The synthesis and photophysical properties of polyether substituted phthalocyanines of potential use in photodynamic therapy

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The synthesis, photophysical properties and singlet oxygen yields of a range of polyether substituted metallo and free-base phthalocyanines are reported and discussed in the context of the potential use of these compounds as alternatives to haematoporphyrin derivatives (HpD) in the photodynamic therapy (PDT) of cancer. The triplet states of the phthalocyanines have been studied in benzene and methanol using nanosecond laser flash photolysis and pulse radiolysis. Triplet state absorption maxima occur at *ca.* 510 to 525 nm and the quantum yields of triplet formation (φ_T) lie in the range 0.14 to 0.32. Triplet state lifetimes are in the range 26 to 155 μs. Energy transfer from the triplet state (T_1) of the phthalocyanines to ground state molecular oxygen $O_2\,{}^3\Sigma_g^-$ to produce singlet oxygen $O_2\,{}^1\Delta_g$ is efficient and evidence is presented for the establishment of an equilibrium in perdeuterated benzene, eqn. (*a*).

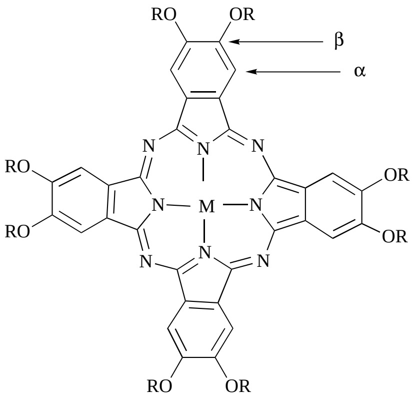
$$\mathrm{Pc}(T_1) + O_2({}^3\Sigma_g^-) \rightleftharpoons \mathrm{Pc}(S_o) + O_2({}^1\Delta_g) \qquad (a)$$

Singlet oxygen quantum yields (φ_Δ), determined by time resolved near infrared luminescence, are comparable with the triplet yield suggesting a high proportion of quenching encounters result in the formation of singlet oxygen.

The photophysical properties of the metallophthalocyanines are dependent on the relative atomic mass and the magnetic properties of the central metal ion.

Introduction

Phthalocyanines are synthetic substances related to the naturally occurring porphyrins. They consist of a macrocycle made up of four isoindole units linked by aza nitrogen atoms in contrast to the methine carbon atoms in porphyrins. Phthalocyanines are stable compounds both chemically and photochemically. Typically they are blue or green in colour and are used as pigments in printing inks, paints and plastics. They also have applications in semiconductors, oxidation catalysts, photochemical solar energy conversion systems and in laser technology.[1]



R = $CH_2CH_2OCH_2CH_3$ (OE)
R = $CH_2CH_2OCH_2CH_2OCH_3$ (OM)
M = $2H^+$, Ni^{2+}, Pb^{2+}, Zn^{2+}

Polyether substituted phthalocyanine structure

Because of their structural resemblance to porphyrins and their superior absorption in the red region of the spectrum[2–4] there has been increasing interest in the last decade in the use of phthalocyanines as photosensitisers for the selective and effective destruction of animal and human malignant tumours. Photosensitisation with a variety of tetrapyrrole compounds has been shown to be an effective method for killing a wide variety of cells including cancerous and bacterial cells. The transfer of electronic energy from the triplet state of large molecules such as phthalocyanines to molecular oxygen has increasingly been investigated by the biomedical community as it is now widely believed that singlet molecular oxygen may be the principal cytotoxic species in tumour necrosis.[5–7]

There is at present considerable interest in the synthesis and application of 'new generation' photosensitisers that contain tetrapyrrole units such as porphyrins, chlorins, phthalocyanines and bacteriochlorins.[4,8–10] The medical application of these tetrapyrrole compounds has given rise to a search for photosensitisers that are more effective than the previously used haematoporphyrin derivative. Such currently used 'second generation' sensitisers must fulfil certain criteria if they are to act efficiently.[11]

The photosensitiser should exhibit strong absorption in the red region. Due to lower scattering and weak absorption by natural chromophores red light is able to penetrate tissue to a greater extent than light of shorter wavelengths. Photophysically, the photosensitiser should possess a high intersystem crossing yield giving rise to the population of a long-lived triplet state, and concomitant efficient generation of singlet oxygen.

The determination of the photophysical properties of these phthalocyanines is therefore desirable in assessing their suitability as photosensitisers for PDT. This paper describes the synthesis and photophysics of polyether substituted phthalocyanines with substitution being in the β position. The function of the peripheral polyether groups is to enhance the solubility of the phthalocyanines in water, rendering them easier to administer in medical applications.

Table 1 Photophysical properties of polyether substituted phthalocyanines in benzene and methanol

			Benzene					Methanol		
Phthalocyanine	λ^{T}_{max}/nm	$\Delta\varepsilon_T$/[a] 10^3 dm^3 mol^{-1} cm^{-1}	τ_T/μs	φ_T(±20%)	φ_Δ[b]	λ^{T}_{max}/nm	$\Delta\varepsilon_T$/[c] 10^3 dm^3 mol^{-1} cm^{-1}	τ_T/μs	φ_T(±20%)	φ_Δ[d,e]
OMPcH$_2$	515	28.5	50	0.15	0.13	520	9.0	32	0.16	0.06 (0.06)
OMPcNi	525	—	—	—	0.0	520	—	—	—	0.0 (0.0)
OMPcPb	520	7.21	32	0.30	0.25	520	—	—	—	0.17 (0.18)
OMPcZn	515	28.2	105	0.32	0.20	520	23.5	64	0.16	0.16 (0.22)
OEPcH$_2$	525	29.3	50	0.15	0.10	520	6.2	26	0.15	0.10 (0.05)
OEPcZn	525	28.0	155	0.28	0.14	510	21.5	39	0.14	0.14 (0.19)

[a] Determined using the energy transfer method. [b] Relative to φ_Δ phenazine = 0.88.[27] [c] Determined using the singlet depletion method. [d] Relative to φ_Δ methylene blue = 0.58.[28] [e] In monodeuterated methanol (CH$_3$OD). φ_Δ values given in parentheses are for acetonitrile solutions.

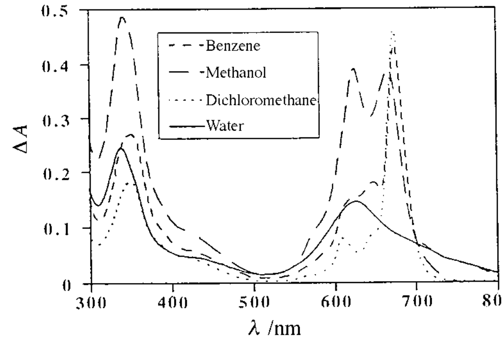


Fig. 1 Ground state electronic absorption spectra of OMPcZn in both polar and non-polar solvents

Results and discussion

Solubility considerations

Unsubstituted phthalocyanines are poorly soluble in most common solvents. However, the addition of polyether groups enhances the solubility of the phthalocyanines and conveys solubility in a range of solvents, both protic polar (methanol and water), aprotic polar (dichloromethane) and non-polar such as benzene.[12] Only those phthalocyanines substituted with the longer polyether side chains are soluble in water. Whilst solubility in the aforementioned solvents is enhanced by the addition of polyether substituents, the phthalocyanines exhibit a degree of aggregation (probably a monomer–dimer equilibrium) in all solvents except dichloromethane.

Ground state absorption spectra

The UV–VIS absorption spectra of the phthalocyanines in benzene have Q-bands (0, 0) ranging from 666 nm for OMPcNi to 714 nm for OMPcPb. The position of λ_{max} is independent of the type of polyether substituent. Alongside the red Q-band additional peaks are present in the regions 640–660, 390–400 and 300–350 nm.

In protic polar solvents such as methanol and water the main spectral Q-bands are blue shifted compared with benzene and are relatively broad due to extensive aggregation. In water the presence of higher associates (trimers *etc.*) is not discounted. In the absorption spectra of the metallophthalocyanines a red shift in the absorption maxima is observed with increasing mass of the central metal ion, irrespective of the solvent.

Fig. 1 shows the absorption spectra of OMPcZn in different solvents where different degrees of aggregation are evident. The position of equilibrium is temperature dependent and by recording the spectrum at different temperatures and subtracting the two spectra (after scaling) the resolved monomer and dimer spectra are obtained. Fig. 2 illustrates the dimer spectra for several polyether substituted phthalocyanines obtained in this way.

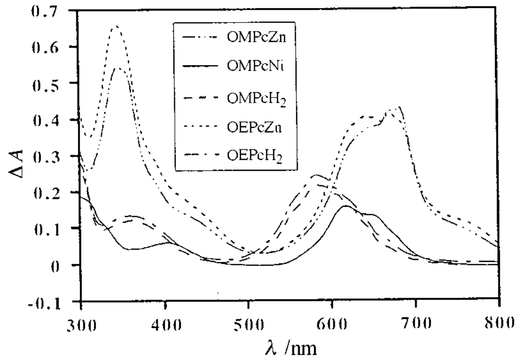


Fig. 2 Dimer spectra of polyether substituted phthalocyanines in benzene (the Zn derivatives show evidence of a monomer peak due to discrepancies in the subtraction of the high and low temperature spectra)

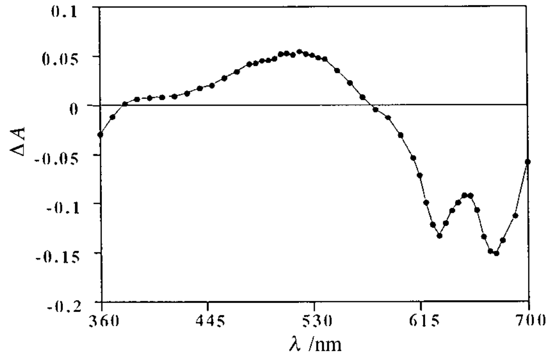


Fig. 3 Triplet minus singlet difference absorption spectrum for OMPcZn in methanol

Triplet state yields and lifetimes

Laser excitation of the phthalocyanines gives rise to a transient absorption in the visible region of the spectrum which is identified as the triplet state since it is quenched by molecular oxygen giving singlet oxygen. Table 1 gives a summary of the triplet state properties for each of the phthalocyanines studied. The maxima in the difference absorption spectra range from 510–525 nm and all exhibit a broad, featureless spectrum as shown in Fig. 3 for OMPcZn. Values of φ_T range from 0.14 to 0.32, with triplet lifetimes τ_T in deaerated solutions ranging from 26–155 μs for OMPcPb and OEPcZn respectively. Such variations are due to enhanced intersystem crossing promoted by heavier metal ions.

Table 2 Polyether substituted phthalocyanine triplet state quenching by O_2

Phthalocyanine	Methanol $k_q/10^9$ dm^3 mol^{-1} s^{-1}	[$^2H_6$]Benzene $k_q/10^9$ dm^3 mol^{-1} s^{-1}
OMPcH$_2$	0.79	1.7
OMPcPb	—	2.2
OMPcZn	1.1	2.0
OEPcH$_2$	1.2	1.7
OEPcZn	1.2	1.8

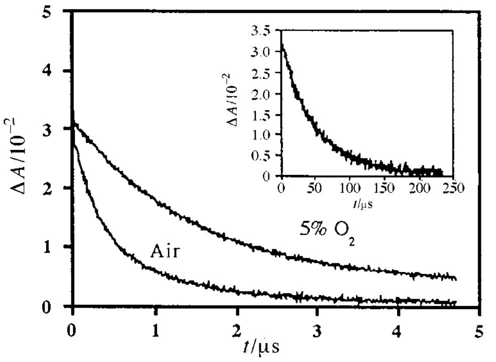


Fig. 4 Decay profiles of triplet OEPcH$_2$ in [$^2H_6$]benzene solutions saturated with air and 5% O_2. (Insert shows the mono-exponential decay of OEPcH$_2$ in [$^2H_6$]benzene when saturated with N_2.)

Triplet state quenching by O_2

Quenching of the phthalocyanine triplet state by ground state molecular oxygen results in the formation of singlet molecular oxygen. In methanol the quenching rate constants (k_q) are *ca.* 1–2 × 10^9 dm^3 mol^{-1} s^{-1} which is typical for porphyrin like compounds[14] (see Table 2). However, in perdeuterated benzene a biexponential decay is observed (see Fig. 4) that is indicative of the establishment of an energy transfer equilibrium. Such observations are similar to observations reported by Rodgers *et al.*[15,16] of reversible energy transfer involving a phthalocyanine triplet state and singlet oxygen (Scheme 1).

$$\begin{tikzcd}
\mathrm{Pc(T_1)} + \mathrm{O_2(^3\Sigma_g^-)} \arrow[r, shift left, "k_f"] \arrow[d, "k_T"] & \mathrm{Pc(S_0)} + \mathrm{O_2(^1\Delta_g)} \arrow[l, shift left, "k_b"] \arrow[d, "k_\Delta"] \\
\mathrm{Pc(S_0)} & \mathrm{O_2(^3\Sigma_g^-)}
\end{tikzcd}$$

Scheme 1

Table 3 Equilibrium constants and triplet energy levels for polyether substituted phthalocyanines in perdeuterated benzene

Phthalocyanine	K_{eq}	E_T/kJ mol^{-1}
OMPcH$_2$	0.31	96.5
OMPcPb	0.12	94.3
OMPcZn	0.54	97.9
OEPcH$_2$	0.29	96.3
OEPcZn	0.51	97.8

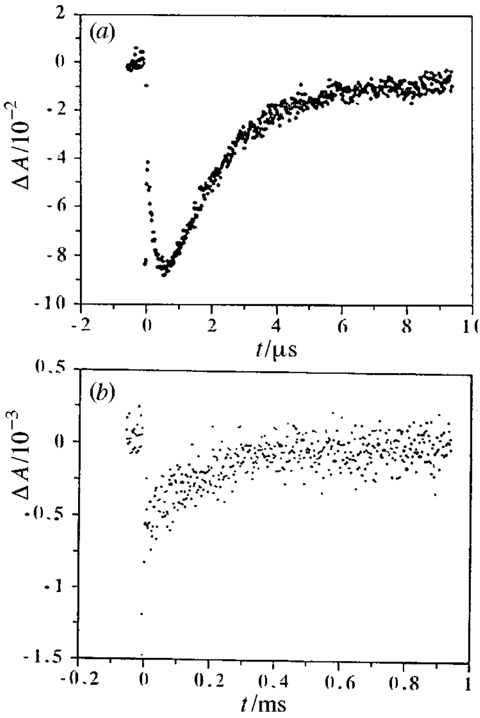


Fig. 5 (*a*) Time profile of the absorbance change at 660 nm of air saturated OEPcH$_2$ in [$^2H_6$]benzene using a short timescale. (*b*) Time profile of the absorbance change at 660 nm of air saturated OEPcH$_2$ in [$^2H_6$]benzene using a long timescale.

Supporting evidence for the existence of such an equilibrium comes from the mono-exponential decay kinetics observed when the solutions are nitrogen saturated (see insert Fig. 4) and the fact that the lifetime of singlet oxygen measured from time-resolved near infrared emission matches the lifetime of the second component of the phthalocyanine triplet state decay. In addition the amplitude of the second component in the triplet state absorption data is sensitive to the oxygen concentration. However, in contrast to Rodgers *et al.*[15,16] the equilibrium lies further to the right, and the equilibrium concentration of phthalocyanine triplet under these experimental conditions is very small, although by monitoring the ground state depletion of the phthalocyanine the short and long-lived components can be seen clearly [see Figs. 5(*a*) and 5(*b*)]. A detailed study of oxygen quenching under these circumstances permits the equilibrium constant ($K_{eq} = k_f/k_b$) to be determined and from this the phthalocyanine triplet state energy, E_T. In these experiments the concentration of oxygen was varied whilst the phthalocyanine concentration was kept constant. Time profiles of the absorption changes at 520 nm showing the decay of the phthalocyanine triplet state at two different oxygen concentrations are reproduced in Fig. 4. A departure from mono-exponential kinetics is clearly observable and the effects of increasing the oxygen concentration on the rate of decay of the first component and the equilibrium triplet state concentration are also apparent. The equilibrium constant may be determined from triplet state absorption measurements using eqn. (1),

$$(A_0 - A_\infty)/A_\infty = K_{eq}([O_2]/[Pc]) \qquad (1)$$

where A_0 is the initial triplet state absorbance and A_∞ is the equilibrium triplet state absorbance extrapolated to $t = 0$. The values of K_{eq} can then be used to evaluate triplet state energies (E_T, see Table 3) using eqn. (2) where the ($\frac{1}{9}$) accounts for the spin statistical factor.[15,17]

$$E_T - E_\Delta + RT\ln(\tfrac{1}{9}) = RT\ln K_{eq} \qquad (2)$$

Singlet oxygen quantum yields and lifetimes

The measured values of φ_Δ for the series of phthalocyanines in acetonitrile, benzene and monodeuterated methanol are collected in Table 1. In all experiments the emission observed at 1270 nm decayed exponentially with a solvent dependent rate constant. The average lifetimes (τ_Δ) observed for singlet oxygen in acetonitrile (55 µs) and benzene (28 µs) are comparable with the published values of 54–68,[18] 27–33 µs[19] for these two solvents. However, in monodeuterated methanol the singlet oxygen lifetimes are reduced to 16.5 and 15 µs in the presence of OMPcH$_2$ and OEPcH$_2$ respectively from which O_2 $^1\Delta_g$ quenching rate constants of 7.5 × 10^8 and 3.8 × 10^8 dm^3 mol^{-1} s^{-1} are deduced in this solvent. No singlet oxygen formation was

Table 4 Efficiency of singlet oxygen formation of polyether substituted phthalocyanines in benzene and methanol

	S_Δ	
Phthalocyanine	Benzene	Methanol
$OMPcH_2$	0.87	0.38
OMPcNi	—	—
OMPcPb	0.83	—
OMPcZn	0.63	1.0
$OEPcH_2$	0.67	0.67
OEPcZn	0.5	1.0

observed for OMPcNi in any of the solvents studied. The φ_Δ/φ_T ratio (S_Δ) gives the efficiency of $O_2\ {}^1\Delta_g$ formation under conditions of complete triplet state quenching by oxygen. As can be seen from Table 4 the values of S_Δ vary from 1.0 to 0.38. Thus, for all the polyether substituted phthalocyanines studied as potential new sensitisers for PDT, triplet state quenching by O_2 leads to efficient $O_2\ {}^1\Delta_g$ formation, even though the triplet energies are rather close to that of $O_2\ {}^1\Delta_g$.

Conclusion

The synthesis of a range of polyether substituted phthalocyanines has been described and their photophysical properties and singlet oxygen quantum yields have been measured in benzene and methanol. The polyether substituted phthalocyanines show intense absorption in the red region of the spectrum and the presence of the polyether groups improves the solubility of these compounds in common solvents including water. With respect to triplet quantum yields and singlet oxygen quantum yields it has been shown that those phthalocyanines which contain a diamagnetic metal centre (Zn and Pb) exhibit greater photoactivity. The efficiency of singlet oxygen formation has been shown to be substantial.

Experimental

Materials

Methylene blue (British Drug Houses Ltd) was used as received. Phenazine (Lancaster) was recrystallized from ethanol. Acetonitrile (spectroscopic grade, Rathburn Chemicals Ltd), benzene (spectroscopic grade, Fisons Scientific), methanol (spectroscopic grade, Rathburn Chemicals Ltd), monodeuterated methanol (CH_3OD) (Cambridge Isotope Laboratories, CIL) and perdeuterated benzene (Aldrich), were used as received.

Instrumentation

Kinetic absorption measurements were made using a JK system 2000 Q switched ruby laser operating on the fundamental (694 nm) and the third harmonic (355 nm) of a Spectron Q switched Nd-YAG laser as described previously.[20] Time resolved singlet oxygen luminescence (1270 nm) was detected *via* the (0, 0) phosphorescence band eqn. (3), centred at 1270 nm using a

$$O_2({}^1\Delta_g) \longrightarrow O_2({}^3\Sigma_g^-) + h\nu\ (1270\text{ nm}) \qquad (3)$$

Judson germanium diode (G-050, active diameter = 0.5 cm) coupled to a Judson preamplifier. Pulse radiolysis measurements were made using a 9–12 MeV Vickers linear accelerator as described previously[21] with pulses of 50 ns duration and doses of between 7 and 8 Gy. Irradiation was in quartz flow-through cells with internal volumes of 2.5 cm^3 and a monitoring optical path length of 2.5 cm.

Absorption spectra were recorded using a Perkin-Elmer Lambda 2 UV–VIS spectrophotometer. Melting points were determined on a heated stage, and are uncorrected. NMR spectra were recorded on a Jeol GS × 270 MHz spectrophotometer for solutions in $CDCl_3$. Mass spectra were determined using an AE1 MS12 mass spectrophotometer.

Methods

Triplet state absorption coefficients ($\Delta\varepsilon_T$) and triplet state quantum yield (φ_T). Triplet state absorption coefficients were obtained using the energy transfer and singlet depletion techniques.[22] In the energy transfer method, a triplet state of unknown $\Delta\varepsilon_T$ is compared with a standard triplet state of $\Delta\varepsilon_T$. In the energy transfer experiments pulse radiolysis was used and the standard was biphenyl for which $\Delta\varepsilon_T{}^{360} = 27\,100\ dm^3\ mol^{-1}\ cm^{-1}$.[23] Solutions of biphenyl (0.1 mol dm^{-3}) were subjected to pulse radiolysis in benzene in the presence and absence of the polyether substituted phthalocyanines (10^{-4} mol dm^{-3}).

The singlet depletion technique depends upon measuring the ground state depletion in a region where it is assumed that $\varepsilon_T = 0$ [see eqn. (4)].

$$\Delta A_T^\lambda = -\varepsilon_S^\lambda[{}^3M^*]l \qquad (4)$$

Triplet quantum yields (φ_T) were obtained by the comparative method[24] using methylene blue in methanol for which $\varphi_T = 0.52$[24] and $\Delta\varepsilon_T = 14\,000\ dm^3\ mol^{-1}\ cm^{-1}$ at 420 nm.[13]

Deaerated solutions of the polyether-substituted phthalocyanines and methylene blue were optically matched at the laser excitation wavelength, and the yields were obtained using eqn. (5).

$$\varphi_T\text{Pc} = \varphi_T\text{Ref} \times \frac{\Delta OD_T^{Pc} \times \Delta\varepsilon_T^{Ref}}{\Delta OD_T^{Ref} \times \Delta\varepsilon_T^{Pc}} \qquad (5)$$

Oxygen quenching rate constants (k_q) measurements. The rate constants (k_q) for oxygen quenching of the triplet states of the polyether substituted phthalocyanines were determined in methanol by kinetic absorption measurements on various O_2/N_2 mixtures. Five single shot kinetic absorption traces were signal-averaged for each measurement and good single exponential fits were obtained for all the phthalocyanines in methanol. However, in perdeuterated benzene there is a departure from monoexponential kinetics and biexponential kinetics are observed (see Results and discussion). The oxygen concentrations in air saturated solvents were taken to be 2.1×10^{-3} and 1.9×10^{-3} mol dm^{-3} in methanol and benzene, respectively.[25]

Singlet oxygen quantum yield measurements (φ_Δ). Air equilibrated solutions of polyether substituted phthalocyanines were optically matched at the laser excitation wavelength, along with that of a reference standard for which the singlet oxygen quantum yield has previously been determined. Solutions were prepared in 1 × 1 cm quartz cells with absorbances of 0.5 at 694 or 355 nm.

For the determination of φ_Δ values time-resolved luminescence at 1270 nm was recorded following laser excitation. At each laser intensity the recorded luminescence trace was obtained by signal-averaging ten single shots. The averaged traces were fitted with a single exponential which was extrapolated to $t = 0$. Plots of I_0 (the extrapolated signal intensity at $t = 0$) *versus* laser intensity were found to be linear up to a laser intensity of 4 mJ pulse $^{-1}$. Within this laser intensity range eight data points were obtained for each plot. Since the gradient of the I_0 *versus* laser intensity plots are proportional to φ_Δ, the values of φ_Δ may be obtained by comparison with the gradient obtained for the reference standard. The standards employed for the three solvents are as follows.

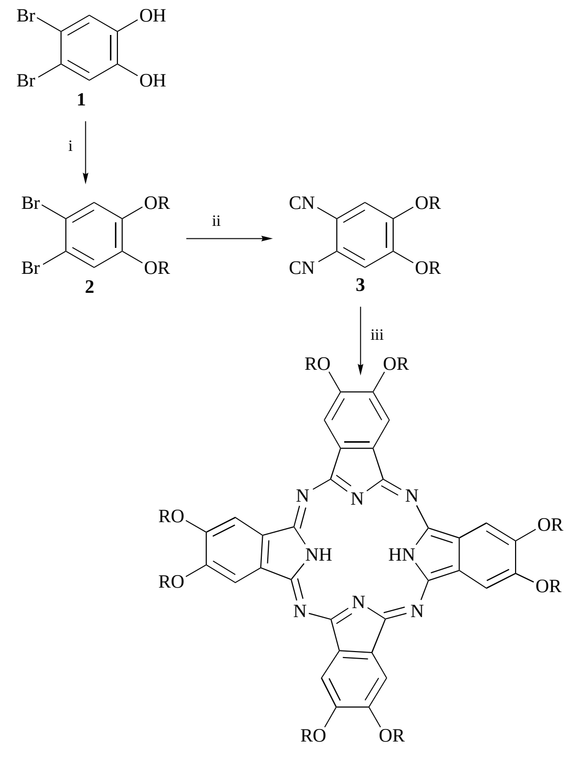
Acetonitrile: methylene blue in air equilibrated acetonitrile for which $\varphi_\Delta = 0.52$.[26]

Benzene: phenazine in air equilibrated benzene for which $\varphi_\Delta = 0.88$.[27]

Methanol: methylene blue in air equilibrated monodeuterated methanol for which $\varphi_\Delta = 0.58$.[28]

Syntheses

The phthalocyanines (**4a** and **4b**) were synthesised as illustrated in Scheme 2.



4a R = $CH_2CH_2OCH_2CH_3$
4b R = $CH_2CH_2OCH_2CH_2OCH_3$

Scheme 2 Synthesis of the polyether-substituted phthalocyanines. *Reagents and conditions:* i, RBr, KOH, EtOH; ii, CuCN, DMF; iii, Li_2CO_3, pentanol, heat.

(*a*) General procedure for ethers 2. Dibromocatechol (0.12 mol) was dissolved in ethanol (300 cm^3), KOH (0.27 mol) was added, and the mixture stirred under nitrogen. The alkyl bromide (0.1 mol) was added, and the solution heated under reflux (15–24 h). The ethanol was removed, the residue extracted with dichloromethane (3 × 80 cm^3) and filtered. The filtrate was washed with 2 M NaOH (2 × 125 cm^3) and water, and the organic layer dried (Na_2SO_4) and evaporated.

4,5-*Dibromo*-1,2-*bis*(2-*ethoxyethoxy*)*benzene* **2a**.—Obtained as an oil in 75% yield. *m/z* 414 ($M^+ + 4$, 1.74%), 412 ($M^+ + 2$, 3.48%), 410 (M^+, 1.87%), 73 ($EtOCH_2CH_2^+$, 44%), 45($C_2H_5O^+$, 100%). δ_H 1.26 (6H, t), 3.62 (4H, q), 3.82 (4H, t), 4.16 (2H, t), 7.18 (2H, s). δ_C 15.02 (CH_3), 66.67 (CH_2), 68.58 (CH_2), 69.20 (CH_2), 115.11 (C4, C5), 118.92 (C3, C6), 148.76 (C1, C2).

4,5-*Dibromo*-1,2-*bis*(3,6-*dioxaheptyloxy*)*benzene* **2b**.—Obtained as an oil in 85% yield. *m/z* 472 ($M^+ + 4$, 19%), 470 ($M^+ + 2$, 37%), 468 (M^+, 19%), 103 ($C_5H_{11}O_2^+$, 95%), 59 ($CH_3OCH_2CH_2^+$, 100%), 45 ($CH_3OCH_2^+$, 50%). δ_H 3.38 (6H, s), 3.55 (4H, m), 3.71 (4H, m), 4.14 (4H, m), 7.14 (2H, s). δ_C 59.05 (CH_3), 69.51 (CH_2), 69.73 (CH_2), 70.93 (CH_2), 72.14 (CH_2), 115.53 (C4, C5), 119.38 (C3, C6), 148.05 (C1, C2).

(*b*) General procedure for synthesis of dinitriles 3. The ether **2** (5.78 mmol) in anhydrous dimethylformamide (DMF) (4 cm^3) was added to a stirred solution of copper(I) cyanide (17.4 mmol) in anhydrous DMF (60 cm^3), and the mixture boiled (8 h). The reaction was monitored by GLC. Removal of the DMF under reduced pressure was followed by chromatography on silica gel, eluting with $CHCl_3$, first mixed with light petroleum, then neat, then small amounts of methanol. In the case of **3a** and **3b** the copper phthalocyanines were also formed, and were eluted after the dinitrile.

4,5-*Bis*(2-*ethoxyethoxy*)*phthalonitrile* **3a**.—Compound **3a** was obtained in 35% yield, colourless crystals from cyclohexane, mp 86–87 °C (Found: C, 62.98; H, 6.51; N, 9.37. $C_{16}H_{20}N_2O_4$ requires C, 63.14; H, 6.62; N, 9.20%) *m/z* 304 (M^+, 7%), 73 (CH_3CH_2 $OCH_2CH_2^+$, 95%), 45 ($CH_3CH_2O^+$, 100%). δ_H 1.23 (6H, t), 3.60 (4H, q), 3.84 (4H, t), 4.23 (4H, t), 7.25 (2H, s). δ_C 15.06 (CH_3), 66.99 (CH_2), 68.41 (CH_2), 69.43 (CH_2), 108.74 (CN), 115.75 (C1, C2), 116.90 (C3, C6), 152.38 (C4, C5). ν_{max}/cm^{-1} 2233 (CN).

4,5-*Bis*(3,6-*dioxaheptyloxy*)*phthalonitrile* **3b**.—Obtained in 21% yield, mp 47 °C (from CCl_4) (Found: C, 59.28; H, 6.57; N, 7.81. $C_{18}H_{24}N_2O_6$ requires C, 59.33; H, 6.64; N, 7.69%). *m/z* 364 (M^+, 2.6%), 103 ($CH_3OCH_2CH_2^+$, 28%), 59 ($CH_3OCH_2CH_2^+$, 100%). δ_H 3.39 (6H, s), 3.56 (4H, t), 3.72 (4H, t), 3.91 (4H, t), 4.27 (4H, t), 7.28 (2H, s). δ_C 58.99 (CH_3), 69.27 (CH_2), 69.37 (CH_2), 70.83 (CH_2), 71.83 (CH_2), 108.71 (CN), 115.69 (C1, C2), 117.05 (C3, C6), 152.31 (C4, C5). ν_{max}/cm^{-1} ($CHCl_3$) 2234.

(*c*) General procedure for making phthalocyanines 4. The dinitrile **3** (3.45 mmol) and lithium carbonate (17.16 mmol) were dissolved in hot stirred *n*-pentanol (10 cm^3) and the solution boiled (66 h). The alcohol was removed (50 °C, water pump, then 75 °C, 0.01 mmHg), the residue treated with dichloromethane, and then filtered. The crude phthalocyanine was purified by Chromatotron, (neat CH_2Cl_2, then 2% ethanol). In some cases further chromatography was necessary, on a silica gel column, loaded in ethanol and eluted with ethanol–CH_2Cl_2, (8 : 2).

2,3,9,10,16,17,23,24-*Octakis*(2-*ethoxyethoxy*)*phthalocyanine* **4a**.—This was obtained in 32% yield (Found: C, 63.25; H, 6.77; N, 9.03. $C_{64}H_{82}N_8O_{16}$ requires C, 63.04; H, 6.78; N, 9.19%). δ_H 1.45 (24H, t), 3.89 (16H, q), 4.16 (16H, t), 4.44 (16H, t), 7.63 (8H, s). δ_C 15.41 (CH_3), 66.96 (CH_2), 68.66 (CH_2), 69.10 (CH_2), 104.27 (CH), 128.99, 150.26. λ_{max}/nm (C_6H_6) (ε/dm^3 mol^{-1} cm^{-1}) 344.2 (29.0 × 10^3), 391.5 (11.4 × 10^3), 660.7 (26.3 × 10^3) and 699.99 (25.1 × 10^3).

2,3,9,10,16,17,23,24-*Octakis*(3,6-*dioxaheptyloxy*)*phthalocyanine* **4b**.—This was obtained in 34% yield (Found: C, 59.25; H, 6.86; N, 7.64. $C_{72}H_{98}N_8O_{24}$ requires C, 59.25; H, 6.77; N, 7.68%). δ_H 3.53 (24H, s), 3.78 (16H, s), 4.04 (16H, s), 4.31 (16H, s), 8.24 (8H, s). δ_C 59.16 (CH_3), 69.06 (CH_2), 69.95 (CH_2), 71.08 (CH_2), 72.27 (CH_2), 104.88 (CH), 129.64, 150.87. λ_{max}/nm (C_6H_6) (ε/dm^3 mol^{-1} cm^{-1}) 350.9 (33.7 × 10^3) 391.5 (11.5 × 10^3), 660.7 (35.9 × 10^3) and 699.9 (37.5 × 10^3).

Nickel phthalocyanine. The appropriate phthalonitrile (1.38 mmol), nickel chloride·$6H_2O$ and quinoline (1 cm^3) were heated and stirred under nitrogen at 200–220 °C (6 h). Evaporation of quinoline under reduced pressure was followed by extraction with ethyl acetate, filtration and evaporation. The residue was chromatographed on silica gel, then for analysis on a further column, loading with ethanol, eluting with CH_2Cl_2–ethanol mixtures. This procedure was applied to all metal phthalocyanines.

Nickel phthalocyanine (**4b**–Ni^{II}).—This was obtained in 56% yield (Found: C, 57.21; H, 6.66; N, 7.15. $C_{72}H_{96}N_8NiO_{24}$ requires C, 57.03; H, 6.38; N, 7.39%). λ_{max}/nm (C_6H_6) (ε/dm^3 mol^{-1} cm^{-1}) 286.0 (73.9 × 10^3), 391.5 (20.1 × 10^3), 618.7 (38.0 × 10^3) and 666.0 (38.9 × 10^3).

Zinc(II) phthalocyanines. A solution of phthalonitrile (1.74 mmol) and anhydrous zinc acetate (1.74 mmol) in DMF (5 cm^3) was boiled under nitrogen (72 h). The metal derivatives, isolated by evaporation of the DMF, were purified as described above.

Zinc phthalocyanine (**4a**–Zn^{II}).—This was obtained in 24% yield (Found: C, 59.80; H, 6.06; N, 8.45. $C_{64}H_{80}N_8O_{16}Zn$ requires C, 59.93; H, 6.29; N, 8.74%). λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 350.9 (36.8 × 10^3), 675.6 (42.4 × 10^3).

Zinc phthalocyanine (**4b**–Zn^{II}).—This was obtained in 42% yield (Found: C, 56.61; H, 6.06; N, 7.16. $C_{72}H_{96}N_8O_{24}Zn$ requires C, 56.78; H, 6.35; N, 7.36%). λ_{max}/nm (C_6H_6) (ε/dm^3 mol^{-1} cm^{-1}) 291.4 (54 × 10^3), 350.9 (68.1 × 10^3) and 676.9 (110.9 × 10^3).

Lead phthalocyanine. Phthalonitrile (1.41 mmol) and lead(II) oxide (1.41 mmol) in chloronaphthalene (4 cm^3) were stirred at

180–200 °C under nitrogen (66 h), and the product purified as described above. Lead phthalocyanine (**4b**–Pb^{II}) was obtained in 33% yield (Found: C, 51.70; H, 5.47; N, 6.46. $C_{72}H_{96}N_8O_{24}Pb$ requires C, 51.95; H, 5.81; N, 6.73%). λ_{max}/nm (C_6H_6) (ε/dm^3 mol^{-1} cm^{-1}) 401.0 (48.6 × 10^3) 640.4 (19.5 × 10^3) and 713.5 (112.8 × 10^3).

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References

1 F. H. Moser and A. L. Thomas, *The Phthalocyanines, Vol I and II*, CRC Press, Inc., Boca Raton, 1968.
2 C. Prinze, L. C. Penning, T. M. A. R. Dubbelman and J. Van Steveninck, *Cancer Res.*, 1992, **52**, 117.
3 B. W. Henderson, S. M. Waldow, T. S. Mang, W. R. Potter, P. B. Malone and T. J. Dougherty, *Cancer Res.*, 1988, **45**, 572.
4 G. A. Kostenich, I. N. Zhuravkin, A. V. Furmanchuk and E. A. Zhavrid, *J. Photochem. Photobiol., B: Biol.*, 1993, **7**, 187.
5 I. Rosenthal, C. Murali Krishna, P. Riesz and E. Ben-Hur, *Radiation Res*, 1986, **107**, 136.
6 I. Rosenthal and E. Ben-Hur, *Int. J. Radiat. Biol.*, 1995, **67**, 85.
7 K. R. Weishaupt, C. J. Gomer and T. J. Dougherty, *Cancer Res.*, 1976, **36**, 2326.
8 E. Zenkevich, E. Sagun, V. Knyukshto, R. Bonnett, S. P. Songea and M. Kassem, *J.Photochem. Photobiol., B: Biol.*, 1996, **133**, 171.
9 D. Wöhrle, N. Isklander, G. Graschew, H. Sinn, E. A. Freidrich, W. Maier-Borst, J. Stern and P. Schlag, *Photochem. Photobiol.*, 1990, **51**, 351.
10 K. R. Adams, M. C. Berenbaum, R. Bonnett, A. N. Nizhnik, A. Salgado and M. A. Valles, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1465.
11 J. Moan, *J. Photochem. Photobiol., B: Biol.*, 1990, **5**, 521.
12 M. J. Cook, A. J. Dunn, S. D. Howe, A. J. Thomson and K. J. Harrison, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2453.
13 I. Carmichael and G. L. Hug, *J. Phys. Chem. Ref. Data*, 1986, **15**, 1.
14 R. Bonnett, A. A. Charalambides, E. J. Land, R. S. Sinclair, D. Tait and T. G. Truscott, *J. Chem. Soc., Faraday Trans 1*, 1980, **76**, 852.
15 B. D. Rhiter, M. E. Kenney, W. E. Ford and M. A. J. Rodgers, *J. Am. Chem. Soc*, 1990, **112**, 8064.
16 P. A. Firey, W. E. Ford, J. R. Sounik, M. E. Kennedy and M. A. J. Rodgers, *J. Am. Chem. Soc*, 1988, **110**, 7626.
17 W. E. Ford, B. D. Rhiter, M. E. Kenney and M. A. J. Rodgers, *Photochem. Photobiol*, 1989, **50**, 277.
18 A. A. Gorman, I. R. Gould, I. Hamblett and M. C. Standen, *J. Am. Chem. Soc.*, 1984, **106**, 6956.
19 M. A. J. Rodgers, *J. Am. Chem. Soc.*, 1983, **105**, 6201.
20 J. H. Tinkler, S. M. Tavender, A. W. Parker, D. J. McGarvey, L. Mulroy and T. G. Truscott, *J. Am. Chem. Soc.*, 1996, **118**, 1756.
21 J. Butler, B. W. Hodgson, B. M. Hoey, E. J. Land, J. S. Lea, E. J. Lindey, F. A. P. Rushton and A. J. Swallow, *Radiat. Phys. Chem.*, 1989, **34**, 633.
22 R. V. Bensasson, E. J. Land and T. G. Truscott, *Flash photolysis and pulse radiolysis: Contributions to the chemistry of biology and medicine*, Pergamon Press, Oxford, 1983.
23 R. Bensasson and E. J. Land, *Trans. Faraday Soc.*, 1971, **67**, 1904.
24 M. Nemoto, H. Kokbun and M. Koizumi, *Bull. Chem. Soc. Jpn.*, 1969, **42**, 1223.
25 S. L. Murov, I. Carmichael and G. L. Hug, *Handbook of Photochemistry*, Marcel Dekker, Inc. New York, 1993.
26 Y. Usui, H. Koike and Y. Hurimura, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 3373.
27 F. Wilkinson, *J. Phys. Chem. Ref. Data*, 1993, **22**, 113.
28 J. N. Chacon, J. McLearie and R. S. Sinclair, *Photochem. Photobiol.*, 1987, **46**, 647.

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