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Synthesis of Porphyrins with ABAB Symmetry from Dipyrromethanes as Potential Phototherapeutic Agents †

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Abstract: Asymmetrically *meso*-substituted porphyrins were synthesized with ABAB symmetry patterns. The approach required the formation of dipyrromethanes, which were obtained from the condensation of an aldehyde (pentafluorobenzaldehyde, 4-nitrobenzaldehyde or *N*,*N*-diphenylaminobenzaldehyde) with a large excess of pyrrole (1:47 aldehyde/pyrrole mol ratio), catalyzed by trifluoroacetic acid in 70–94% yields. Then, acid-catalyzed condensation of these dipyrromethanes with an aldehyde (*N*,*N*-dimethylaminobenzaldehyde, 4-carboxymethyl benzaldehyde or *N*-ethyl-3-carbazolecarbaldehyde) (1:1 mol ratio) in dichloromethane, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone affords the diseased porphyrins in 10–42% yields. These ABAB-porphyrins are interesting starting materials to obtain photoactive molecular structures as potential phototherapeutic agents.

Keywords: porphyrin; tetrapyrrolic macrocycle; pyrrole; pentafluorophenyl; dipyrromethane; photosensitizer

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1. Introduction

Porphyrin derivatives have been proposed as photosensitizers in the photodynamic inactivation of microorganisms [1,2]. However, depending on the substituents on the periphery of the tetrapyrrolic macrocycle, these molecules tend to aggregate, producing a loss of photodynamic activity. Thus, to achieve effective photoinactivation, these compounds can bind to different supports forming photoactive materials [3,4]. In this sense, it is interesting to develop porphyrins asymmetrically substituted in the *meso* positions by two different structures (A and B). In these compounds, structure A has a functional group that allows covalent attachment to other molecules, while B is substituted by groups, allowing changes in the properties of the tetrapyrrolic macrocycle [5,6].

A major limitation of available methods to synthesize porphyrins tetrapyrrole macrocycles is related to the possibility of attaching different groups at the four *meso*-positions of tetrapyrrole macrocycle. Porphyrins containing two types of *meso*-substituents can be synthesized by condensation of binary mixed aldehyde catalyzed by acid. However, this procedure is statistical in nature and frequently multiple porphyrins are formed [7]. In this case, six porphyrins can be obtained and the workup is complex due to the presence of subproducts. In general, the purification involves slowly chromatographic separation and no pure porphyrin is always possible, resulting in low yields of the desired product. More direct approaches to obtain *trans*-substituted porphyrins (ABAB-porphyrins) are provided by condensation of dipyrromethanes with aldehydes. This approach needs to

obtain *meso*-substituted dipyrromethane that can be formed by the reaction of an aldehyde with pyrrole [8].

In the present work, ABAB-porphyrins were synthesized from the condensation of *meso*-(substituted)dipyrromethanes with benzaldehyde derivatives catalyzed by acid. These porphyrins are interesting starting materials to obtain photoactive molecular structures as potential phototherapeutic agents.

2. Materials and Methods

2.1. Equipment and Chemical Substances

Proton nuclear magnetic resonance (^{1}HNMR) spectra were carried out on an FT-NMR Bruker Avance DPX400 spectrometer (Bruker BioSpin, Rheinstetten, Germany). Mass spectra were performed on a Bruker micrO-TOF-QII (Bruker Daltonics, MA, USA), using an ESI source (ESI-MS). Absorption and fluorescence spectra were achieved on a Shimadzu UV-2401PC spectrometer (Shimadzu Corporation, Tokyo, Japan) and a Spex FluoroMax spectrofluorometer (Horiba Jobin Yvon Inc, Edison, NJ, USA), respectively. Chemical substances were purchased from Sigma-Aldrich (Milwaukee, WI, USA). These compounds were used without further purification. Silica gel thin-layer chromatography (TLC, 250 microns) plates were obtained from Analtech (Newark, DE, USA), while silica gel 60 (0.040–0.063 mm, 230–400 mesh) was acquired from Merck (Darmstadt, Germany).

2.2. Synthesis

meso-(Pentafluorophenyl)dipyrromethane (**1**). Pentafluorobenzaldehyde (0.55 mL, 4.45 mmol) and pyrrole (14.5 mL, 209 mmol) were purged with argon for 15 min. Then, trifluoroacetic acid (TFA) (70 L, 0.90 mmol) was added. The mixture was stirred for 45 min at room temperature. After that, the sample was diluted with 25 mL of dichloromethane (DCM) and three washes of 15 mL each were carried out with NaOH (0.1 M). The solvent and excess pyrrole were removed under reduced pressure using a rotary evaporator. The product was purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate/triethylamine (TEA) 80:20:1), obtaining 1.31 g (94%) of **1**. TLC (silica gel, cyclohexane/ethyl acetate/TEA 80:20:1) R_f = 0.46. ^{1}HNMR ($CDCl_3$, TMS) δ [ppm] 5.88 (s, 1H, *meso*-H), 6.00 (m, 2H, pyrrole-H), 6.15 (q, 2H, pyrrole-H), 6.74 (m, 2H, pyrrole-H) 8.10 (brs, 2H, pyrrole NH). ESI-MS [m/z] 310.0534 [M^+] (310.0529 calculated for $C_{15}H_7F_5N_2$).

meso-(4-Nitrophenyl)dipyrromethane (**2**). A solution of 4-nitrobenzaldehyde (2.50 g, 16.6 mmol) and pyrrole (55 mL, 780 mmol) was degassed by bubbling with argon for 15 min, and then TFA (321 μL, 4.17 mmol) was slowly added. The solution was stirred for 20 min at room temperature. The crude product was diluted with DCM. The organic phase was washed with aqueous 0.1 M NaOH. After that, the sample was washed with water. The solvent was removed under reduced pressure. The unreacted pyrrole was removed by vacuum distillation at room temperature. The product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate/triethylamine; 80:20:1) yielded 3.19 g (72%) of **2**. ^{1}HNMR (300.08 MHz, $CDCl_3$, TMS) δ [ppm] 5.58 (s, 1H, *meso*-H); 5.86 (m, 2H, pyrrole-H); 6.17 (q, 2H, pyrrole-H); 6.74 (m, 2H, pyrrole-H); 7.37 (d, 2H, J = 9.0 Hz); 8.01 (s, brs, 2H, pyrrole NH); 8.16 (d, 2H, J = 9.0 Hz). ESI-MS [m/z] 267.1014 [M^+] (267.1008 calculated for $C_{15}H_{13}N_3O_2$).

meso-[4-(*N*,*N*-Diphenylaminophenyl)]dipyrromethane (**3**). A solution of 4-(*N*,*N*-diphenylamino)benzaldehyde (1.98 g, 7.24 mmol) and pyrrole (24 mL, 340 mmol) was stirred under an argon atmosphere. This mixture was kept for 15 min at room temperature. Then, 140 μL (1.82 mmol) of TFA was added and the mixture stirred for 30 min. After that, 780 μL (5.60 mmol) of triethylamine (TEA) was added and the solution was diluted with 50 mL of DCM. The solvent and pyrrole were removed by distillation under reduced pressure. The compound was isolated by flash column chromatography (silica gel, cyclohexane/ethyl acetate/TEA 80:20:1), yielding 1.97 g (70%) of **3**. TLC (silica gel, cyclohexane/ethyl acetate/TEA 80:20:1) R_f = 0.26. ^{1}H NMR ($CDCl_3$, TMS) [ppm] 5.43 (s, 1H, *meso*-

H); 5.94 (m, 2H, pyrrole-H); 6.17(q, 2H, pyrrole-H); 6.72 (m, 2H, pyrrole-H); 6.94–7.12 (m, 10 H, ArH); 7.22 (m, 4 H, ArH); 7.98 (s, brs, 2H, pyrrole NH). ESI-MS [m/z] 389.1887 [M^+] (389.1892 calculated for $C_{27}H_{23}N_3$).

5,15-di(4-(*N*,*N*-dimethylaminophenyl)-10,20-di(pentafluorophenyl)porphyrin (**4**). A solution of 4-(*N*,*N*-dimethylamino)benzaldehyde (3.4 mmol) and dipyrromethane **1** (974 mg, 3.4 mmol) in 250 mL of DCM was bubbled with argon for 15 min. Then, boron trifluoride etherate ($BF_3{\cdot}OEt_2$, 1.1 mmol) was added. The solution was stirred for 80 min at room temperature. After that, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 2.25 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. The solvent was removed under reduced pressure and purification was performed by flash column chromatography (silica gel, DCM) giving **4** in 24% yield.^{1}HNMR ($CDCl_3$, TMS) δ [ppm] −2.86 (s, brs, 2H, N-H), 3.05 (s, 6H, $N(CH_3)_2$), 7.05 (d, 4H, J = 8.2 Hz, 3,5-ArH), 7.97 (d, 4H, J = 8.2 Hz, 2,6-ArH), 8.81–8.94 (m, 8H, -pyrrole-H). ESI-MS (m/z) 881.2447 $[M+H]^+$ (881.2451 calculated for $C_{48}H_{30}F_{10}N_6$ + H).

5,15-bis(4-Methoxycarbonylphenyl)-10,20-bis(pentafluorophenyl)porfirin (**5**). A solution of methyl 4-formylbenzoate (632 mg, 3.85 mmol) and dipyrromethane **1** (1.37 g, 4.38 mmol) in 450 mL of DCM was stirred for 15 min under argon atmosphere at room temperature. Then, TFA (0.50 mL, 6.54 mmol) was added and the solution was kept stirring for 45 min. The mixture was subsequently oxidized with DDQ (885 mg, 3.90 mmol) and stirred for 2 h in an atmosphere of air. Then, 20 mL of MeOH was added to remove excess DDQ and the mixture was kept stirred for 30 min. The solvent was removed under reduced pressure. The product was purified by silica gel filtration and flash column chromatography (silica gel, cyclohexane/DCM 40%), obtaining 90 mg (10%) of **5**. ^{1}HNMR ($CDCl_3$, TMS) δ [ppm] -2.86 (s, brs, 2H, N-H), 4.13 (s, 6H, $COOCH_3$), 8.31 (d, 4H, J = 8.0 Hz, 2,6-ArH), 8.47 (d, 4H, J = 8.0 Hz, 3,5-ArH), 8.83–8.93 (m, 8H, -pyrrole-H). ESI-MS (m/z) 911.1720 $[M+H]^+$ (911.1716 calculated for $C_{48}H_{24}F_{10}N_4O_4$ + H).

5,15-bis(4-Methoxycarbonylphenyl)-10,20-bis(4-nitrophenyl)porphyrin (**6**). A solution of methyl 4-formylbenzoate (2.46 g, 15 mmol) and dipyrromethane **2** (4.0 g, 15 mmol) in 1.5 L of DCM was purged with argon for 15 min. Then, TFA (1.85 mL, 24 mmol) was added slowly over 30 s. The solution was stirred for 30 min at room temperature. After that, DDQ (3.4 g, 15 mmol) was added and the mixture was stirred for 2 h at room temperature. The solvent was removed under vacuum and flash column chromatography (silica gel, DCM) yielded 1.29 g (21%) of **6**. ^{1}HNMR ($CDCl_3$, TMS) δ [ppm] -2.77 (s, brs, 2H, N-H), 4.14 (s, 6H, $COOCH_3$), 8.31 (d, 4H, J = 8.0 Hz, 2,6-ArH-COOEt), 8.40 (d, 4H, J = 8.3 Hz, 2,6-ArH-NO_2); 8.47 (d, 4H, J = 8.0 Hz, 3,5-ArH-COOEt), 8.65 (d, 4H, J = 8.3 Hz, 3,5-ArH-NO_2), 8.80–8.97 (m, 8H, -pyrrole-H). ESI-MS (m/z) 820.1720 $[M+H]^+$ (820.1716 calculated for $C_{48}H_{32}N_6O_8$ + H).

5,15-Bis[4-(*N*,*N*-diphenylamino)phenyl]-10,20-bis[3-(*N*-ethylcarbazoyl)]porphyrin (**7**). A solution of *N*-ethyl-3-carbazolecarbaldehyde (0.56 g, 2.50 mmol) and dipyrromethane **3** (1.00 g, 2.50 mmol) in 310 mL of DCM was purged with argon for 15 min. After that, TFA (425 µL, 5.50 mmol) was slowly added and the solution was stirred for 60 min at room temperature. Then, DDQ (1.50 g, 6.61 mmol) was added and the mixture was stirred for an additional 18 h, open to the atmosphere. The solvent was removed under reduced pressure. The obtained product was purified by flash column chromatography (silica gel, hexane/DCM/TEA 6:93.8:0.2) obtaining 622 mg (42%) of **7**. TLC (silica gel, hexane/DCM/TEA 6:93.8:0.2) Rf = 0.68. ^{1}HNMR ($CDCl_3$, TMS) δ [ppm] -2.60 (brs, 2H, pyrrole N-H), 1.68 (t, 6H, $-CH_3$, J = 7.1 Hz), 4.64 (q, 4H, $-CH_2-$, J = 7.1 Hz), 7.15 (d, 4H, J = 7.8 Hz), 7.34–7.50 (m, 22 H), 7.52–7.64 (m, 4 H), 7.75 (d, 2H, J = 8.3 Hz), 8.02 (d, 4H, J = 7.8 Hz), 8.20 (d, 4 H, J = 7.7 Hz), 8.34 (d, 2H, J = 8.3 Hz), 8.82–9.06 (m, 8H, -pyrrole-H). ESI-MS [m/z] 1183.5169 $[M+H]^+$ (1183.5176 calculated for $C_{84}H_{62}N_8$ + H).

2.3. Spectroscopic Studies

Absorption and fluorescence spectra were performed in a quartz cell of 1 cm path length using *N*,*N*-dimethylformamide (DMF) at 25.0 ± 0.5 °C. Absorbances (<0.05) were

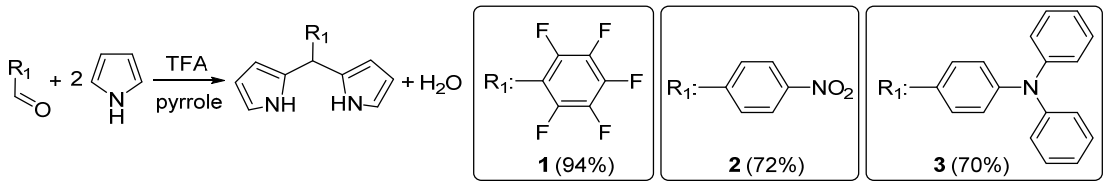
matched at the excitation wavelength (550 nm) and the areas of the emission spectra were integrated in the range 600–800 nm. The fluorescence quantum yield (Φ_F) of the porphyrins was calculated by comparison of the area below the corrected emission spectrum of 5,10,15,20-tetrakis(4-methoxyphenyl)porphyrin (TMP) as a reference [5].

3. Results and Discussion

3.1. Synthesis of Dipyrromethanes

Aldehydes and pyrrole undergo acid-catalyzed condensation at room temperature. Therefore, the condensation of substituted benzaldehydes with a large excess of pyrrole (1:47 aldehyde/pyrrole mol ratio) catalyzed by TFA affords *meso*-(substituted)dipyrromethane (**1–3**). After 25 min of stirring at room temperature, the reaction mixture showed complete consumption of the starting aldehyde. In this procedure, pyrrole was used as a reactant in excess and as the solvent of the condensation, which yielded the corresponding dipyrromethane (Scheme 1).

The dipyrromethanes were purified by flash chromatography on silica gel in a mildly basic medium, using *n*-hexane/ethyl acetate/TEA (80/20/1). The presence of 1% TEA was necessary to avoid the acidolysis of the dipyrromethane on silica gel column. Dipyrromethanes **1**, **2** and **3** were obtained in 94, 72 and 70%, respectively. These compounds are stable upon storage at 0 °C in nitrogen atmosphere and absence of light. Therefore, dipyrromethanes can be easily synthesized with good yield and high purity, which is crucial for the formation of asymmetric *meso*-substituted porphyrins.



Scheme 1. Synthesis of dipyrromethanes **1** and **3**.

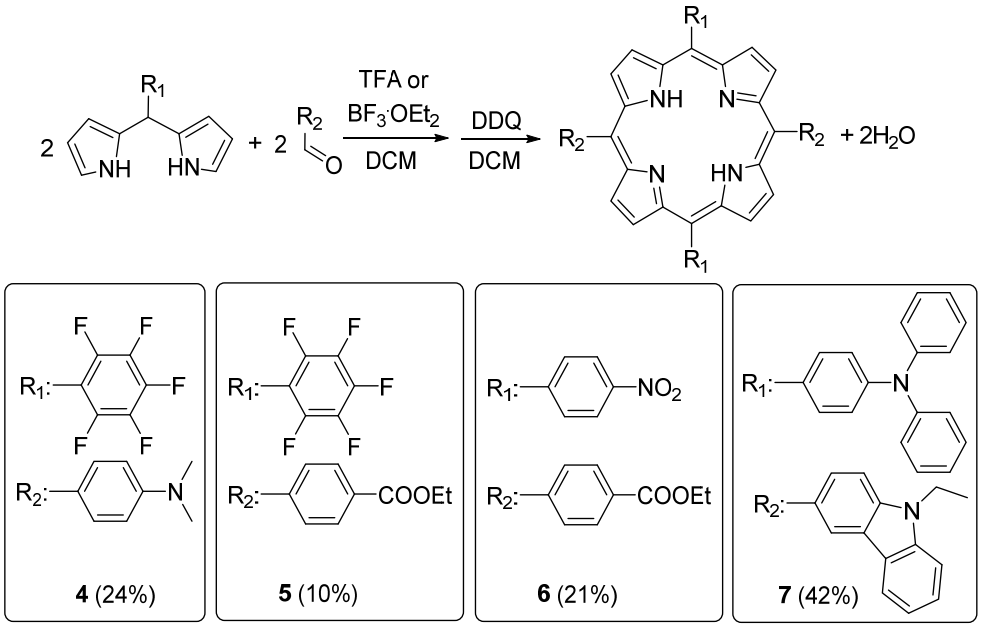
3.2. Synthesis of ABAB-Porphyrins

ABAB-porphyrins **4–7** were synthesized by the acid-catalyzed condensation of dipyrromethane **1–3** and the correspondent substituted benzaldehyde (Scheme 2). Mixed-benzaldehyde dipyrromethane condensations were performed using about [1:1] molar relation of dipyrromethane and substituted benzaldehyde. The reaction was performed using catalytic among of TFA or $BF_3{\cdot}OEt_2$ and DCM as solvent at room temperature. The reaction mixture was subject to oxidation with DDQ. Thus, this mixed condensation affords the corresponding ABAB-porphyrin.

These porphyrins were easily separated by flash chromatography with high purity using DCM/methanol gradient. In all these cases, the first purple band corresponds to the ABAB-porphyrin. Under these conditions, ABAB-porphyrins **4**, **5**, **6** and **7** were obtained in 24, 10, 21 and 42% yields, respectively.

This procedure was previously used to obtain ABAB-porphyrins from the condensation of a dipyrromethane bearing a sterically hindered substituent with an aldehyde [9].

The pentafluorophenyl group linked to the *meso* position of the compounds **4** and **5** can be used to obtain porphyrin derivatives by nucleophilic aromatic substitution reaction of the *para*-fluorine atom [3,10]. Thus, this substituent was used to covalently link the porphyrin ring to several functionalized structures [4]. In porphyrin **4**, *N*,*N*-dimethylaminophenyl substituent can be used to obtain cationic intrinsic charge by methylation [5]. In addition, aminophenyl substituents can be obtained in porphyrin **6** by reduction of nitrophenyl group [11]. Moreover, porphyrin **5** and **6** can be hydrolyzed to form carboxylic acid groups, which can be linked to several structures [11]. Finally, both electroactive substituents of porphyrin **7** can form different polymers [12].



Scheme 2. Synthesis of ABAB-porphyrins **4–7**.

3.3. UV-Visible Absorption Spectroscopic Properties

Porphyrin **4–7** showed the typical Soret band at ~420–430 nm and the four Q-bands between 512–653 nm, which are characteristics of *meso*-tetraphenylporphyrin derivatives [5,6]. The spectroscopic properties of the porphyrins are summarized in Table 1. The Q band of the free base porphyrin moiety consists of four components: $Q_x(0,0)$, $Q_x(1,0)$, $Q_y(0,0)$ and $Q_y(1,0)$, which are associated with D_{2h} symmetry [13]. The maximum of the Soret band of carbazoyl porphyrin derivative **7** showed a 10 nm bathochromic shift with respect to 5,10,15,20-tetrakis(phenyl)porphyrin in DMF due to the auxochromic effect of the carbazoyl groups [14].

The steady-state fluorescence emission spectra of these porphyrins were obtained in DMF (Table 1). The two bands are characteristic for similar *meso*-substituted porphyrin, which were assigned to $Q_x(0\text{-}0)$ and $Q_x(0\text{-}1)$ transitions [5,6]. Free-base porphyrins with D_{2h} symmetry displayed vibronic structure unchanged upon excitation. Moreover, Stokes shifts of ~10 nm were obtained for the tetrapyrrolic macrocycles from the intersection of the absorption and fluorescence $Q_x(0\text{-}0)$ band. Therefore, the spectroscopic energies of these porphyrins were similar to the relaxed energies of the lowest singlet excited state S_1. This behavior was in accordance with a rigid planar structure of tetrapyrrolic macrocycles. Fluorescence quantum yields (Φ_F) of these photosensitizers were calculated by comparison with TMP as a reference. The values of Φ_F for these porphyrins agree with values previously reported by similar porphyrin derivatives [5,15].

Table 1. Spectroscopic properties of porphyrins **4–7** in *N*,*N*-dimethylformamide (DMF).

PS	Absorption$_{max}$ (nm)	ε^{Soret} [a]	Fluorescence$_{max}$ (nm)	Φ_F [b]
4	418 510 542 589 647	4.67×10^5	651 712	0.063 ± 0.003
5	420 512 543 590 648	4.72×10^5	652 712	0.054 ± 0.002
6	421 516 551 591 647	4.72×10^5	652 717	0.10 ± 0.01
7	428 520 563 596 653	3.15×10^5	668 729	0.12 ± 0.01

[a] molar absorption coefficient (L mol^{-1} cm^{-1}), [b] fluorescence quantum yield.

4. Conclusions

The following two basic steps were used sequentially in the synthesis of ABAB-porphyrin: (1) *meso*-(4-substituted) dipyrromethane was formed from correspondent benzaldehyde derivative and pyrrole catalyzed by acid, (2) condensation of dipyrromethane with appropriate benzaldehydes yields the ABAB-porphyrin, which was easily purified by flash chromatography. Thus, the desired ABAB-porphyrins **4–7**, bearing different substituents were obtained with appreciable yields of 10–42%. Thus, the dipyrromethanes react with an aldehyde under the conditions of the two-step one-flask porphyrin synthesis, affording direct access to ABAB-porphyrins. Moreover, it has a relatively simple reaction workup and high yields. These *trans*-substituted porphyrins contain precursor groups of positive charges, which can be used to obtain cationic photosensitizers. Moreover, these tetrapyrrolic macrocycles can be covalently attached to molecular structures and be used to form polymeric materials. Therefore, these ABAB-porphyrins are interesting starting materials to obtain photoactive molecular structures as potential phototherapeutic agents.

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