Metallotexaphyrins: A New Family of Photosensitisers for Efficient Generation of Singlet Oxygen

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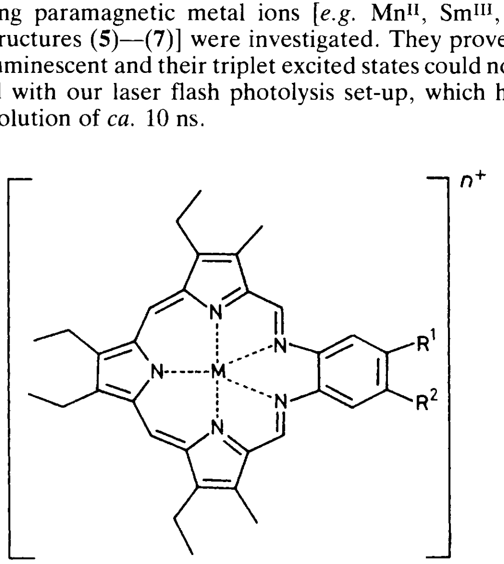
The photophysical properties of a new series of tripyrroledimethine-derived 'expanded porphyrins' ('texaphyrins') are reported; these compounds show strong low energy optical absorptions in the 730—770 nm spectral range as well as a high triplet quantum yield, and act as efficient photosensitizers for the production of singlet oxygen in methanol solution.

Photodynamic therapy is among the more promising of methods currently being considered for the treatment of localised neoplasia[1] and eradication of viral contaminants in blood.[2] As a result, considerable effort has been devoted to the development of effective photochemotherapeutic agents.[3] To date, porphyrins and their derivatives, phthalocyanines, and naphthalocyanines have been among the most widely studied compounds in this regard. Unfortunately, all these dyes suffer from critical disadvantages. While porphyrin derivatives have high triplet yields and long triplet lifetimes (and consequently transfer excitation energy efficiently to triplet oxygen),[3b,3g] their absorption in the Q-band region often parallels that of haem containing tissues. Phthalocyanines and naphthalocyanines absorb in a more convenient spectral range but have significantly lower triplet yields;[4] moreover, they tend to be quite insoluble in polar protic solvents, and are difficult to functionalize. Thus at present the development of more effective photochemotherapeutic agents appears to require the synthesis of compounds which absorb in the spectral region where living tissues are relatively transparent (*i.e.*, 700—1000 nm),[1d] have high triplet quantum yields, and are minimally toxic. We have recently reported[5] the synthesis of a new class of aromatic porphyrin-like macrocycles, the tripyrroledimethine-derived 'texaphyrins,' which absorb strongly in the tissue-transparent 730—770 nm range. We now report that the photophysical properties of metallotexaphyrins (**1**)—(**7**) parallel those of the corresponding metalloporphyrins and that the diamagnetic complexes (**1**)—(**4**) sensitize the product of $^1O_2$ in high quantum yield.

The absorption spectrum of (**1**) Cl is shown in Figure 1. This spectrum, which is representative of this class of compounds (*cf.* Table 1), is characterized by strong Soret- and Q-type bands, the latter being of particular interest. The fluorescence excitation spectrum of this complex, monitored at the emission maximum (*ca.* 780 nm; see inset to Figure 1), and the absorption spectrum are superimposable in the visible region (370—800 nm) showing that internal conversion to the first excited singlet state is quantitative upon photoexcitation in the Soret or Q-band regions. While the fluorescence quantum yields (ϕ_f) for (**1**)—(**4**) are only 0—1%, the quantum yields for triplet formation (ϕ_t) of these diamagnetic metallotexaphyrins can approach unity and resemble those found for metalloporphyrins.[6] The triplet–triplet transient spectrum of (**1**) Cl, given in Figure 2, shows bleaching in the Soret- and Q-bands of the ground state and a positive absorbance change in the 450—600 nm region, again reminiscent of metalloporphyrin triplet spectra.[7] The inset of Figure 2 shows the decay of this triplet state in deoxygenated methanol, from which a lifetime (τ_t) of 67 μs is calculated. Similar triplet spectra, lifetimes, and quantum yields were found for other diamagnetic metallotexaphyrin derivatives in methanol and for (**1**) Cl in mixed methanol–water solutions. Interestingly, low temperature phosphorescence could not be observed for any of the compounds in methanol glasses. Finally, several complexes containing paramagnetic metal ions [*e.g.* Mn^{II}, Sm^{III}, and Eu^{III}, structures (**5**)—(**7**)] were investigated. They proved to be nonluminescent and their triplet excited states could not be detected with our laser flash photolysis set-up, which has a time resolution of *ca.* 10 ns.



(**1**) M = Zn, $R^1 = R^2 = H, n = 1$
(**2**) M = Zn, $R^1 = H, R^2 = Cl, n = 1$
(**3**) M = Cd, $R^1 = R^2 = H, n = 1$
(**4**) M = Cd, $R^1 = H, R^2 = Cl, n = 1$
(**5**) M = Mn, $R^1 = R^2 = H, n = 1$
(**6**) M = Sm, $R^1 = R^2 = Me, n = 2$
(**7**) M = Eu, $R^1 = R^2 = Me, n = 2$

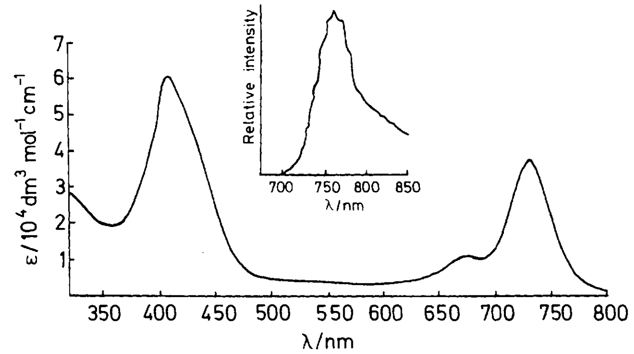


Figure 1. Absorption spectrum of complex (**1**) Cl in deoxygenated methanol. The inset shows the fluorescence emission spectrum recorded in this same solvent.

In methanol solution, the triplet excited states of (**1**)—(**4**) were quenched by molecular oxygen with bimolecular rate constants of (2.6 ± 0.2) × 10^9 dm^3 mol^{-1} s^{-1}. In aerated solution, the triplet state decay profile could be described in terms of a single exponential process with an average lifetime of (175 ± 20) ns; thus, interaction between the triplet species and O_2 is quantitative. Laser excitation (355 nm, 80 mJ, 10 ns) of the compound in aerated methanol gave no redox products (*e.g.* texaphyrin cation and superoxide anion) but, using a Ge diode,[8] the production of $^1O_2$ was observed clearly from its characteristic luminescence at 1270 nm. This luminescence decayed with a lifetime of (12.5 ± 0.3) μs and its initial intensity, as extrapolated to the centre of the laser pulse, was a linear function of the number of photons absorbed by the texaphyrin complex. Comparison of the initial intensity with that obtained using tetrakis-(4-hydroxyphenyl)porphyrin (THPP) as photosensitizer[3b] under identical conditions allowed calculation of the quantum yields for production of singlet oxygen, $\phi(^1O_2)$. The derived values are seen to parallel the triplet quantum yields (Table 1); the triplet state reaction

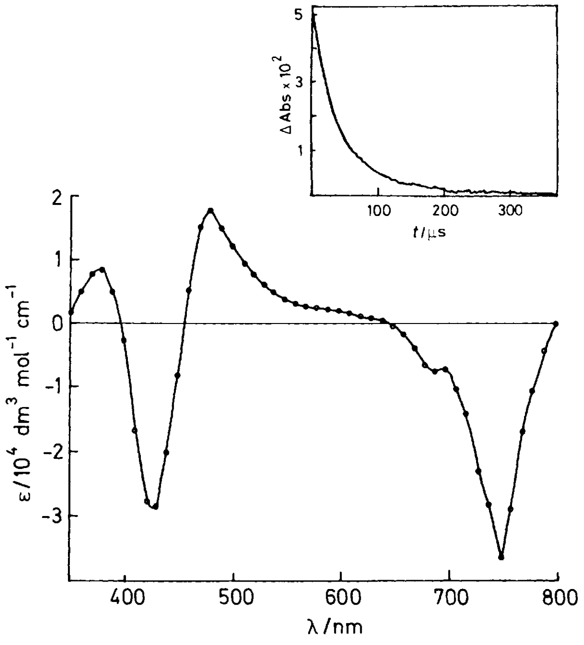


Figure 2. Triplet–triplet transient difference spectrum of (**1**) Cl in deoxygenated methanol recorded 1 μs after irradiation with a 10 ns pulse of 355 nm light (80 mJ). The inset shows the rate of return to ground state, as monitored at 480 nm, and corresponds to a triplet lifetime of 67 μs.

Table 1. Optical and photophysical properties of metallotexaphyrins in MeOH.

Complex	Absorption λ_{max}/nm		Emission λ_{max}/nm	ϕ_f (±10%)	ϕ_t (±5%)	τ_t/ μs	$\phi(^1O_2)$ (±10%)	S^a
(**1**) Cl	410	732	767	0.013	0.82	67	0.61	0.74
(**2**) Cl	412	738	765	0.012	0.88	37	0.65	0.73
(**3**) NO_3	417	759	780	0.011	0.88	55	0.69	0.78
(**4**) NO_3	421	760	788	0.009	0.97	36	0.74	0.76
(**5**) OH	420	760	—	<0.001	ND^b	—	<0.05	—
(**6**) $(OH)_2$	450	763	—	<0.001	ND	—	<0.05	—
(**7**) $(OH)_2$	451	762	—	<0.001	ND	—	<0.05	—
SiNC^c	310	776	780	—	0.39	331	0.35	0.90

[a] $S = \phi(^1O_2)/\phi_t$. [b] ND = not detected. [c] SiNC = bis(tri-n-hexylsiloxy)(2,3-naphthalocyaninato)silicon in benzene; see ref. 4.

appears to partition between generation of $^1O_2$ (74—78%) and formation of vibrationally excited O_2 (22—26%). These $\phi(^1O_2)$ values compare favourably with those observed with porphyrins[3b] and are much superior to values obtained with phthalocyanines and naphthalocyanines[4] due to the improved triplet state yields. Thus diamagnetic texaphyrin complexes appear to be highly efficient photosensitizers for the formation of $^1O_2$.

In summary, the new metallotexaphyrin complexes discussed here show three important optical properties which make then unique among existing porphyrin-like macrocycles. They absorb strongly in a physiologically important region (*i.e.* 730—770 nm), form long-lived triplet states in high yield, and act as efficient photosensitizers for the formation of singlet oxygen. These properties, coupled with their high chemical stability and appreciable solubility in polar media, suggest that these cationic complexes could serve as viable photosensitizers in emerging photodynamic protocols. Preliminary *in vitro* studies of (**3**)·NO_3 in 10% human serum, in which a significant decrease in herpes simplex (HSV-1) infectivity and lymphocyte mitogenic activity are observed upon irradiation at 767 nm,[9] suggest that this is a realistic possibility.

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