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Comparative studies of photophysical and photochemical properties of solketal substituted platinum(II) and zinc(II) phthalocyanine sets

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ABSTRACT

A complete set of platinum(II) solketal substituted phthalocyanines has been synthesized and characterized. To evaluate their potential as Type II photosensitizers for photodynamic therapy, comparative studies of their photophysical and photochemical properties with analogous zinc(II) series have been achieved: electronic absorption, fluorescence quantum yields, lifetimes, and fluorescence quenching by benzoquinone, as well as singlet oxygen generation and photodegradation. It appears that platinum(II) phthalocyanines are worth being used as Type II photosensitizers, as they exhibit good singlet oxygen generation and appropriate photodegradation.

1. Introduction

Phthalocyanines are among the best photosensitizers currently used in photodynamic therapy.[1–10] Their photosensitizing properties are related to the nature of the coordinating central metal or pseudo-metal,[4] giving a diamagnetic complex. Zn(II), Al(III), Ga(III), Si(IV) phthalocyanines are among the most commonly used.

Different molecular mechanisms exist in photodynamic therapy, depending on the type of photosensitizer. Phthalocyanines are Type II photosensitizers: upon irradiation, they induce the conversion of oxygen from its basic state to its excited state, i.e., singlet oxygen. Phthalocyanines are said to be second-generation photosensitizers, offering multiple advantages, mainly absorption at long wavelengths compatible with the biological window, biocompatibility and photostability.[1–10] Their efficiency in generating singlet oxygen is strongly related to their central metal. Transition metals, such as palladium or platinum, despite being rarely introduced in photodynamic therapy agents, are worthy of more study, as available results are promising: palladium(II) and platinum(II) have recently been introduced at the centre of chlorin derivatives with a very positive effect on singlet oxygen generation, hence on tumour cell elimination.[11] The effect of heavy metals, and more generally heavy atoms, is indeed known to enhance fluorescence and intersystem crossing (ISC), enhancing singlet oxygen generation, a key property of efficient photosensitizers.[12–16] Platinum phthalocyanines have been described to generate singlet oxygen effectively when used as oxidation catalysts.[17]

This prompted us to prepare a series of platinum(II) phthalocyanines, substituted by solketal moieties, in order to evaluate the contribution of platinum to the photosensitizing properties of the phthalocyanine macrocycle. Solketal is the protected form of glycerol, a cheap and versatile chemical.[18] Solketal substituted phthalocyanines are easily convertible into the corresponding glycerol substituted phthalocyanines, offering the advantage of being possibly water soluble.[19] This will be the next step of our research, as the results of the present studies confirm the interest of using platinum(II) phthalocyanines as photodynamic therapy agents.

We therefore prepared a complete set of platinum(II) phthalocyanines, designated hereafter as **Pt-set**: unsubstituted **1-Pt**, peripherally and non-peripherally tetra- and octa-substituted, respectively, **2-Pt**, **3-Pt**, **4-Pt** and **5-Pt**, presented in Figure 1.

Our final future aim, after obtaining water-soluble platinum phthalocyanines, is to benefit from the combined advantages of the heavy nature of platinum, of platinum's innocuousness and even its anti-tumour effect,[20–24] associated with the invaluable efficiency of phthalocyanine macrocycles for the required photophysical and photochemical effects implied in photodynamic therapy treatments. The present investigations may be considered

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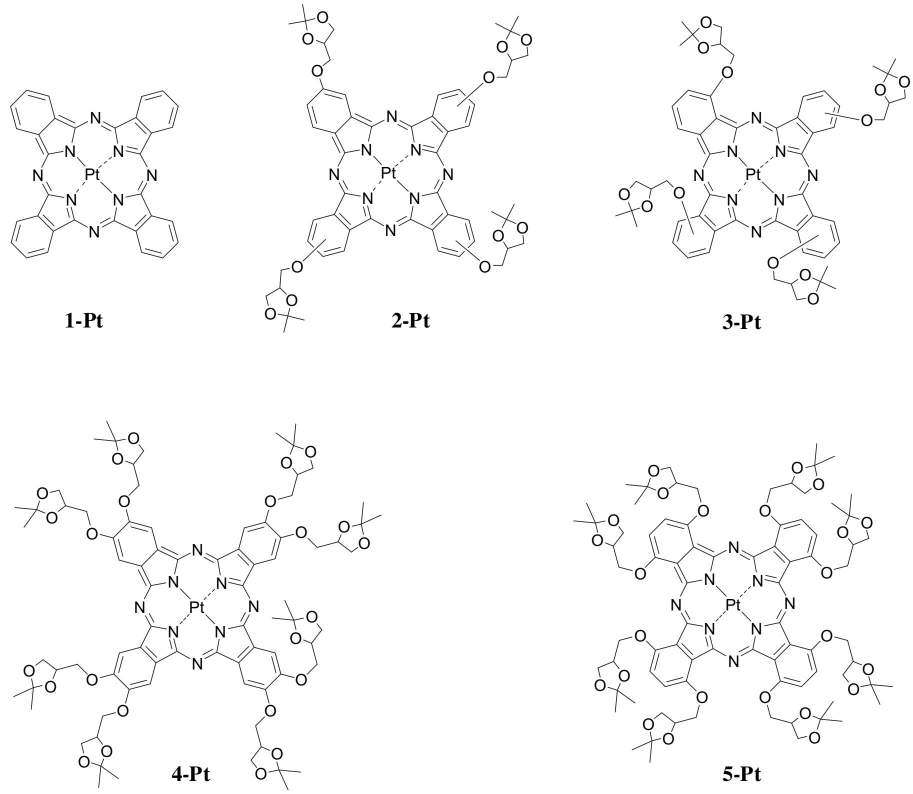


Figure 1. Representation of the platinum phthalocyanines (**Pt-set**).

as preliminary studies in the quest for more efficient photodynamic therapy agents, based on platinum(II) phthalocyanines. The photosensing properties of the **Pt-set** have been compared with those of an analogous series of Zn(II) phthalocyanines, designated hereafter as **Zn-set**. These were chosen as reference because Zn is one of the most common and efficient metals in photosensitizing phthalocyanines used in photodynamic therapy.

2. Results and discussions

2.1. Syntheses and characterizations

Compound **1-Zn** was purchased from Aldrich and used as received. The synthesis of **2-Zn**,[19,25,26] **3-Zn**,[19] **4-Zn**[27–29] and **5-Zn**[29] have been performed following the reported procedures.

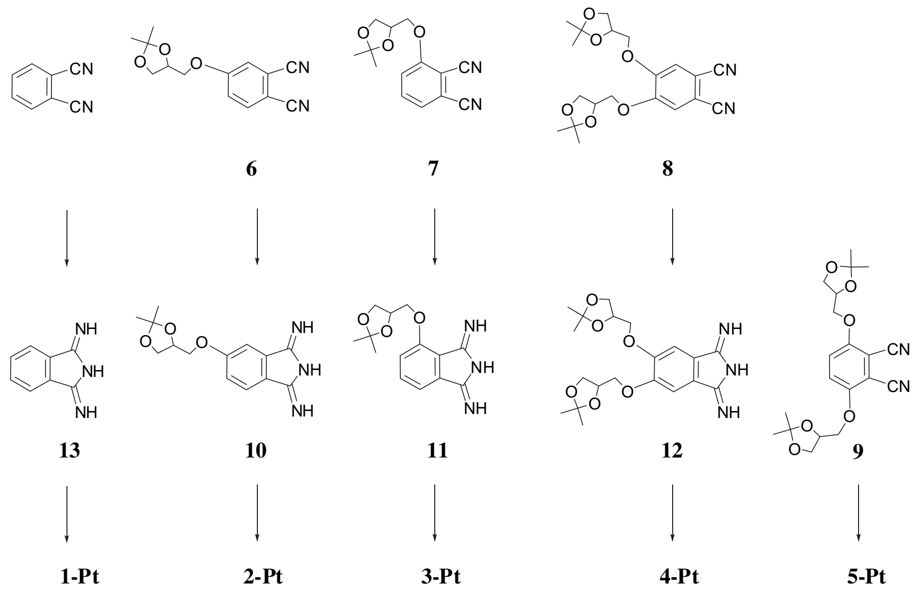
The very few descriptions of substituted platinum phthalocyanine syntheses report the difficulty in synthesis and purification.[30] Most of the reported data about platinum phthalocyanines concerned so far their crystallography.[31] Their electrochemical properties also aroused strong interest.[32] Syntheses of unsubstituted platinum phthalocyanines are described in harsh conditions,[32–34] conditions not applicable for substituted derivatives. Use of microwaves recently optimized the yields, starting from platinum tetrachloride to yield platinum(II) phthalocyanines.[35] It appeared in addition that the insertion of platinum in the centre of a free-based phthalocyanine remains unsuccessful, the metal-assisted tetramerization being more efficient.[36] We therefore chose this strategy to optimize the synthesis of **2-Pt**.

Among the available platinum salts, $PtCl_2$ was the most suitable, being more reactive than $Pt(acac)_2$ or $Pt(OAc)_2$. It has been reported that dimethylaminoethanol is the best solvent for platinum(II) phthalocyanine synthesis.[36] The use of phthalonitrile **6** following described methods[37] lead anyway to **2-Pt** in poor yields ($<2\%$), even under an ammoniacal atmosphere. Use of in situ prepared diiminoisoindoline has been described to give satisfactory yields under ammoniac atmosphere: yields were similar to those obtained with previously purified diiminoisoindoline **10**[38] under an inert atmosphere.[37] We chose to work from isolated diiminoisoindoline, as compounds **11** and **12** are new and had to be fully characterized.

Several experiments on **2-Pt** synthesis proved that, at least with our substituents, yields of isolated phthalocyanines are better when using diiminoisoindoline **10** in *N*,*N*′-dimethylaminoethanol under an ammoniacal atmosphere than under argon atmosphere. It probably enhances the reactivity of the diiminoisoindoline and prevents its eventual decomposition.[37] Except for the octa non-peripheral derivative **5-Pt**, all the platinum phthalocyanines have been prepared using diiminoisoindoline as a precursor, under an ammoniacal atmosphere, with a ratio of 2:1 phthalonitrile/$PtCl_2$, in 10–20% yields, satisfactory regarding the simplicity of the procedure and purification. Under these conditions, no free base phthalocyanine was detected by mass spectroscopy and UV–vis spectrophotometry, saving us from the tedious separations of a metallated phthalocyanine from the analogous free one. The phthalonitrile **9** couldn't be converted to the corresponding diiminoisoindoline, probably due to steric hindrance, and **5-Pt** was therefore prepared directly from **9**.

Compounds **10**,[38] **11** and **12** have been, respectively, prepared from phthalonitriles **6**,[28] **7**[29] and **8**[28] (Scheme 1), following a procedure previously described by us,[38] in nearly quantitative yields.

All the substituted phthalocyanines of the **Pt-set** have been characterized by NMR, mass spectrometry (MALDI) and high performance liquid chromatography (HPLC). Mass spectroscopy analyses of phthalocyanines have previously been challenging, especially for unsubstituted ones.[39,40] In our case, MALDI experiments, using dihydroxybenzoic acid as the matrix, allowed us to observe the molecular ion (see Supplementary data). The purity of the four substituted **Pt-set**'s phthalocyanines: **2-Pt**, **3-Pt**, **4-Pt** and **5-Pt**, has been established by HPLC experiments, on a silica column



Scheme 1. Preparation of platinum phthalocyanines.

eluted by a mixture of dichloromethane/isopropanol (detection from 190 to 950 nm). Respective retention times were 16.78, 17.44, 14.59 and 31.35 min. The unique peak on the profile certifies to the purity of the phthalocyanines (see profiles in Supplementary data). ^{13}C NMR spectra have been recorded (see Supplementary data). They are similar to those of similar solketal substituted phthalocyanines.[29] In the case of **4-Pt** and **5-Pt**, the effect of the platinum on chemical shifts can be compared to the similar Ni, Zn and metal free phthalocyanines:[29] the peak corresponding to the internal carbon of the phthalocyanine macrocycle is observed at 138.70 for **4-Pt** and at 140.48 for **5-Pt**. Compared to analogous zinc(II) and free-based phthalocyanines, this peak is shifted to higher fields, as are those of analogous nickel derivatives. This is coherent with the fact that nickel and platinum belong to the same group on the periodic table. Due to its heavy atom character, the effect of platinum is even more pronounced than for nickel (5 ppm more shielded for **4-Pt** and **5-Pt** compared with the analogous nickel phthalocyanines).

2.2. Photophysical and photochemical parameters

2.2.1. Ground state electronic absorption. Comparative studies of the electronic absorption behaviour of **Zn-set** and **Pt-set** have been performed in *N*,*N*′-dimethylformamide (DMF), a solvent that offers convenient solubility for all of the studied phthalocyanines, except for **1-Pt**, which is insoluble in common organic solvents. Reported electronic absorption spectra of **1-Pt** were recorded in strong inorganic acids such as concentrated sulfuric acid,[35] not suitable for the other molecules of this study. The insolubility of **1-Pt** unfortunately prevented us from achieving further photophysical and photochemical investigations, despite the interest it would have presented.

Electronic absorption spectra of the **Zn-set** phthalocyanines showed non-aggregated monomeric behaviour, as evidenced by a single and narrow Q band, typical of metallated phthalocyanines[41] (Fig. 2a).

The maximum absorptions in the Q band region and extinction coefficients for **Zn-set** and **Pt-set** are summarized in Table 1. The B band region was observed between 300 and 350 nm for all the phthalocyanines. The maximum absorption in the Q band area for the substituted zinc(II) phthalocyanines (**2-Zn** to **5-Zn**) are red-shifted relative to that of the unsubstituted **1-Zn**, implying that the Highest Occupied Molecular Orbital (HOMO)–Lowest Unoccupied Molecular Orbital (LUMO) energy gap of the phthalocyanine ring is reduced when introducing electron-donating substituents. As said above, we couldn't check if similar effects appear in the **Pt-set**, due to the insolubility of **1-Pt** in DMF, while the solketal substituents can't survive in acidic media, prohibiting measurements in the inorganic acids in which **1-Pt** is soluble.

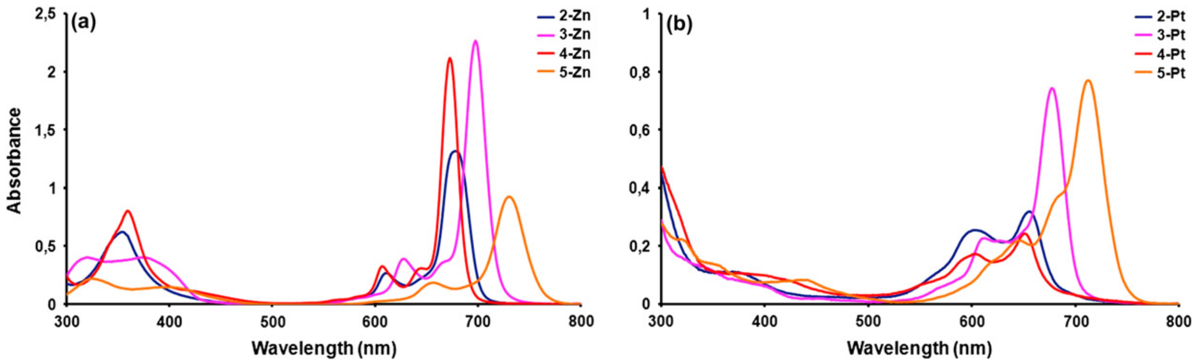


Figure 2. Absorption spectra of tetra- and octa-substituted (a) zinc (**2-Zn**, **3-Zn**, **4-Zn** and **5-Zn**) and (b) platinum (**2-Pt**, **3-Pt**, **4-Pt** and **5-Pt**) phthalocyanines in DMF. Concentration=1×10^{-5} mol dm^{-3}.

Table 1
Maximum electronic absorption and extinction coefficient for the **Zn-set** and the **Pt-set** in the Q band area, in DMF: Q band (λ_{max}, nm, log ε)

Compound	**1**	**2**	**3**	**4**	**5**
Zn	670 (5.37)	677 (5.09)	696 (5.30)	672 (5.28)	729 (4.99)
Pt	—	654 (4.34), 602 (4.40)	676 (4.80)	650 (4.30), 601 (4.24)	711 (4.89)

Platinum (II), when introduced in the centre of a phthalocyanine macrocycle, is known to strongly enhance aggregation.[42] On the other hand, non-peripheral substitution is known to inhibit aggregation.[42] Substituents in non-peripheral positions prevent macrocycles from getting too close to each other, thanks to an intercalative steric hindrance. The fact that peripherally substituted **2-Pt** and **4-Pt** derivatives present cofacial aggregation, as evidenced by the presence of two non-vibrational peaks in the Q band region, when the non-peripheral derivatives **3-Pt** and **5-Pt** show minimal aggregation as judged by the little broadening of their Q band, is in accordance with this hypothesis. The lower energy (red-shifted) bands at 654 nm for **2-Pt** and 650 nm for **4-Pt** are due to the monomeric species, while the higher energy (blue-shifted) bands at 602 nm for **2-Pt**, and at 601 nm for **4-Pt** are due to the aggregated species (Fig. 2b). Compared to analogous substituted phthalocyanines of the **Zn-set**, those of the **Pt-set** are all more aggregated, offering one more illustration of the aggregation tendencies induced by platinum.

The same comparison between the two sets about the maximum absorption in the Q band area results in the general observation of a blue-shift of approximately 20 nm for the **Pt-set** compared to the **Zn-set** (Table 1). This could be due to the larger size and heavy nature of the platinum atom. A π–π^* transition upon photon irradiation occurs at the Q band energy levels and implies the d orbitals of the molecule. The electronic structures of zinc(II) and platinum(II) are of different energy, explaining the hypsochromic shift of the **Pt-set**'s Q-band compared to the **Zn-set**'s ones. It must be noted in addition that extinction coefficients of the **Pt-set** are lower than those of the **Zn-set**.

The effect of peripheral substitution compared with non-peripheral is the same for the two sets, with a red-shift of the Q band for non-peripheral substituted phthalocyanines compared to the peripheral ones. These red spectral shifts are typical of phthalocyanines with substituents at the non-peripheral positions: they are due to the linear combinations of the atomic orbitals (LCAO) coefficients at the non-peripheral positions of the HOMO. These coefficients are greater than those for peripherally substituted phthalocyanines.[43,44] The energy gap (ΔE) between the HOMO and LUMO becomes smaller, resulting in bathochromic shifts. The value of these red-shifts depends on the peripheral or non-peripheral position of the substituents and is the same for the two sets with no influence of the metal. Red-shifts are observed of ~20 nm for tetra-substituted phthalocyanines (**2-Zn** and **2-Pt** vs **3-Zn** and **3-Pt**) and of ~60 nm for octa-substituted phthalocyanines (**4-Zn** and **4-Pt** vs **5-Zn** and **5-Pt**).

*2.2.2. Aggregation behaviour of the **Pt-set** compared to the **Zn-set***. Aggregation results from the coplanar association of the phthalocyanine rings, progressing from monomer to dimer then to complexes of higher order. It depends on several parameters: temperature, concentration, nature of the solvent, nature, central complexed metal ions, number and position of the substituents.[45] In the aggregated state, the electronic structure of the phthalocyanine rings is perturbed, resulting in an alternation of the ground and excited state electronic structures.[46] These perturbations modify the electronic absorption events and are therefore visible in the UV–vis spectra: the peak due to aggregation is blue-shifted with respect to the monomer's one.

Keeping in mind that compared to zinc, platinum is a metal strongly enhancing aggregation,[37,42] we chose to investigate the

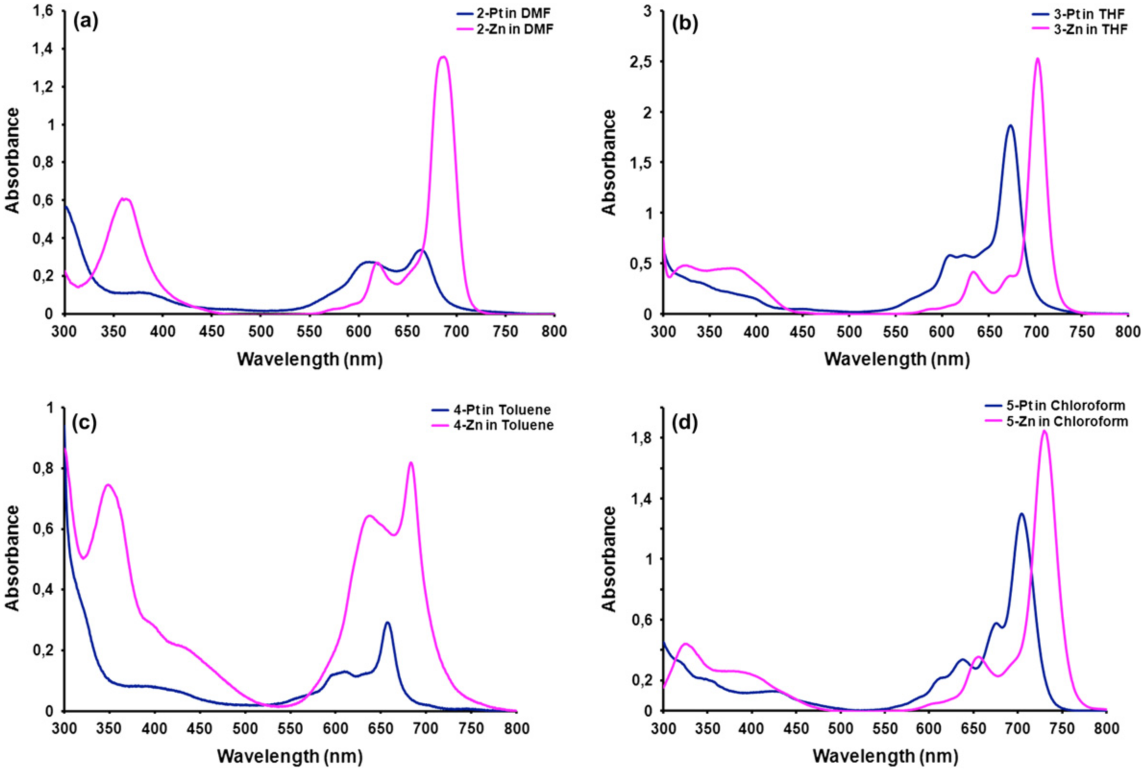


Figure 3. Comparative aggregation behaviour of (a) **2-Zn** and **2-Pt** in DMF, (b) **3-Zn** and **3-Pt** in tetrahydrofuran, (c) **4-Zn** and **4-Pt** in toluene, (d) **5-Zn** and **5-Pt** in chloroform. Zn derivatives are in pink, Pt derivatives in blue.

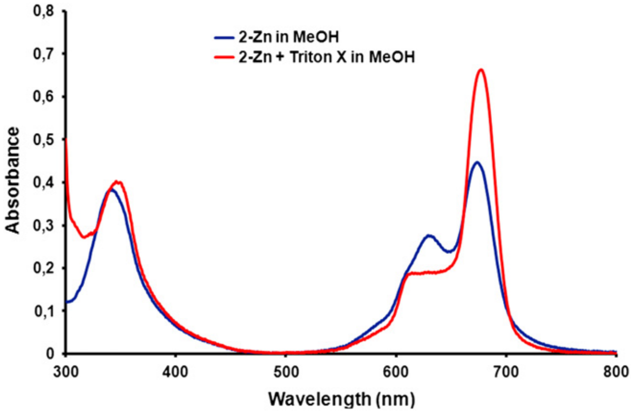


Figure 4. Absorption spectral changes for **2-Zn** in methanol upon the addition of Triton X-100.

aggregation behaviour of the substituted phthalocyanines of the **Pt-set** and of the **Zn-set** in the most common organic solvents: chloroform, DMF, methanol, tetrahydrofuran, toluene and DMSO. Non-peripheral substituted phthalocyanines are known to show less aggregation than peripheral substituted ones:[47] these trends were followed by all the molecules in the two sets.

While all the substituted **Zn-set**'s phthalocyanines are soluble in the selected solvents, the substituted **Pt-set**'s phthalocyanine aren't soluble in methanol and DMSO, and much more aggregated in other solvents than the corresponding zinc derivatives (Fig. 3).

The inhibiting effect of non-peripheral substituents on aggregation is strong enough to limit the aggregation of **3-Zn**, **5-Zn**, **3-Pt** and **5-Pt** in all the solvents: **3-Zn** and **5-Zn** are in their monomeric form in all the solvents, as are **3-Pt** and **5-Pt** in chloroform, DMF, THF and toluene. Peripheral **2-Pt** and **4-Pt** exhibit aggregation in chloroform, DMF, THF and toluene.

The addition of surfactants such as Triton X-100 can reduce aggregation. The aggregated molecules are dissociated thanks to the intercalation of the surfactant. Addition of Triton X-100 to solutions of **2-Zn** and **4-Zn** in methanol, a solvent in which they are aggregated, resulted in their dissociation, as evidenced by the increased intensity and red-shift of the monomer peak, while the peak for the aggregated species decreases in intensity (Fig. 4 for **2-Zn**).

The aggregation behaviour of the substituted Pt(II) phthalocyanines (**3-Pt** and **5-Pt**) and Zn(II) phthalocyanines (**2-Zn** to **5-Zn**) were also investigated at different concentrations in DMF (Fig. 5, case of **4-Zn** and **5-Pt**). The intensity of the Q band increased with the concentrations, obeying the Beer–Lambert law at concentrations ranging from 1.4×10^{-5} to 4×10^{-6} mol dm^{-3}.

2.2.3. Fluorescence studies. Fluorescence measurements have been recorded in DMF, the solvent offering the best average solubility for all the molecules.

2.2.3.1. Absorption, excitation and emission experiments. The non-peripheral octa-substituted phthalocyanines **5-Zn** and **5-Pt** showed less fluorescence emission than the other complexes. In the case of **5-Pt**, the emission of the complex was even not detectable.

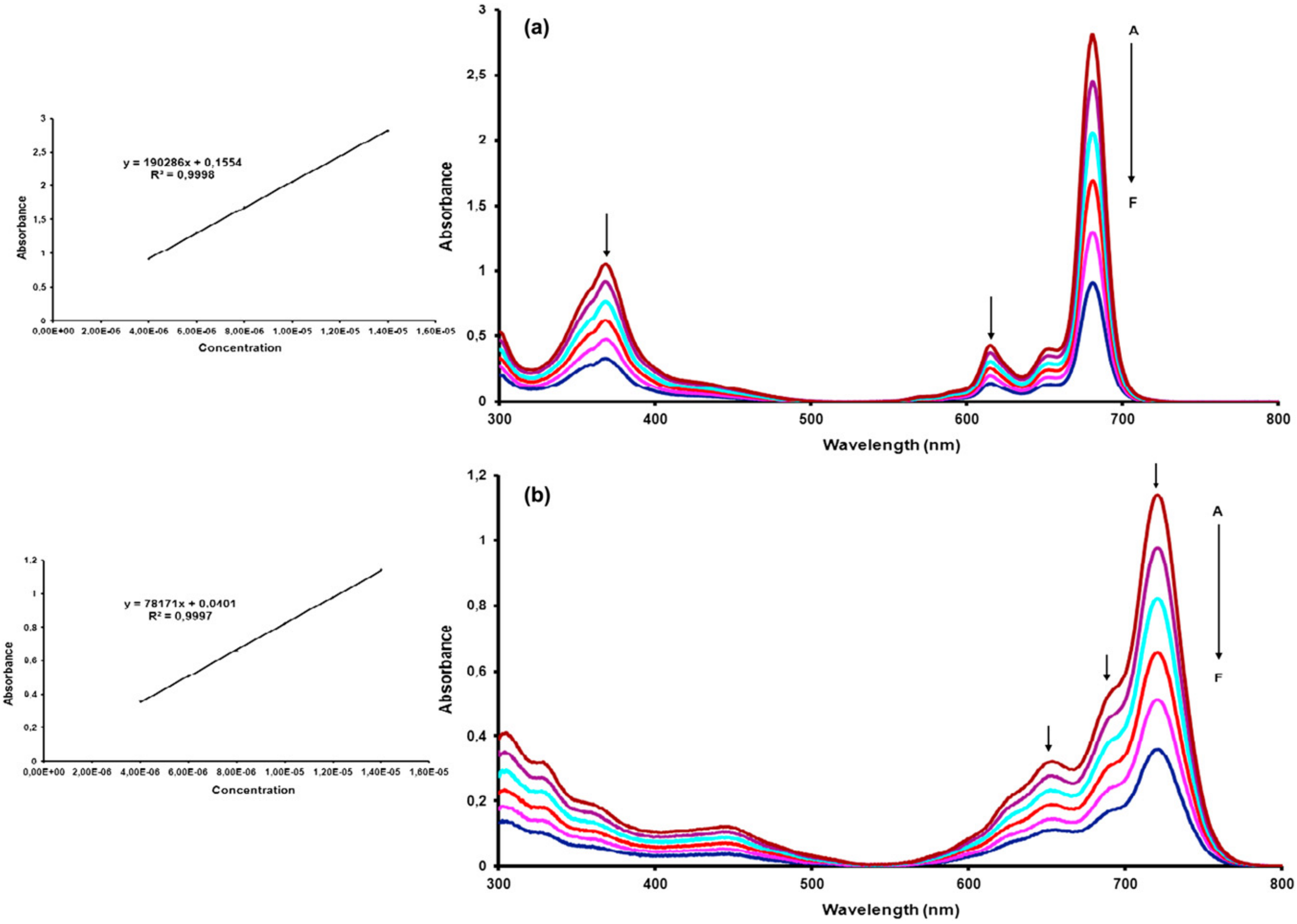


Figure 5. Aggregation behaviour of (a) **4-Zn** and (b) **5-Pt** in DMF at different concentrations: 14×10^{-6} (A), 12×10^{-6} (B), 10×10^{-6} (C), 8×10^{-6} (D), 6×10^{-6} (E), 4×10^{-6} mol dm^{-3} (F). (Inset: plot of absorbance vs concentration).

Figure 6 shows the fluorescence emission, absorption and excitation spectra for **2-Zn** and **2-Pt**. Fluorescence emission peak data are summarized in Table 2. The Stokes shifts are of 13, 14, 10 and 17 nm, respectively, for **2-Zn**, **3-Zn**, **4-Zn** and **5-Zn**, and of 22, 24 and 28 nm, respectively, for **2-Pt**, **3-Pt** and **4-Pt** (Table 2).

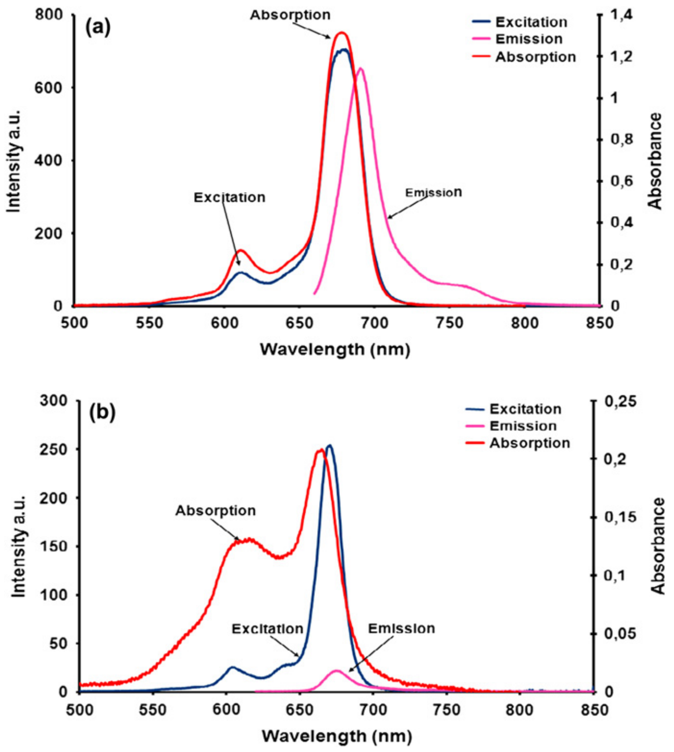


Figure 6. Absorption, excitation and emission spectra of (a) **2-Zn** and (b) **2-Pt** in DMF. Excitation wavelength: 650 nm.

Table 2
Absorption, excitation and emission spectral data for **Zn-set** and **Pt-set** in DMF

Compound	Q band λ_{max} (nm)	Excitation λ_{Ex} (nm)	Emission λ_{Em} (nm)	Stokes shift Δ_{Stokes} (nm)
1-Zn	670	670	676	6
2-Zn	677	680	690	13
3-Zn	696	700	710	14
4-Zn	672	673	682	10
5-Zn	729	736	746	17
2-Pt	654, 602	671	676	22
3-Pt	676	676	700	24
4-Pt	650, 601	673	678	28
5-Pt	711	—	—	—

The shape of the excitation spectra is similar to the absorption spectra's shape for all the **Zn-set** phthalocyanines (**2-Zn** to **5-Zn**). This suggests that the nuclear configurations of the ground and excited states are not affected by excitation. In the case of **Pt-set**, the shape of the excitation spectra appear to be different from the absorption spectra (Fig. 6b, example of **2-Pt**). This is probably due to modifications such as loss of the symmetry of the molecule upon excitation. The difference in the excitation behaviour of **Pt-set** phthalocyanines from **Zn-set** phthalocyanines could be due to the fact that the larger platinum atom is out of the plane of the phthalocyanine ring, inducing a loss of symmetry.[31]

2.2.3.2. Fluorescence quantum yields and lifetimes. The fluorescence quantum yields (Φ_F) are given in Table 3. The fluorescence quantum yields (Φ_F) of **2-Zn**, **3-Zn** and **4-Zn** are typical of metallated phthalocyanines, except for non-peripheral octa-substituted **5-Zn** (Table 3). The Φ_F value for **5-Zn** is lower compared to other substituted Zn(II) complexes (**2-Zn**, **3-Zn** and **4-Zn**). As **5-Zn** is less aggregated than **2-Zn**, **3-Zn** and **4-Zn**, it enhances the energy transfer via the intersystem crossing (ISC), thus limiting Φ_F. The Φ_F values of substituted **Pt-set**'s phthalocyanines were lower than those of the analogous **Zn-set**'s phthalocyanines (Table 3). This is due to intersystem crossing enhanced by the presence of the heavy atom: platinum.[48]

Table 3
Photophysical and photochemical parameters of **Zn-set** and **Pt-set** phthalocyanines in DMF

Compound	Φ_F	τ_F (ns)	τ_0 (ns)	^ak_F (s^{-1}) ($\times 10^7$)	Φ_d ($\times 10^{-4}$)	Φ_Δ
1-Zn	0.17	1.03	6.05	16.53	0.23	0.56
2-Zn	0.20	2.10	10.31	9.69	1.38	0.50
3-Zn	0.13	1.09	8.68	11.50	1.58	0.57
4-Zn	0.17	1.69	9.50	10.53	0.87	0.54
5-Zn	0.085	1.33	15.66	6.38	1.19	0.48
2-Pt	0.0051	0.18	36.09	2.77	1.32	0.35
3-Pt	0.0086	0.17	19.79	5.07	0.62	0.63
4-Pt	0.013	0.55	42.22	2.37	8.58	0.65
5-Pt	—	—	—	—	0.87	0.35

Fluorescence lifetime (τ_F) refers to the average time a molecule remains in its excited state before returning to its ground state. This value is related to that of Φ_F: the longer the fluorescence lifetime is, the higher the quantum yield of fluorescence. Any factor shortening the fluorescence lifetime reduces the value of Φ_F. Among such factors are internal conversion and intersystem crossing events, influenced by the nature and the environment of the fluorophore. The τ_F values (Table 3) were calculated using the Strickler–Berg equation. The τ_F values of the **Zn-set**'s phthalocyanines are higher compared to those of **Pt-set**, as the natural radiative lifetime (τ_0) and the rate constants for fluorescence (k_F) values also given in Table 3. Once again, this is due to the heavy atom effect.[48]

2.2.3.3. Fluorescence quenching studies by benzoquinone [BQ]. Fluorescence quenching by benzoquinone of the **Zn-set** was investigated. The **Pt-set**'s behaviour was not studied because of the very low fluorescence emission. In the presence of a quencher (BQ), energy transfer occurs between the fluorophore (the excited Zn(II) phthalocyanine) and the quencher. The fluorescence quenching of Zn(II) phthalocyanine by BQ obeyed Stern–Volmer kinetics. This is consistent with diffusion-controlled bimolecular reactions. Figure 7 shows the quenching

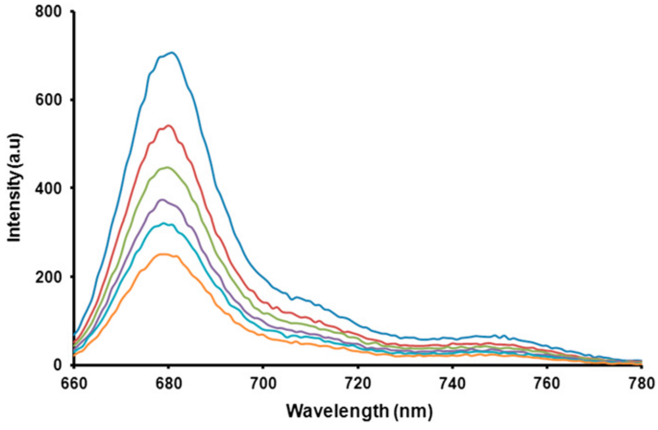


Figure 7. Fluorescence emission spectral changes of **4-Zn** (1.00×10^{-5} mol dm^{-3}) on addition of different concentrations of BQ in DMF. [BQ]=0, 0.008, 0.016, 0.024, 0.032, 0.040 mol dm^{-3}.

of **4-Zn** by BQ. The slope of the plots shown at Figure 8 gave the Stern–Volmer constant (K_{SV}) values. The K_{SV} and bimolecular quenching constant (k_q) values for the BQ quenching of the **Zn-set** are listed in Table 4. The K_{SV} values of the substituted **2-Zn** to **5-Zn** are lower than those of unsubstituted **1-Zn**. The K_{SV} values decreased as follows: **3-Zn**>**2-Zn**>**4-Zn**>**5-Zn**. The bimolecular quenching constant (k_q) values of the substituted phthalocyanines (**2-Zn** to **5-Zn**) are also lower than those of unsubstituted **1-Zn.** The bimolecular quenching rate constants were found to be close to the diffusion-controlled limits, $\sim 10^{10}$ M^{-1} s^{-1}. The k_q values for the substituted complexes decreased as follows: **3-Zn**>**4-Zn**>**2-Zn**>**5-Zn** (Table 4).

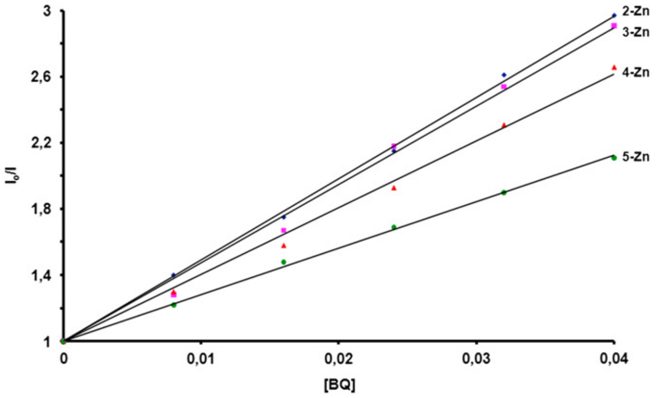


Figure 8. Stern–Volmer plots for benzoquinone (BQ) quenching of **2-Zn**, **3-Zn**, **4-Zn** and **5-Zn** in DMF. [ZnPc] $\sim 1.00 \times 10^{-5}$ mol dm^{-3}. [BQ]=0, 0.008, 0.016, 0.024, 0.032, 0.040 mol dm^{-3}.

Table 4
Fluorescence quenching data of the **Zn-set** in DMF

Compound	K_{SV} (M^{-1})	$k_q/10^{10}$ (dm^3 mol^{-1} s^{-1})
1-Zn	57.60	5.59
2-Zn	48.68	2.31
3-Zn	52.46	4.79
4-Zn	42.83	2.53
5-Zn	26.65	2.00

2.2.4. Singlet oxygen quantum yields. A good photosensitizer must be very efficient in generating singlet oxygen, the active species of a photodynamic therapy treatment. Energy transfer between the triplet state of a photosensitizer (here the metallated phthalocyanine) and the ground state of molecular oxygen leads to its conversion into singlet oxygen. This transfer must be as much efficient as possible to generate large amounts of singlet oxygen. This is quantified by the singlet oxygen quantum yield (Φ_Δ), a parameter giving an indication of the potential of molecules to be used as photosensitizers in applications where singlet oxygen is required (e.g., for Type II mechanism). The Φ_Δ values were determined in DMF using a chemical method and 1,3-diphenylisobenzofuran (DPBF) as a quencher. The disappearance of DPBF was monitored using UV–vis spectrophotometer (Fig. 9: example of **3-Pt**).

Many factors are responsible for the magnitude of the determined quantum yield of singlet oxygen, including: the triplet excited state energy, the ability of substituents and solvents to quench singlet oxygen, the triplet excited state lifetime and the efficiency of the energy transfer between the triplet excited state and the ground state of oxygen. There was no decrease in the Q band and no appearance of new bands during Φ_Δ determinations (Fig. 9): this indicates that the phthalocyanines were not damaged by the generated singlet oxygen. It is believed that during photosensitization, the phthalocyanine is firstly excited to the singlet state, then reaches the triplet state through intersystem crossing, then transfers its energy to ground state oxygen, O_2 ($^3\sum_g$), itself converted into its excited state (singlet oxygen), O_2 ($^1\Delta_g$). This singlet oxygen is the chief cytotoxic species, which subsequently oxidizes the surrounding substrates: this oxidation is the key of the Type II mechanism.

Compound **1-Zn** was used as the reference and the measurements were performed in DMF. Table 3 shows that the all substituted Zn(II) phthalocyanines have roughly the same Φ_Δ values than the unsubstituted **1-Zn**, the number and position of substituents having a very moderate influence.

While the Φ_Δ values of **3-Pt** and **4-Pt** are higher than those of **1-Zn**, **2-Pt** and **5-Pt** exhibit lower Φ_Δ values than **1-Zn** in DMF. Although the non-peripheral **3-Zn** and **3-Pt** showed higher Φ_Δ values than peripheral **2-Zn** and **2-Pt**, the **5-Zn** and **5-Pt** showed lower Φ_Δ values than peripheral **4-Zn** and **4-Pt** (Table 3).

The differences in the observed values are due to the different nature of zinc and platinum, which belong to different groups on the periodic classification table and have different outermost electronic configuration.

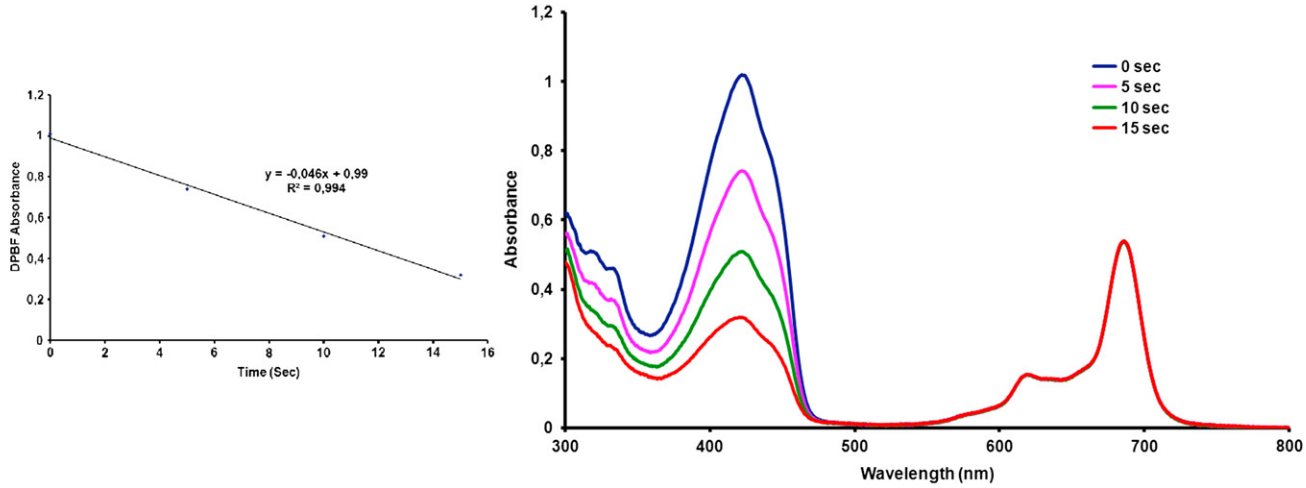


Figure 9. A typical spectrum for the determination of singlet oxygen quantum yield of **3-Pt** in DMF using DPBF as the singlet oxygen quencher. Concentration=1×10^{-5} mol dm^{-3} (Inset: plots of DPBF absorbance vs time.).

We at least established the efficiency of platinum(II) phthalocyanines to generate singlet oxygen. This confirms that further investigations are worth to be achieved.

2.2.5. Photodegradation studies. Degradation of the molecules upon irradiation lowers their availability, thus their photosensitizing efficiency, and is expressed by their photodegradation quantum yield values. The loss of the absorption peaks without distortion of their shape corresponds to clean photodegradation events, not associated with phototransformation. Photodegradation measurements have been recorded in DMF. Examples of spectral changes observed during irradiation for all the substituted phthalocyanines (**2-Zn** to **5-Zn** and **2-Pt** to **5-Pt**) are given in Figure 10 (example of **5-Zn** and **5-Pt**) and hence confirms that photodegradation occurred without phototransformation.

3. Conclusions

We prepared a full set of solketal substituted platinum(II) phthalocyanines, precursors of potentially water-soluble platinum(II) phthalocyanines utilizable as photodynamic therapy agents. Preliminary studies of their interest as Type II photosensitizers, and comparison with analogous zinc(II) phthalocyanines' photophysical and photochemical properties, demonstrated that these complexes are efficient singlet oxygen generators. In addition, their photodegradation parameters are suitable for potential photodynamic therapy agents.

These promising results confirm the interest of platinum(II) phthalocyanines as photodynamic therapy agents. The next steps of this work: obtaining water-soluble platinum(II) phthalocyanines is currently being achieved by our team.

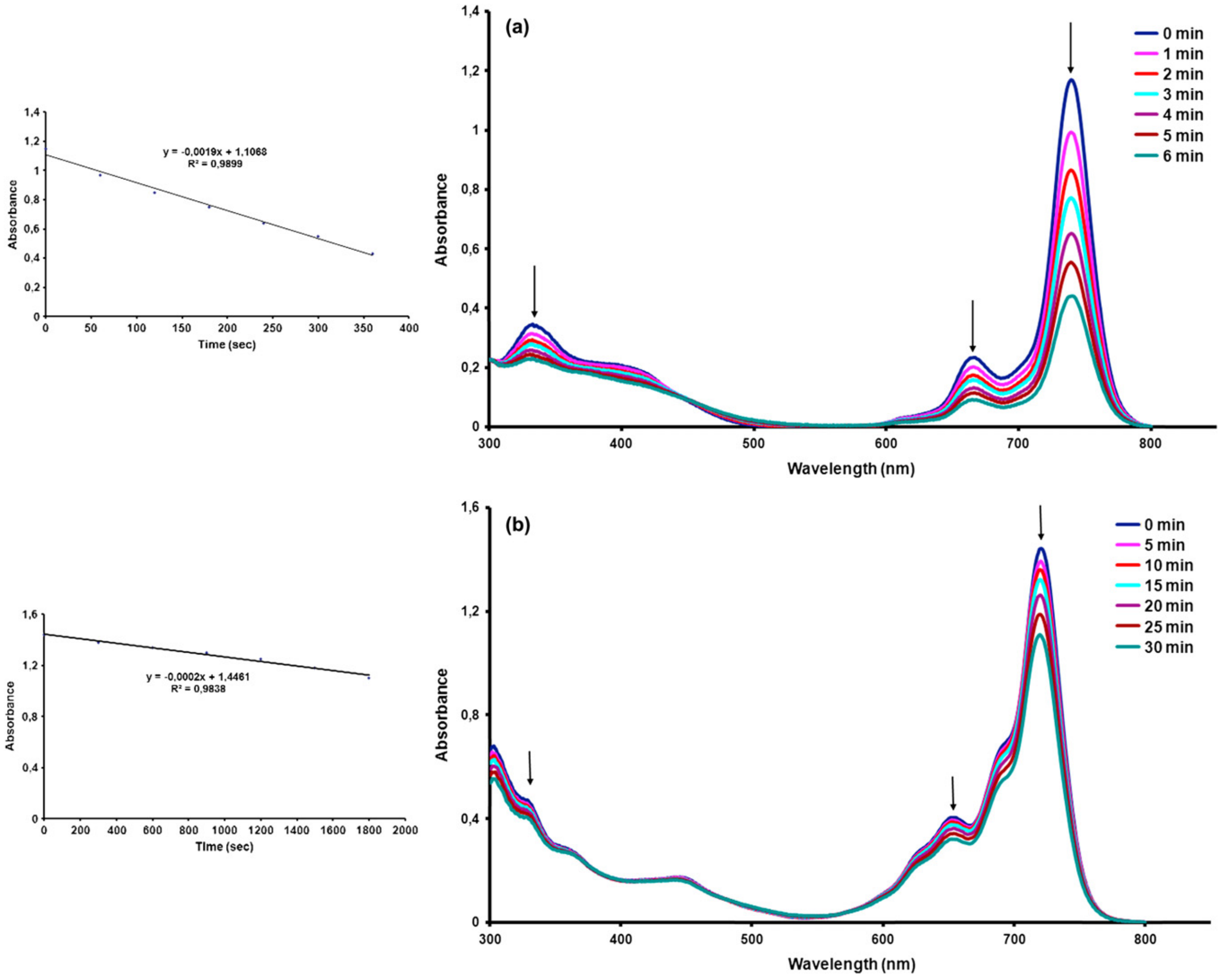


Figure 10. The photodegradation of (a) **5-Zn** and (b) **5-Pt** in DMF showing the disappearance of the Q band and the appearance of the reduction band at 1 min intervals for **5-Zn** and 5 min intervals for **5-Pt** (Inset: plot of Q band absorbance versus time).

All the substituted complexes, **2-Zn** to **5-Zn** and **2-Pt** to **5-Pt**, have roughly similar stability with photodegradation quantum yield (Φ_d) of the order of 10^{-4} (Table 3). Stable complexes show Φ_d values as low as 10^{-6}. Molecules are considered unstable with values around 10^{-3}.[49] Our two sets of molecules have an intermediate photostability. This is particularly required for photodynamic therapy applications: very unstable molecules degrade before having time to act, but on the other hand, highly stable molecules aren't easily eliminated by the host organism.

4. Experimental

4.1. Materials

Unsubstituted zinc phthalocyanine (**1-Zn**) was purchased from Aldrich and used as received. Zinc(II) phthalocyanines (**2-Zn** to **5-Zn**), phthalonitriles **6**, **7**, **8** and **9**, diiminoisoindolines **10** and **13** have been prepared following described procedures.[19,25,26,28,29,38]

4.2. Equipments

HPLC profiles have been recorded using an HPLC system Agilent 1100 series (ChemStation software) equipped with a G 1311A pump, a G1315B diode array detector monitoring the 190–950 nm range and a normal phase column Lichrosorb-SI-60 (250×4.6 mm) from Alltech. Associates, Inc. LC–ESI mass spectra were recorded with a Bruker microTOF spectrometer equipped with electrospray ionization (ESI) source. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) measurements were performed on a Bruker Daltonics microTOF. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ solutions on a Varian 500 MHz spectrometer. Absorption spectra in the UV–visible region were recorded with a Shimadzu 2001 UV spectrophotometer using a 1 cm pathlength cuvette at room temperature. Fluorescence excitation and emission spectra were recorded on a Varian Eclipse spectrofluorometer using 1 cm pathlength cuvettes at room temperature.

Photo-irradiations were done using a General Electric quartz line lamp (300 W). A 600 nm glass cut off filter (Schott) and a water filter were used to filter off ultraviolet and infrared radiations, respectively. An interference filter (Intor, 670 nm with a band width of 40 nm) was additionally placed in the light path before the sample. Light intensities were measured with a POWER MAX5100 (Molelectron detector incorporated) power meter.

4.3. Syntheses

*4.3.1. 3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-methoxy-1,3-dihydro-1,3-diiminoisoindole (**11**).* Prepared following described procedure for **10**,[38] from **7** (1 g, 3.88 mmol). Yield 85% (900 mg). Greenish solid. ^{1}H NMR (DMSO-d_6): 7.64, 7.62, 7.35, 7.34 (m, 3H, aromatics), 4.02–4.60 (m, 5H, CH_2CHCH_2), 3.55 (br s, NH), 1.36, 1.42 (2br s, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6): 154.30, 137.60, 133.87, 120.16, 116.02, 114.79, 108.90, 73.28, 69.49, 65.34, 26.35, 24.86. ESI–LC–MS m/z: calcd 275.1; found 276.2 [M+H]. Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.11; H, 6.24; N, 15.18.

*4.3.2. 5,6-Di-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]-1,3-dihydro-1,3-diiminoisoindole (**12**).* Prepared following described procedure for **10**,[38] from **8** (400 mg, 1.03 mmol). Yield 96% (400 mg). Greenish solid. ^{1}H NMR ($CDCl_3$): 7.20 (s, 2H, aromatics), 4.62 (br s, 1H, CH), 3.92–4.16 (4H, m, $(OCH_2)_2$), 1.37, 1.42 (2br s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$): 165.05, 151.49, 127.80, 109.65, 105.84, 73.66, 66.64, 66.39, 26.54, 25.27. ESI–LC–MS m/z: calcd 405.2; found 406.2 [M+H]. Anal. Calcd for $C_{20}H_{27}N_3O_6$: C, 59.25; H, 6.71; N, 10.36. Found C, 59.22; H, 6.72; N, 10.33.

*4.3.3. Procedure for the synthesis of **Pt-set** phthalocyanines.* Precursor and $PtCl_2$ (0.5 equiv) were refluxed in *N*,*N*-dimethylaminoethanol under ammonia atmosphere for 24 h. The cooled reaction mixture was then poured into hexane. The solid product was filtered, dissolved in a minimum amount of dichloromethane and precipitated in hexane (several times). On silica gel column chromatography, initial elution by hexane/ethyl acetate (2:1) eliminated the remaining organic impurities. The platinum phthalocyanine was then eluted by tetrahydrofuran.

*4.3.3.1. Phthalocyaninato platinum (**1-Pt**).* Obtained following the above procedure, from **13** (1.73 mmol/250 mg). Yield 32% (98 mg).

*4.3.3.2. 2,9(10),16(17),23(24)-Tetra((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phthalocyaninato platinum (**2-Pt**).* Obtained following the above procedure, from **10** (3.64 mmol, 1 g). Yield 35% (392 mg). ^{1}H NMR ($CDCl_3$): δ, ppm 5.99–6.85 (m, 12H, Ar), 3.48–4.38 (m, 20H, $4CH_2CHCH_2$), 1.51, 1.46 (br m, 24H, $8CH_3$). ^{13}C NMR ($CDCl_3$): δ, ppm 158.55, 135.17, 126.92, 121.29, 115.64, 109.64, 102.32, 73.98, 68.55, 66.90, 26.96, 25.45. MALDI-TOF-MS m/z: calcd 1227.32; found 1228.33 [M+H]. Retention time: 16.78 min. UV–vis, λ_{max} nm ($\log \varepsilon$): $CHCl_3$, 654 (4.84), 605 (4.49); THF 654 (4.77), 602 (4.57); DMF 654 (4.34), 602 (4.40). HRMS (ESI) m/z: calcd for $C_{56}H_{57}N_8O_{12}Pt$: 1228.3738; found: 1228.3700.

*4.3.3.3. 1,8(11),15(18),22(25)-Tetra((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phthalocyaninato platinum (**3-Pt**).* Obtained following the above procedure, from **11** (1.82 mmol, 0.5 g). Yield 10% (55.8 mg). ^{1}H NMR ($CDCl_3$): δ, ppm 6.36–8.45 (m, 12H, Ar), 3.65–5.20 (m, 20H, $4CH_2CHCH_2$), 1.57, 1.68 (br m, 24H, $8CH_3$). ^{13}C NMR ($CDCl_3$): δ, ppm 156.05, 139.33, 129.98, 125.00, 121.61, 117.06, 114.04, 111.34, 110.02, 74.95, 74.21, 67.45, 27.51, 25.98. MALDI-TOF-MS m/z: calcd 1227.32; found 1228.46 [M+H]. Retention time: 17.44 min. UV–vis, λ_{max} nm ($\log \varepsilon$): $CHCl_3$, 675 (5.23), 607 (4.58); THF, 674 (5.27), 608 (4.76); DMF, 676 (4.80). HRMS (ESI) m/z: calcd for $C_{56}H_{57}N_8O_{12}Pt$: 1228.3744; found: 1228.3746.

*4.3.3.4. 2,3,9,10,16,17,23,24-Octa((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phthalocyaninato platinum (**4-Pt**).* Obtained following the above procedure, from **12** (1.98 mmol, 0.8 g). Yield 35% (302 mg). ^{1}H NMR ($CDCl_3$): δ, ppm 7.98 (s, 8H, Ar), 4.29–4.90 (m, 40H, $8CH_2CHCH_2$), 1.62, 1.71 (br m, 48H, $16CH_3$). ^{13}C NMR ($CDCl_3$): δ, ppm 150.61, 138.70, 129.92, 109.83, 106.03, 74.38, 70.44, 67.29, 27.03, 25.68. MALDI-TOF-MS m/z: calcd 1747.62; found 1749.16 [M+2H]. Retention time: 14.59 min. UV–vis, λ_{max} nm ($\log \varepsilon$): $CHCl_3$, 651 (5.09), 589 (4.46); THF, 650 (4.81), 602 (4.55); DMF, 650 (4.30), 601 (4.24). HRMS (ESI) m/z: calcd for $C_{80}H_{97}N_8NaO_{24}Pt$: 1771.6156; found: 1771.6100.

*4.3.3.5. 1,4,8,11,15,18,22,25-Octa((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phthalocyaninato platinum (**5-Pt**).* Obtained following the above procedure, from **9** (0.52 mmol, 0.2 g). Yield 8% (18 mg). ^{1}H NMR ($CDCl_3$): δ, ppm 7.71 (s, 8H, Ar), 4.20–5.08 (m, 40H, $8CH_2CHCH_2$), 1.41, 1.47 (br m, 48H, $16CH_3$). ^{13}C NMR ($CDCl_3$): δ, ppm 152.09, 140.58, 127.24, 120.62, 109.59, 74.52, 73.68, 67.21, 27.00, 25.42. MALDI-TOF-MS m/z: calcd 1747.62; found 1748.93 [M+H]. Retention time: 31.35 min. UV–vis, λ_{max} nm ($\log \varepsilon$): $CHCl_3$, 705 (5.11); THF 706 (5.11); DMF, 711 (4.89). HRMS (ESI) m/z: calcd for $C_{80}H_{97}N_8O_{24}Pt$: 1748.6258; found: 1748.6321.

4.4. Photophysical and photochemical parameters

4.4.1. Fluorescence quantum yields and lifetimes. Fluorescence quantum yields (Φ_F) were determined by the comparative method (Eq. 1).[50,51]

$$\Phi_F = \Phi_F(Std)\frac{F \cdot A_{Std} \cdot \eta^2}{F \cdot A_{Std} \cdot \eta_{Std}^2} \tag{1}$$

where F and F_{Std} are, respectively, the areas under the fluorescence curves of the samples (**2-Zn** to **5-Zn** and **2-Pt** to **5-Pt**) and the standard. A and A_{Std} are the respective absorbances of the sample and of the standard at the excitation wavelengths. η and η_{Std} are the refractive indices of solvents used, respectively, for the sample and the standard. Compound **1-Zn** in DMSO (Φ_F=0.18)[52] was employed as the standard.

Natural radiative lifetimes were (τ_0) were determined using PhotochemCAD Program,[53] which uses the Strickler–Berg equation, and fluorescence lifetimes (τ_F) are given by Eq. 2.

$$\Phi_F = \frac{\tau_F}{\tau_0} \tag{2}$$

Using the τ_F values, rate constants for fluorescence (k_F), intersystem crossing (k_{ISC}), internal conversion (k_{IC}) and photodegradation (k_d) were estimated.

4.4.2. Singlet oxygen quantum yields. Singlet oxygen (Φ_Δ) quantum yield determinations were carried out using the experimental set-up described in literature.[54,55] Typically, a 2 mL portion of the phthalocyanine solutions (absorbance ~1 at the irradiation wavelength) containing the singlet oxygen quencher was irradiated in the Q band region. Φ_Δ values were determined in air using the relative method with 1,3-diphenylisobenzofuran (DPBF) as a singlet oxygen chemical quencher in DMF (Eq. 3):

$$\Phi_\Delta = \Phi_\Delta^{Std}\frac{R\cdot I_{abs}^{Std}}{R^{Std}\cdot I_{abs}} \tag{3}$$

where $\Phi_\Delta^{\mathrm{Std}}$ is the singlet oxygen quantum yield for the standard **1-Zn** ($\Phi_\Delta^{\mathrm{Std}} = 0.56$ in DMF).[56] R and R_{Std} are the DPBF photobleaching rates in presence of the studied phthalocyanines (**2-Zn** to **5-Zn** and **2-Pt** to **5-Pt**) and of the standard, respectively; I_{abs} and $I_{\mathrm{abs}}^{\mathrm{Std}}$ are the rates of light absorption by the samples (**2-Zn** to **5-Zn** and **2-Pt** to **5-Pt**) and the standard, respectively. The concentrations of DPBF in the solutions were calculated using the determined value of log ε=4.36 at 417 nm (DPBF in DMF). The light intensity used for Φ_Δ determinations was found to be 9.27×10^{15} photons $\mathrm{s^{-1}\,cm^{-2}}$. The error in the determination of Φ_Δ was ~10% (determined from several Φ_Δ values).

4.4.3. Photodegradation quantum yields. Photodegradation quantum yields were determined using Eq. 4,

$$\Phi_d = \frac{(C_0 - C_t)\cdot V\cdot N_A}{I_{abs}\cdot S\cdot t} \tag{4}$$

where C_0 and C_{t} are the samples (**2-Zn** to **5-Zn** and **2-Pt** to **5-Pt**) concentrations before and after irradiation, respectively, V is the reaction volume, N_{A} the Avogadro's constant, S the irradiated cell area and t the irradiation time. I_{abs} is the overlap integral of the radiation source light intensity and the absorption of the samples (**2-Zn** to **5-Zn** and **2-Pt** to **5-Pt**). A light intensity of 3.09×10^{16} photons $\mathrm{s^{-1}\,cm^{-2}}$ was employed for Φ_{d} determinations.

4.4.4. Fluorescence quenching by benzoquinone (BQ). Fluorescence quenching experiments on the substituted Zn(II) phthalocyanines (**2-Zn** to **5-Zn**) were carried out by the addition of different concentrations of BQ to a fixed concentration of the complexes, and the concentrations of BQ in the resulting mixtures were 0, 0.008, 0.016, 0.024, 0.032 and 0.040 mol $\mathrm{dm^{-3}}$. The fluorescence spectra of substituted Zn(II) phthalocyanines (**2-Zn** to **5-Zn**) at each BQ concentration were recorded, and the changes in fluorescence intensity related to BQ concentration by the Stern–Volmer (S–V) equation[57] (Eq. 5):

$$\frac{I_0}{I} = 1 + K_{SV}[BQ] \tag{5}$$

where I_0 and I are the fluorescence intensities of fluorophore in the absence and presence of quencher, respectively; [Q] is the concentration of the quencher, and K_{SV} is the Stern–Volmer constant; and is the product of the bimolecular quenching constant (k_{q}) and the fluorescence lifetime τ_{F}, i.e.,

$$K_{SV} = k_q\cdot\tau_F \tag{6}$$

The ratios I_0/I were calculated and plotted against [BQ] according to Eq. 5, and K_{SV} determined from the slope.

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Supplementary data

HLPC profiles, ^{13}C NMR and mass spectra of **2-Pt**, **3-Pt**, **4-Pt** and **5-Pt** are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.02.079.

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