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Authors: Małgorzata Cyza, Arkadiusz Gut, Łukasz Łapok, Jędrzej Solarski, Valeri Knyukshto, Mariusz Kępczyński, Maria Nowakowska



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Dr. Łukasz Łapok

Jagiellonian University, Faculty of Chemistry, Gronostajowa 2, Kraków 30-387, Poland, lapok@chemia.uj.edu.pl phone: 0048-12-686-27-50

For the attention of: Mir Wais Hosseini,

Editor of New Journal of Chemistry,

Please find enclosed the manuscript entitled "lodinated zinc phthalocyanine – the novel visible-light activated photosensitizer for efficient generation of singlet oxygen" by Łapok et al., which is submitted to be considered for publication in your journal.

The manuscript describes the method of preparation of a novel photosensitizer from the class of phthalocyanines. The synthesis is accompanied by an in-depth photophysical characterization with special attention paid to the ability of this new phthalocyanine to generate singlet oxygen. Also, the possibility of excited triplet state formation of this new photosensitizer is investigated by both transient absorption spectroscopy and phosphorescence measurement.

We recently developed an interest in the synthesis of phthalocyanines as useful photosensitizers in photodynamic cancer therapy (PDT). There is a quest for new photosensitizers for PDT with improved properties compared to the photosensitizers that have currently been used in clinical practice.

We believe that this paper and the results presented within will be of interest to chemists who are involved in the synthesis of new photosensitizers and are interested in developing new therapies for cancer treatment.

Respectfully yours,

Dr. Łukasz Łapok

Kraków, 17/11/2017

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Iodinated zinc phthalocyanine – the novel visible-light activated photosensitizer for efficient generation of singlet oxygen

Małgorzata Cyza¹, Arkadiusz Gut¹, Łukasz Łapok¹*, Jędrzej Solarski², Valeri Knyukshto³, Mariusz Kępczyński¹, Maria Nowakowska¹

¹Faculty of Chemistry, Jagiellonian University, Gronostajowa 2, 30-387 Kraków, Poland.
²Institute of Physical Chemistry, Polish Academy of Science, 44/52 Kasprzaka, 01-224 Warsaw, Poland.
³B. I. Stepanov Institute of Physics, National Academy of Science, Independence Avenue 68, 220072, Minsk, Belarus.

*Corresponding author: lapok@chemia.uj.edu.pl, Tel.: +48 12 686 25 31, Fax: +48 12 686 27 50.



Graphical abstract

Highly desirable photophysical and photochemical properties were induced in novel nonaggregating zinc phthalocyanine by iodination of the aromatic rings.

Highlights

- Iodinated zinc phthalocyanine is described with the purpose of applying it as a photosensitizer to eradicate cancerous cells.
- The photosensitizer exhibits absorption band within the so-called "therapeutic window" with a very high molar absorption coefficient of 295 000 [M⁻¹cm⁻¹].
- Iodinated zinc phthalocyanine produces singlet oxygen with an excellent quantum yield of 0.76 via Type II mechanism.
- Iodinate zinc phthalocyanine exhibits moderate stability in the presence of oxygen with quantum yield of photodegradation (Φ_d) equal 4.01 x 10⁻⁴
- Moderate photostability of the dye is advantageous for the PDT to promote rapid breakdown and clearance after treatment.
- The dye is phosphorescent with λ_P 1103 nm and it exhibits excited triplet state lifetime of τ_T 3.3 μ s.

Abstract

Phthalocyanines are promising photosensitizers for photodynamic therapy (PDT). A novel zinc 1,8(11),15(18),22(25)-tetraiodo-3,10(9),17(16),24(23)-tetra-*tert*-butylphthalocyanine has been synthesized and characterized. The synthesis of iodinated phthalocyanine was achieved through templated cyclotetramerization of 6-*tert*-butyl-4-iodo-1,3-diiminoisoindoline around zinc ions (Zn²⁺). A six step route leading to 6-*tert*-butyl-4-iodo-1,3-diiminoisoindoline was proposed. The synthesis started with a regiospecific iodination of 4-*tert*-butyl-o-xylene to 5-*tert*-butyl-2,3-dimethyl-iodobenzene, followed by oxidation of the methyl groups to phthalic acid, conversion of phthalic acid to phthalimide, hydrolysis of phthalimide to phthalamide, conversion of phthalamide to phthalonitrile, followed by conversion of phthalonitrile to a more reactive 6-*tert*-butyl-4-iodo-1,3-diiminoisoindoline. Highly desirable photophysical and photochemical properties were induced in zinc phthalocyanine by iodination of the aromatic rings, while the presence of *tert*-butyl groups rendered the compound non-aggregating in solution. The photosensitizer studied exhibits absorption band within the so-called "therapeutic window", with λ_{max} at 689 nm and very high molar absorption coefficient of 295 000 [M⁻¹cm⁻¹] in DMF. Transient absorption experiment revealed T₁ \rightarrow T_n absorption spanning from ca. 400 nm to ca.

600 nm and allowed determination of the excited triplet state lifetime (τ_T). The estimated τ_T in THF equaled 3.3 µs. The phosphorescence maximum was found to be located at λ_P 1103 nm and the excited triplet state energy (E_T) equaled 1.12 eV in 2-methyltetrahydrofuran at 77 K. The photosensitizer studied is characterized by a high value of singlet oxygen quantum yield (Φ_{Δ}) of ca. 0.76 and the photooxygenation process proceeds via Type II mechanism under the experimental conditions applied. The photodegradation studies revealed that the iodinated phthalocyanine was moderately stable in the presence of oxygen with quantum yield of photodegradation (Φ_d) equaled 4.01 x 10⁻⁴. Moderate photostability of photosensitizer is advantageous from a PDT point of view where rapid breakdown and fast clearance from the patient's system is necessary to avoid prolonged skin photosensitivity following treatment.

Keywords: phthalocyanine, photosensitizer, singlet oxygen, heavy atom effect, PDT, triplet sensitizer,

1. Introduction

Photodynamic therapy (PDT) is a well-established treatment for certain forms of cancer and skin diseases [1]. It is a noninvasive alternative to conventional treatments like surgical tumor resection, chemo- and radiotherapy [2]. Cancerous and other pathologically changed cells are eradicated by the combined action of light, oxygen present in the tissues and intravenously or topically administered dye molecule termed as photosensitizer [3]. Photosensitizers, due to their ability to transfer the energy acquired by absorption of light to molecules of oxygen resulting in the formation of highly cytotoxic reactive oxygen species (ROS), have proven to be useful tools in photodynamic cancer therapy (PDT) [4,5].

For a given molecule in order to be called an efficient photosensitizer the following criteria must be met: (1) possibly high absorption coefficient in the spectral region suitable for PDT; (2) sufficient energy of the triplet state ($E_T \ge 0.985$ eV) to facilitate energy transfer to the triplet state oxygen (ground state oxygen); (3) high quantum yield of triplet state formation ($\Phi_T > 0.4$) accompanied by a long triplet state lifetime ($\tau_T > 1 \mu_s$); (4) reasonable photostability [4,5].

When all these criteria are met high values of the quantum yield of singlet oxygen formation (Φ_{Δ}) and other ROS are observed. Another key factor, often discussed in the literature, is the location of maximum absorption of a photosensitizer [6]. Studies have shown that tissuepenetration depth of light is strongly dependent on the light wavelength and it increases with the increase of the light wavelength. Light characterized by the wavelength shorter than 550 nm is unsuitable for PDT. However, ability of light to penetrate tissue doubles from 550 nm to 650 nm and it doubles further as the wavelength moves to 700 nm. Between 700 nm and 800 nm light penetration further increases of 10%. This observations have some practical implications, viz. in order to treat more deeply seated tumors one needs photosensitizers possessing long-wavelength absorption. The "therapeutic window" for PDT was defined as 600-1100 nm [6]. A great deal of attention has been paid by researchers to develop next generation photosensitizers that would possess ability to absorb light from the visible and near-IR region of the spectrum while maintaining other parameters important for PDT, such as photostability, lack of dark cytotoxicity or high singlet oxygen and other ROS quantum yield.

The first photosensitizer to win approval by regulatory agencies in many countries was Photofrin, a complex mixture of hematoporphyrin oligomers. Although Photofrin is successfully used to treat certain forms of cancer it possesses severe limitations and these include poor absorption in the "therapeutic window", compositional complexity, tendency to be retained by the patient's body and thus to produce a prolonged skin photosensitivity [7]. These limitations have inspired a world-wide research aimed at developing a second-generation photosensitizers. These new photosensitizers usually share a tetrapyrrole, or less often tripyrrole (e.g. Lutrin), framework and belong to the class of porphyrins, chlorins (e.g. Foscan, Purlytin, NPe6), bacteriochlorins (Tookad), porphycenes or phthalocyanines [5,6,7]. Among all aforementioned classes of photosensitizers a considerable attention has been paid over past decades to phthalocyanines; a blue/green dyes closely related to the porphyrins and tetraazaporphyrins [8,9].

Given the indisputable advantages of the phthalocyanine dyes over conventional first generation photosensitizers in terms of range of light absorption, very high absorption coefficient in the "therapeutic window" and photophysical properties, a tremendous effort has

been made by researchers to develop novel PDT drugs based on this class of dyes [10]. Currently, one of the silicon containing phthalocyanine, known as Pc 4, has been approved in several countries (the USA, Japan, the Netherlands and France) as a photosensitizer for photodynamic treatment of certain forms of cancer [5,11,12,13]. Pc 4 was first invented at Case Western Reserve University followed by its clinical trials at University Hospitals Case Medical Center.

At the core of development of the next generation photosensitizers is a thorough understanding of the photophysical and photochemical characteristics of the dye molecule that govern its PDT efficacy [4,7]. We report herein the synthesis, photophysical and photochemical characterization of novel zinc phthalocyanine complex **9** (Scheme 2). Substitution of the peripheral positions of the phthalocyanine, Pc, with four bulky *tert*-butyl groups, through the steric hindrance, protects the Pc organic ligand from aggregation while greatly enhancing its solubility in organic solvents, facilitating purification and spectroscopic characterization. At the same time, replacement of four aromatic H atoms at the positions closer to the organic ligand core with four iodine atoms, leads, through the heavy atom effect, to the formation of a dye with increased singlet oxygen formation capacity [14,15]. The presence of heavy iodine atoms in the Pc molecule reflects on both intersystem crossing quantum yield (Φ_{ISC}) and triplet lifetime (τ_T) in both cases by increasing them [16].

2. Results and discussion

2.1. Synthesis and characterization

The starting point for the synthesis of **9** was the phthalonitrile **7** (Scheme 1). The stepwise synthesis of **7** started with regiospecific electrophilic introduction of iodine substituent into 4-*tert*-butyl-*o*-xylene (**1**) to give 5-*tert*-butyl-2,3-dimethyl-iodobenzene (**2**) in 81 % yield. A protocol described elsewhere was adopted [17]. In the next step the methyl groups in **2** were oxidized to give the corresponding phthalic acid **3**. This was achieved by using potassium permanganate in water/pyridine mixture at 90 °C. After 16 hours reaction time the phthalic acid **3** was obtained in 80 % yield. The IR spectrum of **3** was dominated by a sharp absorption band at 1713 cm⁻¹ (C=O) and a broad absorption band spanning 3300 cm⁻¹ to 2250 cm⁻¹ (OH), while

the ¹H-NMR spectrum revealed a broad signal centered at 13.26 ppm accounting for the two protons of the carboxylic groups.

Initially, it was planned to follow the classical protocol known for the preparation of phthalonitriles, which requires the phthalic acid to be converted into phthalic anhydride. Thus, phthalic acid **3** was reacted with either acetyl chloride or acetic acid anhydride as dehydrating agents to give the corresponding phthalic anhydride 4 in 74 % yield upon crystallization from hexane. Strong bands at 1858 cm⁻¹, 1837 cm⁻¹, 1815 cm⁻¹ and a very strong band at 1776 cm⁻¹ observed in the IR spectrum, along with the disappearance of the previously observed broad absorption band characteristic of the OH group of the carboxylic acid, corroborated unambiguously the formation of cyclic anhydride 4. However, in the course of our experiments we found that the reaction pathway leading to the phthalonitrile 7 could be shorten by omitting the step in which phthalic anhydride intermediate was formed. It was found that simple heating of the phthalic acid in formamide at 180-190°C for 45 minutes allowed obtaining of the phthalimide 5 in 95 % yield. The reaction was straightforward and afforded a high purity product, meaning, no chromatographic separation was needed. A strong absorption in the IR spectrum at 3207 cm⁻¹ indicated the presence of an N-H stretching vibration, while two strong absorption bands at 1769 cm⁻¹ and 1713 cm⁻¹ were assigned to C=O stretching vibrations. In addition, in the ¹H NMR spectrum a broad peak centered at 7.92 ppm was observed for the N-H hydrogen of phthalimide 5. The classical protocol used to obtained phthalonitriles requires the phthalimide to be transformed to phthalamide which is then converted to phthalonitrile. It was found that a strict control of the temperature and more importantly reaction time of the ammonolysis was crucial for the reaction yield of the phthalonitrile 7. A prolonged reaction time favours gradual hydrolysis of the phthalamide 6 into ammonium carboxylate (diammonium phthalate or/and ammonium 1-(aminocarbonyl)benzoate or/and 2-(aminocarbonyl)benzoate). This in turn significantly lowers overall reaction yield of the phthalonitrile **7**. To provide the key precursor 7 in the highest possible yield we studied the scope and limitations of the phthalamide 6 formation. Thus, when the ammonolysis of phthalimide was carried out at 80 °C for 1 h and 45 min it was found that the phthalonitrile 7 was obtained in a 24 % yield. Lowering of the reaction time to 1 h and 15 min allowed the phthalonitrile 7 be formed in 28 % yield.

Further lowering of the reaction time of the ammonolysis caused drop of the reaction yield of the phthalonitrile 7. Treatment of phthalamide 6 with a phosphorus oxychloride POCl₃ in anhydrous pyridine afforded 5-tert-butyl-3-iodophthalonitrile (7) in 28 % yield (reaction yield calculated based on the phthalimide 5 used). The 1 H NMR spectrum confirmed unambiguously the assigned structure of 7. In the ¹H NMR spectrum, two doublets were observed in the aromatic region of the spectrum with equal intensities and coupling constants of ca. 1.80 Hz. The measured coupling constant clearly indicated that both aromatic protons were located in meta positions, thereby the 1,2,3,5-substitution pattern was unambiguously corroborated. The integration of the proton signals observed for the *tert*-butyl group and aromatic ring gave, as expected, a 9:2 ratio. The IR spectrum of the product showed a sharp peak at 2231 cm⁻¹ clearly indicating the presence of the CN groups (aromatic nitriles). Finally, we tested the possibility of transforming phthalonitrile 7 into its more reactive form, viz. 1,3-diiminoisoindoline 8. This intermediate is widely used whenever phthalocyanines with less reactive metals or non-metals are to be obtained. Treating of a methanolic solution of 7 with an ammonia gas in the presence of sodium methoxide at room temperature afforded 1,3-diiminoisoindoline 8 with a quantitative yield. The ESI-MS clearly confirmed that 8 was formed as two peaks were discernible in the mass spectrum, viz. m/z 328 [M+H]⁺ and m/z 350 [M+Na]⁺.

An attempt to use phthalic acid **3**, phthalic anhydride **4**, phthalimide **5** or phthalamide **6** with urea as a nitrogen source and ammonium molybdate as a catalyst did not allow obtaining of phthalocyanine **9**. Thus, only phthalonitrile **7** and 1,3-diiminoisoindoline **8** proved to be reactive enough to form zinc phthalocyanine complex **9**. The rearrangement of 1,3-diiminoisoindoline **8** into phthalocyanine **9** was performed in boiling 2-dimethylaminoethanol in the presence of zinc acetate (Scheme 2). Phthalocyanine **9**, after chromatographic purification, was obtained in 42 % yield. Due to the symmetry of the phthalonitrile **7**, phthalocyanine **9** is formed as a mixture of four regioisomers with C_{4h}, C_{2v}, C_s and D_{2h} symmetry, respectively. Phthalocyanine **9** is a deep blue/green compound that thanks to the *tert*-butyl groups, possesses an excellent solubility in nearly every organic solvent. The formation of phthalocyanine **9** was unambiguously corroborated by mass spectrometry, IR and ¹H NMR spectroscopy (see Supporting Information).

MALDI-TOF analysis revealed a molecular ion peak at m/z 1304.936 [M+H]⁺ with isotope pattern matching the calculated isotope pattern. In the ¹H NMR spectrum, a set of peaks was observed in the aromatic region of the spectrum, viz. between 8 ppm and 9.5 ppm, due to non-equivalent aromatic protons and another set of peaks between 1.6 ppm and 1.9 ppm due to nonequivalent aliphatic protons of the different regioisomers of **9**. The integration of the signals observed for the *tert*-butyl group and aromatic ring gave, as expected, a 9:2 ratio.

2.2. Optical properties

The normalized UV-Vis absorption and emission spectra of **9** in DMF are displayed in Figure 1 and the data are collected in Table 1. The UV-Vis absorption spectrum of **9** shows typical for non-aggregating phthalocyanines features, viz. very intense, sharp Q(0,0) band with λ_{max} 689 nm, accompanied by a markedly weaker B band with λ_{max} 348 nm. The compound presented in this paper possess a structural feature, viz. presence of bulky *tert*-butyl substituents, that renders this phthalocyanine non-aggregating in solution. Consequently, phthalocyanine **9** obeys the Lambert-Beer law in a wide range of concentrations. Compound **9** is a very good absorber of light from the so-called "therapeutic window" with high molar absorption coefficient (ε) of 295 000 [M⁻¹cm⁻¹] in DMF. This value is slightly higher compared to that of the unsubstituted ZnPc, viz. 235 000 [M⁻¹cm⁻¹] at 670 nm in DMF [18]. Phthalocyanine **9** is emissive at room temperature and the fluorescence maximum was found at λ_f 696 nm. However, the heavy atom effect exerted by the iodine atoms present in the structure of **9** lowers the fluorescence quantum yield (Φ_f) to merely the value of 0.015 [19]. A mono-exponential fluorescence decay was found for **9** with time constant of 0.42 ns in DMF. Based on the fluorescence spectrum the excited singlet state (E_s) energy for **9** was calculated: $E_s = 1.78$ eV.

2.3. Excited triplet state decay dynamics and phosphorescence

We have investigated the excited triplet state decay dynamic of **9** by nanosecond time-resolved transient absorption spectra. The transient absorption spectra, transient decays and triplet state lifetimes are presented in Figure 2 and Table 1. The transient absorption spectrum of **9** recorded in deaerated THF, feature broad positive triplet-triplet absorption spanning from ca. 400 nm to

ca. 600 nm. The decay of the transient $T_1 \rightarrow T_n$ absorption and the recovery of the absorption $S_0 \rightarrow S_1$ in the singlet state (bleaching) were used to calculate triplet state lifetimes (τ_T) of **9**. Both methods gave similar values of triplet lifetimes. A mono-exponential decays of the transient absorption and recovery of the ground state absorption were observed for **9**. Phthalocyanine **9** was found to have the triplet lifetime (τ_T) of **3**.3 ± 0.005 µs.

Phosphorescence of phthalocyanines, due to the hurdles in detecting such signals and the spinforbidden nature of such transition, is rarely reported [20,21]. Phthalocyanines for which phosphorescence spectra and triplet state energies (E_7) are reported are either palladium or platinum complexes [22-25]. The normalized phosphorescence spectrum of **9** is displayed in Figure 2. Phthalocyanine **9** exhibit strong NIR emission in oxygen-free, glass forming 2methyltetrahydrofuran at 77 K. The phosphorescence maximum was found to be located at λ_P 1103 nm. The value of the lowest triplet excited state (E_7) was calculated directly from the phosphorescence spectrum. Phthalocyanine **9** was found to have its lowest triplet state energy (E_7) at 1.12 eV.

2.4. Singlet oxygen generation

One of the most important features of a given photosensitizer, whether it be for photocatalytic or biomedical applications, is its ability to form singlet oxygen (${}^{1}O_{2}$) and other reactive forms of oxygen (viz. OH[•], HO₂[•], O₂^{•-}). Singlet oxygen is formed via energy transfer between the photosensitizer in the excited triplet state (${}^{3}Sens^{*}$) and the molecular oxygen (${}^{3}O_{2}$) itself in the triplet ground state (Type II mechanism). Formation of superoxide radical anions (O₂^{•-}), hydroxyl radicals (OH[•]), hydroperoxyl radicals (HO₂[•]) and alkoxy radicals (RO[•]) is the result of an electron transfer (Type III mechanism). The measure of the efficacy of a given photosensitizer is known as singlet oxygen quantum yield (ϕ_{Δ}). The singlet oxygen quantum yield (ϕ_{Δ}) of phthalocyanine **9** was measured in DMF and we employed two methods to find the value of ϕ_{Δ} . First method rely on the chemical reaction between singlet oxygen and/or other reactive forms of oxygen with the acceptor molecule, viz. 1,3-diphenylisobenzofuan (DPBF). The decay of the absorption band at λ_{max} 417 nm of the acceptor molecule is monitored upon irradiation with light absorbed by

the investigated compound and by the standard molecule with known value of singlet oxygen quantum yield. Second method is based on the observation of the phosphorescence of singlet oxygen (${}^{1}O_{2}$) at λ_{P} 1270 nm. The intensity of the singlet oxygen emission at 1270 nm as a function of energy of the exciting laser pulses is observed and compared for the investigated compound and for the standard molecule with known value of ϕ_{Δ} . This method allows exclusive detection of singlet oxygen, while the chemical quencher, that is DPBF, reacts indistinguishable with all reactive oxygen species. High values of singlet oxygen quantum yield were found for compound **9**. The method that utilizes the chemical quencher gave the value of ϕ_{Δ} 0.76 ± 0.02, while the method that is based on the singlet oxygen luminescence gave the value of ϕ_{Δ} 0.74 ± 0.03. Both methods gave similar values of singlet oxygen quantum yield (ϕ_{Δ}), meaning that phthalocyanine **9** sensitizes formation of singlet oxygen via energy transfer and that no radicals were formed (Type II process) [4].

We indicated in the Introduction of this paper that a good photosensitizer should possess sufficient energy of the excited triplet state, viz. $E_T \ge 0.985$ eV, triplet state lifetimes (τ_T) longer than 1 µs and high absorption coefficient in the spectral region of the excitation [4]. The phosphorescence measurements revealed that phthalocyanine **9** fulfilled the first requirement set for an efficient photosensitizer; the E_T equals 112 kJ/mol (1.12 eV). The energy separation between phthalocyanine **9** excited triplet state and singlet oxygen ($^{1}\Delta_g$) is roughly 0.14 eV (13.06 kJ/mol). Also, compound **9** fulfills second requirement, viz. its triplet lifetime (τ_T) equals 3.3 µs, facilitating the energy transfer between the photosensitizer (3 Sens^{*}) and ground state oxygen ($^{3}O_2$). Moreover, phthalocyanine **9** is a very good visible light absorber with high molar absorption coefficient of 295 000 [M⁻¹cm⁻¹]. Combination of these photophysical parameters resulted in high singlet oxygen quantum yield (ϕ_Δ) measured for compound **9**.

2.5. Photostability

We studied the light driven degradation processes of photosensitizer **9** in an effort to understand its potential in biomedical applications. In general, this process can proceed either via phototransformation or clean photodegradation. In the case of a phototransformation a

decrease of the intensity of the absorption spectrum of the photosensitizer is observed with concomitant evolution of new absorption bands, while in the case of photodegradation a gradual depletion of the spectrum is discernible over time without formation of new absorption bands in the UV-Vis spectrum [26]. Figure 3, left panel, presents the change of the intensity of the absorption spectrum of phthalocyanine **9** over time in an oxygen saturated DMF solution. Prolonged exposure of the DMF solution of **9** to the light resulted in gradual decrease of the absorption spectrum without appearance of new absorption bands, meaning that the photobleaching of **9** proceeds via clean photodegradation and not via phototransformation (both in an oxygen and oxygen-free atmosphere). This observation is in agreement with the results presented by other researchers indicating that photobleaching of phthalocyanines tends to proceed via clean photodegradation without phototransformation [27-29].

Monitoring the decay of the Q band at λ 689 nm in DMF over time allowed to study the kinetics of the photodegradation of **9** and establish the exact values of both the photodegradation quantum yield (Φ_d) and photobleaching constant (K_d) in the presence of oxygen and in an oxygen-free atmosphere (Figure 3, right panel). The photodegradation of **9** proved to be a two stage process with the initial step proceeding faster followed by a second slower stage. Firstorder kinetics were fitted to both stages and the values of K_d and Φ_d were summarized in Table 2. Moreover, we noticed that the presence of an oxygen accelerates the photodegradation process of **9**, meaning that singlet oxygen ($^{1}O_{2}$) and other ROS participate in the decomposition of this photosensitizer [30].

In general compounds having quantum yields of photodegradation (Φ_d) higher than 10⁻³ are considered to be unstable. Phthalocyanine **9** is characterized by a Φ_d equal 4.01 x 10⁻⁴, thus it could be regarded as a moderately stable photosensitizer. Moderate photostability of **9** can be advantageous from a PDT point of view where rapid breakdown and fast clearance from the patient's system is necessary to avoid prolonged skin photosensitivity following treatment. Photosensitizer used for PDT with high photostability (e.g. Photofrin) are known to be problematic in clinical application as they may cause skin photosensitivity that last up to several weeks [31-33].

3. Experimental

4.1. Materials and methods

¹H-NMR and ¹³C-NMR spectra were recorded on Bruker Avance II 300 and 75 MHz, respectively, in deuterated solvents. Electrospray mass spectrometer microTOF II (Bruker Daltonics, Bremen/Germany) with a resolution of > 16 500 FWHM and a mass accuracy of < 2 ppm was used to obtain the high resolution mass spectra. FT-IR spectra were recorded using a Bruker Equinox 55. UV-Vis absorption spectra at 298 K were measured using a Hewlett-Packard 8452A diode-array spectrophotometer equipped with a HP 89090A Peltier temperature control accessory. Steady-state fluorescence spectra of the samples were recorded on an SLM-AMINCO 8100 Instruments spectrofluorimeter at room temperature. Emission spectra were corrected for the wavelength dependency of the detector response by using an internal correction function provided by the manufacturer. For the elemental micro analysis the CHNS Vario Micro Cube analyzer combined with the electronic microbalance was used. Reaction progress was controlled using TLC on silica gel (Supelco). All reagents were obtained from commercial sources (Sigma Aldrich and TCI) and solvents were used without prior purification, unless stated otherwise. Pyridine was dried with NaOH and distilled under inert gas atmosphere.

4.2. Synthesis

4-tert-butyl-o-xylene (1): see references [34,35]. Yield: 85%.

5-tert-butyl-2,3-dimethyl-iodobenzene (2): see reference [36]. Compound **1** (25 g; 154.2 mmol), periodic acid (7.13 g; 31.28 mmol) and iodine (15.69 g; 61.82 mmol) were added to a mixture of glacial acetic acid (79 mL), concentrated sulphuric acid (2.8 mL) and water (14 mL). The reaction mixture was stirred at 60-65 °C. The iodine was consumed after 6 hours and a heavy oil collected at the bottom of the flask. Water (200 mL) and sodium thiosulfate (1 g; 6.32 mmol) were added to the reaction mixture. The product was extracted with diethyl ether (3 x 80 mL), and the ethereal solution was washed with water (3 x 100 mL). Ether was removed on a rotary evaporator. The crude product was finally purified by distillation under reduced pressure (92 °C, 10^{-2} mbar). Everything that distilled off before the main fraction was discarded. The main

fraction was collected and identified as product. Yield: 36 g (81%), colourless oily liquid. ¹H NMR (300 MHz, CDCl₃) δ [ppm]: 1.28 (s, 9H, *t*-Bu), 2.35 (s, 3H, CH₃), 2.38 (s, 3H, CH₃) 7.13 (d, 1H, ⁴J_{meta} 1.9 Hz), 7.68 (d, 1H, ⁴J_{meta} 2.0 Hz). ¹³C NMR (75 MHz, CDCl₃) δ [ppm]: 22.39 (CH₃), 24.85 (CH₃), 31.40 (*t*-Bu), 34.24 (*t*-Bu), 102.97, 127.38, 134.27, 136.57, 136.99, 150.61. **GC-MS** (electron impact): *m/z* 288 [M]⁺, 273 [M-CH₃]⁺. **FT-IR** (film): v = 3020, 2964, 2907, 2866, 1598, 1543, 1478, 1465, 1442, 1395, 1362, 1276, 1250, 1222, 1202, 1161, 999, 922, 869, 817, 785, 705, 686, 614 cm⁻¹.

5-tert-butyl-3-iodophthalic acid (3): $KMnO_4$ (51.93 g; 328.61 mmol) was added in 4 portions to a solution of 2 (20 g; 69.41 mmol) in pyridine (200 mL) and water (25 mL). Reaction mixture was kept at 90 °C for 16 h. A water (100 mL) solution of NaOH (8 g) was added to the reaction mixture and stirred. Reaction mixture was diluted with ethanol (80 mL) and the formed MnO₂ was filtered off and washed with ethanol. On a rotary evaporator pyridine and ethanol were removed. The remaining water solution was concentrated to around 50 mL and acidified with concentrated HCl (until pH 1-2) and left for 0.5 h under vigorous stirring to well crush the solidifying phthalic acid 3. The formed precipitate was filtered off (G-4) and washed thoroughly with water until neutral pH. The product was washed out with acetone leaving behind the rest of MnO₂. Acetone was removed and the product was dried. Yield: 19.23 g (80%) of white powder. ¹H NMR (300 MHz, d₆-DMSO) δ [ppm]: 1.29 (s, 9H, *t*-Bu), 7.89 (d, 1H, ⁴J_{meta} 1.89 Hz), 8.03 (d, 1H, ⁴J_{meta} 1.89 Hz), 13.26 (bs, 2H, COOH). ¹³C NMR (75 MHz, d₆-DMSO) δ [ppm]: 30.56 (t-Bu), 34.36 (t-Bu), 94.13, 126.04, 129.48, 139.47, 139.57, 153.00, 165.88 (COOH), 169.35 (COOH). **ESI-MS** (positive mode): *m*/*z* = 333 [M-CH₃]⁺, 349 [M+H]⁺, 371 [M+Na]⁺. **ESI-MS** (negative mode): *m*/*z* = 348 [M]⁻. **FT-IR** (KBr): v = 3300-2250 broad vs (OH), 2966 vs, 2905 vs, 2870 vs, 2660 s, 2564 s, 1779 m, 1713 (C=O) vs, 1696 (C=O) vs, 1594 s, 1543 m, 1475 s, 1462 s, 1424 s, 1388 s, 1365 s, 1296 vs, 1276 vs, 1257 vs, 1165 m, 1138 m, 924 s, 888 s, 806 m, 795 s, 698 vs cm⁻¹. Anal. Calcd for C₁₂H₁₃O₄I: C, 41.40; H, 3.76. Found: C, 42.63; H, 3.96.

5-tert-butyl-3-iodophthalic anhydride (**4**): Phthalic acid **3** (2 g; 5.75 mmol) was refluxed with acetyl chloride (4 mL; 4.42 g; 56.25 mmol) for 1 h. The unreacted acetyl chloride was removed on a rotary evaporator under vacuum. Crude product was dissolved in hot hexane and crystallized to give pure product. Yield: 1.39 g (74%), white solid. Alternatively, acetic acid

anhydride can be used to obtain **4**. It requires heating of the starting material **3** (2 g, 5.75 mmol) with acetic acid anhydride (6 mL, 63.53 mmol) at 100 °C for 18 h. The crude product, after removal of the unreacted acetic acid anhydride, was purified by crystallization from hexane. Yield: 1.39 g (74 %), white solid. **ESI-MS** (positive mode): m/z = 331 [M+H]⁺. **FT-IR** (KBr): v = 3421 w, 3078 w, 2965 s, 2928 s, 2872 s, 1858 (C=O) s, 1837 (C=O) s, 1815 (C=O) m, 1776 (C=O) vs, 1605 s, 1573 m, 1478 m, 1456 m, 1399 m, 1367 m, 1328 m, 1276 m, 1243 s, 1232 s, 1148 m, 1130 m, 924 s, 898 s, 824 s, 740 s, 717 s, 683 s, 655 m cm⁻¹.

5-tert-butyl-3-iodophthalimide (5): Method I: Phthalic acid 3 (15.73 g, 45.18 mmol) was heated in formamide (7.5 mL, 188.8 mmol) at 180 - 190 °C for 45 min. Upon cooling to room temperature the product solidified. Reaction mixture was vigorously stirred while water was added dropwise until reaction mixture was diluted to the volume of 100 mL. White precipitate was filtered off, washed thoroughly with water and dried in vacuum to give the product. Yield: 14.13 g (95 %). No further purification was necessary as the compound was obtained with a very good purity as judged by TLC (acetone/hexane, 2:3). However, in case the purification is needed, a column chromatography can be used to purify the material (silica gel; acetone/hexane, 1:4 v/v). Yield: 76 %. Method II: Phthalic anhydride 4 (0.5 g; 1.51 mmol) was mixed with urea (2 g; 33.32 mmol) and placed in a 50 mL round-bottom flask. Reaction mixture was immersed in a preheated oil bath. The melt was kept at 160 °C for 15 min. After that time starting material was no longer present in the reaction mixture as judged by TLC (toluene/hexane, 1:2 v/v). The reaction mixture was cooled followed by a dropwise addition of water (50 mL) and vigorous stirring for 30 minutes to crush the solidified product. The precipitate formed was filtered and washed with copious volume of water to remove unreacted urea. The product was dried under vacuum and crystallized from CHCl₃. Yield: 0.44 g (89 %), white solid. ¹H NMR (300 MHz, CDCl₃) δ [ppm]: 1.37 (s, 9H, *t*-Bu), 7.88 (d, 1H, ⁴J_{meta} 1.6 Hz), 7.92 (s, 1H, NH), 8.11 (d, 1H, ⁴J_{meta} 1.6 Hz). ¹³CNMR (75 MHz, CDCl₃) δ [ppm]: 31.15 (*t*-Bu), 35.82 (*t*-Bu), 89.08, 121.10, 134.55, 142.84, 160.27, 161.88, 166.32 (CO), 166.67 (CO). **ESI-MS** (negative mode): *m/z* = 329 [M]⁻. **FT-IR** (KBr): v = 3207 (N-H) s, 3061 m, 2962 vs, 2872 s, 1769 (C=O) s, 1731 (C=O) s, 1713 (C=O) s, 1607 m, 1566 m, 1479 m, 1457 m, 1404 m, 1368 m, 1339 s, 1301 s, 1266 m, 1235 m, 1169 m, 1093 s, 1043 s,

725 s, 699 s, 684 s, 660 s, 638 m cm⁻¹. **Anal. Calcd** for C₁₂H₁₂O₂NI: C, 43.79; H, 3.67; N, 4.26. Found: C, 44.39; H, 3.78; N, 4.09.

5-tert-butyl-3-iodophthalamide (6): Method I: Phthalimide 5 (0.8 g; 2.43 mmol) was dissolved in methanol (150 mL). Ammonia gas was passed through the solution at 0 $^{\circ}$ C for 2 hours. No amide 6 was formed under this reaction conditions. *Method II:* Phthalimide 5 (250 mg; 0.76 mmol) was dissolved in methanol (50 mL) followed by addition of 25% ammonia solution (30 mL). The formed mixture was stirred for 1 hour and 15 minutes at 80 °C. The course of the reaction was followed by TLC (acetone/hexane, 1:4). The reaction was stopped immediately after the unreacted phthalimide 5 was consumed. Caution: prolonged reaction time should be avoided as it promotes hydrolysis of the amide to the ammonium carboxylic salt (COONH₄). Water and methanol were removed on a rotary evaporator under vacuum at 60 °C. The white solid obtained, despite being contaminated with a major admixture of ammonium carboxylic salt, was used for the next reaction without additional purification. ¹H NMR (300 MHz, d_6 -DMSO) δ [ppm]: 1.25, 1.26 (s, t-Bu, salt and amide), 7.26 (br s, NH₂), 7.63 (d, ⁴J_{meta} 2.0 Hz), 7.76 (d, ⁴J_{meta} 2.0 Hz), 7.79 (d, ⁴J_{meta} 2.0 Hz), 7.80 (d, ⁴J_{meta} 2.0 Hz), 8.35 (br s, NH₂). **ESI-MS** (negative mode): $m/z = 330 [M-NH_2]^{-}$. FT-IR (KBr): $v = 3394 \text{ cm}^{-1}$ (N-H) vs, 3203 (N-H) vs, 2960 (t-Bu) vs, 2867 s, 1665 (C=O) vs, 1611 vs, 1569 (N-H) vs, 1458 vs, 1367 vs, 1351 vs, 1264 s, 1068 w, 880 m, 817 m, 911 m cm⁻¹.

5-*tert*-butyl-3-iodophthalonitrile (7): Anhydrous pyridine (10 mL) was added to the phthalamide **6** (obtained from 250 mg of phthalimide **5**) followed by injecting of POCl₃ (0.25 mL; 2.68 mmol). The reaction mixture was stirred under an inert gas atmosphere for 1 h at 0 °C, and then for 1 h at room temperature. The reaction mixture was quenched by pouring it onto crushed ice and stirred for 10 min, followed by extraction with CH_2Cl_2 (3 x 30 mL). The organic phase was washed with 5 % HCl solution (2 x 50 mL) to remove the pyridine and then with water until neutral pH was obtained. After solvent evaporation the residue was purified by column chromatography (silica gel; toluene). The first colorless fraction was collected and identified as the product. Yield: 66 mg, (28%). ¹H NMR (300 MHz, CDCl₃) δ [ppm]: 1.34 (s, 9H, *t*-Bu), 7.77 (d, 1H, ⁴J_{meta} 1.80 Hz), 8.13 (d, 1H, ⁴J_{meta} 1.80 Hz). ¹³C NMR (75 MHz, CDCl₃) δ [ppm]: 30.74 (*t*-Bu), 35.75 (*t*-Bu), 100.00, 115.22 (CN), 116.70 (CN), 117.64, 120.59, 130.47, 141.01, 158.52. **ESI-MS**:

m/*z* = 311 [M+H]⁺, 333 [M+Na]⁺. **MALDI-TOF-MS**: *m*/*z* = 333.075 [M+Na]⁺. **FT-IR** (KBr): *v* = 3422, 3073 (Ar-H), 2971 (*t*-Bu), 2873, 2231 (CN), 1581, 1532, 1478, 1467, 1395, 1367, 1275, 1242, 1210, 1158, 1086, 887, 818, 778, 724 cm⁻¹. **Anal. Calcd** for C₁₂H₁₁N₂I: C, 46.40; H, 3.50; N, 9.00. Found: C, 48.58; H, 3.87; N, 8.52.

6-tert-butyl-4-iodo-1,3-diiminoisoindoline (8): Phthalonitrile **7** (200 mg; 0.645 mmol) was dissolved in methanol (9 mL). A catalytic amount of sodium methoxide MeONa was added to the reaction mixture. A stream of ammonia gas was passed through the solution until saturation. The ammonia saturated solution was then left to stand for two days. After this time the solution was saturated again with a stream of ammonia gas and left to stand for additional two days. Reaction progress was followed by TLC (silica gel;, toluene). After the substrate was completely consumed solvent was removed under reduced pressure at 55 °C. The substrate was quantitatively converted into 1,3-diiminoisoindoline and could be used as a precursor for phthalocyanine without prior purification. **ESI-MS**: m/z = 328 [M+H]⁺, 350 [M+Na]⁺, 655 [2M+H]⁺, 677 [2M+Na]⁺.

Zinc 1,8(11),15(18),22(25)-tetraiodo-3,10(9),17(16),24(23)-tetra-*tert*-butylphthalocyanine (9) (a mixture of four regioisomers): Diiminoisoindoline 8 (obtained from 200 mg of phthalonitrile 7; 0.645 mmol) and Zn(CH₃COO)₂ ·2H₂O (42 mg; 0,192 mmol) were reacted in DMAE (6 mL). Reaction mixture was brought slowly to boiling and then it was kept refluxing for 24 hrs. Upon heating formation of green product was observed. Reaction mixture was cooled down, water was added dropwise under stirring and the precipitate formed was filtered off. The solid residue was washed with a mixture of acetonitrile and water (7:3) in order to remove yellow impurities. Finally, product was purified by column chromatography on silica gel. Toluene with 1 % of acetone (v/v) was used as an eluent. The green fraction was collected. Upon solvent removal 88 mg (42 %) of dark-green product was obtained. **FT-IR** (KBr): v = 2954 (*t*-Bu), 2901, 2864, 1602 (C_{Ar}-H), 1543, 1474 (C_{Ar}-H), 1360, 1349, 1330, 1302, 1259, 1201, 1099, 1048, 1022, 929, 874, 831, 768, 744, 667 cm⁻¹. **UV/Vis** (DMF): λ = 689 (ε = 295 200 [M⁻¹ cm⁻¹]), 346 nm. **MALDI-TOF MS**: *m/z* 1304.924 (calculated); 1304.936 [M+H]⁺ (found). ¹H **NMR** (300 MHz, CDCl₃) δ [ppm]: 1.65 – 1.84 (m, 9H, *t*-Bu), 8.22 – 9.35 (m, 2H). Anal. Calcd for C₄₈H₄₄N₈I₄Zn 1305.92 g/mol: C, 44.15; H, 3.4; N, 8.58. Found: C, 45.15; H, 3.77; N, 8.72.

4.3. Measurements

Determination of fluorescence quantum yield (\Phi_F): The fluorescence quantum yield (Φ_F) of phthalocyanine ZnPc(*t*-Bu)₄I₄ **9** in DMF was determined using the comparative method according to the equation

$$\Phi_{\rm F} = \Phi_{\rm F}^{\rm Std} \, \frac{F \, A_{\rm Std} \, n^2}{F_{\rm Std} \, A \, n_{\rm Std}^2},$$

where *F* and *F*_{Std} are the areas under the fluorescence emission curves of the sample and the standard, *A* and *A*_{std} are the absorbance of the sample and the standard and *n* and *n*_{std} are the refractive indices of the solvent used for the sample and the standard, respectively [37]. Unsubstituted zinc phthalocyanine ZnPc ($\Phi_F^{Std} = 0.2$ in DMSO) was employed as the standard [38]. The absorbance of the solutions at the excitation wavelength was in the range of 0.02 - 0.04.

Fluorescence lifetimes: Time-resolved fluorescence decays in the nanosecond range were obtained using a modular time-correlated single-photon-counting (TCSPC) system (HORIBA Jobin Yvon Inc.), consisting of a Nano LED pulsed diode (340 nm, <1.2 ns pulse), a picosecond photon counting detector (HORIBA Jobin Yvon Inc.), and Fluoro Hub TCSPC module. Fluorescence decays were analyzed using Data Station v2.3 software.

Transient triplet-triplet absorption spectra and triplet state lifetimes: A home-built laser flash photolysis setup has been used. The pump pulses of 25 ns duration and energy of 5 mJ are provided by a home-build dye laser, pumped by excimer laser (Labda Physik LPX100) working at 1-10 Hz. The continuous light of laser-driven Xe lamp (Energetiq EQ-99-Plus-EU) and pump pulses of Xe flash lamp (PerkinElmer 1100 Series) have been involved for kinetic and spectral data acquisitions, respectively. The setup is equipped with the two-channel CCD spectrometer (Avantes AvaSpec-ULS2048-2-USB2) for spectral measurements and allows registration of time-resolved spectra from 1 ms to seconds. The acquisition of kinetic data has been performed by home-built monochromator equipped with fast photomultiplier tube (Hamamatsu H6780) and

oscilloscope (Tektronix TDS 3032). Prior to the measurement all sample solutions were deoxygenated using the freeze-pump-thaw technique (five cycles). Samples were irradiated in 1 cm path-length quartz cell. To ensure accuracy of the obtained data upon collecting the first set of transient triplet-triplet absorption spectra and triplet state lifetimes the solutions were diluted down to half of the initial concentration and all measurements were repeated.

Phosphorescence spectra: Corrected phosphorescence spectra, as well as phosphorescence excitation spectra were recorded by a two-disk phosphoroscope driven by two synchronous motors. The operating spectral region was from 200 nm to 1100 nm, and the exciting light sources were xenon and tungsten lamps or several different photodiodes (Thorlabs, Inc.). The experimental set-up was equipped with a thermocooling system for the photomultiplier (FEU-83 or FEU-100). The reproducibility of the system is 5%. The apparatus has been described in details elsewhere [39].

Determination of singlet oxygen quantum yield (Φ_{Δ} **):** *Chemical method.* The quantum yield of singlet oxygen (Φ_{Δ}) of phthalocyanine **9** in DMF solution was measured indirectly according to the procedure described elsewhere [40-42]. DPBF was applied as acceptors of singlet oxygen and zinc phthalocyanine (Φ_{Δ} = 0.56 in DMF) was used as a reference [43,44]. Typically, 2 mL of the DMF solution containing the sensitizer (2.8×10^{-7} M), and the acceptor (5×10^{-5} M) was introduced into the quartz cuvette and irradiated using an Osram[®] xenon lamp (XBO 75W/2). A 630 nm glass cut-off filter was used to filter the ultraviolet radiation. The value of Φ_{Δ} was measured in the air and the following equation was employed for the calculations:

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

where $\Phi_{\Delta}^{\text{Std}}$ is the quantum yield of singlet oxygen formation for the standard, *R* and *R*^{Std} are the DPBF photobleaching rates in the presence of the phthalocyanine **9** and in the presence of the reference molecule, viz. zinc phthalocyanine, respectively. I_{abs} and $I_{\text{abs}}^{\text{Std}}$ are the rates of light

absorption by the measured sample and the respective standard. The mean intensity of the light absorbed by the samples (I_{abs} , I_{abs}^{std}) was calculated according to the following equation:

$$I_{\rm abs} = \int_{\lambda} T(\lambda) I(\lambda) \left(1 - 10^{-A(\lambda)} \right) d\lambda$$

where $T(\lambda)$ is the transmittance of the filter, $A(\lambda)$ is the absorbance of the sensitizer and $I(\lambda)$ is the light intensity emitted by the lamp. The photosensitizer absorbance was maintained at about 0.1. Each experiment was repeated at least four times.

Direct method. The photogeneration of singlet oxygen was measured directly by detecting its phosphorescence at 1270 nm, as described elsewhere [45]. Photosensitizer absorbance was maintained at about 0.3.

Photostability: The kinetics and quantum yield (Φ_D) of photodegradation of the phthalocyanine **9** were measured both in an atmosphere of oxygen and argon. Before the irradiations, the solution containing phthalocyanine **9** (4.1 × 10⁻⁶ M) was purged with the appropriate gas and tightly sealed. The sample was irradiated with a xenon lamp. A 630 nm glass cut-off filter was used for this experiment. The kinetics of the dye degradation was followed with absorption spectroscopy. Photobleaching constants were calculated in accordance with first order reaction kinetics. The intensities of the light absorbed by the samples were determined using a potassium reineckate actinometer K[Cr(NH₃)₂(SCN)₄], using a procedure described in detail elsewhere [46,47].

4. Conclusions

In conclusion, we have outlined a synthesis pathway leading to a novel photosensitizer from the class of phthalocyanines. The synthesis of iodinated phthalocyanine was achieved through templated cyclotetramerization of 6-*tert*-butyl-4-iodo-1,3-diiminoisoindoline around zinc ions (Zn²⁺). A six step route leading to 6-*tert*-butyl-4-iodo-1,3-diiminoisoindoline was proposed. The

synthesis started with a regiospecific iodination of 4-tert-butyl-o-xylene to 5-tert-butyl-2,3dimethyl-iodobenzene. The methyl groups of the latter were oxidized by potassium permanganate to phthalic acid. The phthalic acid was directly and conveniently transformed to phthalimide, followed by its hydrolysis to phthalamide. Conversion of phthalamide to phthalonitrile was achieved by treating the phthalimide with POCl₃ in dry pyridine. Finally, the phthalonitrile was transformed to a more reactive 6-tert-butyl-4-iodo-1,3-diiminoisoindoline. Due to the combination of iodine substituents, tert-butyl groups and diamagnetic zinc ion incorporated into the phthalocyanine ligand, the novel photosensitizer possesses outstanding photophysical and photochemical properties important from the PDT point of view. The phthalocyanine studied is an extremely efficient absorber of visible light, as evidenced by the very high molar absorption coefficient (ε) equaled 295 000 [M⁻¹cm⁻¹] at 689 nm. The compound studied exhibits absorption band within the so-called "therapeutic window", with λ_{max} located at 689 nm. By recording the time-resolved transient absorption spectra we determined the excited triplet state lifetime ($\tau_{\rm T}$) of the iodinated zinc phthalocyanine. The excited triplet state lifetime equaled 3.3 μ s. The phosphorescence maximum was found to be located at λ_P 1103 nm and it was used to calculate the lowest triplet excited state energy (E_7) . The iodinated phthalocyanine was found to have its lowest triplet state energy (E_T) at 1.12 eV. Upon excitation the molecules of the photosensitizer studied efficiently transfer their excited triplet state energy (E_T) to the ground state oxygen (³O₂), resulting in high values of quantum yields of singlet oxygen formation (Φ_{Δ}) equaled to 0.76. To determine the value of Φ_{Δ} we resorted to two methods, viz. direct and indirect method. A comparison of the results obtained by both methods indicate that the photooxygenation process induced by iodinated zinc phthalocyanine proceeds via Type II mechanism, with singlet oxygen being the only reactive oxygen species formed under the experimental conditions applied. The compound studied is moderately photostable in the presence of oxygen (Φ_d = 4.01 x 10⁻⁴). A moderate stability can be advantageous in PDT of cancer as rapid breakdown and clearance from the patient's system after treatment is desirable. In summary, the triplet state properties of iodinated zinc phthalocyanine, lack of aggregation in solution and its ability to generate singlet oxygen with high Φ_{Δ} combined with moderate

photostability, render this novel photosensitizer a promising candidate for a photosensitizer for biomedical applications.

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Figure 1. Left: absorption (blue) and fluorescence (read) normalized spectra of **9** measured in DMF. Right: concentration dependent spectra of **9** in DMF (concentration range: $5.9 \times 10^{-6} - 6.3 \times 10^{-7}$ M).



Figure 2. Left: transient absorption spectrum of phthalocyanine **9** measured in THF at room temperature, excitation wavelength 643 nm. Transient decay is shown in the inset. Right: phosphorescence spectrum recorded in 2-methyltetrahydrofuran (2-mTHF) at 77 K.



Figure 3. Left panel: UV-Vis absorption spectra of phthalocyanine **9** recorded after different irradiation times in oxygen saturated DMF. Right panel: the photodegradation kinetics of phthalocyanine **9** in DMF measured as a decrease of the Q-band intensity at a 5 min intervals (A₀ stands for the initial absorption intensity and A stands for the intensity of the Q-band after a given irradiation time).





Scheme 1. Reagents and conditions: a) H₅IO₆, I₂, CH₃COOH, H₂SO₄, H₂O, 60-65°C, 6 h, 81%; b) KMnO₄, py/H₂O, 16 h, 90 °C, 80 %; c) acetyl chloride, reflux, 1 h, 74%; d) urea, 160 °C, 15 min., 89%; e) formamide, 180-190 °C, 1 h, 95%; f) NH₃, H₂O, 80 °C, 1 h 15 min., 28%; g) POCl₃, py, 0 °C to RT, 2 h, 28%; h) MeOH, NH₃, NaOMe, RT, 48 h, quantitative yield.



Scheme 2. Reaction of 1,3-diiminoisoindoline 8 with zinc acetate yielding corresponding phthalocyanine
9 (a mixture of four regioisomers). Reaction conditions: Zn(CH₃COO)₂•H₂O, 2-dimethylaminoethanol, reflux, 24 h, 42 %.

Compound	λ _{abs} [nm]	ε [M⁻¹cm⁻¹]	λ _f [nm]	Es [eV]	τ _f [ns]	$\mathbf{\Phi}_{f}$	λ _P [nm]	<i>Е</i> т [eV]	ΔE _{S-T} [eV]	τ ₇ [μs]	ΦΔ
9	689	295 000	696	1.78	0.42	0.015 ± 0.001	1103	1.12	0.673	3.3 ± 0.005	0.76 ± 0.02 ^a 0.74 ± 0.03 ^b

Table 1. Summary of photophysical and photochemical data for zinc phthalocyanine 9.

 λ_{abs} : absorption maximum in DMF; ε : molar absorption coefficient at λ_{abs} in DMF; λ_{f} : fluorescence maximum in DMF; E_s : excited singlet state energy; τ_{f} : fluorescence lifetime in DMF; Φ_{f} : fluorescence quantum yield in DMF; λ_{P} : phosphorescence maximum in 2-methyl-tetrahydrofuran at 77 K; E_T : excited triplet state energy; τ_{T} : triplet lifetime in THF; Φ_{Δ} : singlet oxygen quantum yield in DMF (^a luminescence method, ^b DPBF method).

Table 2. Photobleaching constant (K_d) and photodegradation quantum yield (Φ_d) of phthalocyanine **9** in DMF in the presence of O₂ and Ar, respectively.

		Oxygen		Argon	
		Stage I	Stage II	Stage I	Stage II
<i>K</i> _d x 10	0⁴ [s⁻¹]	1.61 ± 0.04	1.03 ± 0.03	0.22 ± 0.02	0.01 ± 0.01
Ф _d х 1	.0 ⁻⁴	4.01 ± 1.00	3.00 ± 0.30	0.10 ± 0.03	0.10 ± 0.01