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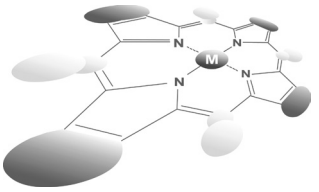

Synthesis and characterization of 5-(4-carboxyphenylspermine)-10,15,20-triphenylporphyrin

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Dedicated to Professor Roberto Paolesse on the occasion of his 60th birthday.

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ABSTRACT: We synthetized and characterized a mono spermine porphyrin derivative by NMR, UV-vis and fluorescence spectroscopy. The photophysical properties and the protonation equilibria of 5-(4-carboxyphenylspermine)-10,15,20-triphenylporphyrin have been investigated, showing that porphyrin does not aggregate in acidic solutions, differently from what occurs as soon as the core of the porphyrin is deprotonated. These aggregation processes have been detected by the rising of new fluorescence band and a significant splitting of the Soret band.

KEYWORDS: spermine porphyrin, self-assembly, synthesis, fluorescence spectroscopy, pK determination.

INTRODUCTION

Porphyrins are widely studied for their unique and fascinating optical and electronic properties. The extensive electronic delocalization due to the aromatic core leads these molecules to work as light-harvesting and energy- or electron-transfer systems in several biological processes, making these macrocycles essential for life. By attempting to mimic these processes, one can obtain porphyrin-based systems useful in different applications ranging from sensing [1–2], to photocatalysis [3–5] and biology [6–7]. Although porphyrins are mainly hydrophobic macrocycles, by exploiting their extreme synthetic versatility it is possible to introduce peripherally charged substituents making them soluble in water [8–12]. As a consequence of the solvophobicity of the porphyrins, their application in biomedical fields, *e.g.* photodynamic therapy (PDT) is increased exponentially [13–15]. With this purpose, synthetic efforts are centered around making water-soluble porphyrins also biocompatible. Indeed, due to the great tendency of porphyrins to aggregate it is difficult to use them in media with increasing lipophilicity. To overcome this issue, the renowned ability of the polyamine transport system of the cell which affords a selective accumulation of polyamine analogues in neoplastic tissues [16–19] could be exploited. Indeed several porphyrin-poliamine-conjugated molecules have been reported in the literature with the aim to make porphyrin more biocompatible for several applications ranging from boron delivery agents for boron neutron capture therapy, to PDT and DNA cleavage [20–27].

In particular, very recently, our group developed a synthetic strategy to obtain a tetra-spermine porphyrin derivative which showed interesting features in the formation of supramolecular assemblies, depending on the pH, solvent and the solution preparation method [28]. We demonstrated that tetra-spermine porphyrin and its Zn(II) derivative show an interesting affinity towards different structures of poly-nucleotides [29]. Indeed, exploiting the ability of both Zn(II) porphyrin derivatives to axially coordinate and spermine as a groove binder, we realized an inducer, stabilizer and probe for the Z form of DNA [30]. Moreover, we studied also the stabilizer/destabilizer effect of naked tetraspermine derivative

◊ SPP full member in good standing.

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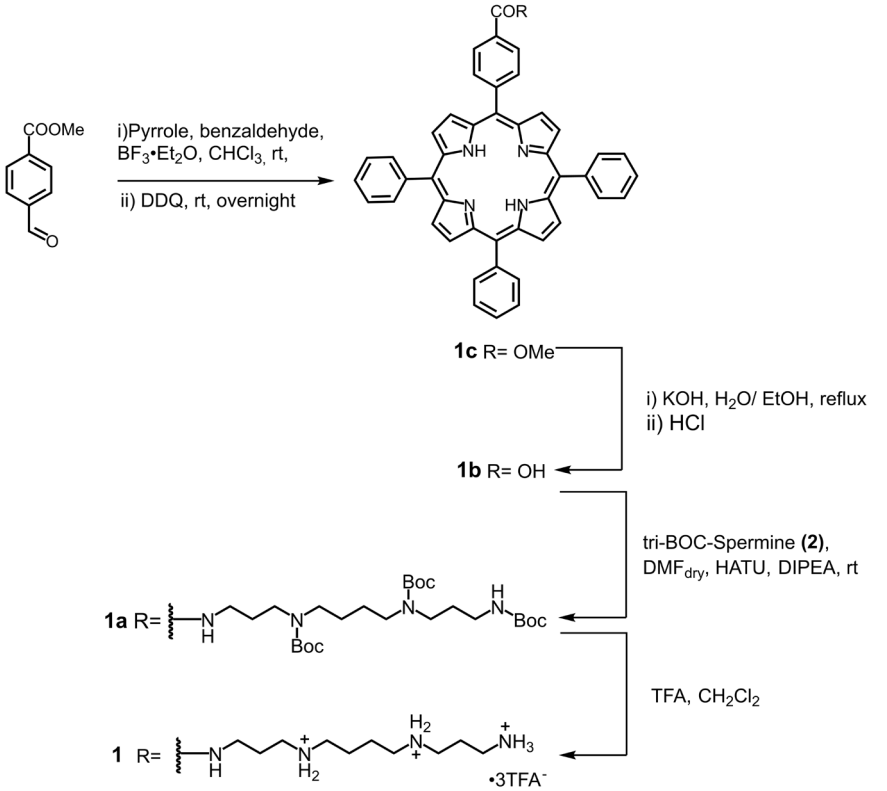

Scheme 1. General synthetic procedure to obtain the compound **(1)**

on both telomeric and aptamer sequences forming G-quadruplex structures [31–32].

The possibility of introducing a variable number of poly-amine pendants in the *meso*-position through simple amidation reaction broadens the perspectives to obtain a great variety of supramolecular structures [33] useful for different purposes from biological to material application fields. In the present work, we designed, synthetized and characterized a new mono-spermine tri-phenyl porphyrin derivative (Fig. 1). The desired compound carrying one single spermine arm, 5-(4-carboxyphenylspermine)-10,15,20-triphenylporphyrin H_2MCPSpmTPP **(1)** (Scheme 1) was achieved using a modified literature procedure [28].

RESULTS AND DISCUSSION

Synthesis of 5-(4-carboxyphenylspermine)-10,15,20-triphenylporphyrin (1)

The first step of the synthetic procedure consists in the preparation of 5-(4-methoxycarbonylphenyl)-10,15,20-triphenylporphyrin **(1c)**, using a Lindsey's method [34–35]. Then, we remove the methyl protecting group [36–37], and after activation *in situ* using HATU as a coupling agent with the free carboxylic group in compound **(1b)**, we attach the primary amine group of the pendant forming an amide derivative **(1a)**. The poly-amine pendant tri-BOC-spermine **(2)** was previously obtained after differential protection/deprotection reactions of primary and secondary amine groups in spermine [38–40]. The mono-functionalized derivative 5-(4-carboxyphenyl-tri-BOC-spermine)10,15,20-triphenylporphyrin **(1a)**, was then treated with trifluoroacetic acid in CH_2Cl_2 in order to remove the BOC-protecting groups in the spermine pendant and to obtain the corresponding trifluoracetic salt H_2MCPSpmTPP **(1)**. Unfortunately, the presence of only one hydrophilic spermine pendant does not guarantee the complete solubility in water (directly from solid at neutral pH) of our porphyrin derivative. However it is perfectly soluble in DMSO, allowing us to prepare stock solutions in DMSO and to perform characterization in water solution of compound **(1)**.

Spectroscopic measurements

Our porphyrin derivative was spectroscopically characterized by UV-vis and fluorescence spectroscopy techniques. In Fig. 1 the UV-vis absorption spectra of **(1)** [1 μM] in water shows at pH = 1.5 a Soret band at 434 nm (black line), due to the core-protonated porphyrin derivative, which is stable even after one hour. In contrast, at pH = 6.9 we observe a Soret band at 414 nm (Fig. 1, blue line) ascribed to the core non-protonated derivative, which in just one hour starts to aggregate as highlighted by the hypochromic effect of the Soret band at 414 nm (Fig. 1, red dotted line). Upon performing a

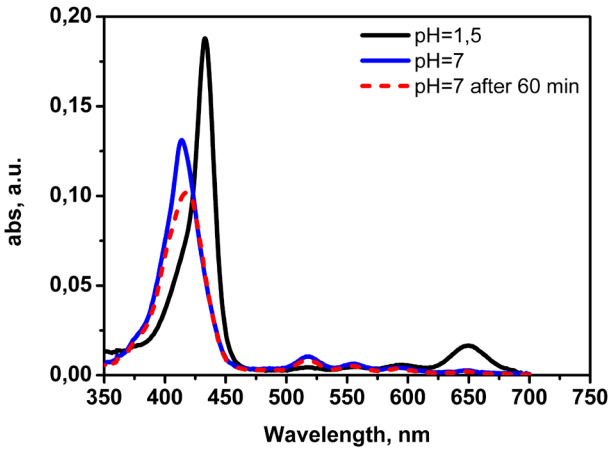

Fig. 1. UV-vis absorption spectra of compound **(1)** 1 μM in water at pH = 1.5 (black line); at pH = 7 fresh prepared (blue line) and after 60 min (red dotted line)

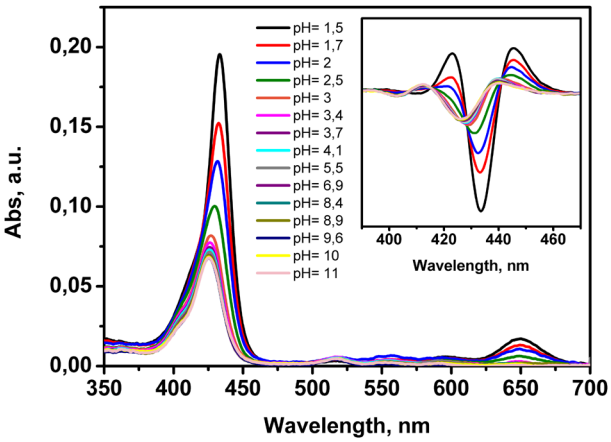

Fig. 2. UV-vis titration of compound **(1)** 1 μM in water

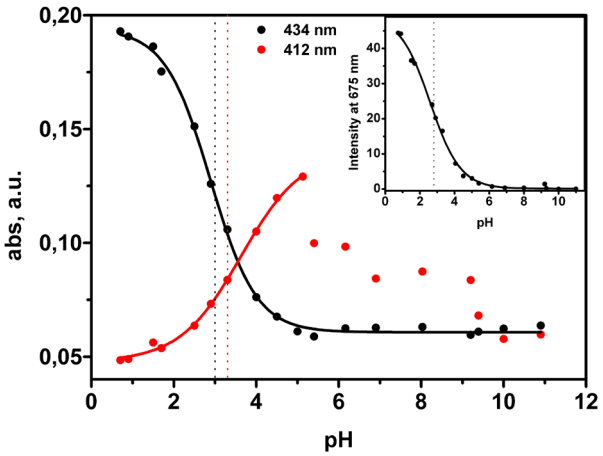

Fig. 3. Plot of absorbance at 434 nm (black circle) and at 412 nm (red circle) and fluorescence emission at 675 nm (inset) of 1 μM solution of (**1**) *vs*. pH values

preliminary UV-vis characterization, we determined the molar extinction coefficients both in DMSO and in water at pH = 1.5 per HCl, obtaining respectively $\varepsilon_{418.5\ nm}$ = $3.20 \times 10^5\ M^{-1} \cdot cm^{-1}$ and $\varepsilon_{434\ nm} = 1.72 \times 105\ M^{-1} \cdot cm^{-1}$ (see Figs S12 and S13 in the Supporting information).

Taking into account the possible aggregation phenomena, we studied the protonation equilibria and aggregation both through slow titration increasing the pH values and through independent solution methods. In the first method, a solution of **(1)** [1 μM] at pH = 1.5 was slowly titrated, adding increasing amounts of NaOH solution and recording the UV-vis spectra at different pH (Fig. 2). The decreasing intensity of the Soret band at 434 nm with increasing pH values, without the appearance of a band at 414 nm, confirms the possibility of aggregation, which should occur as soon as deprotonation of the porphyrin core happens. Indeed, we think that the positive charges of the spermine arm alone are not sufficient to hold the porphyrin in its monomeric form. The Soret band decreases in intensity up to pH 3, suggesting that at this pH the deprotonation of the core of (**1**) and the aggregation process start. As a result, the second derivative of the Soret band after pH 3 shows two absorption bands, one at ~400 nm and the second at ~425 nm, suggesting a splitting of the non-protonated band (414 nm, Fig. 2 inset). As proof of the inertness of these aggregates, decreasing the pH with one single fast addition of HCl up to 1.5 value, it was not able to restore the initial absorbance at 434 nm (Fig. S14).

The independent solutions method allows us to detect the pKa value of the porphyrin core (Fig. 3). We prepared different solutions of **(1)** at distinct pH values, diluting with water the desired amount of the stock solution of **(1)** (previously dissolved in DMSO), in order to reach a 1 μM concentration. Then UV-vis spectra were recorded for each solution. At acidic pH, the absorption spectra show only one band centered at 434 nm, in line with what was reported in the continuous titration, confirming the absence of any evidences of aggregation (Fig. S15). Starting from pH 3, it is possible to note the well-defined band at 412 nm, indicating the presence of the non-protonated form of **(1)** (Fig. S15). Through the plot of absorbances intensities at 434 nm and 412 nm *vs*. the pH values Fig. 3, is possible to evidence the pKa value for the inner core protonation process, which is around pH ~3.

After pH 5, we detect aggregation processes, highlighted by the hypochromic effect and broadening of the Soret band (Figs 4 and S14). As observed previously in the continuous titration, in the independent solution experiments the second derivatives of spectra at higher pH (ranging from 5.5 and 8.5) show the presence of two bands centered at ~400 nm and ~424 nm (inset, Fig. 4). From pH 8.6 the band at 424 nm shifts to ~440 nm, suggesting the formation of a new family of aggregates. These aggregation processes hinder the possibility of

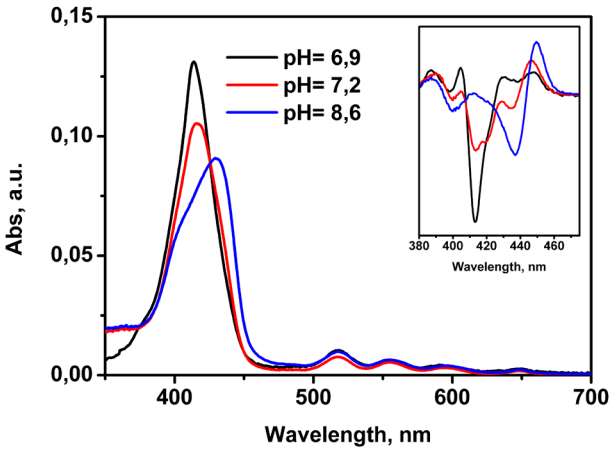

Fig. 4. UV-vis absorption spectra of compound **(1)** 1 μM in water at pH = 6.9 (black line); at pH = 7.2 (red line) and at pH = 8.6 (blue line). In the inset the second derivatives of the same spectra are reported

determining the pKa values of the poly-amine pendant, even if, from the graph reporting the intensity of absorbances at 412 nm *vs*. the pH values (Fig. 3), three steps at around pH 5.5, 6.5 and 9 might be ascribed to the pKa values of the spermine arm. In order to validate our hypothesis about the pendant pKa values, we performed simulation through the MoKa program [41–43]. The pKa values of the poly-amine pendant result at around ~7 and ~8 for the inner secondary amine groups and ~10 for the primary ones. These results are in line with what was observed in the experimental data, which are slightly shifted due to aggregation processes. Noteworthy, in the presence of 10% of DMSO it is possible to reduce the aggregation process as indicated by comparison of porphyrin UV spectra at pH 8.6 with different solvent (Fig. S16).

To further investigate the behavior of our compound, fluorescence, RLS and excitation experiments were conducted. From the plot of fluorescence spectra (Fig. S17) at 675 nm *vs*. pH values, we can confirm the pKa of the porphyrin core which in this case also is ~3 (inset Fig. 3). RLS spectra performed at different pH also confirm the formation of aggregates from pH 6 which evolve into more structured aggregates at pH 9 as indicated by the intense band at 450 nm (Fig. S18). From the comparison of fluorescence spectra at pH = 0.9, at pH = 6.3 with λ_{ex} = 422 nm and λ_{ex} = 412 nm (Fig. 5) it is possible to note the presence of emission band at 605 nm, detectable only at pH 6.3 with λ_{ex} = 422 nm. In order to investigate the origin of the 605 nm emission band, we recorded excitation spectra. Noteworthy, the excitation spectrum at λ_{em} = 605 nm shows a Soret band centered at 420 nm, ascribed to non-protonated aggregated species. This emission is, in fact, undetectable at the same pH when the fluorescence is recorded with λ_{ex} = 412 nm (Fig. 5a blue line).

EXPERIMENTAL

General

All chemicals were purchased from Sigma–Aldrich as reagent grade and were used without further purification. Ultra-pure water (18.2 MΩ.cm) was obtained from the Elga Purelab Flex system by Veolia. NMR experiments were carried out at 27 °C on a Varian UNITY Inova 500MHz spectrometer (^{1}H at 499.88 MHz, ^{13}C NMR at 125.7 MHz) equipped with a pulse field gradient module

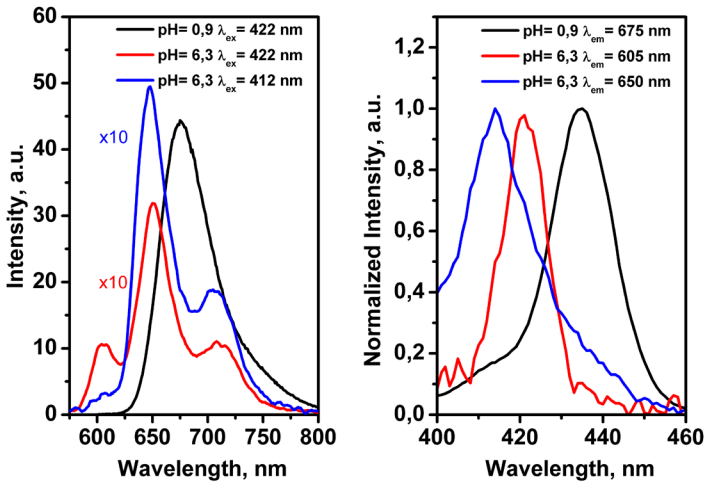

Fig. 5. (a) Fluorescence spectra of **(1)** 1 μM at pH = 0.9 (λ_{ex} = 422 nm; black line) and at pH = 6.3 (λ_{ex} = 422 nm; red line and λ_{ex} = 412 nm blue line). (b) Excitation spectra of **(1)** 1 μM at pH = 0.9 (λ_{em} = 675 nm; black line) and at pH = 6.3 (λ_{em} = 605 nm; red line and λ_{em} = 650 nm blue line).

(Z axis) and a tunable 5 mm Varian inverse detection probe (ID-PFG). ESI mass spectra were acquired on a API 2000TM AB Sciex system using MeOH (positive ion mode). A JASCO V-560 UV-vis spectrophotometer equipped with a 1 cm path-length cell was used for UV-vis measurements. Luminescence measurements were carried out using a Cary Eclipse fluorescence spectrophotometer with different excitation wavelength and a 0.5 nm resolution, at room temperature. The emission was recorded at 90° with respect to the exciting line beam using 5/5 nm slit-widths for all measurements.

Synthesis of 5-(4-carboxyphenylspermine)-10,15,20-triphenylporphyrin (1) (H_2MCPPSpm1) (1)

***Synthesis of* 5-(4-*methoxycarbonylphenyl*)-10,15,20-*triphenyl*-21,23*h*-*porphyrin* (1*c*).** To a solution of pyrrole (2.52 mL, 36 mmol), in $CHCl_3$ (500 mL) benzaldehyde (3.64 mL, 36 mmol) and methyl-*p*-formylbenzoate (985.0 mg, 6 mmol) were added and purged with nitrogen (1 h) in the dark. Then boron trifluoride etherate (0.69 mL, 5.4 mmol) was added and the reaction was allowed to stir at room temperature. After one h, DDQ (8.14 g, 36 mmol) was added and stirred for 16 h. The reaction mixture was concentrated in vacuum and was purified by double column chromatography (CH_2Cl_2) to give a solid purple powder **1c**, yield 135.7 mg (3%). ^{1}H NMR (500 MHz; $CDCl_3$): δ_H, ppm 8.88 (m, 6H), 8.80 (d, J = 5.0 Hz, 2H), 8.45 (d, J = 8.0 Hz, 2H), 8.32 (d, J = 8.0, 2H), 8.23 (d, J = 7.0 Hz, 6H), 7.78 (m, 9H), 4.12 (s, 3H), -2.76 (2H).

***Synthesis of* 5-(4-*carboxyphenyl*)-10,15,20-*triphenylporphyrin* (1*b*).** To a suspension of **1c** (77.5 mg, 0.12 mmol) in EtOH (5 mL) was added a solution of KOH (2N, 10 mL) and the suspension was refluxed for 24 h. Cooled to room temperature, the reaction mixture was acidified with HCl_{acq} up to a pH ≈ 5. The compound is extracted with ethyl acetate (3 × 20 mL). The organic phase was collected and dried with anhydrous Na_2SO_4. The solvent was removed in vacuum obtaining desired product **1b** as a violet powder. Yield 75.7 mg (95%). ^{1}H NMR (500 MHz; Acetone-d_6) δ_H, ppm 8.90–8.91 (m, 8H), 8.52 (d, J = 8.0 Hz, 2H), 8.43 (d, J = 8.0 Hz, 2H), 8.28 (m, 6H), 7.86 (m, 9H).

***Synthesis of* 5-(4-*carboxyphenyl-tri-BOC-spermine*)-10,15,20-*triphenylporphyrin* (1*a*)**. To a solution of compound **1b** (75.7 mg, 0.115 mmol) in DMF_{dry} (1 mL), under nitrogen atmosphere and at room temperature, HATU (50.7 mg, 0.133 mmol) in DMF_{dry} (1 mL) was added dropwise and stirred for 20 min. Then to the reaction mixture a solution of tri-BOC-Spm (57.8 mg, 0.115 mmol) in DMF_{dry} (500 µL) was added. After 40 min *N*,*N*-diisopropylethylamine (20 µL, 0.115 mmol) was added to reaction mixture and it was stirred at room temperature under nitrogen atmosphere for 54 h. Then H_2O was added and the precipitate was dried and after purified by double chromatographic column (from $CHCl_3$ 100% to $CHCl_3$/EtOH 98:2) to give desired compound **1a**. Yield 36.5 mg (28%). UV-vis (CH_3OH) λ_{max}, nm (log ε) 413 (5.57), 512 (4.29), 548 (4.00), 590 (3.81), 645 (3.60). ^{1}H NMR (500 MHz; Acetone-d_6) δ_H, ppm 8.87 (br s, 8H), 8.31–8.29 (dd, 4H), 8.24 (m, 6H), 7.82 (m, 9H), 5.95 (br s, 1H), 3.60–3.40 (br m, 4H), 3.35–3.22 (m, 6H), 3.08 (m, 2H), 1.93 (m br, 2H), 1.71 (m br, 2H), 1.60 (m br, 4H), 1.51 (s, 9H), 1.47 (s, 9H), 1.39 (s, 9H), -2.72 (s, 2H). ^{13}C NMR (125MHz; Acetone-d_6) δ_C, ppm 166.0, 155.7, 150.1, 149.6, 146.2, 144.7, 143.3, 141.9, 134.5, 134.3, 131.7, 131.6, 131.6, 131.3, 127.9, 127.4, 126.8, 126.5, 125.6, 125.2, 120.72, 120.4, 120.3, 119.2, 78.5, 77.5, 46.7, 44.2, 37.5, 27.8, 27.8. ESI-MS: *m/z* 1143.87 $[M + H]^+$.

***Synthesis of* 5-(4-*carboxyphenylspermine*)-10,15,20-*triphenylporphyrin* (1).** To a solution of 5-(4-carboxyphenyl-tri-BOC-spermine)-10,15,20-triphenylporphyrin **1a** (20.6 mg, 0.018 mmol) in CH_2Cl_2 (3 mL) was added 40 µL of TFA (0.52 mmol). After about 8 h, were added another 60 µL of TFA and 4 mL of CH_2Cl_2 and allowed to react overnight. After about 24 h the solvent was removed in vacuum to obtain the desired product **1** as trifluoracetic acid salt yield 20.3 mg (95%). ^{1}H NMR (500 MHz; CD_3OD) δ_H, ppm 8.87 (m, 8H), 8.71 (d, J = 8.0 Hz, 2H), 8.60 (m, 6H), 8.53 (d, J = 8.0, 2H), 3.74 (t, J = 6.5 Hz, 2H), 3.27 (t, J = 7.0 Hz, 2H), 3.18 (m, 6H), 3.08 (t, J = 7.5 Hz, 2H), 2.20 (m, 2H), 2.12 (m, 2H), 1.92 (m,4H). ^{13}C NMR (125 MHz; CD_3OD) δ_C, ppm 169.3, 150.1, 143.7, 143.3, 140.4, 136.4, 134.3, 132.6, 131.3, 130.5, 129.6, 129.3, 129.1, 128.1, 127.0, 126.4, 126.0, 122.3, 122.1, 120.2, 46.9, 45.3, 44.5, 36.4, 29.3, 29.0, 26.5, 23.9, 23.0, 22.9. ESI-MS: *m/z* 843.73 $[M + H]^+$.

Spectroscopic measurements

Stock solutions of compound **(1)** in DMSO ~mM concentrations were obtained by dissolving the purple solid directly in dry DMSO. For continuous titration we diluted the calculated amount of stock solution in DMSO to obtain a 1 µM working solution, at ~pH 1. Then, every 10 min we added small amounts of NaOH to increase the pH of the solution and we recorded the spectrum. To prepare independent solutions, we diluted into aqueous solutions at different pH, obtained using HCl and/or NaOH solution, the needed amount of porphyrin stock solution to achieve 1 µM concentration. After preparation of the samples we waited 10 min before recording the spectra. All experiments were conducted by using 1cm four face plastic cuvettes in order to avoid the porphyrin sticking on the cuvette walls.

CONCLUSION

In conclusion, an interesting and simple synthetic strategy was used to obtain a single spermine pendant porphyrin derivative with good solubility in water after dissolving it in a DMSO stock solution. The

derivative was spectroscopically characterized and showed fascinating behavior in water at different pH. The presence of a single spermine pendant gave us the opportunity to exploit the well-known capability of polyamine to interact with biological targets without giving up on the hydrophobic features of the porphyrin core. Thus, combining these properties it is possible to use this compound both as single molecules and as aggregates for further studies towards different applications in material or biological fields.

Acknowledgments

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Supporting information

Synthetic scheme and spectral data (Figs S1–S18) are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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