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Coordination Chemistry Reviews 233–234 (2002) 351–371

COORDINATION CHEMISTRY REVIEWS

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Photosensitized singlet oxygen and its applications

Maria C. DeRosa, Robert J. Crutchley *

Department of Chemistry, Ottawa-Carleton Chemistry Institute, Carleton University, 2240 Herzberg Building, 1125 Colonel By Drive, Ottawa, ON, Canada K1S 5B6

Received 18 September 2001; accepted 15 February 2002

Contents

Abstract

The study of singlet molecular oxygen production and reactivity has emerged as a rich and diverse area with implications in fields ranging from polymer science to cancer therapy. In this review, we address the photophysical properties of singlet oxygen and of the photosensitizers used in its generation. Photosensitizers based on organic molecules and coordination compounds are examined and compared. Recent advances in the photosensitized production of singlet oxygen and its uses in photochemistry and photobiology are highlighted, with particular focus on its role in wastewater treatment, fine chemical synthesis, and photodynamic therapy (PDT). Future directions in photosensitizer development and singlet oxygen applications are also explored.

Keywords: Singlet oxygen; Photosensitizers; Photodynamic therapy

* Corresponding author. Tel.: +1-613-520-2600; fax: +1-613-520-2659.
E-mail address: robert_crutchley@carleton.ca (R.J. Crutchley).

0010-8545/02/$ - see front matter
PII: S0010-8545(02)00034-6

1. Introduction

Despite being discovered in 1924, singlet molecular oxygen only became the focus of intense laboratory study after 1963 when Khan and Kasha interpreted the chemiluminescence of the hypochlorite-peroxide reaction as caused by liberated singlet oxygen [1]. Since then, the physical, chemical, and biological properties of this energetically rich form of molecular oxygen have garnered serious attention. In particular, the photosensitized production of singlet oxygen has significance in a range of areas from photooxidation, DNA damage, photodynamic therapy (PDT) of cancer, to polymer science. Recently, important treatises by Wasserman and Murray [2], and Rånby and Rabek [3] have provided the impetus for further study of this field.

This review will survey the literature regarding the photosensitized generation of singlet oxygen and its applications, focusing mainly on the latest results from 1995 to early 2001. It will begin with an introduction to the electronic structure of singlet oxygen and its reactivity, followed by the sources of singlet oxygen with particular attention to photosensitized reactions. The groups of photosensitizers that will be examined are: (1) the organic dyes and aromatics; (2) the porphyrins, phthalocyanines, and related macrocycles; (3) semiconductors; and (4) transition metal complexes. The effect of immobilizing photosensitzers in a polymer matrix will also be discussed. The section on applications will explore the recent literature regarding the use of singlet oxygen in several main areas: wastewater treatment, fine chemical synthesis, and photodynamic applications such as blood sterilization, sunlight-activated herbicides and insecticides, as well as photodynamic cancer therapy. Finally, the section on future studies will summarize the research that is needed to expand the current understanding of photosensitized singlet oxygen generation and the application of this research.

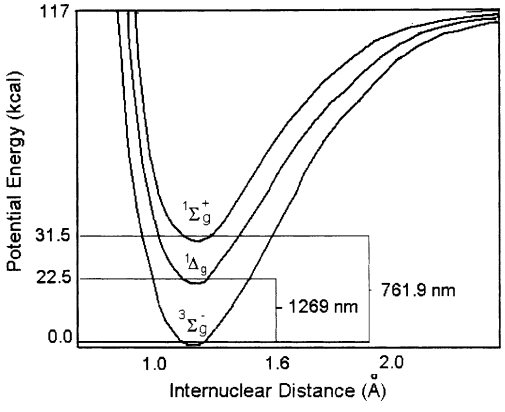


Fig. 1. Potential energy curves for the three low-lying electronic states of molecular oxygen.

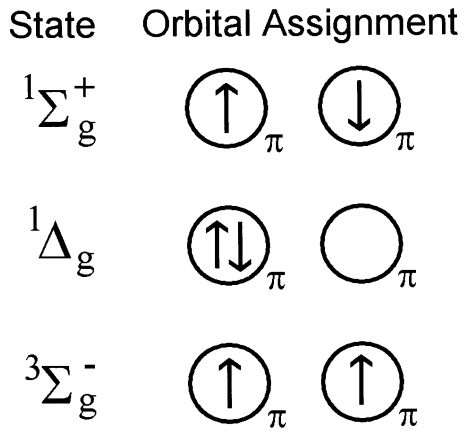


Fig. 2. Primitive representations of molecular oxygen lowest singlet and triplet states.

2. Properties of singlet oxygen

2.1. Electronic structure of singlet oxygen

Molecular oxygen has two low-lying singlet excited states, $^1\Delta_g$ and $^1\Sigma_g^+$, 95 (22.5 kcal mol^{-1}) and 158 kJ mol^{-1} (31.5 kcal mol^{-1}) above the triplet state, respectively, as shown in Fig. 1 [4].

Electronic configurations of these states differ only by the structure of the π-antibonding orbitals. The configuration of the molecular orbitals of the first excited state, $^1\Delta_g$, is as follows: $O_2KK(2\sigma_g)^2(2\sigma_u)^2(3\sigma_g)^2(1\pi_u)^4(1\pi_g^+)(1\pi_g^+)]$. In the second excited state, $^1\Sigma_g^+$, the electronic configuration is identical to that of the ground state, except that the last two electrons have antiparallel spins (see Fig. 2).

The transition from the $^1\Delta_g$ state to the $^3\Sigma_g^-$ state is spin forbidden, thus the $^1\Delta_g$ O_2 is a relatively long-lived species. The second excited state of oxygen, on the other hand, is short-lived due to a spin-allowed transition to the $^1\Delta_g$ state. This difference in stability is confirmed by the radiative lifetimes of $O_2(^1\Delta_g)$ and $O_2(^1\Sigma_g^+)$, which are 45 min and 7–12 s in the gas phase [5] and 10^{-6}–10^{-3} s, and 10^{-11}–10^{-9} s in solution [6], respectively. Due to the metastability of the $^1\Delta_g$ state, the $^1\Delta_g \leftrightarrow {}^3\Sigma_g^-$ transitions at 1268.7 nm are observed in absorption and emission spectra despite being spin and symmetry forbidden. For a more detailed treatise on the spectral properties of $^1O_2$, see Ref. [7].

2.2. Quenching of $^1O_2$

Once dioxygen is in its singlet excited state, it can be deactivated by other species to return to its ground state. This quenching can take place in two major ways [8]:

1) *Physical quenching:* $^1O_2 + A \xrightarrow{k_p} {}^3O_2 + A$, in which interaction leads only to deactivation of singlet

oxygen with no O_2 consumption or product formation, and

2) *Chemical quenching:* $^1O_2 + A \xrightarrow{k_c} P$, where the quencher reacts with singlet oxygen to give a new product.

Early work with singlet oxygen found that this active species could oxidize substrates that were unaffected by oxygen in its normal energy state. Oxygen is ca. 1 V more oxidizing in its singlet excited state and is therefore significantly more electrophilic, reacting rapidly with unsaturated carbon–carbon bonds, neutral nucleophiles such as sulfides and amines, and as well as with anions. Consequently, organic chemists have found utility in singlet oxygen as a versatile synthetic reagent [9]. The common reactions of singlet oxygen will be described below. The application of these reactions to fine chemical synthesis and wastewater treatment can be found in Section 4.1.

The 1,3 addition of singlet oxygen to dienes and conjugated *cis*-dienes, [4+2] cycloaddition, is similar to the Diels–Alder reaction, where singlet oxygen is the dienophile. An example of the utility of this reaction is given by the synthesis of dibenzoyl benzene from 1,3-diphenylisobenzofuran [10]. Singlet oxygen can also react with olefins having two or more allylic substituents causing a double bond shift and the formation of an allylic hydroperoxide. This reaction is particularly relevant to biological systems in the reaction of singlet oxygen with tryptophan [11], histidine [11], and unsaturated fatty acids [10].

The formation of dioxetanes is possible via the cycloaddition of singlet oxygen with π-electron rich olefins. Dioxetanes, which are generally only stable at low temperatures, will undergo decomposition to form two carbonyl groups [12].

Singlet oxygen, due to its high electrophilicity, is capable of oxidizing phenols, sulfides, and amines. The reaction of singlet oxygen with phenol results in the formation of hydroperoxides that dehydrate to form *p*-benzoquinones [8b]. The oxidation of organic sulfides, disulfides, and amines has also been intensely studied [13]. Sulfides are generally oxidized to sulfoxides, while disulfides react to form thiolsulfinates [14]. Amines with low ionization potentials can be oxidized by singlet oxygen, possibly through a charge transfer intermediate [15].

It is possible that some singlet oxygen reactions may proceed by electron transfer from the electron rich compound to the electrophilic singlet oxygen. Phenols can react with singlet oxygen via electron transfer [16]. It has also been suggested that the photooxidation of polystyrene by singlet oxygen may occur via a radical mechanism as well as by formation of a hydroperoxide [17].

Many metal complexes have been shown to possess singlet oxygen quenching ability, particularly Ni(II) chelates [18]. Reactions of $^1O_2$ to form energetic and reactive metal–dioxygen complexes have also been explored. Foote and Selke made the preliminary report that singlet oxygen reacts with *trans*-$Ir(CO)X(PPH_3)_2$, where X = Cl, Br, or I to form an Ir(III) peroxo complex at ca. 10^9 times faster rate than when reacted with triplet oxygen [19]. Singlet oxygen has also been used to produce the rhodium complex *trans*-$Rh(CO)Cl(PPh_3)_2O_2$ from the Rh analogue of the Vaska's complex [20]. More recently, cationic complexes $[M(PPh_3)_2(CO)S]^+$, where $S = CH_3CN$ and M = Ir, Rh can also quench singlet oxygen to form the corresponding peroxo complex, $[M(CO)S(PPh_3)_2O_2]^+$ [21].

While excited triplet state molecules can be efficient sensitizers of singlet oxygen (see Section 2.3), in many cases they are also efficient quenchers of this species once formed. Consequently, there can be situations where the sensitizers used to generate singlet oxygen will themselves react to quench it. This could lead to photobleaching and -degradation, where photodegradation refers to the process in which singlet oxygen reacts with a material, resulting in its degeneration, and photobleaching refers specifically to the degradation of dyes by singlet oxygen.

The photodegradation of polymers by $^1O_2$ is a significant industrial problem. The yellowing of lignin in paper, for example, has been attributed to the effects of $^1O_2$. Singlet oxygen can be generated by energy transfer from impurities within a polymer or from specially added dyes which can act as photosensitizers. Once generated, singlet oxygen can react with the polymer to form dioxetanes, hydroperoxides, and/or endoperoxides, which could lead to further decomposition and loss of polymer properties [17]. The addition of quenchers of singlet oxygen can serve to stabilize polymers against these effects [17].

2.3. Generation of singlet oxygen

There are many known sources of $^1O_2$ [13], however, this review will focus only on the photosensitized method of generation. Photosensitized generation is a simple and controllable method for the production of $^1O_2$, requiring only oxygen, light of an appropriate wavelength, and a photosensitizer capable of absorbing and using that energy to excite oxygen to its singlet state. Sensitizer excitation is generally achieved via a one-photon transition ($h\nu$) between the ground state, S_0, and a singlet excited state S_n. Relaxation of the S_n state yields the lowest excited singlet state of the sensitizer S_1. Intersystem crossing generates the sensitizer triplet state, T_1. The lifetime of the T_1 state is longer (μs) than that of the S_1 state (ns) allowing this excited state to react in one of two ways, defined as Types I and II mechanisms. A

Type I mechanism involves hydrogen-atom abstraction or electron-transfer between the excited sensitizer and a substrate, yielding free radicals. These radicals can react with oxygen to form an active oxygen species such as the superoxide radical anion. In a Type II mechanism, singlet oxygen is generated via an energy transfer process during a collision of the excited sensitizer with triplet oxygen. See Scheme 1, below:

$$P(S_0) \xrightarrow{h\nu} P(S_1) \xrightarrow{k_{ISC}} P(T_1) \quad (1)$$

$$P(T_1) + {}^3O_2 \xrightarrow{k_{en}} P(S_0) + {}^1O_2 \quad (2)$$

where P, photosensitizer; S_0, singlet ground state; S_1, first excited singlet state; T_1, first excited triplet state; k_{ISC}, rate constant of intersystem crossing; k_{en}, rate constant of energy transfer; $^3O_2$, ground state triplet oxygen; and $^1O_2$, singlet oxygen.

Each photosensitizer molecule can typically produce 10^3–10^5 molecules of $^1O_2$ before being degraded through photobleaching by $^1O_2$ or by some other process. These processes are illustrated in the extended Jablonski diagram shown in Fig. 3.

The singlet oxygen generating ability of a photosensitizer is measured by its quantum yield. Quantum yield of singlet oxygen production arising from oxygen quenching can be found by considering the various photophysical and photochemical pathways involved. Competing with reactions (1) and (2) are monomolecular radiative and non-radiative processes:

$$P(T_1) \xrightarrow{k_r} P(S_0) + h\nu' \quad (3)$$

$$P(T_1) \xrightarrow{k_{nr}} P(S_0) \quad (4)$$

Bimolecular reactions, such as physical deactivation by molecular oxygen or electron transfer, also compete with energy transfer:

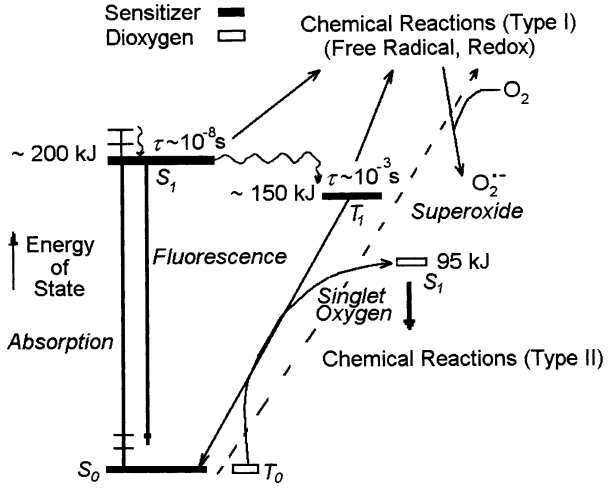


Fig. 3. Generation of excited photosensitizer states and reactive dioxygen species. [Reproduced with permission from Ref. [33]. Copyright (1995) Royal Chemical Society.]

$$P(T_1) + O_2 \xrightarrow{k_{dO_2}} P(S_0) + O_2 \quad (5)$$

$$P(T_1) + O_2 \xrightarrow{k_{et}} P^+ + O_2^{\bullet -} \quad (6)$$

Considering Eqs. (1)–(6), the quantum yield of $^1O_2$ production Φ_Δ is defined as [9],

$$\Phi_\Delta = \Phi_T \phi_{en} = \Phi_T \left(\frac{k_{en}[O_2]}{k_r + k_{nr} + k_q[O_2]} \right) \quad (7)$$

where Φ_T is the quantum yield of triplet formation; ϕ_{en}, efficiency of energy transfer; k_{en}, rate constant of energy transfer; and k_q, sum of rate constants from the quenching of $P(T_1)$ by O_2 ($k_{en} + k_{dO_2} + k_{et}$). An alternate way of expressing the quantum yield of singlet oxygen formation is given by

$$\Phi_\Delta = \Phi_T \left(\frac{k_q[O_2]}{k_r + k_{nr} + k_q[O_2]} \right) \left(\frac{k_{en}}{k_q} \right) = \Phi_T f_\Delta^T P_{O_2}^T \quad (8)$$

where $f_\Delta^T = (k_{en}/k_q)$ signifies the fraction of triplet states quenched by oxygen which yield $^1O_2$ (or the efficiency of singlet oxygen formation) and $P_{O_2}^T = k_q[O_2]/(k_r + k_{nr} + k_q[O_2])$ represents the fraction of triplet states quenched by oxygen.

The methodology used to measure the quantum yield of singlet oxygen generation (Φ_Δ) ranges from direct detection of the luminescence produced (at 1270 nm) upon relaxation of singlet oxygen (time-resolved or steady-state infrared luminescence), calorimetric techniques (photoacoustic calorimetry and time resolved thermal lensing), and quantitative analysis of photooxidation reactions (loss of absorbance, or fluorescence of a probe molecule, or oxygen uptake). An excellent description of these techniques can be found in a review by Wilkinson et al. [22]. A more recent but complementary review of singlet oxygen yields can be found in a review by Redmond and Gamlin [23].

3. Types of photosensitizers

There are several groups of UV–vis absorbing molecules that have shown singlet oxygen generating ability. Photosensitizers should exhibit the following properties: (1) high absorption coefficient in the spectral region of the excitation light; (2) a triplet state of appropriate energy ($E_T \geq 95$ kJ mol^{-1}) to allow for efficient energy transfer to ground state oxygen; (3) high quantum yield of the triplet state ($\Phi_T > 0.4$) and long triplet state lifetimes ($\tau_T > 1$ μs), since the efficiency of the photosensitizer is dependent on the photophysical properties of its lowest excited triplet state; and (4) high photostability.

Table 1
Some examples [23] of common organic dyes and their photophysical properties

Dye	Triplet energy E_T (kcal mol^{-1})	Φ_Δ (aqueous)		Φ_Δ (EtOH)	Φ_Δ (CH_3OH)
		D_2O	H_2O		
Rose bengal	42.0	0.76	0.75	0.68	0.76
Fluorescein	47.2		0.03	0.03	0.1
Eosin blue	45.5		0.52	0.37	
Methylene blue	32.0			0.52	0.5
Erythrosin blue			0.63	0.69	

3.1. Organic dyes and aromatic hydrocarbons

Dyes such as rose bengal, eosin, and methylene blue are very effective photosensitizers, as they possess triplet states of appropriate energies for sensitization of oxygen (see Table 1). Methylene blue is a phenothiazinium dye with a strong absorbance in the range of 550–700 nm, and a significant quantum yield ($\Phi_\Delta = 0.52$) [23]. Xanthene dyes such as rose bengal and eosin exhibit intense absorption bands in the green area of the visible spectrum (480–550 nm) and produce singlet oxygen with high yields. Rose bengal for example has a $\Phi_\Delta = 0.76$ [23]. Increasing the number and atomic mass of halogen substituents on the xanthene skeleton causes the peak maximum to red shift. Likewise, the presence of heavier halogens increases the yield of intersystem crossing to the triplet state of the dye, which is an important criterion for a photosensitizer. For this reason, tetraiodo xanthene derivatives, like rose bengal and erythrosin B, are generally more efficient photosensitizers than other halogenated derivatives (Fig. 4).

Aromatic hydrocarbons such as napthalenes, anthracenes, and biphenyls have also been studied for their photosensitizer ability [24]. These studies found that the competition of charge transfer interactions with the energy transfer pathway was of greater importance for biphenyls than for the napthalenes. Changing the nature of the substituents on the biphenyl ring affects the oxidation potential, E^{Ox}, of these compounds, changing their free energy of charge transfer, ΔG_{CT}. The higher the oxidation potential of the photosensitizer, the lower the k_q and the higher f_Δ^T, leading more exclusively to quenching via the energy transfer pathway in these photosensitizers. A solvent dependence was also noted in these studies, whereby decreasing the polarity of the solvent leads to an increase in ΔG_{CT}.

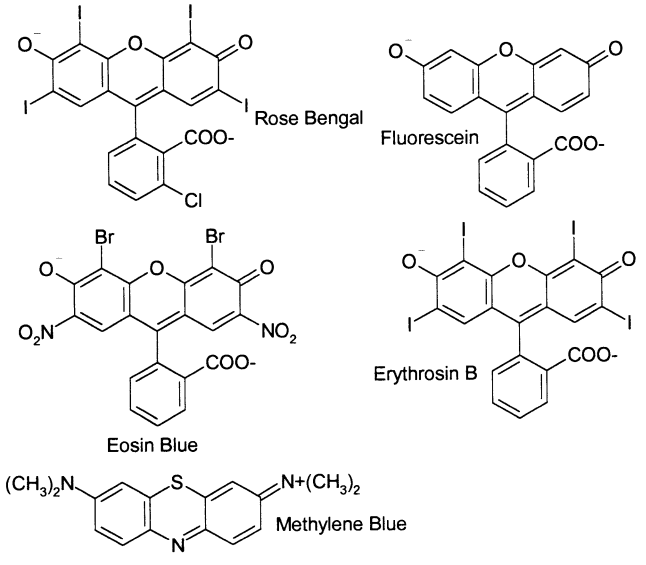


Fig. 4. Some common organic photosensitizers.

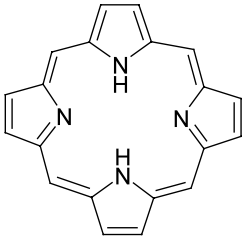
Quinones play an important role in biological processes and these compounds have been studied for their photosensitizer ability. Guiterez et al. have obtained the singlet oxygen quantum yields from a range of quinone and anthraquinone derivatives and these compounds were found to be excellent sensitizers for singlet oxygen in aprotic solvents ($\Phi_\Delta = 0.69$ for anthroquinone-2-sulfonic acid and 1,8-dihydroxyanthraquinone, for example), as well as moderate quenchers of $^1O_2$ by physical deactivation [25]. Photosensitized production of $^1O_2$ by water soluble quinones occurs with reasonable quantum yields (from 0.11 for 2-methyl-1,4-benzoquinone to 0.44 for sodium 9,10-anthraquinone-2-sulfonate) [26]. Particular interest has been paid to the small group of natural pigments known as the 3,10-dihydroxy-4,9-perlyenequinones, of which the hypocrellin compounds are a part. Hypocrellins have received attention as potential photosensitizers for PDT [27]. These compounds have sizeable Φ_Δ values, for example $\Phi_\Delta = 0.76$ for hypocrellin B, but unfortunately, they lack strong absorptivity at energies greater than 600 nm, which has limited their application to date. Amino derivatives of hyprocrellins, however, demonstrate significantly enhanced red absorption and show comparable singlet oxygen generating ability [28].

3.2. Porphyrins, phthalocyanines, and related tetrapyrroles

Recently, the attention on photosensitizers has been focused on porphyrins and their analogues because their presence in natural systems makes them ideal candidates

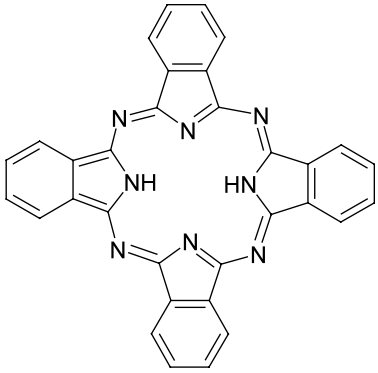
for use in biological singlet oxygen generation. As a result of their biological roles, these photosensitizers generally lack cytotoxicity in the absence of light, which proves important in certain applications (see Section 4.2.2). The porphyrins and their derivatives have the ability to absorb several wavelengths in the UV–vis range. The Soret band in the blue and the Q-band in the red are major bands, which represent important components of sunlight. The long-lived triplet states of many porphyrins allow for high quantum yields, and substituents on the macrocycle, metal ions coordinated at its centre, and ligands attached to the axial positions of the metal ion allow for tuning of the porphryins properties (see Table 2). Finally, some porphyrins undergo rapid decomposition in the presence of $^1O_2$ (photobleaching). Admittedly, this can be deleterious in some industrial applications; however, it could be an advantage in biological systems where rapid breakdown of the photosensitizer after use is necessary (see Section 4.2). A well-studied porphyrin used in the photosensitized production of singlet oxygen is haematoporphyrin (discussed further in Section 4.2.2). While its triplet quantum yield and singlet oxygen production quantum yields are high (0.83 and 0.65, respectively), its absorption at 630 nm ($\varepsilon = 3500\ M^{-1}\ cm^{-1}$) is weaker than the ideal for a photosensitizer [29].

The most commonly encountered derivatives of porphyrin,



are the symmetrically substituted analogues such as octaethylporphine (OEP) and tetraphenylporphine (TPP). Water-soluble porphyrins can be synthesized by sulfonation, carboxylation, or by alkylation of *N*-pyridyl-substituted compounds. Generally, these compounds, both free or metallated, tend to remain monomeric in solution and can absorb a significant portion of the solar spectrum (e.g. TPP, 46%; MgTPP, 40%; PdTPP, 25%) [31].

Phthalocyanines, derivatives of the porphyrin skeleton,



are an important class of intensely colored macrocycles [30]. Phthalocyanines differ from porphyrins by having nitrogen atoms link the individual pyrrole units. Extended conjugation, afforded by the peripheral benzene rings, strengthens its absorption at longer wavelengths. Their strong absorption in the red (Q-band) overlaps the region of maximum light penetration in tissues, thus making them ideal candidates for PDT (see Section 4.2.2).

A long triplet lifetime and a relatively high triplet quantum yield, which are useful qualities for a photosensitizer, characterize metallophthalocyanines containing diamagnetic metal ions such as Al^{3+} or Zn^{2+} (see Table 3) [31]. For example, Zn(II)PcTS, where PcTS = phthalocyanine tetrasulfonate, has a long triplet lifetime, $\tau_T = 245$ μs, and high triplet quantum yield, $\Phi_T = 0.56$ [31]. Complexes with paramagnetic transition metal ions, however, have much shorter triplet lifetimes (e.g. Cu(II)PcTS, $\tau_T = 0.06$ μs), and this difference is reflected in the quantum yields of singlet oxygen formation in these complexes: M(PcTS) for M = Zinc(II), Al(III), $2H^+$, Cu(II), and Co(II), $\Phi_\Delta = 0.45$, 0.34, 0.14, 0, and 0, respectively [22].

As seen with the porphyrins, tuning of photophysical behavior can be achieved through the selection of macrocycle substituents. In water-soluble derivatives such as MPcTS and MPcTC, where PcTC = phthalocyanine tetracarboxylate, the formation of dimers and higher order aggregates in solution are commonplace.

Table 2
Photophysical properties for some metalloporphyrins [23,31]

Complex	Φ_T	τ_T (μs)	Φ_Δ
H_2TPP	0.82	1380 (300 K)	0.63 (C_6H_6)
MgTPP		1350 (300 K)	0.62 (C_6H_6)
ZnTPP	0.88	1200 (300 K)	0.83 (C_6H_6)
CdTPP		260 (300 K)	
PdTPP	1	380 (300 K)	0.88 (C_6H_6)
ZnOEP		57 000 (77 K)	
PdOEP	1	300 (300 K)	

Table 3
Photophysical properties of some metal phthalocyanines [23,31]

Complex	λ_{max}	log ε	τ_T (μs)	Φ_T	Φ_Δ
Pc	698	5.21	140	0.14	0.16 (CH_3OD)
$PcTS^{4-}$	702		170	0.22	0.17 (CH_3OD)
CuPc	678	5.34	0.035	0.7	0
ZnPcTS	690	5.47	245	0.56	0.45
CuPcTS	670		0.06	0.92	0

Equilibrium constants for dimerization usually range from 10^5 to 10^7 M^{-1} [31]. Aggregation can be controlled through the use of peripheral substituents and axial ligands, an important factor since aggregation has a direct influence on photophysical behavior, rendering normally active photosensitizers inactive through self-quenching [29]. Substituents and axial ligands also play a key role in the hydrophilic/hydrophobic nature of the dye and this helps determine the extent of its localization certain tissues.

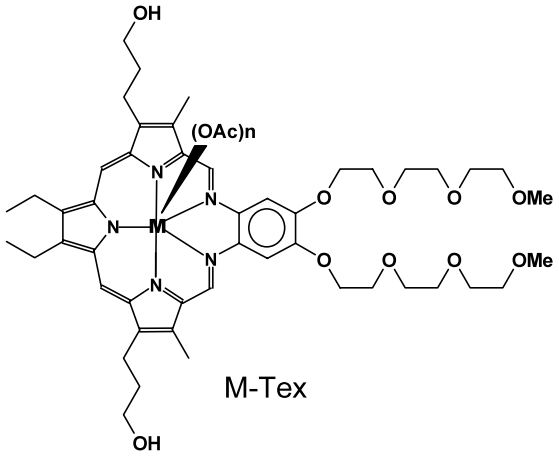
Napthalocyanines are macrocycles with a second benzene ring added on the periphery of the phthalocyanine ring. This additional conjugation leads to the absorption of longer wavelength light than the phthalocyanines (770 compared with 680 nm) that could prove useful in the treatment of highly pigmented tumors in PDT [32].

Chlorins and bacteriochlorins are other members of the porphyrin family. These too have cores based on the porphyrin skeleton, with saturation of one or two double bonds, respectively. These compounds absorb further into the red, advantageous in biological uses. Chlorin absorbs 10 times more light in the 'phototherapeutic window', the range of light wavelengths that are useful and accessible in biological applications, then corresponding porphyrins [33]. The further reduced compounds known as bacteriochlorins are even stronger absorbers, but are generally less stable in solution [33].

Texaphyrins are related macrocycles with two main features that distinguish them from porphyrins. Firstly, they have five, rather than four, nearly coplanar nitrogen-donor atoms. Also, the atomic periphery consists of a 22π-electron system, instead of the 18π-electron system of the porphyrins, causing a red-shift in absorption. A number of complexes of texaphyrins containing paramagnetic and diamagnetic metal ions have recently been investigated [34]. Once again, the paramagnetic complexes of this macrocycle have shorter fluorescence lifetimes than their diamagnetic counterparts and this difference is reflected in their singlet oxygen quantum yields (Table 4).

A more detailed look at porphyrin and related photosensitizers with respect to their application to PDT can be found in Section 4.2.2.

Table 4
Singlet oxygen quantum yields for a range of diamagnetic and paramagnetic texaphyrin complexes



M-Tex

Complex	Φ_Δ
Cd(Tex)(Oac)	0.24
Y(Tex)$(OAc)_2$	0.58
In(Tex)$(OAc)_2$	0.48
Lu(Tex)$(OAc)_2$	0.31
Nd(Tex)$(Oac)_2$	0
Eu(Tex)$(OAc)_2$	0.091
Gd(Tex)$(Oac)_2$	0.08
Tb(Tex)$(OAc)_2$	0
Dy(Tex)$(Oac)_2$	0
Tm(Tex)$(Oac)_2$	0
Yb(Tex)$(Oac)_2$	0

3.3. Transition metal complexes

Most studies in singlet oxygen photosensitization involve organic molecules. However, some inorganic complexes have also been shown to be efficient photosensitizers. Transition metal complexes of Ruthenium(II), for example, have relatively strong absorption in the UV–vis regions of the spectrum. Long lifetimes of emission from the triplet metal-to-ligand charge transfer (^{3}MLCT) states of many Ru(II) complexes allow oxygen quenching to be an efficient process in aerated solutions. Furthermore, it is thermodynamically possible for many Ru(II) diimine complexes to sensitize oxygen. Many of the ruthenium-based photosensitizers have been found to be more efficient $^1O_2$ producers than the well-studied organic photosensitizer methylene blue, and comparable to the widely used rose bengal.

Early work by Demas et al. [35] studied the oxygen quenching of 16 luminescent diimine (2,2′-bipyridine, 1,10-phenanthroline and/or substituted phenanthroline) metal complexes of Ru(II), Os(II), and Ir(III). This work found quantum yields of singlet oxygen formation of 0.68–0.86 for Ru(II) and Os(II) complexes. Ru(II) tris-bipyridine, $[Ru(bpy)_3]^{2+}$, in particular, was shown to be an effective photosensitizer of singlet oxygen with a quantum yield Φ_Δ of 0.86 in oxygen-saturated methanol at 1 atm. In studies by Mulazzani et al. [36] on RuL_3^{2+} complexes, where L was any combination of bipyridine, bipyrazine, and 2,2′-bipyrimidine, all except for $Ru(bpy)_3^{2+}$ showed quantum yields of unit efficiency, relative to tetrakis(4-sulfonatophenyl)porphine, in aqueous media.

More recent work by Garcia-Fresnadillo et al. [37] examined the photosensitizer ability of a series of complexes $[RuL_3]^{2+}$ where L is 2,2′-bipyridine (bpy),

Table 5
Quantum yields of singlet oxygen formation of several Ru(II) complexes

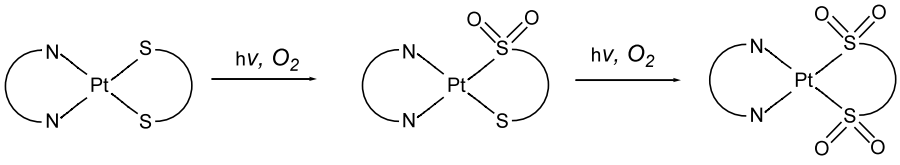
	Φ_Δ (in CD_3OD)	Φ_Δ (in D_2O)
$Ru(bpy)_3^{2+}$	0.73	0.22
$Ru(phen)_3^{2+}$	0.54	0.24
$Ru(bpz)_3^{2+}$	0.28	0.19
$Ru(dip)_3^{2+}$	0.97	0.42
$Ru(dpds)_3^{4-}$	1	0.43
$Ru(poda)_3^{2+}$	0.54	Insoluble

1,10-phenathroline (phen), 2,2′-bipyrazine (bpz), 4,7-diphenyl-1,10-phenanthroline (dip), diphenyl-1,10-phenanthroline-4,7-disulfonate (dpds), and 1,10-phenanthroline-5-octadecanamide (poda) in water and methanol. In this series of complexes, a wide range of quantum yields of singlet oxygen formation were found, from 0.22 for $[Ru(bpy)_3]^{2+}$ in D_2O and 1.0 for $[Ru(dpds)_3]^{2+}$ in CD_3OD, (see Table 5). Complexes of ligands substituted with aryl groups in the 4,7-positions were found to have longer excited-state lifetimes, and were the most efficient photosensitizers. Of importance is that, in methanol, changes in Φ_Δ reflected variations of $P^T_{O_2}$, which means that both Φ_T and f^T_Δ are unity (see equation 8) and energy transfer leading to singlet oxygen production is the only quenching pathway of the excited RuL_3 complexes by molecular oxygen. In water, however, Φ_Δ was found to be about half of $P^T_{O_2}$, thus energy transfer must not found be the only quenching pathway available to the excited RuL_3 complexes. Tanielian et al. [38] have found that oxygen quenching of the $[Ru(bpy)_3]^{2+}$ excited state is solvent dependent, with Φ_Δ ranging from 0.41 to 0.87 and f^T_Δ values ranging from 0.58 to 0.92 upon changing the solvent from water to methanol.

investigated by Abdel-Shafi et al. [40]. Using acridine in acetonitrile as a comparison for relative Φ_Δ calculation, these polypyridine complexes had quantum yields that ranged from 0.21 to 0.54. All showed less singlet oxygen generating ability than $[Ru(bpy)_3]^{2+}$ (quantum yield = 0.56). The mixed ligand complexes showed much lower triplet lifetimes. This was ascribed to increased conjugation, which results in the availability of lower excited state energy levels for non-radiative deactivation of the triplet MLCT state. Complexes containing at least one benzoaza-15-crown-5-bipyridine substituent had much lower oxidation potentials and lower f values, in the range of 0.26–0.31. The authors suggest that those ligands with extended conjugation and with low oxidation potentials could be physically quenching the singlet oxygen in the precursor molecule, before dissociation occurs [39].

Ruthenium transition metal complexes are not alone in their ability to photosensitize oxygen. The quenching of luminescent excited states of polypyridyl complexes of Cr(III) has also been the subject of interest for some time [41]. In the case of ^2E $Cr(bpy)_3^{3+}$, quenching by $^3O_2$ leads to energy transfer and $^1O_2$ formation with a quantum yield of 0.86 [42].

Photosensitization by platinum and palladium complexes has also been investigated. Complexes of the form (NN)Pt(II)(SS), where N–N = bipyridine and 4,4′-di-tert-butyl-2,2′-bipyridine, and S–S = 3,4-toluenedithiolate (tdt), *meso*-1,2-diphenyl-1,2-ethanedithiolate or 1,2-ethanedithiolate produce singlet oxygen with moderate efficiency [43]. In these complexes, the fraction of triplet states quenched by oxygen ranged from 0.11 to 0.20. The complex Pt(bpy)(bdt), where bdt = 1,2-benzenedithiolate, reacts with ground state oxygen to form singlet oxygen, and then can quench singlet oxygen to form sulfinated products [44].



Substituted ethoxybenzene or vinyl-linked benzo-crown-ether-2,2′-bipyridine Ru(II) complexes have been tested for singlet oxygen producing ability, with efficiencies in the range of 0.18–0.47 [39]. A related series of aza-15-crown-5-vinyl-2,2′-bipyridine Ru(II) complexes and multinuclear Ru(II) complexes were

Platinum (II) and Pd(II) mixed-ligand complexes with various diimines and dioxolene ligands are also capable of acting as photosensitizers. 2,2′-Dipyridylamine (DPA) complexes of Pt(II) and Pd(II) with dioxolenes produce singlet oxygen with reasonable yields upon excitation of its π–π* and MLCT-bands [45]. In

particular, Pt(DHBA)(DPA), where DHBA = 3,4-dihydroxybenzoic acid demonstrated $^1O_2$ production efficiencies of ca. 32.6% of that of haematoporphyrin IX. Anbalagan and Srivastava have also examined mononuclear and dinuclear Pt(II) and Pd(II) complexes with the formula M(DHB)(N–N), where DHB = 3,4-dihydroxybenzaldehyde, and N–N = 2,2′-bipyridine (bpy), 2,2′-biquinoline (biq), 4,7-diphenyl-1,10-phenanthroline (dpp) or 1,10-phenanthroline (phen), and [{M(bpy)}$_2$-(THB)], where THB = 3,3,4,4-tetrahydroxybenzaldehyde [46]. The photosensitizing ability of the dinuclear complexes was about 4× greater than that of the corresponding mononuclear complexes. Also, the Pt(II) complexes were better sensitizers than the analogous Pd(II) complexes. This difference is attributed to the increase in crystal field splitting from Pd(II) to Pt(II). As a result, the $^3A_2$ or $^1A_2$ state has a much higher energy than the ^{3}(d, π)* state and is less available for radiationless decay in the Pt(II) complexes.

3.4. Photobleaching of organic and metal complex photosensitizers

As mentioned earlier in Section 2.2, singlet oxygen is a powerful electrophile and can react rapidly with an olefin, generating a dioxetane, or with a diene by the 1,3 addition of singlet oxygen. For a highly conjugated organic photosensitizer, (the dyes in Table 1, porphyrins, phthalocyanines, etc.), this reaction destroys conjugation and with it the ability to absorb visible light and to photosensitize the formation of singlet oxygen. Unfortunately, there have been no quantitative studies comparing the resistance of organic and metal complex photosensitizers to photobleaching.

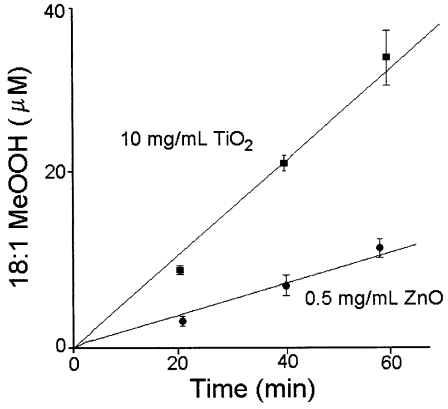


Fig. 5. Formation of methyl oleate hydroperoxides (18:1 Me-OOH) during the photooxidation of methyl oleate (100 μM) in ethanol in the presence of 10 mg ml^{-1} TiO_2 or 0.5 mg ml^{-1} ZnO under aerobic conditions at room temperature. [Reproduced with permission from Ref. [47]. Copyright (2000) Academic Press.]

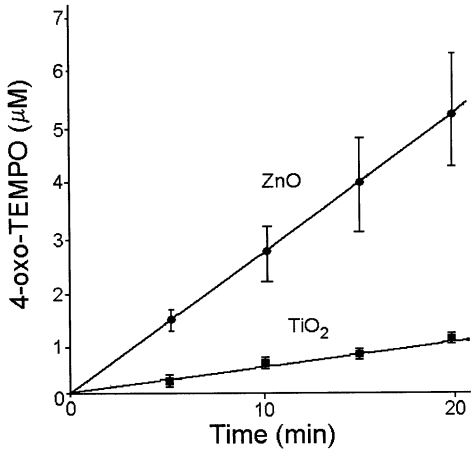


Fig. 6. Formation of 4-oxo-TEMPO upon irradiation of 4-oxo-TMP with 1.6 mg ml^{-1} TiO_2 or ZnO at room temperature under aerobic conditions. [Reproduced with permission from Ref. [47]. Copyright (2000) Academic Press.]

3.5. Semiconductors

Singlet oxygen production from photoexcited semiconductors such as a TiO_2 and ZnO has received little attention compared to that of active oxygen species such as hydroxyl radicals and superoxide anion. Recently, Yamamoto et al. re-examined the production of these oxygen species from UV-irradiated TiO_2 and ZnO [47]. They demonstrated photosensitized singlet oxygen production by these semiconductors by monitoring the photooxidation of methyl oleate (Fig. 5) and 2,2,6,6-tetramethyl-4-piperidone (4-oxo-TMP) (Fig. 6). The oxidation of methyl oleate by singlet oxygen is known to give 9- and 10-hydroperoxydecenoates. No hydroperoxides were detected in the absence of the semiconductors, and the predominance of the 9- and 10-hydroperoxides in the GC of the reaction products provides strong evidence for the photosensitized production of singlet oxygen by these semiconductors. Singlet oxygen can also cause the oxidation of 4-oxo-TMP to give the paramagnetic *N*-oxide (4-oxo-TEMPO) that can be detected via EPR. ZnO showed a greater quantum efficiency for $^1O_2$ production in this reaction.

3.6. Immobilized photosensitizers

Recent work has begun to focus on immobilized photosensitizers for singlet oxygen generation. There are several advantages to the use of immobilized photosensitizers in practical applications. For use in water purification, for example, the ability to recover and reuse photosensitizers makes environmental and economic sense. In the case of photochemical synthesis, immobilization of the photosensitizers allows for easy isolation of the reaction products from the photosensi-

tizer. Moreover, because these photosensitizers are used heterogeneously, immobilized photosensitizers can be employed in a number of solvents, allowing flexibility in fine chemical synthesis. In general, immobilized photosensitizers show reduced quantum yields than their unbound counterparts, due in part to the need for oxygen to diffuse into and out of the polymer matrix in order to be sensitized and detected. Nevertheless, the ease of reuse of these systems tends to outweigh this shortcoming.

Work by Schaaps et al. [48] compared the efficiency of singlet oxygen production of free rose bengal to rose bengal immobilized on merrifield polymer. Results found that the free photosensitizer had a 100-fold higher production rate of singlet oxygen, due most likely to diffusion problems. Recently, work by Nowakowska and Kepcynski [49] has resulted in the development of a poly(sodium styrenesulfonate-co-vinylbenzyl chloride) polymer with covalently attached rose bengal chromophores (PSSS-VBC/RB). The photosensitizer ability of this polymer was studied through the oxidation of phenol to benzoquinone in aqueous solution. The quantum yield of singlet oxygen formation was determined to be 0.73 [50] and the efficiency of phenol oxidation was found to range from 0.002 to 0.423% with increasing pH. The photobleaching of PSSS-VBC/RB was found to occur at a rate of 6×10^{-7} mol dm^{-3} h^{-1}, which was considerably slower than the oxidation of phenol allowing for the possibility of multiple use.

A recent study by Gerdes et al. [51] focused on the photooxidation of phenol, cyclopentadiene, and citronellol by ionically bound anionic photosensitizers such as rose bengal, and Zn(II), Al(III)OH, Ga(III)OH, and Si(IV)$(OH)_2$ complexes of tetrasulfthalocyanines (PcTS) onto Amberlite® IRA 400. The immobilized photosensitizers showed comparable activities to those of the homogenous analogues. While the rose bengal system was readily decomposed by photodegradation, the photostability of the immobilized phthalocyanines was considerably improved, allowing the reuse of the photosensitizer without considerable loss of activity (see Figs. 7 and 8).

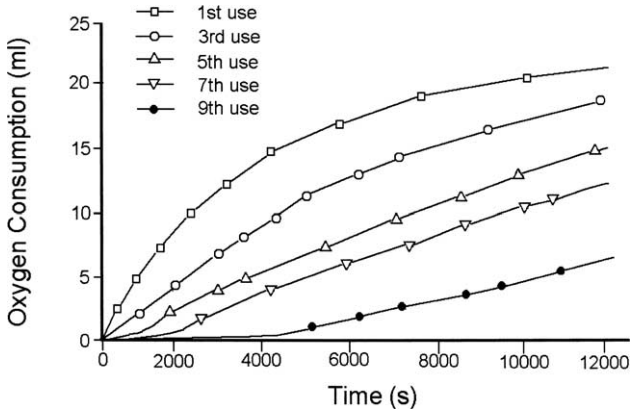


Fig. 7. Photooxidation of 1 mmol of citronellol in methanol with immobilized rose bengal on Amberlite IRA 400 employed nine times. [Reproduced with permission from Ref. [51]. Copyright (2001) John Wiley and Sons.]

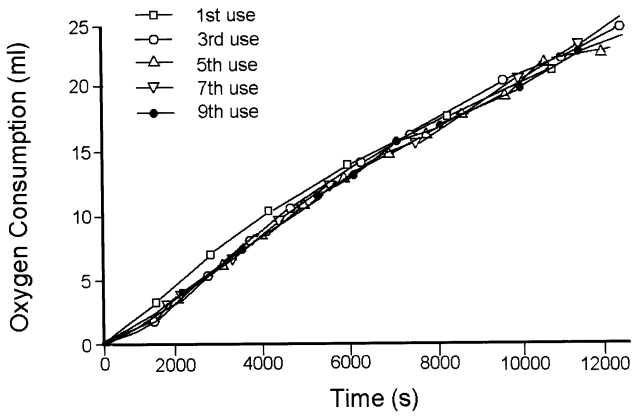


Fig. 8. Photooxidation of 1 mmol of citronellol in methanol using immobilized Si(PcTS)$(OH)_2$ on Amberlite IRA 400 employed nine times. [Reproduced with permission from Ref. [51]. Copyright (2001) John Wiley and Sons.]

Derivatives of Zn(II)-porphyrins with a functional alcoholic group, Zn(II)-5-(4-hydroxyphenyl)-10,15,20-tris(*N*-methyl-4-pyridinium)porphyrin and Zn(II)-5-(4-hydroxyphenyl)-10,15,20-tris(4-sulfonatophenyl)porphyrin, were synthesized by Faust et al. [52] and were linked covalently to polymethylmethacrylate (PMMA) with a concentration of 1%. Normalized production rates of singlet oxygen of the two polymers were 1.34×10^{-4} and 3.77×10^{-5} M s^{-1}, respectively. This is lower than homogeneous solutions of the rose bengal (2.96×10^{-2} M s^{-1}), but higher that of immobilized rose bengal in merrifield polymer (5.26×10^{-6} M s^{-1}).

Suzuki et al. have studied the partially quaternized poly(1-vinylimidazole)-bound Ru(II) complex (C_{12}RuQPIm) in the photooxidation of 1,3-cyclopentadiene [53]. Oxygen consumption measurements confirmed the oxidation of cyclopentadiene. Because oxygen was not consumed in the absence of the polymer, and no reaction between the polymer and cyclopentadiene occurred under an argon atmosphere, the conclusion can be made that singlet oxygen is responsible for this reaction. Fig. 9 shows the change in oxygen consumption during visible light irradiation for the C_{12}RuQPIm system. Reaction activity of the polymer bound Ru(II) gradually decreased with repeated reactions and reaction time was increased to 30 min to ensure complete photooxidation of cyclopentadiene. During these reactions, changes to the absorption maximum of the complex indicated that one imidazole ligand was substituted by chloride. Fortuitously, the new polymer displays a marked improvement in photostability, allowing for numerous repetitions of the photooxidation without degradation of the sensitizer.

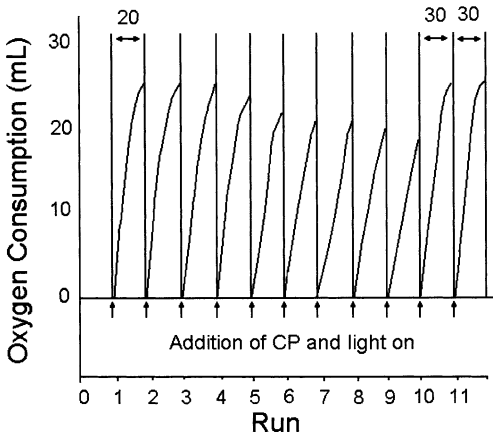


Fig. 9. Repeated cyclopentadiene (CP) photooxidation experiments using C_{12Q}Pim as the photosensitizer ([Ru(II)] = 5.0×10^{-5} M; [CP] = 2.5×10^{-2} M). Irradiation time of one cycle was 20 min in runs 1–9 and 30 min in runs 10 and 11. [Reproduced with permission from Ref. [53]. Copyright (1999) Chemical Society of Japan.]

Recent work by Bourdeland et al. [54] studied the efficiency of singlet oxygen production in water suspensions of a Ru(II) complex, $[Ru(bpac)_3]^{2+}$ where bpac = 4,4′-dicarboxy-2,2′-bipyridine, free in solution and covalently bound to sephadex G-25 to form an insoluble hydrophilic polymer. The rate constants for the molecular oxygen quenching of the lowest excited triplet state of the polymer and the free $[Ru(bpac)_3]^{2+}$ was found to be 4.4×10^8 and 2.4×10^9 M^{-1} s^{-1}, respectively, while quantum yields were 0.1 and 0.28, respectively.

Immobilized zinc phthalocyanine and SALEN (1,6-bis(2-hydroxyphenyl)-2,5-diaza-1,5-hexadiene), complexes have been studied as photocatalysts for the oxidation of 2-mercaptoethanol and sodium thiosulfate [55]. The complexes were anchored on silica or intercalated in the galleries and cavities of layered double hydroxides and zeolite. The photostability of the complexes in these materials was improved but this was thought by the authors as being due to the reduced rate of diffusion of dioxygen and the subsequent quenching of the photosensitized singlet oxygen by the material.

4. Applications of photosensitized $^1O_2$

After $^1O_2$ is generated, it can either lose its energy through a radiative process, a non-radiative process, i.e. heat, or it can react with a substrate. The reactivity of singlet oxygen can be detrimental, as is the case in the photodegradation of polymers, but can also be beneficial as is illustrated in this section.

4.1. Fine chemicals synthesis and wastewater treatment

The use of singlet oxygen in the synthesis of fine chemicals and in the treatment of wastewater is gaining increasing interest. The versatility and the high degree of stereoselectivity of singlet oxygen make it a useful synthetic reagent. The use of solar energy in the treatment of wastewater could be an economical solution to a difficult environmental problem. Research into photosensitized detoxification and treatment of industrial and urban waste-waters using light concentrated directly from the sun is currently underway at the Plataforma Solar de Almeria (PSA, Spain) [56]. Likewise, work has begun at the PSA on project 'SOLFIN' and at the PROPHIS [57] reactor in Germany, both dedicated to photosensitized fine chemical synthesis. For example, work from the PSA has demonstrated the synthesis of 5-hydroxy-5*H*-furan-2-one from furfural in the presence of methylene blue or rose bengal photosensitizers in ethanol [56].

Endoperoxide products of the [4+2] reaction, and allylic hydroperoxide products of the ene reaction are important building blocks for synthetic organic chemistry, allowing the efficient introduction of oxygen into a variety of organic substrates. Substituent, and environmental effects of these reactions are thoroughly described in a recent review by Clennan [9]. For example, endoperoxide synthesis using the novel zinc-seco-porphazine, a very good singlet oxygen sensitizer with a quantum yield of $\Phi_\Delta = 0.54$ was recently studied by Trabanco et al. [58]. A range of endoperoxides were synthesized from the appropriate dienes, with yields greater than or equal to similar reactions using rose bengal as the photosensitizer.

The reaction of cyclopentadiene with singlet oxygen resulting endoperoxide formation is well described in the literature. Depending on the reaction conditions, the endoperoxide converts to other products such as 4,5-epoxy-2-penten-1-one, 1,3-dihydroxy-2-cyclopentene, or 3-hydroxy-2-cyclopentenone [51].

Gerdes et al. studied this photooxidation using phthalocyanines immobilized on Amberlite as the photosensitizers [51]. Fig. 10 shows complete oxidation

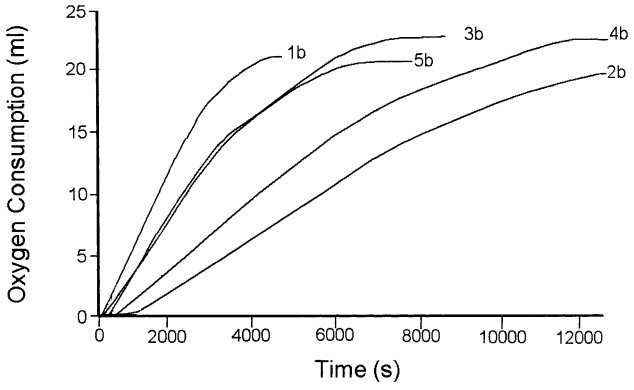


Fig. 10. The photooxidation of 1 mmol of cyclopentadiene in ethanol with immobilized photosensitizers. (**1b** = ZnPcTS; **2b** = Al(OH)PcTS; **3b** = Ga(OH)PcTS; **4b** = $Si(OH)_2$PcTS; **5b** = $Ge(OH)_2$PcTS). [Reproduced with permission from Ref. [51]. Copyright (2001) John Wiley and Sons.]

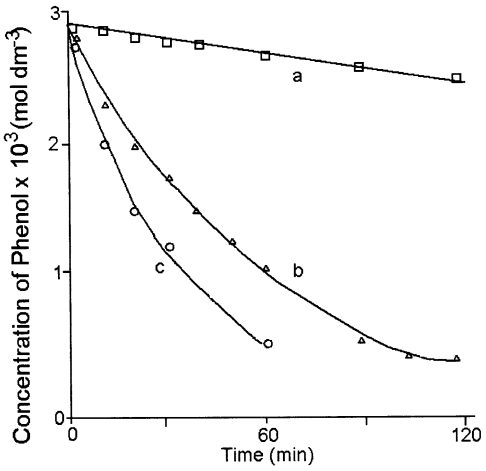


Fig. 11. Changes in the concentration of phenol upon irradiation of aqueous solutions of PSSS-VBC/RB and phenol at various pH. (a) pH 7.2; (b) 10.3; and (c) 11.3. [Reproduced with permission from Ref. [49]. Copyright (1998) Elsevier Science.]

of the cyclopentadiene (24.4 ml of oxygen consumed) is achieved by the immobilized photosensitizers.

Suzuki et al. used poly(1-vinylimidazole)-bound Ru(II) complexes as sensitizers for the oxidation of cyclopentadiene, as shown in Fig. 9 (Section 3.6) [53].

A great deal of work has been done on the use of photosensitized singlet oxygen in oxidation reactions for use in wastewater treatment. Phenol and its derivatives are a class of toxic compounds that are found in the wastewater of paper and dye manufacturing industries, as well as oil refineries. The oxidation of phenols in organic solvents has been studied for some time, using photosensitizers such as eosin, rose bengal, methylene blue, riboflavin, and Zn(II) tetraphenylporphyrin. The use of immobilized rose bengal in the oxidation of phenol was studied by Nowakowska and Kepcynski [49] as was described in Section 3.6 and immobilized

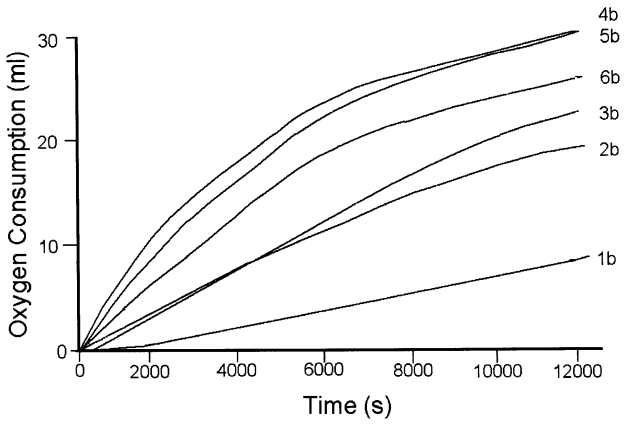


Fig. 12. Photooxidation of 0.36 mmol of phenol in aqueous solutions at pH 10 with different immobilized photosensitizers. **1b** = ZnPcTS; **2b** = Al(OH)PcTS; **3b** = Ga(OH)PcTS; **4b** = Si(OH)$_2$PcTS; **5b** = Ge(OH)$_2$PcTS; **6b** = rose bengal. [Reproduced with permission from Ref. [51]. Copyright (2001) John Wiley and Sons.]

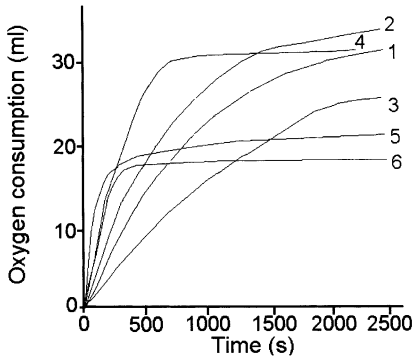


Fig. 13. Photooxidation of 0.71 mmol of sodium sulfide using 0.5 μmol of different catalysts in solutions containing 0.1 M CTAC. (1) Zn(II)PcTS; (2) Al(III)(OH)PcTS; (3) Al(III)(OH)PcTS without CTAC; (4) H_2PcTS; (5) Co(II)PcTS; (6) Co(II)PcTS (not irradiated). [Reproduced with permission from Ref. [61]. Copyright (1998) Elsevier Science.]

phthalcyanines were studied for the same purpose by Gerdes [51] (see Figs. 11 and 12).

More recently, phenols and monochlorophenols in aqueous solution have been investigated by Gerdes et al. [59] using photosensitizers such as Al(III), Zn(II), and Ga(III) complexes of 2,9,16,23-tetrasulfophthalocyanine, as well as 5,10,5,20-tetrakis(4-carboxyphenyl)porphyrin, rose bengal, methylene blue, and di(*N*,*N*,-trimethylammonium-propylene)-3,4,9,10-perylenebis-carboxyimide. The results demonstrated that a monomeric state of the photosensitizer in solution is crucial to its activity in photoreactions. The addition of oppositely charged detergents to discourage aggregation, especially in the Zn(II) phthalocyanine and the carboxyimide, improved Φ_Δ and phenol oxidation.

The oxidation of sulfide salts to sulfate in aqueous solution is also important in wastewater treatment, due to its occurrence as a byproduct of industrial processes such as petroleum refining, tanning, coking, natural gas purification, and food processing. In a study by Iliev et al. [60] Zn(II)-2,9,16,23-phthalocyanine tetracarboxylic acid was found to be effective in the photosensitized oxidation of both sulfide and thiosulfate to sulfate. A study by Spiller et al. [61] examined the photooxidation of sodium sulfide by sulfonated phthalocyanine and the effects of added detergents and latexes. Fig. 13 shows the photosensitizers used and their oxygen consumption over time. All phthalocyanines, with the exception of the Co(II) complex, showed oxygen consumptions consistent with complete conversion of the sulfide to sulfate and photosensitized singlet oxygen was thought to be responsible for the photooxidation. Once again, the use of detergents such as cetyl trimethyl ammonium chloride (CTAC) strongly enhances the photoactivity of sensitizers that have high aggregation tendency. Latexes appear to increase the photoactivity, but also the photodegradation, of the photosensitizers due to the

high local concentration of generated singlet oxygen in the latex.

4.2. Singlet oxygen in photodynamic processes

The photodynamic effect describes the damage of living tissue by the combination of a photosensitizer, visible light, and oxygen. Singlet oxygen is understood to play the major role in this effect, and application of this effect to blood sterilization, cancer therapy, and insecticides and herbicides is of increasing importance.

Direct spectroscopic evidence of singlet oxygen in PDT is difficult to find, presumably due to the rapid reaction of singlet oxygen with biomolecules. Nevertheless, it is generally agreed that $^1O_2$ is the major participant. It is important, however, to note that the role of Type I (radical) mechanisms in PDT cannot be discounted.

4.2.1. Blood sterilization

The Swiss and German Red Cross use methylene blue as a photosensitizer for the decontamination of freshly frozen plasma units [62]. Known for its lack of toxicity to humans, the dye is effective at destroying extracellulary-enveloped viruses. Unfortunately, cellular enzymes reduce this dye to a photodynamically inactive colorless form, thus limiting its use as an in vivo photosensitizer. Silicon-based phthalocyanines [63] are also being studied for the sterilization of blood components by V.I. Technologies at the New York Blood Center.

4.2.2. Photodynamic therapy of cancer (PDT)

This new form of cancer therapy is gaining research attention due to the promise of selectivity for diseased tissue. In PDT, visible light, a light-sensitive drug (photosensitizer), and oxygen are combined, leading to the production of lethal agents to inactivate tumor cells. It is generally accepted that singlet oxygen is the primary cytotoxic agent responsible for photobiological activity, [33], however, Type I (radical) reactions could play a supporting role. The dual selectivity of PDT comes from both the localization of the sensitizer in the tumor and the ability to confine activation of the photosensitizer by illumination of only the tumor region. This allows for the possibility of tumor destruction without effect on normal tissue, a major goal in cancer therapy.

The process of photodynamic cancer therapy is as follows [33]: the photosensitizer is administered (orally, topically, or intravenously) and the drug equilibrates for a certain period of time (drug-light interval), allowing for maximum tumor/normal tissue differentiation. The tumor is then irradiated directly by a light source with the desired wavelength. The light source can be as simple as a projector lamp, although lasers and fibre optics are often used. Finally, cytotoxic products generated by the excited photosensitizer cause the desired tumor destruction, preferably without consequence on healthy tissue.

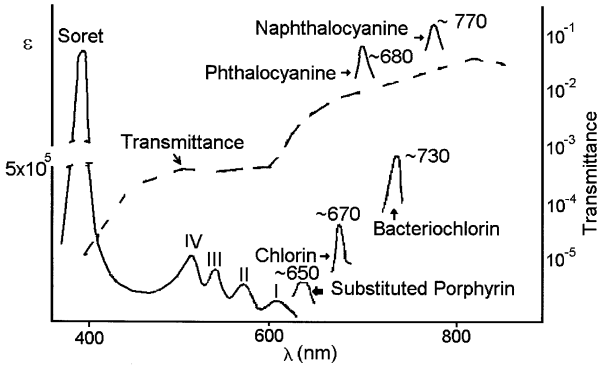


Fig. 14. Photosensitizer absorbance compared to tissue transmittance. The Soret, and I, II, III, IV bands represent those of porphyrin. The transmittance curve is obtained from a sample of human scrotal sac (7 mm thick). The broad absorbance from 500 to 600 nm is attributed to haemoglobin. [Reproduced with permission from Ref. [33]. Copyright (1995) Royal Chemical Society.]

The potential candidates for biological photosensitizers for PDT of cancer must fulfil several criteria in addition to those for general photosensitizers. The compounds should have low dark toxicity and should selectively accumulate in tumor tissue, in order to minimize skin sensitivity. The distribution of the photosensitizer is important in photodynamic processes and is influenced by its chemical structure. It is particularly useful if the photosensitizer is amphiphilic, water-soluble but containing a hydrophobic matrix which should facilitate the crossing of cell membranes. Limited in vivo stability is preferred to allow for rapid removal from tissues. Absorption in the red region of the visible spectrum with high extinction coefficient ($\varepsilon \geq 50\,000$ M^{-1} cm^{-1}) is also an important criterion to increase the number of photons absorbed and to take advantage of the increase in the penetration depth of light into tissue at longer wavelengths. Moreover, the absorption band of the sensitizer should not overlap the absorption bands of other chromophores present in the tissues (see Fig. 14).

Photosensitizers for PDT of cancer have been classed into three generations:

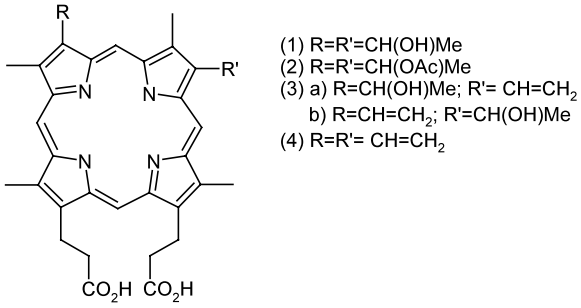
First generation: Haematoporphyrin derivative (HpD) and its analogues.

Second generation: Structurally distinct compounds with long-wavelength absorption.

Third generation: Second generation photosensitizers bound to carriers for selective accumulation in the tumor.

Haematoporphyrin derivative (HpD), and its commercial analogues, such as Photofrin and Photoheme,

are the first generation of photosensitizers. It was with these compounds that the first results and authorizations for clinical use were obtained. Reports on the tumor killing potential and the efficiency of HpD in PDT [64] appeared in the 1970s and 80s. The HpD was prepared in order to solubilize haematoporphyrin in neutral aqueous solution [33]. Haematoporphyrin (**1**) is treated with 5% sulfuric acid in acetic acid at ambient temperature for 30 min and the resulting purple solid, known as HpD stage 1, is a mixture of about 10 components.



The major component is haematoporphyrin diacetate (**2**). The solid is treated with aqueous base and then neutralized forming HpD stage 2. This regenerates haematoporphyrin and produces 3-hydroxylethyl-8-vinyldeuteroporphyrin (**3a**) or 3-vinyl-8-hydroxylethyldeuteroporphyrin (**3b**) and protoporphyrin (**4**).

These monomer compounds are not in fact the components responsible for the photonecrotic behavior of HpD stage 2. Instead, a mixture of porphyrin dimers and oligomers connected by ether, ester, and carbon–carbon interporphryin linkages appears to be the active components, perhaps due to their ability to localize within certain tissues. Photofrin, for example, consists of a complex mixture of dimers and oligomers ranging from two to nine porphyrin units linked mostly by ether bonds. Commercial purified PDT agents such as Photofrin 18 [33] are prepared by removing the monomer fractions of HpD stage II by HPLC or gel permeation chromatography. This PDT photosensitizer has been accepted in clinical trials in several countries for the treatment early and late-stage lung cancer, oesophageal cancer, bladder cancer, early stage cervical cancer for some examples [62].

These first generation photosensitizers have been studied extensively and have been used in experimental clinical work. Unfortunately, there are several disadvantages associated with them. Selectivity of these photosensitizers is poor. In fact, only 0.1–3% of injected photosensitizer is found in tumor tissue [29]. The cutaneous tissue can take up and retain these compounds for up to 10 weeks after intake, thus causing photosensitivity in the patient. These compounds only absorb weakly in the red. For example, Photofrin has a number of absorption bands between 400 and 650 nm, but its weakest band at 630 nm, is most often used for excitation. Irradiation at this wavelength can only penetrate tissue to a depth of ca. 5 mm [29]. Also, the first generation photosensitizers are complex mixtures and it has not been possible to isolate a single highly active component. This makes synthesis and biological activity difficult to reproduce. Despite these disadvantages, first generation photosensitizers have become a useful means for fighting against cancer and have stimulated the search for new, second generation photosensitizers with improved characteristics.

The second generation photosensitizers were sought with certain new criteria in mind. These photosensitizers should be single substances, for simplicity of interpretation and ease of reproduction. Furthermore, these substances should have greater selectivity for tumor tissue and be rapidly excreted from the body. Absorption in the range of 675–800 nm is desired, since it would allow for light penetration of up to 2–3 cm. A great deal of research has been focused on the discovery and testing of the second generation of PDT photosensitizers. Many of these classes of photosensitizers have been previously introduced (Section 2.2), but their results in relation to PDT will be expanded upon here.

4.2.2.1. Porphryins. The modification of readily available porphyrins, haematoporphyrin and protoporphyrin, was an obvious first step in the search for new photosensitizers. Ether, thioether, ester, and amino substituted haematoporphyrin derivatives have been synthesized and most show biological activity [33]. *meso*-Tetraphenylporphyrins are synthetically accessible and can be easily substituted in the phenyl group to add to the hydrophilicity. Unfortunately, the *ortho* hydroxy phenyl isomer causes skin sensitivity, but the *meta* and *para* isomers show improved tumor phototoxicity and selectivity over haematoporphryin derivative [33,65]. The methyl pyridinium salt causes significant tumor photodamage, attributed to the increase in hydrophilicity imparted by the cationic substituent [66]. A series of asymmetric amide protoporphyrin derivatives studied by Haylett et al. [67] was found to be efficient sensitizers of singlet oxygen with quantum yields of 0.01–0.64. Tetrakismethoxyphenyl porphyrins have favorable photophysical properties such as high triplet quantum yield (0.63–0.84 depending on the number and position of the MeO groups) and can produce singlet oxygen with high quantum yield ($\Phi_\Delta \cong 0.7$) [68]. The second-generation photosensitizer verteporfin (benzoporphyrin-derivative monoacid ring A) is presently undergoing clinical trials for cutaneous non-melanoma skin cancer and against other non-melanoma skin cancers [62]. Interested researchers can search the web site of QLT PhotoTherapeutics (www.qlt-pdt.com) for the progress of these clinical trials. Verteporfin has a strong absorbance at long wavelength (690 nm), has good selectivity,

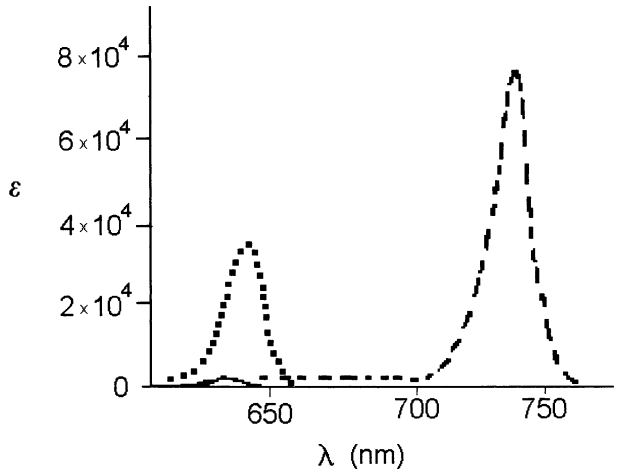


Fig. 15. Absorption spectra of *m*-THPP (solid line), *m*-THPC (small dashed line), and *m*-THPBC (large dashed line). [Reproduced with permission from Ref. [33]. Copyright (1995) Royal Chemical Society.]

and is rapidly excreted from the body, resulting in skin photosensitivity that only lasts a few days [69].

Another interesting approach to the search for photosensitizers is the use of the body's biosynthetic capability to produce large amounts of photosensitizer. The rate-limiting step in the synthetic pathway for haem is the conversion of glycine and succinyl coenzyme A to ALA, a step under negative feedback control by haem. If ALA concentration is artificially enhanced, this can bypass the negative feedback, leading to a build-up of protoporphyrin [33]. This excess photosensitizer can then cause a photonecrotic effect. Interestingly, the endogenous protoporphyrin seems to be remarkably sensitive to photobleaching, thus reducing skin sensitivity to only 1–2 days. In clinical trials, ALA cream can be applied topically [70] to superficial basal cell or squamous cell carcinomas, and it has also been possible to administer ALA orally or intraveneously with positive results [71].

Despite the progress with analogues of HpD, search for photosensitizers with more intense bands in the red region required research into other types of macrocycles. One major group, the chlorins and bacteriochlorins, has been investigated as possible PDT agents. The natural compounds chlorophyll *a* and bacteriochlorophyll *a* have been used as starting materials for a number of amphiphilic chlorins with PDT activity.

Synthetic chlorins, *meso*-tetrakis(*m*-hydroxyphenyl)chlorin (*m*-THPC), *meso*-tetrakis(*o*-hydroxyphenyl)chlorin (*o*-THPC), *meso*-tetrakis(*o*-hydroxyphenyl)-chlorin (*p*-THPC) and *meso*-tetrakis(*m*-hydroxyphenyl)bacteriochlorin (*m*-THPBC) were synthesized by Bonnett [33] to build upon the initial success of the tetrakis(hydroxylphenyl)porphyrins, but at the same time increase absorption in the red region of the visible spectrum. These porphyrins could be prepared in good yields and purity and as expected, increased absorption in the red was noted (see Fig. 15).

In vivo studies have indicated that activity increases in the sequence porphyrin, chlorin, bacterochlorin [72,73].

m-THPC, also known as Temoporfin, in particular, was found to have a high Φ_Δ and good biological activity, less photosensitization of normal skin than Photofrin, and thus was considered to be a good candidate for clinical work. This photosensitizer may be one of the most phototoxic sensitizers currently being investigated. Doses as low as 0.1 mg kg^{-1}, and light doses as low as 10 J cm^{-2} can be effective, making it 100 times more photobiologically active than Photofrin, which typically requires drug doses of 2–5 mg kg^{-1} and light doses of 100–200 J cm^{-2} [62]. This increased photoactivity can be attributed to both its improved optical properties, and more importantly, to its subcellular localization [74].

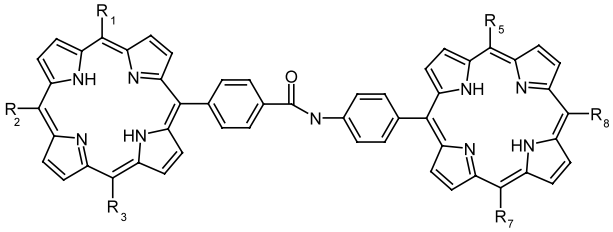
Tetra- and octa-glycogenated tetraphenyl chlorins and porphyrins have been synthesized and studied by Mikata et al. [75]. All these derivatives showed comparable singlet oxygen producing ability, thus differences in photocytotoxicity against HeLa cells reflected the extent of incorporation of the photosensitizers in the cell. The octa-glycosated derivative showed little phototoxicity, likely due to its excessive hydrophilicity. The tetra-glycosated porphyrin derivative was the most effective photosensitizer, likely due to its membrane permeating ability.

Halogenated chlorins such as TDFPC = 5,10,15,20-tetrakis(2,6-difluorophenyl)chlorin, ToCPC = 5,10,15,20-tetrakis(2-chlorophenyl)chlorin, TDCPC = 5,10,15,20-tetrakis(2,6-dichlorophenyl)chlorin have recently been investigated as potential new PDT agents [76]. The quantum yields of these complexes when excited at 655 or 660 nm are considerable: TDFPP $\Phi_\Delta = 0.88$, ToCPP $\Phi_\Delta = 0.89$, TDCPP $\Phi_\Delta = 0.98$. A particular advantage of these chlorins is that their absorptivities are ca. 10 times larger than those of related porphyrins.

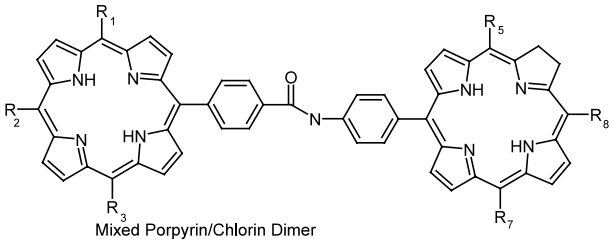
meso-Tetraphenylporphyrin and chlorin dimer derivatives were studied by Faustino et al. as potential photosensitizers for PDT [77]. Study of the photo-

Table 6
Photophysical and biological properties of a series of chlorin and porphyrin dimers

	λ_{max} (nm)	ε (M^{-1} cm^{-1})	Φ_Δ	Tumor to skin accumulation ratio
D1	647	8200	0.72	24
D2	646	7600	0.71	5
D3	648	8200	0.67	24
D4	651	31 600	0.73	5



Porphyrin Dimers
(D1) $R_1=R_2=R_3=C_6H_5$; $R_5=R_7=R_8=3\text{-}MeOC_6H_4$
(D2) $R_1=R_2=R_3=R_5=R_7=R_8=C_6H_5$
(D3) $R_1=R_2=R_3=C_6H_5$; $R_5=R_7=R_8=3\text{-}MeOC_6H_4$



Mixed Porpyrin/Chlorin Dimer
(D4) $R_1=R_2=R_3=C_6H_5$; $R_5=R_7=R_8=3\text{-}MeOC_6H_4$

physical properties of the amide-linked dimers showed moderate absorption coefficients in the red portion of the visible spectrum and high quantum yields of singlet oxygen formation, ranging from 0.67 for D3 to 0.73 for D4 (see Table 6). High tumor selectivity, especially in D1 and D3, could mean little or no induced photosensitivity. Irradiation of these dimers over a 30-min period, however, caused negligible photobleaching.

The purpurin series of tetrapyrroles has also been investigated for use in PDT. These compounds are generally hydrophobic and need to be administered in an emulsifying agent. Tin etiopurpurin, for example, is a biologically active compound under intensive study [62]. It has a reasonably strong absorption in the red (660 nm, 2.8×10^4 M^{-1} cm^{-1}) and is currently in clinical and preclinical trials for a number of cancers. Interested researchers can search the web site of Miravant Medical Technologies (http://www.miravant.com) for an update of the progress of these trials. Unfortunately, patients can experience skin sensitivity of up to one month when given this PDT agent.

4.2.2.2. Phthalocyanines and Naphthalocyanines. Complexes of phthalocyanine (Pc) and napthalocyanine (NPc) with closed *d*-electron shell elements produce singlet oxygen with high quantum yields (Φ_Δ (Zn(II)Pc) = 0.56; Φ_Δ (Zn(II)NPc) = 0.45) [23] and show strong photobiological activity against tumors. These hydrophobic compounds can be administered in a transport agent, such as unilamellar liposomes like dipalmitoyl phosphatidyl choline (DPPC). This method is effective at keeping these strongly aggregating photosensitizers monomeric in solution [29]. In clinical trials, Zn phthalocyanine has been studied for its application to the treatment of squamous cell carcinomas of the upper aerodigestive tract [78].

It is thought that tumor localization and selectivity in phthalocyanines can be improved by adding polar groups to the hydrophobic macrocycle skeleton to improve its amphiphilicity. For example, groups like carboxylic acids, hydroxyls, sulfonic acids, and quaternary ammonium salts are being investigated [29,33] but a balance between hydrophobic and hydrophilic properties is essential. Amphiphilic phthalocyanines, such as sulfonic acid derivatives have been studied and activity seems to be related to the degree of sulfonation. In a series of aluminum phthalocyanines, biological activity increased by an order of magnitude in the series $AlPcS_4 < AlPcS_3 < AlPcS_2$ (S = sulfonic acid groups in the peripheral benzenoid positions) [29]. Mono and disulfonated phthalocyanine complexes have displayed uniform cytoplasmic fluorescence, indicating their monomolecular state in the cell [29]. Trials are underway to study these sulfonated aluminum phthalocyanine derivatives against skin, breast, lung, and gastrointestinal cancer [62,79].

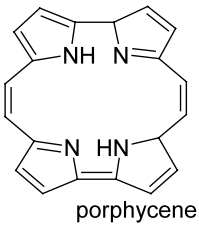
4.2.2.3. Other macrocyclic systems. Texaphyrins have strong absorptions in the 600–900 nm region whose energy can be tuned via substitution, and have high quantum yields. Lanthanum and lutecium complexes with $R = CH_2OH$ and $R' = O(CH_2)_3OH$ show photobiological activity in vivo [80]. The lutecium texaphryin, under the trade name Lutrin™, is undergoing clinical trials as a possible therapy for breast cancer [62].

Porphycene has a strong absorption band at 630 nm ($\varepsilon = 52\,000$ M^{-1} cm^{-1}) and the derivative [9-acetoxy-2,7,12,17-tetrakis-(β-methoxyethyl)porphycene] has undergone extensive examination [81]. The methoxy ethyl

Table 7
Comparison of the photophysical properties of the first and second generations of photosensitizers [61,33]

Photosensitizer	ε (M^{-1} cm^{-1})	λ_{max} (nm)	Φ_T	Φ_Δ
Haematoporphyrin [a]	3500	630	0.83	0.65
Photofrin II [a]	~3000	~630		~0.2
Zn phthalocyanine [a]	150 000	675	0.6	0.59
Al phthalocyanine–tetrasulfonic acid [b]	105 000	675	0.38	0.38
Zn naphthalocyanine [a]	160 000	764		0.45
Benzoporhyrin [a]	118 000	685		0.6
Bacteriochlorin [a]	150 000	785	0.32	0.32
Zn etiopurin [a]	~70 000	~690	0.83	0.57
Porphycene [a]	52 000	630	0.42	0.3

[a] Determined in an organic solvent.
[b] Determined in water.

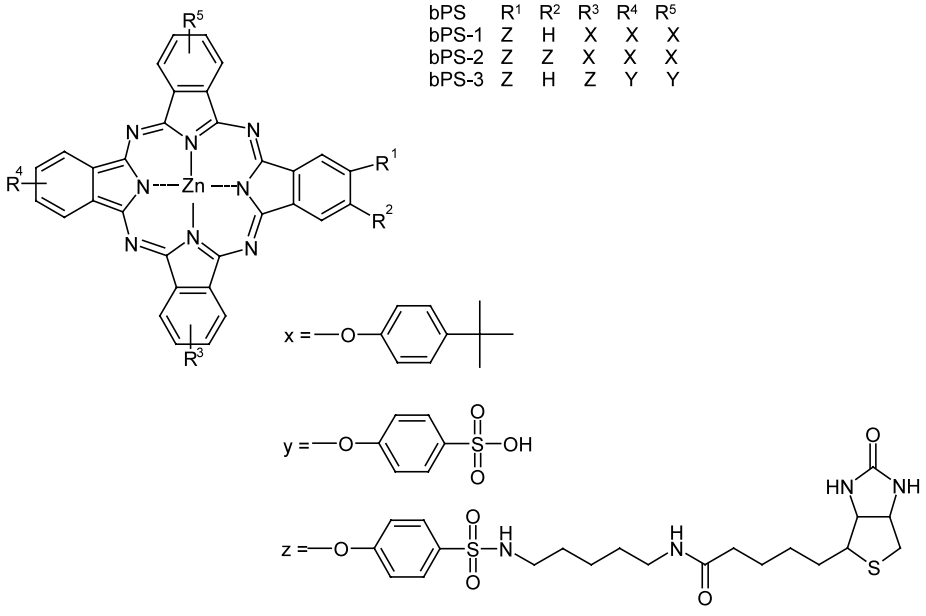


porphycene

side-chains accelerate cellular uptake while the acetoxy-group appears to increase the hydrophilicity of the molecule [81].

In general, second generation photosensitizers show improved photophysical properties and address some of the problems associated with the first generation. Table 7 compares some of the better known first and second generation photosensitizers.

4.2.2.4. Third generation photosensitizers. Photosensitizers of this generation have properties allowing for their selective delivery to the tumor tissue. This could occur through the conjugation to biomolecules such as monoclonal antibodies (mAB). It is known that tumor cells have cell surface antigens that are different from those



of normal cells. If the mAB bound photosensitizer will bind specifically to the tumor tissue, this would allow selective photodamage without affecting normal tissue [82]. The current strategy for binding photosensitizers uses polyphasic tumor therapy to accumulate up to 10^8 photosensitizer molecules on the tumor, assuming ca. 10^5 antigen binding sites [29]. This strategy overcomes difficulties in reproducibility in the molecule binding site and in accumulation of photosensitizer on the tumor, found in previous approaches [29] (see Fig. 16). For example, the properties of the avidin–biotin system could be used for the delivery of a photosensitizer (PS) onto specifically labelled tumor cells [29]: (1) tumor cells are treated with biotinylated mAB; (2) the excess mAB is removed, and avidin or streptavidin (SA) is added which binds to the biotin linked to mAB; (3) the excess avidin is removed, and biotinylated photosensitizer (bPS) is added, which binds to the free sites of the mAB-avidin conjugate; and (4) multiple repetitions of steps 2–4 allows for a high accumulation of PS on the surface of the tumor cell.

Binding tests using the different bPS systems (bPS-1, -2, and -3) showed excellent binding in an enzyme-linked immunosorbent assay. Tests were done on breast carcinoma cells and colon carcinoma cells treated first with biotinylated antibody BM7, then streptavidin (SA) and finally bPS-1. Irradiation with a light dose of 5 J cm^{-2} caused ca. 90% cell lysis of the breast carcinoma cells and ca. 45% cell lysis of the colon carcinoma cells. These results are quite promising and should lead to the further development of third generation photosensitizers.

The use of delivery vehicles in PDT is another promising development in the study of third generation photosensitizers. In a recent study by Allen et al. [83] metallated phthalocyanines have been covalently linked to adenovirus Type 2 capsid proteins, known to bind

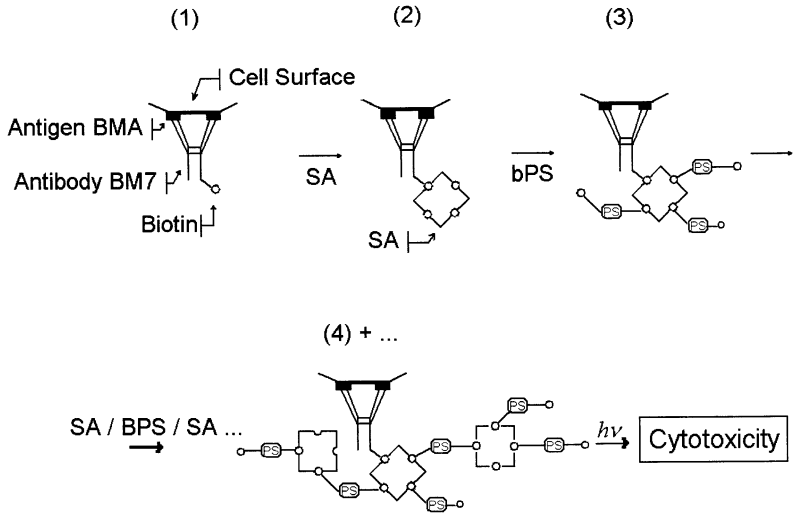


Fig. 16. Reaction scheme for the selective attachment of third-generation photosensitizers to the surface of a tumor cell (SA, streptavidin; bPS, biotinylated photosensitizer). [Reproduced with permission from Ref. [29]. Copyright (1998) Kluwer.]

with great affinity and high specificity to integrin receptors, expressed by several types of cancer. A mixture of adenovirus Type 2 soluble proteins covalently labeled with $AlPcS_4$ required half the drug dose of free $AlPcS_4$ needed to induce complete tumor damage, suggesting that the linked complex is able to target the tumor.

4.2.3. Insecticides and herbicides

Akin to the work done in the PDT of cancer, photodynamic herbicides and insecticides use the toxic effects of singlet oxygen to destroy unwanted plants and pests. Photodynamic herbicides cause the undesirable accumulation of chlorophyll and heme metabolic intermediates, tetrapyrroles, in green plants [84]. Once exposed to light, these accumulated tetrapyrroles act as photosensitizers for the production of singlet oxygen,

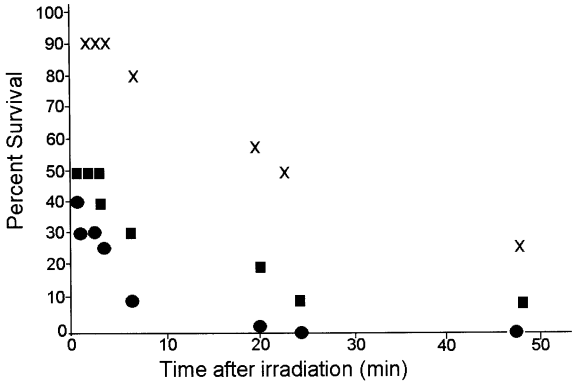


Fig. 17. Percent survival of three diptera *Ceratitis capitata* (circles), *Bactrocera* (*Dacus*) *oleae* (×), and *Stomoxys calcitrans* (squares) after 1 h irradiation with white light. The flies had been exposed to a bait containing 8 μM haematoporphyrin. [Reproduced with permission from Ref. [85]. Copyright (2000) Elsevier Science.]

which kills the treated plants through oxidation of their tissues. These tetrapyrrole-dependent photodynamic herbicides (TDPH) generally consist of δ-aminolevulinic acid (ALA), which is a precursor of all tetrapyrroles in plant and animal cells and modulators, which can alter the tetrapyrrole accumulation.

As a direct continuation of this work, the insecticidal effects of photosensitizers have been studied. For more in depth reviews on photodynamic insecticides see those by Ben Amor [85] and Rebeiz [86]. Organic dyes, such as the xanthenes, have been intensely studied for this purpose due to their photosensitizing ability. The poor photostability of the xanthene dyes is an advantage as this eliminates the problem of persistence in the environment that is a serious issue with conventional insecticides.

Porphyrin-based photosensitizers have been more recently studied for use as insecticides [87]. Due to their absorption bands in various regions in the UV–vis spectrum, these compounds can be activated by a range of wavelengths and have been found to be effective as insecticides (see Fig. 17).

Different approaches for the use of porphyrin based insectides have been followed. Similar to the TDP herbicides, large excesses of ALA have been administered to insects, resulting in the accumulation of significant amounts of protoporphyrin IX [88]. Photosensitivity is sufficient in the insects 3–4 h after exposure to the ALA. A second approach involves the direct administration of a porphyrin from a bait [87]. One hour after exposure the insects are photosensitive and this persists about 48 h after adminstration of the porphyrin has stopped. Highly water soluble porphyrins, such as *meso*-*N*-methylpyridylporphine or *meso*-sulfonatophenyl porphine are inefficient photoinsecticides despite

being efficient generators of singlet oxygen [87]. The ineffectiveness of these complexes must be related to the spatial distribution in the insects. The most effective agents were amphiphilic derivatives such as *meso*-[di-*cis*(4*N*-methylpyridiyl)]*cis*-diphenylporphine ditosylate (DDP). This mirrors the results from PDT, which has found that very hydrophilic photosensitizers are ineffective at destroying tumor cells.

5. Future studies

The chemistry of singlet oxygen is rich and we have only begun to realize its potential uses. Much remains to be done to modify and improve existing photosensitizers to better suit their properties to desired applications. This, of course, requires an improved understanding of mechanisms of photosensitizer quenching, photobleaching, and localization in tissues. The investigation of new photosensitizers is also crucial to further development in this field.

Semiconductors with band gaps in the visible range have been investigated for use in light-emitting diodes and photovoltaic devices. The possibility that their excited states may be quenched by molecular oxygen has not been fully explored and could lead to new applications. Luminescent Ru(II), Pt(II), Pd(II), Ir(III), and Rh(III) complexes possess 'tuneable' properties through ligand substitution that may offer photosensitization and photostability advantages. Understandably, the synthesis of these metal complexes could be too costly for industrial use, however, this may not be a major issue in biological applications, and thus, their biological activity and cytotoxic nature should be investigated.

The problem of aggregation in phthalocyanine photochemistry has been described previously. This seems to have detrimental effects to the industrial use of phthalocyanines in applications such as wastewater treatment, as additives such as detergents are often needed to improve singlet oxygen formation and waste decomposition. Free and metallated porphyrins, however, show comparable singlet oxygen yields and have less tendency to aggregate. The main advantage that phthalocyanines hold over porphyrins, their absorption at lower wavelengths, is only truly important in photodynamic applications with regards to the depth of light penetration into tissue, and thus should not affect their use in waste treatment and fine chemical synthesis.

The immobilization of photosensitizers in a polymer matrix also requires further study. The covalent linking of complexes to a polymer backbone should eliminate the problem of photosensitizer aggregation, however, difficulties with the diffusion of oxygen into and out of the polymer beads appears to reduce their efficiency. The question remains of whether the improved photostability of these sensitizers is a factor of their immobilization, or simply a result of lower singlet oxygen yields. This problem needs to be addressed before industrial application of these systems can occur.

Selectivity remains a major issue in PDT, as photosensitivity of the patient during PDT is a serious problem. Two major routes of research should be followed in order to resolve this difficulty: (1) the study of photobleaching in photosensitizers to determine the optimal rate of decomposition that maximizes tumor damage, while minimizing photosensitivity in patients; and (2) the study of new third generation photosensitizers. With regards to strategy 1, further work into photosensitizers with appropriate singlet oxygen quenching substiutents (e.g. amines) is necessary. Strategy 2 is likely the more promising of the two routes. The avidin–biotin interaction should be applied to a wide range of organic and inorganic photosensitizers to attempt the selective administration of the sensitizer to the tumor cells. Similarly, the use of covalently bound adenoviruses should be tested systematically for various sensitizers. Undoubtedly, other biological interactions that could be applied to the selective administration of photosensitizers to tumor tissue exist and it is here that a major contribution to PDT can be made.

With the wealth of possible photosensitizers that are currently described in the literature, the focus on new applications for photosensitized singlet oxygen offers many research possibilities. This research could address problems as varied as the removal of sulfides from mining effluent to the destruction of viruses and bacteria in drinking water. The study of the generation and application of singlet oxygen is still in its infancy and presents numerous research opportunities to biologists and chemists alike.

Acknowledgements

The authors wish to thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support. M.C.D. thanks NSERC for the award of a postgraduate scholarship.

References

[1] A.U. Khan, M. Kasha, J. Chem. Phys. 39 (1963) 2105.
[2] H.H. Wasserman, R.W. Murray, in: H.H. Wasserman, R.W. Murray (Eds.), Singlet Oxygen, vol. 40, Academic Press, New York, 1979.
[3] B. Rånby, J.F. Rabek (Eds.), Singlet Oxygen: Reactions with Organic Compounds and Polymers, John Wiley and Sons, New York, 1978.
[4] G. Herzberg, Molecular Spectra and Molecular Structure I: Spectra of Diatomic Molecules, 2nd ed., VonNostrand, New York, 1950.

[5] S.J. Arnold, M. Kubo, E.A. Ogryzlo, Adv. Chem. Ser. 77 (1968) 133.
[6] P.B. Merkel, D.R. Kearns, J. Am. Chem. Soc. 94 (1972) 1029.
[7] C.A. Long, D.R. Kearn, J. Am. Chem. Soc. 97 (1975) 2018.
[8] (a) C.S. Foote, in: H.H. Wasserman, R.W. Murray (Eds.), Quenching of Singlet Oxygen in Singlet Oxygen, vol. 40, Academic Press, New York, 1979;
(b) D. Bellus, Quenchers of Singlet Oxygen in Singlet Oxygen: Reactions with Organic Compounds and Polymers, John Wiley and Sons, New York, 1978.
[9] E.L. Clennan, Tetrahedron 56 (2000) 9151.
[10] H.R. Rawls, P.J. Vansanten, J. Am. Oil Chem. Soc. 47 (1970) 121.
[11] E.G. Adams, R.L. Willson, Trans. Faraday Soc. 65 (1969) 2981.
[12] (a) J.W. Hasting, T. Wilson, Photochem. Photobiol. 23 (1976) 461;
(b) S. Mazur, C.S. Foote, J. Am. Chem. Soc. 92 (1970) 3225.
[13] I. Kruk, Environmental Toxicology and Chemistry of Oxygen Species Handbook of Environmental Chemistry, vol. 2, Hutzinger, New York, 1998.
[14] C.S. Foote, R.W. Murray, R.D. Smetana, E. Block, Tetrahedron Lett. (1971) 299.
[15] K. Gollnick, in: B. Rånby, J.F. Rabek (Eds.), Singlet Oxygen: Reactions with Organic Compounds and Polymers, John Wiley and Sons, New York, 1978, p. 111.
[16] C.S. Foote, R.W. Denny, L. Weaver, Y. Chang, J. Peters, Ann. N.Y. Acad. Sci. 171 (1970) 139.
[17] J.F. Rabek, Photodegradation of Polymers, Springer-Verlag, New York, 1996.
[18] C.A. Gruperhaus, Acc. Chem. Res. 31 (1998) 451.
[19] M. Selke, C.S. Foote, J. Am. Chem. Soc. 115 (1993) 1166.
[20] M. Selke, C.S. Foote, W.L. Karney, Inorg. Chem. 32 (1993) 5425.
[21] M. Selke, L. Rosenberg, J.M. Salvo, C.S. Foote, Inorg. Chem 35 (1996) 4519.
[22] F.W. Wilkinson, W.P. Helman, A.B. Ross, J. Phys. Chem. Ref. Data 22 (1993) 113.
[23] R.W. Redmond, J.N. Gamlin, Photochem. Photobiol. 70 (1999) 391.
[24] (a) F. Wilkinson, A.A. Abdel-Shafi, J. Phys. Chem. Sect. A 103 (1999) 5425;
(b) D.J. McGarvey, P.G. Szekeres, F. Wilkinson, Chem. Phys. Lett. 199 (1992) 314;
(c) C. Grewer, H. Brauer, J. Phys. Chem. 98 (1994) 4230;
(d) A.F. Olea, F. Wilkinson, J. Phys. Chem. 99 (1995) 4518.
[25] I. Gutierrez, S.G. Bertolotti, M.A. Biasutti, A.T. Soltermann, N.A. García, Can. J. Chem. 75 (1997) 423.
[26] A.E. Alegría, A. Ferrer, G. Santiago, E. Sepúlveda, W. Flores, J. Photochem. Photobiol. A: Chem. 127 (1999) 57.
[27] Z.J. Diwu, J. Photochem. Photobiol. 61 (1995) 529.
[28] T. Wu, S. Xu, J. Shen, A. Song, S. Chen, M. Zhang, T. Shen, Anti-Cancer Drug Des. 15 (2000) 287.
[29] D. Wöhrle, A. Hirth, T. Bogdahn-Rai, G. Schnurpfeil, M. Shopova, Russ. Chem. Bull. 47 (1998) 807.
[30] C.C. Leznoff, A.B.P. Lever (Eds.), Phthalocyanines: Properties and Applications, VCH Publishing, New York, 1996.
[31] J.R. Darwent, P. Douglas, A. Harriman, G. Porter, M.C. Richoux, Coord. Chem. Rev. 44 (1982) 83.
[32] M. Soncin, J. Photochem. Photobiol. B: Biol. 42 (1998) 202.
[33] R. Bonnett, Chem. Soc. Rev. (1995) 19.
[34] D.M. Guildy, T.D. Mody, N.N. Gerasimchuk, D. Magda, J.L. Sessler, J. Am. Chem. Soc. 122 (2000) 8289.
[35] J.N. Demas, E.W. Harris, R.P. McBride, J. Am. Chem. Soc. 99 (1977) 3547.
[36] Q.G. Mulazzani, H. Jiun, M.Z. Hoffmann, W.E. Ford, M.A. Rodgers, J. Phys. Chem. 98 (1994) 1145.
[37] D. Garcia-Fresnadillo, Y. Georgiadou, G. Orellana, A.M. Braun, E. Oliveros, Helv. Chem. Acta 79 (1996) 1222.
[38] C. Tanielian, C. Wolff, M. Esch, J. Phys. Chem. 100 (1996) 6555.
[39] A.A. Abdel-Shafi, P.D. Beer, R.J. Mortimer, F. Wilkinson, J. Phys. Chem. Sect. A 104 (2000) 192.
[40] A.A. Abdel-Shafi, P.D. Beer, R.J. Mortimer, F. Wilkinson, Phys. Chem. Chem. Phys. 2 (2000) 3137.
[41] M.A. Jamesian, N. Seron, M.Z. Hoffman, Coord. Chem. Rev. 39 (1981) 121.
[42] Y. Zhang, L.P. Ley, K.S. Schanze, Inorg. Chem. 35 (1996) 7102.
[43] A. Tiyabhorn, O.K. Zahirk, Can. J. Chem. 74 (1996) 336.
[44] W.B. Connick, H.B. Gray, J. Am. Chem. Soc. 119 (1997) 11620.
[45] V. Anhalagan, T.S. Srivastava, J. Photochem. Photobiol. A: Chem. 77 (1994) 141.
[46] V. Anhalagan, T.S. Srivastava, J. Photochem. Photobiol. A: Chem. 89 (1995) 113.
[47] Y. Yamamoto, N. Imai, R. Mashima, R. Konaka, M. Inoue, W. Dunlap, Methods in Enzymology, vol. 319, Academic Press, New York, 2000, p. 29.
[48] A.P. Schaap, A.L. Thayer, E.C. Blossey, D.C. Neckers, J. Am. Chem. Soc. 97 (1975) 3741.
[49] M. Nowakowska, M. Kepcynski, J. Photochem. Photobiol. A: Chem. 116 (1998) 251.
[50] M. Nowakowska, M. Kepcynski, K. Szczubialka, Macromol. Chem. 196 (1995) 2073.
[51] R. Gerdes, O. Bartels, G. Schneider, D. Wöhrle, G. Schulz-Ekloff, Polym. Adv. Technol. 12 (2001) 152.
[52] D. Faust, K.H. Funken, G. Horneck, B. Milow, J. Ortner, M. Sattlegger, M. Schafer, C. Schimtz, Solar Energy 65 (1999) 71.
[53] M. Suzuki, O. Bartels, R. Gerdes, G. Schneider, D. Wöhrle, G. Schulz-Ekloff, M. Kimura, K. Hanabusa, H. Shirai, Chem. Lett. (1999) 579.
[54] J.L. Bourdelande, J. Font, G. Marques, A.A. Abdel-Shafi, F. Wilkinson, D.R. Worrall, J. Photochem. Photobiol. A: Chem. 138 (2001) 65.
[55] V. Iliev, A. Ileva, L. Bilyarska, J. Mol. Catal. A: Chem. 126 (1997) 99.
[56] P. Esser, B. Pohlmann, H.D. Scharf, Angew. Chem. 106 (1994) 2093.
[57] P. Wagler, B. Heller, O. Orther, K.H. Funkn, G. Oehme, Chem. Ing. Technol. 68 (1996) 823.
[58] A.A. Trabanco, A.G. Montalban, G. Rumble, A.G.M. Barrett, B.M. Hoffmann, Synlett 7 (2000) 1010.
[59] R. Gerdes, D. Wöhrle, W. Spiller, G. Schneider, G. Schrurpfeil, G. Schulz-Ekloff, J. Photochem. Photobiol. A: Chem. 111 (1997) 65.
[60] V. Iliev, L. Prahov, L. Bilyarska, H. Fischer, G. Schulz-Ekloff, D. Wöhrle, L. Petrov, J. Mol. Catal. A: Chem. 151 (2000) 161.
[61] W. Spiller, D. Wohrle, G. Schulz-Ekloff, W.T. Ford, G. Schneider, J. Stark, J. Photochem. Photobiol. A: Chem. (1996) 161.
[62] W.M. Sharman, G.M. Allen, J.E. VanLier, Drug Discov. Today 4 (1999) 507.
[63] N.L. Olenick, A.K. Antunez, M.E. Clay, B.D. Rihter, M.E. Kenney, J. Photochem. Photobiol. 57 (1993) 242.
[64] T.J. Dougherty, J. Photochem. Photobiol. 45 (1987) 879.
[65] D.A. James, D.P. Arnold, P.G. Parsons, J. Photochem. Photobiol. 59 (1994) 441.
[66] A. Villaneuva, L. Caggiari, G. Jori, C. Milanesi, J. Photochem. Photobiol. B: Biol. 33 (1994) 49.
[67] A.K. Haylett, F.I. McNair, D. McGarvey, N.J.F. Dodd, E. Forbes, T.G. Truscott, J.V. Moore, Cancer Lett. 112 (1997) 233.
[68] Z. Katona, A. Grofcsik, P. Baranyai, I. Bitter, G. Grabner, M. Kubinyi, T. Vidóczy, J. Mol. Struct. 450 (1998) 41.
[69] G.I. Stables, D.V. Ash, Cancer Treat. Rev. 21 (1995) 311.
[70] J.C. Kennedy, R.H. Pottier, J. Photochem. Photobiol. B: Biol. 14 (1992) 275.
[71] C.S. Lok, A.J. MacRobert, J. Bedwell, J. Regula, N. Krasner, S.G. Bown, Br. J. Cancer 68 (1993) 41.

[72] R. Bonnett, R.D. White, V.J. Winfield, M.L. Berenbaum, Biochem. J. 261 (1989) 277.
[73] R. Bonnett, P. Charlesworth, B.D. Djelal, S. Foley, D.J. McGarvey, T.G. Truscott, J. Chem. Soc. Perkin Trans. 2 (1999) 325.
[74] H.J. Hopkinson, D.I. Vernon, S.B. Brown, Photochem. Photobiol. 69 (1999) 482.
[75] Y. Mikata, Y. Onchi, M. Shibata, T. Kakuchi, H. Ono, S. Ogura, I. Okura, S. Yano, Bioorg. Med. Chem. Lett. 8 (1998) 3543.
[76] M. Pineiro, M.M. Pereira, A.M.D.R. Gonsalves, L.G. Arnaut, S.J. Formosinho, J. Photochem. Photobiol. A: Chem. 138 (2001) 147.
[77] M.A.F. Faustino, M.G.P.M.S. Neves, J.A.S. Cavaleiro, M. Neumann, H.D. Brauer, G. Jori, J. Photochem. Photobiol. 72 (2000) 217.
[78] M. Oeshner, J. Photochem. Photobiol. B: Biol. 32 (1996) 3.
[79] W.M. Sharman, C.M. Allen, J. Porphyrins Pthalocyanins 5 (2001) 161.
[80] J.L. Sessler, G. Hemmi, T.D. Mody, T. Murai, A. Burrell, S.W. Young, Acc. Chem. Res. 27 (1994) 43.
[81] R.M. Szeimes, J. Photochem. Photobiol. B: Biol. 34 (1996) 67.
[82] A. Bamias, P. Keane, T. Krausz, G. Williams, A.A. Epenetos, Cancer Res. 51 (1991) 724.
[83] C.M. Allen, W.M. Sharman, C. La Madeleine, J.M. Weber, R. Langlois, R. Ouellet, J.E. vanLier, J. Photochem. Photobiol. 70 (1999) 512.
[84] C.A. Rebeiz, K.N. Reddy, O.B. Nadihalli, J. Velu, J. Photochem. Photobiol. 52 (1990) 1099.
[85] T. Ben Amor, G. Jori, Insect Biochem. Mol. Biol. 30 (2000) 915.
[86] C.A. Rebeiz, L.J. Gut, K. Lee, J.A. Juvik, C.C. Rebeiz, C.E. Bouton, Crit. Rev. Plant Sci. 14 (1995) 329.
[87] (a) T. Ben Amor, M. Tronchin, L. Bortolotti, R. Verdiglione, G. Jori, J. Photochem. Photobiol. 67 (1998) 206;
(b) T. Ben Amor, L. Bortolotti, G. Jori, J. Photochem. Photobiol. 71 (2000) 123.
[88] C.A. Rebeiz, J.A. Juvick, C.C. Rebeiz, Pestic. Biochem. Physiol. 36 (1988) 201.