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Graphical Abstract

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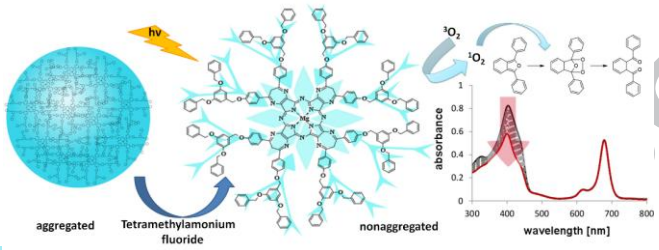

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First Example of a Diazepinoporphyrazine with Dendrimeric Substituents

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ABSTRACT

The synthesis and physicochemical properties of a novel diazepinoporphyrazine possessing G1-dendrimeric substituents are presented. Initially, diaminomaleonitrile was condensed with 1,3-bis-(4-hydroxyphenyl)-1,3-propanedione to give a novel 1,4-diazepine-2,3-dicarbonitrile derivative which was subjected to an alkylation reaction with 3,5-bis(benzyloxy)benzylbromide furnishing a 1,4-diazepine-2,3-dicarbonitrile derivative with bulky substituents. Subsequent macrocyclization led to the desired diazepinoporphyrazine with conjugated, hyperbranched G1-dendrimeric substituents, which was characterized by MS MALDI and NMR. The potential photosensitizing activity of the novel porphyrazine was evaluated by measuring its ability to generate singlet oxygen. This measurement was performed with and without addition of the anti-aggregation agent tetramethylamonium fluoride to determine the role of the monomeric form in singlet oxygen generation.

1. Introduction

Derivatives of 1,4-diazepine-2,3-dicarbonitrile were discovered by Begland,[1,2] Ohtsuka[3] and their co-workers. These compounds in their parent form or after further modifications have been studied in various aspects, especially as dyes[4-9] and/or intermediates for macrocyclization reactions to give porphyrazines with annulated diazepine,[10-13] tetrahydrodiazepine,[14,15] and styryldiazepine,[15-18] rings. Initially, Ercolani, Stuzhin and their co-workers applied 5,7-diphenyl- and 5,7-di(4-*tert*-butylphenyl)-2,3-dicyano-6*H*-1,4-diazepines in the synthesis of porphyrazines and tribenzoporphyrazines with annulated diazepine rings and investigated their electronic properties.[10-13,19,20] More recently, novel homoleptic double-decker sandwich-type complexes with rare earth metal ions (La, Nd, Ce) have been electrochemically studied.[21,22]

Previously, we reported the synthesis of porphyrazines bearing styryldiazepine and bis(styryl)diazepine substituents, and evaluated their electronic properties, tendency for aggregation and photodegradation, singlet oxygen generation efficiency, and *in vitro* photodynamic activity at a nanomolar level using two oral squamous cell carcinoma cell lines.[15,17,18]

Herein, we report the synthesis, characterization and photochemical properties of dendrimer-substituted diazepinoporphyrazine **1**.

2. Result and discussion

Novel magnesium diazepinoporphyrazine with bulky and hyperbranched 4-[3,5-bis(benzyloxy)benzyloxy]phenyl substituents at the C5 and C7 positions **1** (Fig. 1) was synthesized and characterized.

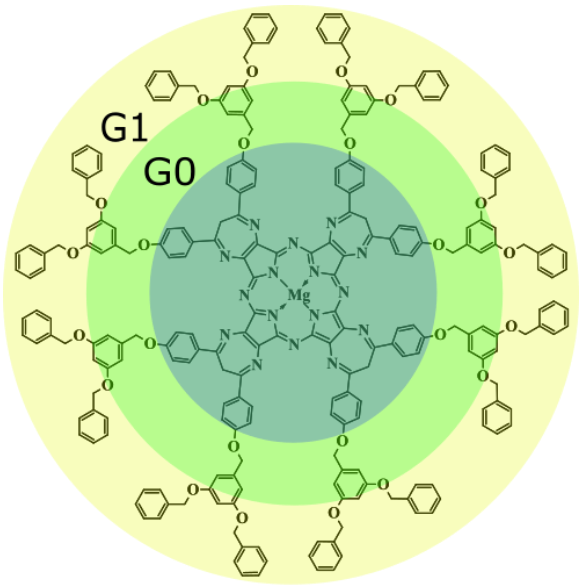

Figure 1. Magnesium diazepinoporphyrazine with G1-dendrimeric substituents **1**.

Following the procedure of Begland and co-workers,[2] diaminomaleonitrile **2** was subjected to a condensation reaction in the presence of phosphorus pentoxide with the known compound 1,3-bis-(4-hydroxyphenyl)-1,3-propanedione **4**[23]

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(obtained following the literature procedure[24]) to give the corresponding 1,4-diazepine-2,3-dicarbonitrile derivative with 4-hydroxyphenyl substituents **5**[25] (Fig. 2). Then, compound **5** was alkylated with 3,5-bis(benzyloxy)benzylbromide **7** to give the 1,4-diazepine-2,3-dicarbonitrile derivative with bulky substituents **8**.[26] The alkylating agent **7**[27] was prepared from 3,5-bis[(phenylmethoxy)phenyl]methanol **6** using the conditions reported by Hawker and co-workers.[28] Derivative **8** was used for the Linstead macrocyclization with magnesium *n*-butanolate in *n*-butanol to give novel diazepinoporphyrazine **1**[29] in 39% yield.[30] Porphyrazine **1** was carefully purified by column chromatography and further analyzed using HPLC (see ESI).

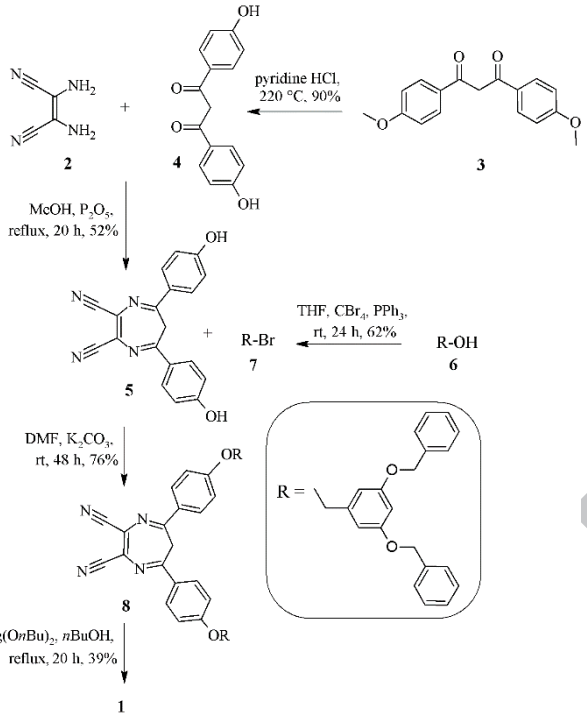

Figure 2. Synthesis of porphyrazine **1.**

The ^{1}H NMR spectrum of **1** revealed three signals at 7.39, 7.33 and 7.28 ppm from eighty protons belonging to the outer, peripheral phenyl rings, two signals at 6.83, 6.68 ppm from twenty four protons of the middle phenyl rings and two signals at 7.05, 8.16 ppm from thirty two protons belonging to the inner phenyl rings directly attached to the diazepine rings (Fig. 3). Aliphatic protons from the outer and inner methyleneoxy bridges were found at 5.04 and 5.14-5.20 ppm, respectively. Additionally, two characteristic broad signals resonating at 5.96 and 5.13 ppm from C6-CH_2 eight geminal protons were observed (ESI). Moreover, variable-temperature NMR experiments showed that the pseudoquartet signal of the outer methyleneoxy bridges in the range of 4.94-4.99 ppm at 298K was shifted downfield when the temperature was raised to 353 K and appeared as a sharp singlet at 5.04 ppm (Fig. 3). The broad, flat, unresolved signal of the equatorial protons from C6-CH_2^{eq} of the diazepine rings at 5.96 ppm (298K) appeared as a doublet with an estimated ^2J value of 12 Hz when the temperature was raised to 353K. The C6-CH_2^{ax} protons were overlapped by 5.14-5.20 ppm signals of protons from the inner sphere methyleneoxy bridges of the G1-dendritic moieties according to 2D-NMR spectra. It is worth noting that the presence of these signals from C6-CH_2 indicates that all diazepine rings are in the 6*H* tautomeric form.[11]

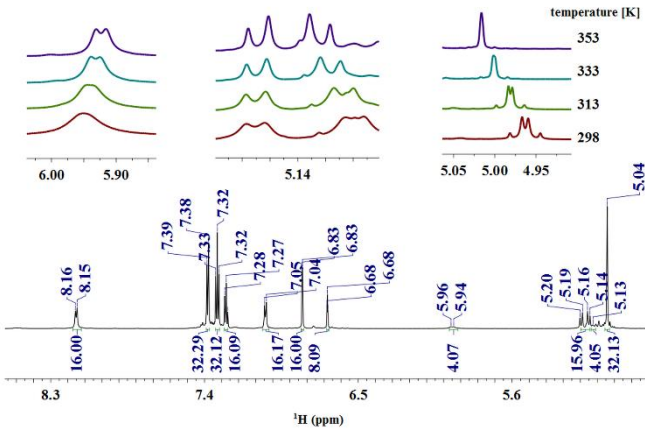

Figure 3. ^{1}H NMR spectrum of **1** in DMSO-d_6 at 353 K. Variable temperature ^{1}H NMR spectra expansions of the regions: 4.94–5.05 ppm, 5.10-5.18 ppm and 5.85–6.00 ppm are presented in the insets.

The tendency of porphyrazine **1** to aggregate was evaluated in DMSO following the procedure of Stuzhin and co-workers.[16] Figure 4 presents the changes in the UV-Vis spectra of **1** in DMSO after the addition of 10% water and tetramethylammonium fluoride (TMAF), which is a known anti-aggregation agent. It can be seen that the addition of water increased the intensity of the short wavelength sub-band with λ_{max} at ~640 nm and decreased the intensity of the long wavelength band with λ_{max} at ~675 nm. Moreover, the addition of TMAF caused the disappearance of the short wavelength band and only the single intensive band with λ_{max} at ~675 nm was observed. It was found that the long wavelength band corresponded to the monomeric form of **1**, whereas the short wavelength band results from the presence of the aggregated form.

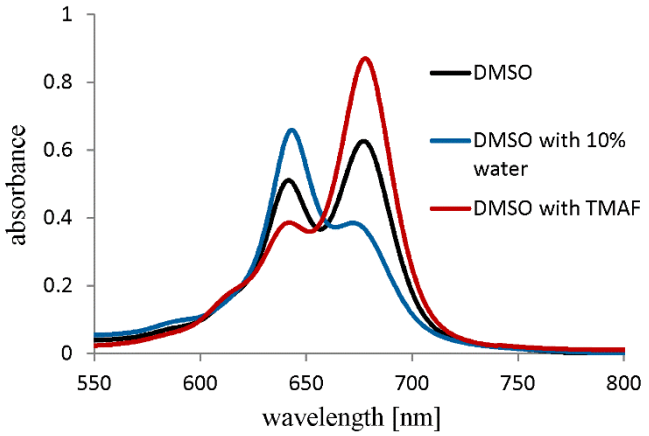

Figure 4. Aggregation studies of **1** in DMSO.

The potential photosensitizing activity of the obtained porphyrazine, which is crucial for application in photodynamic therapy, was evaluated by measuring its ability for singlet oxygen generation, which is the result of interaction between the activated photosensitizer and oxygen. 1,3-Diphenylisobenzofuran (DPBF) was used as a chemical quencher, which undergoes a cycloaddition reaction with singlet oxygen to produce endoperoxide.[15,31] DMSO solutions containing porphyrazine **1**, or a reference zinc(II) phthalocyanine, with DPBF were irradiated with monochromatic light at wavelengths corresponding to their monomeric forms Q-band maxima (Fig. 5). The kinetics of DPBF decomposition by photogenerated singlet oxygen was studied in the UV-Vis spectra as a decrease of the absorbance at 417 nm, and was further used to calculate the singlet oxygen

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generation yield (Φ_Δ). Measurements of singlet oxygen generation efficacy were performed with and without the addition of TMAF to determine the role of the monomeric form of **1**. The calculated value of singlet oxygen quantum yield for **1** in the presence of TMAF was 0.295 ± 0.024 ($\Phi_\Delta \pm \Delta\Phi_\Delta$*), whereas in its absence it was 0.090 ± 0.007 ($\Phi_\Delta \pm \Delta\Phi_\Delta$*). The Φ_Δ values of **1** in DMSO were higher after the addition of TMAF, indicating that a decreased generation of singlet oxygen is the result of aggregation.

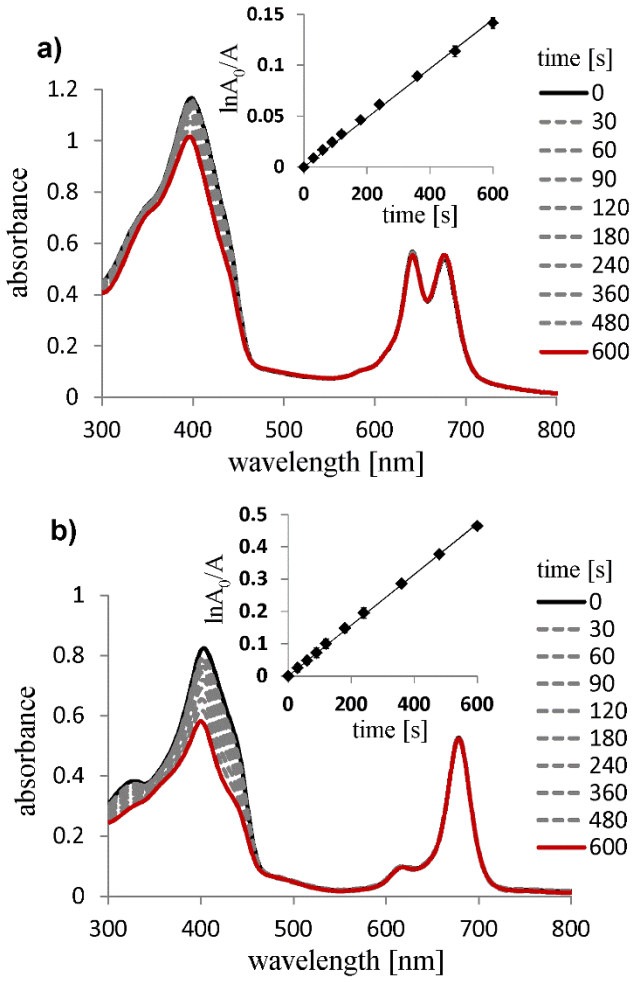

Figure 5. Changes in the UV–Vis spectra during irradiation of **1** and DPBF in DMSO without (a) or with TMAF (b) and first-order plots of DPBF degradation by photosensitized **1**.

Conclusion

The first example of a diazepinoporphyrazine possessing G1-dendrimeric substituents was presented. The novel macrocycle was characterized using UV-Vis, MS MALDI and various NMR techniques. The potential photosensitizing activity of the novel porphyrazine was evaluated by measuring its ability to generate singlet oxygen in DMSO, with and without addition of the anti-aggregation agent TMAF. The obtained value of singlet oxygen quantum yield of 0.295 makes it a potential photosensitizer for application in photodynamic therapy. Considering the successful results obtained within our group for dendrimeric sulfanyl porphyrazines,[32] the direction of this research for diazepinoporphyrazines will be continued and reported in due course.

Acknowledgments

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25. 5,7-Bis(4-hydroxyphenyl)-6*H*-1,4-diazepine-2,3-dicarbonitrile (**5**) Diketone **4** (0.8 g, 3.12 mmol), diaminomaleonitrile **1** (0.337 g, 3.12 mmol) and P_2O_5 (0.15 g, 1.56 mmol) in anhydrous MeOH (40 mL) were stirred for 1 h at room temp. After the addition of further P_2O_5 (0.15 g, 1.56 mmol), the reaction mixture was heated at reflux for 20 h. The solvent was evaporated and the residual solid purified by column chromatography (dichloromethane-methanol, 20:1) to give a yellow solid (0.525 g, 52%). mp 140 °C dec. R_f (dichloromethane:methanol 20:1) 0.54. UV-Vis (dichloromethane): λ_{max}, nm (log ε) 388 (4.77), 313

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(5.03). MS (ES pos) m/z 329 $[M+H]^+$, 351 $[M+Na]^+$, 367 $[M+K]^+$, (ES neg) m/z 327 $[M-H]^-$. HRMS (ES pos) found: 329.1016 [M+H]+, requires 329.1038 $[M+H]^+$. HRMS (ES neg) found: 327.0877 $[M-H]^-$, requires 327.0882 [M-H]-. Limited solubility of compound in organic solvents and water effectively hampered purification by column chromatography and identification (NMR, combustion analysis) leading to the use of the crude product in the next step.

26. 5,7-Bis-[4-[3,5-bis(benzyloxy)benzyloxy]phenyl]-6*H*-1,4-diazepine-2,3-dicarbonitrile (**8**) The reaction mixture of **7** (397 mg, 1.20 mmol), **5** (1.38 g, 3.60 mmol), and K_2CO_3 (663 mg, 4.80 mmol) in DMF (10 mL) was stirred for 48 h at room temp. The solvent was evaporated and the residual solid diluted with water (20 mL) then extracted with dichloromethane (total amount 150 mL). The organic layers were combined and evaporated to give a yellow oil, which was purified by column chromatography (dichloromethane) to give a yellow solid **8** (0.850 g, 76% yield). mp 105-108 °C. R_f (dichloromethane) 0.66. UV-Vis (dichloromethane): λ_{max}, nm (log ε) 380 (4.73), 314 (5.01) 230 (4.9). ^{1}H NMR (799.926 MHz, DMSO-d_6); δ_H, ppm 8.08 (d, 4H, ^3J=9 Hz, C3, C5 ArH), 7.40 (d, 8H, ^3J=7 Hz, C2``, C6``, ArH), 7.36 (t, 8H, ^3J=7.3 Hz, C3``, C5``, ArH), 7.30 (t, 4H, ^3J=7 Hz, C4``, ArH), 7.06 (d, 4H, ^3J=9 Hz, C2, C6 ArH), 6.67 (s, 4H, C2`, C6`, ArH), 6.62 (s, 2H, C4` ArH), 5.99 (s, 1H, N=C-CH$^{eq}$), 5.09 (s, 4H, O-$CH_2$), 5.06 (s, 8H, O-$CH_2$), 2.21 (s, 1H, N=C-CH$^{ax}$). $^{13}$C NMR (201.162 MHz, DMSO-$d_6$): $\delta_C$, ppm 162.1 (C1`, ArC), 159.5 (C3`, C5`, ArC), 150.0 (C1, ArC), 138.4 (C4, ArC), 136.7 (C1``, ArC), 132.3 (C3, C5, ArC), 128.1 (C3``, C5``, ArC), 127.5 (C4``, ArC), 127.3 (C2``, C6``, ArC), 125.8 (N=C), 122.5 (C-C≡N), 115.8 (C≡N), 115.1 (C2, C6, ArC), 106.6 (C2`, C6`, ArC), 101.5 (C4`, ArC), 69.3 (O-CH_2), 38.5 (N=C-CH_2). MS (ES pos) m/z 956 $[M+Na]^+$, (ES neg) m/z $[M-H]^-$ 932. HRMS (MALDI) found: 933.3730 $[M+H]^+$, requires 933.3652 $[M+H]^+$. Anal. calcd for $C_{61}H_{48}N_4O_6$: C, 78.52; H, 5.19; N, 6.00, O, 10.29. Found: C, 78.45; H, 5.24; N, 6.15; O, 10.15.
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29. Tetrakis[5,7-bis-[4-[3,5-bis(benzyloxy)benzyloxy]phenyl]-6*H*-1,4-diazepino][2,3-b;2',3'-g;2'',3''-l;2''',3'''-q]porphyrazinato magnesium(II) (**1**) Magnesium turnings (10.0 mg, 0.4 mmol) and a small crystal of iodine were heated at reflux in *n*-butanol (15 mL) for 4 h. After cooling to room temperature, **8** (400 g, 0.4 mmol) was added. The reaction mixture was then heated at reflux for 20 h. The reaction mixture was cooled to room temp., filtered through Celite, then washed with toluene and dichloromethane. The filtrates were evaporated to dryness, and the solid residue purified by column chromatography (dichloromethane, dichloromethane-methanol, 20:1; then reversed-phase silica gel, methanol to dichloromethane-methanol, 2:1) (0.148 g, 39% yield). mp > 300 °C. R_f (dichloromethane-methanol 20:1) 0.57. UV-Vis (dichloromethane): λ_{max}, nm (log ε) 276 (5.14), 348 (5.25), 652 (5.02), 672 (4.95). ^{1}H NMR (799.926 MHz, DMSO-d_6): δ_H, ppm 8.16 (d, 16H, ^3J=8.1 Hz, C2, C6 ArH), 7.39 (d, 32H, ^3J=7 Hz, C2``, C6``, ArH), 7.33 (t, 32H, ^3J=7.6 Hz, C3``, C5``, ArH), 7.28 (t, 16H, ^3J=8 Hz, C4``, ArH), 7.05 (d, 16H, ^3J=8 Hz, C3, C5 ArH), 6.83 (d, 16H, *J*=2 Hz, C2`, C6`, ArH), 6.68 (t, 8H, *J*=2 Hz, C4` ArH), 5.96 (d, 4H, $^2J$=12 Hz, N=C-CH$^{eq}$), 5.14-5.20 (m, 16H, O-$CH_2$), 5.13 (overlapped, 4H, N=C-CH$^{ax}$), 5.04 (s, 32H, O-$CH_2$). $^{13}$C NMR (201.162 MHz, DMSO-$d_6$): $\delta_C$, ppm 159.6 (C4, ArC), 159.5 (C3`, C5`, ArC), 152.4, 143.7 (C1, ArC), 140.6, 138.8 (C1`, ArC), 136.6 (C1``, ArC), 130.4 (C2, C6, ArC), 129.4, 127.9 (C3``, C5``, ArC), 127.3 (C4``, ArC), 127.0 (C2``, C6``, ArC), 114.3 (C3``, C5``, ArC), 106.8 (C2`, C6`, ArC), 101.6 (C4`, ArC), 69.3 (O-CH_2), 69.4 (O-CH_2), 35.8 (N=C-CH_2). HRMS (MALDI) m/z found: $[M+H]^+$ 3754,4053 requires 3754,4219.
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Highlights

- Diazepinoporphyrazine possessing G1-dendrimeric substituents is presented
- The potential photosensitizing activity of novel porphyrazine was evaluated
- The aggregation study for diazepinoporphyrazine was performed

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