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Efficient Singlet Oxygen Photogeneration by Zinc Porphyrin-Dimers Upon One- and Two-Photon Excitation.

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ABSTRACT

The development of photodynamic therapy at depth requires photosensitizers which have both sufficient quantum yield for singlet oxygen generation and strong two-photon absorption. Here we show that this can be achieved by conjugated linkage of zinc porphyrins to make dimers. We determined the quantum yield of generation of $^1\text{O}_2$, ϕ_{Δ} , by measuring emission at 1270 nm using a near infra-red streak camera and found it to increase from 15% for a single porphyrin unit to 27-47% for the dimers with a conjugated linker. Then, we measured the spectra of two-photon absorption cross section, σ_2 , by a focus-tunable Z-scan method, which allows for nondestructive investigation of light-sensitive materials. We observed a strong enhancement of the two-photon absorption coefficient in the dimers, especially those with an alkyne linker. These results lead to an excellent figure of merit for two-photon production of singlet oxygen (expressed by the product $\sigma_2 \times \phi_{\Delta}$) in the porphyrin dimers, of around 3700 GM, which is very promising for applications involving treatment of deep tumors by photodynamic therapy.

1. INTRODUCTION

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4 Photodynamic therapy (PDT) is a widely killing *Propionibacterium acnes*),
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6
7 used cancer treatment, particularly for the periodontology⁶, treatment of viral lesions⁷
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10 treatment of superficial cancers such as and age-related macular degeneration⁸.

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12
13
14 many skin cancers¹. PDT involves the use In order to efficiently photogenerate
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17 of light in combination with a singlet oxygen, a material should fulfill a
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20 photosensitizer to cause a photochemical few criteria. It needs to absorb excitation
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23 reaction, leading to the generation of light and have a triplet energy level higher
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26 reactive oxygen species (ROS)², which than 397 kJ/mol to allow for efficient
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29 then kill neighboring tumor cells. Whilst energy transfer to ground state oxygen
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32 most often used to kill cancer cells, the and hence the generation of singlet
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35 reactive oxygen species can also be used oxygen. Moreover, it should have high
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38 to kill bacteria thereby providing a triplet quantum yield and long triplet state
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42 powerful alternative to antibiotics in the lifetime². Despite these requirements,
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44
45 management of topical infections^{3, 4}. For there are many materials capable of
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48 example, in addition to cancers, PDT has photogenerating singlet oxygen, they can
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52 been used in the treatment of acne⁵ (by be grouped into: (1) the organic dyes and
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3 aromatics⁹; (2) the porphyrins, chlorins, wavelengths in the biological
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6 phthalocyanines, and related transparency windows of tissue at
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10 macrocycles¹⁰; (3) semiconductors¹¹; and 650-950 nm and 1000-1250 nm¹⁴. As only
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14 (4) metal nanoparticles^{12, 13}. Among these few photosensitizers have a linear
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17 photosensitizers, porphyrin derivatives absorption band in this wavelength
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20 attracted significant attention and some of region¹⁵, two-photon excitation in which
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24 them are already in clinical use. two longer wavelength photons are
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28 Photodynamic therapy has been widely simultaneously absorbed is a natural way
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31 used to kill tumor cells, which are located to achieve the desired excitation energy
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34 close to skin surface, due to the fact that with longer wavelength light that can
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37 the photosensitizers are excited with penetrate further into tissue. The
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40 wavelengths which are strongly absorbed photosensitizers which aim to be used in
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43 and scattered by the tissue. PDT could two-photon excited PDT should be
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45
46 treat a much wider range of conditions if it characterized by high quantum yield of
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49 could work at greater depth which could singlet oxygen generation, ϕ_{Δ} , and large
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52 be achieved by using excitation two-photon absorption cross-sections.
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4 Typical porphyrin derivatives¹⁶⁻¹⁸, even consider this figure of merit when
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6 those accepted for clinical use like normalized by molecular weight i.e.
7
8 Photofrin[®], Verteporfin[®] or Foscan[®] are $\sigma_2 \times \phi_{\Delta} / M$, marked as $(\sigma_2 \times \phi_{\Delta})^*$ to facilitate
9
10 indeed efficient singlet oxygen generators comparison of large and small candidate
11
12 but suffer from low two-photon absorption photosensitizers. In the case of
13
14 cross-sections, on the order of 1 GM^{19, 20}. porphyrins, in order to maximize the
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16 In that context, there is a need to design parameter $\sigma_2 \times \phi_{\Delta}$, insertion of a metal ion
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18 and synthesize new molecules with leads to a trade-off as it causes reduction
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20 excellent figure of merit for two-photon of the singlet oxygen quantum yield²¹ and
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22 production of singlet oxygen (expressed increase of the 2PA cross-section.
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24 by the product $\sigma_2 \times \phi_{\Delta}$). It is also relevant to
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42 In the field of nonlinear optics, the been shown that centrosymmetric
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44 general rules for molecular design to quadrupolar compounds have larger
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46 maximize 2PA cross-section exist in the values of σ_2 than their dipolar
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48 literature and are supported by both counterparts²². In addition, introducing
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50 theoretical and experimental work. It has strong electron donating (D) or electron
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3 withdrawing (A) groups to yield the
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7 structures like D-A-D or A-D-A further
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9
10 improves 2PA properties²³. Finally, the
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13 process of simultaneous absorption of two
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17 photons requires strong overlap of the
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20 π -orbitals over a large system, making it
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23 sensitive to molecular conformation
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27 changes, which may alter the electronic
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30 coupling.

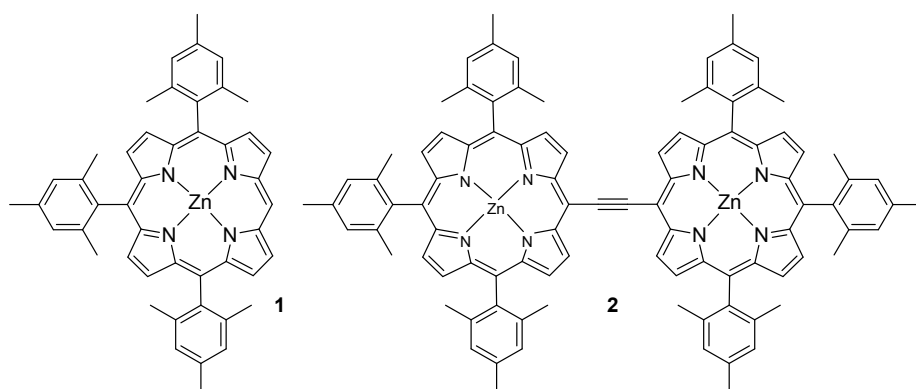
31
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35 The general structure-property rules can
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38 be applied to porphyrin based
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42 compounds. It has been shown that 2PA
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45 properties may be tuned by metal
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48 insertion, adding electron donating or
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51 withdrawing groups and expanding the
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54 π -conjugated system by creating dimers

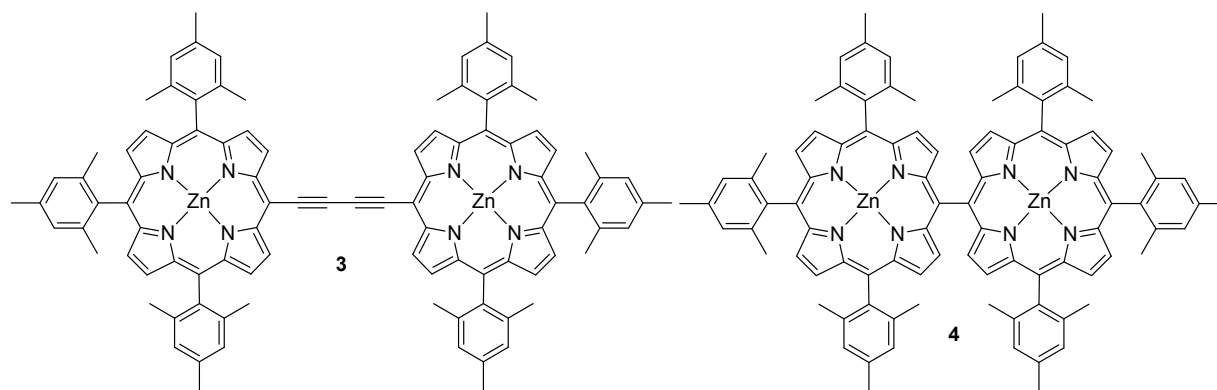
or higher order oligomers^{17, 23, 24}. In the
present work we use metal containing
porphyrins and explore the effect of
increasing electron delocalization by
conjugated links between macrocycles. In
particular, we explore the photogeneration
of singlet oxygen and two-photon
absorption in a series of zinc porphyrins,
either being a monomer (compound **1**), or
a dimer, linked by ethyne (**2**) or di-ethyne
link (**3**) or by a single bond (**4**), as depicted
in Scheme 1.

There are numerous papers
investigating either the two-photon
absorption or singlet oxygen
photogeneration properties of porphyrin

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3 based compounds, but not so many where
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7 the combination of these two effects is
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10 presented²⁵⁻²⁷. Our goal was to carry out
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13 interdisciplinary research covering the
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16 nonlinear optical properties and singlet
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18 oxygen photogeneration, thus providing
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21 strong support to the results and
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24 conclusions concerning the structure-
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26
27 property optimization. Singlet oxygen
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30 generation was studied using an infra-red
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streak camera. The two-photon absorption
properties were investigated by the focus-
tunable Z-scan method, which has the
important advantage over alternative
methods of being quick, thereby avoiding
photodegradation which is a particular
consideration in the measurement of
materials intended to cause
photochemistry.





Scheme 1. Structures of investigated compounds.

2. EXPERIMENTAL SECTION

The molecules used in this work were synthesized and purified according to the protocols described in²⁸. The molecules were dissolved in chloroform (Sigma-Aldrich) and quartz cuvettes were filled with the solutions for the photophysical measurements. UV-vis absorption spectra were measured using a Perkin Elmer Lambda 1050 UV/Vis/NIR

spectrophotometer. The concentration of the solution was adjusted to reach optical densities suitable for the PL and emission from singlet oxygen experiments. Steady-state PL spectra were recorded using an automated spectrofluorometer (Fluorolog, Horiba Jobin-Yvon), with a 450 W Xenon lamp excitation source. The solution singlet oxygen quantum yield (SOQY) (ϕ_{Δ})

values were determined using PHAROS regenerative amplifier (output tetraphenylporphyrin (H₂TPP) from Fisher Scientific in chloroform solution as a standard reference because of its well-known SOQY of 55%²⁹. The direct emission of singlet oxygen at 1270 nm was detected by a NIR streak camera from Hamamatsu Photonics. The camera was working in Photon Counting mode and the experiment was automatically stopped after 50 000 frames for each sample. In order to prevent the degradation, the samples solutions were placed in a rotating cell, placed in such a way that the exciting beam was shifted from the center.

The beam from a Light Conversion

PHAROS regenerative amplifier (output wavelength 1028 nm, pulse duration 290 fs, repetition rate 5 kHz) was directed to an optical parametric amplifier (OPA, a Light Conversion OPHEUS-F). The OPA generated 828 nm, which was further frequency doubled to obtain 414 nm used to excite the samples. The output pulse duration was less than 100 fs. The quantum yield of singlet oxygen generation may be determined using the modified method used by Tanielian and Heinrich³⁰ and using equation 1²¹:

$$\phi_{\Delta x} = \phi_{\Delta r} \frac{A_r(\lambda_r) I(\lambda_r) D_x \tau_r}{A_x(\lambda_x) I(\lambda_x) D_r \tau_s} \quad (1)$$

1
2
3 where ϕ_{Δ} stands for the quantum yield of
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7 singlet oxygen generation, the subscripts
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10 x and r refer to the compound to be
11
12
13 characterized and to the reference
14
15
16 solutions, respectively. λ is the excitation
17
18
19 wavelength, $A(\lambda)$ is the absorbance, $I(\lambda)$ is
20
21
22 the relative intensity of the excitation light,
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27 τ is the lifetime of singlet oxygen emission
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31 in the sample and reference solvent, and
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35 D is the integrated area under the
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emission spectra.

As, the samples and reference solutions
are excited at the same conditions and
they are dissolved in chloroform, the
above equation can be simplified to:

$$\phi_{\Delta x} = \phi_{\Delta r} \frac{A_r(\lambda_r) D_x}{A_x(\lambda_x) D_r} \quad (2)$$

The two-photon absorption cross-sections were determined by f-scan method described in³¹. The laser system used for this study was a Quantronix Integra Ti:Sapphire regenerative amplifier (output wavelength: 800 nm; pulse duration: 130 fs; repetition rate: 1 kHz) that pumped an optical parametric amplifier (OPA, a Quantronix Palitra) to provide tunable excitation. The sample solution was prepared by dissolving the corresponding chromophore in chloroform at concentration of 0.5% (w/w) and placed in a glass cell with 1 mm optical path-

length. The measurements were carried out in a relative manner, calibrating all the data against f-scans carried out on a fused silica plate and taking into account the nonlinear signals obtained from a cell containing pure solvent.

3. RESULTS AND DISCUSSION

Steady-state electronic absorption.

The absorption and photoluminescence spectra of the investigated compounds were measured in dilute CHCl_3 solutions with 1×10^{-6} mol/L concentration. Maximum absorption wavelengths and maximum emission wavelengths are listed in Table 1. The absorption spectra are displayed in Figure 1. For the monomeric

porphyrin, compound **1**, (Figure 1a), two absorption bands are clearly visible. The Soret band is located at 414 nm and so called Q-band at 543 nm. For the dimers, the Q-bands are intensified they show bathochromic shift compared to molecule

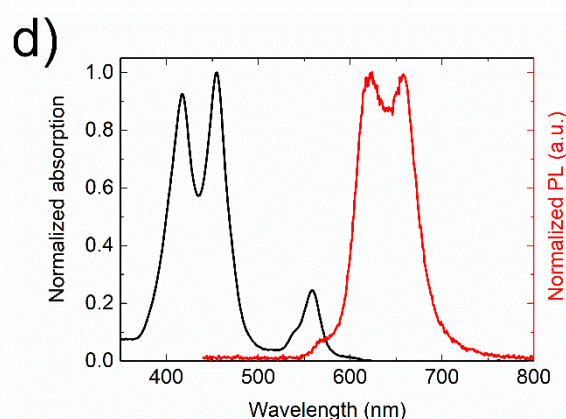
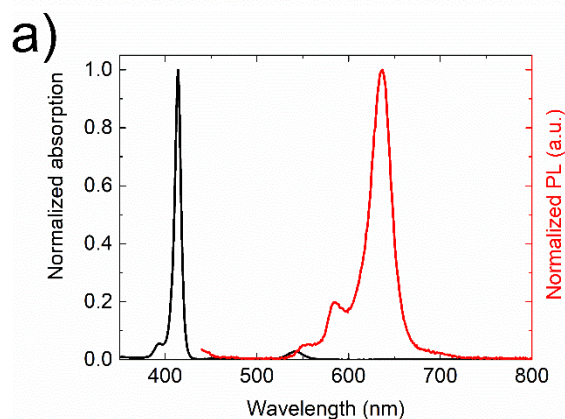
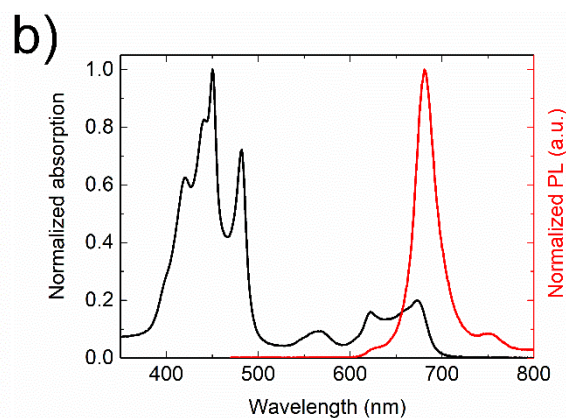
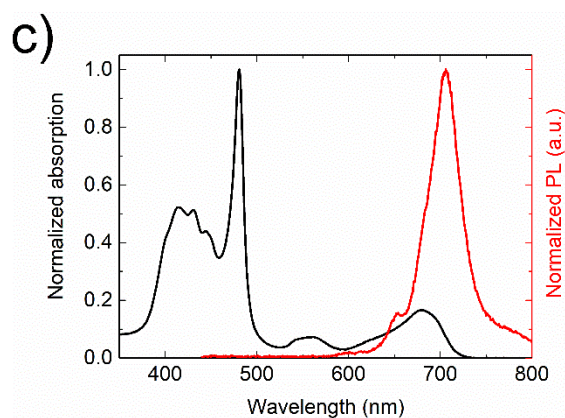
1. Moreover, both Soret and Q-bands are much broader with additional peaks visible in the absorption spectra for compounds **2-4**. It is worth to mention that the stronger Q-band absorption is responsible for enhanced 2PA properties in the NIR. Fluorescence occurs from the Q-band, whichever band is excited. The fluorescence bands of compounds **2** and **3** show a bathochromic shift with respect

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2
3 to compound **1** (Figure 1a-c). The as $B_x(0-0)$ transition. There are also other
4 bathochromic shift of the absorption and B_x and B_y transitions which span a wide
5
6 fluorescence bands can be explained by region to the blue from the $B_x(0-0)$
7 the decreased HOMO-LUMO gap due to transition. In the case of compound **4** the
8 π -delocalization between the neighboring molecule is no longer planar due to steric
9 hindrance, and so the dimerization does
10 not lead to increased electron
11 delocalization. There is an almost equally
12 intense split in the Soret absorption and Q-
13 band emission of **4** (Figure 1d), which can
14 be explained by the excitonic coupling
15 between the two parallel strong dipole
16 transitions of each porphyrin ring^{28, 32}. The
17 magnitude of the absorption band split is
18 equal to 2002 cm^{-1} and the emission band
19 split is equal to 854 cm^{-1} .
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The crystallographic structure analysis performed by another group yielded the torsional angle of the porphyrin dimer linked by a single bond to be $69.1(2)^{\circ}$ ³³.

The torsional angle of the dimers linked by ethyne and di-ethyne bonds were

determined by DFT calculations to be zero, which means that the molecules are planar³⁴, which enhances both 2PA and singlet oxygen photogeneration due to faster intersystem crossing (S_1-T_1), compared to twisted conformers³⁵.



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4 **Figure 1.** Normalized absorption (black curves) and steady-state fluorescence spectra
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6
7 (red curves) of investigated porphyrins. Figures a) to d) correspond to molecules **1** to **4**,
8
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10 respectively.

15 **Singlet oxygen detection.**

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18 The singlet oxygen quantum yield, ϕ_{Δ} , emission. The spectra obtained for sample
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20 was determined by recording direct **4** and the reference are shown in Figure 2.
21
22 emission from singlet oxygen centered at Finally, the spectra were integrated to
23
24 1270 nm by a NIR streak camera. The obtain the D factors necessary to calculate
25
26 transition from first excited singlet state the quantum yield of singlet oxygen
27
28 $^1\Delta_g$ to ground state being triplet, $^3\Sigma_g^-$, is photogeneration. The values of ϕ_{Δ} of all
29
30 spin forbidden². This is the reason for the investigated compounds are summarized
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32 emission lifetime on the order of μ s, which in Table 1. The least efficient is the
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34 strongly depends on the solvent²¹. monomeric unit (**1**). The dimerization
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49 The signals were integrated from 8 to leads to enhanced properties of singlet
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52 50 μ s to obtain the spectra of $^1\text{O}_2$ oxygen photogeneration, regardless the
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3 type of the link. One can notice that the
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7 value of ϕ_{Δ} for compound **4**, which is not
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10 conjugated due to steric hindrance, is
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13 approximately doubled, compared to **1**.
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16
17 On the other hand, compounds **2** and **3**,
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20 which have large π -delocalization and are
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22
23
24 close to planar, are characterized with
25
26
27
28 much larger ϕ_{Δ} being equal to 35 and
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30
31 47 %. These findings are in good
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33
34 agreement with other works on porphyrins
35
36
37 dimers, e.g. with porphyrin units linked by
38
39
40 butadiyne bond linked to TIPS-protected
41
42
43 ethynyl groups³⁶. The determined ϕ_{Δ} of
44
45
46 such porphyrin dimer in DCM was
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48
49 reported to be 37 %, which means that the
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52
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54 structural design of compounds **2** and **3**

are more efficient in terms of singlet
oxygen production.

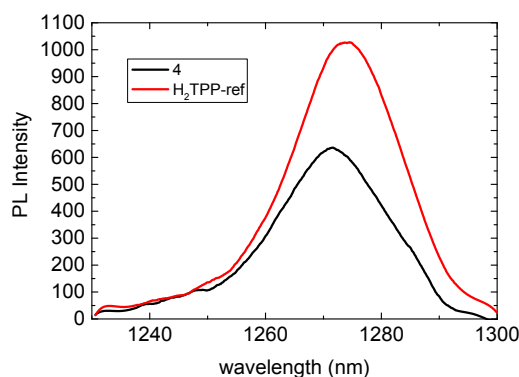


Figure 2. Singlet oxygen emission spectra of **4** and H₂TPP, obtained by integrating the streak camera images from 8 to 50 μ s.

Table 1. Steady-state photophysical properties of the investigated compounds (**1-4**) and their singlet oxygen quantum yields. The positions of the most intensive bands are given in bold.

porphyrins	λ_{abs} (nm)	λ_{em} (nm)	ϕ_{Δ} (%)
-------------------	-----------------------------	----------------------------	---------------------

	Soret band	Q-band		
1	393 414	542	554 585 637 700	15
2	420 441 450 482	566 622 673	627 681 751	35

Two-photon absorption cross-section spectra.

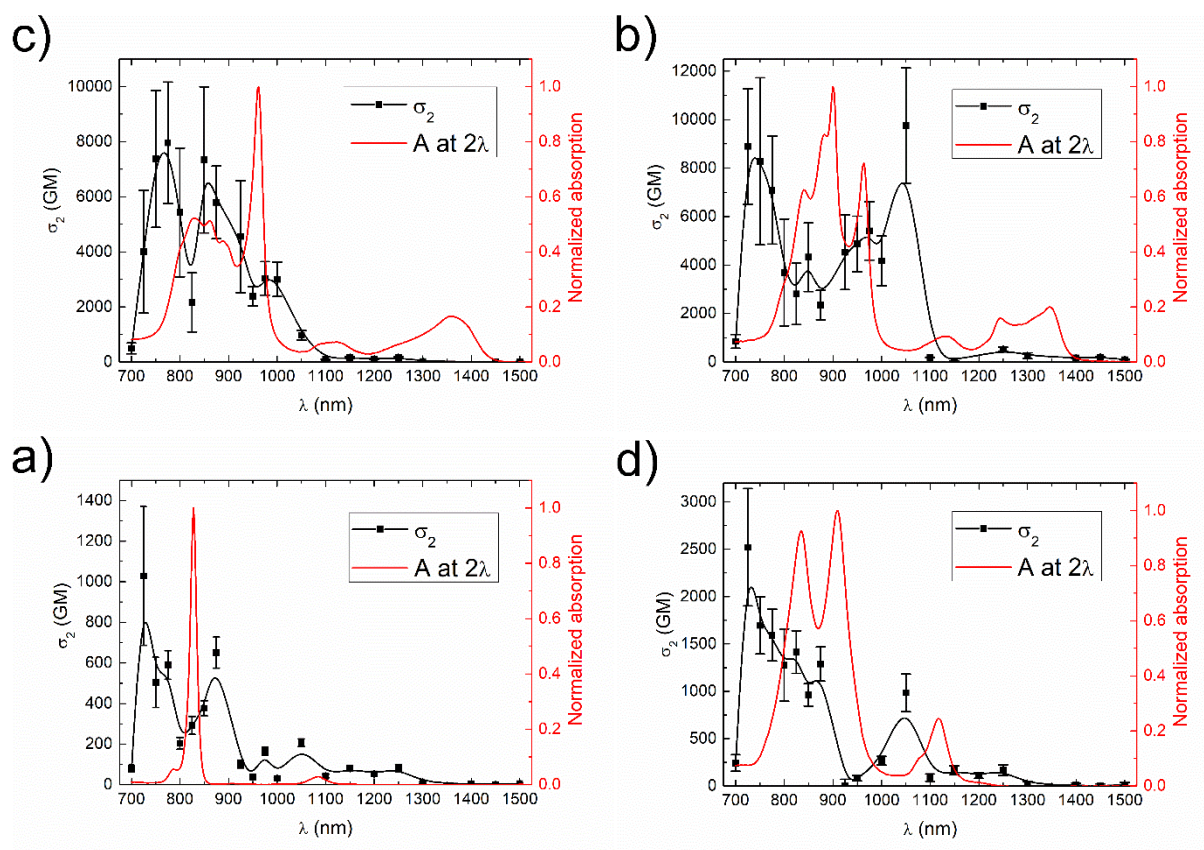
The spectra of two-photon absorption cross-section may be obtained by many methods, two-photon excited fluorescence (TPEF)³⁷ and fs Z-scan³⁸⁻⁴¹ being the most common nowadays. They strongly differ from each other, as in TPEF one detects fluorescence spectrum at various wavelengths and compares the integrated PL with a standard reference with known PLQY and σ_2 . In Z-scan one

3	414 431 444 481	562 681	599 654 706 785	47
4	417 455	538 558 600	567 624 658	27

measures the changes of sample transmission as a function of the sample position in Z direction and fit the data recorded on so called Open Aperture curve as described in the literature^{38, 41} to determine the value of two-photon absorption cross-section at the specific wavelength. In order to obtain reliable data by these two aforementioned techniques, the samples have to be perfectly photostable.

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4 Upon photoexcitation with one- and the f-scan technique, instead of translating
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7 two-photons the singlet oxygen which is the sample, the focal point is shifted by an
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10 generated by the investigated porphyrins electrically controlled lens³¹. Combined
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14 causes their degradation. It is important to with improved data acquisition technique,
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16
17 mention that each photosensitizer this method reduces the time necessary
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20
21 molecule can typically produce 10^3 - 10^5 for a single scan from a few minutes to
22
23
24 molecules of $^1\text{O}_2$ before being degraded several seconds, thus limiting the
25
26
27
28 through photobleaching by $^1\text{O}_2$ or by some possibility of photodegradation. While the
29
30
31 other process². Thus, it is crucial to vast majority of published papers
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33
34
35 minimize the time of irradiation especially described only the singlet oxygen
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37
38 with high power laser used to study the photogeneration process, or two-photon
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40
41
42 nonlinear effects. Hence we use the so- absorption properties of the studied
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44
45 called “f-scan” technique which is a photosensitizers, in this work both are
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47
48 modification of the standard Z-scan treated with equal attention and detail,
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51
52 method, to determine the spectra of allowing for more reliable conclusions.
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54
55
56 two-photon absorption cross-section. In

The spectra of two-photon absorption cross-sections of investigated porphyrins obtained by f-scan technique are shown in Figure 3. They are overlaid with linear absorption spectra, shown as red curves, plotted vs. twice the wavelength. For all porphyrins, both the monomer (1) and dimers (2-4) the maximum of two-photon absorption cross-sections is within first biological window which exists at wavelengths between 650 nm and 950 nm¹⁴.



1
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3 **Figure 3.** Spectra of two-photon absorption cross-sections of the investigated porphyrins
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6
7 (1-4). The spectra were overlaid with linear absorption (red curves) plotted vs. twice the
8
9
10 wavelength. Figures a) to d) correspond to compounds 1 to 4.

16 In case of the monomer 1, the maximum means that it is favorable for the
17 value of σ_2 is around 1000 GM at 725 nm, molecules to be excited to higher vibronic
18 as shown in Figure 3. a). One can see that state upon 2PA excitation, compared to
19 the band of 2PA is split into two, even 1PA process. Despite the fact that linear
20 though the linear absorption shows only absorption of 4 is split into two equally
21 intense bands, the 2PA spectrum is
22 one peak at 414 nm. It is caused by different. One can see that the band at
23 different selection rules for one- and
24 two-photon absorption, as described in the 725 nm is much more intensive than that at
25 literature²². It is worth noticing that the high 875 nm. The maximum value of σ_2 ,
26 energy 2PA band at 725 nm is observed measured at 725 nm is approximately
27 for all the compounds and has the highest doubled compared to those of compound
28 value of σ_2 among other 2PA bands. It 1 and is equal to 2500 GM. In the studies

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3 of two-photon absorption cross-sections but its position remains the same, the
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6 various normalization factors are used, wavelength of maximum σ_2 is equal to
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9 among which the normalization to molar 725 nm. However, the low energy band,
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11 mass is the most popular. If the maximum which is located at 875 nm for other
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13 σ_2 is divided by molar mass, a similar investigated compounds, is
14
15 value is obtained, which means that such bathochromically shifted to 1050 nm.
16
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18 structural change does not impose neither Similarly to compound 1, there is a dip in
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20 cooperation nor deleterious effects on the the two-photon absorption cross-section
21
22 multiphoton absorption properties of the spectra at twice the wavelength of
23
24 investigated compounds 1 and 4. In case maximum 1PA band. The 2PA spectrum
25
26 of compounds 2 and 3, the spectra of of compound 3 is presented in Figure 3. c).
27
28 two-photon absorption cross-section show The higher energy band is
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30 more complex structures, similarly to their bathochromically shifted by 50 nm to
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32 1PA spectra. For compound 2 775 nm and the value of σ_2 is around 8000
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34 (Figure 3. b), the higher energy 2PA band GM being slightly lower than for
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36 is broader than for compounds 1 and 4, compound 2. For both compounds 2 and
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3, the maximum value of two-photon absorption cross-section is enhanced few times, while keeping the molar mass similar to compound **4**. The results prove that a simple modification of the linker, from single bond (**4**) to ethyne (**2**) and di-ethyne (**3**) links between the zinc porphyrins cores cause cooperation effect, enhancing the σ_{2^*} figure of merit.

The values of maximum two-photon absorption cross-section and the figure of merit are listed in Table 2. The dimers of zinc porphyrins, especially connected by ethyne and di-ethyne link, are much more effective two-photon photosensitizers than tetraphenyl porphyrin, or other porphyrin derivatives that are commercially used for PDT.

Table 2. Two-photon absorption cross-section, merit factors and two-photon excited oxygen sensitization properties of the investigated porphyrins (**1-4**).

	λ_{2PA}^{max} (nm)	σ_2^{max} (GM)	σ_2^{max*} (GM·mol/g)	$\sigma_2^{max} \cdot \phi_{\Delta}$ (GM)	$\sigma_2^{max} \cdot \phi_{\Delta}^*$ (GM·mol/g)	Two-photon excited oxygen sensitization enhancement factor ^[c]
1	725	1030	1.4	155	0.21	21
2	725	8900	6.1	3115	2.15	433
3	775	7950	5.4	3737	2.53	519
4	725	2500	1.7	675	0.45	94
H ₂ TPP	790	12 ^[a]	0.02	7.2 ^[b]	0.01	1

^[a] taken from reference ⁴²

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3 [b] taken from reference ²⁷
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5 [c] Enhancement factor: $\sigma_2^{max} \cdot \phi_{\Delta}$ of the compound normalized to that of H₂TPP.
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8 It was previously shown e.g. by TPEF conditions in the three-level system and
9 measurements¹⁷, that dimerization of dramatic enhancement of the excited-
10 porphyrin units leads to enhanced 2PA state singlet-singlet transition due to linear
11 cross-sections and enhanced two-photon elongation of the π -conjugated system.
12 production of singlet oxygen. The σ_2 Insertion of side groups, being either
13 determined for the porphyrin dimer linked electron acceptors (A) or donors (D)
14 by ethyne and di-ethyne bonds were on influence the σ_2 in a way that two-photon
15 the order of 8200 and 5500 GM, which is absorption cross-section is the lowest for
16 similar to the values found in the current neutral porphyrins, higher for the
17 work for similar porphyrin derivatives. The porphyrins extended with A and the
18 cooperative effect was explained by a highest for compounds with D groups⁴³.
19 combination of several factors, including Even though the vast majority of
20 strong enhancement of the lowest one- molecules targeted to be used in 2PA PDT
21 photon Q-transition, better resonance are based on the porphyrin structure,
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4 there are some alternative approaches
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7 with reasonable figures of merit. One
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10 example is a macromolecular
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13 photosensitizer, which was obtained via
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16 the covalent anchoring of several
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19 molecular PS based on a
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22 dibromobenzene (DBB) core onto a water-
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25 soluble polymer chain based on
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28 poly(N-acryloylmorpholine). It resulted in
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31 large 2PA cross-section up to 2600 GM at
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35 740 nm and was proved to be an efficient
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37
38
39 candidate to cause melanoma cells death
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42 upon photo irradiation⁴⁴.
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49 4. CONCLUSIONS

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52 In this work, we investigated two-photon
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55 absorption and singlet oxygen
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photogeneration properties in a series of
zinc porphyrins, either in a monomer or
dimer form. The dimers were connected
by single bond, or by ethyne, or di-ethyne
link. We observed strong enhancement of
the obtained quantum yields for
two-photon excited singlet oxygen
generation (expressed by the product
 $\sigma_2^{max} \phi_{\Delta}$) in the porphyrin dimer
connected by di-ethyne link, around
3700 GM, which is around 500 times more
efficient than tetraphenyl porphyrin. It can
be seen that in case of zinc porphyrin
derivatives, structure optimization towards
high two-photon absorption cross-section
simultaneously enhances the properties of

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4 singlet oxygen photogeneration. Thus, in
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7 order to obtain a material capable of
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10 efficient production of singlet oxygen upon
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13 two-photon excitation, one should
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17 increase the conjugation length, so that
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21 π -delocalization is maximized, while
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24 maintaining planar structure, as shown for
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28 compounds **2** and **3**. The results are very
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31 promising for applications involving
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35 treatment of deep tumors by
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38 photodynamic therapy.
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Conflict of interest statement

There are no conflicts to declare.

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