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Novel fully-BODIPY functionalized cyclotetraphosphazene photosensitizers having high singlet oxygen quantum yields

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ABSTRACT

Novel fully-BODIPY functionalized dendrimeric cyclotetraphosphazenes (**FBCP 1** and **2**) have been synthesized and characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopies. The photophysical and photochemical properties of **FBCP 1** and **2** are investigated in dichloromethane solution. The effectiveness of singlet oxygen generation was measured for **FBCP 1** and **2** by UV–Vis spectra monitoring of the solution of 1,3-diphenylisobenzofuran (DPBF), which is a well-known trapping molecule used in detection of singlet oxygen. **FBCP 1** and **2** show high molar extinction coefficients in the NIR region, good singlet oxygen quantum yields and appropriate photo degradation. The data presented in the work indicate that the dendrimeric cyclotetraphosphazenes are effective singlet oxygen photosensitizers that might be used for various areas of applications such as photodynamic therapy and photocatalysis.

1. Introduction

Singlet oxygen ($^{1}O_2$), the lowest excited state of the molecular oxygen, plays a number of different and important roles in biological systems [1]. $^{1}O_2$ can oxidize various kinds of biological molecules such as DNAs, proteins and lipids [2–4]. Also, singlet oxygen has been proposed to be involved in the induction of gene expression, the cell signaling cascade and the mitochondrial membrane pore transition [5,6]. Currently most cited application of singlet oxygen is photodynamic therapy which is used to destroy malignant cancer cells [7–10]. Although there are many known sources of $^{1}O_2$, photosensitized generation is the simplest and controllable method for the production of singlet oxygen, requiring a, light of an appropriate wavelength and oxygen [7]. Commonly used photosensitizers are highly conjugated molecules such as porphyrin, phthalocyanine, methylene blue and BODIPY dyes that can be monitored by various optical imaging techniques [10–15].

Cyclophosphazenes are an important class of heterocyclic ring systems containing phosphorus and nitrogen repeating units [16]. The best known members of the cyclophosphazenes are hexachlorocyclotriphosphazene ($N_3P_3Cl_6$) and octachlorocyclotetraphosphazene ($N_4P_4Cl_8$) and they are of interest as starting materials in the synthesis of small molecules or polymers [16–20]. Many different types of cyclotetraphosphazene derivatives have been designed and assembled via substitution reactions of various nucleophilic reagents with $N_4P_4Cl_8$ in recent years [21–24]. $N_4P_4Cl_8$ is a very valuable core for synthesizing dendrimeric molecules that can directly afford eight functional units [21,25–27]. Its eight membered ring is inert and stable to a variety reaction conditions, so it can be used as scaffold for the preparation of multisite ligands [28]. Furthermore, the chemical features of cyclotetraphosphazenes can be modulated by the type, number and orientation of the functional groups. This leads to the emergence of the new applications such as organic light emitting diodes, flame retardant additives to polymers, fluorescence probes and anticancer agents [26,27,29,30]. Recently, we reported that the BODIPY decorated dendrimeric cyclotriphosphazenes are efficient singlet oxygen photosensitizers [31]. To the best of our knowledge, no attempts have been made to develop cyclotetraphosphazene derivatives as a singlet oxygen generator. The success of the previous results has encouraged us to extend the research with the combination of BODIPY and cyclotetraphosphazene core.

The aims of the present research are (*i*) synthesis of the new dendrimeric systems containing eight BODIPY units on the same molecule, (*ii*) investigation of the singlet oxygen generation ability of the first BODIPY functionalized cyclotetraphosphazene derivatives, (*iii*) demonstration of the advantages of dendrimeric systems such as the reducing the concentration range for practical applications, (*iv*) comparison of the results obtained with previous work [31]. For this purpose, novel fully-BODIPY functionalized cyclotetraphosphazenes (**FBCP 1**–**2**) have been successfully synthesized (Fig. 1) and characterized by ^{1}H, ^{13}C, ^{31}P NMR spectroscopies. The photophysical (fluorescence lifetime and fluorescence quantum yield) and photochemical (the singlet oxygen generation capabilities and appropriate photo degradation by light irradiation) properties of the novel compounds are also investigated.

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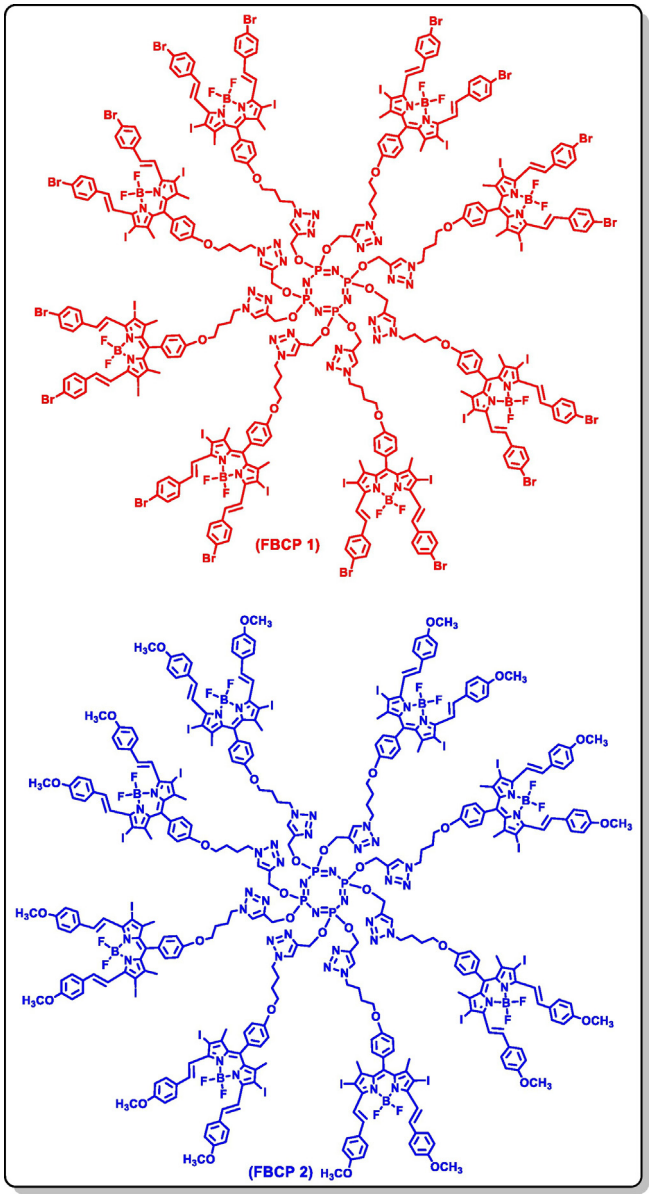

Fig. 1. Structure of fully-BODIPY functionalized cyclotetraphosphazenes (**FBCP 1–2**).

2. Experimental section

2.1. General methods

All reagents have been purchased from Aldrich and used without further purification and all solvents were obtained from Merck. All reactions have been monitored by thin layer chromatography using Merck TLC Silica gel 60 F_{254}. Silica gel 60 (particle size: 0.040–0.063 mm, 230–400 mesh ASTM) for column chromatography are obtained from Merck. Elemental analyses were obtained using a Thermo Finnigan Flash 1112 Instrument. Positive ion and linear mode MALDI-MS of complexes have been obtained in 2,5-dihydroxybenzoic acid as MALDI matrix using nitrogen laser accumulating 50 laser shots using Bruker Microflex LT MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization-Time-Of-Flight) mass spectrometer. ^{1}H, ^{13}C and ^{31}P NMR spectra are recorded for all compounds in $CDCl_3$ solutions on a Varian INOVA 500 MHz spectrometer. Electronic absorption spectra in the UV–Vis. region are recorded with a Shimadzu 2101 UV–Vis spectrophotometer. Fluorescence excitation and emission spectra are recorded on a Varian Eclipse spectrofluorometer using 1 cm path length cuvettes at room temperature. Fluorescence lifetimes have been measured using a time correlated single photon counting setup (TCSPC) (Horiba Fluorolog 3 equipment.) HORIBA Model: FLUOROLOG 3. Signal acquisition has been performed using a TCSPC module (NanoLED −390 emitting 390 nm). Photo-irradiations have been done using a General Electric quartz line lamp (300 W). A 600 nm glass cut off filter (Schott) and a water filter are used to filter off ultraviolet and infrared radiations respectively. An interference filter (Intor, 600 nm with a band width of 40 nm).

2.2. Synthesis

Compound **1**–**3** were synthesized according to literature [29,31].

2.2.1. Synthesis of FBCP 1

Compound **1** (135.0 mg, 0.132 mmol) was dissolved in CH_2Cl_2 (4.0 mL), CH_3OH (1.0 mL) and H_2O (1.0 mL). Compound **3** (10.0 mg, 0.016 mmol), sodium ascorbate (7.5 mg, 0.03 mmol), $CuSO_4.5H_2O$ (6.0 mg, 0.03 mmol), and 2 drop of Et_3N were added and the mixture was stirred at room temperature for 2 days. The solvent was evaporated and the crude product was purified by silica gel column chromatography using MeOH-CH_2Cl_2 (5:100) as mobile phase. Fraction containing compound **FBCP 1** was collected then the solvent was removed under reduced pressure (43.0 mg, 0.004 mmol, 30%). Elemental analyses: Calc. (%) for $C_{320}H_{264}B_8Br_{16}F_{16}I_{16}N_{44}O_{16}P_4$: C, 43.65; H, 3.02; N, 7.00; found C, 43.58; H, 2.98; N, 6.91. MS (MALDI-TOF) *m/z* Calc. 8805.21; found 8806.45 $[M + H]^+$ (Fig.S1). ^{31}P NMR (proton decoupled) (202 MHz, $CDCl_3$) δ_P −0.57 (s, 4P), ppm (Fig.S2). ^{1}H NMR (Phosphorus coupled) (500 MHz, $CDCl_3$) δ_H 8.09 (d, J = 16.6 Hz, 16H), (*trans*-CH); 7.67 (d, J = 16.60 Hz, 16H), (*trans*-CH); 7.61 (s, 8H), (NCH); 7.56 (d, J = 8.60 Hz, 32H), (Ar-CH); 7.52 (d, J = 8.60 Hz, 32H), (Ar-CH); 7.19 (d, J = 8.61 Hz, 16H), (Ar-CH); 7.04 (d, J = 8.61 Hz, 16H), (Ar-CH); 4.63 (s, 16H) ($POCH_2$); 4.51 (t, J = 7.08 Hz, 16H), (NCH_2); 4.09 (t, J = 5.94 Hz, 16H), (OCH_2); 2.25–2.18 (m, 16H), (CH_2); 1.95–1.89 (m, 16H), (CH_2); 1.53 (s, 48H), (CH_3) ppm (Fig. 2b). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 159.9, 150.2, 146.4, 145.4, 140.0, 138.1, 135.5, 133.6, 132.5, 132.0, 129.5, 129.1, 127.1, 123.4, 122.2, 119.4, 115.4, 67.1, 66.1, 58.5, 27.3, 26.2, 17.8 ppm (Fig.S4).

2.2.2. Synthesis of FBCP 2

Compound **2** (150.0 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (4.0 mL), CH_3OH (1.0 mL) and H_2O (1.0 mL). Compound **3** (12.50 mg, 0.02 mmol), sodium ascorbate (7.5 mg, 0.03 mmol), $CuSO_4.5H_2O$ (6.0 mg, 0.03 mmol), and 2 drop of Et_3N were added and the mixture was stirred at room temperature for 2 days. The solvent was evaporated and the crude product was purified by silica gel column chromatography using MeOH-CH_2Cl_2 (5:100) as mobile phase. Fraction containing compound **FBCP 2** was collected then the solvent was removed under reduced pressure (56.0 mg, 0.006 mmol, 34%). Elemental analyses: Calc. (%) for $C_{336}H_{312}B_8F_{16}I_{16}N_{44}O_{32}P_4$: C, 50.30; H, 3.92; N, 7.68; found C, 50.18; H, 3.89; N, 7.60. MS (MALDI-TOF) *m/z* Calc. 8023.29; found 8024.12 $[M + H]^+$ (Fig.S5). ^{31}P NMR (proton decoupled) (202 MHz, $CDCl_3$) δ_P −0.56 (s, 4P), ppm (Fig.S6). ^{1}H NMR (Phosphorus coupled) (500 MHz, $CDCl_3$) δ_H 8.15 (d, J = 16.73 Hz, 16H), (*trans*-CH); 7.66–7.61 (m, 32H + 16H), (Ar-CH, *trans*-CH); 7.59 (s, 8H), (NCH); 7.19 (d, J = 8.41 Hz, 16H), (Ar-CH); 7.03 (d, J = 8.41 Hz, 16H), (Ar-CH); 6.97 (d, J = 8.80 Hz, 32H); 4.63 (s, 16H) ($POCH_2$); 4.52 (t, J = 7.16 Hz, 16H), (NCH_2); 4.09 (t, J = 5.95 Hz, 16H), (OCH_2); 3.89 (s, 48H), (OCH_3); 2.25–2.16 (m, 16H), (CH_2); 1.95–1.88 (m, 16H), (CH_2); 1.52 (s, 48H), (CH_3) ppm (Fig.S7). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 160.8, 159.7, 150.4, 145.7, 139.0, 138.9, 138.5, 133.2, 129.7, 129.6, 129.3, 129.2, 127.5, 122.2, 116.8, 115.2, 114.3, 67.1, 66.1, 58.4, 55.4, 27.3, 26.2, 17.7 ppm (Fig.S8).