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Tetrapyrazinoporphyrazine with eight peripheral adamantanylsulfanyl units – Synthesis and physicochemical study

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ABSTRACT

A novel, (1-adamantylsulfanyl)-octasubstituted tetrapyrazinoporphyrazine has been synthesized and analyzed for its key physicochemical properties. Also, two 1-adamantylsulfanyl-substituted pyrazine derivatives were compared, and their crystallographic structures as well as chemical reactivity were assessed and discussed. Porphyrazine macrocycle showed good fluorescence and singlet oxygen generation properties as well as photostability. In addition, studied adamantylsulfanyl porphyrazine, despite its hydrophobic nature, revealed good solubility in polar solvents. Electrochemical studies revealed that the macrocycle underwent oxidation by one one-electron process and reduction with two one-electron processes.

1. Introduction

Tetrapyrazinoporphyrazines (TPyzPz) constitute a broad class of macrocyclic compounds, which may be regarded as porphyrazines with four annulated pyrazine rings, or as 1,4,8,11,15,18,22,25-octaazaphthalocyanines. They have been first reported by Linstead et al. [1] in 1937 and have been recently expertly reviewed [2,3]. Phthalocyanines, porphyrazines (Pzs) and related macrocycles may be used in various biomedical areas, including probes for DNA/RNA detection [4], photodynamic therapy (PDT) [5,6], fluorescent imaging [7] and magnetic resonance imaging (MRI) agents [8].

The potential of phthalocyanines and porphyrazines comes not only from their remarkable stability and easy accessibility by chemical synthesis but foremost by the possibility of fine-tuning of their spectral and physicochemical properties. Numerous approaches of chemical modifications have been reported so far, including the exchange of the central metal ion, attachment of functional groups to the peripheral or axial positions as well as coupling of the dye to other, biologically active molecules [9–12]. Another important group of derivatives includes porphyrazines with directly attached heteroatom substituents or fused heterocyclic rings [13–15].

The most critical factor for prospective applications of novel macrocycles as photosensitizers in PDT or fluorescent probes in imaging is their ability to generate reactive oxygen species and high values of their fluorescence quantum yield. Furthermore, the ideal PDT agent should absorb light from the wavelength range between 650–850 nm, which shows the best tissue penetration [16]. A common drawback of porphyrinoid dyes, in general, is their susceptibility to form aggregates in solution, which is a result of their large, hydrophobic structure and π-π bond stacking. This undesired phenomenon contributes to self-quenching of the excited state of the macrocycle and results in a decrease of both fluorescence and singlet oxygen generation [17,18]. The self-association of Pzs can be significantly decreased by an endowment of the macrocycle ring with bulky peripheral substituents [19,20]. Concerning our previous research on designing of the molecules for biomedical use, one has to consider their solubility in polar solvents. The highly hydrophobic nature of TPyzPz ring can be successfully countered by the introduction of suitable peripheral groups. Highly water-soluble macrocycles have been obtained by decorating their periphery with anionic (sulfate) [21], cationic (tertiary ammonium salts) [22], ester and carboxylic acid groups [23].

Adamantane moiety raises much interest in modern medicinal chemistry for two reasons. Firstly because of the increase of the lipophilicity and secondly due to the steric hindrance [24,25]. The adamantyl substituent has had especially attracted our interest, regarding many reports on the porphyrinoid macrocycles and adamantane

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conjugates. There have been obtained and subjected to physicochemical study various adamantane-substituted porphyrazines [26], including pyrazinoporphyrazines [27]. Moreover, interesting studies have been reported for adamantane-appended phthalocyanines [28–30] and their incorporation into various nanostructures and supramolecular complexes, including nanoemulsions and liposomes [31,32]. The most important feature of highly lipophilic adamantane is its ability to form a stable host-guest complex with β-cyclodextrin. These interactions have been used for obtaining of supramolecular complexes between adamantane-appended macrocycles and β-cyclodextrin derivatives. Also, these complexes have revealed many essential features, including an improved solubility (of generally lipophilic macrocycle) and a possibility to use them in biomimetics of various enzymes [33–37].

In this paper, the synthesis of tetrapyrazinoporphyrazine octa-substituted with 1-adamantylsulfanyl units is reported. The macrocycle was subjected to a series of photochemical, photophysical and electrochemical studies, including singlet oxygen and fluorescence quantum yields evaluation, assessment of its aggregation and photobleaching tendency. Obtained porphyrazine complex showed promising results for future applications in biomedical and engineering applications.

2. Experimental

Additional experimental details are presented in supplementary materials.

2.1. Chemicals and instrumentation

All reactions were conducted in oven dried glassware under argon atmosphere using Radleys Heat-On heating system. All solvents were rotary evaporated at or below 60 °C under reduced pressure. All solvents and reagents were obtained from commercial suppliers and used without further purification, unless otherwise stated. Flash column chromatography was carried out on Merck silica gel 60, particle size 0.040–0.063 mm. Thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F 254 plates and visualized with UV (λ_{max} = 254 or 365 nm). UV–vis spectra were recorded on a Hitachi UV–vis U-1900 and Shimadzu PC-160 spectrophotometers. The NMR spectra were acquired on Agilent DD2 800 spectrometer operating at resonance frequencies of 799.903 and 201.146 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are quoted in parts per million (ppm) and are referred to a residual solvent peak. Coupling constants (*J*) are quoted in hertz (Hz). The abbreviations s, bs, d, and m refer to singlet, broad singlet, doublet, and multiplet, respectively. ^{1}H and ^{13}C NMR resonances were unambiguously assigned on the basis of ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra. All NMR experiments were carried out at 298 K. Mass spectra (ES, MALDI TOF, HRMS) were carried out by the Advanced Chemical Equipment and Instrumentation Facility at the Faculty of Chemistry and the Wielkopolska Center for Advanced Technologies at Adam Mickiewicz University in Poznan. Melting points were obtained on a “Stuart” Bibby apparatus and are uncorrected.

2.2. Synthesis

2.2.1. 5,6-Bis(1-adamantylsulfanyl)pyrazine-2,3-dicarbonitrile (2)

5,6-Dichloropyrazine-2,3-dicarbonitrile (**1**) (0.610 g, 3 mmol), 1-adamantanethiol (1.03 g, 6 mmol) and triethylamine (0.8 mL, 6 mmol) were stirred in 25 mL of THF at room temperature for 18 h. Afterward, the reaction mixture was concentrated, dissolved in 20 mL of DCM and extracted several times with water. The organic layer was subsequently dried with $MgSO_4$ and vaporized to dryness. The crude product was put on a top of a Celite plug, washed with an excess of methanol and diethyl ether, then collected by rinsing down with DCM. After vaporization of 0.94 g (68% yield) of pure compound **2** was obtained. M.p. (THF/MeOH): 220–230 °C (slow dec.). R_f (DCM/hexanes, 1:5): 0.21. ^{1}H NMR (800 MHz, pyridine-d_5) δ 2.34 (bs, 12H), 1.97 (s, 6H), 1.68 (d, *J* = 12 Hz, 6H), 1.60 (d, *J* = 13 Hz, 6H). ^{13}C NMR (201 MHz, pyridine-d_5) δ 161.0, 125.8, 115.2, 55.6, 42.2, 36.6, 30.7. HRMS (MALDI) *m/z* found: 462.1906 $[M]^+$ $C_{26}H_{30}N_4S_2$ requires 462.1912 $[M]^+$.

2.2.2. 3,5,6-Tris(1-adamantylsulfanyl)pyrazine-1-carbonitrile (3)

5,6-Dichloropyrazine-2,3-dicarbonitrile (**1**) (1.0 g, 5 mmol), 1-adamantanethiol (2.524 g, 15 mmol) and K_2CO_3 (6.9 g, 50 mmol) were stirred in 30 mL of THF at 60 °C for 18 h. Afterwards, reaction mixture was cooled down, filtered through a Celite plug, and vaporized to dryness. Crude product was washed with excess of methanol, then purified by means of column chromatography (DCM/hexanes, 1:2–2:1) to give compound **4** as a yellow powder (0.755 g, 25% yield). M.p. (THF/MeOH): 223 °C. R_f (DCM/hexanes, 1:5): 0.36. ^{1}H NMR (800 MHz, $CDCl_3$) δ 2.35 (bs, 6 H), 2.31 (bs, 6H), 2.09-2.07 (m, 15H), 1.78 (m, 6H), 1.74 (m, 6H), 1.68 (m, 6H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 158.8, 155.1, 146.4, 127.6, 116.8, 54.0, 53.9, 52.8, 44.2, 41.9, 41.9, 36.3, 36.2, 36.0, 30.3, 30.1, 30.1. HRMS (MALDI) *m/z* found: 626.2665 $[M+Na]^+$ $C_{35}H_{45}N_3S_3$ requires 626.2673 $[M+Na]^+$.

2.2.3. Zinc(II) 2,3,9,10,16,17,23,24-octakis(1-adamantylsulfanyl)-1,4,8,11,15,18,22,25-(octaaza)phthalocyanine (4)

Compound **2** (0.6 g, 1.3 mmol), zinc acetate (0.238 g, 1.3 mmol) and DBU (0.2 mL, 1.3 mmol) were stirred in DMF at 140 °C for 2 h. After cooling down, the reaction mixture was poured into 50% (v/v) AcOH solution and stirred for 30 min. The formed green precipitate was then filtered off on a Celite plug and washed with methanol and acetone. The crude product has been collected by rinsing down with DCM and THF and subjected to purification by column chromatography (DCM/CH_3CN, 100:1) to give porphyrazine **4** as a green powder (0.110 g, 17% yield). R_f (DCM/CH_3CN, 100:1): 0.43. UV–vis (DMF): λ_{max}, nm (log ε) 385 (4.92), 601 (4.35), 663 (5.22). ^{1}H NMR (800 MHz, pyridine-d_5) δ 2.85 (bs, 48H), 2.21 (s, 24H), 2.03 (d, *J* = 12 Hz, 24H), 1.84 (d, *J* = 12 Hz, 24H). ^{13}C NMR (201 MHz, pyridine-d_5) δ 160.0, 152.1, 146.9, 54.5, 44.0, 37.1, 31.2. HRMS (MALDI) *m/z* found: 1915.7104 $[M+H]^+$ $C_{104}H_{120}N_{16}S_8Zn$ requires 1915.7025 $[M+H]^+$.

2.3. X-ray studies

X-ray diffraction data for crystals **2** and **3** have been performed at 130 K. Reflection intensities for both crystals were measured with a SuperNova Dual diffractometer equipped with a Cu and Mo microfocus sources. Data were processed with the *CrysAlis PRO* software [38]. The structures were solved by direct methods using SHELXT [39] and refined by the full-matrix least-squares techniques based on F^2 with SHELXL [40]. Non-H atoms were refined anisotropically. The positions of H atoms were calculated geometrically and refined using a riding model with isotropic temperature factors 20% higher than the isotropic equivalent for the atom to which the H-atom was bonded. Interpretation of the results has been performed using Mercury program [41]. The crystal and refinement data are given in Table 1. The CIFs files have been deposited with the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk, deposition numbers 1842714 and 1842715 for **2** and **3**, respectively).

2.4. Electrochemistry

Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) measurements were performed with an Autolab (PGSTAT-30) electrochemical analyzer (Eco Chemie, Netherlands). Glassy carbon (GC, area 0.00785 cm^2) was used as working electrode. Platinum wire served as a counter electrode, and Ag/AgCl wire was employed as a pseudo-reference electrode. Concentration of Pz **4** was 1 mg cm^{-3}. Tetrabutylammonium perchlorate (0.1 M) dissolved in tetrahydrofuran (TBAP/THF) was employed as the supporting electrolyte. The potential was adjusted against the $E_{1/2}$ of ferrocenium/ferrocene couple (Fc^+/Fc) measured after experiments in the same electrolyte.