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Paper
Статья

Photosensitizers Based on Bacteriopurpurinimide Derivatives and Silica Nanoparticles: Synthesis and Photophysical Properties

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We report the synthesis and optical characterization of photosensitizers related to bacteriopurpurin-N-propoximide and its derivative substituted with aminoethylamide surface attachment group, and their conjugates with silica nanoparticles. The obtained supramolecular complexes are characterized by long-wavelength fluorescence band and the ability to photogeneration of long-lived triplet states with high quantum yield.

Keywords: Bacteriopurpurinimide derivatives, photosensitizers, silica nanoparticles.

Фотосенсибилизаторы на основе производных бактериопурпуринимида и наночастиц кремнезема: синтез и фотофизические свойства

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Описаны синтез и фотофизические свойства фотосенсибилизаторов на основе N-пропоксиимида бактерио-пурпурина, его аминоэтиламидного производного и наночастиц кремнезема. Полученные супрамолекулярные комплексы характеризуются длинноволновой полосой флуоресценции и способностью к фотогенерации долго-живущих триплетных состояний с высоким квантовым выходом.

Ключевые слова: Производные бактериопурпуринимида, фотосенсибилизаторы, наночастицы кремнезема.

Introduction

In the last years, significant advances in fighting cancer have been made due to the development of highly selective and safe bimodal treatments, *i.e.* sonodynamic therapy (SDT), boron neutron capture therapy (BNCT), photodynamic therapy (PDT). PDT combines three essential components: photosensitizer (PS), light, and oxygen to generate cytotoxic singlet oxygen.[1-3] Destruction of tumor tissue results from direct photoinduced cytotoxic effect in the cells, indirect vascular shutdown of the blood vessels surrounding the diseased tissue, and by invoking an immune response.[4-6] PDT is minimally invasive, can selectively destroy malignant tissues, due to low toxicity of used PS it is a relatively benign procedure with minimal local and systemic side effects. However, the technique has its limitations, specifically, PDT efficacy strongly depends on the depth of penetration of light into tissue. Another limitation is a relatively low selectivity of accumulation of PS in the tumor tissue characteristic of classical photosensitisers in clinical PDT.

Of particular interest is a group of naturally occurring chlorophylls and their derivatives having strong light absorption in the red and near IR spectral region as their therapeutic absorption window between about 660-800 nm enables to ablate tumors which cannot be accessed with PS absorbing at shorter wavelengths. Light of such wavelength penetrates into tissue to the depth of more than 20 mm allowing treatment of deep-seated and pigmented tumors.[7-9]

The choice of natural pigments to be used for synthesis of new PS is influenced by several factors, including their natural occurrence, strong long-wavelength absorption, convenient substitution on side-chain functional groups, structural similarity with endogenous porphyrins which is thought to ensure low toxicity of PS and its rapid elimination from the body. However, due to high hydrophobicity, low chemical and photo stability, limited tumor uptake of chlorins and bacteriochlorins, efforts are currently underway to modify them further in a way to enhance photophysical properties, reach higher solubility in aqueous medium and polar solvents, and improve tumor affinity.[10,11]

The use of silica nanoparticles (SNP) with immobilized PS opens up new approaches to improve the efficacy of PDT.[12] The nanoparticles of silica possess a number of unique characteristics, such as optical properties, stability, high specific surface, chemical and photochemical inertness in ultrafine (nano-scale) state.[13,14] An important advantage of SNP is their ability to penetrate into the tumor tissue by passive targeting due to extravasation through defective tumor vessels.[15]

In this work, *O*-propyloxime *N*-propoxybacteriopurpurinimide methyl ester (PS-1), which showed good bioassay result,[16] and its novel derivative carrying ethylenediamine moiety (PS-2) were used as lead compounds. Photophysical properties and values of the quantum yield of the generation of triplet excited states of the obtained water-soluble supramolecular complexes based on bacteriopurpurinimide derivatives and silica nanoparticles (PS-SNP-1 and PS-SNP-2) were studied. A possibility of photodynamic activity of silica nanoparticles modified PS-1 and PS-2 as potential agents for PDT was estimated.

Experimental

NMR spectra were recorded with a Bruker DPX-300 (Germany) instrument at 300 MHz using deuterochloroform. MALDI mass spectra were acquired on a Bruker Ultraflex TOF/TOF mass spectrometer (UK) using 2,5-dihydroxy benzoic acid (DHB) as the MALDI matrix. TLC was performed on plates precoated with Kieselgel 60 F$_{254}$ silica gel (Merck, Germany) plates using methylene chloride as a solvent.

The absorption spectra and the formation and decay kinetics of intermediate products were measured on a nanosecond laser photolysis apparatus.[17] A nitrogen laser (PRA LN 1000, with 1 ns pulse duration and 337 nm radiation wavelength), operating in the frequency mode of ≤10 Hz was used as an excitation source. Rate curves were averaged (by ≥16 laser pulses) with a UF258 high-speed digitizer (Sweden) connected to a personal computer. Each rate curve contained 12-14 bits of points with a distance between points of 4-400 ns. The data presented in the work are average values obtained by processing of no less than ten rate curves measured under the aforementioned conditions. Dissolved oxygen was removed by evacuation. All measurements were carried out at 20 °C in a quartz cell with an optical path length of 2 mm. Electronic absorption spectra were measured on a UV-VIS-NIR UV-3101PC (Shimadzu, Germany) spectrophotometer. Fluorescence spectra were measured on a Shimadzu RF5000 spectrofluorophotometer using standard 10 mm quartz cuvettes in steps of 1 nm.

An estimation of the fluorescence quantum yields and triplet states generation was performed using solutions of zinc complex of tetraphenylporphyrin in toluene and 4-carboxybenzophenone in DMF as standards. Experimental accuracy is ±2%. Calculation of photophysical parameters was performed by known formulas.[18] The binding constants of PS-1 and PS-2 with NP were determined by spectrophotometric titration using Scatchard equation.[19]

Oxime N-hydroxybacteriopurpurinimide (2). The solution of bacteriopurpurin **1** (50 mg) in pyridine (20 ml) was treated with hydroxylamine hydrochloride (25 mg). The mixture was stirred at room temperature for 15 h. The course of the reaction was followed using spectrophotometry. Then the resulting mixture was diluted with 50 ml chloroform, neutralized with diluted HCl, and transferred to a separatory funnel. The lower red-colored organic layer was drained off and washed with water (3×40 ml). The aqueous upper layer was extracted with 3×50 ml chloroform to full decolorization. The pooled extracts were dried over anhydrous sodium sulfate and concentrated to afford product **2** in 68 % yield. UV-Vis (CH$_2$Cl$_2$) λ_{max} nm: 363, 412 (Soret), 547 and 809 (relative intensity 1:0,75:0,35:0,9).

O-Propyloxime N-propoxybacteriopurpurinimide methyl ester (4). To the solution of purpurinimide **2** (10 mg) in THF (3 ml) propyl iodide (4 ml) was added dropwise. The mixture was stirred at room temperature for 1 h, whereupon potassium carbonate was added (10 mg). The reaction mixture was then stirred for more 24 h. The course of the reaction was followed using TLC and spectrophotometry. The resulting mixture was treated with 150 ml water followed by 1 N HCl (5 ml) and extracted with 5×30 ml chloroform to full decolorization. The pooled extracts were dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The residue was chromatographed on silica eluting with CHCl$_3$:CH$_3$OH (50:1, vol/vol). To solution of *O*-propyloxime *N*-propoxybacteriopurpurinimide **3** (10 mg) in diethyl ether solution of diazomethane in diethyl ether was added. The reaction mixture was then stirred for 30 min and then concentrated with a rotary evaporator. The residue was chromatographed on silica eluting with CHCl$_3$:CH$_3$OH (50:1, vol/vol). Yield 53 % of product **4**. ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm: 8.65 (s, H, 5-H), 8.58 (s, H, 10-H), 8.40 (s, H, 20-H), 5.21 (m, H, 17-H), 4.59 (m, 4H, -OC*H*$_2$CH$_3$), 4.18 (m, 2H, 7-H, 18-H), 4.00 (m, H, 8-H), 3.64 (s, 3H, 12-CH$_3$), 3.58 (s, 3H, 17³-COOCH$_3$), 3.30 (s, 3H, 2-CH$_3$), 2.78 (s, 3H, 3²-CH$_3$), 2.75

(m, H, 17²-CH₂), 2.40 (m, 3H, 8¹-CH₂, 17¹-CH₂, 17²-CH₂), 2.08 (m, 2H, 8¹-CH₂, 17¹-CH₂), 1.80 (d, 3H, *J*=7.24 Hz, 7-CH₃), 1.70 (m, 9H, 18-CH₃, -OCH₂C*H₃*), 1.10 (t, 3H, *J*=7.38 Hz, 8²-CH₃), 0.00 (s, NH), -0.26 (s, NH). UV-Vis (CH₂Cl₂) λ_{max} nm ($\varepsilon \cdot 10^{-3}$, M⁻¹·cm⁻¹): 368 (100), 418 (53), 541 (40), 800 (49).

17³-Aminoethylamide O-propyloxime N-propoxybacterio-purpurinimide (5). To the solution of purpurinimide **3** (30 mg, 0.043 mmol) in methylene chloride (5 ml) was added ethylenedi-amine (15 µl, 0.43 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-di-hydroquinoline (EEDQ) (21 mg, 0.86 mmol). The reaction mixture was stirred at 0 °C for 40 h. The course of the reaction was followed using TLC. The resulting mixture was treated with 150 ml water followed by 1 N HCl (5 ml) and extracted with 5×30 ml chloroform to full decolorization. The combined extracts were dried over anhy-drous sodium sulfate and concentrated with a rotary evaporator. The residue was chromatographed on silica eluting with CHCl₃:CH₃OH (20:1, vol/vol) to afford product **5** (yield 77 %). ¹H NMR (300 MHz, CDCl₃) δ ppm: 8.65 (s, H, 5-H), 8.58 (s, H, 10-H), 8.40 (s, H, 20-H), 5.21 (m, H, 17-H), 4.68 (s, H, 17³-COON*H*CH₂CH₂NH₂), 4.59 (m, 4H, -OC*H₂*CH₃), 4.18 (m, 2H, 7-H, 18-H), 4.00 (m, H, 8-H), 3.64 (s, 3H, 12-CH₃), 3.54 (m, 2H, 17³-COONHC*H₂*CH₂NH₂), 3.54 (dt, 2H, 17³-COONHCH₂C*H₂*NH₂), 3.30 (s, 3H, 2-CH₃), 2.78 (s, 3H, 3²-CH₃), 2.75 (m, H, 17²-CH₂), 2.40 (m, 3H, 8¹-CH₂, 17¹-CH₂, 17²-CH₂), 2.08 (m, 2H, 8¹-CH₂, 17¹-CH₂), 1.80 (d, 3H, *J*=7.24 Hz, 7-CH₃), 1.70 (m, 9H, 18-CH₃, -OCH₂C*H₃*), 1.17 (m, 2H, 17³-COONHCH₂CH₂N*H₂*), 1.10 (t, 3H, *J*=7.38 Hz, 8²-CH₃), 0.00 (s, NH), -0.26 (s, NH). UV-Vis (CH₂Cl₂) λ_{max} nm ($\varepsilon \cdot 10^{-3}$, M⁻¹·cm⁻¹): 367 (101), 418 (54), 541 (39), 799 (48).

Silica nanoparticles with diameter of 60 nm were prepared in ISPM RAS by the method described elsewhere.[20] Solution SNP of 0.25 % by weight in distilled water was used in the experiment. Water solutions of PS-SNP-1 and PS-SNP-2 were prepared by adding 0.2 ml of solutions PS-1 or PS-2 in DMF with concentration of 0.06 M to 9.8 ml of SNP stock solution with intensive stirring. Thus, the amount of organic solvent in the PS-SNP-1 and PS-SNP-2 samples did not exceed 2 % (vol.). In some cases, in order to suppress the aggregation of modified nanoparticles Cremophor® was used. For this 0.2 ml of PS-1 or PS-2 solution in DMF with concentration of 0.06 M and 9.4 ml of SNP solution were mixed and then 0.4 ml of Cremophor® in bidistilled water was added. For spectral measurements the solutions of PS-SNP-1 and PS-SNP-2 were diluted by bidistilled water to a concentration $\leq 10^{-5}$ M. In comparative experiments, the solutions of PS-1 and PS-2 in DMF, ethanol and water with 2 % (vol.) DMF were used.

Results and Discussion

Earlier we have synthesized bacteriopurpurinimide **3** by reacting bacteriopurpurin **1** with propoxyamine.[16] How-ever, the latter is not commercially available, and its prepara-tion from hydroxylamine can hardly be regarded as a robust synthetic procedure. Therefore, the two-step approach to the target product **3** proposed herein is to convert bacteriopur-purin **1** to bacteriopurpurin-*N*-hydroxyimide **2** by reaction with hydroxylamine followed by treatment of **2** with pro-pyl iodide in the presence of potassium carbonate affording dipropoxy-substituted bacteriopurpurinimide **3** in 55 % yield (Scheme 1). The reaction with hydroxylamine was direct-ly monitored by detecting a hypsochromic shift of 817 nm Q_2-absorption band of bacteriopurpurin **1** to 800 nm. Alkyla-tion of purpurinimide **2** with propyl iodide was accompa-nied by band shift in the absorption spectrum of product **3** by 9 nm. Treatment of the latter with diazomethane gave the methyl ester **4** (PS-1) in quantitative yield.

To promote coupling of photosensitizer to the hydroxyl groups on silica surface, purpurinimide **3** was functionalized with the aminoethylamide moiety introduced by reaction with ethylenediamine in the presence of condensing agent, EEDQ (yield is 77 %).

The use of supramolecular complexes of hydrophobic PS and silica nanoparticles (Scheme 2) allows to solve a number of tasks, including water solubility, the ability to regulate the aggregation behavior of the photosensitizer and increase the selectivity of PS accumulation.[21,22]

Electronic absorption spectra of solutions of PS-1 in DMF and water are shown in Figure 1. In water solutions of PS-1 the absorption spectrum contains a band with a maximum of 894 nm in addition to the main Q_2-band at 806 nm. A similar situation is observed for PS-2 solution in water (corresponding to the absorption peaks are arranged at 804 and 894 nm). The presence of the new band at 894 nm indicates finding PS-1 and PS-2 in an aggregate form in water,[23,24] in contrast to solutions of PS-1 and PS-2 in DMF, ethanol and other organic solvents. The presence of aggregates of PS-1 and PS-2 was accompanied by the absence of the fluorescence in these water solutions. However, no absorption band at 894 nm is observed in aqueous solution of the nanostructured photosensitizers PS-SNP-1 and PS-SNP-2, indicating that pigments form a monomer species on the surface of SNP. The interaction of PS-1 and PS-2 with silicon nanoparticles is manifested in the significant decrease of intensity of Q_2-band.

Figure 1 for the case of PS-SNP-1 shows that Q_2-band in the electronic spectrum is broadened somewhat, which may be a result of partial aggregation of the SNP modified by photosensitizers. This corresponds to reduction in the lifetime of the PS-2 singlet state t_0, equal to 3.4 ns in water, as opposed to 14.8 ns for PS-SNP-2 in the presence of Cremophor®. The assumption about SNP aggregation is also supported by fluorescent spectroscopy data. Thus, the PS-1 and PS-2 in ethanol possess a fluorescence spectrum with maximum at 815 nm and a quantum yield of 11 %. At the same time PS-SNP-1 and PS-SNP-2 in aqueous solutions do not possess fluorescence.

The addition of Cremophor® as a solubilizer leads to a change in shape of the Q_2-band (Figure 1) and the appearance of fluorescence in the 817 nm with quantum yield of 20 % for the PS-SNP-1 and 23 % for the PS-SNP-2. The increase of fluorescence quantum yield of PS-1 and PS-2 in the complexes with SNP is observed as compared with their solutions.

Therefore, the presence of fluorescence in the PS-SNP-1 and PS-SNP-2 allows to consider these complexes promising fluorescent agents for tumor imaging.

To study a stability of complexes of PS-SNP-1 and PS-SNP-2 binding constant (K_B) values were estimated at concentrations of PS-1 and PS-2 of $2.7 \cdot 10^{-5}$ M in solutions containing nanoparticles at concentrations of 0.01-2.5 % by weight. The values of K_B were $5.7 \cdot 10^7$ and $3.4 \cdot 10^8$ M⁻¹ for PS-SNP-1 and PS-SNP-2, respectively. A higher value of K_B of PS-SNP-2 can be explained by structural differences of molecules of PS-1 and PS-2. Apparently, the presence of the aminogroup in PS-2 molecule provides more strong binding due to the additional electrostatic interaction of SiO⁻…NH₃⁺ type on SNP surface. It should be noted that
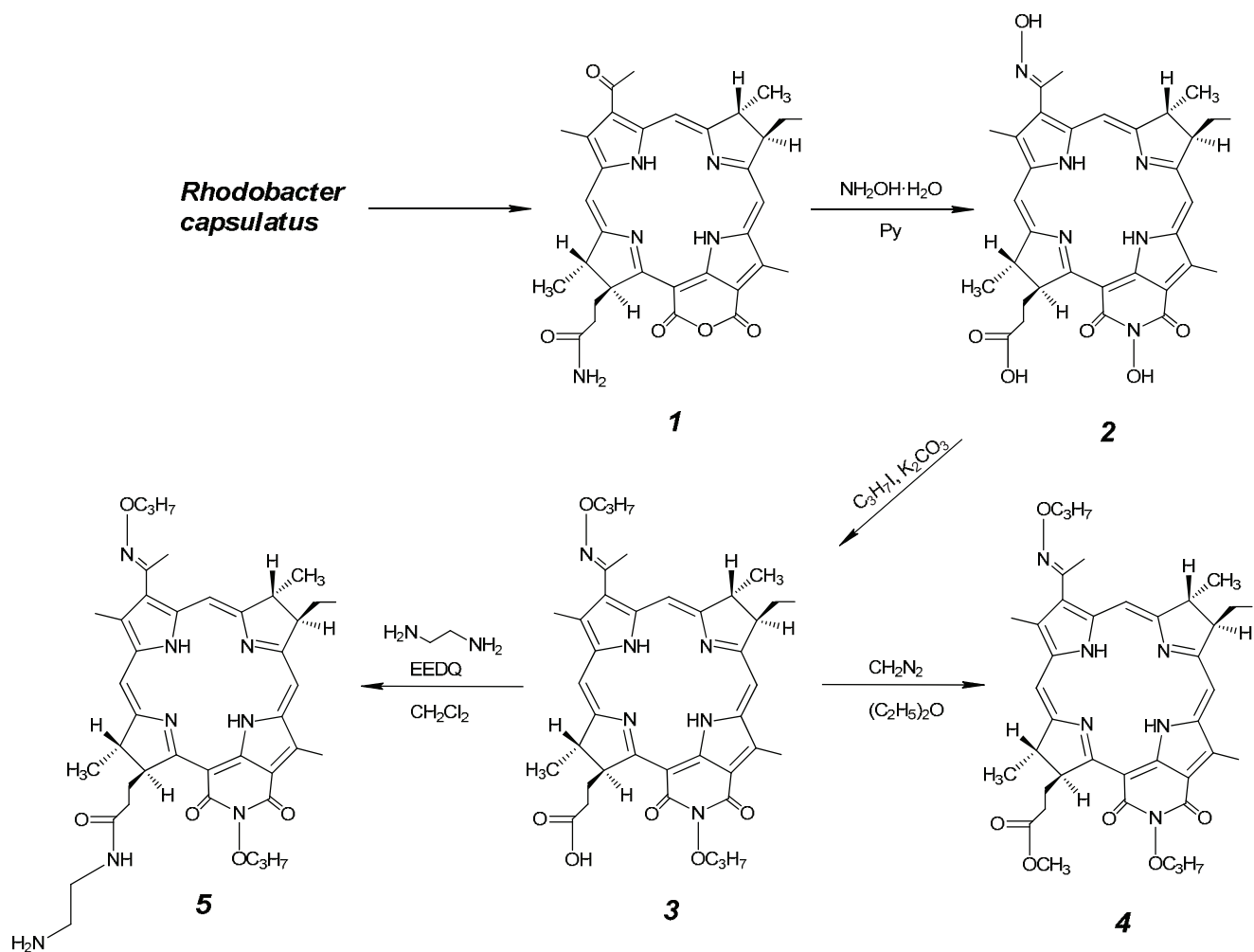
Scheme 1. Synthesis of photosensitizers PS-1 **4** and PS-2 **5** based on bacteriopurpurinimide derivatives.
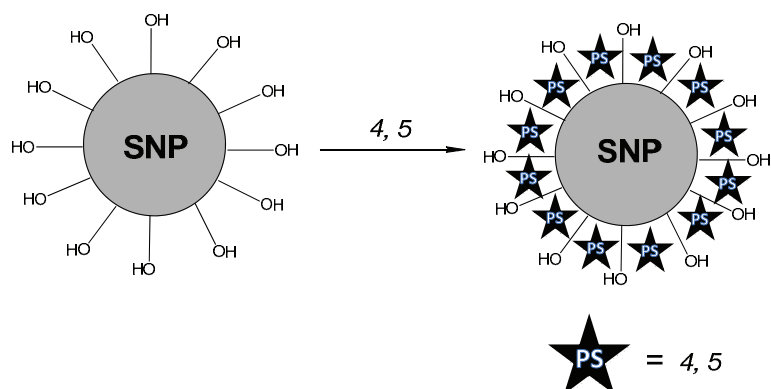
Scheme 2. Preparation of PS conjugates with silica nanoparticles, PS-SNP-1 and PS-SNP-2.
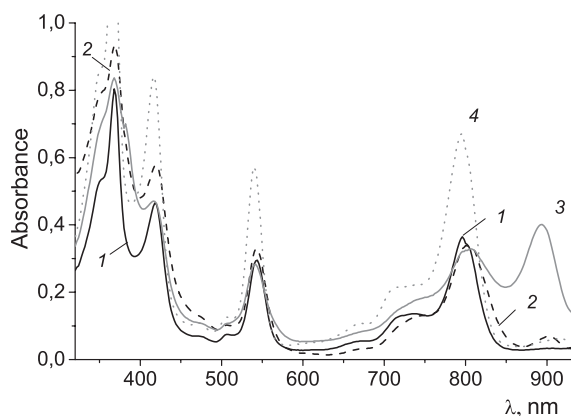
Figure 1. Electronic spectrum: *1* – PS-SNP-1 in 4 % water solution of Cremophor®, *2* – PS-SNP-1 in water, *3* – PS-1 in water, *4* - PS-1 in DMF. Concentration of PS-1 7.4·10⁻⁵ M in all cases.

Table 1. The parameters of the triplet states of PS-1, PS-2, PS-SNP-1, and PS-SNP-2.

Compound/ Solvent	t, μs[*]	$k_{TT} \cdot 10^{-4}$, s⁻¹	$k_q(O_2) \cdot 10^{-9}$, M⁻¹·s⁻¹	Φ_T
PS-1/DMF	83	1.2	1.0	0.17
PS-2/DMF	83	1.2	1.0	0.17
PS-1/ethanol	52	1.9	1.1	0.19
PS-2/ethanol	59	1.7	1.0	0.16
PS-SNP-1/ water with 4 % Cremophor®	48	2.1	2.6	0.44
PS-SNP-2/ water with 4 % Cremophor®	56	1.8	2.4	0.41

[*] t – the lifetime of the triplet state; k_{TT} – the death rate constant of the triplet state; $k_q(O_2)$ – bimolecular rate constant for the death of the triplet state in the oxygenated solutions; Φ_T – quantum yield of the generation of the triplet state.

SNP-PS interaction is not 1:1 and is described by Poisson distribution.[25]

To determine the photosensitizing activity of the synthesized photosensitizers the parameters of their triplet excited states were determined. Laser photolysis of solutions of PS-1 and PS-2 in ethanol and DMF and in SNP complexes leads to the formation of triplet states characterized by T-T absorption spectrum in the range 540-660 nm, shown in Figure 2 for the case of PS-SNP-2.
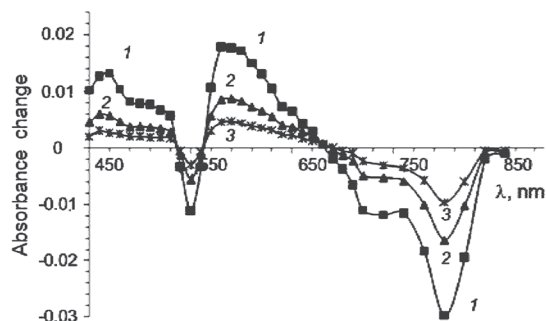

Figure 2. Difference absorption spectra of the intermediate products obtained upon laser photolysis of deoxygenated solutions of PS-SNP-2 (7.7·10⁻⁵ M) in 4 % water solution of Cremophor® within 10 (*1*), 50 (*2*), and 200 μs (*3*) after the laser flash.

The similar spectra are observed for the PS-1 and PS-SNP-1. Kinetics of triplet state death in deoxygenated ethanol solution obeys first order k_{TT} with constant rate of (1.7-1.9)·10⁴ s⁻¹ (Table 1). The main channel of the triplet state death in these experimental conditions is the quenching reaction by molecular oxygen.

The bimolecular rate constant k_q estimated by comparison of the kinetics of death in deoxygenated and oxygenated solutions based on the concentration of O_2 in ethanol of 2·10⁻³ M is 1.1·10⁹ M⁻¹·s⁻¹. Similar values of k_{TT} and k_q were obtained for PS-1 and PS-2 in DMF, and PS-SNP-1 and PS-SNP-2 in Cremophor® water solution (Table 1).

The calculation of the quantum yield of the generation of triplet states (Φ_T) of PS-SNP-1 and PS-SNP-2 in Cremophor® water solution gives the respective values 44 and 41 %. Apparently the increase in Φ_T as well as the fluorescence quantum yield of PS-1 and PS-2 in the complexes with SNP is associated with decrease in thermal molecular mobility of immobilized photosensitizers. The values of Φ_T correspond to the order of the expected quantum yield of singlet oxygen generation, which, depends on the microenvironment and could reach 30-55 % within the cell.[26,27]

Conclusions

Thus, here we extend the *de novo* route to long-wave absorbing analogues of the fundamental bacteriopurpurinimide and their conjugates with silica nanoparticles. Novel supramolecular complexes are characterized by long-wavelength fluorescence band and the ability to photogeneration of long-lived triplet states with high quantum yield that makes them promising agents for *in vivo* study in the field of photodynamic therapy and diagnosis of tumors.

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