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Light and metal complexes in medicine

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Contents

Abstract

This article surveys some medical aspects of inorganic photochemistry, in particular those involving the use of coordination compounds. Examples of beneficial (therapeutic, diagnostic) and deleterious effects of the interaction between light and metallopharmaceuticals have been selected for presentation. The use of light as a tool in studying and modeling the different biochemical processes is also discussed. © 1998 Elsevier Science S.A.

Keywords: Light; Metal complexes; Metallopharmaceuticals; Medicine; Photomedicine

1. Introduction

Biochemical processes can either proceed naturally, contributing to Darwinian evolution with molecular and macroscopic assemblies and compartments so derived

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that reaction follows the biologically desirable pathway, or they can be adventitious, like xenobiotic metabolism which can follow a multiplicity of pathways and lead to different biological targets. This division is also valid for the photobiochemical processes. In this case, photochemically produced excited states and active molecules increase the number of metabolic pathways and macromolecular targets. Medicinal photochemistry deals with the reactions which pharmaceuticals (drugs or diagnostic agents) undergo when exposed to UV or visible light. Quite often a photoexcited pharmaceutical displays toxic or therapeutic effects towards biological systems. The aim of medicinal photochemistry is to gain insight into: (i) the relation between photoreactivity of a pharmaceutical *in vitro* and its biological activity *in vivo*; (ii) the relation between the molecular and electronic structure of a pharmaceutical and its photoreactivity *in vivo*. Those relationships are important for drug design as they can be used to promote a phototherapeutic effect or to define a phototoxicity potential. There is much current interest in the design of metal complexes as drugs and diagnostic agents and in understanding the molecular mechanism of action of metallopharmaceuticals already in clinical use.

2. Light and health

Light is essential to our health and is useful as a tool for therapy and diagnosis and in preventive medicine [1–27]. There are many beneficial effects of sunlight on the body, from warmth to recovery from states of depression. One of the most important functions of light is transmission of information about the environment resulting in movement, orientation, and vision. 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 by the action of some UV components of sunlight.

Unfortunately, light, and 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. Light penetrates through the skin to some extent and the melanin pigments filter out much of the ultraviolet effect. However, chronic sunburn is injurious to the skin; it results in premature aging, and prolonged sunburn can lead to skin cancer. The skin cancer is initiated by radiation within the range 260–300 nm that brings about alterations of the DNA molecule. Damaging effects of near-ultraviolet or visible light can also be brought about indirectly by a photosensitization of the molecule, which can be a species naturally occurring in the cell or exogenous metallopharmaceutical or pollutant.

We are just beginning to explore and understand the medicinal uses of light. The use of visible light or near-visible light as a therapeutic agent in clinical medicine is called phototherapy. It falls into two categories: direct, when biological molecules, like proteins, nucleic acids or smaller molecules (like glutathione), absorb light and undergo a change; and indirect, when the effect is achieved via an administered photosensitizer which is the effective light absorber. Phototherapy is generally considered to have originated with Finsen [2], who at the beginning of the 20th century

treated tubercular conditions of the skin with heat-filtered light from a carbon arc lamp. The direct use of light as a therapeutic agent is important currently in the treatment of vitamin D deficiency, neonatal jaundice, autoimmune system diseases, and manic depression, etc. [1].

The sequence of events that leads to the therapeutic effect in indirect phototherapy starts with the absorption of UV or visible light by an administered drug. Subsequently, the photoexcited drug molecule undergoes a number of primary processes, such as photochemical reaction of the drug itself, photoreaction with endogenous molecules, or energy transfer to endogenous species. One of the most active research fields of indirect phototherapy at present is tumour phototherapy called photodynamic therapy (PDT) [3–27]. The basic idea of PDT is to inject a photosensitizer which shows some selectivity for tumour tissue and then, when maximum differentiation in concentration of this photosensitizer in normal and tumour tissue is achieved, the tumour is irradiated by visible light. The excited species of the phototherapeutic agent then undergo different reactions, among which electron transfer (ET) and energy transfer processes are the most important. Radicals or singlet oxygen produced in these processes are the species mostly responsible for the photonecrosis [4]. Using fibre optics and a laser source it is possible to irradiate internal tumours, so that the method is not restricted to tumours at, or near, the surface of the skin. Since the photosensitizer is chosen to have some selectivity for the tumour, and since light is highly directional, it is possible to target the tumour with some precision.

3. Metal complexes in medicine

Metal complexes important for our health are both endogenous (like metalloproteins) and exogenous in origin. Exogenous metal complexes can be administered to our body desirably in a controlled way, as is the case of pharmaceuticals (drugs and diagnostic agents) or undesirably (uncontrolled) as by air or dietary pollutants. It is notable that some organic pharmaceutical agents or pollutants may be directed towards metal targets in the body, or require metal binding to function (e.g. the anticancer agent bleomycin requires iron and dioxygen). The pharmacological activity of metal complexes depends on the metal, its ligands or both. Two factors, i.e. maximum thermodynamic stability and large degree of selectivity, are important in the design of metal complexes or ligands for medical application. The reason for this is interaction between exogenous metal ions and natural ligands present in the body which are engaged in storage, transport and the regulation of the activity of endogenous metal ions that are needed for various metabolic purposes [28].

A wide variety of metal compounds are already in clinical use (Fig. 1) [28–34]. These include mineral supplements containing metals essential for mammalian life, e.g. Fe, Zn, Mn, Cu, Mo, Ca, Mg. Cobalt comes in the form of vitamin B_{12}, which is the physiologically effective complex. Widely used are antacids, many of which are simple inorganic salts of Group 1, 2 or 13 metals (sodium bicarbonate, magnesium oxide, trisilicate or carbonate, aluminium hydroxide).

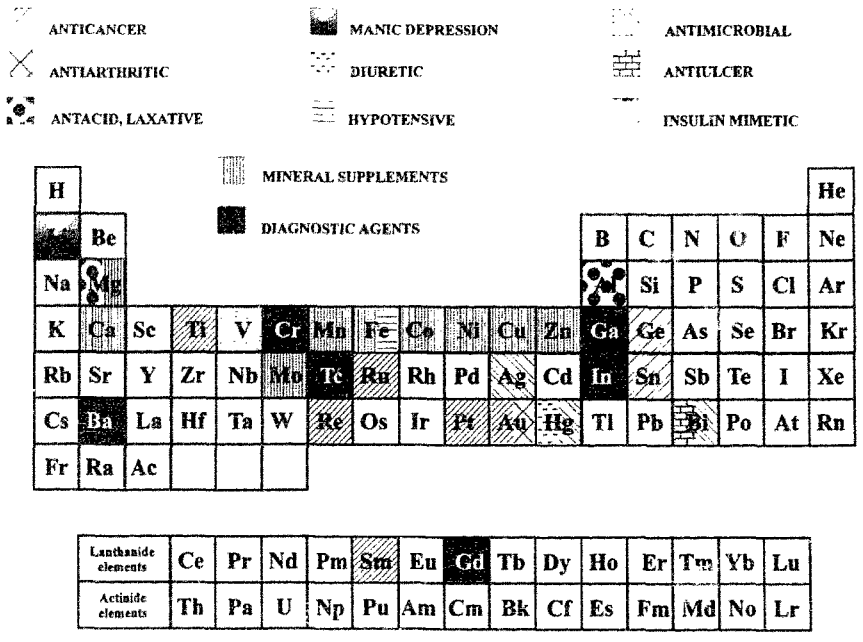

Fig. 1. Some biomedical applications of metal compounds (drugs, diagnostic agents).

At the beginning of this century, a gold complex, $K[Au(CN)_2]$, was introduced for the treatment of tuberculosis. Today several injectable gold(I) thiolates (e.g. aurothiomalate, aurothiopropanol sulphonate) and also the orally active drug auranofin, (2,3,4,6-tetra-*O*-acetyl-1-thio-1-β-D-glucopyranosato triethylphosphine gold(I)) are used for the treatment of rheumatoid arthritis [28,29,31].

The introduction of the platinum(II) complexes *cis*-$[PtCl_2(NH_3)_2]$ (cisplatin) and *cis*-$[Pt^{II}(CBDCA)(NH_3)_2]$ (where CBDCA is 1,2-dicarboxycyclobutane) has dramatically improved the success rate for the treatment of certain types of cancer, notably testicular cancer. The main target site for platinum is DNA and, specifically, intrastrand cross-links involving guanine and adenine bases. Sulphur ligands, such as the amino acid L-methionine and glutathione are also involved in the metabolism of platinum drugs. There is current interest in the development of orally active platinum complexes which are active against a wider range of cancer types. Although platinum complexes have been the most intensively investigated, research has been extended to practically all metals, among which the coordination compounds of gallium, titanium, iron, ruthenium, rhodium, palladium, copper and gold and organometallic compounds of germanium, tin, titanium, vanadium, iron and rhodium seem to be the most promising [28,29,31,33].

The iron compound, disodiumpentacyanonitrosylferrate, $Na_2[Fe(CN)_5NO]\cdot 2H_2O$ (sodium nitroprusside, SNP), which is used in the control of blood pressure (vasodilation), especially as an emergency drug in the case of hypertension crises that can no longer be influenced by any other drugs, is an example of a metal complex which carries a reactive ligand (nitrosyl ligand) to its target site [35–44].

Simple inorganic salts are also in clinical use. Lithium salts are used in psychiatry for the treatment of manic depressions. Metal compounds are often found in dermatology (e.g. Zn, Ag, Hg, Sb, Al).

Metal compounds have a number of diagnostic uses. Insoluble barium sulphate is used as an X-ray contrast agent for imaging the gastrointestinal tract. NMR contrast agents approved for clinical use include Gd(III) complexes with DTPA (diethylenetriaminepentaacetate) and DOTA (1,4,7,10-tetra(carboxymethyl)-1,4,7,10-tetraazacyclododecane) as ligands. Radioisotopes ^{99m}Tc and ^{111}In are widely used as radiodiagnostic agents, e.g. for imaging myocardial and cerebral perfusion and monitoring kidney function, depending on the types of ligand and the overall charge on the complex [28,31].

4. Interaction of light and metal complexes in medicine

Light can interact with medicinally important metal complexes *in vivo* or *in vitro*. This interaction can be both controlled and uncontrolled, which brings positive (physiological, therapeutic, diagnostic) or negative (pathological, toxic) effects.

In this article we will provide a sampling of the approaches that have been developed. Among others, vitamin B_{12}, SNP and its analogue, pentacyanonitroferrate(III), ($[Fe(CN)_5NO_2]^{3-}$) have been chosen to illustrate some aspects of the light and metal complex interactions in medicine.

4.1. Photobiological targeting

Research in the area of medicinal chemistry concerns persistent questions of drug resistance, toxicity and the need for better targeting to the sites of actions. In this respect light offers the unique possibility of triggering the desired action at the desired point. In fact, PDT is based on this concept [3,4].

Another field where the possibility of point irradiation can be very useful is drug and diagnostic-agent delivery systems. The pharmaceutical can be packaged in the form of a thermally stable compound and released from this compound at the desired place by point irradiation (using a laser and fibre optics). The carrier molecule should be easy to prepare, have minimal toxicity in the dark, should undergo efficient photochemical reaction leading to the release of the pharmaceutical in the appropriate form and generate only non-toxic, easily excreted by-products.

The only cobalt complexes which seem to be essential to humans, vitamin B_{12} and its derivatives, can be considered as potential carrier molecules. The B_{12} family, among others the cobalamins with the general formula B_{12}–X, where B_{12} is Co(III)(corrin)(N-base), meets most of the aforementioned requirements. Light sensitivity is one of their outstanding features. The photochemical reactions of the cobalamins involve the bond breaking between the cobalt centre and the axial X ligand [45–58]. This can be realized by either a heterolytic or homolytic pathway.

In aqueous media the heterolytic mode leads to photoaquation.

$$B_{12}X + H_2O \xrightarrow{h\nu} B_{12}\text{–}H_2O^+ + X^- \quad (1)$$

The homolytic fission generates two reactive products the X· radical and Co(II) complex ($B_{12\,r}$).

$$B_{12}\text{–}X \xrightarrow{h\nu} B_{12\,r}(II) + X^{\cdot} \quad (2)$$

The vitamin $B_{12\,r}$ readily undergoes oxidation and aquation.

$$B_{12\,r} + O_2 \xrightarrow{H_2O} B_{12}\text{–}H_2O^+ \quad (3)$$

The B_{12}–X complexes can be easily prepared from aquaocobalamin (B_{12}–H_2O^+) owing to high lability of the aqua ligand [59,60]. Moreover B_{12}–X derivatives and their side photoproduct, B_{12}–H_2O^+, are non-toxic and the excess of B_{12}–H_2O^+ is easily excreted from the body.

The metallocobalamins B_{12}–X with a second metal complex such as $[Fe(CN)_5NO]^{2-}$ [59], $[Pt(CN)_4]^{2-}$ or $[Au(CN)_2]^-$ [61] as the sixth ligand X have already been considered as useful models for this new medical application of vitamin B_{12}. These metallocobalamins can be prepared by direct synthesis from $[B_{12}\text{–}H_2O]^+$ and the appropriate complex. Upon irradiation, all three compounds ($[B_{12}$–μ-$NCFe(CN)_4NO]^-$ [62], $[B_{12}$–μ-$NCPt(II)(CN)_3]^-$ and $[B_{12}$–μ-NCAu(I)(CN)] [61]) undergo photosolvation

$$[B_{12}\text{–}\mu\text{-}NCFe(CN)_4NO]^- + H_2O \xrightarrow{h\nu} [B_{12}\text{–}H_2O]^+ + [Fe(CN)_5NO]^{2-} \quad (4)$$

$$[B_{12}\text{–}\mu\text{-}NCAu(CN)] + H_2O \xrightarrow{h\nu} [B_{12}\text{–}H_2O]^+ + [Au(CN)_2]^- \quad (5)$$

$$[B_{12}\text{–}\mu\text{-}NCPt(CN)_3]^- + DMSO \xrightarrow{h\nu} [B_{12}\text{–}DMSO]^+ + [Pt(CN)_4]^{2-} \quad (6)$$

Since $[Fe(CN)_5NO]^{2-}$ is used as a vasodilator, and certain Pt(II) and Au(I) complexes are used in the chemotherapy of cancer and rheumatism, it is feasible that metallocobalamins bound to $[Fe(CN)_5NO]^{2-}$ or suitable Pt(II) and Au(I) complexes can serve as physiological carriers for bioactive metal complexes. Moreover, a controlled photochemical release of the bioactive metal complex might lead to a new type of phototherapy.

A few years ago nitric oxide was recognised as a biologically important molecule, among others regulating blood pressure, acting as neurotransmitter and participating in the ability of the immune system to kill tumour cells and intracellular parasites [35–44]. The release of nitric oxide from different donor compounds by photochemical methods is a phenomenon studied recently [63,64]. The possibility of using

nitrosocobalamin (B_{12}–NO) and nitrocobalamin (B_{12}–NO_2) as NO-donors from which nitric oxide can be released by point irradiation is under investigation [62].

4.2. Phototherapeutic effects

Some metal complexes are used as photosensitizers in PDT [4–27]. The choice of a photosensitizer and its subsequent phototherapeutic treatment is based on its physicochemical properties in the ground and excited states, its pharmacokinetic and pharmacodynamic behaviour, and its photoactivity *in vivo*. A good photosensitizer for PDT should meet the criteria mentioned above, plus be a single substance with constant composition and a high degree of chemical purity, be as non-toxic as possible in the dark and be sufficiently stable kinetically and thermodynamically. It must have strong absorption bands within the "phototherapeutic window" (650–850 nm range), which includes the wavelengths with maximum penetration power into mammalian tissue (Fig. 2). It must exhibit significant excess uptake by tumour relative to normal tissue, and undergo efficient generation of reactive, cytotoxic species by either energy transfer or ET [4].

At present, porphyrins, chlorins, bacteriochlorins, phthalocyanines and naphthalocyanines are the most important photosensitizers in PDT. Their complexes with metals such Sn, Zn, Sb, Mg, Al., Ga, etc., are of clinical interest [4–27]. Protoporphyrin (PP) is a potent sensitizer in cell culture and in cell-free systems. Its metalloporphyrin analogue, tin PP (SnPP), is an equally effective photosensitizer and has other interesting biological properties. The hydrophobic PP first encounters the cell membrane, where it concentrates and, on irradiation, catalyses alterations

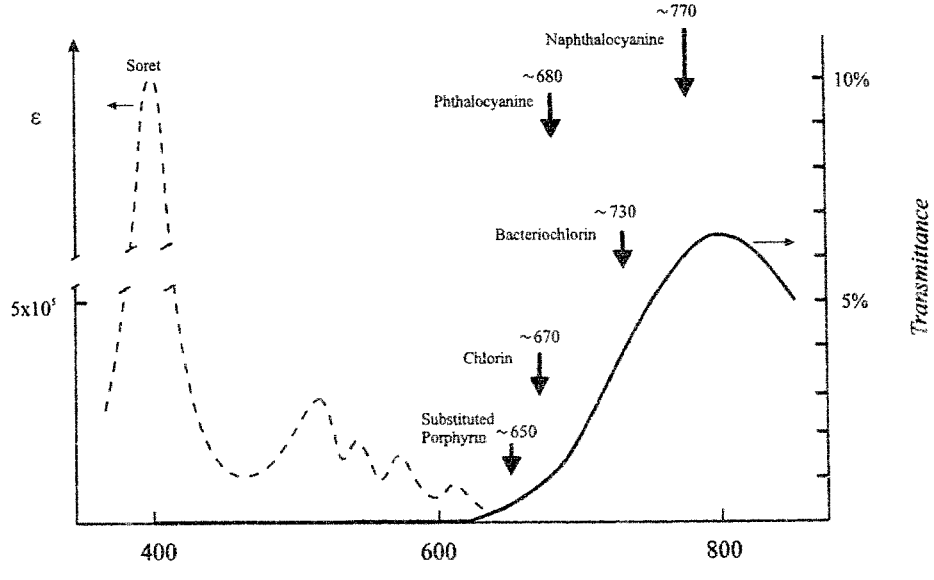

Fig. 2. Typical tissue transmittance in relation to photosensitizer absorbances: porphyrin (dashed line) and others mentioned in figure with the I band parameters (adapted from Ref. [4]).

in membrane hydrophobicity and transport, whereas the more hydrophilic SnPP is less effectively accumulated and causes photodamage of species of hydrophilic character at an intracellular site [4,12].

It has been shown that several non-photosensitizing metalloporphyrins and metallophthalocyanines bound with paramagnetic central metal ions can be accumulated and retained by tumours *in vivo*. These compounds have short triplet lifetimes and very low fluorescence quantum yields; therefore, decay from the electronic excited state to the ground state occurs mainly by non-radiative pathways, releasing energy as heat. These so-called photothermal sensitizers can thus produce local hyperthermal effects leading to specific damage of cell and tissues (e.g. alteration in membrane permeability, tissue shrinkage, cell mortality, tissue coagulation, vaporization and ablation of tissue) [13].

Phthalocyanines and naphthalocyanines can form chelates with many metal ions (aluminium, zinc, gallium, cadmium, thorium) and these complexes show photobiological activity against tumours. Metallocomplexes of naphthalocyanines (for example zinc naphthalocyanine) are surely more hydrophobic than phthalocyanine complexes. They show significant activity *in vivo* only after intraperitoneal delivery in liposomes. This activity depends strongly on the substituents [4,7].

Texaphyrins are sensitizers with high singlet oxygen quantum yields. Such ligands readily form complexes with diamagnetic metal ions. These complexes absorb at the long-visible and near-IR wavelengths (600–900 nm). Complexes with lanthanum and lutetium show phototumouricidal activity *in vivo*, whereas those with cadmium and gadolinium appear promising in this application [1].

4.3. Photoabatement of therapeutic effect and phototoxicity

Irradiation of drugs, either *in vitro* or *in vivo*, can lead to the abatement of the therapeutic effect or even cause toxic effects. In toxicology, a drug is defined as phototoxic if light represents an essential condition for causing an unwanted biological effect.

Although nitroprusside is a valuable drug, there have been many reports [65–69] that it is metabolized in red blood cells with a rapid release of cyanide into the blood-stream. Photochemical study has revealed, however, that it is also light and not only blood which is responsible for the release of the cyanide [60,70–76]. Moreover, relaxation of the rabbit aortic strips and inhibition of blood platelet achieved by administration of the irradiated aqueous solutions of nitroprusside ion, $[Fe(CN)_5NO]^{2-}$, or its analogue $[Fe(CN)_5NO_2]^{3-}$ complex was found to be considerably lower than effects caused by the unirradiated solutions [73]. The photochemistry of SNP and pentacyanonitroferrate, $[Fe(CN)_5NO_2]^{3-}$, (Fig. 3) has been the subject of many investigations [70–78]. Photo-oxidation of the metal centre and solvation of the NO ligand is known as the predominant primary mode for both aqueous and non-aqueous solutions of SNP ($h\nu_1$), whereas photoreduction followed by rapid loss of CN^- ligand is the mode induced only by more energetic radiation ($h\nu_2$) [70–72,77,78]. Irradiation of $[Fe(CN)_5NO_2]^{3-}$ within the $\lambda \leqslant 440$ nm range

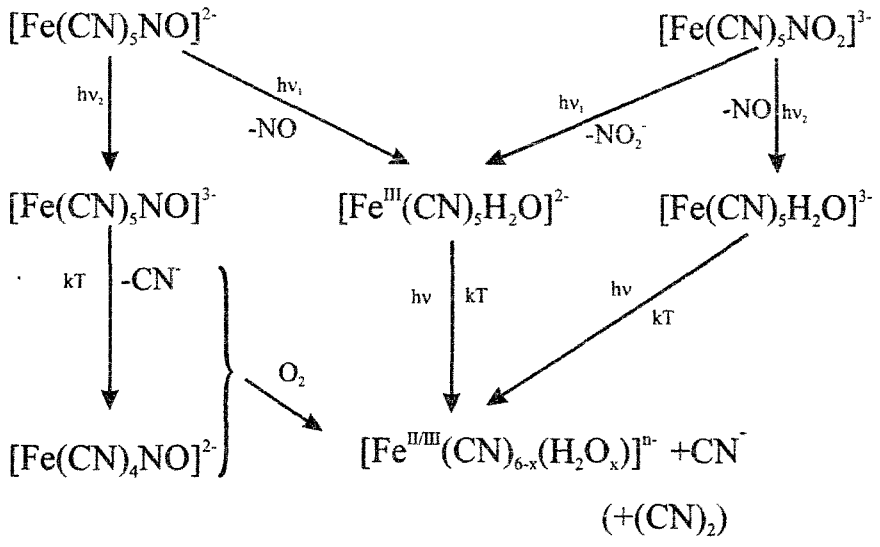

Fig. 3. Main primary photochemical and secondary thermal and photochemical pathways for the $Fe(CN)_5NO^{2-}$ and $Fe(CN)_5NO_2^{3-}$ ions irradiated in aqueous solutions with UV/vis light.

induces both photosubstitution ($h\nu_1$) of the NO_2^- ligand and intramolecular photoreduction ($h\nu_2$), with quantum yield dependent on energy of radiation [79].

Ready liberation of cyanide occurs both thermally and photochemically from the primary photoproducts of both the complexes studied. The former is observed in the case of the labile $[Fe(CN)_5NO]^{3-}$ complex, whereas for aquapentacyanoferrates(II) and (III) it is mainly secondary photoaquation which is responsible for the release of free CN^-. Irradiation with unfiltered light ($\lambda > 230$ nm) results in simultaneous generation of photo-oxidation and photoreduction products and, at longer times, generation of different aquacyanocomplexes of Fe(II) and Fe(III), as well as of NO, CN^-, $(CN)_2$ products, have been reported [70–72,75–79].

4.4. Photoprotection of metallopharmaceuticals

In the case of photosensitive drugs, extreme care must be taken in manipulating their solutions. Injectable preparations in multidose or single-dose vials must be labelled with the cautionary statement "protect from light". Photoprotective covers (bottles, drains, syringes) should be used throughout the preparation and administration process. Less photosensitive derivatives with the same biological activity should be tested.

Physicochemical stabilization of the drug solution against photolysis is another photoprotective procedure. The stabilization can be achieved, for example, by addition of a strong light absorber. The coadministred species should be non-toxic (or of low toxicity), have strong absorption within the same range as the drug, not be photosensitive (or little), and be easily excreted from the body.

The photodecomposition of SNP (a disadvantage for its clinical use) has been the subject of study in order to formulate more stable pharmaceutical preparations

[74,80–83]. Leeuwenkamp et al. [74] found that the addition of small amounts of vitamin B_{12} to 5% dextrose solution of SNP retards the decomposition process caused by normal daylight as well as by 350 nm light. The effect was particularly significant in the latter case owing to the high molar absorptivity of B_{12}–CN in that wavelength region. Another possible protective action is administration of a substance consuming photochemically generated radicals. This is especially important for the red blood cells which are very sensitive to oxygen free radicals. Recent evidence has shown the damaging effects of radicals generated photochemically from PP IX, 2(3-benzoxyphenyl) propionic acid or chlorobenzoic acid [84–86]. The photohaemolysis was found to be reduced by some Cu(II) complexes, $[CuL_2]$ with 72-methylaminopyridine and various anions (Cl^-, Br^-, NO_3^-, ClO_4^-, SO_4^{2-}) [84].

Addition of viscosigens to an aqueous solution of SNP can be another method of photoprotection [71,87,88]. The primary photochemical reaction of SNP

$$[Fe(CN)_5NO]^{2-} \xrightarrow[h\nu]{\text{solv}} [Fe(CN)_5solv]^{2-} + NO \tag{7}$$

was studied in H_2O, H_2O+glycerol mixtures, CH_3OH, CH_3CN, DMF, Me_2SO, and C_5H_5N as solvents [71,88].

The quantum yields were found [71] to correlate inversely with solvent viscosity (Tables 1 and 2), suggesting a cage recombination mechanism:

$$[Fe(CN)_5NO]^{2-} \xrightarrow{h\nu} \{[Fe(CN)_5NO]^{2-}\}^* \tag{8}$$

$$\{[Fe(CN)_5NO]^{2-}\}^* \xrightarrow{k_1} [Fe(CN)_5NO]^{2-} \tag{9}$$

$$\{[Fe(CN)_5NO]^{2-}\}^* \xrightarrow{k_2} \{[Fe(CN)_5]^{2-}\ldots NO\}_{\text{cage}} \tag{10}$$

$$\{[Fe(CN)_5]^{2-}\ldots NO\}_{\text{cage}} \xrightarrow{k_3} [Fe(CN)_5NO]^{2-} \tag{11}$$

$$\{[Fe(CN)_5]^{2-}\ldots NO\}_{\text{cage}} \xrightarrow[k_4]{\text{solv}} [Fe(CN)_5solv]^{2-} + NO \tag{12}$$

Table 1
Quantum yields for photogeneration of $[Fe(CN)_5solv]^{2-}$ from $[Fe(CN)_5NO]^{2-}$ in various solvents at 298 K [71]

solvent	Φ (mol einstein^{-1})		Solvent viscosity η ($\times 10$ cP)
	$\lambda = 436$ nm	$\lambda = 313$ nm	
CH_3CN	0.44 ± 0.01	0.84 ± 0.02	3.41
CH_3OH	0.39 ± 0.01	0.63 ± 0.01	5.43
DMF	0.40 ± 0.02	0.46 ± 0.01	7.96
Me_2SO	0.33 ± 0.02	0.42 ± 0.02	19.6
H_2O	0.17 ± 0.01	0.37 ± 0.02	8.90
C_5H_5N	~ 0.05	~ 0.15	8.83

Table 2
Influence of the viscosity of the medium (water–glycerol mixtures) on quantum yields for the formation of $[Fe(CN)_5H_2O]^{2-}$ ($\lambda_{irr}=313$ nm and $T=298$ K) [71]

Glycerol (%)	Φ_{313} (nm)	η (cP)
60	0.14	9.48
50	0.16	5.34
45	0.18	4.16
40	0.23	3.24
30	0.25	2.16
20	0.30	1.54
10	0.31	1.15
0	0.37	0.89

In this mechanism, the reaction in Eq. (10) is visualized as a radical pair formation step as a result of an excited state decay which is of MC+LC character [71,77,78]. The observed photo-oxidation yield for such a mechanism is given by

$$\Phi=\left(\frac{k_2}{k_1+k_2}\right)\left(\frac{k4}{k_4+k_3}\right)=\Phi_0\left(\frac{k_4}{k_3+k_4}\right) \tag{13}$$

where Φ_0 presents the primary quantum yield for radical pair formation/bond cleavage. The values of Φ_0 and k_3 should not depend on viscosity η, whereas k_4 is expected to decrease with increasing viscosity, i.e. $k_4=(A/\eta)$, where A is a constant. Substitution and rearrangement of Eq. (13) results in

$$\Phi^{-1}=\Phi_0^{-1}+(k_3\eta/A\Phi_0) \tag{14}$$

A plot of Φ^{-1} versus η was found to be linear, which supports a cage recombination mechanism (Table 2). Highly viscous solutions will decrease diffusion, favouring recombination of the radicals and thereby stabilizing SNP solution against photolysis.

Addition of viscosigens to therapeutic aqueous preparations was also suggested in the case of vitamin B_{12} [87]. The photolytic instability of vitamin B_{12} (cyanocobalamin) and its biologically active alkylocobalamin derivatives (methyl- and adenozylcobalamins) is due to the low enthalpy of the Co–C bond. The photolysis of alkylcobalamins (B_{12}–R) is known [45–58] to produce a geminate radical pair (Fig. 4).

Absorption of ultraviolet or visible light leads to formation of an excited state that can either undergo vibrational relaxation (k_1) to the original substrate, or homolytic cleavage of the Co–C bond (k_2), yielding a cobalamin(II)/R$^{\cdot}$ radical pair in the singlet spin state. Hyperfine coupling with the cobalt nucleus can result in rapid intersystem crossing to the triplet spin state (k_3). Radical pairs, in both the singlet and triplet states, are trapped within a solvent cage. This cage slows the diffusion and separation of the radical pair (k_4 k'_4). Under anaerobic conditions the free cobalamin(II) efficiently recaptures the alkyl radical (R$^{\cdot}$), regenerating alkylcobalamin cofactor (k_{-4}, k'_{-4}, k_1). In the presence of an efficient radical quenching

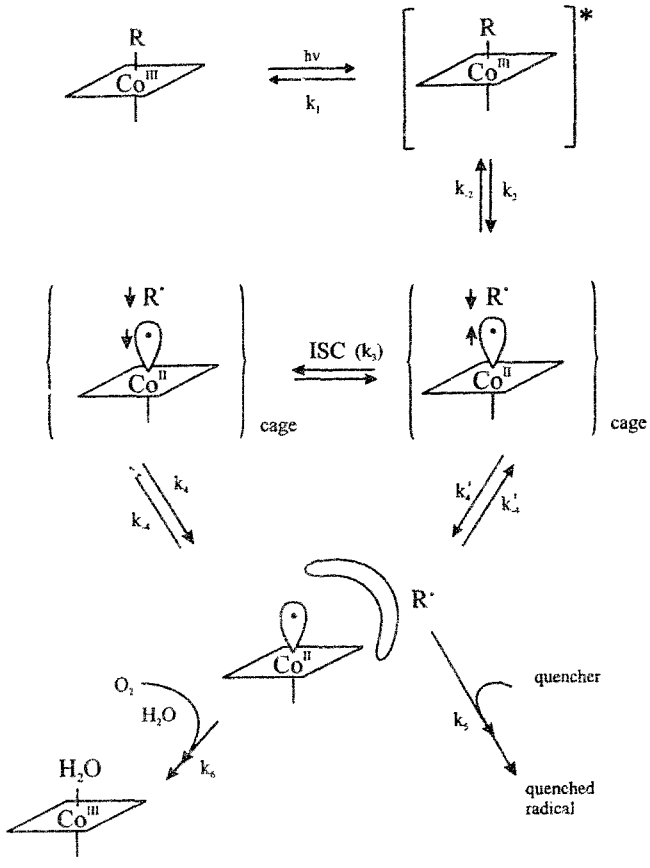

Fig. 4. Reaction scheme for photolysis of alkylocobalamins (adapted from Ref. [52]).

agent, alkyl radical is irreversibly quenched (k_5). The cobalamin(II) is oxidized to aquacobalamin(III) by oxygen (k_6). In both cases, efficient progress of the photolysis is observed.

For vitamin B_{12} (cyanocobalamin), two photolytic pathways were suggested: homolytic cleavage of the Co–C bond, resulting in radical pair formation (cobalamin(II)/$CN^{\cdot}$) [87], and photosubstitution of CN^- ligand, leading to aquacobalamin (III) [45]. Grissom et al. [87] reported that glycerol stabilizes cyanocobalamin(III) (vitamin B_{12}) against anaerobic photolysis by a high-intensity UV light source or a low-intensity fluorescent light source. The likely mechanism for stabilization by viscosigens is a decrease in diffusion and an enhancement of radical pair recombination. Glycerol stabilizes therapeutic doses of vitamin B_{12} in single-dose injection vials against adventitious photolysis by diffused light.

5. Light and metal complexes in model studies

The applications of inorganic photochemistry, particularly of transition metal complexes, to study nucleic acid and metalloporphyrin chemistry have led to the

solution of many problems, not only of structural and mechanistic importance, but also for drug design strategies and for getting rapid information about their binding to targets.

Metal complexes interact with the DNA polyanion electrostatically, by classical intercalation, or by a combination of both [89–92]. The most commonly studied are Ru(II) complexes with *N*-heterocyclic ligands, but complexes of other metals (Re, Co, Pt, Rh) have also been found to be useful [93–101]. The DNA site- and shape-selective interactions were investigated by direct emission from MLCT excited states [92,98,102–110], in chromophore-quencher systems [89,111,112], by emission quenching [89,92,113,114] or by electrogenerated chemiluminescence [89,115–117]. The light-induced emission studies have revealed DNA bonding characteristics [89] and electronic properties of nucleobase ligands [118]. Also obtained from this analysis is the strategy for designing nucleobase-targeting complexes [118]. Electrogenerated chemiluminescence studies allowed for the differentiation between single- and double-stranded DNA [119].

The activity of transition metal complexes to oxidize organic compounds via hydrogen abstraction was used to modify DNA [120–122]. The reaction starts at the sugar moiety of nucleotides and leads to cleavage of DNA or RNA and generation of products dependent on the oxidation site. When a transition metal complex in an excited state is used as an oxidant, its lifetime provides a lower limit for the rate of hydrogen abstraction, leading to a faithful reflection of the binding pattern of the complex; in particular, for Co(III) or Rh(III) [123,124].

The second approach to using light-induced hydrogen abstraction by transition metal complexes involves a "protein footprinting technique" [125–127]. The technique involves complexes that cleave DNA or RNA in a sequence-independent manner, whereas some nucleotides are protected from cleavage by binding of the protein; this protected region is referred as the "footprint". The excited-state of the $[Pt_2(pop)_4]^{4-}$ ($pop=P_2O_5H_2^{2-}$) or $[Rh(phi)_2(bpy)]^{3+}$ (phi = 9,10-phenanthrenequinonediimine) complexes was used as the photo-oxidant [122,128–131].

Another way of modifying DNA was developed during research on the chemotherapeutic mechanism of cytotoxic effects of cisplatin. In these studies a set of cisplatin analogues was prepared in which one of the ammine ligands was substituted by a photoreactive tethered aryl azide ligand. It was discovered that DNA modified by these complexes can undergo photoinduced cross-linking to HMG1 when irradiated with 300 nm light [132]. For application in cancer therapy the photochemical potential of platinum complexes in general [133], and platinum porphyrins [134] in particular, has been evaluated quite recently.

Inorganic photochemistry has also recently been used to model the NO-donation mechanism of a vasodilator drug, $[Fe(CN)_5NO]^{2-}$, and other complexes of the $[M(CN)_xNO_y]^{n-}$ formula (where M = Cr(I), Mn(I), Mn(II), Fe(I), Fe(II), Fe(III)) [73]. Comparison of the pharmacological effects measured in the dark and under irradiation with unfiltered light, consistent with other findings, allowed the metabolism of nitroprusside and other pharmacologically active iron complexes to be interpreted in terms of the NO^+-donation [73,135].

Transition metal complexes in their excited states can be a source of ET processes.

The photoinduced ET between a chromophore and substrate of biological importance is an area of intense current interest because it is responsible for many important processes, the most important of which is photosynthesis in plants and bacteria.

One of the well-developed methods for studying these very fast processes is rapid generation of reactive states by pulse radiolysis or by laser flash photolysis [89,90,136–141]. The metalloproteins, represented mainly by cytochrome-*c*, bound to Ru(II) polypirydyl complex, are probably the most intensively studied systems [123]. The photoinitiated ET in the Ru(II) compounds enabled measurement of the kinetics of intraprotein and interprotein ET reactions of cytochrome-*c* with cytochrome-*c* oxidase [142–144], cytochrome-*c* peroxidase [145], cytochrome-b_5 [146], cytochrome-c_1 [147] and phthalocyanine [148].

Considering interaction of light with nucleic acids from the health perspective, radiation can damage DNA and generate different reduced and oxidized ET products. In addition to DNA modification, photoadduct formation was also detected [89,149]. The ET between metal centres over long distances in proteins or protein pairs is the subject of interest because of its importance with regard to nucleic-acid-based diseases. Measurements of the ET rates were made as a function of distance, driving force and intervening medium [150–153]. The results were consistent with a model involving fast long-range photoinduced ET between intercalators through the DNA helix. The efficiency of the photosensitized DNA cleavage was found to be influenced by the nature of the ligand in Ru(II) complexes [150].

6. Concluding remarks

The aim of the article was to show that inorganic photochemistry not only contributes essentially to vital functions, but also can be used in many important scopes as diagnosis, drug design, treating diseases or as a tool in studying and modelling the different biochemical processes. The unique applications of light and metal complexes create a real challenge for the development of a new generation of drugs and diagnostic agents.

Unfortunately, the pathway leading to the desired results is often a very complex one and, in general, the species which reaches the target site is not the same as that which was administered. That is why the understanding of the biological phototransformations of metallodrugs and diagnostic agents is, as yet, very poor compared with organic compounds. We are just beginning to explore and understand the medical uses of inorganic photochemistry, but currently the topic is among the most important fields of the research.

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