The synthesis, fluorescence behaviour and singlet oxygen studies of new water-soluble cationic gallium(III) phthalocyanines

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Abstract

The preparation of cationic water-soluble gallium phthalocyanine derivatives are described for the first time. Peripheral and non-peripheral 3-hydroxypyridine tetrasubstituted gallium(III)phthalocyanines (**5a**, **6a**) and their quaternarized derivatives (**5b** and **6b**) have been synthesized and characterized by elemental analysis, IR, ^{1}H NMR spectroscopy, electronic spectroscopy and mass spectra. The quaternarized compounds (**5b** and **6b**) are soluble in water and not aggregated (in water and in organic solvents) within a wide concentration range. General trends are described for singlet oxygen quantum yields, fluorescence quantum yields and fluorescence lifetimes of these compounds. These complexes showed better singlet oxygen quantum yields in water than the related quarternarized porphyrazine complexes.

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Phthalocyanines exhibit a number of unique properties that make them of great interest in different scientific and technological areas. Recently, they have also found applications in many fields in materials science, especially in nonlinear optical (NLO) devices, liquid crystals, Langmuir–Blodgett films, electrochromic devices, gas sensors, and photosensitizers, among others [1,2].

One of the most important characteristic of a photosensitizing drug is the perfect balance between its hydrophobic and hydrophilic properties. Phthalocyanine skeletons are essentially hydrophobic due to intermolecular interactions between the macrocycles. The solubility of phthalocyanines can be improved by introduction of substituents on the periphery of the molecule, which increase the π-electron density and make solvation easier [3]. Some water-soluble phthalocyanine compounds have potential for use as photosensitizers in photodynamic therapy (PDT) since they can be injected directly into the bloodstream. The water solubility of these photosensitizers is an additional advantage despite the fact that the aggregation tendency in such polar medium, in particular, is very high [4].

Hydrophilic and non-aggregated phthalocyanines are therefore important and potentially useful materials. A substantial number of water-soluble tetra- and octasubstituted phthalocyanines have been reported. The hydrophilic moieties which have been incorporated on the peripheral of phthalocyanine ring include sulfonates [5], carboxylates [6], phosphonates [7], and quaternarized amino groups [8]. Another type of water-soluble phthalocyanines contains hydrophilic groups as axial ligands coordinated to the central metal ion [9].

The PDT properties of the phthalocyanine dyes are strongly influenced by the presence and nature of the central metal ion. Complexation of phthalocyanine with transition metals gives dyes with short lifetimes. Closed shell, diamagnetic ions, such as Zn^{2+}, Al^{3+} and Ga^{3+}, give phthalocyanine complexes with both high triplet quantum yields and long triplet lifetimes [10]. MPc complexes containing metals

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such as Ga^{3+}, which can coordinate axial ligands are useful in that axial ligation prevents aggregation.

To our knowledge, only water-soluble anionic tetrasulfogallium phthalocyanine is known in the literature [11,12], cationic gallium phthalocyanines have not been reported before. This study is the first report on tetrapyridyloxy cationic substituted water-soluble gallium(III)phthalocyanine compounds. The aim of our ongoing research is to synthesise water-soluble gallium phthalocyanines to be used as potential PDT agents, since gallium(III)phthalocyanine complexes show good photophysical and photochemical properties which are very useful for PDT studies [13,14]. Herein, we report the synthesis, characterization and spectroscopic properties of ClGaPcs tetra-substituted at the non-peripheral (complex **5a**) and peripheral (complex **6a**) positions with 3-pyridyloxy group (Scheme 1a) and their quaternarized (**5b** for non-peripheral and **6b** for peripheral) derivatives (Scheme 1b).

Generally, substituted phthalocyanines are prepared by cyclotetramerization of substituted phthalonitriles or 1,3-diimino-1*H*-isoindoles. 2(3), 9(10), 16(17), 23(24)-tetrasubstituted phthalocyanines can be synthesized from 4-substituted phthalonitriles while 1(4), 8(11), 15(18), 22(25)-tetrasubstituted phthalocyanines are obtained from 3-substituted analogues. In both cases a mixture of four possible structural isomers are obtained. The four probable isomers can be designed by their molecular symmetry as C_{4h}, C_{2v}, C_s and D_{2h}. In this study, synthesized phthalocyanine compounds are obtained as isomeric mixtures as expected. No attempt was made to separate the isomers of **5a–b** and **6a–b**. 3-Nitrophthalonitrile (**1**) and 4-nitrophthalonitrile (**2**) were used recently to prepare 3-monosubstituted and 4-monosubstituted phthalonitrile derivatives respectively, through base catalysed nucleophilic aromatic displacement [15]. The same route was applied to prepare 3-pyridyloxyphthalonitrile (**3a**) from 3-hydroxypyridine

and 3-nitrophthalonitrile (**1**) (Scheme 1a). Similarly, the reaction of 3-hydroxypyridine under same conditions with 4-nitrophthalonitrile (**2**) resulted in the expected compound **4a** (Scheme 1a). The reactions were carried out in dimethyl formamide (DMF) at room temperature and gave yields about 80–90%.

The preparation of phthalocyanine derivatives from the aromatic nitriles occur under different reaction conditions. The syntheses of metallophthalocyanine complexes (**5a** and **6a**) were achieved by treatment of phthalonitriles **3a** and **4a** with anhydrous $GaCl_3$ in freshly distilled quinoline (Scheme 1a). Because gallium is a large atom, high energy is required to insert the metal ion into the phthalocyanine ring, thus a high-boiling solvent (such as quinoline) is used to achieve this purpose. Complex **5a** is non-peripherally (α) substituted, whereas complex **6a** is peripherally (β) substituted. Preparative thin layer chromatography with silica gel was employed to obtain the pure products from the reaction mixtures.

Quaternarization of the gallium phthalocyanine compounds were achieved by reaction with dimethylsulphate (DMS) as quaternarization agent in DMF (as a solvent) at 120 °C (Scheme 1b). Yields of the products were 73% for **5b** and 80% for **6b**.

Generally, phthalocyanine complexes are insoluble in most organic solvents; however introduction of substituents on the ring increases the solubility. All complexes (**5a–b** and **6a–b**) exhibited excellent solubility in DMF and dimethylsulfoxide (DMSO). Quaternarized complexes (**5b** and **6b**) are soluble in water as well. For comparative purposes, the pyridyloxy group was tetrasubstituted at the α and β positions of the ring. The new compounds were characterized by UV–vis, IR, NMR spectroscopies, MALDI-TOF mass spectra and elemental analysis. The analyses are consistent with the predicted structures. The sharp peak in the IR spectra for the C≡N vibrations of
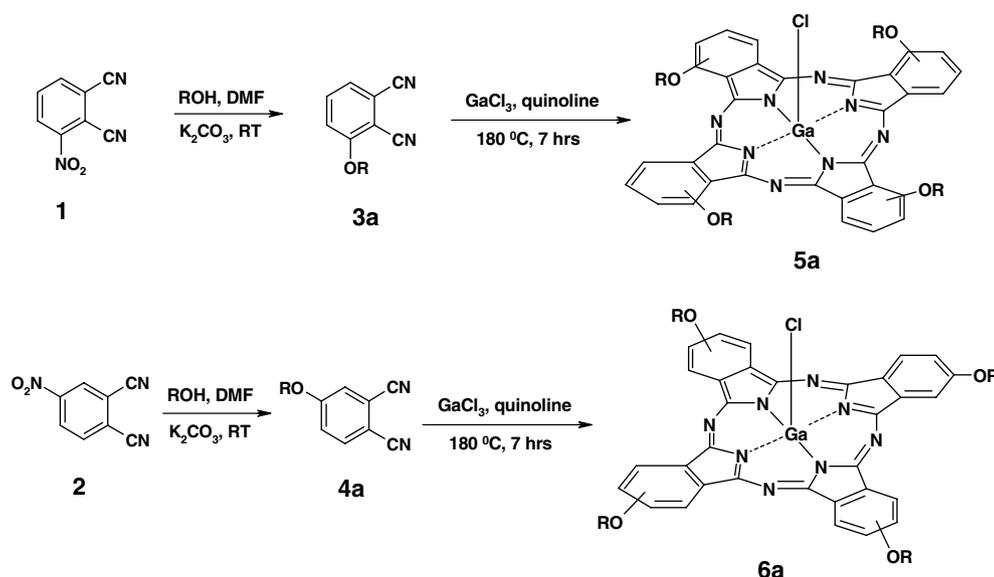
Scheme 1a. Synthesis of tetrasubstituted 3-pyridyloxy(phthalocyaninato)gallium(III) substituted at the α and β positions.
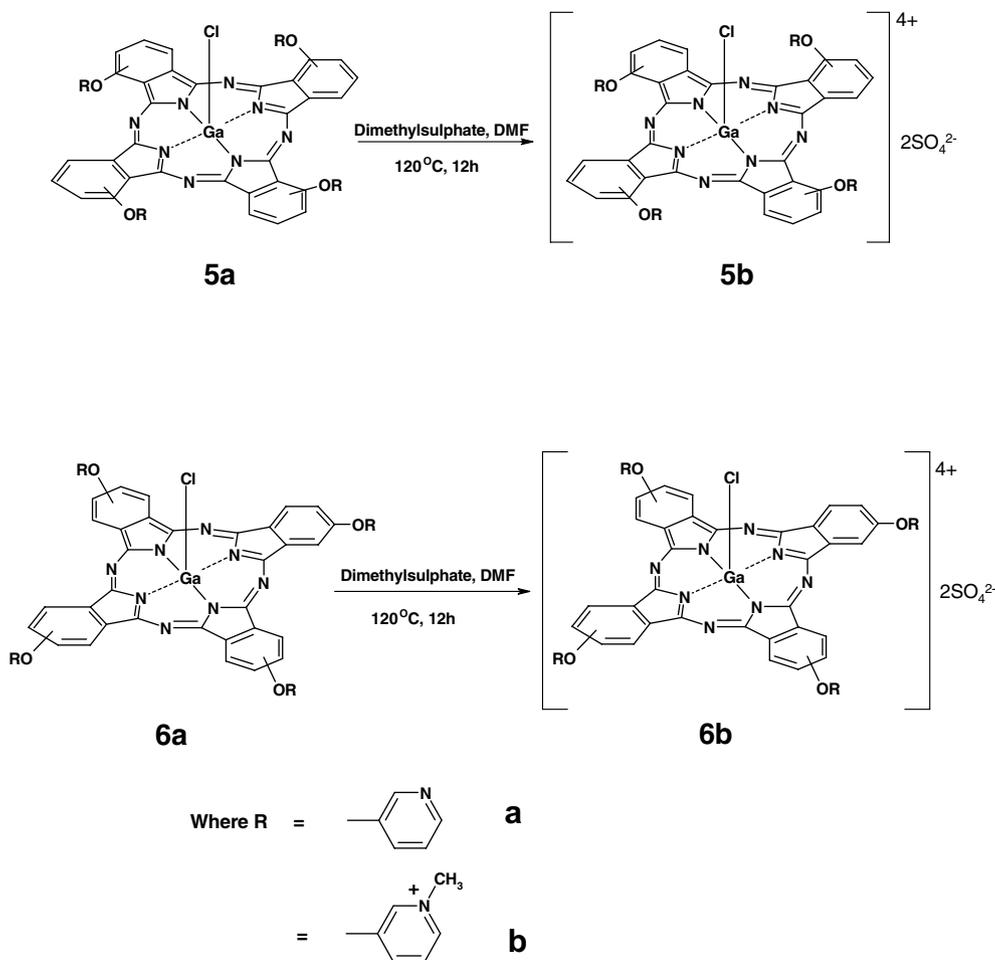
Scheme 1b. Synthesis of quaternarized tetrasubstituted 3-pyridyloxy (phthalocyaninato) gallium(III) substituted at the α and β positions.

phthalonitriles **3a** and **4a** at ~2230 cm^{-1} disappeared after conversion into gallium phthalocyanines, indicative of metallophthalocyanine formation. The characteristic vibrations corresponding to ether groups (C–O–C) were observed at 1082–1084 cm^{-1} and aromatic CH stretching at ca. 3050 cm^{-1} for all complexes. Aliphatic CH stretching at ca. 2942 cm^{-1}, S=O stretching at 1277 cm^{-1} and 1192 cm^{-1} and S–O stretching at 591 cm^{-1} for **5b** and **6b**. The latter peaks are indicative of quaternarization.

The ^{1}H NMR spectra of tetrasubstituted phthalocyanine derivatives (**5a–b** and **6a–b**) showed complex patterns due to the mixed isomer character of these compounds, Fig. 1. The complexes were found to be pure by ^{1}H NMR with all the substituents and ring protons observed in their respective regions. The pyridyloxy substituted complexes **5a** and **6a** showed different behaviour in that the peripherally substituted complex (**6a**) showed more resolved and split bands for the phthalocyanine ring. The resonances belonging to ring protons were observed between 9.51 and 9.73 ppm, 9.05 and 9.18 ppm, and 8.84 and 8.97 ppm for **6a** (Fig. 1b) integrating for four protons each, making a total of 12 protons expected for both peripheral and non-peripheral protons. The pyridyloxy protons were observed between 8.60 and 8.79 ppm, 7.98

and 8.38 ppm, and 7.66 and 7.91 ppm for **6a**, integrating for 4, 8, 4 protons each, respectively, making a total of 16 protons as expected (Fig. 1b). For the non-peripherally substituted complex (**5a**) similar splitting of bands was not observed most likely due to the presence of isomers. The ^{1}H NMR spectrum of **5a** showed unresolved multiplets; 9.22 and 10.11 ppm integrating four protons for ring protons, 8.31 and 9.18 ppm integrating eight protons for ring protons and four protons for pyridyloxy groups, 7.34 and 8.28 ppm integrating twelve protons due to pyridyloxy groups. Both complexes (**5** and **6**) are expected to have positional isomers due to the presence of a single substituent on either the peripheral and non-peripheral positions. Less positional isomers are expected for the non-peripherally substituted complex (**5a**) compared to the peripherally substituted complex (**6a**) due to steric effects in the former. Thus, the observed split in the ^{1}H NMR spectra could be due to lack of symmetry which may result in unresolved (**5a**) and split (**6a**) spectra for the complexes. The resonances for the pyridyl ring are also split for **6a** and not for **5a**, for the same reasons.

The NMR spectra of the quaternarized phthalocyanine complexes (**5b** and **6b**) showed more unresolved patterns compared to non-quaternarized derivatives due to the use
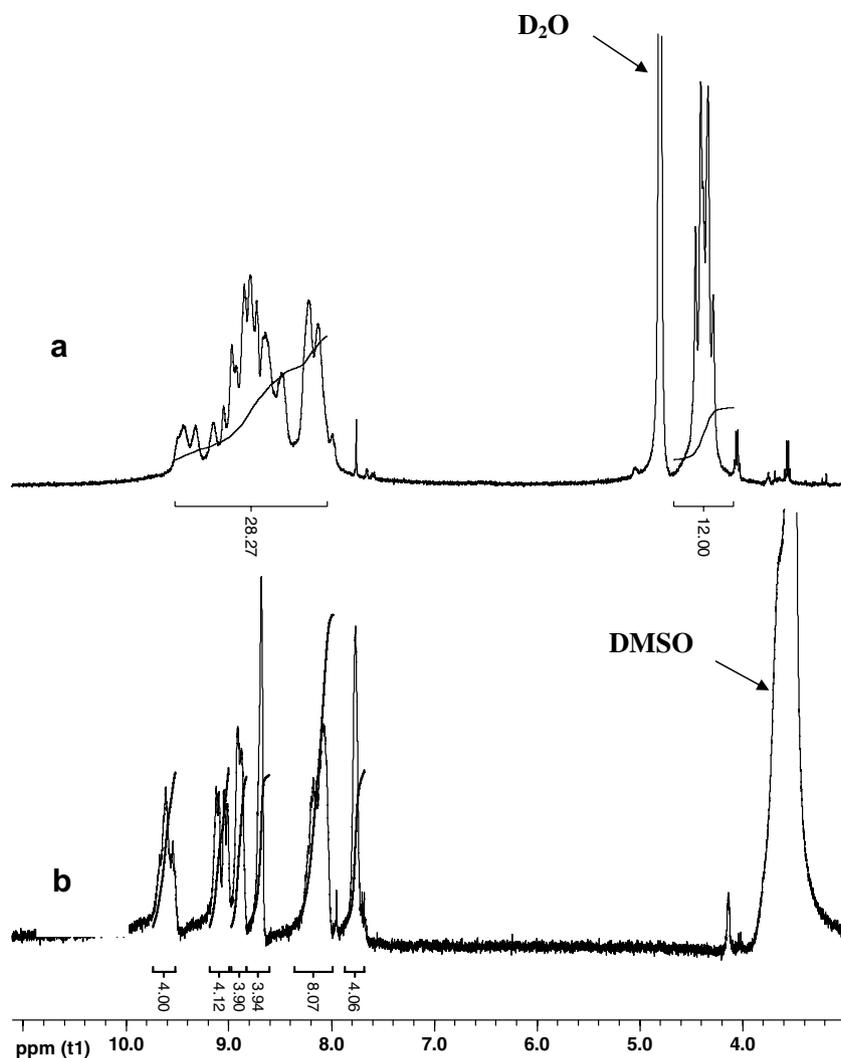
Fig. 1. ^{1}H NMR spectra of complexes (a) **6b** in D_2O and (b) **6a** in DMSO-d_6.

of deuterated water for NMR solvent. These complexes (**5b**, non-peripheral **6b**, peripheral) showed the phthalocyanine ring protons and pyridyl group protons as unresolved multiplets integrating for a total of 28 protons each. For complex **5b**, phthalocyanine ring and pyridyl protons were observed between 7.91 and 9.56 ppm, and for **6b** between 7.78 and 9.63 ppm as multiplets (Fig. 1a). The methyl protons which integrated for 12 protons were observed between 3.86 ppm and 4.44 ppm for **5b**, and between 4.09 ppm and 4.71 ppm for **6b** as multiplets (Fig. 1a). Although the presence of isomers as well as phthalocyanine aggregation at the concentrations used for the NMR measurements may lead to broadening of the aromatic signals, the observed spectra of all the complexes were relatively well-resolved.

The electronic spectra of the complexes showed characteristic absorption in the Q band region at around 700 nm for **5a** and **5b**, and 680 nm for **6a** and **6b** in DMSO, Table 1. The B bands were observed at around 350–360 nm (Fig. 2). The spectra showed monomeric behaviour evidenced by a single (narrow) Q band, typical of metallated

phthalocyanine complexes [16]. In DMSO, the Q bands were observed at: 706 (**5a**), 697 (**5b**), 688 (**6a**) and 683 (**6b**), Table 1. Thus, the quaternization caused 9 nm and 5 nm blue-shifts for **5b** and **6b** compared to **5a** and **6a** in DMSO, respectively. The Q bands of the α-substituted complexes (**5a** and **5b**) are red-shifted by 18 and 14 nm, respectively, when compared to the corresponding β-substituted complexes (**6a** and **6b**) in DMSO (Fig. 2). The observed red spectral shift is typical of phthalocyanines with substituents at the α positions and has been explained [17] to be due to linear combinations of the atomic orbitals (LCAO) coefficients at the α (non-peripheral) positions of the HOMO being greater than those at the β (peripheral) positions. As a result, the HOMO level is destabilized more at the α position that it is at the β position. Essentially, the energy gap (ΔE) between the HOMO and LUMO becomes smaller, resulting in ~20 nm bathochromic shift. The B-bands are broad due to the superimposition of the B_1 and B_2 bands in the 350–360 nm region. These quaternarized complexes showed narrow absorption in Q band region at 693 nm for **5b** and 681 nm for **6b** in water.

Table 1
Electronic absorption and photophysical data of peripheral and non-peripheral substituted gallium(III)phthalocyanines in DMSO and water

Compound	Solvent	Q band λ_{max}, (nm)	Excitation λ_{Ex}, (nm)	Emission λ_{Em}, (nm)	τ_F (ns)	Φ_F	Φ_Δ
5a	DMSO	706	719	725	1.28	0.12	0.48
	H_2O^a	–	–	–	–	–	–
5b	DMSO	697	695	712	1.50	0.19	0.53
	H_2O	693	694	709	0.72	0.07	0.41
6a	DMSO	688	688	705	2.05	0.19	0.59
	H_2O^a	–	–	–	–	–	–
6b	DMSO	683	690	699	1.93	0.24	0.51
	H_2O	681	691	695	1.06	0.12	0.44

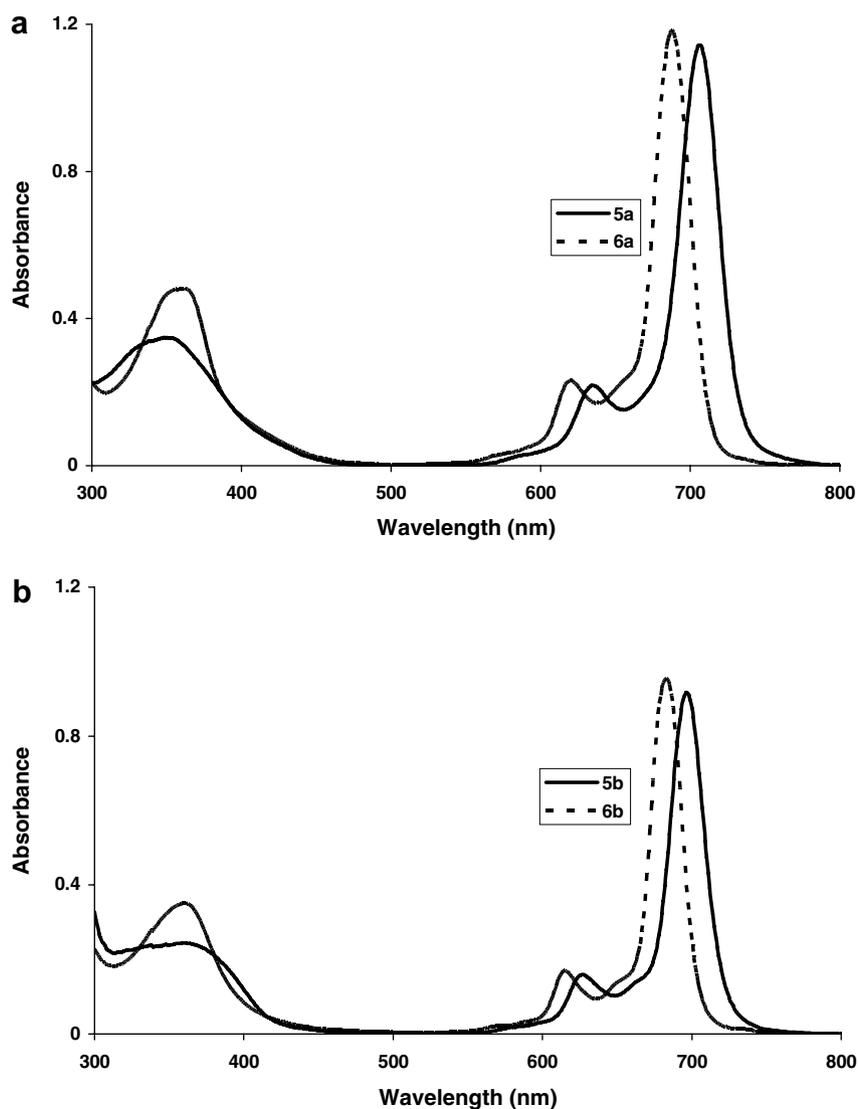[a] Compounds **5a** and **6a** are insoluble in H_2O.

Fig. 2. Absorption spectra of: (a) **5a** and **6a**; (b) **5b** and **6b** in DMSO. Concentration $= 4 \times 10^{-6}$ mol dm^{-3}.

Aggregation is usually depicted as a coplanar association of rings progressing from monomer to dimer and higher order complexes. It is dependent on concentration, nature of the solvent, nature of the substituents, complexed metal ions and temperature [18]. In the aggregated state the electronic structure of the complexed phthalocyanine rings are perturbed resulting in alternation of the ground and excited state electronic structures [19]. In this study, the aggregation behaviour of the phthalocyanines derivatives (**5a–b** and **6a–b**) were investigated in DMSO for **5a** and

6a, and in both of DMSO and water for **5b** and **6b** at different concentrations (Fig. 3). As the concentration was increased, the intensity of absorption of the Q band also increased and there were no new bands (normally blue shifted) due to the aggregated species [20]. The phthalocyanine derivatives (**5a–b** and **6a–b**) did not show aggregation in these solvents. Beer-Lambert law was obeyed for all of these compounds in the concentrations ranging from 1.4×10^{-5} to 4×10^{-6} mol dm^{-3}. Non-aggregated water-soluble compounds are very useful for PDT applications.

All complexes showed similar fluorescence behaviour. Fig. 4 shows the fluorescence excitation and emission spectra for complex **5b** as an example in water. The excitation spectra were similar to absorption spectra and both were mirror images of the fluorescent spectra. The proximity of the wavelength of each component of the Q-band absorption to the Q band maxima of the excitation spectra

for all complexes suggest that the nuclear configurations of the ground and excited states are similar and not affected by excitation.

The fluorescence quantum yields (Φ_F) of all complexes are typical of MPc complexes, Table 1. The peripherally substituted complexes (**6a** and **6b**) show marginally higher Φ_F values in DMSO, compared to non-peripherally substituted derivatives (**5a** and **5b**), suggesting not as much of quenching of the excited singlet state by peripheral substitution compared to the non-peripheral substituents. Quaternarized cationic complexes (**5b** and **6b**) show larger Φ_F values compared to the corresponding non-ionic complexes (**5a** and **6a**) in DMSO. Comparing DMSO and water, the cationic complexes (**5b** and **6b**) show larger Φ_F values in DMSO than in water. This is attributed to the higher viscosity of DMSO than that of water. Lifetimes of fluorescence (τ_F) (Table 1) were calculated using the Strickler-
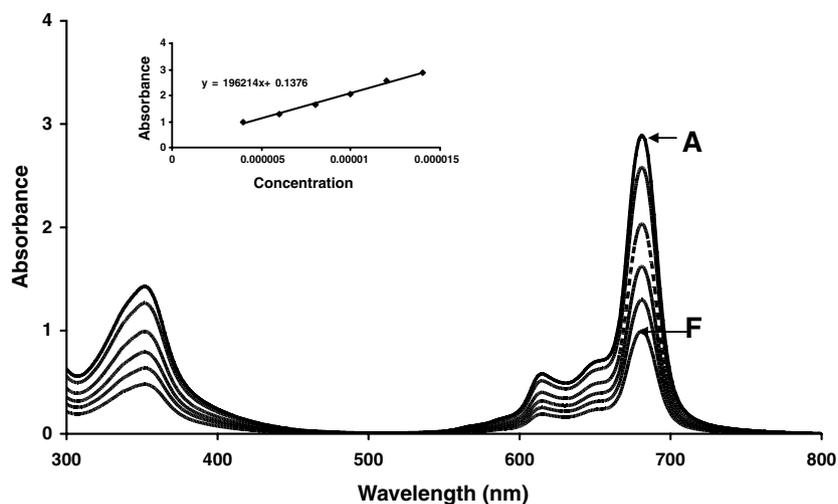

Fig. 3. Absorption spectra of **6b** in H$_2$O at different concentrations: 14×10^{-6} (A), 12×10^{-6} (B), 10×10^{-6} (C), 8×10^{-6} (D), 6×10^{-6} (E), 4×10^{-6} (F) mol dm^{-3}.
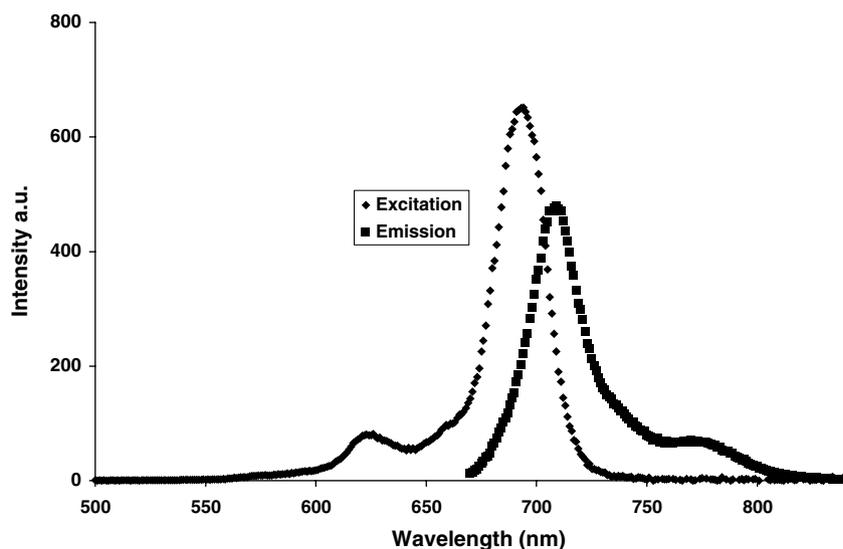

Fig. 4. Fluorescence excitation and emission spectra of **5b** in H$_2$O. Excitation wavelength = 660 nm.

Berg equation. τ_F values are lower for non-peripheral complexes (**5a–b**) when compared to peripheral complexes (**6a–b**), Table 1, suggesting more quenching by peripheral substitution compared to non-peripheral substitution. However, the τ_F values are typical for MPc complexes [21]. The τ_F values were lower in water when compared to in DMSO for complexes **5b** and **6b**.

The singlet oxygen quantum yields (Φ_Δ), give an indication of the potential of the complexes as photosensitizers in applications where singlet oxygen is required, (e.g. for Type II mechanism). Table 1 shows that singlet oxygen quantum yield (Φ_Δ) value for **6a** is higher than **5a** in DMSO, and both are higher than for ClGaPc with $\Phi_\Delta = 0.41$ [14]. However the values for **5b** and **6b** are almost the same in water and they are lower than in DMSO. These complexes have good singlet oxygen quantum yield values. Thus, we believe that these complexes can be potential as photodynamic therapy of cancer. The Φ_Δ values in water for complexes **5b** and **6b** are much larger than those observed for the quaternarized tetramethyl-tetra-2,3-pyridinoporphyrazine complexes containing Ge, Sn and Si metals [22]. The latter which gave a similar value of $\Phi_\Delta = 0.01$, which is an order of magnitude lower than the values shown in Table 1.

In summary, we have prepared and characterized four new gallium phthalocyanine complexes, tetrasubstituted at the peripheral and non-peripheral positions. The synthesis of cationic water-soluble gallium(III)phthalocyanines (**5b** and **6b**) have been achieved for the first time in this study. All synthesized gallium(III)phthalocyanine complexes (**5a–b** and **6a–b**) are monomeric in solution. The gallium phthalocyanine complexes (**5a–b** and **6a–b**) have better singlet oxygen quantum yields (Φ_Δ ranging from 0.41 to 0.59) in water than the related quarternarized porphyrazine complexes ($\Phi_\Delta \sim 0.01$). Thus, these complexes show potential as Type II photosensitizers for photodynamic therapy of cancer.

Acknowledgement

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.inoche.2006.11.012.

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