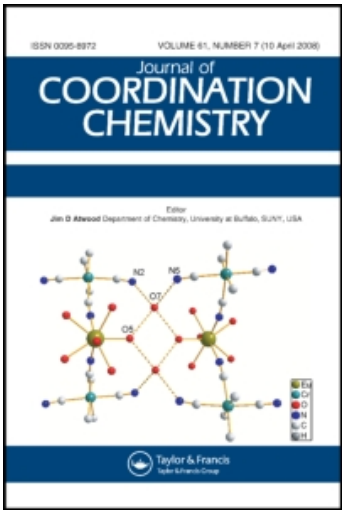

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The photodegradation of a zinc phthalocyanine

M. K. Gümüştaş[a]; B. S. Sesalan[b]; P. Atukeren[a]; B. Yavuz[a]; A. Gül[b]
[a] Department of Biochemistry, Istanbul University, 34093, Istanbul, Turkey [b] Department of Chemistry, Technical University of Istanbul, 34469, Istanbul, Turkey

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The photodegradation of a zinc phthalocyanine

M.K. GÜMÜŞTAŞ†, B.S. SESALAN*‡, P. ATUKEREN†,
B. YAVUZ† and A. GÜL‡

†Department of Biochemistry, Istanbul University, 34093, Istanbul, Turkey
‡Department of Chemistry, Technical University of Istanbul, 34469, Istanbul, Turkey

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A water-soluble zinc phthalocyanine (Pc), ZnPc (**3**), bearing 12 dimethylamino groups, which enhance the solubility of the macrocycle was synthesized and characterized. Photobleaching of the compound was examined both *in vivo* and *in vitro*. Laser irradiation causes photo-oxidation of the newly synthesized ZnPc. A photobleachable phthalocyanine can be an alternative in imaging; phthalocyanine dyes are used in imaging the cardiovascular system. Besides, it can be used in fluorescein angiography in some cases. When compared to stable ones, a photobleaching ZnPc (**3**) might be an attractive compound for imaging in medicine.

Keywords: Phthalocyanine; Dye; Cationic; Mice; Photobleaching

1. Introduction

Phthalocyanines with their unique electronic, spectroscopic, and chemical properties are used in a very wide range of areas. Recently, water-soluble phthalocyanines became very popular in medicine. Phthalocyanines are good photosensitizers due to their unique electronic properties and, in addition, photobleaching might be realized by further irradiation. The photo-oxidation of the sensitizer may represent a positive factor in reducing the risk of photosensitivity after photodynamic therapy. Besides, easily degradable dyes are preferred for imaging in medicine to minimize skin sensitivity [1–3].

In immunohistochemistry, stains and dyes which are easily degradable are preferred for highlighting structures in biological tissues for viewing [4]. For instance, double staining protocol is followed in imaging any disorder in heart arteries. Phthalocyanines as dyes are used in imaging the area at risk in heart arteries [5–10]. Another use of phthalocyanines is in fluorescein angiography, which is a routine retinal diagnostic procedure, giving information on the retinal and optic nerve blood vessels at the back of the eye [11, 12].

A stable, radical (e.g., superoxide) generator pc initiates lipid peroxidation mechanism of cellular injury and this is used as an indicator of oxidative stress in

*Corresponding author. Email: sungurs@itu.edu.tr

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cells and tissues. Lipid peroxides are unstable and decompose to form a complex series of compounds. These include reactive aldehydes, of which the most abundant is malondialdehyde (MDA). Therefore, measurement of MDA is widely used as an indicator of lipid peroxidation [13].

Our group has been engaged with synthesis of phthalocyanines and porphyrazines with different functional moieties serving many different purposes; substituents include heterocyclic groups, porphyrazine–phthalocyanine hybrid units, and quaternized amino groups [14–18].

In the present work, a photobleachable ZnPc (**3**) bearing 12 dimethylamino groups was synthesized and its photodegradation investigated both *in vitro* and *in vivo*. Photobleaching was evaluated by UV-Vis spectra in different conditions (i.e., hypoxic conditions as well as in the presence of oxygen). Oxidative stress in cells was evaluated by the values of MDA. A superoxide scavenger, superoxide dismutase (SOD), catalyzes the oxidation of O_2^- to O_2. SOD activity is measured as the inhibition of the rate of reduction of cytochrome c by the superoxide radical, observed at 550 nm [19]. Measurement of MDA (TBARS, thiobarbituric acid reacting substances method) and SOD levels in biological samples were determined by the methods reported previously [20].

2. Experimental

Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum One Fourier transform infrared (FT-IR) spectrophotometer and electronic spectra on Scinco Neosys 2000 double beam UV-Vis spectrophotometer. Tumor cell count was performed using Olympus Light Microscope Thoma Lam. ^{1}H-NMR spectra were recorded on a Bruker 250 MHz spectrophotometer using tetramethylsilane (TMS) as internal reference. Elemental analysis was performed by the Instrumental Analysis Laboratory of TUBITAK Gebze Research Centre; 2,4,6-*tris*(*N*,*N*-dimethylaminomethyl)phenoxy-4,5-dicyanobenzene (**1**) was synthesized according to the procedure previously reported [18]. All chemicals except cytochrome c were purchased from Merck. Cytochrome c from horse heart was purchased from Sigma–Aldrich Chemicals and stored at −20°C.

The irradiation source used was a diode laser with a beam diameter of 5 mm whose wavelength is in the range 600–700 nm. All samples were stirred (100 rpm Heidolph) during illumination at 25.0 ± 0.5°C. Spectra were recorded using quartz cuvettes with path length 1 cm. Light doses with 6, 30, 60, 90, and 180 J cm^{-2} were obtained for different exposure times at a fluence rate of 100 m W cm^{-2}. Samples were positioned 15 cm from the slit. After 5 min of bubbling with oxygen or nitrogen, irradiations and the measurements of absorbance intensity were performed on each sample in the same cuvette.

2.1. *Synthesis*

2.1.1. 2,9,16,23-Tetrakis[2,4,6-*tris*(*N*,*N*-dimethylaminomethyl)phenoxy] phthalocyaninato zinc(II) (2). 200 mg (0.51 mmol) of **1** was reacted with 46 mg (0.255 mmol) of zinc acetylacetonato in *n*-pentanol with two drops of DBU under N_2 at 130°C for 24 h.

The reaction mixture was stirred with 35 mL of acetone for 2 h at room temperature. Then, it was filtered and the filtrate evaporated till dryness. 40 mL of acetonitrile was added to the crude product and stirred for 3 h at room temp. To remove impurities, the reaction mixture was filtered and the filtrate was evaporated to dryness. Then, it was dissolved in 20 mL of acetone and added dropwise into cold 50mL of petroleum ether to precipitate. The precipitate was dried *in vacuo*. Yield: 40 mg (19.23%). ^{1}H-NMR (acetone-d_6): δ 7.78–6.85 (m, 20H, Ar–H), 3.27 (s, 16H, *o*–N–CH_2), 2.70 (s, 8H, *p*–N–CH_2), 2.32 (s, 48H, *o*–N–CH_3), and 2.06 (s, 24H, *p*–N–CH_3) (spectrum was given as "Supplementary material"); IR, ν (cm^{-1}): 2931–2776, 1608, 1455, 1355, 1277, 1029, 836, and 730; UV-Vis λ_{max} (nm) (log ε) in CH_2Cl_2: 358 (5.37), 617 (4.90), and 692 (5.59). Anal. Calcd for $C_{92}H_{116}N_{20}O_4Zn$ (%): C, 67.32; H, 7.01; and N, 16.85. Found %: C, 67.67; H, 7.11; and N, 17.16.

2.1.2. 2,9,16,23-Tetrakis[2,4,6-*tris*(*N*,*N*,*N*-trimethylammoniummethyl) phenoxy] phthalocyaninato zinc(II) dodecaiodide (3). In this study, 100 mg (0.061 mmol) of **2** was dissolved in CH_2Cl_2 (30 mL) and stirred with 208 mg (1.46 mmol) of CH_3I at room temperature for 4 h. Then, the mixture was filtered and the precipitate was washed with CH_2Cl_2. The precipitate was dried *in vacuo*. Yield: 52 mg (25.49%). IR, ν (cm^{-1}): 3008, 2933, 2761, 1607, 1405, 1393 (N–CH_3), 1215, 1040, 942, 842, and 745; UV-Vis λ_{max} (nm) (log ε) in water: 349 (4.43), 614 (4.03), and 683 (4.67) (spectrum was given as "Supplementary material"). Anal. Calcd for $C_{104}H_{152}N_{20}O_4I_{12}Zn$ (%): C, 37.42; H, 4.56; and N, 8.39. Found %: C, 37.35; H, 4.62; and N, 7.95. MS (ES) *m*/*z*: 3334.70 $[M]^+$ (spectrum was given as Supplementary material). ^{1}H-NMR (D_2O): δ 7.67–7.08 (m, 20H, Ar–H), 3.38 (s, 24H, N–CH_2), and 3.28 (s, 108H, N–CH_3) (spectrum was given as "Supplementary material").

2.2. *Preparation of solutions*

In this study, 3.64 μ mol L^{-1} stock solution of **3** and 1.72 μ mol L^{-1} stock solution of cytochrome c (Fe^{+3}) were prepared in distilled water. The reaction mixture containing 0.117 μ mol L^{-1} of **3** and 1.66 μ mol L^{-1} of cytochrome c (Fe^{+3}) was irradiated with different doses of light and the change in absorbance at 550 nm which is characteristic of cytochrome c (Fe^{+2}) was followed [19]. The change in absorbance of Q band of **3** was monitored after irradiation of 3 mL of 3.64 μ mol L^{-1} stock solution which is bubbled with O_2. A second 3 mL of the same stock was saturated with N_2 for 5 min and then the solution was exposed to different doses of light. To test the stability of **3** in the presence of axial binding ligands, 4 μ mol L^{-1} stock solution of **3** was prepared in DMF. First half of this stock was bubbled with O_2, the second half was bubbled with N_2 and irradiated by laser at different times and the decrease in absorbance intensity followed.

2.3. *Animal experiments*

All experiments were performed on 8–12–week old, 24 male BALB/c mice (body weight 20–24 g). The protocol was approved by Cerrahpasa Medical Faculty Local Ethics Committee. The animals had free access to water and food throughout

the course of experiment. Abdomen hair was epilated prior to irradiation. Groups that were employed during the experiment were:

(1) Group I: Tumor was inoculated ($n = 8$).
(2) Group II: Tumor was inoculated, **3** and irradiation applied ($n = 8$).
(3) Group III: Loaded with saline ($n = 8$).

EAC was maintained in Group I and II by intraperitoneal (i.p.) transplantation of $1.0 \pm 0.2 \times 10^6$ cells suspended in 0.2 mL ascite fluid. Tumor growth was followed using Thoma Lam. After 1 week, abdominal fluid of mice in Group I and II reached a volume of more than 15.000 mm^{-3}. Group II was injected i.p. with 1 $\mu mol\,kg^{-1}$ of ZnPc that was dissolved in saline and Group III was only loaded with saline. Considering the tumor uptake, irradiation of Group II was performed with a red light diode laser (650–700 nm) delivering 180 $J\,cm^{-2}$ light dose with a fluence rate of 100 $mW\,cm^{-2}$ at 24 h post-injection of the dye **3**. Irradiation source was positioned such a distance that whole abdomen of the mouse was uniformly irradiated. After 6 h, peritoneal ascite fluids were collected under etheral anesthesia. Ascite fluid cell counts were performed and all tumor cells were observed as intact. Thus, mice were sacrificed by cervical dislocation. Blood samples were collected from right ventricule. Heparinized blood samples were centrifuged ($3000 \times g$) for 5 min and plasmas were separated. Ascite fluid samples were centrifuged ($3000 \times g$) for 5 min. Pellets and ascite fluids were separated. Pellets were diluted with phosphate buffer saline (PBS; pH = 7.4) and sonicated. TBARS and SOD levels were analyzed by spectrophotometric methods in lysised tumor cell contents and heparinized plasmas [20].

Statistical analyses were conducted using Unistat 5.1 software. All numerical values are reported as means ± SD. A comparison of variables between two groups was performed using Student's *t*-test; *p*-values less than 0.05 were considered significant.

3. Results and discussion

ZnPc (**2**) (figure 1) was synthesized directly by cyclotetramerization of the phthalonitrile derivative (**1**) in the presence of anhydrous zinc acetate and an N-donor base DBU in a high-boiling solvent such as *n*-pentanol. One important point which should be always taken into account during this synthesis was that temperatures higher than 130°C led to decomposition of the precursor and totally diminished the yield of the reaction.

In the IR spectrum of **1**, alkyl C–H vibrations around 2941–2767 cm^{-1} were observed. The characteristic CN vibration at 2230 cm^{-1} in the spectrum of **1** disappeared after Pc formation in **2**.

^{1}H-NMR spectrum of **1** showed two different singlets for N–CH_2 protons at 3.49 ppm and at 3.16 ppm corresponding to *ortho*- and *para*-substitutions. Similarly, N–CH_3 protons were observed also as two singlets at 2.18 and 2.12 ppm indicating the *ortho*- and *para*-position of the substituents. Between 7.66 and 6.91 ppm, aromatic protons were observed.

Since a monosubstituted phthalonitrile (**1**) was the precursor for the synthesis of phthalocyanines in this study, all products were obtained as isomer mixtures. Strong adsorption of the molecules with tertiary amino groups on both alumina and silica hindered the possibility of using column chromatography in purification and also

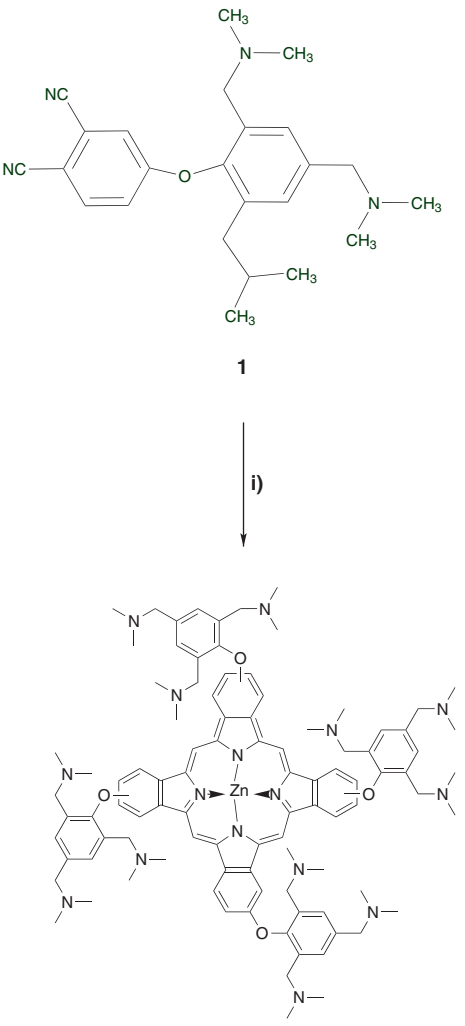
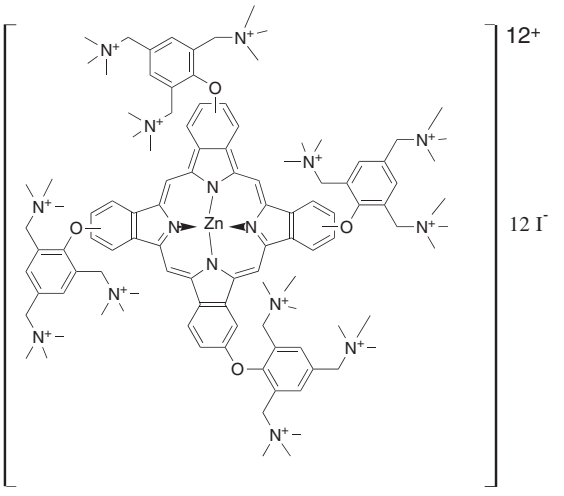


Figure 1. Synthesis of **2**.

isomer isolation of phthalocyanines. As a consequence of the presence of the isomers, it is difficult to differentiate the distinct protons. However, the multiplet around 7.78–6.85 ppm can be ascribed to aromatic protons. Also between 3.27–2.70 ppm *o*–N–CH_2 and *p*–N–CH_2; and 2.23 and 2.07 between *o*–N–CH_3 and *p*–N–CH_3 were observed.

^{1}H-NMR spectrum of **3** (in deuterium oxide) indicated that the shift of *o*- and *p*–N–CH_2 protons was close to the shift of *o*- and *p*–N–CH_3 protons. The shift of the aromatic protons were very close to the ones of **2**. Elemental analysis of **3** (figure 2) showed good agreement with the calculated values. Since the molecular weight of **3** was 3334.64 g mol^{-1}, mass spectrum of the compound ($[M]^+ = 3334.70$) led us to the



3

Figure 2. Structure of **3**.

conclusion that this compound can be used for biological applications. While the electronic spectrum of **2** measured in CH_2Cl_2 showed maxima at 349 nm in Soret and 683 nm in Q band region, quaternized zinc phthalocyanine (**3**) with positive charges on the periphery again gives the typical spectrum corresponding to monomeric species in aqueous solution (figure 3).

3.1. *Photochemical experiments*

To test the effect of O_2 on the rate of photobleaching, solutions were saturated either with O_2 or N_2. After an exposure of $6\,J\,cm^{-2}$ dose of light to the solution, which was bubbled either with O_2 (figure 4) or N_2 (figure 5), the decay in N_2-saturated solution (before irradiation $\log \varepsilon_0 = 4.81$ and after 1 min irradiation $\log \varepsilon_1 = 4.48$) was more than the O_2 bubbled solution ($\log \varepsilon_0 = 4.81$ and $\log \varepsilon_1 = 4.66$).

Axial binding of solvent to metal in pc ring can also affect bleaching. For this purpose, $4\,\mu mol\,L^{-1}$ stock solution of **3** was prepared in DMF. First half of this stock was bubbled with O_2 and then irradiated by diode laser at different times with a fluence rate of 100 mW (figure 6a). After 1-min irradiation, there was a decrease in Q band absorption ($\log \varepsilon_0 = 4.37$; $\log \varepsilon_1 = 4.34$). The second half was purged with nitrogen before exciting by different doses of light. As opposed to the previous state, first an increase ($\log \varepsilon_0 = 4.37$, $\log \varepsilon_1 = 4.48$) was observed (figure 6b). Then 7 min-irradiation caused a decrease ($\log \varepsilon_7 = 4.46$) in the absorbance at 682 nm. There was very little change in absorbance for further irradiation.

Figure 7 illustrates that zinc can enlarge the coordination sphere and bind DMF axially. A pentacoordinate structure can be more stable. Thus, binding an axial ligand to the molecule was more effective than nitrogen or oxygen gas on photodecomposition in donor solvents like DMF.

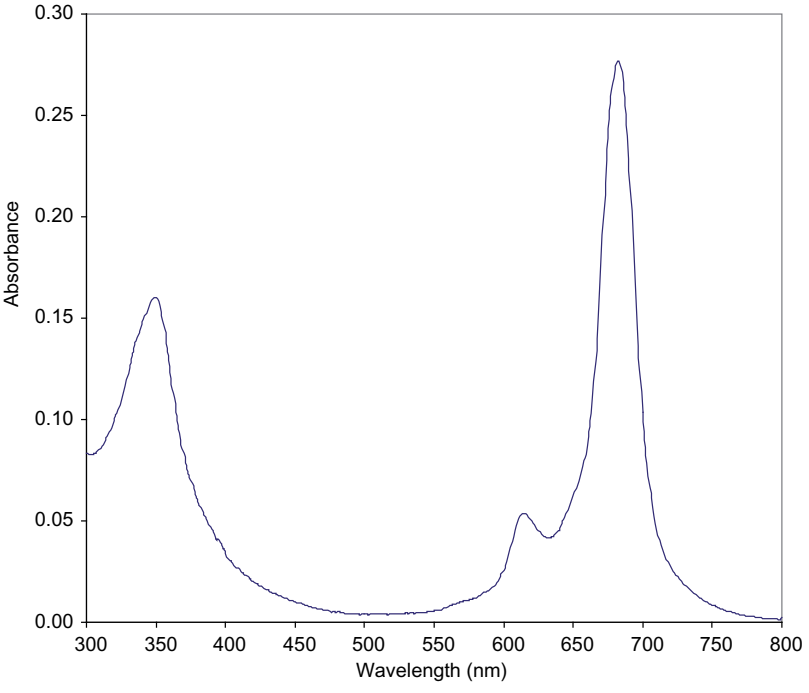


Figure 3. The UV-Vis spectrum of **3** in H_2O.

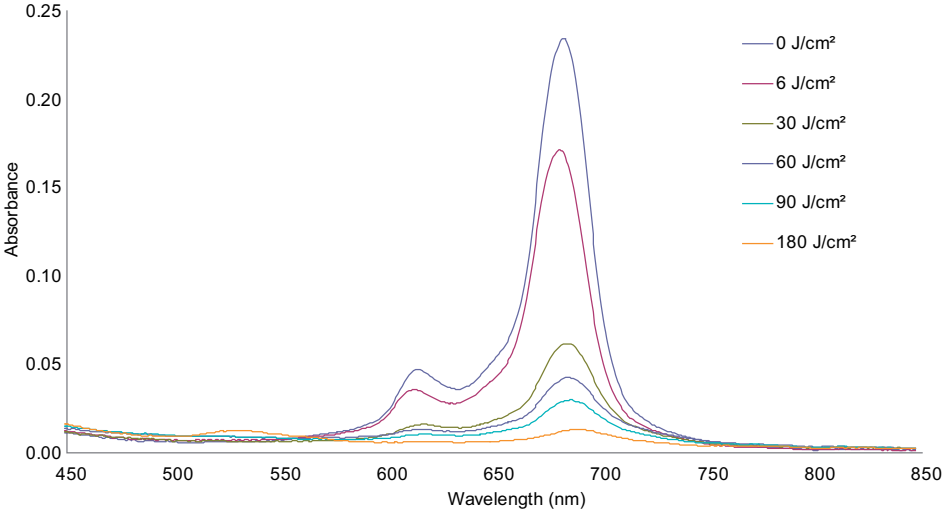


Figure 4. The UV-Vis spectrum of **3** in O_2-saturated aqueous solution.

In contrast, in water, the conversion of triplet state of the macrocycle to ground state in the presence of O_2 yielding excited oxygen species (figure 8) results in less decomposition. However, in the presence of nitrogen, the triplet state of the macro ring undergoes singlet state and causes decomposition of the ground state dye molecules instead of generating singlet oxygen or superoxide.

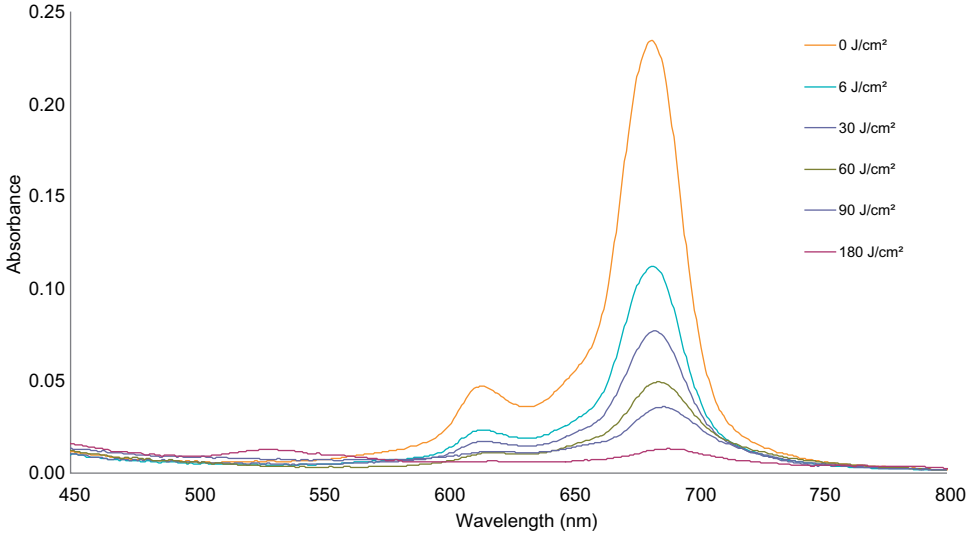


Figure 5. The UV-Vis spectrum of **3** in N_2-saturated solution.

To test the generation of superoxide radicals, cyctochrome c method was used. Cytochrome (Fe^{+3}) is reduced to cytochrome c (Fe^{+2}) in the presence of superoxide radicals. In UV-Vis spectrum, the absorbtion at 550 nm is characteristic of cytochrome c (Fe^{+2}) [19]. Thus, the solution which contained 0.117 μ mol L^{-1} **3** and 1.66 μ mol L^{-1} of cytochrome c (Fe^{+3}) was exposed to light. Figure 9 indicates that the macrocycle decomposed and **3** did not undergo Type I mechanism to generate superoxide radicals.

In general, the greatest initial decrease in rate of bleaching occurred at the lowest laser power (after 6 J cm^{-2} dose of light). On increasing laser power, the proportion of excited molecules increased and the effective ground state population at a given time decreased. The reactive species that cause photobleaching of **3** might attack ground state **3** molecules [21]. The pc was more photobleachable in the presence of nitrogen, suggesting that the excited triplet state of the dye (conversion from singlet to triplet *via* intersystem crossing) was involved in the bleaching process. In this case, the quenching of triplet dye by molecular oxygen with simultaneous formation of singlet oxygen would prevent the triplet state from initializing electron transfer events that cause bleaching [22, 23]. In the case of axial binding of solvent to central metal ions in pcs, photobleaching can be reduced with the effect of donor ability of solvent preventing decomposition of the macrocycle [24, 25]. Here, coordination of DMF to Zn might result in a more stable pc ring for photooxidation.

3.2. *Animal experiments*

As stated before, the synthesis of a photobleachable pc was aimed in this study. According to the results of *in vitro* studies, **3** was unstable and did not generate any superoxide radicals when irradiated. Thus, EAC tumor model on 24 male BALB/c mice (20–24 g, 8–12 week old) was used to confirm the photo-oxidation *in vivo*.

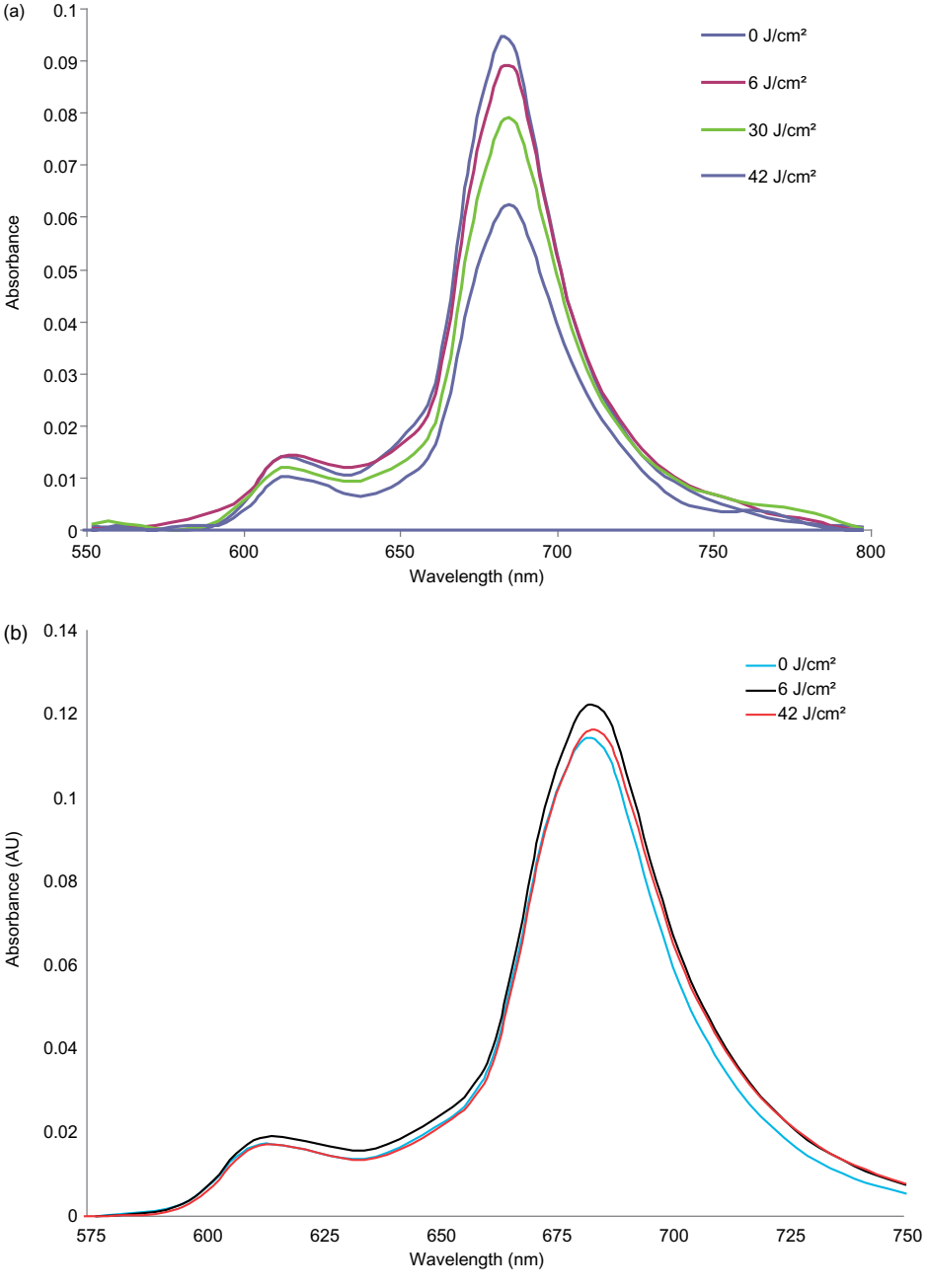


Figure 6. Photobleaching of **3** in DMF under (a) O_2 and (b) N_2.

The effect of **3** and irradiation on tumor as a marker of oxidative stress in Group II was evaluated by TBARS and SOD levels with spectrophotometric methods. Since the bleaching process has two components, the photosensitizer **3** and irradiation, control groups like tumor and **3**, or tumor and irradation were not employed.

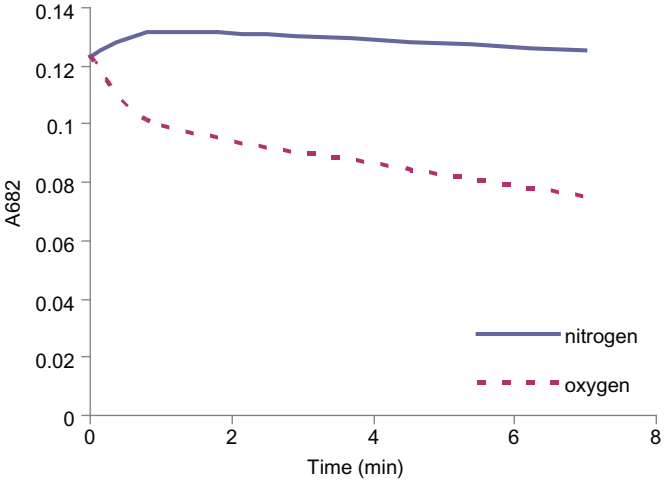


Figure 7. Photobleaching of **3** in DMF under N_2 (—) or O_2 (···) with respect to time.

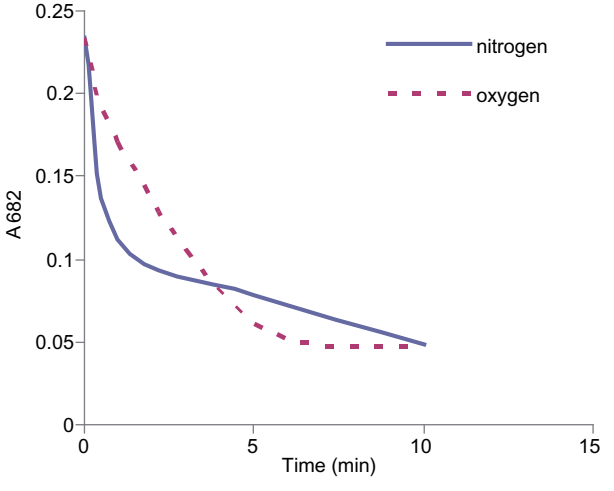


Figure 8. Photobleaching of **3** in water under N_2 (—) or O_2 (···) with respect to time.

After 1 week from injection, when compared with Group III, in Group I and II, abdominal fluid volume and tumor count increase indicated that EAC was inoculated successfully (figure 10a and b).

For more tissue penetration, only 180 J cm^{-2} light dose was applied to each mouse. In plasma, in Group II, TBARS levels increase because of EAC and caused an oxidative stress in blood. The application of **3** and irradiation to peritoneum resulted in a mild increase in oxidative stress in mice plasma. However, statistically, it was not significant. A significant oxidative stress would result in tumor cell lysis. Thus, TBARS levels both in pellets and fluids would increase by statistically significant amounts. Furthermore, if **3** had generated superoxide radicals, tumor cell count would decrease and cell

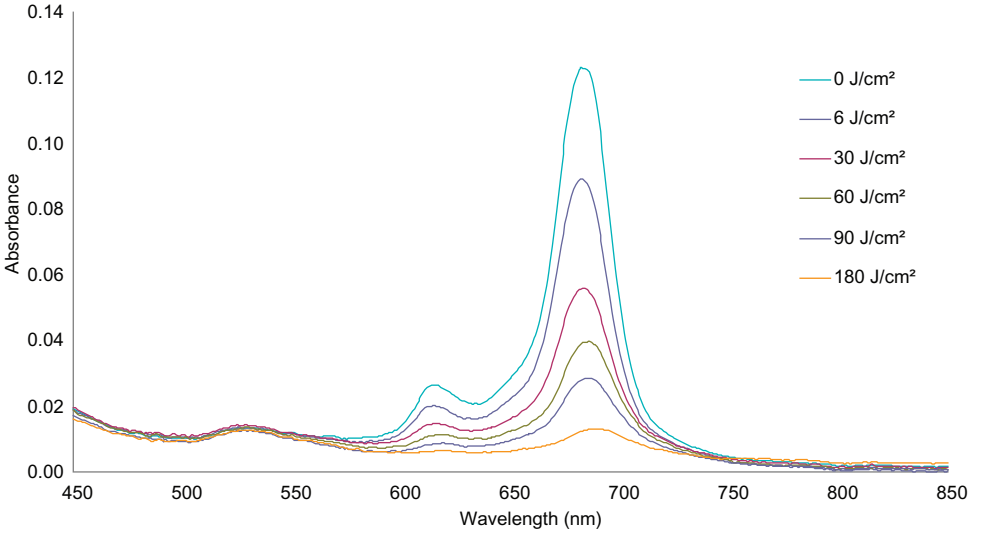


Figure 9. The UV-Vis spectrum of the aqueous solution containing **3** and cytochrome c.

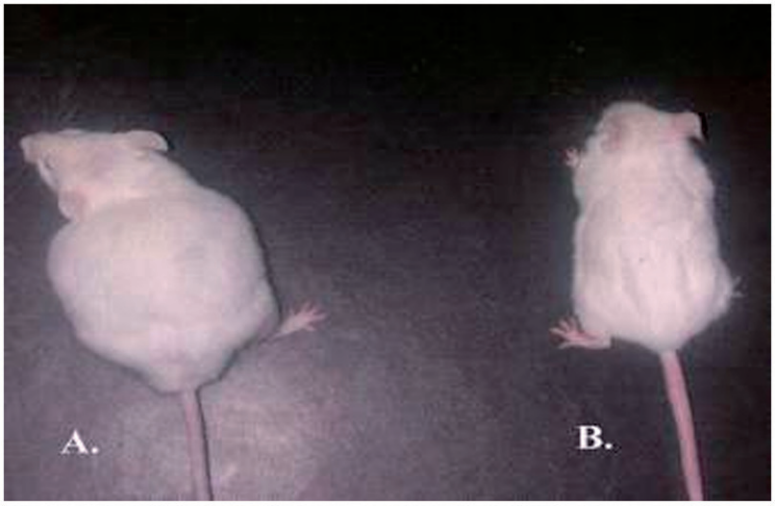


Figure 10. Mice with EAC; (A) 1 week after inoculation of EAC in Groups I and II and (B) Group III.

destruction would be observed under microscope. Since the pellet was the indicator of tumor cell lysis, the fluid content would be affected directly by the pellet. TBARS levels in fluid was not significant depending on the pellet. Since there was no significant oxidative stress, SOD levels did not significantly change (table 1).

It was thought that irradiation of **3** did not cause an additive oxidative stress on metabolism. In other words, **3** did not photobleach *via* radical formation. This was in accord with the results obtained from the cytochrome c method.

Table 1. The results of TBARS and SOD levels.

	TBARS plasma ($nmol\,mL^{-1}$)	TBARS pellet ($nmol\,mg^{-1}$)	SOD ascite fluid ($U\,mL^{-1}$)	SOD pellet ($U\,mg^{-1}$)
Group II	163 ± 29	159 ± 38	0.126 ± 0.02	0.227 ± 0.03
Group I	149 ± 23	132 ± 37	0.135 ± 0.02	0.243 ± 0.01

4. Conclusion

Phthalocyanines, which undergo Type I or Type II mechanism, can be easily excited even by sunlight causing skin irritation and sometimes scrab. Thus, the main side effect of this kind of photosensitizers is skin and eye sensitivity to daylight or bright indoor lighting. The subcellular localization of chemicals can be minimized by using easily degradable drugs.

Rather than the pcs which have moieties that enable them to dissolve in organic solvents [26–29], water-soluble derivatives are preferred for biological applications. Here, a new water-soluble bulky ZnPc (**3**) was synthesized. Its photochemical and photobiological properties indicated that it was not stable under irradiation both *in vivo* and *in vitro*. Products of photodegradation could be aromatic compounds, mainly phthalimide [30–32]. The aim of this study was to introduce a new photobleachable phthalocyanine dye as an alternative to those used presently in medicine (e.g., angiography) with the advantage of shorter skin sensitivity.

Supplementary material

^{1}H-NMR spectrum of **2**; and mass, UV-Vis electronic, and ^{1}H-NMR spectra of **3** are provided as supplementary material.

Acknowledgments

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