands; (iii) easily modified size of the desired supramolecules by utilizing various lengths of bridging ligands; and (iv) incorporation of their distinct spectral, magnetic, redox, photophysical, and photochemical properties.[46] Moreover, the diverse bonding angles imported by the transition-metal centers and the high directionality of the bonding between the ligands and metals also

provide superior features over weak electrostatic, van der Waals, and $\pi-\pi$ interactions. Another interesting aspect is that thermodynamically driven spontaneous self-assembly of individual molecular components into well-defined molecular structures in solution is expected to be rather similar for both coordination chemistry and biology, and this enables transition-metal complexes to be valuable mimics of the more complicated biological systems.[46,51]

Nanostructured materials offer many new opportunities to study fundamental processes in a controlled manner, and this in turn leads to fabrication of numerous photonic and optoelectronic devices.[11,17] The design of photochemical molecular devices requires the ability to organize molecules on a nanometric scale with the fine control of their arrangement/distribution, mobility, and spectral and redox properties. Several types of heterogeneous multiphase systems have been proposed and tested. Mesoporous membrane-type films with a large surface area can be prepared from nanosized colloidal semiconductor dispersions. Nanocrystalline semiconductor films of oxide or chalcogenide particles such as TiO_2, ZnO, ZnS, Nb_2O_5, WO_3, Ta_2O_5, CdS, CdSe, and CdTe have been used for that purpose.[17] By suitable molecular engineering the metal complexes can be readily attached to the surface. These films with anchored photoactive complexes find increasing use in energy-conversion devices such as dye-sensitized photoelectrochemical solar cells, intercalation batteries, optical displays, and optical sensors.[17,19,20] For application in photonic and optoelectronic devices, the photoactive component has to meet several stringent requirements. The first is the intensity and spectral range of light absorption in the UV, visible, and near-IR regions. The second is tunability of the absorption band. The third are photophysical properties: types and number of accessible excited states and their lifetimes and quantum yields of radiative and nonradiative decays. The fourth are redox properties of the ground and excited states. For redox sensitizers or redox mediators there are further requirements of stability of the both redox forms and reversibility of the redox processes. In all cases transition-metal complexes with polypyridines or polypyrrolic macrocycles as ligands come out clearly as the sensitizers of preferred choice.[17]

Application of inorganic photophysics generates challenging new areas in bioscience and biotechnology. Optical and, especially, fluorescence spectroscopy are widely used research tools in biochemistry, molecular biology, and environmental studies. Fluorescence has also become the dominant method enabling the revolution in medical diagnostics, DNA sequencing, and genomics. To date, all fluorescence observables, including spectral shifts, anisotropies, quantum yields, and lifetimes, have found both scientific and analytical applications.[36] Lakowicz, in his forward-looking paper,[37] describes new opportunities in fluorescence and radiative decay engineering, e.g., modification of the fluorophores emissions by changing nonradiative decay rates. Transition-metal complexes have many potential advantages including numerous excited states of long lifetimes and high luminescence quantum yields.[37,38,46−48,52] Luminescent polynuclear transition-metal complexes containing multichromophoric ligands with extended conjugation have been extensively studied in recent years, partly because of their potential use as sensors, probes, and photonic devices.[23,46] Many are easily excited by visible light with low-cost light-emitting diodes (LEDs) or inexpensive red diode lasers. They show large spectral shifts between the excitation and emission bands which minimize the difficulty of isolating the excitation and emission wavelengths. Long lifetimes allow efficient time discrimination from the ubiquitous background fluorescences. Importantly, the longer lifetimes also allow the excited state ample time to sample its environment, making these materials particularly sensitive reporters.[29,38,47,48]

3. Light and Metal Compounds in Medicine

Light is essential to our health and useful as a tool in therapy, diagnosis, and preventive medicine.[34,40,42] There are many beneficial effects of sunlight on the body, from warmth to recovery from depression. One of the most important functions of light is transmission of information about the environment enabling spatial orientation and motion. Photoreceptor systems affect growth, hormonal stimulation, clocking mechanism, and others. A well-known example of the positive light effect is the photosynthesis of vitamin D upon exposition to UV components of sunlight. Unfortunately, light, in particular sunlight, can also be hazardous to our health. Prolonged exposure to the sun produces sunburn, the result of UV radiation on the human skin. This can cause premature aging, while prolonged sunburn can even lead to skin cancer.[42,53−55]

Although light has been used for medical purposes since ancient times, we have just begun to explore and understand the medical potential of light. Light can bring the desired biological effects by acting either directly on tissue, where endogenous species such as proteins, nucleic acids, or other molecules absorb light and undergo changes, or indirectly via an administrated exogenous species which there are effective light absorbers. Modern phototherapy is generally considered to be originated by Finsen, who at the end of the 19th century treated tubercular conditions of skin with heat-filtered light from a carbon arc lamp,[44] and for this innovation he was awarded a Nobel Prize in 1903. The direct use of light as a therapeutic agent is currently important in the treatment of vitamin D deficiency, neonatal jaundice, autoimmune system diseases, manic depression, and others. The sequence of events leading to the therapeutic effect of indirect phototherapy starts with the absorption of light by an administered drug. Subsequently, the photoexcited drug molecule can undergo a number of primary processes, such as photochemical reactions of the drug itself, photoreactions with endogenous molecules, energy or electron transfer. The use of light and exogenous dyes to treat medical conditions can be traced back to ancient Egypt and Greece, where vitiligo was treated with the combination of orally ingested psoralen-containing plants and sunlight. At the very beginning of the 20th century

the term "photodynamic therapy" was introduced into specialized literature.[56] Nowadays, one of the most active research fields of indirect phototherapy is the photodynamic therapy of tumors. In the beginning photomedicine was focused mainly on cancer and dermatological diseases treatment. Now it is obvious that several new areas of application have become accessible for this young field of medicine. Photomedical methodologies have the intrinsic advantage of dual selectivity since the photoprocess is the result of the combined effect of two factors: light and the photoactive chromophore. Photomedicine extends nowadays to such different fields as phototherapy, photodiagnosis, phototargeting, photodelivery, photoprotection, etc.

The unique properties of metal compounds, especially very rich photochemistry and photophysics of transition-metal compounds, make them suitable candidates for selected applications in photomedicine.[5,6,24,25,27,29,30,32] Metal ions or metal compounds important for our health are of both endogenous and exogenous origin.[1−6,32,57,58] Endogenous metal compounds are required for many critical processes such as respiration, much of metabolism, development, neural transmission, muscle contraction, signal transduction, gene expression, protection against toxic and mutagenic agents. Exogenous compound can be introduced into the organism through the diet, via interaction with the environment, or in order to induce a predetermined alteration of the system. It is notable that some organic pharmaceuticals or pollutants may be directed toward metal targets in the body or require metal binding to function. The biological activity of metal complexes depends on the metal, its ligands, or both. Light can interact with biologically and medically important metal ions and complexes in vivo or in vitro. These interactions can be both controlled and uncontrolled, bringing positive (physiological, therapeutic, diagnostic, etc.) or negative (pathological, toxic, etc.) effects.[25−28,32,58]

3.1. Cells, Tissues, and Light

Light upon interaction with a tissue surface can be reflected, scattered, transmitted, or absorbed (Figure 4) depending on optical features of the tissue and on the light properties (absorption coefficient, photon energy, power density, exposition time, etc.). Light propagation in the tissue is affected by scattering occurring at inhomogenity sites e.g., membranes, nuclei, etc. Also, the presence of water and highly absorbing endogenous dyes such as melanin and hemoglobin strongly influences light penetration depth into the tissue. Therefore, light penetration depth is highly dependent on the tissue type; however, in the case of most tissues light of the spectral range 600−700 nm penetrates 50−200% deeper than light of the range 400−500 nm.[59,60] The maximum of skin permeability occurs in the range of ca. 620−850 nm; thus, light of this spectral range (so-called "phototherapeutic window") is predominantly used in phototherapy (Figure 5).

Nowadays there are various artificial light sources. Their choice is determined by the lesion location, the spectral range, and the light power density and dose

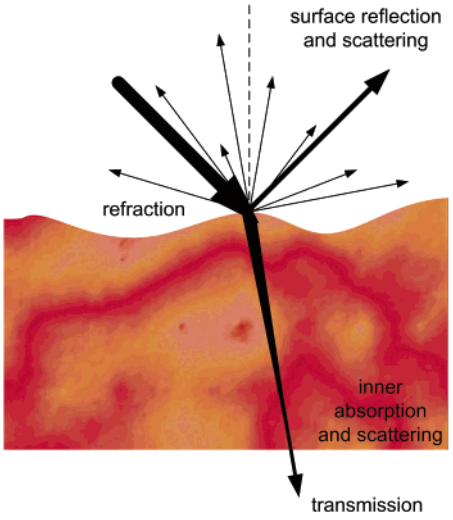

Figure 4. Light interactions with a tissue.

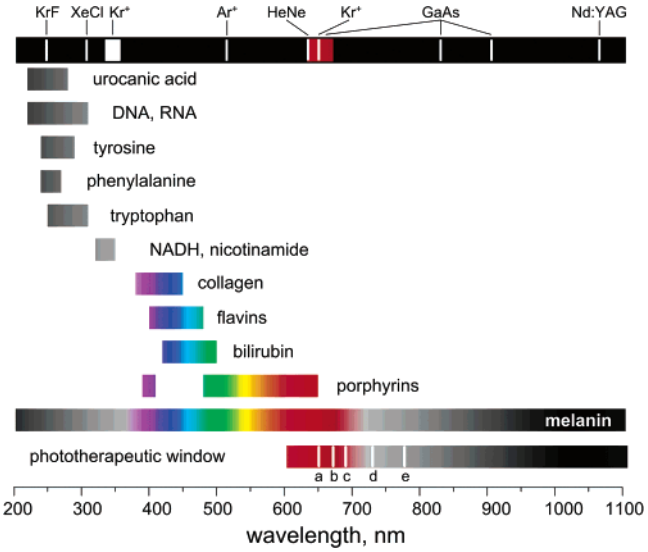

Figure 5. Medically relevant spectral characteristics of common lasers, endogenous chromophores, the phototherapeutic window, and exogenous photosensitizers: substituted porphyrins (a), chlorin (b), phthalocyanine (c), bacteriochlorin (d), and naphthalocyanin (e).

to be delivered. The most common coherent light sources include argon and argon-pumped lasers, metal vapor-pumped dye lasers, solid-state lasers, and optical parametric oscillators lasers.[61] There are several types of the noncoherent light sources such as halogen lamps, xenon arc lamps, metal halide lamps, phosphor-coated sodium lamps, and fluorescent lamps. Two novel light sources—light-emitting diodes (LED) and femtosecond solid-state lasers—may find applications in the future.[59] Although lasers are the most commonly used devices for treatment, noncoherent light sources have become more and more popular because of their price and simplicity of handling. Instead of a high-intensity monochromatic light emitted by lasers, lamps support high-intensity light distributed over a broader spectral range. Since the lamp cannot be easily coupled with small optic fibers without significant loss of its output power, applications of lamps have been limited to irradiation of wide skin lesions, whereas lasers are used for endoscopic purposes also.[59,62]

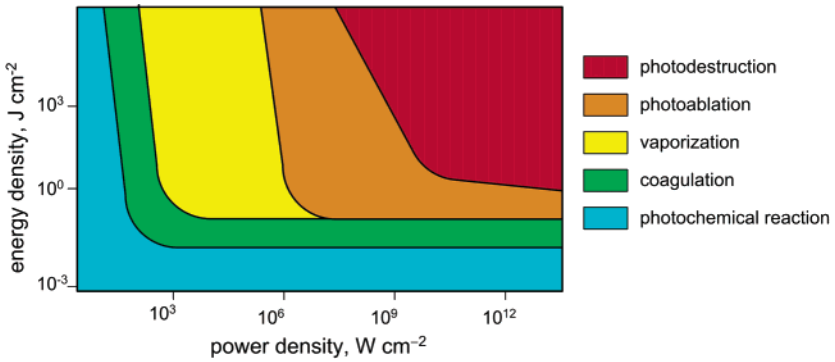

Figure 6. Types of laser radiation interactions with a tissue. (Adapted from refs 60 and 105.)

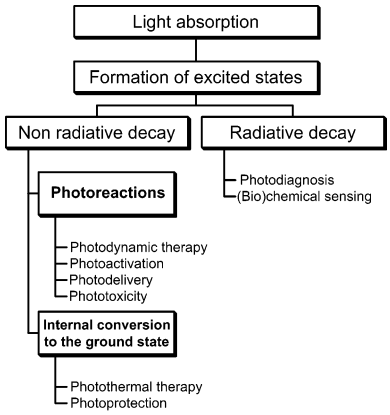

Figure 7. Application of photophysical and photochemical processes in photomedicine.

Generally, there are three main types of interactions between laser radiation and tissue (Figure 6) depending on the irradiation power density and irradiation time: photochemical (biostimulation, phototherapy), thermal (coagulation, vaporizing, and photoablation), and electromechanical (photodestruction). All of these effects are used in medicine. The most frequently used mechanism of the photon-energy conversion in laser medicine is heating. Local heating of irradiated samples occurs with all the other effects (cutting, vaporization, coagulation, and ablation).[61] At low light intensities the photochemical conversion of energy absorbed by a photoacceptor prevails.[63] This type of reaction is well known for specialized photoreceptor pigment species such as rhodopsin. In medicine, light absorption by nonspecific photoacceptor molecules is used rather extensively. Photoexcitation of endogenous or exogenous chromophores can result in either the re-emission of light (this may be used in photodiagnosis) or partial conversion of the absorbed radiation into thermal or chemical energy (Figure 7). The last two processes generate photothermal and photochemical sensitization, respectively, leading to the irreversible damage of cells and tissues; hence, they can be used for phototherapeutic purposes. The efficacy and scope of photodiagnostic and phototherapeutic techniques improve as knowledge about the influence of biological microenvironments on the mechanisms of photoprocesses is developed. New approaches are developed for controlling the biodistribution of photosensitizing agents in vivo and the depth of incident light penetration into tissues. In particular, even the localized and sublethal damage of cells can often be modulated to generate intracellular signaling in order to either induce a programmed cell death (apoptosis) or accelerate cell metabolism (photostimulation).[63]

Irradiation of cells in the range of 380−1000 nm in the absence of an exogenous dye can alter the whole metabolism by activation of some cellular native components.[63,64] Irradiation can activate or inactivate enzymes,[65−72] induce an electron transfer and in consequence folding of proteins,[73,74] cause topical heating (e.g., heme),[75] generate superoxide anion and singlet oxygen,[63] or have a biostimulating effect[64,76] by affecting the redox chain in mitochondria.[63] Low-energy and low-intensity optical irradiation has stimulating effects on various biological systems. Irradiation of blood vessels induces local vasodilatation, which results in improved microcirculation and therefore improved blood supply in organs. Moreover, several effects are observed on cellular and subcellular levels: (i) increased activity of lysosomes and phagocytes, (ii) enhanced cell division and growth, (iii) activation of the proteins and cytokines synthesis. These beneficial effects are widely used in various fields of medicine. Some of those effects can be associated with the photochemistry of metal-containing biomolecules, like superoxide dismutase, nitric oxide synthase, or nitrosohemoglobin.[77] Such visible and near-infrared light absorption by nonspecialized photoacceptor molecules is also used in medicine in so-called low-level laser radiation therapy[64,78] for pain treatment,[79] in stimulation of collagen synthesis,[80] as well as in photothermolysis.[75] Photothermolysis requires several visible-light-absorbing endogenous chromophores (e.g., heme, melanin) usually devoid of photodynamic activity. The radiationless decay of their excited states leads to heat evolution. The highly localized hyperthermal effect can induce important chemical (e.g., bond cleavage) and mechanical (e.g., ultrasonic shock) damage of the biological system.[81] Selective photothermolysis with oxyhemoglobin as the molecular target allows the treatment of some epidermal and dermal lesions such as port-wine stains[82,83] and chronic plaque psoriasis.[84] This therapy is limited to treatment of pigmented or highly vascularized tissues. Recently it has been proved that nitrosyl−hemoglobin (Hb−NO) may be one of the possible targets for visible light in the systemic blood.[85] Laser light irradiation at the Soret band leads to NO release in both Hb−NO solution[86] and red blood suspensions.[85] NO released from the nitrosyl complex may cause vasodilatation in vivo (vide infra).

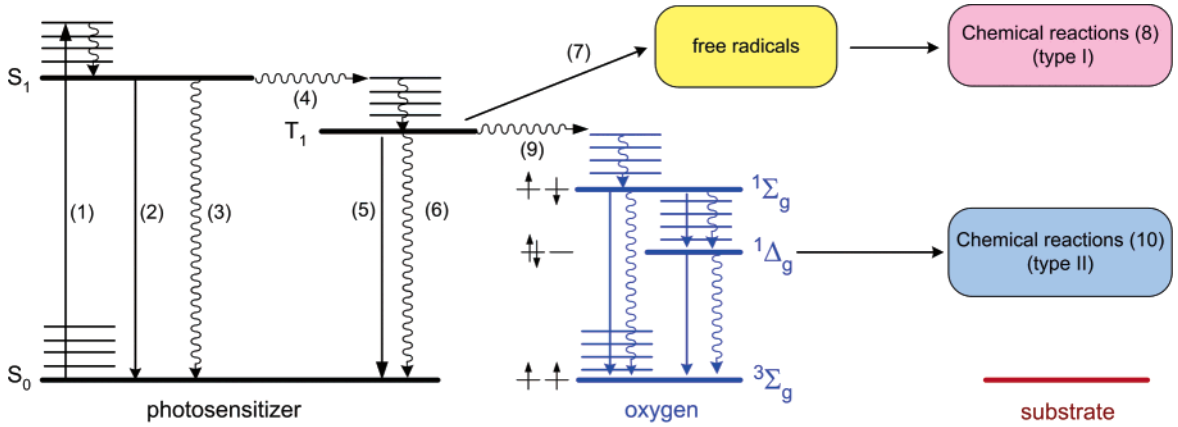

Figure 8. Physical and chemical processes involved in PDT (7−9), PTT (3, 6), and PD (2, 5).

3.2. Photodynamic Therapy, Photothermal Therapy, and Photodiagnosis

Careful design of the exogenous photoactive molecule together with extensive photophysical and photochemical studies enables excited-state engineering and channeling the excitation energy in vivo to the desired mode of action (Figure 7).[37,87] Thus, in photodiagnosis (PD; also called "photodynamic diagnosis" (PDD)), widely used in clinical detection of cancer lesions,[88−90] the photoactive molecule re-emits the excitation energy as fluorescence. During photothermal therapy (PTT) the excited photoactive molecule undergoes internal conversion to the ground state, leading to local heating of the tissue.[75] Excitation of the photoactive molecule can also induce different types of photoreactions including the direct photoactivation of a pharmaceutical (see section 3.3.) or its indirect photodynamic action. The latter so-called photodynamic effect is used in photodynamic therapy (PDT), which is one of the most promising anticancer therapies still under investigation.[25,44,90−92] The photodynamic effect has been also applied in antimicrobial therapies and blood sterilization.[93,94]

3.2.1. Mechanisms

The detailed photophysical processes involved in PD, PDT, and PTT are illustrated in Figure 8. The electronic ground state of the photosensitizer is a singlet state (S_0). Upon light absorption the photosensitizer is excited to a short-lived first excited singlet state (S_1) (1). The photosensitizer can return to the S_0 state by emitting the absorbed energy as fluorescence (2) or internal conversion (3). Alternatively, S_1 can undergo conversion (with a reasonably high quantum yield) to the first excited triplet state (T_1) by intersystem crossing (4). From the T_1 state the photosensitizer can also release energy by emitting phosphorescence (5) or return to the ground state through a nonradiative path (6). The sufficiently long-lived T_1 state is able to take part in chemical reactions based on electron (or hydrogen) transfer (7) with generation of radical intermediates involved in photodynamic reactions of type I (8). Energy transfer (9) from the triplet state of the photosensitizer to a suitable acceptor, most frequently oxygen, results in generation of highly reactive singlet oxygen involved in photodynamic reactions of type II (10). Radical intermediates (mainly reactive oxygen species (ROS)) and singlet oxygen are highly cytotoxic agents. In most cases the type II mechanism is dominant in PDT.[95,96] However, the type I reactions are most efficient at low oxygen and high substrate concentrations.[97] Photosensitizers should also act as catalysts, i.e., their ground state should be ultimately regenerated. Otherwise, "photobleaching" (destruction of the absorbing chromophore) is generally observed upon irradiation.[98]

PDT in vivo acts through at least three principal modes: (i) direct cell killing by lethal oxidative damage of tumor cells (necrosis, apoptosis); (ii) indirect cell killing due to photodynamic damage or shutdown of the (neo)vasculature with loss of oxygen and nutrients supply to the tumor; and (iii) additional antitumor contributions from the inflammatory and immune responses.[99] There are many organelles such as cellular membranes, nuclei, mitochondria, and others which can be affected by photogenerated reactive species. In consequence, apoptosis, necrosis, or a combination takes place.[95,100,101]

3.2.2. Photosensitizers: General Remarks

The choice of a photosensitizer and its subsequent phototherapeutic effect depends on its physicochemical properties in the ground and excited states, pharmacokinetic and pharmacodynamic behavior, and photoactivity in vivo.[25,32,102] A good photosensitizer should be a single substance with constant composition and a high degree of chemical purity, nontoxic in the dark, and sufficiently stable under physiological conditions. It should show intensive absorption bands within the phototherapeutic window (ca. 620−850 nm), but its absorption in the range 400−600 nm should be as low as possible. This requirement is necessary to avoid prolonged skin sensitivity toward solar irradiation following drug administration. As the efficiency of PDT photosensitizer depends on the photophysical properties of the first excited triplet state, this state should be generated with a high quantum yield and have an appropriate energy and long enough lifetime to allow efficient energy or electron transfer to the oxygen molecule. The photosensitizer must be photostable, and it should not be easily oxidized by singlet oxygen or other ROS generated in situ. It should be selectively accumulated into malignant and easily re-

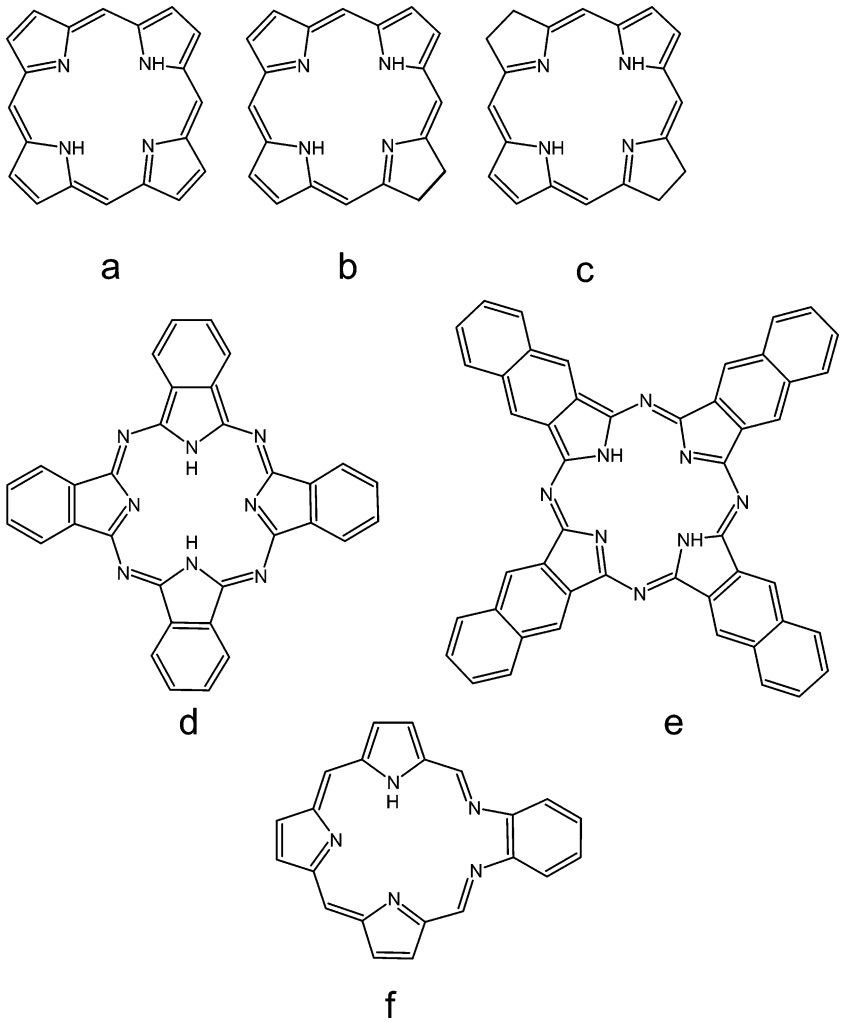

Figure 9. Skeleton structures of polypyrrolic photosensitizers: (a) porphyrin, (b) chlorin, (c) bacteriochlorin, (d) phthalocyanine, (e) naphthalocyanine, and (f) texaphyrin.

moved from healthy tissues. The amphiphilic character of the compound is advantageous, enabling its accumulation and acting both in membranes and physiological fluids.[25,60,87,91,103−105] When PD applications are concerned, it should exhibit an intensive fluorescence, whereas for PTT purposes the internal conversion to the ground state should dominate.

The first-generation photosensitizers are based on chemically modified natural hematoporphyrin.[102,106] They possess certain limitations such as weak absorption in the phototherapeutic window as well as a relatively poor specificity of uptake and retention with respect to malignant and healthy tissues. In addition, they cause prolonged skin photosensitivity (usually 2−3 months).[107] Subsequent extensive research helped to develop modern photosensitizers of the second and third generations. The second-generation PDT sensitizers are mainly based on engineered, synthetic, and semisynthetic porphyrins with various substituents at at the pyrrole rings and the methylene bridges.[32,108] They are structurally homogeneous compounds with long-wavelength absorption bands of high intensity. Thus far many compounds have been tested as potential photosensitizers for application in PDT.[25,32,102] They can be divided into five groups: organic dyes (eosin, rose bengal, methylene blue), aromatic hydrocarbons (naphthalenes, anthracenes, biphenyls, quinines), polypyrrolic and metallopolypyrrolic compounds,[25,32] transition-metal complexes (see section 3.2.4), and semiconductors (see section 3.2.5).[103] The third-generation photosensitizers consist of the photosensitizer moiety linked to biomolecules such as monoclonal antibodies, polypeptide chains, proteins, etc., which allow their selective delivery.[109] This strategy overcomes difficulties in molecule recognition and specific binding to the tumor.

Nowadays, the most investigated photosensitizers are various porphyrins, chlorins, bacteriochlorins, phthalocyanines, naphthalocyanines, and texaphyrins (Figure 9).[32,102,104] Photosensitizers currently approved for clinical use belong to various groups. The first accepted photosensitizer is Photofrin, which is a mixture of hematoporphyrin monomers, dimers, and oligomers. Other photosensitizers consist of a precursor of protoporphyrin IX−5-aminolevulinic acid (Levulan) and its methyl (Metvix), hexyl (Hexvix), and benzyl (Benzvix) ester derivatives. The synthetic *m*-tetrahydroxyphenylchlorin (*m*THPC, Foscan) as well as the luthetium texaphyrin complex (Lutex, Motexafin Lutetium) have been already accepted for clinical applications.[104]

3.2.3. Macrocyclic Photosensitizers Modified by Metal Ions

In the case of many polypyrrolic photosensitizers, inserting a metal ion (through metalation, transmetallation, or template synthesis) seems to be an obvious way to change the properties of the compound and causes various therapeutic (photodynamic vs photothermal) or diagnostic effects (cf. Figure 7) by changing the properties of both the ground and the excited states of a compound.

In this way not only can the photophysical and spectroscopic properties of the photosensitizer be modulated, but also their hydrophobicity, degree of aggregation, stability, and consequently route of photosensitizer transport into the cell and further distribution as well.[25,97] Generally, the properties of compounds with a porphyrin or porphyrin-like skeleton in both the ground and the excited states are affected by the electronic configuration of the central metal ion. The properties of these compounds containing metal ions with d^0 or d^{10} configurations (closed shell) are determined essentially by the π electrons of the tetrapyrrolic ring with only minor perturbations from the electrons of the central ion. In contrast, in the case of metal ions with not fully occupied d orbitals (open shell), the d electrons can significantly integrate with the π and π^* orbitals of the macrocycle.[110,111]

Ground-State Properties.

Stability. Generally, metalloporphyrins and metallophthalocyanines are thermodynamically stable. Considering different polypyrrolic ligands, the stability of the corresponding metallocomplexes decreases in a series: phthalocyanines > porphyrins > chlorins. Texaphyrins are capable of coordinating larger cations because of the expanded cavity of a central hole. To asses the thermodynamic stability of metalloporphyrins, the empirical "stability index", $S_i = 100\chi(Z/r_i)$ (where χ = Pauling electronegativity, Z = oxidation number, r_i = effective ionic radius (pm) of a central metal ion), was suggested by Buchler.[112] It includes both the covalent bonding capacity and electrostatic interactions. Accordingly, metal complexes with high values of χ and Z and small r_i, such as, e.g., Ru^{III}, Al^{III}, and Sn^{IV}, are more stable than these of low χ and Z and big r_i (e.g., Mg^{II}, Cd^{II}).[25] The other effect with a large impact on the stability of porphyrins and porphyrin-like systems is susceptibility to one-electron oxidation. The redox properties of metalloporphyrins and metallochlorins depend significantly on the nature of the coordinated metal ion and have been linearly correlated to χ.[113] Generally, complexes of metals of a higher positive charge exhibit higher half-wave potentials for ring oxidation. For metal ions with the same charge, various effects are observed, e.g., Pd^{II}(tpp) ($E_{1/2}$ = 1.02 V) is harder to oxidize than the free base ($E_{1/2}$ = 0.95 V) in contrast to Mg^{II}(tpp) ($E_{1/2}$ = 0.54 V) and Cd^{II}(tpp) ($E_{1/2}$ = 0.63 V).[25,114] Thus, inserting of a metal ion into the porphyrin ring influences its susceptibility to photobleaching during PDT.

Aggregation. In general, porphyrin and porphyrin-like compounds have a tendency to aggregate, causing a decrease of singlet oxygen generation and a reduction of the photosensitizing efficiency of a compound.[115] The presence of additional ligands in the axial position obviously influences, both electronically and sterically, the environment of a metal complex. The presence of closed-shell metal ions, which can support octahedral d^2sp^3 hybrid orbitals (e.g., Zn^{II}), guarantees a reasonable yield of $^1O_2$ generation because axial ligands generate steric hindrance to intermolecular aggregation. Additionally, if the ligand is hydrophilic, the solubility of the complex in aqueous phases is enhanced, which is important as the amphiphilic character of the photosensitizer is advantageous for PDT.

Selectivity. The selectivity of photosensitizers can also be affected by the central metal ion and substituents at the macrocycle. For instance, tetrasulfonated chloroaluminum phthalocyanine [Al(pcS_4)Cl] localizes well in the tumor, while tetrasulfonated zinc phthalocyanine [Zn(pcS_4)] (and disulfonated zinc phthalocyanine [Zn(pcS_2)]) shows a relatively poor tumor localization.[116] The sulfonated aluminum phthalocyanines are in clinical trials for treatment of breast, mouth, lung, skin, and pharyngeal cancer, as well as zinc phthalocyanines are in trials for photodynamic therapy of skin cancers.[102]

UV−Vis Absorption Spectra. The main effect of the metal on the spectrum comes from conjugation of its d electrons with the π electrons of the ring. Complexation of a metal ion by the porphyrin macrocycle causes strong charge transfer and electrostatic interactions.[111] Porphyrins with the central metal, which have a d^0 or d^{10} electronic configuration, show a three-banded spectra (α, β, Soret). The α-band is localized within the range 570−630 nm, while the Soret band is in the region 395−405 nm.[117] The lowest energy β band shows a hypsochromic shift induced by metal ions.[32] The absorption spectra of chlorins and chlorophylls are characterized by a strong Soret band close to 400 nm, a relatively strong—as compared to the fully unsaturated porphyrins—Q_y band around 660 nm, and two weak bands in the central part of the visible spectrum.[113] Metal coordination by chlorophylls results in a hypsochromic shift of the Q_y band. In the case of metal-substituted bacteriochlorophylls, four bands are observed: B_y (~330−370 nm), B_x (~380−390 nm), Q_x (~520−610 nm), and Q_y (~750−780 nm). The most important for photodynamic therapy one, the Q_y band, is slightly affected by coordination of various metals.[113] The insertion of a metal to purpurin (e.g., tin) causes a red shift of about 20−30 nm, in contrast to porphyrins where a blue shift is observed upon metalation.[118]

Excited-State Properties.

Emission. The fluorescence properties of metalloporphyrin and porphyrin-like compounds depend on the character of the central metal ion. Fluorescence of porphyrins is generally observed from the free base or closed-shell metal complexes. The longest fluorescence lifetime (τ_F) and its high quantum yield (Φ_F) are observed for the first- and second-row elements (e.g., Mg, Al) and decrease going to the third-row elements (e.g., Zn). Both τ_F and Φ_F are significantly decreased in the case of the fourth-row elements (e.g.,

Cd, In). This is caused by spin−orbit coupling on the central atom, which increases intersystem crossing. Complexes with open-shell central metals can be divided into three groups. One contains complexes of the second- and third-row transition-metal ions such as Ru^{II}, Pt^{II}, and Pd^{II} which are diamagnetic and show an intense phosphorescence. The second group covers the first-row transition-metal complexes (e.g., Cu)—luminescent and paramagnetic, whereas the third group contains nonluminescent complexes of Ni^{II}, Co^{II}, Fe, and others. Emission is not observed because of the enhancement of internal conversion to the ground state.[110] For metal-substituted bacteriochlorophylls (Pd^{II}, Co^{II}, Ni^{II}, Cu^{II}, Zn^{II}, Mg^{II}, Cd^{II}, and Mn^{II}), no emission was detected for Co^{II}, Ni^{II}, Cu^{II}, and Mn^{II}.[119] Fluorescent photosensitizers have the advantage of being therapeutic agents and diagnostic tools at the same time, which allows monitoring therapy progress. Water-soluble lutetium(III) texaphyrin complex has been proved to be an excellent fluorescent marker for tissues, such as atheromatous plaque and tumors.[120,121] It is also an efficient generator of singlet oxygen.[122] [Lu(tex)$(OAc)_2$]-mediated phototherapy was shown in an experimental fibrosarcoma tumor model to be highly selective for tumor microvasculature while leaving the normal vessels in the surrounding tissue unharmed.[123]

IC and ISC Quantum Yield. Introduction of a heavy metal ion strongly affects intersystem crossing in the complex via enhancement of spin−orbit coupling, which influences the formation and decay of triplet states. As a result, the rate of intersystem crossing is enhanced. In extreme cases, as in, e.g., Pt^{II}-porphyrins, it results in intense phosphorescence even at room temperature, which can be used in optical sensors for oxygen in vivo.[124] In series of bacteriochlorins, short S_1 lifetimes (H_2bchl = 2.6 ns; [Zn(bchl)] = 2.1 ns; [Pd(bchl)] = 65 ps) result from an efficient intersystem crossing to the triplet state, leading to an increase of triplet quantum yields: 76%, 85%, and >99%, respectively.[125] Recently, the palladium(II) derivative of bacteriochlorophyll was shown to be photodynamically active in vivo on rat C6 glioma xenografts.[126] In the case of open-shell metal ions, the d electrons can significantly integrate with the π and π^* orbitals of the macrocycle. In consequence, the triplet excited states of these compounds are usually short lived and the quantum yields of the triplet state formation are very low. This effect can be observed, e.g., in the case of Ni^{II} (d^8)-substituted bacteriochlorophyll where the excited-state lifetime is extremely short (less than 40 fs) compared to Mg−bacteriochlorophyll (tens of microseconds) due to an enhanced internal conversion rate.[127] Such dyes exhibit photophysical and photochemical features which appear to be optimal for photothermal sensitization. A high molar extinction coefficient, a very low quantum yield of fluorescence, and a short-lived (picosecond range) and low-energy triplet state predestinate these materials for PTT. Among them porphyrinoid dyes with paramagnetic transition-metal ions constitute a large group of well-characterized compounds.[128−130] Vibrational de-excitation of the triplet excited states generates locally heat, which may induce local "selective cooking" of malignant tissue.[131] In this context the use of Cu^{II}-hematoporphyrin, a chromophore that is devoid of any appreciable photodynamic activity, for photothermally sensitized inactivation of amelanotic melanoma cells by irradiation at 532 nm, was reported.[132] Natural dyes used in PTT include hemoglobin and melanin, while only a few synthetic dyes have been studied. Semisynthetic Cu^{II}-hematoporphyrin and indocyanine green are believed to act through the PTT mechanism.[132] Ni^{II}-octabutoxynaphthalocyanine [Ni(nc$(OBu)_8$)] showed neither fluorescence nor $^1O_2$ and other ROS generation upon photoexcitation. This material can be a potential photothermal sensitizer due to the high molar absorption coefficient in the far-red spectral region that corresponds to the phototherapeutic window.[133] The Ni^{II}− and Pd^{II}−octabutoxynaphthalocyanine complexes were reported to be efficient PTT chromophores against amelanotic melanoma and mammary adenocarcinoma cells.[131,133−140−146]

Table 1. Photophysical Properties of Selected Porphyrins and Metalloporphyrins

complex	solvent	Φ_F	τ_T (μs)	Φ_T	Φ_D	ref
H_2tpp	toluene	0.10	>10	0.73	0.67	134
[Zn(tpp)]	toluene	0.033	>10	0.86	0.68	134
[Cu(tpp)]	toluene	0	0.00178	0.88	0.03	134
	toluene			0.9		135
[Cd(tpp)]					0.98	136
	$C_6H_{11}CH_3$	0.0004	265	265		137
	$C_6H_{11}CH_3$	0.0002	380			137
[Pd(tpp)]				1		103
	C_6D_6	C_6D_6	C_6D_6		0.88	138
H_2tppS_4	H_2O		414	0.76		139
					0.62	140
[Zn(tppS_4)]	H_2O		2040	0.86		139
					0.74	140
[Cu(tppS_4)]	D_2O				0	138
[Cd(tppS_4)]	H_2O		149	0.88		139
	H_2O		268	0.63		139
[Pd(tppS_4)]					0.49	140
	D_2O				1	136

Singlet Oxygen Generation. Closed-shell metalloporphyrins show some advantages compared to free-base porphyrins, e.g., an increase of the quantum yield of singlet oxygen generation (Table 1). In this case the major nonradiative decay route is the intersystem crossing from the first excited singlet state to the first excited triplet state, while the internal conversion to the ground state is minor. The photophysical effects of metalation are notable in a series of phthalocyanines (Table 2). Phthalocyanine derivatives with coordinated zinc and aluminum (diamagnetic, closed shell) show high singlet oxygen formation yields, higher compared to metal-free phthalocyanine. Thus, metalated phthalocyanines are more convenient for PDT use. Most of the naphthalocyanines and their metalloderivatives show the type II mechanism of photosensitization; however, diamagnetic Ru^{II}−phthalocyanines are thought to undergo the type I mechanism (electron transfer, cf. Figure 8).[147] A series of complexes of the *trans*-[Ru^{II}(nc)L_2] type exhibit activity against HeLa cells already at micromolar concentrations.[148] Apart from use in PDT,[149] phthalocyanines have shown a significant potential in the area of blood product disin-

Table 2. Photophysical Properties of Selected Phthalocyanines and Metallophthalocyanines

complex	solvent	Φ_F	τ_T (μs)	Φ_T	Φ_D	ref
H_2pc	$C_{10}H_7Cl$	0.7				141
			140	0.14		142
					0.16	103
[Al(pc)Cl]	$C_{10}H_7Cl$	0.58	500	0.4		142
	dmso				0.29	138
[Zn(pc)]	$C_{10}H_7Cl$	0.3	125	0.65		141
	dmso				0.4	138
[Cu(pc)]	$C_{10}H_7Cl$	<0.0001				143
			0.035	>0.70		144
					0	145
H_2pcS_4	H_2O	0.62	170	0.22		142
					0.14	146
[Al(pcS_4)]	H_2O		500			142
	CH_3OD			0.42	0.30	138
[Zn(pcS_4)]	H_2O	0.32	245	0.56		142
	CH_3OD				0.36	138
[Cu(pcS_4)]	$C_{10}H_7Cl$	0.0001	0.065	0.92		142
					0	138

fection.[150] Enveloped viruses such as HIV are generally amenable to photoinactivation, in contrast to the nonenveloped viruses, indicating that the viral envelope may be a target for phthalocyanine photosensitization rather than nucleic acid.[94,151] The use of free base, aluminum and silicon phthalocyanines against viruses in blood has been reported to show high efficiencies of singlet oxygen production.[150,152] Cationic zinc tetra(*N*-methylpirydynium-4-yl)phthalocyanine showed the ability to photoinactivate both Gram-negative and Gram-positive bacteria.[153] The photosensitization of *E. coli* with aluminum(III) phthalocyanine has been shown recently.[154]

3.2.4. Transition-Metal Complexes as Photosensitizers

Metal compounds can act as prospective photosensitizers through both energy and electron transfer to the oxygen molecule. Most of the studies on photogeneration of singlet oxygen involve polypyrrolic dyes (porphyrins, porphycenes, phthalocyanines, etc.) and their metalloderivatives, but there is a significant number of other metal complexes capable of photosensitized singlet oxygen generation. A low-energy triplet excited state with a long lifetime is a prerequisite for this phenomenon. Many ruthenium(II) complexes undergo efficient oxygen quenching.[103] Quantum yields of the singlet oxygen generation are relatively high; depending on the complex and solvent they span from 0.19 ($[Ru(bpz)_3]^{2+}$ in D_2O) to unity ($[Ru(dpds)_3]^{2+}$ in CD_3OD) (for ligands structures see Figure 10).[103] Other transition-metal complexes, like $[Cr(bpy)_3]^{3+}$ ($\Phi_\Delta = 0.86$) or Pt^{II} complex with bpy and 3,4-toluenedithiolate, were found to give moderate quantum yields of singlet oxygen ($\Phi_\Delta = 0.11-0.20$). Also, mono- and dinuclear Os^{II}, Ir^{III}, and Pd^{II} complexes with polypyridines, 3,4-hydroxybenzoic acid, or di- and tetrahydroxybenzaldehyde can be used as singlet oxygen photogenerators.[103] These complexes have not been fully explored, but their photostability and facile tuning of the excited-state properties may lead to prospective PDT applications.

Another possible application of metal complexes in photodynamic therapy involves not singlet oxygen generation but photoinduced redox processes. In this context ruthenium(II) complexes with heterocyclic ligands are promising agents for PDT.[147,155] The excitation of Ru^{II} polypyridyls leads to the ^{1}MLCT state, which undergoes an efficient (quantum yield close to unity) intersystem crossing to the ^{3}MLCT state, which in turn can be deactivated by (i) radiative emission, (ii) radiationless decay with heat evolution, (iii) radiationless thermal conversion to the higher energy ^{3}MC state, and (iv) chemical reaction (Figure 11).

The molecule in the ^{3}MLCT state is a better oxidant and better reducer than in the ground state and may initiate some redox reactions. In contrast, the ^{3}MC state involves populating a higher energy d orbital of antibonding character, thereby weakening one or more Ru−N bonds, which may result in ligand substitution. The photoredox properties of Ru^{II} polypyridyls can be modulated by changing the nature or combination of ligands. Some examples of polyazaheteroaromatic ligands are shown in Figure 10. To obtain highly oxidizing complexes it is necessary to use ligands with strong π-acceptor properties, such as tap, hat, bpz, or phehat (Figure 10). Photoreaction of $[RuL_3]^{2+}$ with DNA results in photocleavage of DNA strands with quantum yields correlating with the redox potentials of the Ru^{II} complexes.

In the case of analogous Os^{II} complexes, thermal activation to the ^{3}MC state is not possible; therefore, the selective photoredox reactivity of osmium(II) complexes is superior to ruthenium(II) compounds. The oxidation power of the ^{3}MLCT Os^{II} excited state is lower than that of ruthenium, so the osmium species can selectively oxidize guanine (the strongest reducer among nucleic bases) while other bases remain intact.[156]

3.2.5. Semiconductors as Photosensitizers

Photogeneration of reactive oxygen species can be achieved not only in homogeneous systems. There are reports on trials of semiconducting heterogeneous photocatalysts application in antitumor therapy.[157] The studies are focused mainly on TiO_2.

Reactive oxygen species may damage the cellular membrane,[158,159] including altered permeability of cellular membranes to potassium and calcium ions,[160] and may cause further damage inside the cell. In particular, the targets are nucleic acids[161−164] and enzymes.[165] Oxidation of proteins and amino acids photocatalyzed by TiO_2 was observed by Muszkat et al.[166] This process, responsible for cell damage, can also be applied for purification of biocontaminated waters.

TiO_2 particles exhibit no or weak genotoxicity in the dark; however, upon UV light irradiation TiO_2 photogenotoxicity was observed.[162] Anatase and rutile crystalline forms of titania particles showed photoenhanced DNA damage associated with decreased cell survival. Photoexcited TiO_2 particles induced primary DNA damage and structural chromosome aberrations in mouse lymphoma L5178Y cells. These genotoxic activities depended on TiO_2 dose and light intensity. Only high concentrations of TiO_2 particles induced DNA damage in the absence of light, but no

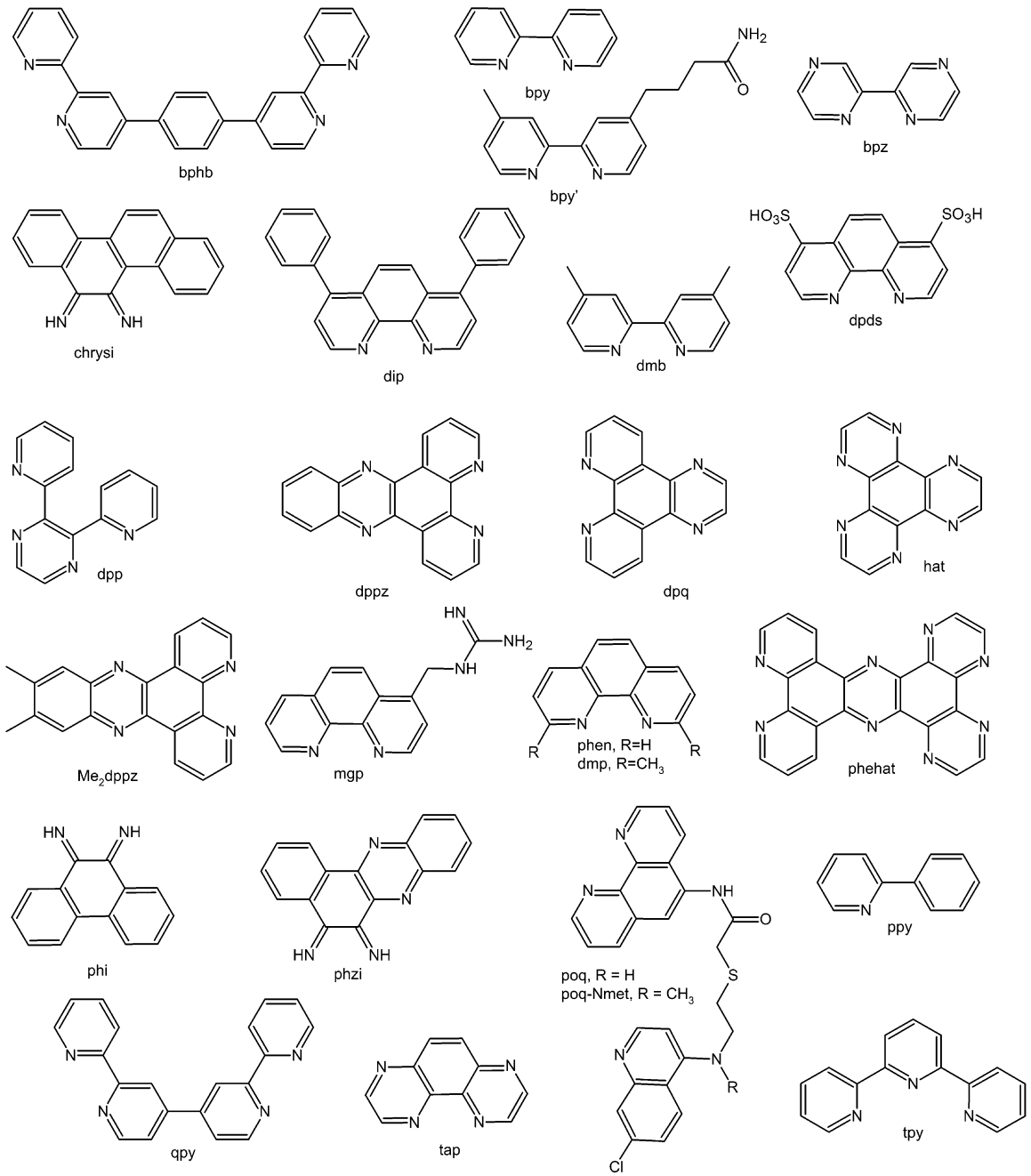

Figure 10. Structures of selected ligands appearing in sections 3 and 4 (see Abbreviations for systematic names).

significant cytotoxic response was observed. No induction of gene mutations by photoexcited TiO_2 particles was observed in microbial or mammalian cells systems. Therefore, it was suggested that DNA lesion catalyzed by photoexcited TiO_2 particles resulted in chromosomal aberration rather than gene mutations.

The cytotoxicity of TiO_2 upon UVA irradiation was observed also against Chinese hamster ovary cells.[167,168] The observed cytotoxicity was attributed to photogenerated $^{\bullet}OH$ radicals. Photoinduced killing of T-24 human bladder cancer cells in the presence of TiO_2 was reported by Fujishima et al.[160,169,170] Inoue et al. reported formation of both singlet oxygen and superoxide anion.[171] They assumed formation of singlet oxygen to proceed in photosensitization process, i.e., energy transfer from recombination of photogenerated electron/hole pair to an adsorbed oxygen molecule.

Other systems of possible application in photodynamic therapy are nanomaterials. Nanomaterials are extensively used in life sciences, e.g., in histological studies, diagnostic assays, drug-delivery systems, and separation techniques. As nanoparticles can effectively penetrate tissues and are generally absorbed by cells, they are considered mainly as carriers of photosensitizers. However, some of them, e.g., TiO_2 (vide infra), ZnO, and fullerenes, are capable of generating singlet oxygen themselves. For PDT purposes, ceramic-based, metallic (e.g., gold), and biodegradable nanoparticles with phthalocyanins were tested in order to improve hydrophilicity, increase yield of singlet oxygen generation, as well as enhance cell affinity of the photosensitizer.[172]

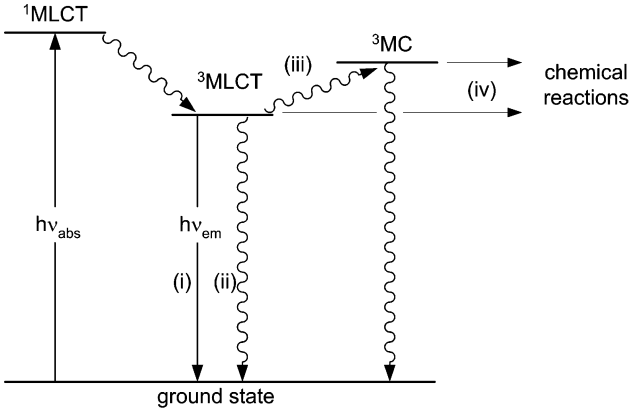

Figure 11. Photophysical processes in the ruthenium(II) polypyridine complexes.[156]

3.2.6. Supporting Role of Metal Ions in Photodynamic Therapy

The effectiveness of the photodynamic action of a photosensitizer is also affected by the presence of various metal ions in the cellular environment, in particular iron, which is essential for the proper functioning of all living cells. In the presence of molecular oxygen, labile iron complexes are able to cycle between the two most stable oxidation states, generating oxygen-derived free radicals such as the hydroxyl radical, which results in peroxidative tissue damage. The production of such highly reactive species is undesirable in normally functioning cell, and thus, a number of protective strategies are adopted by cells to prevent their formation. As the protection mechanisms are not effective enough in the presence of an excess amount of iron ions, the synergistic action of the photosensitizer, Photofrin, and exogenous Fe^{III} in the presence of ascorbate was tested.[173,174] The ascorbate reduces Fe^{III} to Fe^{II}, which readily donates an electron to lipid hydroperoxides generated previously upon photosensitization and the free radical chain reactions are initiated. This prooxidant combination of iron and ascorbate was proved to enhance cytotoxicity of PDT on L1210 leukemia cells and human squamous cell carcinoma cells as well.

The other therapeutic strategy is based on selective inhibition of iron-containing enzymes.[175] The inhibition of ferrochelatase by iron chelating agent, 1,2-diethyl-3-hydroxy-4-pirydione, increases the level of its substrate protoporphyrin IX, which acts as an endogenous photosensitizer formed during PDT from 5-aminolevulinic acid.[176]

3.2.7. Combination of Polypyrrolic Photosensitizers and Metallopharmaceuticals

The high binding affinity of cisplatin toward DNA has led to its popularity as an anticancer agent.[58] However, due to cumulative drug resistance, low tumor selectivity, and toxic side effects of this classical anticancer drug, researchers have explored other related metallodrugs. As established before, a combination of chemotherapy and PDT has a significantly additive antitumor effect,[177,178] which suggests a new way of classic antitumor drug modification.

Nowadays, extensively studied systems involve porphyrin moieties linked to a peripheral platinum moiety (Figure 12a−c).[179−183] Both synthetic (sulfonated pyridinetriphenylporphyrin) and natural (hematoporphyrin) PDT photosensitizers were successfully coupled with complexes structurally similar to already used classical antitumor drugs such as cisplatin (Figure 12a and b) and carboplatin (Figure 12c). The presence of a light absorber allows excitation of these systems, which then can act as photodynamic and chemotherapeutic agents at the same time. The solubility, reactivity, and selectivity of these complexes can be modulated by changing the first Pt^{II} coordination sphere or peripheral substituents at both the porphyrin ring and the chelating ligands.[179−184] The antitumor activity of these complexes was tested with mammary carcinoma cell line,[180] human bladder cancer cells,[179] and leukemia L1210 cell line.[183]

Another promising combination of metallodrug with polypyrrolic photosensitizers was reported very recently by Conrado and co-workers. Iron−sulfur−nitrosyl cluster, acting as photoinducible NO donor (vide infra) is covalently linked with strongly absorbing chromophore, protoporphyrin IX (Figure 12d). Irradiation with low-energy light induces efficient photodestruction of the cluster and liberation of nitric oxide. Moreover, at the same time the porphyrin moiety can act as a traditional photosensitizer in photodynamic therapy.[185,186]

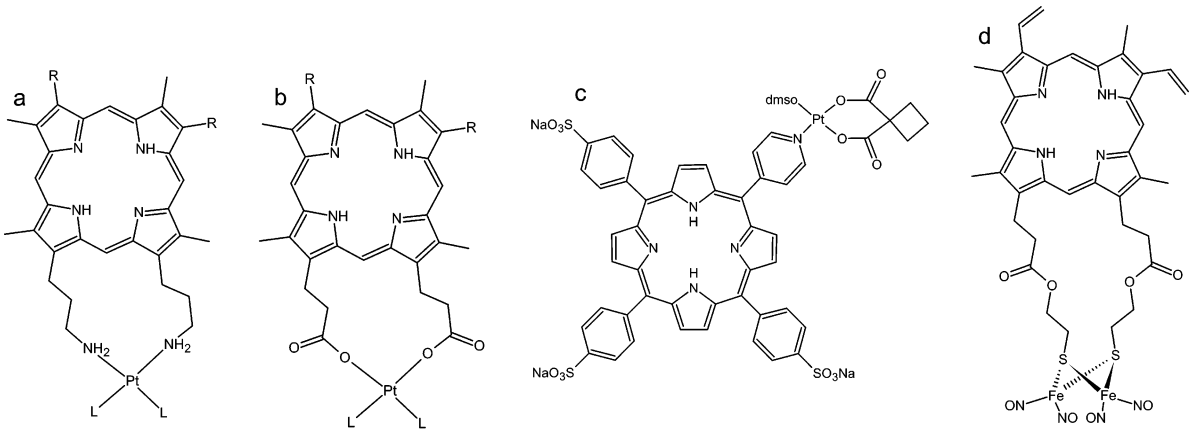

Figure 12. PDT photosensitizers incorporating the metallodrug moieties: (a, b) cisplatin-like (L = NH_3, 1,2-diamines, 1,2-dicarboxylates); (c) carboplatin-like; (d) iron−sulfur−nitrosyl cluster.

3.3. Photoactivation of Metallopharmaceuticals

Photosensitization used in photodynamic therapy is not the only possible approach toward phototherapeutic action. Photosensitizer should act as a catalyst, i.e., it should be ultimately regenerated in its electronic ground state. Photoreactions leading to biologically active products and proceeding directly from the metallopharmaceutical excited state are the other possibility of photoactivation. Depending on the excited-state character (CT, LF, or IL), various types of photoreactions (redox, dissociation, substitution, and rearrangement) occur and can be used for medical applications. Photoactivation of metallopharmaceuticals may thus consist in photodissociation of the coordinated ligand (which may be a consequence of the photoredox process), redox transformation of the metal center (eventually accompanied with changes in the first coordination sphere), isomerization, or others. All these processes finally lead to an increase of the pharmacological activity of the prodrug. The strategy based on light application as a trigger of pharmacological activity of the prodrug enables precise control of the drug action in both a temporal and a spatial domain, which reduces side effects and restricts the drug activity to desired tissue and/or organ.

3.3.1. Active Ligand

NO donors are good examples of prospective pharmaceuticals activated via their photodissociation, photosubstitution, and photoredox processes. During the last 20 years nitric oxide has been recognized as a key molecule in many physiological processes.[187−194] Among others, it is a messenger molecule in cardiovascular, nervous, and immune system.[192] Since nitric oxide plays many important roles in mammalian bioregulation and immunology, it is not surprising that a breakdown in the regulation of its biosynthesis and metabolism results in a number of diseases such as hypertension, diabetes, arthritis, epilepsy, septic shock, or others. One of the therapeutic approaches involves application of external sources of nitric oxide.[195−197] Release of the active forms of nitric oxide from the NO donor drug may proceed by spontaneous, enzyme-catalyzed, and light-induced pathways. Among the various NO donors, only one metal nitrosyl complex is used in clinical practice (sodium nitroprusside, $Na_2[Fe(CN)_5NO]\cdot 2H_2O$) under the commercial name Nipride.[198] There have been attempts to use other iron nitrosyls, both monomeric complexes and clusters.[199−204] Photochemical liberation of nitric oxide follows three main reaction pathways: (i) photooxidation−substitution, (ii) photoreduction, and (iii) ligand rearrangement or decomposition as a result of photoreaction.

The $Na_2[Fe(CN)_5NO]\cdot 2H_2O$ complex is the effective hypotensive drug. Various mechanisms of its in vivo metabolism were suggested.[197,203] The photoreactivity of $[Fe(CN)_5NO]^{2-}$ has been the subject of extensive studies.[205−209] The complex was found to release nitric oxide upon irradiation within 300−600 nm with high quantum yields (up to 0.4, depending on conditions).[207,209,210] The reaction follows the photooxidation of iron and subsequent substitution of NO by a solvent molecule.[206,209]

The reactivity of the coordinated nitrosyl enables fine tuning of the spectroscopic and photochemical processes of the nitrosyl complex. The complex reacts with a large variety of nucleophiles yielding complexes of the $[Fe(CN)_5N(O)L]^{n-}$ type, where L depicts C-, N-, O-, S-, or Se-nucleophiles. Especially important from a biomedical point of view are the S-nucleophiles.[211−213] The thermal stability of the $[Fe(CN)_5N(O)SR]^{3-}$ complexes can be tuned by variations of the ligand structure.[210,212,214−217] Thermally stable $[Fe(CN)_5N(O)SR]^{3-}$ complexes undergo photodecomposition via the unstable $[Fe^{III}(CN)_5\{N(O)SR^{\bullet -}\}]^{3-}$ charge-separated state, which in turn decomposes via heterolytic cleavage of the Fe−N and N−S bonds.[210,211,214,215] The general reaction mode is thus similar to that of $[Fe(CN)_5NO]^{2-}$, but in the case of $[Fe(CN)_5N(O)SR]^{3-}$, the nitrosothiyl anion radical is generated instead of NO. Photogenerated nitrosothiyl anion radical may decompose to the thiolate anion and nitric oxide or undergo oxidation yielding nitrosothiol.[215] The change in photosensitivity range from UV to visible upon addition of the RS^- to NO ligand in nitroprusside may be understood as a thiolate-induced photosensitization of the nitrosyl complex. Moreover, the nucleophilic attack changes the nature of the bioactive species that are photogenerated. Instead of nitric oxide itself, other NO donors are produced. This system is an example of a tunable NO donor releasing different bioactive species on demand.[210,211,214,215,218] Moreover, nucleophilic modification of the nitrosyl ligand results in a well-pronounced photoreactivity close to the phototherapeutic window.[211]

The photooxidation mode was also observed in the case of other nitrosyl complexes containing linear nitrosyl ligand (formally NO^+). Various iron complexes with polypyridine−carboxamide ligands were found to be good NO donors upon visible irradiation. These complexes are also reported to *S*-nitrosate thiols with good yield.[219,220] Nitrosyl complexes of ruthenium have been found to be good NO donors.[221−223] Two NO complexes, trichloronitrosylruthenium $[RuCl_3(NO)]$ and dipotassium pentachloronitrosylruthenate ($K_2[RuCl_5(NO)]$), have been shown to be thermally stable but photolabile, releasing nitric oxide on exposure to near-UV light.[224,225] They are water soluble and thereby unlikely to cross biological membranes. Among the various nitrosyl ruthenium complexes an important class is represented by salen complexes.[226] They undergo photochemically activated labilization of nitric oxide. Preliminary studies on the photoreactivity of a representative member of this family, [RuCl(salen)(NO)], demonstrate that this complex undergoes NO labilization upon near-UV irradiation to give the solvento species, [RuCl(salen)(solv)]. Thus, this system may serve as a precursor for photochemical NO generation.[226] Other transition-metal macrocyclic complexes, like $[Ru^{II}X(NO)(cyclam)]^{2+}$ (X = halogen) and $[Cr^{III}(ONO)_2(cyclam)]^+$, were also found to photoactivate NO.[227,228] Recently a series of new ruthenium nitrosyls with a very high quantum yield of NO release was reported.[229−231] These complexes contain various N-ligands (tetraazacyclopentadecane, polypyridyls or

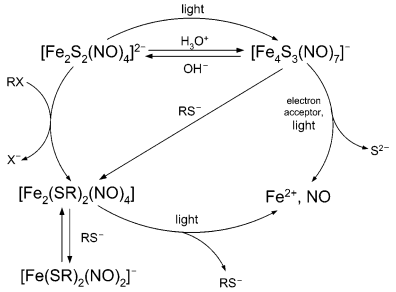

Figure 13. Thermal and photochemical transformations of iron−sulfur−nitrosyl clusters leading to nitric oxide release.

pyridine ligands, amino acids, and alkyl phosphites). Irradiation within the LMCT absorption band results in photolabilization of coordinated nitrosyl with a quantum yield up to 0.6.[229−231] A family of ruthenium−sulfoxide−nitrosyl complexes represents dual biological activity. Not only do they serve as NO donors, but the sulfoxide−ruthenium fragment shows a strong antitumor activity in animal tumor models.[147,222]

The photoreduction mode is important in complexes containing bent (formally NO^-) nitrosyl ligand. Good examples of this class of NO donors are iron−sulfur nitrosyl monomers and clusters. The most studied complexes belonging to the $[Fe_xS_y(NO)_z]^{n-}$ family are Roussin's red salt, $[Fe_2S_2(NO)_4]^{2-}$, and Roussin's black salt, $[Fe_4S_3(NO)_7]^-$. These compounds contain a large number of nitrosyl ligands within a single anion and are known as highly effective nitrovasodilators with unusual pharmacological profiles.[195,199,200] They are thermally stable, but irradiation of these species results in photodegradation of the cluster accompanied with almost quantitative nitric oxide release.[201,202,232−235] DFT calculations made for model monomeric compounds indicated that these complexes consist of Fe^{III} centers and NO^- ligands which are strongly antiferromagnetically coupled.[236] Although ionic, they enter endothelial cells remarkably quickly and accumulate therein, slowly releasing NO. The selectivity of the iron−sulfur nitrosyl clusters may be enhanced due to their lipophilicity—they can be easily bound within hydrophobic pockets, e.g., inside the cyclodextrin cavity.[237] Easy interconversion between $[Fe_4S_3(NO)_7]^-$, $[Fe_2S_2(NO)_4]^{2-}$, $[Fe_2(SR)_2(NO)_4]$, and $[Fe(SR)_2(NO)_2]^-$ makes the system susceptible to ligand-controlled NO photogeneration (Figure 13). Important structural modification was achieved via incorporation of a longer bridge between iron centers, which results in changes in solubility, magnetic properties, photochemical behaviors, and physiological action.[238,239] The NO photogeneration quantum yield depends strongly on oxygen concentration. Solubility of the Fe−S−NO cluster compounds is in turn controlled by the ligand structure (hydrophilic vs lipophilic effect depending on the R group polarity). All these may lead to the tissue-selective NO photogeneration, which is important from a photomedical point of view.[211,238,239]

An interesting class of compounds considered as potential photochemical precursors from which NO can be released by point irradiation are metalloporphyrins.[240−245] Depending on the coordination mode (linear MNO vs bent MNO) the photoinduced denitrosylation process can be regarded as a photooxidation or photoreduction process (vide infra). Metalloporphyrin and heme protein nitrosyl complexes have been the subject of photochemical studies for a long time.[61,246−252] It is known that these complexes release nitric oxide with quantum yields varying from virtually zero to unity when photons are absorbed by the porphyrin macrocyclic π system. Electronic excited states in these systems are inherently short lived because empty d orbitals of transition metals can couple with the porphyrin π orbitals, forming states of intermediate energy.[252] It was found that metalloporphyrin−ligand systems with d^6 electronic configuration are highly photolabile, whereas systems with a higher d occupancy are not (for instance $\Phi \approx 1$ for $[MbFe^{III}NO]$ complex and $\Phi \leq 10^{-4}$ for $[MbCo^{II}NO]$ complex). More recently, Morlino and Rodgers investigated photodissociation of two protein-free nitrosylmetalloporphyrins, [Fe(tpp)(NO)] and [Co(tpp)(NO)]. They showed that the difference in the denitrosylation yields of these nitrosyl adducts (Φ = 0.5 and 1 for [Fe(tpp)NO] and [Co(tpp)NO], respectively) is the result of energy partitioning in the upper excited states of the porphyrin. Only those excited states which relax via the CT state result in loss of nitric oxide.[253,254] It was found that utility of the nitrosyl porphyrin complexes of the first-row transition metals in photochemical NO delivery to specific targets is severely hampered by their lability and oxygen sensitivity.[252,255] In this respect most attention was turned to the nitrosyl ruthenium porphyrin complexes, which were anticipated to be more stable. This has directed the investigations toward the synthesis, structural characterization, and photochemical reactivities of several ruthenium porphyrin complexes of the [RuL(ONO)(NO)] type where L = tpp, oep, tmtp, and fttp.[201,252,255,256]

Several examples of nitric oxide (or unstable NO donor) photogeneration involving complex reactions of coordinated ligands have also been reported. This phenomenon was observed in the case of the molybdenum(0) complex [Mo(dtc)(CO)(diphos)(NO)]. Upon excitation within the LLCT band (dtc → NO) at 520 nm it releases unstable nitrosodithiocarbamate species, which acts as a powerful NO donor.[257] Nitric oxide can be photogenerated also by photodecomposition of coordinated cupferronate ligand as it was observed in the case of an iron(III) complex.[258] The ligand itself is photoactive and releases nitric oxide upon ultraviolet (254 nm) irradiation.[259−261] Formation of the cupferron−Fe^{III} complex results in a significant extension of the photosensitivity range to the whole LMCT band (approximately 550 nm). Low solubility in water and lipophilicity of the complex may be also significant for biomedical applications.

It is worth mentioning here that transition-metal centers are among the most important receptors of nitric oxide in all living organisms,[85,192,262−265] and these reactions are responsible for a majority of all physiological actions of NO, both direct and indirect, beneficial, and deleterious. It creates the unique possibility of controlling natural physiological pro-

cesses by light. Coordination of nitric oxide to metalloproteins results in activation (guanylate cyclase, hemoxygenase) or deactivation (cytochromes, catalase, ferritin, nitrile hydratase) of their biological functions.[66,264] Selective irradiation of chosen NO−metalloproteins induces photolabilization of nitric oxide.[85] This may have important medical applications and serve as a tool in elucidation of biochemical pathways involving nitric oxide and metalloproteins. Recently the same approach was used to control the activity of an industrially important enzyme, nitrile hydratase.[66,266−268]

Photodissociation of 4-aminopyridine from ruthenium polypyridyl complex was reported recently.[269] It was found that the complex does not interact with neurons, while the photoliberated ligand gives a strong physiological response. Photodissociation occurs at a low-energy excitation. This research opens the new possibility for optical control of the activity of selected groups of neurons for neurobiochemical studies.

3.3.2. Active Metal Center or Complex

Biological activation of Pt^{IV} complexes via their photoreduction to Pt^{II} species has been suggested recently.[270−274] The photoactive Pt^{IV} analogues of the anticancer drug cisplatin [$PtCl_2(NH_3)_2$], such as [$Pt(OAc)_2I_2$en] and [$Pt(OAc)_2(N_3)_2$en] compounds, have recently been designed and investigated.[270−274] It has been shown that iodo complexes of Pt^{IV} can platinate a nucleotide (5′-GMP) and DNA under illumination. The cytotoxicity is slightly enhanced by photolysis of these compounds in comparison to the dark control.[271,272] However, slow photoreactions and low stability in serum due to high reactivity toward reducing agents limit the use of these complexes in anticancer therapy. Recently developed Pt^{IV} diazidediamine complexes which are highly stable in human blood plasma and react very slowly with reducing agent (e.g., glutathione) seem to be more promising.[274] It has been reported that visible light photoactivation of these compounds results in a very reactive Pt^{II} species which binds rapidly to nucleotides (5′-GMP, d(GpG)) and DNA forming cisplatin−nucleotide cross links. Transcription mapping of plasmid DNA showed the platination sites to be similar to those obtained for cisplatin, mainly GG sequences.[273]

Photorearrangement reactions can also find application in prospective drug activation. Photoisomerization of *cis*-[$RuCl_2(dmso)_4$] to the trans isomer leads to enhancement of its antimetastatic and antitumor activity.[28]

The ruthenium complexes photoreacting with DNA (described in detail in section 4.3.4) are also known to have significant effects on DNA functions and therefore disturb gene expression.[275−281] The photocleavage of DNA as well as formation of photoadducts with DNA can inhibit the binding of enzymes involved in transcription and replication processes or prevent the progression of these enzymes along DNA. As a consequence, these processes inhibit the transcription and replication processes. The complexes which possess such activity could be other candidates for phototherapy. Several compounds have been found to inhibit growth of the tumor cells. Ruthenium complexes of the [$Ru(tap)_2(phen)]^{2+}$ and [$Ru(tap)_2$-(poq-Nmet)]$^{2+}$ type inhibit gene transcription by direct photoinduced electron transfer between the oxidizing complex (containing π-deficient ligands) and DNA with a concomitant formation of covalent photoadducts with DNA.[275] The real advantage is that the activity is no longer based on the presence of dioxygen. Another complex of the Λ-1-[$Rh(mgp)_2$-(phi)]$^{3+}$ type can inhibit site-specifically the binding of transcription factor to the DNA.[276] Recently it has been shown that *cis*-[$RhCl_2(dppz)(phen)]^+$ is phototoxic toward tumor cells and Sindbis Virus. The primary target for the latter is viral genome.[277] The use of modified oligonucleotides with tethered photoactive ruthenium(II) complexes allows precisely driving the metal complex reactivity to the desired DNA or RNA sequence. Subsequently, the metal complex can be selectively activated by light, leading to formation of interstrand cross link or oxidizing nearby guanine base and results in inhibition of gene expression.[278−281]

Additionally, DNA photometallocleavers can be useful as diagnostic tools. The great advantage of the photocleavage agents is the fact that the desired reaction is triggered by light while in the dark the reaction does not occur. The design of new agents especially for base pair mismatches detection based on combination of the shape-selective metal complexes with their photocleaving activity has great therapeutic potential and can be useful in genetic diagnosis. Particularly useful for this purpose are Rh^{III} complexes such as [$Rh(bpy)_2(chrysi)]^{3+}$, [$Rh(ppy)_2(chrysi)]^+$, or [$Rh(bpy)_2(phzi)]^{3+}$ which can be appropriate mismatch recognition agents.[282−286]

3.4. Photodelivery and Phototargeting

Light-assisted drug delivery and phototargeting gives a possibility of triggering drug action at the desired site, which helps to avoid unwanted side effects. The pharmaceutical can be packed and transported in the form of a thermally stable compound and released at the target site by point irradiation (using laser or fiber optics). The carrier molecule should be easy to prepare, have minimal toxicity in the dark, undergo efficient photochemical reaction leading to release of the pharmaceutical in the appropriate form, and generate only nontoxic, easily excreted byproducts. There are two main approaches to photodelivery. They are based on photodissociation of the drug−carrier complex or photoinduced drug release from vesicle structures.

As a possible carrier molecule vitamin B_{12} and its derivatives were considered, since they meet most of the aforementioned requirements. Since the photochemical reactions of the cobalamins involve bond breaking between the cobalt center and the axial ligand,[287−298] the model assemblies of metallocobalamins with a second metal complex (such as [$Pt(CN)_4]^{2-}$ or [$Au(CN)_2]^-$)[27,291,299] as the sixth ligand have been synthesized. Upon irradiation these cobalamin derivatives undergo photosolvation with the concomitant metal complex release. Described in the

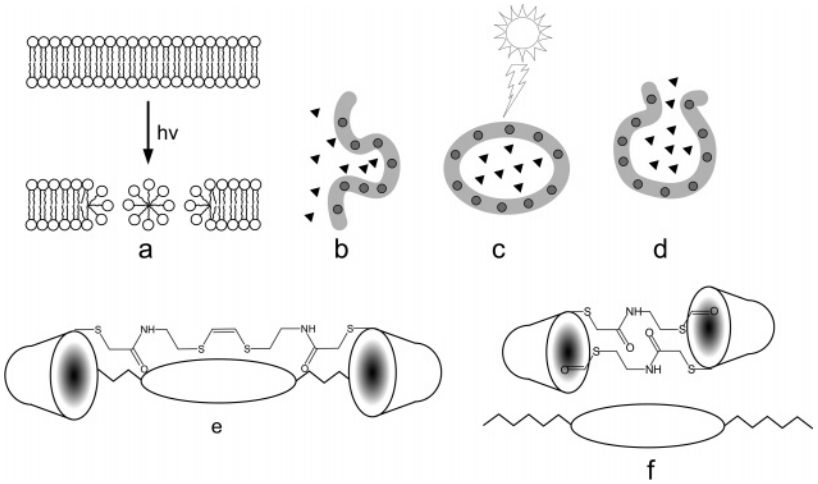

Figure 14. Light-assisted drug delivery with photosensitive liposomes and cyclodextrin cages: (a) photoinduced lamellar-to-micellar phase transition in the liposome bilayer, (b) encapsulation of the drug (triangles) inside the liposome-containing photosensitizer (circles), (c) irradiation of the liposome, (d) drug release from opened liposome, (e) hydrophobic photosensitizer encapsulated in a water-soluble cyclodextrin cage, and (f) liberation of the photosensitizer due to cleavage of the linker.

previous section, nitric oxide photodissociation from metallonitrosyl complexes can be regarded as another example of light-assisted drug delivery (vide supra).

Light activation is an exceptionally promising method for triggering a vesicle contents release since it provides a variety of adjustable parameters (photosensitizer, vesicle-forming components, irradiation wavelength and time, etc.) which can be optimized for biological compliance. Light may induce phase transitions within lipid bilayers, resulting in vesicle opening, or can lead to direct interactions of liposomes with target sites.[300,301] Lamellar-to-micellar phase transitions may be induced by photoisomerization of liposome-bound photoreceptors or by oxidation of some membrane components with singlet oxygen or other reactive oxygen species (Figure 14a). The drug can be encapsulated in light-sensitive liposomes containing a photosensitizer (aluminum phthalocyanines, bacteriochlorophylls, etc.) incorporated into membrane (Figure 14b). After liposome administration, point irradiation leads to photodynamic opening of lipid membrane and subsequently to topical drug release (Figure 14c and d). In some cases liposomes can be opened with the strategies characteristic of the PTT approach.[300,301]

Another strategy for drug photodelivery was proposed by Breslow et al.[302] The new strategy involves encapsulation of the hydrophobic phthalocyanine photosensitizer in cyclodextrine dimer with sulfur-containing olephine linker (Figure 14e). The supramolecular complex shows good solubility, but irradiation generates singlet oxygen and thus induces liberation of the hydrophobic photosensitizer (Figure 14f), which can effectively bind to neighboring cells or other biological structures.

3.5. Phototoxicity and Photoprotection

Many organic and inorganic drugs are apt to undergo photochemical reactions both in vivo and ex vivo. Ex vivo photochemistry may lead to the abatement of physiological reactivity or generation of harmful and toxic photoproducts, while in vivo photochemistry may also induce photoallergies and undesired phototoxic effects. A drug is phototoxic if light represents an essential condition causing deleterious biological effects ranging from photoirritation to photocarcinogenicity.[303−306] Photoirritation is a light-induced, nonimmunologic skin response to a photoreactive chemical, applied directly to the skin or via the circulatory system following systemic administration. Photoallergy is an immunological response to a photoproduct itself or adduct of photoproduct with proteins or nucleic acids. Photogenotoxicity is a genotoxic response observed after exposure to a chemical photoactivated by UV or visible light. Photocarcinogenicity focuses on the potential of a drug to induce skin tumors in combination with UV. This may be either an indirect enhancement of UV-induced carcinogenic effects or a carcinogenic effect of a drug photoactivated under UV irradiation (also termed photochemical carcinogenesis). It was also found that some photosensitizers enhance UV-associated skin carcinogenesis. Also, alteration in optical properties of skin is responsible for photocarcinogenicity. Various phototoxic effects may be associated with several photochemical processes: direct interaction of excited molecule with biological targets, fragmentation of drug molecule into toxic species, photogeneration of reactive forms of oxygen (oxygen-centered radicals and singlet oxygen).[304]

Drug photoprotection includes both physical protection against light (proper materials for immediate and market packages such as bottles, syringes, boxes, etc.) as well as additives preventing photochemical reactions by switching the photoreactivity of the excited state to the alternative pathways or changing the solution viscosity. The third possibility includes addition of chemical species acting as scavengers for toxic photoproducts (drug reformulation).[307] The role of various metal compounds is significant in all three abovementioned approaches.

Most of the drugs are packed in plastic or glass containers; however, any of these materials itself does not ensure sufficient protection against UV and visible irradiation. One of the possibilities includes formation of proper optical filters directly on the

surface of the container. The filter can be composed of a silicate xerogel doped with titania or zirconia and organic pigments.[308] Optical and mechanical properties of these coatings make them well suited for drug packages, vials, syringes, etc. Other strategies assume changes in the composition of drug preparation. The simplest strategy involves addition of dyes and pigments, acting as inner filters, to the pharmaceutical preparations. The most important additives are iron oxides and titanium dioxide. Also, addition of quenchers may successfully prevent photoreactions by efficient energy transfer from the excited drug molecule to the quencher. In the case of photoisomerizable drugs, cyclodextrins are good "molecular containers" which enforce preservation of molecular geometry/conformation and in this way help to maintain the desired physiological activity of the drug. An increase of the solution viscosity also constitutes an efficient way to photostabilize some drugs, especially those which undergo photodissociation.[303]

One of the best known examples of metallodrugs showing photochemical reactivity ex vivo, which leads to generation of toxic photoproducts and abatement of physiological reactivity, is sodium nitroprusside.[27,203] Its phototoxicity is well recognized and photoprotection strategies well developed. Extensive photolysis of the nitroprusside complex first leads to liberation of nitric oxide (see section 3.3.1), and subsequently free cyanide is released in secondary photochemical steps. Highly energetic UV irradiation induces photoreduction of the complex yielding $[Fe(CN)_5NO]^{3-}$, which in turn spontaneously liberates axial cyanide in the fast thermal process. Other common metallopharmaceuticals which undergo photodecomposition upon prolonged exposure to UV or visible light are cisplatin and cobalamin derivatives. Irradiation of cisplatin in aqueous solution leads to photoaquation, while irradiation of cobalamins leads to the loss of axial ligands and corrin ring opening.[303] In the case of sodium nitroprusside, simultaneous administration of vitamin B_{12}, which is a powerful cyanide scavenger, prevents cyanide poisoning.[309] An increase of the drug solution viscosity (addition of glycerol, glucose, etc.) also prevents photodissociation due to disturbed diffusion of primary photoproducts from the solvent cage.[27]

Phototoxicity, however, does not concern the drugs only. Numerous natural (endogenous) chromophores may act as photosensitizers (generating thus reactive oxygen species upon irradiation) or undergo photoreactions yielding deleterious products. Nature has evolved complex systems for free radical scavenging, frequently based on transition-metal complexes. To prevent an overload of free radicals and peroxides, aerobic organisms have elaborate defense mechanisms against ROS. The effectiveness of that system can be modulated by the presence of redox transition-metal ions and their complexes. The Cu^{2+}, Mn^{2+}, and Co^{2+} ions can act as redox scavengers of photochemically generated radicals.[310] Therefore, these ions and their complexes exert an antioxidant activity and a radical blocking action, which protects them from -drug-photoinduced DNA cleavage and lipid peroxidation. As a result the photoinduced damage of a cell is reduced. However, high concentrations of these ions lead to toxic effects.[303,311,312] Another approach to increase the photoprotective potential of a cell is the use of complexes which can mimic enzyme superoxide dismutase (SOD), catalyzing the reduction of the superoxide anion to less toxic H_2O_2. Various types of SOD enzymes are known: Cu,Zn−SOD in cytoplasm of eukaryotic cells,[313] Mn−SOD in mitochondria, Mn−SOD and Fe−SOD in prokaryotic cells. Therefore, some Mn^{II}, Fe^{II}, and Cu^{II} complexes with oligopeptides, salicylates, and polyazamacrocycles were tested as efficient SOD models.[58] Use of many copper(II) complexes in vivo is limited by dissociation of Cu^{II} and binding to natural ligands such as albumins.[314] Some Mn^{II}−macrocycle complexes are biologically active;[315] however, Mn^{II} complexes are much less stable than analogous Cu^{II}−macrocycle complexes.[58]

Since natural photoprotection strategies are sometimes insufficient, artificial photoprotection systems have been developed. Nowadays, numerous cosmetic preparations with optical filters and radical scavengers are readily available, among them those based on metal compounds. The spectral properties of titanium dioxide and zinc oxide allow using these materials as sunscreen agents.[55] Their absorption onset localized around 400 nm agrees with the border between the UV and visible regions. A good sunscreen agent should absorb UV without causing any photochemical or postirradiation thermal effects such as ROS generation, photodecomposition of organic molecules, and other undesired processes. There are a few reports on titania application in UV protection.[316,317] Scaiano et al. observed mineralization of widely used UVB organic sunscreens in the presence of TiO_2.[318] Mixtures of organic and inorganic sunscreens commonly used in the cosmetic industry should be therefore carefully tested for their photostability. Since UVC irradiation causes DNA damage observed as a pyrimidine dimer formation,[319] the effect of TiO_2 in combination with UVC was examined.[320] As demonstrated on normal human cells (TIG-1) and human cancer cells (T24), pyrimidine dimer formation decreased in the presence of titania (*Degussa* P25) when irradiated at 254 nm. Under experimental conditions photogenerated ROS at the titania surface did not manage to penetrate efficiently inside the cell—which would lead to the cell damage—but TiO_2 acted rather as an efficient UVC filter.[316,317]

4. Biochemical and Bioanalytical Applications of Inorganic Photochemistry

4.1. Artificial Photosynthesis

An increasing demand for cheap and clean energy has stimulated development of novel chemical systems capable of efficient solar energy conversion. Until now natural photosynthesis has been the cleanest and most efficient process. It involves a large array of chromophores (antennae) to harvest visible light, a charge-separation system, and redox centers. Photosynthetic systems of green plants are very complex assemblies of light-harvesting antennae (photosystems I and II), energy- and electron-transfer systems, redox centers capable of water oxidation,

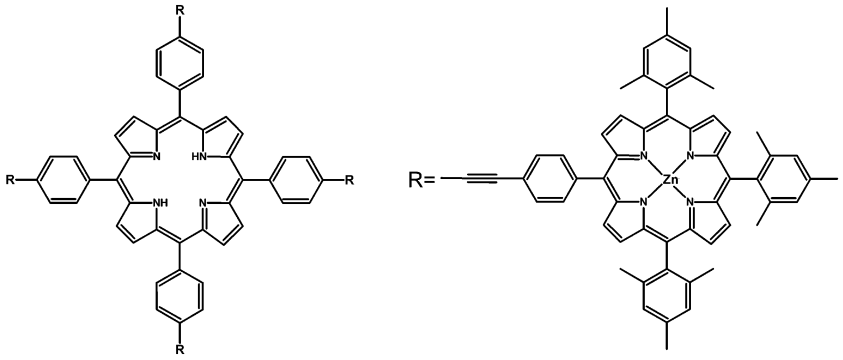

Figure 15. Starlike pentameric array of porphyrins for light harvesting.[340]

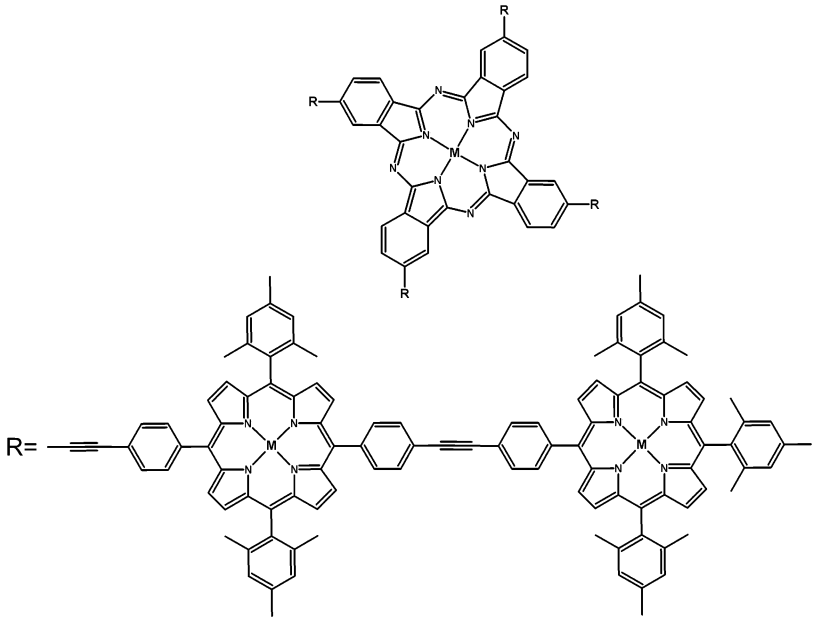

Figure 16. Light-harvesting antenna composed of eight metalloporphyrin units and a phthalocyanine core (M = Mg, Zn).[343]

and protomotoric-force-powered ATP synthase.[321−323] Photosynthesis is powered by visible photons, and the light-harvesting antennae is tuned to the maximum light intensity available in habitat. Electronic excitation in the antenna migrates from chromophore to chromophore and ultimately to the reaction center, where it is converted into chemical energy in the form of charge separation across the membrane.

Even a relatively simple bacterial photosynthetic system is very complex, and its synthetic imitation is a challenging task. Mimicking the natural photosynthetic process requires synthetic models of all the crucial components and linking them together into a working molecular assembly. All the elements (antenna, charge separation, and reaction centers) may involve transition metals. Application of metal complexes facilitates mimicking of this complex chemical system due to rich and versatile photochemical processes typical for transition-metal complexes.[16]

4.1.1. Light-Harvesting Antennae

An antenna for light harvesting is an organized multicomponent system in which an array of chromophoric molecules absorbs the incident light and channels the excitation energy to the common acceptor component.[324−332] The antenna effect can only be obtained in supramolecular arrays suitably organized in space, time, and energy domains. Each molecular component must absorb the incident light, and the excited state obtained this way must transfer electronic energy to the nearby component before undergoing radiative or nonradiative deactivation.[31]

One of the obvious candidates for light-harvesting antennae chromophores are porphyrin and phthalocyanine arrays,[333−341] synthetic analogues of natural chlorophyll arrays present in photosystems of green plants. Porphyrins are characterized by high molar absorption coefficients and fast energy/electron transfer to other components of the system, and they can be easily used as building blocks in large supramolecular systems.[129,339,342] Widely studied antenna systems consist of an array of various metalloporphyrin units linked with free-base porphyrin (Figure 15) or phthalocyanine (Figure 16) with bridges that ensure good energy transfer and weak electronic coupling (e.g., diarylethynes).[339,343] Arrays comprised of weakly coupled pigments are ideally suited for energy-transfer studies as the energy-transfer process does not depend on the state of other chromophores.[344] In the systems containing Mg or Zn porphyrin energy donors and free-base porphyrin

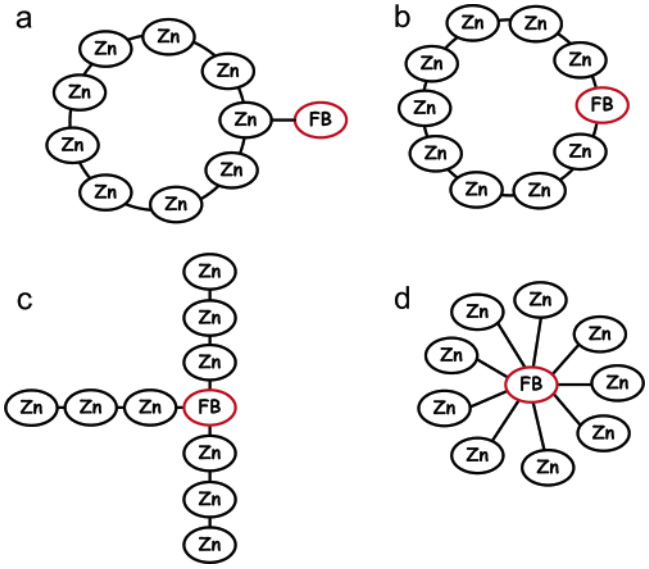

Figure 17. Various architectures of the porphyrin arrays for light harvesting: (a) cyclic array with peripheral acceptor; (b) cyclic array with integral acceptor; (c) tribranched array with central acceptor; (d) starburst array with central acceptor. FB denotes the free-base porphyrin, while Zn denotes the zinc−porphyrin complex. (Adapted from ref 344.)

acceptor the energy transfer occurs with a lifetime of 25−115 ps and high quantum efficiency (>95%).[344] The energy-transfer quantum efficiency depends on the geometrical arrangement of chromophores and varies from 76% for a cyclic array with peripheral acceptor, 84% for a cyclic array with integral acceptor, 91% for a tribranched array with central acceptor, to 98% for starburst arrays with the acceptor in the center (Figure 17).[344]

Another class of extensively studied artificial antennae encompasses metallodendrimers and multimetal arrays based on polypyridine ligands.[330,332,345−348] Especially promising, due to high molar absorptivity, photostability, and excited-state properties, are polypyridine complexes of ruthenium(II) and osmium(II). Irradiation of the abovementioned complexes within the MLCT absorption band leads to formation of a long-lived excited state, which can efficiently transfer electronic energy to other metal center of the same or lower energy. This process can by used in a dendritic structure to focus energy within the core of the dendrimer or transport it from the inner part of the dendrimer to the edge (Figure 18). The electronic energy transfer within metallodendrimers may follow two independent pathways: superexchange along the dendritic framework or direct Coulombic interaction via the dendritic folding. The direction of energy transfer can be tuned with the structure of the bridging and terminal ligands and by proper selection of metal ions present in the branching points and on the edge of the dendrimer. The efficiency of the energy transfer is close to unity. The excitation of the mononuclear complexes to the ^{1}MLCT state is followed by immediate intersystem crossing to the lowest ^{3}MLCT state, which luminesces with high quantum yield. In the case of multinuclear supramolecular assemblies the energy transfer is so efficient that the luminescence of the unit with higher ^{3}MLCT energy cannot be observed and the quantum yield of energy transfer is unity.[35,349]

Other interesting biomimetic light-harvesting antennae were developed by Calzaferri et al.[324−326,350−357] In these systems the role of the metal ions is, however, very different; they provide scaffolds for multichromophoric systems (Figure 19). The antenna itself consists of a series of organic chromophores embedded within zeolite channels. The mutual orientation of dye molecules ensures an efficient energy transfer from the interior of the zeolite crystal to its sidewalls perpendicular to the channel axis.[324−326,356,357] The excitation energy can be subsequently utilized to excite the "stopper" molecules,[353] partially embedded inside the channel with the bulky head remaining outside. Fullerenes, metal chelates, or other chromophoric or catalytic units may be used as energy acceptors. The main purpose of the stopper molecule is to ensure contact of the zeolite crystal with its environment: they may trap the excitation energy from inside the crystal or inject the energy to the dyes inside the channels. Some examples of dyes and headgroups are shown in Figure 19.

An alternative to these solid-state antennae was shown by Kumar, Chaudhary, and Mallouk et al.[358,359] The light-harvesting system was built on the surface of zirconium phosphate by chemisorption of transition-metal ions or construction of complex lamellar

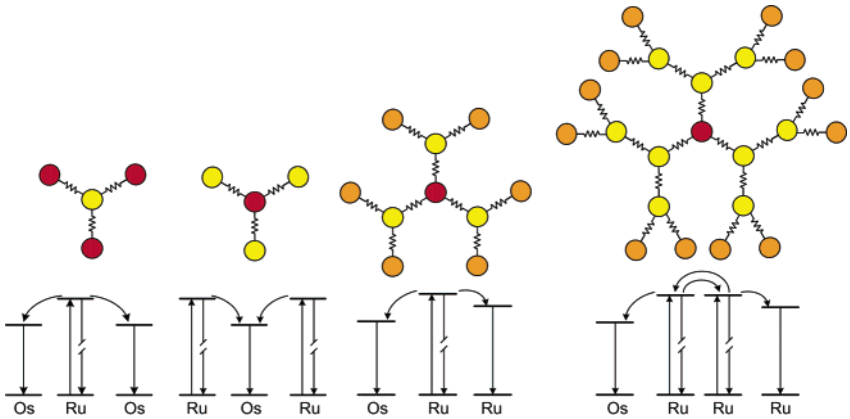

Figure 18. Schematic structures of several Ru^{II}- and Os^{II}-based polypyridine dendrimers together with schematic energy diagrams indicating the energy-transfer processes. Ruthenium centers are marked in yellow and orange, while osmium centers are in red. The terminal ligands are omitted for clarity.[11,345,346]

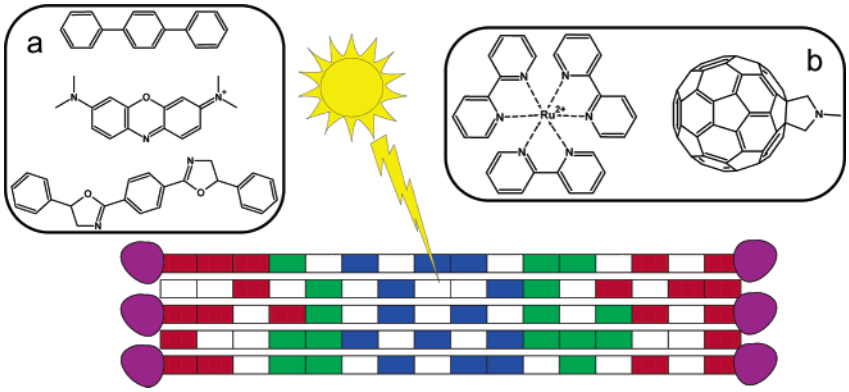

Figure 19. Schematic representation of the dye-loaded zeolite with channel openings blocked with stopper molecules. (Insets) Examples of the dye (a) and stopper moieties (b). (Adapted from refs 326 and 352).

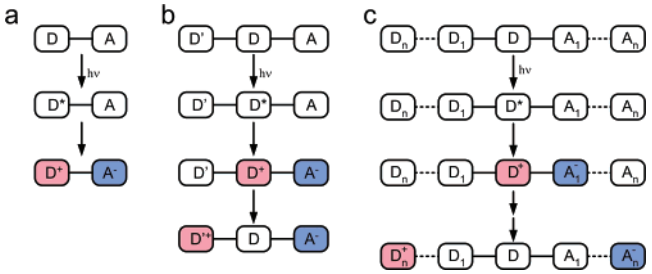

Figure 20. Photoinduced charge-separation processes in dyads (a), triads (b), and polyads (c).[361]

assemblies with incorporated chromophores. The solid support provides both mechanical stabilization of the artificial photosynthetic system as well as proper coupling between donors and acceptors. Clay minerals were also found to be efficient inorganic supports for photoinduced electron-transfer reactions.[360]

4.1.2. Charge-Separation Systems

Once the solar energy is harvested and focused in the reaction center it must be converted into a more useful form, i.e., chemical energy. This goal can be achieved in the systems that allow formation of the charge-separated state with a significant lifetime. The simplest system to achieve this goal is a dyad molecule (Figure 20a), where donor (D) and acceptor (A) counterparts are covalently linked to form one molecule.[361] Photoinduced charge separation occurs here in a single step. It is obvious that in such a structure charge recombination will occur readily. To slow the recombination it is necessary to introduce an additional reaction step in which the charges are moved far apart. The simplest way to do so is to introduce the secondary donor (D′) or secondary acceptor (A′) (Figure 20b). One can envision more complex systems containing an array of donors and acceptors, separating charges as fast and as far as possible (Figure 20c).

In natural systems it is achieved by the carotene-containing system as a terminal electron donor and quinone as a terminal electron acceptor with a series of porphyrin moieties in between. Artificial systems based on the same structural units are characterized with relatively short lifetimes of the charge-separated state. The design of artificial photosynthetic systems is, however, not restricted to naturally occurring building blocks. Redox-active sites may give, in principle, new interesting properties to the synthetic assemblies and expand their usefulness as potential solar energy conversion devices. The C_{60} bucky ball seems to be especially well suited for application as a component of artificial photosynthetic device. They constitute good electron acceptors (up to six electrons) with a reduction potential very similar to that of quinones. The solubility of fullerenes in lipid membranes facilitates construction of biomimetic structures for charge-separation systems.[328,362] Metalloporphyrin−fullerene arrays are also used in solid-state photovoltaic devices.[334] The most successful artificial systems contain porphyrin chromophore (or chromophores) linked with fullerene as an electron acceptor.[328,333−336,362] Among the different systems containing series of electron donors (porphyrins, ferrocene) and acceptors (pyromellitimide, quinones, fullerene) the longest lifetime (380 ms) of the charge-separated state was observed for the tetrad Fc−ZnP−H_2P−C_{60} (Figures 21 and 22).[336] The lifetime of this state is more than 1 order of magnitude longer than in any other synthetic system and is comparable to that observed for the bacterial photosynthetic center. Recently an even longer lifetime has been recorded for the zinc chlorin−fullerene dyad at −150 °C.[338] The quantum yield of the charge-separated state amounts to only 0.12.

Conceptionally different charge-separation biomimetic systems are photovoltaic cells[17,18,363,364] and other photovoltaic devices.[328,334] These devices usually contain a photosensitized mesoporous semiconductor (e.g., titanium dioxide) supported on the transparent electrode, the redox-active electrolyte (usually the I_3^-/I^- couple), and a counter electrode (Figure 23). In some other systems the charge-separating molecule (e.g., fullerene−porphyrin dyad) is attached directly to the surface of the conductor (ITO electrode) via silyl groups.[328,334] The excited state of the photosensitizer[17,365−368] (cyanometalate, polypyridine ruthenium complex, organic dye, etc.) injects the electron to the conduction band of the semiconductor. The oxidized form of the photosensitizer is reduced in turn with the redox couple present in the solution. The cycle is completed upon reduction of the redox mediator at the counter electrode. The liquid electrolyte containing the redox mediator may be replaced with the organic hole conductor.[369] The process is a biomimetic model of photosynthesis in the sense

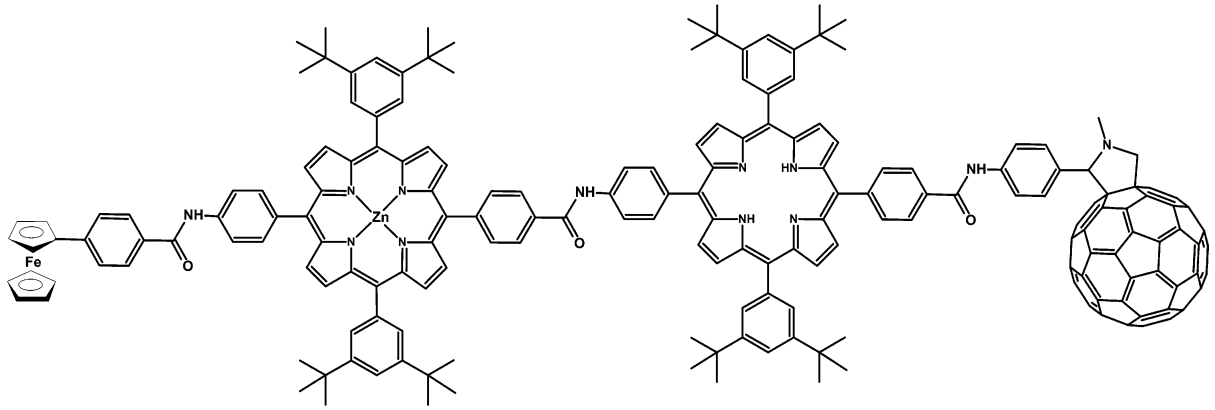

Figure 21. Structure of the ferrocene−porphyrin−fullerene tetrad capable of efficient light-induced charge separation.[336]

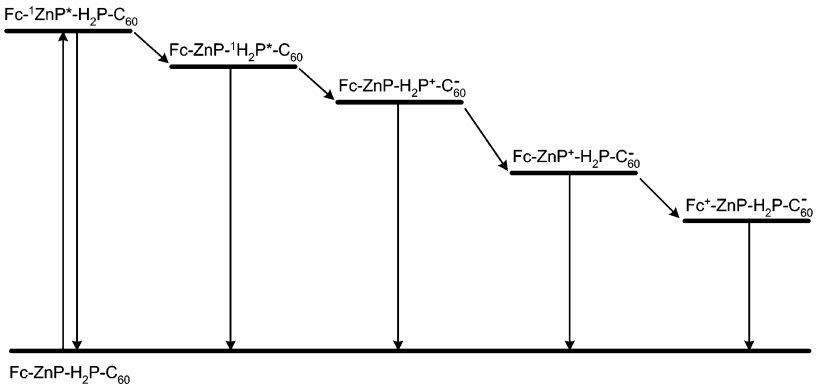

Figure 22. Energy levels and photophysical processes in the ferrocene−porphyrin−fullerene tetrad.[336]

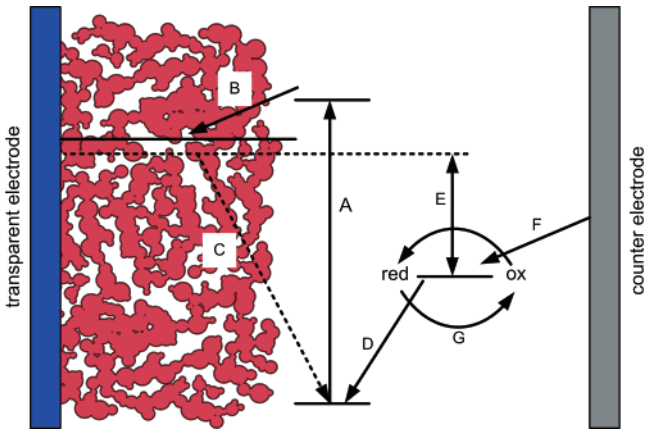

Figure 23. Schematic representation of the principle of the nanocrystalline photovoltaic cell indicating the energy levels in different phases. The cell voltage observed under illumination corresponds to the difference in the quasi-Fermi level of TiO_2 and the electrochemical potential of electrolyte. The latter is equal to the Nerstian potential of the I^-/I_3^- redox couple used to mediate charge transfer between the electrodes (A, excitation; B, electron injection; C, recombination; D, interception; E, maximum voltage; F, reduction of the mediator; G, mediator diffusion). (Adapted from ref 369.)

that it uses the energy harvested in the antenna (photosensitizer) to generate the charge-separated state (mesoporous semiconductor) and transfers the energy to the receiver (external load).

4.1.3. Biomimetic Reaction Centers

In natural photosynthetic systems the excitation energy migrates from the antenna and initiates a cascade of electron-transfer reactions between the reaction center cofactors. Photosystem II contains the primary donor, P_{680} chlorophyll, which in the excited state transfers one electron to the nearby pheophytine moiety. The resulting P_{680}^+ cation is a strong oxidant and abstracts one electron from the tyrosine residue. It oxidizes, in turn, the manganese cluster, which is comprised of four manganese atoms. Four sequential oxidation steps induce, in turn, oxidation of two water molecules and generation of molecular oxygen.

This part of the photosynthetic chain can be mimicked by ruthenium−tyrosinate and manganese−tyrosinate complexes.[370−372] In the excited state the ruthenium polypyridine complex abstracts one electron from the tyrosinate moiety, yielding the tyrosyl radical. More advanced models contain ruthenium polypyridine antenna linked with manganese phenolate or manganese−polyamine complexes containing mono-, di-, and trimeric Mn centers. Subsequent excitation of the Ru^{II} antenna results in oxidation of the Mn^{II} center to Mn^{III} and Mn^{IV}. Di- and trinuclear complexes can provide more electrons to the system.

The other approach toward artificial photosynthesis does not model the natural photosystems directly but instead links natural and synthetic components to achieve a system capable of photochemical water reduction and synthesis of molecular oxygen.[373]

4.2. Artificial Photoenzymes

Photocontrol of the activity of naturally occurring enzymes by modulation of the redox states of the active sites by photoinduced electron injection or

abstraction is one of the most attractive approaches in recent protein engineering.[374,375] Some biomimetic systems have been constructed on the basis of the natural enzymes with artificial photosensitive cofactors.[67−72] These systems allow precise photochemical control of enzyme activity, which have already found applications in biosensors[70] or can lead to new features, like artificial photosynthetic centers or enzyme-like catalysts.[72]

A photoactive glucose sensor was built on the basis of covalently modified glucose oxidase.[70] The native enzyme was transformed to the apoenzyme by the FAD cofactor extraction, and subsequently the enzyme was reconstituted with synthetic merocyanine−FAD cofactor. The enzyme was covalently anchored to the gold surface with thiolate-containing linker. The modified enzyme oxidizes glucose to gluconic acid and reduces ferrocenium to ferrocenecarboxylic acid. The modified cofactor efficiently controls the conformation of the enzyme and hence its activity. Photoisomerization of the merocyanine to the spiropyrane form inhibits glucose oxidation and ferrocenium reduction. If the cofactor contains the spiro form, the contact between the electron mediator (ferrocene) and the protein redox center (FAD) is blocked, while photoisomerization to the merocyanine form activates contact between the reagents. The system may work as an electrochemical glucose sensor or a transducer converting optical signals into electrical ones.[70]

4.3. Light and Metal Compounds in (Bio)chemical Sensing and Studies

The crucial recognition events of chemistry, biology, and materials science occur at the molecular level. Information about these events can be conveniently transmitted to us via light signals emitted by purpose-built molecular devices. Besides this sensory role, such molecular devices also have potential for information processing since their emission can be switched between two distinguishable states by external stimuli.[376] The advantages of molecular luminescence for sensing and switching can be summarized as follows: high sensitivity of detection down to a single molecule, "on−off" switch ability, feasibility of communication between human and molecule, subnanometer spatial resolution with submicrometer visualization, and submillisecond temporal resolution. Furthermore, many of the structural features which reduce fluorescence efficiency like double-bond torsion, low-energy nπ^* levels, "heavy" atoms, weak bonds, and opportunities for photoinduced electron transfer (PET) or electronic energy transfer have been delineated.[376] Apart from electronic-level related issues, another important factor is the substrate binding ability of the receptor and selectivity of this interaction.[377] The highest stability of the sensor−analyte complex is achieved when the substrate fits perfectly into the "hole" within the receptor. The analyte does not have to fit the receptor cavity perfectly; efficient binding can be achieved by careful design of the receptor. It must contain a proper type and number of donor atoms; angular orientation and directionality of lone electron pairs are also of crucial importance.[377]

The role of metal ions in fluorescent or, more generally, optical chemical sensing is crucial. First, metal ions (alkali, alkaline-earth, and transition-metal ions) are the most frequent targets of chemical sensing, especially in medical and environmental analysis.[29,30,48,378−398] Transition-metal cations serve also as binding sites for different neutral[30,38,378,399−401] and anionic[46,378,400−406] analytes and are used as fluorophores[38,46,400,401,403] (mostly Re^{I}, Ru^{II}, Os^{II}, and lanthanides) and structural elements[38,378,395,405,406] in a large number of applications. Transition-metal- and lanthanide-based fluorophores are of special importance because of the very rich diversity of available fluorescent excited states, large spans of excitation and emission spectral ranges, lifetimes, and quantum yields.[52] Lanthanide fluorophores absorb light in the ultraviolet and emit in the visible range with broad absorption and very narrow emission bands. The luminescence does not depend significantly on temperature and variation of the environment. A long fluorescence lifetime allows time-resolved measurements and separation of different optical signals in the time domain.[407] Some sensors can also probe chirality of the substrate, polarity, rigidity, solvent exposure, and molecular dynamics.[38,408] Recently special attention was paid to fluorescent imaging of distribution of biologically important ions and molecules (Mg^{2+}, Ca^{2+}, Fe^{2+}, Zn^{2+}, NO) in organs, tissues, and cells[30,376,409−419] and labeling antibodies and oligonucleotides.[26]

Photophysical processes of metal compounds are important not only for bioanalytical applications. Inorganic photochemistry due to its diversity, time scale, and selectivity is a unique tool in studying and elucidating biomolecule functions and structures. It has been particularly useful for studying electron-transfer processes in biopolymers (e.g., nucleic acids, proteins) and ligand binding to or dissociation from biologically active centers.[420−425]

4.3.1. Metal-Ion Sensors

Most of the reported metal-ion chemosensors are based on the photoinduced electron transfer (PET) phenomenon. The principle of the PET-based sensor is shown in Figure 24. In most cases the sensor consists of a receptor, which selectively and reversibly binds a substrate, a fluorophore that provides optical communication between the sensor and the environment, and a spacer (linker) which binds both components together and provides electronic communication between the receptor and the fluorophore (or chromophore) if the process is thermodynamically and kinetically feasible.[426] In most instances the kinetic restrictions are minor though there are some exceptions. Importantly, the rate of electron transfer is much faster than the luminescence when PET is thermodynamically allowed (Figure 24a). Luminescence and PET are the two main competitors which deactivate the excited state of the fluorophore. Binding of the substrate to the receptor drastically alters the thermodynamics to the endoergonic situation (Figure 24b). In the simplest case the change of the energetics of the system is caused by electrostatic interactions between the receptor and the substrate.

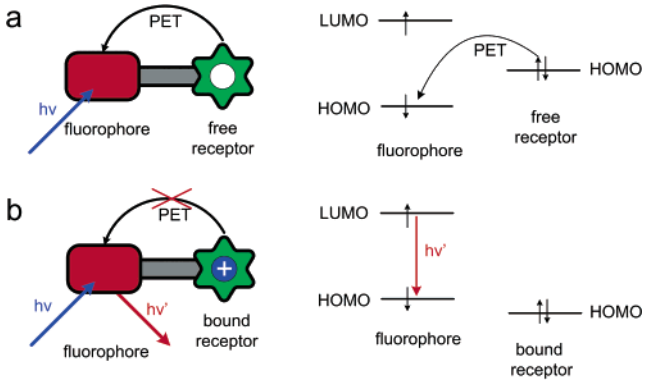

Figure 24. Principle of the PET chemosensor. The HOMO level of the unbound receptor acts as an electron donor and effectively quenches the fluorescence of the sensor (a). Upon coordination of the substrate the energy of the HOMO level of the receptor is decreased due to electrostatic interaction with cationic species and PET quenching is no longer possible (b).

Depending on the desired spectral properties and lifetime of the fluorescent cation sensor the sensing molecule may include various organic (anthracene, pyrene, naphthalimides, pyromellitimide, coumarins, fluoresceins, pyrazolobenzothiazoles, diphenylpyrazoles) or inorganic fluorophores (polypyridine ruthenium(II) complexes, lanthanide complexes).[37,376] Selectivity and sensitivity of the chemosensors are controlled, in turn, by careful design of the receptor part. The large diversity of possible organic ligands enables designing sensors suited for particular applications.

Fluorescent chemosensors suited for in vivo and in vitro analysis of biological samples are now of special importance. Recent developments in neurosciences were possible only due to development in zinc and calcium imaging. Modern zinc chemosensors allow precise determination at subnanomolar concentrations.[411] Most of the complexes contain branched pyridine or edta-like receptors and various fluorophores. These molecules should show good solubility in water and biological fluids, low toxicity, and high fluorescence quantum yield and should not interfere with any natural biological process occurring in the studied tissue. Moreover, to enable gated recording of the chemosensor luminescence, the fluorescence lifetime should be significantly longer than that of the components of the biological sample (e.g., tryptophan residues in proteins).[37,427] These requirements are fulfilled by a several families of compounds. Some examples are shown in Figure 25.

Further development of sensitivity and selectivity of fluorescent sensors can be achieved when bioengineering methods are combined with conventional sensor preparation.[385,398] Metal chelators (edta-like and substituted bipyridines, Figure 26) were used for covalent modification of bovine serum albumin. Upon metal coordination the modified proteins were used to immunize mice. This procedure leads to formation of monoclonal antibodies selectively binding metal-modified protein with very high selectivity and sensitivity.[398] Thus, bioengineered sensors allow accurate determination of Cd^{II}, Pb^{II}, Co^{II}, and U^{VI} at subnanomolar concentrations with high selectivity.

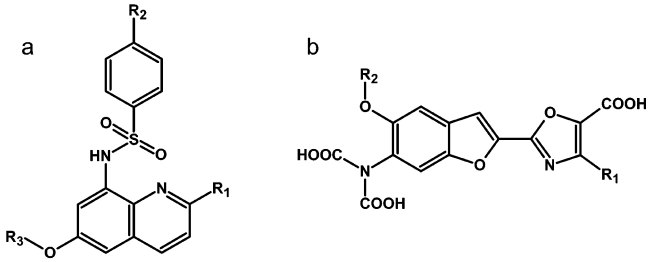

Figure 25. Representatives of two families of zinc chemosensors: TSQ (a) and FURA-ZIN (b). R_1, R_2, and R_3 are hydrogen atoms, methyl groups, and carboxylic or methylcarboxylic groups.[416]

The other biotechnological approach to increase the sensitivity and selectivity of metal sensors involves combinatorial DNA synthesis and evolutionary selection of the most specific, metal-binding sequence. The metal-binding DNA strands are then selected for their catalytic ability to hydrolyze fluorophore-labeled DNA probe. This method allows detection of selected metal ions in the nanomolar range in the presence of a high concentration of other metals.[385]

4.3.2. Sensing of Neutral and Anionic Analytes

More complex receptors are required for sensing of anionic and neutral analytes. While binding of the metal cation requires a specific ligand, anion binding requires a specific receptor in which anionic analyte plays the role of the ligand or is trapped via hydrogen-bonding or electrostatic interactions. The same requirements must be fulfilled for neutral molecules sensing. Anionic substrates include simple inorganic anions (hydroxide, chloride, and phosphate), phenolates, carboxylates, and amino acids. Neutral molecules include oxygen, nitric oxide, amino acids, ATP, sugars, volatile organics, and others.

Anion sensing and recognition in most cases involves coordinatively unsaturated transition-metal or lanthanide complexes[378,400,402−405,419,428] or protonated azapodands or azamacrocycles with the conformation preferably binding only one anion.[378,401,405] The latter chemosensors usually contain a metal-based fluorophore (lanthanide or ruthenium(II) polypyridine complexes), Figure 27.

The output of the sensor depends on the perturbation of the excited-state properties on metal-based fluorophore with the analyte. The nature of excited-state bonding between the receptor and the analyte may change the order of energy levels and switch between luminescent and nonluminescent form.[378] Metal-centered and MLCT excited states are susceptible to stabilization or destabilization through interactions that perturb the energetics of the metal-based or ligand-based orbitals. Changes in the coordination environment of a metal center affect the energetics of the metal-based orbitals, which in turn can alter the energy of the MC, MLCT, or LMCT transition involving these orbitals. Depending on the complexity of the excited-state manifold of the complex the result of such processes can range from subtle changes in emission energies to switching between emissive and nonemissive forms.[378] The latter is especially interesting from an analytical

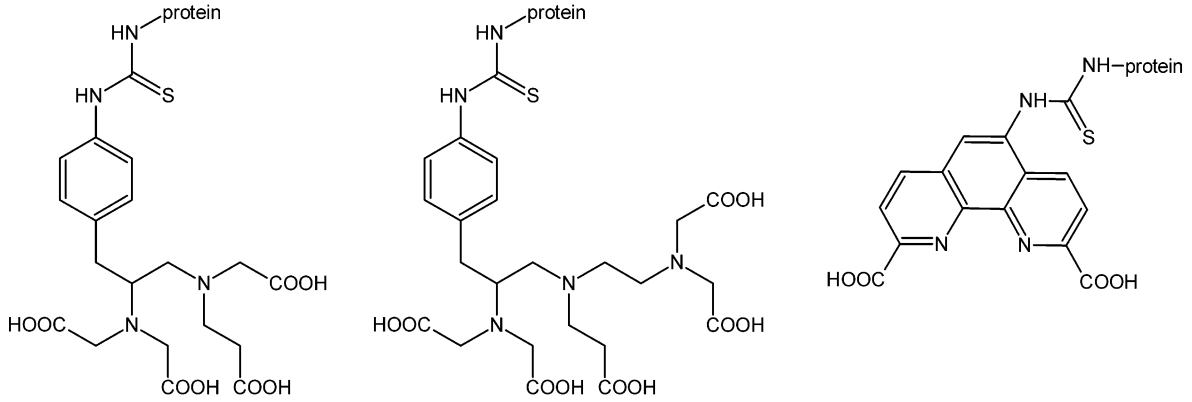

Figure 26. Metal chelators for cadmium (left), cobalt (middle), and uranium (right) used for protein modification.[398]

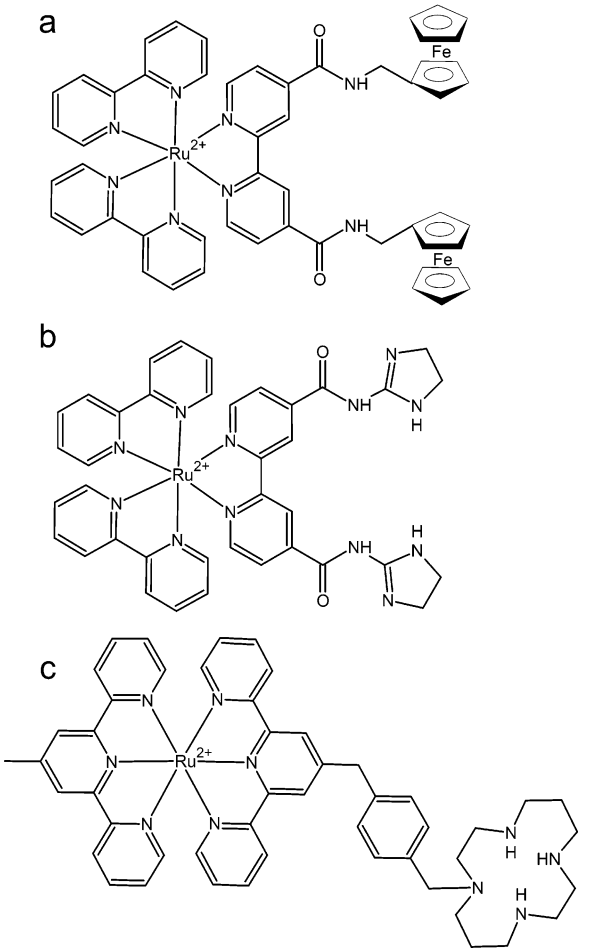

Figure 27. Ruthenium(II) polypyridine-based fluorescent sensors for biologically important phosphate derivatives: hydrogen phosphate (a),[402] phosphodiesters (b),[401] and ATP (c).[428]

chemistry point of view because it can yield the highest signal-to-noise ratio.

The simplest anion receptor design involves direct binding of the anionic analyte to the coordinatively unsaturated metal center. These are common chemosensors, usually based on complexes with polydentate ligands such as tren or macrocyclic derivatives such as cyclams and porphyrins. In many cases the metal plays a dual role as both the receptor and the fluorophore, but more common are the structures where ligand binding affects the photophysical properties of organic lumophore.[378] These structures usually involve late transition elements with unfilled d orbitals such as Cu^{II}, which in the unbound state are able to quench the excited state of the lumophore. The commonly encountered lumophores include aromatic hydrocarbon residues (naphthalene, anthracene, pyrene), acridine, and coumarin, which are susceptible to luminescence quenching via photoinduced electron transfer to the metal ion. Closed-shell metal ions such as Zn^{II} are also commonly used in conjunction with heteroaromatics, whose emission is switched upon formation of a Lewis acid−base adduct. In this case the chemosensor response to metal center coordination arises from quenching mechanics other than electron transfer.[378]

Another strategy assumes coordination of the analyte through displacement of a weakly bound ligand. Lanthanide complexes with a coordinated water molecule are usually weakly fluorescent due to quenching by O−H stretching modes. Coordination of the analyte removes a water molecule from the coordination sphere and gives rise to the intense emission.[378]

Analogous strategies are applied also for sensing of neutral molecules which can serve as ligands. There are numerous amino acid and amine sensors based on Zn^{II} and Cu^{II} complexes[405,429] with fluorescent ligands.[378,401,430] It is possible, however, to detect noncoordinating molecules (e.g., hydrocarbons) based on the same principle of operation. Hydrocarbons do not coordinate to the lanthanide cations, but clever design allowed efficient sensing. The sensor consists of two binding sites linked together: a macrocycle for lanthanide and a cyclodextrin for hydrophobic substrates. Fluorescence enhancement is based on the AETE (absorption/energy transfer/emission) effect, and the analyte acts as a photonic antenna for the lanthanide lumophore.[401] Lanthanide luminescence quenching by molecular oxygen constitutes the basis for several chemosensing systems.[400,431]

More practical oxygen and volatile organics luminescent chemosensors are based on a transition-metal complex embedded in suitable polymers or anchored to solid surfaces.[130,432−445] The sensors are realized by immobilizing a luminescent indicator in a gas-permeable polymeric matrix. The most common lumophores are aromatic hydrocarbons, metalloporphyrins, and transition-metal complexes. Ruthenium(II) polypyridyls[439] and ruthenium(II),[444] rhodium(II),[440] platinum(II),[440−442,444,445] and palladium-

(II)[440,444,445] porphyrins show excellent properties: long fluorescence lifetimes, absorption and emission in the visible range, high luminescence quantum yields, and remarkable sensitivity toward molecular oxygen. Further improvement of sensitivity and selectivity of these chemosensors can be achieved via modification of the solid matrix. Many different polymers, both inorganic and organic, have been tested. The best performance and photostability of the sensor was observed in the case of fluorinated polymers. Due to the high electron affinity of fluorine atoms, they do not undergo porphyrin-catalyzed photooxidation and additionally are characterized by a high oxygen permeability.[440−442]

Various volatile organic substances were found to change the optical properties of free-base porphyrins and metalloporphyrins: absorption spectrum change, the fluorescence switch on or off, and the emission spectrum change.[130,432,434−437,446,447] Metalloporphyrins are a natural choice for detection of metal-ligating vapors because of their open coordination sites for axial ligation, their large spectral shifts upon ligand binding, and their intense coloration. Because of the strong tendency to large color changes induced in metalloporphyrins upon ligand binding, it was possible to develop an easy colorimetric technique which minimizes the need for extensive signal transduction hardware. This represents the first example of a colorimetric array detector for vapor-phase ligands. Simply by taking the difference before and after exposure of scanned images of the array one obtains unique color-change signatures for analytes; these signatures can be used for both qualitative recognition and quantitative analysis.[437] The system constitutes a very efficient olfactory device.[448−450] This method allows distinguishing closely related toxic organics (thiols, phosphines, amines),[437] aliphatic alcohols,[432] and other solvents[435] and checking the quality of food and spices.[434] The same principle was observed in the organic vapor chemosensor based on cyano-bridged rhenium−cobalt cluster complexes, $[Co_2(H_2O)_4][Re_6S_8(CN)_8]\cdot 10H_2O$.[451] The color of the solid sample of these cluster complexes changes from orange (without organic analyte) to red, violet, green, and blue upon interaction with various organic solvents. It is caused by a change in the coordination geometry of the cobalt ions within the crystal framework. This interpretation was confirmed by magnetic studies of these materials.[451] Other vapochromic systems include cyano-bridged coordination polymers based on $[Au(CN)_2]^-$ or Au−phosphine building blocks.[452]

One of the most important biomolecules of which fluorescent sensing[30,399,453] is of great importance is nitric oxide.[187−189,454,455] Nitric oxide can react with several organic dyes, switching on their fluorescence due to triazole ring-closure reaction.[30] There are also useful and selective NO optical sensors based on transition-metal complexes (Figures 28 and 29).[30,399,453]

One of the first metal-containing NO fluorescent sensors contains an Fe^{II} macrocyclic complex connected to a quinoline ligand on the pendant arm (Figure 28). Coordination of nitric oxide to the iron results in labilization of the quinoline moiety and fluorescence decrease.[30] Other nitric oxide sensors are

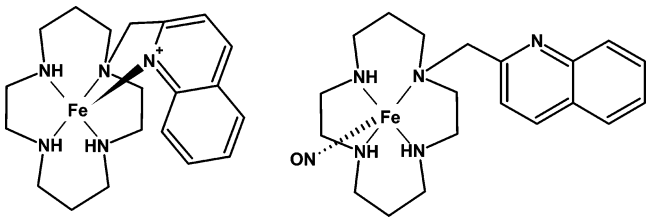

Figure 28. Fluorescent NO sensor. Nitric oxide coordination to the iron quenches the fluorescence.[30]

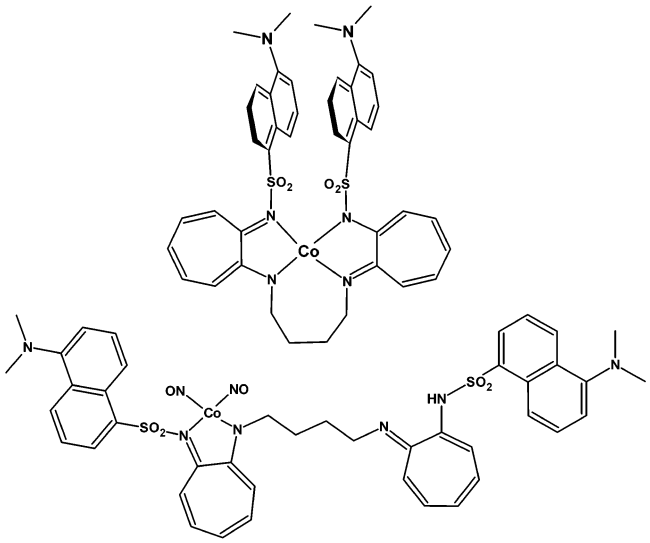

Figure 29. Fluorescent NO sensor. The Co−tropocoronand complex does not emit due to efficient excimer formation (top). Coordination of two nitric oxide molecules changes the geometry, and excimer formation is geometrically inhibited (bottom).[30]

based on Fe,[456] Mn,[453] and Co[457−459] tropocoronand complexes. One example is shown in Figure 29. The tropocoronand ligands incorporate substituted dimethylaminonaphthalenesulfonate (dansyl) fluorophores. Free ligands exhibit strong fluorescence, which is largely diminished upon coordination to transition-metal cations due to excimer formation.[30] The reaction with nitric oxide liberates one arm of the ligand. The new conformation reduces interaction between dansyl fluorophores and hence disturbs excimer formation, which results in a large increase of the fluorescence quantum yield. Nitric oxide can be also determined with an absorptiometric chemosensor based on the Mn^{II} porphyrin complex.[460] The tetrakis(*N*-ethylpyridinium-2-yl)porphyrin complex of manganese reacts with nitric oxide in the presence of ascorbate, yielding the Mn-nitrosylated species. The difference in the absorption spectra of the free and nitrosylated complex allows fast and accurate spectrophotometric determination of nitric oxide in aqueous solutions at the submicromolar level.

4.3.3. Nanoparticles for Optical Sensing and Labeling

Other entirely different methods of optical sensing and imaging utilize not metal complexes but metal and semiconductor nanoparticles.[243,385,461−465] Metal and semiconductor nanoparticles are colored in solution due to the plasmon resonance[461−463,466−468] and possess other size-dependent properties.[462,463,469−473] By controlling their structure at the nanometer scale

one can precisely control and tailor properties of nanoparticles[464] to make them better suited for biological systems, e.g., modify their surface layer for enhanced aqueous solubility, biocompatibility, and biorecognition. There are known surface-modified nanoparticles attached to such biomolecules as sugars,[474−476] peptides,[477] proteins,[478−480] and DNA.[461−463,481−483] These nanoparticle conjugates are used for assembly of new materials, development of homo- and heterogeneous assays, multicolor fluorescent labeling, and high-throughput detection and imaging.[464] Replacement of conventional chromo- and fluorophores with nanoparticles results in higher quantum efficiencies, greater scattering or absorbance cross-section, optical activity at biocompatible wavelengths, and significantly increased chemical and photochemical stability.[464]

The wavelength and half-width of the plasmon resonance absorption strongly depend on the nanoparticle size and shape.[467] This phenomenon was used for specific sensing of metal ions[385] and DNA sequence recognition.[461−463,481,483−486] The molar absorption coefficient is at least 3 orders of magnitude higher than that of any inorganic or organic chromophores ($\sim 2.4 \times 10^8\ M^{-1}\ cm^{-1}$), so it allows using nanomolar concentrations of nanoparticles. DNA surface-modified gold nanoparticles show a characteristic plasmon absorbance similar to that of unmodified nanoparticles. Addition of complementary DNA strands causes aggregation of nanoparticles and hence the color change. The reaction is extremely sensitive to the DNA sequence, and one pair mismatch, deletion, or insertion dramatically changes the aggregation equilibrium. Due to the very high selectivity and sensitivity the nanoparticle-based method of DNA sequence detection was successfully used for anthrax detection.[462]

Semiconductor nanoparticles are powerful fluorescent probes, which can be used for labeling of biomolecules.[487,488] Quantum dots have several advantages over conventional fluorescent dyes. Their emission and absorption spectra are easily tuned by changes in their size and material composition; moreover, they have very narrow emission lines. Fluorescence quantum yields are relatively high (0.3−0.5), and their photostability against photobleaching is 2 orders of magnitude better than that of any other fluorescent labels.[487−489] The fluorescence lifetime is long (few hundreds nanoseconds), which allows time-delayed fluorescence measurements, which can be used to suppress the autofluorescence of biological matrixes.[470]

4.3.4. Nucleic Acids Photocleavage and Charge Transport

The photochemistry of transition-metal complexes has been successfully used in examination of nucleic acids cleavage and charge transport. A proper design of metal complexes by tuning their structural and electronic properties results in selective metallophotocleavers to study the DNA and RNA structures[490−492] and DNA−protein interactions.[493,494]

Mechanisms and Strategies for Advanced Metallophotocleavers.

The photocleavers can cause an immediate strand break or initiate cleavage of nucleic acid which requires further chemical manipulation to recognize the sites and extent of damage.[420] Nucleic acids have two possible targets for photocleavers: sugar moieties or nucleobases. Several mechanisms can be engaged in photoactivated DNA cleavage by metal complexes: (i) oxidation of the base by singlet oxygen formed via energy transfer from the triplet excited state of the photocleaver, (ii) direct electron transfer from the base to the excited state of the photocleaver, (iii) formation of adducts with nucleotide base, or (iv) direct hydrogen abstraction from the sugar moiety by photoexcited metal complex. The formation of photoadduct is usually associated with the electron-transfer process. The DNA photocleavage arising from oxidation of deoxyribose proceeds via hydrogen-atom abstraction from the sugar ring, resulting in formation of sugar radicals. The hydrogen atoms on carbons 1′, 3′, 4′, and 5′ are thermodynamically favored for abstraction due to the presence of heteroatoms at the α positions. The sugar radical can decompose on various pathways, yielding low molecular weight products and DNA fragments.[495] Photocleavage agents, targeting nucleobases, oxidize mainly guanine with formation of 7,8-dihydro-8-oxoguanine, imidazolone, or oxazolone products.[496]

Dramatic growth in the design and development of synthetic nucleic acid photocleavage agents based on metal complexes has been observed during the past decade. Various strategies have been used to improve the sequence selectivity of cleavage which can arise from preferential binding or preferential reactivity at a certain site. One of the approaches involves an increase of DNA-complex affinity by design of metal complexes with extended planar ligands. It leads to an increased surface area of intercalative interactions. A series of ruthenium(II) complexes with phehat and dppz ligands (Figure 10), such as $[Ru(phehat)(phen)_2]^{2+}$ or $[Ru(bpz/tap)_2(dppz)]^{2+}$, was synthesized and applied as photometallocleavers.[155,497,498] These complexes possess high affinity toward DNA with their photoreactivity preserved. Most of the photocleavers of this type can promote photoinduced electron transfer, leading to oxidative damage of nucleic acids. The electron-transfer process between polypyridine ruthenium(II) complexes and DNA arises from formation of the ^{3}MLCT state upon irradiation in the visible region.[155,174] Photoexcited polypyridine ruthenium(II) complexes can be quenched by the electron transfer to a surface-bound electron acceptor like methyl viologen, resulting in formation of Ru^{III} intercalator. This species, which is a potent ground-state oxidant, can be reduced back to Ru^{II} by reaction with the reduced quencher or electron transfer from a nearby guanine base which is the most easily oxidizable one.[499,500] Formation of the neutral radical of guanine, G•(−H), by deprotonation of a guanine cation radical can take place. The oxidized radical of guanine can return to its nonradical form by reaction with reduced quencher or undergo further reaction with O_2 or H_2O leading to formation of stable products (oxidized guanine, vide supra, G^{ox}). The presented procedure, shown schematically in Figure 30, is called the flash quench method and was originally invented to study protein-mediated electron transfer.[501]

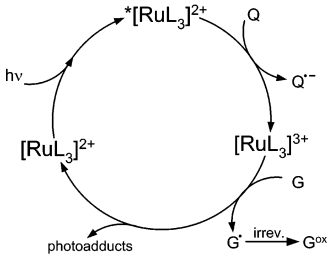

Figure 30. Molecular mechanism of the flash quench method applied for photooxidation of guanine by generated in situ Ru^{III} complex. Q denotes a quencher.[499]

Covalent attachment of the photosensitizer to nucleic acids or oligonucleotides represents a new approach developed in the past decade. The photoactive metallointercalator can be attached to one end of double-stranded DNA. The ruthenium(II) complexes of the type $[Ru(bpy')(phi)_2]^{2+}$, $[Ru(bpy')(Me_2\text{-}dppz)(phen)]^{2+}$, and rhodium(III) complexes, such as $[Rh(bpy')(phi)_2]^{3+}$ and $[Rh(dmb)(phi)_2]^{3+}$ tethered to one strand of the nucleic acid, have been prepared and used to study charge transport in DNA (cf. Figure 10).[500,502−504] The great advantage of this method is that the intercalation of tethered metal complexes takes place a defined distance from the oxidation site.

The synthetic oligonucleotides which have sequence complementary to part of messenger RNA (mRNA) may recognize and react with the target mRNA sequence. In that way they inhibit expression of the targeted sequence. This strategy, so-called the anti-sense or anti-gene strategy, can be used to direct the photoreactive complex to a specific sequence. The photoactive ruthenium(II) complexes ($[Ru(dip)(tap)_2]^{2+}$ or $[Ru(CH_3CN)(dppz)(tpy)]^{2+}$) have been attached to a oligonucleotide and used for irreversible cross linking of the two strands upon irradiation.[279,280,505−507] For the former ruthenium complex it was found that electron transfer from the photoexcited complex to DNA initiates the formation of adducts between the metal complex and DNA (Figure 30). Such behavior was also observed for other complexes such as $[Ru(bpy)_{3-n}(hat/tap)_n]^{2+}$ (n = 2, 3)[174,508] and $[Ru(bpz)_3]^{2+}$.[509] A covalent linkage between the 2-NH_2 group of the guanine nucleobase and one of the organic ligands of the metal complex is formed upon visible light irradiation.[155,508] Other types of photoadducts have been found for $[Ru(tpy)(dppz)(CH_3CN)]^{2+}$ complex tethered to the oligonucleotide. Acetonitrile dissociates from the complex upon irradiation with consecutive formation of a cross link with a guanine base via a coordination bond.[280]

Another strategy for advanced metallophotocleavers is based on shape-selective recognition by proper design of ligands. The series of photoactive Rh^{III} complexes containing a phi ligand represents a class of intercalators which can specifically bind to DNA. The phi ligand is inserted between base pairs, while the ancillary, nonintercalating ligands are oriented in the major groove. Modification of the ancillary ligands allows getting high sequence specificity and reactivity of Rh^{III}-phi complexes with DNA, resulting in new photoactive sequence-specific metallointercalators.[510,511] Another example of shape-selective recognition has been observed for rhodium complexes with chrysi[282] or phzi[284] ligands, which bind preferentially in the destabilized regions at or close to base mismatches. The ligand-centered excited states of Rh^{III} complexes are reductively quenched by guanine or ribose, thus generating carbon-centered radicals with concomitant formation of Rh^{II} complexes.[502,512]

Recently di- and trinuclear complexes to target special DNA geometries or topologies have been designed. DNA binding and photocleavage has been reported for dirhodium complexes such as $[Rh_2(\mu\text{-}OOCCH_3)_4]$[513] and $[Rh_2(\mu\text{-}OOCCH_3)_2(\mu^1\text{-}OOCCH_3)(CH_3OH)(dppz)]^+$.[514] Emphasis has been placed on developing photosensitizers that absorb low-energy light to eliminate the interfering absorbance by other chromophores present in the living systems. Mixed-metal supramolecular complexes that couple ruthenium(II) or osmium(II) light absorbers to a central rhodium(III) core ($[\{(bpy)_2M(dpp)\}_2RhCl_2]^{5+}$ (M = Ru or Os) or $[\{(tpy)_2RuCl(dpp)\}_2RhCl_2]^{3+}$) can promote light-activated DNA cleavage when irradiated with low-energy visible light.[515,516] It has been proposed that the lowest metal to metal charge-transfer excited state (MMCT) of the triad promotes DNA photocleavage.[515,516]

In the search for new advanced metallophotocleavers ligand modification in ruthenium and rhodium complexes has been studied as well as the possibility of application of other transition-metal ions. Among them are complexes of Co^{III} and Co^{II} with mixed-polypyridine ligands such as bpy, phen, and dppz in which one of the ligands has been modified in order to improve DNA-binding properties.[517−523] The exact mechanism of the photocleavage reaction for these complexes is not fully understood. However, it has been suggested that cobalt(III) complexes are capable of photogenerating various radicals, including reactive oxygen species, which can cleave DNA,[517−519,523] while cobalt(II) complexes can act as photooxidants.[521] Some cobalt(III) complexes with non-pyridyl ligands, e.g., bleomycin and its analogues, have been studied as potential DNA photocleavers.[420,524] The tentative mechanism assumes generation of hydroxyl radicals. It has been reported that the tetraanionic diplatinum(II) complexes with pyrophosphito ligands are able to cleave DNA catalytically upon irradiation. Photocleavage proceeds via hydrogen-atom abstraction.[525] Some cyclopentadienyl (Cp) tungsten complexes with covalently attached DNA recognition elements have been tested as metallophotocleavers. In this group of complexes cleavage of DNA is performed by photogenerated methyl or phenyl radicals. Attachment of netropsin analogue (the recognition element) to $[W(CO)_3(Cp)(Ph)]$ complex resulted in an increase of the efficiency as well as selectivity of the strand scission.[526] A new class of DNA photocleavers based on copper(II) complexes containing 9-diazo-4,5-diazafluorene ligands has been suggested as a potential model for the action of Kinamycin anticancer antibiotics.[527] Another group of Cu^{II} and Cu^{I} complexes with ligands containing enediyne units has been found to photocleave DNA.[528] The proposed mechanism involves formation of diradical intermediates as a consequence of photo-Bergman cyclization of copper metalloenediynes. Diradicals enable cleav-

ing DNA via hydrogen-atom abstraction from the sugar moiety.[528] Recently a series of Cu^{II} complexes with polypyridine ligands (phen, dpq, dppz, and dmp) and substituted thiosemicarbazones or aromatic sulfur-containing Schiff bases was reported to be efficient DNA photocleavers. The reactive species involved in DNA cleavage is singlet oxygen formed upon visible or UV light irradiation of Cu^{II} complexes.[529−532]

A large group of photometallocleavers includes metalloporphyrins, discussed in previous sections.[109] Photocleavage proceeds via generation of singlet oxygen by energy transfer from the triplet excited state of metal complexes to triplet oxygen.[533]

The uranyl(VI) ion, UO_2^{2+}, represents another group of photocleavers. It binds to DNA via electrostatic interaction, preferentially to adenine/thymine-rich regions in the minor groove.[534,535] Mechanistic studies indicate that cleavage occurs via hydrogen abstraction from the sugar moiety; however, the detailed mechanism is not completely elucidated.[536] Some studies have shown an important role of singlet oxygen in the cleavage reaction.[537] Uranyl ion can be employed as a probe for a variety of nucleic acid structures as well as an indicator for metal-ion binding to RNA.[538−540] A new approach, based on immobilization of uranyl ion to a polymeric matrix, has been reported recently. The obtained system is amenable to undergo efficient recycling and accelerates the rate of photocleavage.[537,541]

Photoinduced DNA-Mediated Charge Transport.

Charge migration through DNA has been extensively examined.[421−423] Application of metal complexes and light had a great impact on the investigation of this phenomenon. The rate and efficiency of electron transfer through DNA depend on the employed oxidant and unique features of DNA itself. The construction of well-defined DNA assemblies containing donors and acceptors at discrete sites on the helix allows probing DNA as a model of a molecular wire. Study of the long-range oxidation of guanine by strategically placed tethered Ru^{II} or Rh^{III} complexes has shown that the DNA-mediated charge transport can occur over a significant distance (e.g., 20 nm).[500,542,543]

An entirely new approach to study DNA charge transport involves attachment of oligonucleotides to TiO_2 nanoparticles through a dopamine anchor.[544] Photoexcitation of these TiO_2/dopamine/oligonucleotide triads results in charge separation across the nanoparticle interface followed by double-stranded DNA oxidation by holes. This sequential charge separation does not occur when single-stranded oligonucleotides are attached and is sensitive to mismatches in double-stranded oligonucleotides.

The long-range charge transport through the DNA double helix has been found to be sensitive to the sequence and stacking of the intervening bases e.g., mismatches,[545,546] bulges,[500,542,547] crossovers,[504] junctions,[548] and triple strands.[549] In addition, it has been demonstrated that protein binding to DNA can both activate or inhibit charge transfer through the helix.[550−553]

There is an evidence suggesting that DNA is only a marginally better electron conductor as compared to proteins.[554−556] As a result, many studies have been focused on various methods of DNA modification such that conductive properties can be improved. It is possible to enhance the conductivity of DNA by coating it with a thin film of metal atoms, but the molecular recognition properties of DNA are then destroyed. An effective approach to this problem is incorporation of metal ions into the DNA double helix.[557−559] Preliminary results suggest that metal-ion−DNA complex may be a much better conductor than B−DNA, since the former shows a metallic conduction whereas the latter behaves like a wide band gap semiconductor.[560]

4.3.5. Intra- and Intermolecular Electron Transfer in Proteins

Electron transfer is one of the most important and fundamental processes in living systems. Redox-active proteins participate in a number of biological processes such as photosynthesis, respiration, metabolism, and synthesis of bioactive compounds, metabolism of toxic materials, and many others.[425,561−564] A common feature of a large fraction of redox proteins is the presence of metal ions or clusters usually providing an electron sink. The rates of electron transfer to and from metal centers are tuned by the protein matrix.[424,425] Attempts to elucidate the physical and chemical aspects of these complex phenomena require both theoretical and experimental approaches.

Photochemical Methods.

Photochemical methods offer a convenient tool to study intra- and interprotein electron transfer because of their time resolution and selectivity. Various experimental approaches based on the photochemistry of metal complexes have been undertaken. Most of the studies on protein electron-transfer processes have been done for hemoproteins using, among others, (i) photoactive ruthenium complexes, (ii) modified hemoproteins in which heme iron is substituted by other metal ions (Zn, Sn, Mg), and (iii) CO-bound heme proteins.[374,375]

Application of ruthenium complexes as photosensitizers can be realized in several ways: use of the unbound ruthenium complex, attachment of the complex to a protein or its cofactor, and complex tethering to an enzyme substrate. The photoactive ruthenium complexes with polypyridyl ligands have been widely used to study electron transfer in proteins and can be applied for photochemical reduction as well as oxidation of heme proteins. The photoexcited $[Ru^{II}L_3]^{2+}$ complexes can directly reduce ferric heme group in enzymes, and back electron transfer from the ferrous heme to $[Ru^{III}L_3]^{3+}$ can be avoided by addition of the sacrificial electron donor (Figure 31a).[565] When a stronger reducing agent is needed photoexcited $[Ru^{II}L_3]^{2+}$ can be reductively quenched by an electron donor with lower potential, e.g., *p*-methoxy-*N*,*N*-dimethylaniline or *N*,*N*-dimethylaminobenzoate, yielding $[Ru^{II}L_2L^-]^+$.[566] Subsequently, the metal center in the protein can be reduced by the $[Ru^{II}L_2L^-]^+$ complex (Figure 31a). Furthermore, the $[Ru^{II}L_3]^{2+}$ complex can be used for photoinduced oxidation of heme proteins.[567,568] Photoexcited $[Ru^{I}L_3]^{2+}$ can be oxidatively quenched by a suitable

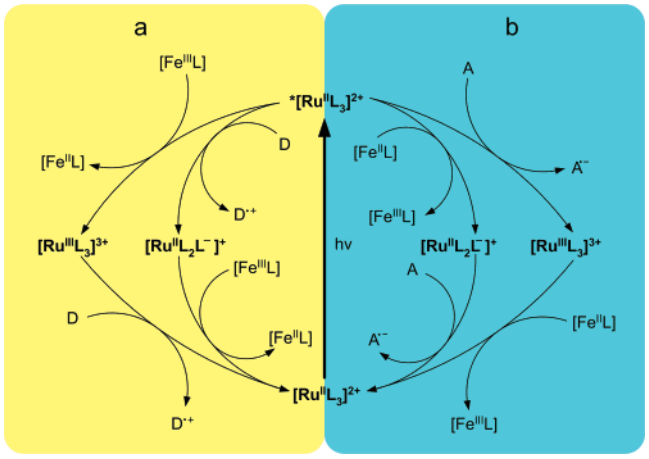

Figure 31. Scheme of the reduction (a) and oxidation (b) of iron centers of hemoproteins with photoexcited ruthenium(II) polypyridine complexes.

sacrificial acceptor ($[CoBr(NH_3)_5]^{2+}$ or $[Ru(NH_3)_6]^{3+}$) yielding $[Ru^{III}L_3]^{3+}$, and subsequently the photogenerated oxidant[569] reacts with Fe^{II} of the heme protein. Alternatively, for some ruthenium complexes (e.g., with bpz ligands) the excited state of ruthenium can be quenched by direct electron transfer from $[Ru^{II}L_3]^*$ to the metal center of the protein, thus forming $[Ru^{II}L_2L^-]^+$ and the oxidized metal center. The back electron transfer from $[Ru^{II}L_2L^-]^+$ to Fe^{III} can be inhibited by addition of an electron acceptor (e.g., $[CoCl(NH_3)_5]^{2+}$), yielding $[Ru^{II}L_3]^{2+}$ and ferric state protein. The oxidative pathway is shown in Figure 31b.

The simple $[Ru(bpy)_3]^{2+}$ complex has been widely used to study the electron-transfer process in proteins.[565−568,570] To improve the binding properties of the complex to proteins and to increase the quantum yields of photoreduction or photooxidation processes novel binuclear ruthenium complexes have been designed ($[\{Ru(bpy)_2\}_2(bphb)]^{4+}$, $[\{Ru(bpy)_2\}_2(qpy)]^{4+}$, $[\{Ru(bpz)_2\}_2(qpy)]^{4+}$).[571−574] They have a net charge of +4, which makes them apt to bind strongly to the negatively charged protein domains and donate/abstract electrons to/from proteins upon irradiation with good quantum yields. These high efficiencies are the consequence of longer MLCT state lifetimes, as compared to the $[Ru(bpy)_3]^{2+}$ complex. Binding properties and selectivity of ruthenium complexes can be further improved by careful design of ligands bearing carboxylate dendrons.[575]

Labeling of proteins with ruthenium complexes has been known for a long time;[576−579] however, design of more effective ruthenium complexes for PET studies and development of modern experimental techniques allow better understanding of the principles and mechanisms of electron transfer occurring in complex biological systems.[374,375,572,580−587] One approach to modify proteins encompasses covalent attachment of the photosensitizer to a specific amino acid (e.g., cysteine,[588] histidine,[589] or lysine[590]) of the protein. A ruthenium complex is usually placed out of the binding domain at the surface of the protein molecule. Another strategy includes attachment of the photosensitizer to the protein using a cofactor-reconstitution.[591−594] A protohemin molecule, the prosthetic group of most hemoproteins, can be modified by binding of $[Ru(bpy)_3]^{2+}$ complex through various spacers followed by incorporation of $[Ru(bpy)_3]$−protohemin into the heme crevice of apoenzyme as shown in Figure 32. To date several proteins have been prepared in this way (e.g., myoglobin, cytochrome b_{562}), and their photoactivation properties and electron-transfer reaction mechanisms have been examined. These semisynthetic proteins can be photoswitched from a resting to an active state by visible light irradiation.

The strategy based on attachment of the photosensitizer via an aliphatic spacer to compounds that bind to the enzyme active site (Figure 33) has been recently applied to a group of cytochromes P450, particularly P450*cam*.[595−597] The ruthenium polypyridine complexes can be attached through hydrocarbon chain substrates (e.g., adamantane, ethylbenzene) or ligands (e.g., imidazole) which have high affinity for the P450 heme pocket and can recognize cytochrome P450 in the presence of other heme proteins. Binding of the Ru^{II}−substrate compounds to the P450 protein can be detected by the decrease of the $[Ru^{II}L_3]^*$−substrate compounds lifetime and the usually monophasic luminescence decay profile becoming biphasic. The substrate with the attached photosensitizer can reduce or oxidize the heme group in protein upon photoexcitation in the presence of the reductive or oxidative quencher (cf. Figure 31).[597] This strategy is particularly useful when the reactive redox center is deeply buried in proteins and the electron transfer between the active site and the external redox agent even covalently attached to the protein is inefficient.

Another approach involves modification of hemoproteins in which heme iron is substituted by other metals. The photoexcited states of heme decay rapidly by thermal dissipation since the iron quenches not only the porphyrin fluorescence but also the fluorescence of tryptophan and tyrosine residues.[374,598] Replacement of Fe^{II} with other metal ions such as Zn^{II}, Sn^{II}, or Mg^{II} triggers, however, the fluorescence of porphyrin and allows population of triplet states.[599] The triplet state of the metal-substituted hemoprotein can act as a good reducing agent. The overall scheme of electron transfer between Zn-substituted heme protein (ZnP) and unmodified heme protein (FeP) is presented in Figure 34. Photoexcitation of the metal-substituted porphyrin yields the singlet excited state of the chromophore, which can be converted to the triplet state, acting as an electron donor. This results in reduction of heme (FeP) and formation of the π-radical cation of the metalloporphyrin (ZnP, cf. Figure 34). The π-radical cation is a strong oxidant which rapidly recaptures the lost electron, thereby returning to the ground state. The Zn-substituted metalloproteins, such as cytochrome *c*,[600−602] myoglobin,[603−607] and hemoglobin,[608] have been extensively used to study photoinduced electron transfer between modified proteins and their physiological redox partners. Interestingly, in hemoglobin it was possible to determine electron-transfer parameters for both α and β subunits.[608]

A more sophisticated method is the combination of metal-substituted proteins with electron acceptors

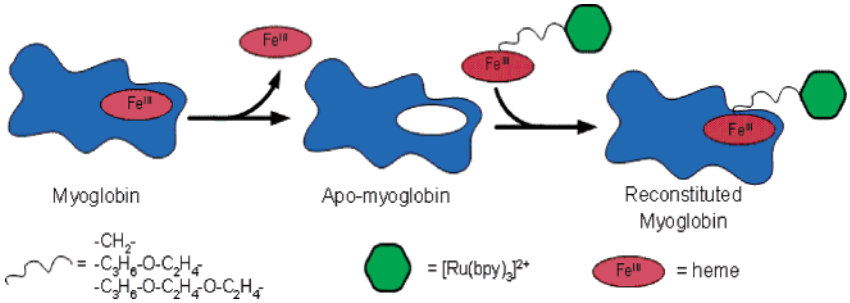

Figure 32. Reconstitution of the ruthenium−tris(bipyridine)-appended heme to apo-myoglobin.[591−593]

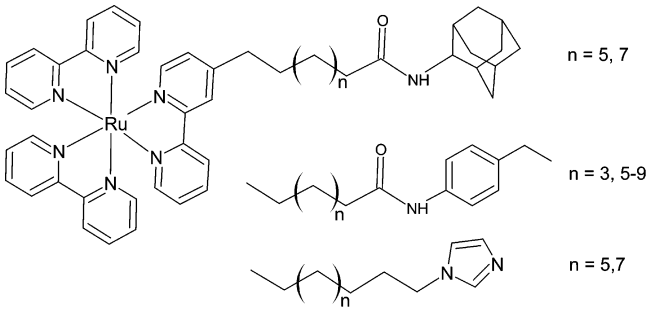

Figure 33. Ruthenium complex linked to enzyme substrates (adamantane, ethylbenzene) or ligand (imidazole).[595−597]

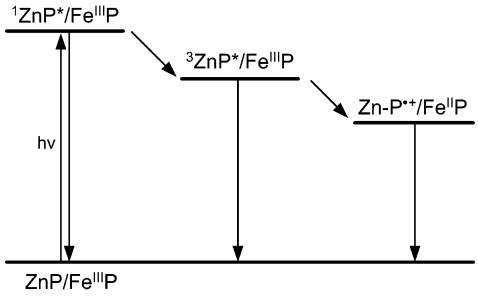

Figure 34. Electron transfer between Zn-substituted porphyrin (ZnP) and unmodified porphyrin in the oxidized state in hemoproteins (FeP).[374]

covalently attached to the amino acid residue located at the protein surface.[609−611] As an electron acceptor the $[Ru(NH_3)_5]^{3+}$ complex attached to the histidine residue has been used in Zn-substituted myoglobin[609,611] or cytochrome b_{562}.[610] This design allows fixing the distance between the donor and acceptor and is very useful for experimental analysis of the intramolecular electron transfer in proteins.

Previously discussed methods of PET studies in proteins assume preservation of the protein redox center properties. An alternative protocol is based on tuning the redox potential of the metal center in protein. This method involves binding of certain ligands to the redox-active metal site in proteins and photolabilization of the ligand.[70] The heme−CO complexes are light sensitive and can be photodissociated with high quantum yield ($\Phi \approx 1$).[612] The light-induced CO dissociation results in lowering of the redox potential and rapidly converts a good electron acceptor (the CO complex) into an electron donor. The intramolecular electron transfer triggered by photodissociation of the CO ligand has been observed for cytochrome *c* oxidase[613,614] and cytochrome cd_1.[615−617] Alternatively, the intermolecular electron transfer has been investigated between carboxymethyl cytochrome *c* and cytochrome *c* oxidase[612] or plastocyanin.[618]

Mechanisms.

The current understanding of intramolecular electron-transfer processes in proteins comes mostly from studies on systems where donors and acceptors are held at fixed distances and orientations. Extensive work on such systems has shown that the dependence of the electron-transfer rate on the distance of redox partners is exponential,[619−622] as expected for tunneling reactions.[620,621,623] Thus, it is likely that the redox centers in these proteins are coupled electronically through the chemical bond framework of the intervening medium.[619,620,623−625]

The interprotein electron-transfer reactions are much more complicated as they involve at least three steps: (i) formation of a reactant complex of the donor and acceptor protein, (ii) electron transfer within the reactant complex, and (iii) dissociation of the product complex. It has often been assumed that the second step, intracomplex electron transfer, takes place within a static reactant complex. However, a number of cases has been observed in which the reactant complex is not static but undergoes dynamic configurational fluctuations (defined as the protein−protein orientation in the bound complex) or conformational changes (defined as the tertiary structure of each protein). If the reaction is rate-limited by dynamic fluctuation rather than by the actual electron-transfer event, then it is said to be gated.[626,627] Kostič and co-workers found that the rate constants for intracomplex electron transfer between zinc−cytochrome *c* and either plastocyanin or cytochrome b_5 decrease significantly with increasing viscosity, indicating gating by dynamic configurational fluctuations.[628] Durham et al.[629] reported evidence supporting configurational gating in the complex of ruthenium-labeled cytochrome *c* and plastocyanin. Hoffman and co-workers[630] studied the concentration dependence of the interprotein electron-transfer rates to demonstrate the conformational heterogeneity of protein complexes. These researchers defined a new dynamic docking paradigm for electron transfer in which interprotein interactions can involve numerous weakly bound conformations of which only a small subset are electron-transfer active.[607] Gated electron transfer in model systems consisting of various ruthenium-labeled peptides and ferricytochrome *c* has been recently studied by Ogawa et al.[631] as a probe of the configurational dynamics of peptide−protein complex.

Studies on the kinetics and structure under the same conditions are needed to probe the interactions

promoting electron tunneling between proteins. A protein crystal containing photoactive donors and acceptors at specific lattice sites is an ideal medium for investigating the dependence of tunneling rates on the structure. Gray and co-workers[632] measured and analyzed the kinetics of electron transfer between native and Zn-substituted cytochrome *c* molecules in crystals of known structures. The results indicate that van der Waals interactions and water-mediated hydrogen bonds are effective coupling elements for tunneling across protein−protein interfaces. Integrating photosensitizers into protein crystals provides a powerful tool for studying biochemical reactions dynamics. Zinc−cytochrome *c* should be an excellent optical trigger for time-resolved X-ray crystallography. Introduction of Zn−porphyrins creates an opportunity to probe the redox-induced structural changes and catalytic intermediates in the protein crystals.

Currently, the design of photoactive reagent which would cross link the associated proteins seems to be a promising method for probing the dynamics of protein−protein interactions.[633−637] The photogenerated excited state of $[Ru(bpy)_3]^{2+}$ in the presence of electron acceptor (ammonium persulfate) yields a Ru^{III} complex, the sulfate radical, and sulfate anion. The proposed mechanism of photoinitiated protein cross-linking involves the formation of tyrosyl radical in reaction with Ru^{III} complex. This is a crucial step of the cross-linking reaction. Subsequently, the nearby nucleophile (lysine or cysteine residue) attacks the tyrosyl radical and the hydrogen atom is abstracted by the sulfate radical. Alternatively, if another tyrosine (or tryptophan) residue is in the vicinity, the coupling with the tyrosyl radical occurs and the sulfate radical is engaged in hydrogen abstraction. The formation of the tyrosyl radical in $[Ru(bpy)_3]^{2+}$/persulfate-mediated protein cross-linking is fast and efficient as compared to the traditional cross-linking techniques[638−640] and can be used in crude extracts as well as in purified proteins. The great advantage of this method is the possibility of cross-linking switching at a desired time, which allows studying dynamic processes.

Spontaneous refolding of proteins occurs in a wide range of time scales: from microseconds to hours. Rapid photochemical methods described above can be utilized to investigate the fast protein folding processes. The refolding process can be triggered by a photoinduced electron transfer from the photosensitizer to unfolded protein.[641−643] Alternatively, the photochemical method based on photoinitiated electron transfer can be used to probe the progress and mode of folding or denaturation processes under solvent conditions favoring the folded or unfolded protein.[644,645] Studies on the folding processes can answer the question of how polypeptide self-assembles into the native structure, which can be helpful in designing an artificial enzyme. Particular interest is focused on enzymes activated by light—photoenzymes.[646,647]

The recent study of Kostič and co-workers[648] showed that interprotein electron transfer between compartmentalized redox proteins is feasible. The rigid sol−gel matrix spatially separates encapsulated proteins from each other. The photoinduced electron transfer between encapsulated redox metalloproteins is possible only in the presence of mobile charge carriers (e.g., metal complexes). The results demonstrate the potential of metalloprotein integration with photocatalytic materials.[648]

4.3.6. Small Molecules Binding to and Release from Biological Metal Centers

Reactions of small molecules (Y = O_2, NO, CO) with metal active centers play an important role in environmental, biological, and medical processes. Despite the extensive studies on metal−Y interactions, the fundamental chemistry of thermal processes in which Y forms and breaks bonds with metals is still not well understood. Laser flash techniques are well suited for investigating the kinetics of binding to and release from metal center reactions. In such studies flash photolysis of an equilibrium mixture of M(L) and M(L)Y leads to labilization of Y from the latter complex, and if no permanent photoproduct is formed, relaxation of the non-steady-state system back to the equilibrium position can be followed by spectrophotometric methods. Mechanistic information on the formation and breaking of the Y−metal bonds has been received with the help of these and other ambient and high-pressure kinetic methods for many systems of biological and medical relevance with such metals as Fe, Cu, Co, Ru, Mn, etc. Kinetic and spectroscopic measurements revealed large differences in the reactivity of metal complexes toward small molecules as well as in the nature of the resulting M(L)Y compounds.[243,245,649−651]

5. Light and Metals in the Environment

Photoprocesses in which metal ions, complexes, or compounds are involved play an important role in the environment and may be used for its remediation. The systems described in this section are divided into two categories: homogeneous and heterogeneous. The first type of system consists of mainly photoredox processes in which soluble metal ions and/or complexes are involved. Some of these systems can be found in the environment; others can be classified as advanced oxidation processes (AOP) which can be applied in solving selected environmental problems. Also, heterogeneous photocatalysis, mainly at titanium dioxide, is an important example of AOP.

The term heterogeneous photocatalysis concerns photoreactions occurring in the presence of a solid catalyst surface.[652,653] Light can be harvested by adsorbed molecules, which then interact with the support in its ground state. The process may be called a catalyzed photoreaction. A sensitized photoreaction takes place when the catalyst after light absorption interacts with adsorbed molecules. In many cases considered in this work a corresponding differentiation is not possible, and therefore, the more general term semiconductor photocatalysis can be used.

5.1. Photochemistry of Transition-Metal Complexes in Homogeneous Systems

Processes using light and metal complexes which proceed in natural waters often involve multiple species.[39] Some of the most common components of these systems are the iron Fe^{III}/Fe^{II} compounds,

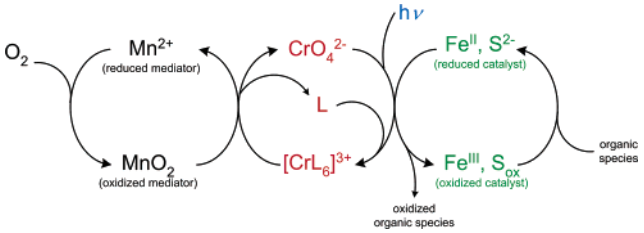

Figure 35. Photosystem with chromium and iron species present in the environment.[211,664]

which are easily converted into each other by thermal redox and/or photoredox processes, and thus, they play a role as either radical sources or their sinks.[654] The excited states of Fe^{III} species are responsible for the oxidation of various organic species present in the environmental compartments. Especially effective are systems containing the Fe^{III}/Fe^{II} pair accompanied by another redox couple, such as Cu^{II}/Cu^{I} [655−663] or Cr^{VI}/Cr^{III}.[664] In next subsections selected aspects of light-induced redox processes of these systems are pointed out.

5.1.1. Photoassisted Fenton Reactions

Photochemical properties of iron complexes/ions in the presence of hydrogen peroxide are tightly connected with hydroxyl radical generation. This opens the possibility of using such systems in AOP.[665] Besides thermal systems which consist of H_2O_2/Fe^{II} (Fenton) or H_2O_2/Fe^{III} (Fenton-like), the photoassisted Fenton system, $H_2O_2/Fe^{II}(Fe^{III})/UV$, is of a particular interest. In the latter case the formation of $^{\bullet}OH$ radicals is significantly accelerated by irradiation (>300 nm) as compared to thermal processes[666,667] due to photogeneration of Fe^{2+}

$$Fe(OH)^{2+} \xrightarrow{h\nu} Fe^{2+} + {}^{\bullet}OH$$

Formation of $^{\bullet}OH$ by Fenton reagent can be described as

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {}^{\bullet}OH$$

At pH values of ca. 2.7−2.8[668]

$$Fe^{3+} + H_2O_2 \rightleftarrows H^+ + FeOOH^{2+}$$

$$FeOOH^{2+} \rightarrow Fe^{2+} + HO_2^{\bullet}$$

To date, oxidation of several organic compounds in photoassisted Fenton and related processes has been reported. Detailed studies include chlorophenols,[669] atrazine,[670] quinoline,[671] detergents,[672] and pesticides.[672,673] The disadvantage of this method is incomplete mineralization[669] and the necessity of using expensive chemicals (e.g., H_2O_2).

5.1.2. Chromium Phototransformations

A variety of chromium species at various oxidation states and forms can be found in the environment. Several parameters such as pH, oxygen concentration, and the presence of oxidants, reducers, and other catalytic systems influence the prevailing forms of chromium-containing ions. The conversion between

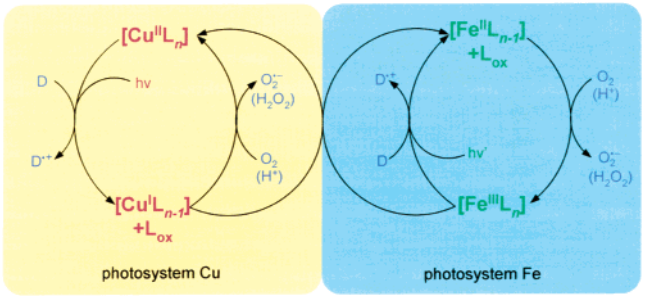

Figure 36. Photooxidation of organic ligands (L) realized in combined Cu^{II}/Cu^{I} and Fe^{III}/Fe^{II} cycles.[211]

chromium(III) and chromium(VI) is relatively easy—Cr^{VI} exists mainly as $HCrO_4^-$ and CrO_4^{2-} ions, while Cr^{III} can form complexes with organic ligands.[664,674−679] An example of the photoredox system present in water is $Cr^{VI}/Cr^{III}-Fe^{III}/Fe^{II}$. In the presence of some organic reducing agents the processes depicted in Figure 35 may occur.[211,664,680] Studies on this type of system[680] with oxalate and citrate gave evidence for photoreduction of Fe^{III} followed by oxidation of Fe^{II} by $O_2^{\bullet-}$, $CO_2^{\bullet-}$, and H_2O_2; the overall reaction can be written as

$$HCrO_4^- + 3C_2O_4^{2-} + 14H^+ \xrightarrow{h\nu,\ Fe^{II}/Fe^{III}} 2Cr^{3+} + 6CO_2 + 8H_2O$$

Dissolved organic matter (alcohols, phenols) can also contribute to the photochemical Cr^{VI} reduction.[681] Reduction of chromium(VI) to chromium(III), called dechromification,[682] is an important process in which strongly toxic and mobile Cr^{VI} anions are transformed into less mobile and less toxic chromium(III) hydroxide.

5.1.3. Photosystems with Copper

The Cu^{II}/Cu^{I} systems photocatalyzing oxidation of phenols,[683−685] amino acids,[661,686] alcohols,[687] and aromatic substrates[687] have been studied in detail. The photoreduction of Cu^{II} is accompanied by ligand (organic substrate) oxidation (Figure 36, photosystem Cu). In the presence of O_2, generated transient Cu^{I} species is reoxidized to Cu^{II} with concomitant formation of superoxide and hydrogen peroxide. The system Cu^{I}/H_2O_2 is able to perform a photoassisted Fenton reaction.

Photogeneration of some reactive oxygen species, like $^{\bullet}OH$, $^{\bullet}OOH$, $O_2^{\bullet-}$, and H_2O_2, is efficiently realized in the environment as well as in systems containing both Fe^{III}/Fe^{II} and Cu^{II}/Cu^{I} redox pairs.[654] The redox reaction between Cu^{I} and Fe^{III} enables coupling of the two photosystems (Cu^{II}/Cu^{I} and Fe^{III}/Fe^{II}, Figure 36).[660,663] Such combination is often found in the environment and is responsible for (photo)degradation of organic pollutants. Several other homogeneous systems capable of organic molecules photooxidation can be found in the environment or used for water purification.[684,685]

5.2. Photochemistry of Transition-Metal Compounds in Heterogeneous Systems

Besides homogeneous systems performing light-induced electron-transfer processes, more and more

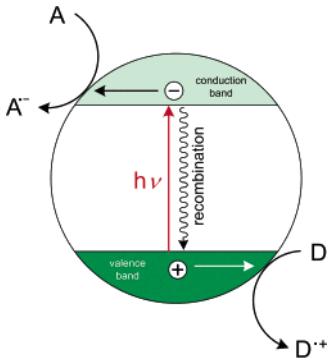

Figure 37. Mechanism of photocatalysis at a semiconductor particle.

studies are dedicated to heterogeneous systems. Light absorption by a semiconductor may be followed by interfacial electron transfer (IFET) between excited material and adsorbed species. This effect opens possibilities to design various materials which can find environmental, biological, and medical applications. Water and air purification, self-cleaning, and self-sterilizing surfaces are only selected examples of photoactive semiconducting materials applications. A semiconductor of particular interest is titanium dioxide due to its appropriate redox properties, low toxicity, good thermal and photostability, and low price.

5.2.1. Primary Processes at Excited Semiconductor Particles

The mechanism of photocatalysis at semiconductor surfaces has been described in many review papers and handbooks.[653,688−692] Hence, it will be discussed here very briefly pointing at some aspects important for further discussion. Irradiation of a semiconductor with photons of energy higher than the band-gap energy results in transfer of an electron (on the femtosecond time scale) from the valence to conduction band of the semiconductor, Figure 37. The fate of generated charges can be various. They can recombine with heat evolution (nonradiative pathway) or light emission (radiative pathway) soon after the separation process or later during their transfer to the surface. The lifetime of excited charges increases after electron and hole trapping in certain states. In the case of titania, electrons are trapped as Ti^{III} centers,[691,693] holes as $\{\equiv Ti^{IV}OH^{\bullet}\}^{+}$.[691] Trapping of holes proceeds in 10−100 ns, while this process is faster for electrons and requires a few hundred picoseconds. Charge-carrier recombination from the trapped states proceeds also in 10−100 ns. The IFET process competes with the recombination processes. An electron localized at a surface site can reduce an electron acceptor (A) adsorbed at the semiconductor. In the case of TiO_2-sensitized photodetoxification the acceptor is usually the oxygen molecule. This process is relatively slow and requires milliseconds to proceed. The hole generated in the valence band oxidizes an electron donor (D) adsorbed at another surface site within hundreds of nanoseconds. Since holes generated in TiO_2 are strong oxidants (about 2.8 V at pH = 0), they are able to oxidize directly most organic compounds as well as water or hydroxyl groups present at the surface (so-called oxidative pathway). Holes and hydroxyl radicals play a crucial role in the process of organic contaminant oxidation.

In the case of small semiconductor particles competition between IFET and recombination is responsible for charge separation. The primary redox products $A^{\bullet-}$ and $D^{\bullet+}$ may also recombine or undergo back-electron transfer

$$A^{\bullet-} + h^{+} \rightarrow A$$

$$D^{\bullet+} + e^{-} \rightarrow D$$

To suppress these undesired processes $A^{\bullet-}$ and $D^{\bullet+}$ should be quickly converted to further products. An increase in the lifetime of charge carriers, IFET rate, and rates of the primary redox product conversion results in higher quantum yields for an overall photocatalyzed reaction.

A semiconductor suitable for organic pollutants photooxidation must fulfill several requirements. Its band gap should allow use of the solar spectrum, i.e., the catalyst has to absorb in the visible or near-UV light region. The redox potential of $^{\bullet}OH/OH^{-}$ and $O_2/O_2^{\bullet-}$ couples should lie within this band gap ($E^{\circ}_{^{\bullet}OH/OH^{-}} = 2.8$ V,[694] $E^{\circ}_{O_2/O_2^{\bullet-}} = -0.16$ V[695]). This is the case for a limited group of semiconducting materials. Out of this group TiO_2 is, however, the best choice due to its high activity and stability (does not undergo photocorrosion), nontoxicity, and low price. The valence and conduction band edges are localized at ca. 3.1 and −0.1 V (vs NHE at pH = 0), respectively.

5.2.2. Reactive Oxygen Species (ROS) Formation

The reductive pathway of semiconductor-catalyzed degradation also plays an indispensable role. An electron from the conduction band of titania reduces adsorbed dioxygen molecule to superoxide anion ($O_2^{\bullet-}$).[696−699] In further steps other moieties, like hydrogen peroxide or $^{\bullet}OH$ radicals, are formed according to the following reactions

$$O_2^{\bullet-} + H^{+} \rightarrow HO_2^{\bullet}$$

$$HO_2^{\bullet} + HO_2^{\bullet} \rightarrow H_2O_2 + O_2$$

$$O_2^{\bullet-} + HO_2^{\bullet} \rightarrow O_2 + HO_2^{-}$$

$$HO_2^{-} + H^{+} \rightarrow H_2O_2$$

$$H_2O_2 + O_2^{\bullet-} \rightarrow {}^{\bullet}OH + OH^{-} + O_2$$

$$H_2O_2 + e_{CB}^{-} \rightarrow {}^{\bullet}OH + OH^{-}$$

Similar to the oxidative pathway, the reactions initiated by e_{CB}^{-} (the so-called reductive pathway) also lead to hydroxyl radical generation. The formation of one $^{\bullet}OH$ requires three electrons from the conduction band (generation of two $HO_2^{\bullet}$ radicals and reduction of H_2O_2).

Another ROS molecule which can be formed upon TiO_2 irradiation is singlet oxygen. The usually dis-

cussed mechanisms of $^1O_2$ formation are (i) energy transfer from the excited semiconductor to O_2 molecule,[171] (ii) $HO_2^{\bullet}$ radical recombination with concomitant H_2O_2 generation,[700] and (iii) $O_2^{\bullet-}/h^+$ recombination.[701,702] The most likely singlet oxygen is formed according to the first mechanism, i.e., in the photosensitization process.[171] Homogeneous sensitizers responsible for ROS generation are described in the section dedicated to photochemistry in medicine (section 3.2).

5.2.3. Photocatalytic Mineralization of Organic Pollutants

Processes based on light utilization for water and air purification have been studied and developed extensively over last two to three decades. The ultraviolet part of solar or artificial light can be used for direct photolysis of organic contaminants alone and in combination with ozonation or hydrogen peroxide.[665] In contrast, heterogeneous photocatalysis based on most commonly used TiO_2 works already at wavelengths shorter than 400 nm. In the latter case UV light and oxygen are consumed. Pollutants containing carbon, hydrogen, nitrogen, sulfur, halogen atoms, and others are usually completely mineralized, i.e., they are converted to CO_2, H_2O, NO_3^-, SO_4^{2-}, halide anions, etc. There are several reports also on photocatalyzed detoxification of selected inorganic ions such as CN^-,[703] NO_3^-,[704] NO_2^-,[704] and others. Due to the very promising features of heterogeneous photocatalysis it has become the subject of many detailed studies and improvements. To date hundreds of organic compounds have been successfully degraded in this process.[691,705] Some pilot plants for water and air cleaning were built and successfully operated, especially in regions with a large number of sunny days. Nevertheless, the efficiency of the photocatalytic process is insufficient. Only ca. 3% of solar light energy, available as UV radiation, can be utilized by TiO_2. Therefore, two main points should be still developed: sensitization toward visible light and improvement of quantum yield of the photooxidation process. Selected aspects of photodegradation under UV and visible light degradation in the presence of TiO_2-based materials are discussed in following sections.

Neat TiO_2 Systems.

One of the most extensively studied compounds in semiconductor-photocatalyzed degradation is 4-chlorophenol (4-CP). The route of 4-CP oxidation at the titania surface, showing the main intermediates, was described in many original and review papers.[691,706−711] This chlorinated, aromatic compound has been commonly accepted as a standard model molecule.[712] The oxidative pathway includes attack of hydroxyl radical or direct oxidation with a hole leading to hydrogen-atom abstraction or introduction of an additional −OH group to the aromatic ring. Further steps include C−Cl bond cleavage, introduction of next hydroxyl groups, and ring opening. Decarboxylation of carboxylic acids and subsequent oxidation reactions lead, finally, to complete mineralization.

Mineralization of numerous organic species cannot be regarded only as oxidation. In many cases oxidation must be preceded by reduction steps. For instance, photocatalyzed transformation of CCl_4 to CO_2 and Cl^- requires first reduction of carbon(IV) to lower oxidation states followed by its reoxidation to CO_2.[691] In this context the redox properties of the excited semiconductor play a crucial role. Photogenerated holes should support a highly oxidative potential, but at the other surface states an efficient reductant (electrons) should be also available.[688,713]

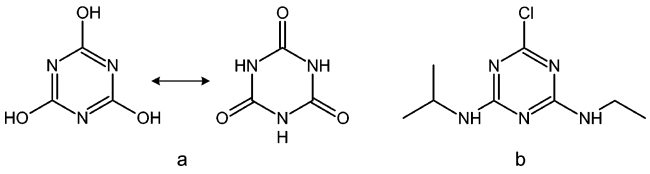

Figure 38. Structures of cyanuric acid tautomers (a) and atrazine (b).

An interesting pollutant attracting particular attention is cyanuric acid (Figure 38). This is an end product of atrazine oxidation in most systems containing TiO_2. The stable molecule of cyanuric acid can be, however, decomposed when the titania surface is modified with Pt^{IV} chlorides[714] or fluoride anions.[715] According to Jenks,[715] hydroxyl radicals formed in the homogeneous phase can degrade cyanuric acid rather than hydroxyl radicals present at the surface of titania.

Metal(0)-Modified TiO_2.

Metal deposition on TiO_2 can be easily achieved by photochemical reduction of the appropriate metal ions in the presence of alcohols as reducing agents. This method can be used for photocatalytic recovery of noble metals from dilute solutions.[716] The presence of Pt^0, Ag^0, Au^0, and other metallic islands on TiO_2 particles also influences other photocatalytic processes. The deposited metal can be regarded as an electron sink.[692,717] Due to better charge separation the lifetime of electron/hole pairs can be prolonged, which enhances the efficiency of the IFET process also observed as higher photocurrents measured at electrodes covered with such materials.[717] The presence of metal at the catalyst surface can influence the product ratio. Platinum deposited at the TiO_2 surface enhances hydrogen evolution, while RuO_2 particles enhance oxygen evolution in the process of photocatalyzed decomposition of water on RuO_2/Pt/TiO_2 photocatalyst.[718] In this system, which can be considered as a short-circuited microphotoelectrochemical cell, platinum plays the role of the cathode while RuO_2 is the anode. Deposited platinum and ruthenium oxide reduce the overpotentials for H_2 and O_2 formation.

Visible-Light-Sensitized Systems.

The inactivity of titania upon visible light irradiation is its main disadvantage. To increase the quantum efficiency during solar light irradiation several photosensitization methods for detoxification and current generation have been applied. A brief overview of the possible photosensitization methods is presented here.

Dye Sensitization. The semiconductor can be modified with a sensitizer (S) absorbing visible light (Figure 39). The redox potential of the excited state (S*) should be lower than the conduction band edge of the semiconductor. The electron transfer from S*

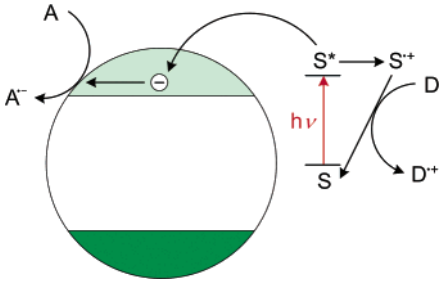

Figure 39. Mechanism of photosensitization with a regenerative sensitizer.

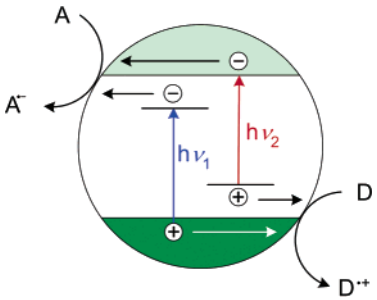

Figure 40. Mechanism of photosensitization with ions.

to the conduction band can occur with subsequent reduction of the oxidized form of the sensitizer ($S^{\bullet+}$) by an electron donor, D. The sensitizer is therefore regenerated, and the catalytic cycle is closed. The semiconductor plays only the role of a support, mediating electron transfer to the acceptor, A. The effect of TiO_2 sensitization was observed in the case of cyanide complexes[719,720] of Fe^{II}, Ru^{II}, Os^{II}, Mo^{IV}, W^{IV}, and Re^{III} or with several $[Ru(bpy)_3]^{2+}$ derivatives used as a dye in photovoltaic cells.[364,369]

A novel version of sensitization was reported for titania containing up to 3% of Pt^{IV}, Rh^{III}, and Au^{III} chlorides in the bulk.[721−723] In aqueous suspensions these hybrid materials sustained visible light activity (>455 nm) for several days. Under such conditions 4-CP was completely mineralized. The surface modification of TiO_2 with $[PtCl_6]^{2-}$ complexes gave even more efficient catalysts.[714,724−726] Upon irradiation the excited platinum complex undergoes homolytic metal−chloride bond cleavage to afford Pt^{III} transient species and an adsorbed chlorine atom. Subsequent ET from the former to titania and from 4-CP to the chlorine atom reforms the sensitizer.

Although the dye sensitization method can be very efficient, its application in photocatalytic water purification is usually very limited due to the low stability of such systems.

Doping with Ions. Some ions, especially transition-metal ions, can provide additional energy levels within the band gap of the semiconductor. The simplest case is presented in Figure 40. Electron transfer from this level to the conduction band requires lower photon energy as compared to the situation of the unmodified semiconductor. The hole photogenerated within the band gap oxidizes the electron donor and primary oxidation products. This type of sensitization was achieved with several metal ions, for instance, Fe^{3+},[704,727] Co^{2+},[704] Li^+, Zn^{2+},[728] Mn^{4+}, Ni^{2+},[729] Cr^{3+},[704,729,730] and others.[731,732] Recently nonmetal doping has attracted more and more attention. Among others, nitrogen-[733−735] and carbon-doped titania[736,737] show interesting visible light activity.

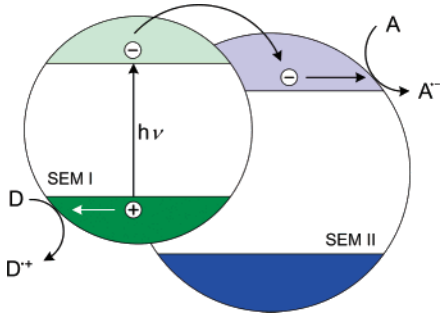

Figure 41. Composite semiconductors.

Composite Semiconductors. Other systems involve hybrid catalysts consisting of two semiconductors characterized by different band gaps and flat band potentials as depicted in Figure 41. Visible light irradiation leads to charge separation only in the semiconductor of lower band gap (SEM I). Then an electron can be transferred to the conduction band of the second semiconductor (SEM II) and later used in reduction of the electron acceptor. On the other hand, oxidation of D takes place at the surface of the first semiconductor. Not only activity upon visible light irradiation, but also an efficient charge separation, suppression of the recombination process, and increased yield of the catalytic reaction are the main advantages of such systems. Examples of this approach are 2-propanol oxidation at semiconductor−zeolite composites[738] or chlorophenol oxidation at CdS/TiO_2.[739,740] Also, Fe_2O_3/TiO_2 colloids were reported to be active toward dichloroacetic acid degradation upon visible light.[741]

Other Semiconducting Systems.

Although titania-based materials are the most commonly used heterogeneous photocatalysts, other systems may also offer interesting activity in oxidation of organic molecules. There are reports on photodegradation of carboxylic acids and phenols at the surface of iron oxides.[742,743] The role of iron-based photocatalysts will be shown in the part dealing with N_2-photofixation (see section 5.2.5). The variety of forms of iron oxides and iron hydroxides enables tuning of their light-induced redox properties and photocatalytic activity. An interesting example is an iron-containing protein—ferritin. This biomolecule consists of 24 protein subunits which create a particular cavity of 7−8 nm internal diameter. This cage can be occupied by one or more nanoparticles of hydrated ferric oxide.[744−746] Studies on the visible light-induced properties of ferritin confirmed the photocatalytic behavior of this material resulting from its semiconducting core. Excitation of the ferritin-encapsulated nanocrystals resulted in e^-/h^+ pair generation followed by some photoredox processes such as reduction of cytochrome *c* and viologens and oxidation of carboxylic acids and thiols.[747] Recently efficient photoreduction of Cr^{VI} species to Cr^{III} catalyzed by ferritin was also demonstrated.[748]

5.2.4. Photocatalytic Microorganism Killing

Reactive oxygen species photogenerated at the surface of excited TiO_2 may be responsible for mi-

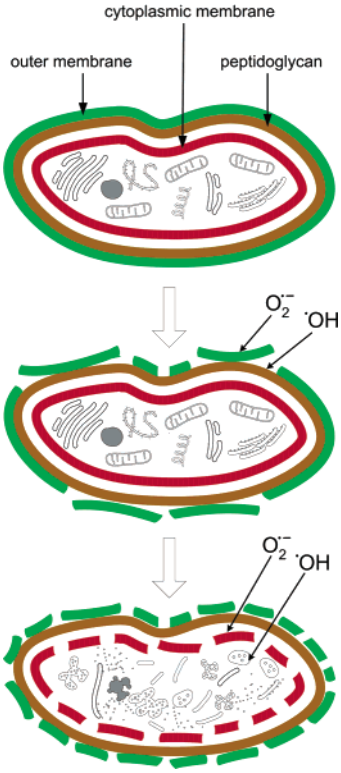

Figure 42. Mechanism of the cellular membrane damage by photogenerated ROS on TiO_2 surface.[751]

croorganism killing. Photokilling of tumor cells by TiO_2 used as a heterogeneous sensitizer in PDT is described in section 3.2.5.

Neat TiO_2 Systems.

Inhibition of growth or killing of bacteria[157,159,749−753] and algae[754] at an irradiated titania surface is well known. This activity of TiO_2 films can be used in sterile surface production, for instance, tiles for medical zones, bathrooms, or pools. The bactericidal effect of the TiO_2 surface results from ROS photogeneration. ROS may attack the cell membrane (mainly by lipid peroxidation), nucleic acids, and proteins (enzyme deactivation). Similar mechanisms are involved in the process of tumor cell photokilling.

The attack of photogenerated ROS on the cell membrane leads to membrane destruction only when its three main layers are broken: the outer membrane, peptidoglycan, and the cytoplasmic membrane (Figure 42).[751] Damage of the outer membrane results in changes of the permeability to ROS. The mechanism for cytoplasmic membrane damage involves mainly lipid peroxidation. This process is possible since ROS generated at the TiO_2 surface has a sufficient lifetime to diffuse at a certain distance. Fujishima et al. demonstrated that the bactericidal effect of irradiated TiO_2 film on *E. coli* can be observed even at a distance of 50 μm from the film.[749] Opening the cellular membrane allows small photocatalyst particles to penetrate the inner part of the cell causing severe, efficient oxidation of the cell content.[161,755]

ROS are efficient oxidants of amino acids, peptides,[166] enzymes,[165] and nucleic acids.[161−164] Nucleic acid destruction can be monitored by pyrimidine dimer formation,[320] DNA structural changes,[164] decrease of DNA molecular weight,[161] or hydroxylation of guanine bases.[163]

Metal(0)-Modified TiO_2.

The influence of metal(0) on the photocatalytic properties of titania was described above. An additional effect can be obtained when TiO_2 is loaded with metal showing bactericidal properties (e.g., Ag, Cu). Tests with Ag/TiO_2 material with 1% w/w silver content showed increased efficiency of *E. coli* killing.[159] The process of lipid peroxidation in this system was significantly faster compared to the system with neat titania. The same effect was achieved with Cu/TiO_2 materials.[157,750] These properties of selected M^0/TiO_2 materials have been used for preparation of bactericidal ceramic tiles. The titania layers were sprayed with metal salt solutions followed by ion photoreduction to form metal islands.[157] The activity of such surfaces is 2-fold: (i) bacteria killing by metal (in dark) and/or by photogenerated ROS; (ii) photodecomposition (photomineralization) of organic material, in particular endotoxins, lipids, etc. The second property of M^0/TiO_2 materials is especially important since removal of a biofilm from the surface prevents it from growth of new microorganisms due to the lack of available nutrients.

5.2.5. Nitrogen Photofixation: Iron Oxide/Titania Systems

In 1977 Schrauzer and Guth reported photocatalyzed reduction of N_2 to ammonia upon irradiation of rutile-TiO_2 doped with 0.2% of Fe_2O_3.[756] Photoreduction was observed only in the presence of humid nitrogen—water vapor was oxidized to molecular oxygen. In general, a higher content of iron oxide resulted in inactive materials. The process was studied in detail also by other groups; however, the nature of the reducing agent remains unclear since in many cases no oxygen formation was detected.[757−763] Typical ammonia concentrations reached in this process were in the range of 1−10 μM. Although the iron-doped material shows visible light absorption, the photoreduction occurred only upon UV light irradiation.

Kisch et al. reported photoreduction of N_2 at iron titanate films with a Ti:Fe molar ratio of 1:1.[764,765] The postulated new semiconducting phase $Fe_2Ti_2O_7$ catalyzed nitrogen photoreduction in the presence of ethanol even upon visible light irradiation. Ammonia and hydrazine formation were observed also when a neat semiconductor and metal ions other than Fe^{III} (Cr, Mn, Co) doped TiO_2 and WO_3 were used as photocatalysts.[766,767] In the presence of oxygen, nitric oxides and nitrates can be formed also.

5.2.6. Carbon Dioxide Photofixation

Reduction of CO_2 photocatalyzed by semiconducting materials may lead to formation of formaldehyde, formic acid, methanol, methane, and oxalate among other products.[692] The earliest report on the photocatalytic reduction of CO_2 with water at TiO_2 was published by Inoue et al.[768] Nearly at the same time the photoreduction of CO_2 to methane at $SrTiO_3$ was reported by Hemminger et al.[769] The same process can be performed also on AgCl/zeolites.[770]

Carbon dioxide photoreduction was observed also at other heterogeneous photocatalysts such as SiC, CdS, GaP, ZnO, WO_3, and $BaTiO_3$.[771] Low yields of the process result from the reverse oxidation reactions. The presence of some metal(0) deposited at the titania surface (vide supra) may enhance yields and the selectivity of the reduction products.[772−774]

Heterogeneous systems similar to those described above capable of CO_2 and N_2 photofixation and catalyzing other transformations of small molecules may be responsible for the genesis of life in interstellar space and on the young Earth. This hypothesis was recently discussed by Serpone et al.[771] and Greenberg.[775] Also, photosynthesis of urea from inorganic compounds of carbon and nitrogen catalyzed by TiO_2 was reported.[776]

6. Conclusion

Inorganic photochemistry is one of the most rapidly growing fields of chemistry. It evolved from simple molecular systems and reached its "adolescence" via convergence with supramolecular chemistry, heterogeneous catalysis, and biochemistry. New trends in inorganic photochemistry explore such diverse areas as medicine, environmental sciences, materials technology, and technology related to new energy sources. In this review we attempted to highlight the recent advances and main frontiers in bioinorganic photochemistry, the interdisciplinary field which intersects inorganic photochemistry with biological, medical, and environmental sciences. Our understanding of the photochemistry and photophysics of metal compounds has matured to the point that solutions to various practical problems of the modern world are accessible.

7. List of Abbreviations

Φ	quantum yield
Φ_F	fluorescence quantum yield
Φ_T	triplet-state quantum yield
τ_T	triplet-state lifetime
Φ_Δ	singlet-oxygen-generation quantum yield
4-CP	4-chlorophenol
5′-GMP	5′-guanosine monophosphate
A	electron acceptor
AETE	absorption/energy transfer/emission
AOP	advanced oxidation processes
ATP	adenosine triphosphate
bchl	bacteriochlorin
bphb	4-[4-(2,2′-bipyridin-4-yl)phenyl]-2,2′-bipyridine
bpy	2,2′-bipyridine
bpy′	4-(4′-methyl-2,2′-bipyridin-4-yl)butanamide
bpz	2,2′-bipyrazine
chrysi	chrysene-5,6-diylidenediamine
CT	charge transfer
cupferron	*N*-nitroso-*N*-phenylhydroxylamine
cyclam	1,4,8,11-tetraazacyclotetradecane
D	electron donor
dip	4,7-diphenyl-1,1-phenanthroline
diphos	*P*,*P*,*P*′,*P*′-tetraphenylethane-1,2-diphosphine
dmb	4,4′-dimethyl-2,2′-bipyridine
dmp	2,9-dimethyl-1,10-phenantroline
dmso	dimethyl sulfoxide
dpds	1,10-phenanthroline-4,7-disulfonic acid
dpp	2,3-dipyridin-2-ylpyrazine
dppz	4,5,9,14-tetraazabenzo[*b*]triphenylene
dpq	dipyrido-[3,2-*d*:2′,3′-*f*]-quinoxaline
dtc	*N*,*N*-diethyldithiocarbamate
edta	ethylenediaminetetraacetate
en	1,2-diaminoethane
FAD	flavin adenine dinucleotide
Fc	ferrocene
fttp	tetrakis(4-trifluoromethylphenyl)porphyrin
G	guanine
GMP	guanine monophosphate
G^{ox}	oxidized guanine
GpG	2′-deoxyguanyl-(3′→5′)-2′-deoxyguanosine
hat	1,4,5,8,9,12-hexaazatriphenylene
Hb	hemoglobin
HOMO	highest occupied molecular orbital
IC	internal conversion
IFET	interfacial electron transfer
IL	intraligand
ISC	intersystem crossing
ITO	indium tin oxide
k_f	fluorescence rate constant
k_{ic}	internal conversion rate constant
k_{isc}	intersystem crossing rate constant
k_r	reaction rate constant
L	ligand
LED	light-emitting diode
LMCT	ligand-to-metal charge transfer
LUMO	lowest unoccupied molecular orbital
M	metal
Mb	myoglobin
MC	metal centered
Me_2dppz	11,12-dimethyl-4,5,9,14-tetraazabenzo[*b*]triphenylene
mgp	*N*-(1,10-phenanthrolin-4-ylmethyl)guanidine
MLCT	metal-to-ligand charge transfer
MMCT	metal-to-metal charge transfer
nc	naphthalocyanine
ncOBu$_8$	octabutoxynaphthalocyanine
OAc	acetate
oep	octaethylporphyrin
P	porphyrin
pc	phthalocyanine
pcS_2	phthalocyanine disulfonic acid
pcS_4	phthalocyanine tetrasulfonic acid
PD	photodiagnosis
PDD	photodynamic diagnosis
PDT	photodynamic therapy
PET	photoinduced electron transfer
phehat	1,4,5,8,9,10,17,18-octaazaphenanthro[9,10-*b*]triphenylene
phen	1,10-phenanthroline
phi	phenanthrene-9,10-diylidenediamine
phzi	benzo[*a*]phenazine-5,6-diylidenediamine
poq	2-{2-(7-chloroquinolin-4-yl-amino)ethylsulfanyl}-*N*-[1,10]-phenantrolin-5-yl-acetamide
poq-Nmet	2-{2-[(7-chloroquinolin-4-yl)methylamino]ethylsulfanyl}-*N*-[1,10]-phenantrolin-5-yl-acetamide
ppy	2-phenylpyridine
PTT	photothermal therapy
qpy	2,2′:4′,4″:2″,2‴-quaterpyridine
ROS	reactive oxygen species
S	sensitizer
salen	*N*,*N*′-bis(hydroxybenzylidene)ethanediimine
SEM	semiconductor
SOD	superoxide dismutase
solv	solvent
tap	pyrazino[2,3-*f*]quinoxaline
tex	texaphyrin
tmtp	tetra(4-methylphenyl)porphyrin

tpp	tetraphenylporphyrin
tpy	2,2′:6′,2″-terpyridine
tren	triethylenetetramine
UV	ultraviolet
UVA	ultraviolet light of wavelength 320−400 nm
UVB	ultraviolet light of wavelength 290−320 nm
UVC	ultraviolet light of wavelength 100−290 nm
X	halide

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