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Synthesis of Highly Substituted Nitro/Halo–*meso*–tetraaryl–porphyrins by Tandem Cyclocondensation/Aromatic Electrophilic Nitration Reactions

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Synthesis of highly functionalized nitro/halo-5,10,15,20-tetraarylporphyrins is described. meso-Tetraphenylporphyrin derivatives (halo-substituted in meso-phenyl rings; with F, Cl, Br, and I), in the reaction with fuming yellow nitric acid (d = 1.52), result in the formation of mono-, di-, tri-, and even tetranitro-substituted porphyrins (with summary yields of 28–81%), depending on the reaction temperature (0 °C to 5 °C or at r.t.), amounts of the acid used, and reaction time. In some cases moderate selectivity was observed. The starting halo-substituted meso-tetraarylporphyrins were prepared in the cyclocondensation reaction of pyrrole with the respective aromatic aldehydes (usually carried out according to known procedures). By this route, the preparation of the synthetic porphyrins (bearing up to ten halo-/nitro-substituents) was demonstrated.

Keywords: Porphyrins, cyclocondensation, electrophilic nitration, halogens.

Синтез высокозамещенных нитро/гало–*мезо*–тетраарил–порфиринов путём тандемных реакций циклоконденсации и ароматического электрофильного нитрования

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Описан синтез высоко функционализированных нитро/гало-5,10,15,20-тетраарилпорфиринов. При взаимодействии галогенпроизводных мезо-тетрафенилпорфирина (F, Cl, Br и I замещенные фенильные кольца) с дымящей азотной кислотой (d = 1.52) образуются моно-, ди-, три- и даже тетранитрозамещенные порфирины (с суммарным выходом 28-81%) в зависимости от количества используемой кислоты, времени и температуры проведения реакции (0-5 °C или комнатная температура). В некоторых случаях наблюдалась умеренная селективность. Исходные галоген-замещенные мезо-тетраарилпорфирины были получены реакцией циклоконденсации пиррола с соответствующим ароматическим альдегидом, часто по известной методике. Таким образом, была показана возможность получения синтетических порфиринов, имеющих в своём составе до десяти галогено/нитро-заместителей.

Ключевые слова: Порфирины, циклоконденсация, электрофильное нитрование, галогены.

Introduction

Porphyrins are intensively studied in recent years.[1] These systems are present in well-known biological materials (*e.g.* chlorophyll, heme, vitamin B_{12}).[2] From the synthetic point of view, the selective functionalization of readily available *meso*-tetraarylporphyrins is of significant importance due to their potential use as sensitizers in photodynamic cancer therapy (PDT),[3] molecular-based multi-bit memory storage,[4] electron-donor parts in artificial photosynthetic models,[5] *etc*.. For example, from this process, the hydrophobic moieties can be transformed into the hydrophilic compounds. The latter, as such, being soluble in physiological milieu, may be considered as potential PDT agents.

We present herein a synthesis of a series of poly-substituted halo/nitro-*meso*-tetraarylporphyrins. The first substituents (in this case, halogens) were introduced to the system due to one-step cyclocondensation of pyrrole with the corresponding aromatic aldehydes. The above macrocyclization usually was realized according to known procedures. Introduction of the next substituent(s) (one or more NO_2 groups) was achieved by the direct electrophilic nitration of the system.

Experimental

^{1}H NMR spectra were recorded with a Varian MR-400 spectrometer operating at 400 MHz. Coupling constants *J* are expressed in hertz [Hz]. Mass spectra were measured with a MARINER (ESI-TOF) PerSeptive Biosystems spectrometer (ESI method), GCT Premier (Waters, FD-TOF) spectrometer (FD method), and 4000 Q-TRAP (Applied Biosystems) spectrometer (APPI-photospray method); *m/z* intensity values for peaks are given as % of relative intensity. UV–Vis spectra were measured with a Beckman DU-68 spectrophotometer and Metertech SP-8001 spectrophotometer. TLC analysis was performed on aluminum foil plates pre-coated with silica gel (60 F-254, Merck AG). The products synthesized were isolated by column chromatography (silica gel, 230–400 mesh; Merck AG).

The starting 5,10,15,20-tetraarylporphyrins used were prepared from pyrrole and the corresponding benzaldehyde derivatives by the method described earlier for *m*-TPP:[6] 5,10,15,20-tetrakis(3-fluorophenyl)porphyrin (**1a**, 37 %), 5,10,15,20-tetrakis(3-bromophenyl)porphyrin (**1b**, 51 %), 5,10,15,20-tetrakis(3-iodophenyl)-porphyrin (**1c**, 42 %), 5,10,15,20-tetrakis(2,6-dichlorophenyl)-porphyrin (**7**, 34 %; according to modified procedure[7]).

They have already been described in the previous literature: (**1a-c**,[8] **7**[7,9]). Herein, their ^{1}H NMR data were given for more detailed characterization.

*5,10,15,20-Tetrakis(3-fluorophenyl)porphyrin (**1a**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.86 (s, 8H, H$^\beta$-pyrrole), 8.02 (d, *J* = 7.2 Hz, 4H, H-6 of C_6H_4F), 7.95 (d, $J_{H\text{-}F}$ = 9.2 Hz, 4H, H-2 of C_6H_4F), 7.73 (apparent q, $J_1+J_2+J_3$ = 22.0 Hz, 4H, H-5 of C_6H_4F), 7.52 (apparent td, "J_1" = *ca* 8.0 Hz, J_2 = 2.0 Hz, 4H, H-4 of C_6H_4F), -2.91 (s, 2H, 2×NH).

*5,10,15,20-Tetrakis(3-bromophenyl)porphyrin (**1b**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.86 (s, 8H, H$^\beta$-pyrrole), 8.38 (s, 4H, H-2 of C_6H_4Br), 8.16 (d, *J* = 7.6 Hz, 4H, H-6 of C_6H_4Br), 7.95 (d, *J* = *ca* 8.0 Hz, 4H, H-4 of C_6H_4Br), 7.64 (apparent t, *J* = 7.6 Hz, 4H, H-5 of C_6H_4Br), -2.92 (s, 2H, 2×NH).

*5,10,15,20-Tetrakis(3-iodophenyl)porphyrin (**1c**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.86 (s, 8H, H$^\beta$-pyrrole), 8.59 (s, 4H, H-2 of C_6H_4I), 8.19 (d, *J* = 7.2 Hz, 4H, H-6 of C_6H_4I), 8.15 (d, *J* = 8.0 Hz, 4H, H-4 of C_6H_4I), 7.50 (apparent t, *J* = 7.6 Hz, 4H, H-5 of C_6H_4I), -2.92 (s, 2H, 2×NH).

*5,10,15,20-Tetrakis(2,6-dichlorophenyl)porphyrin (**7**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.67 (s, 8H, H$^\beta$-pyrrole), 7.79 (part A_2 of A_2B, $|J|$ = 8.3 Hz, 8H, H-3 and H-5 of $C_6H_3Cl_2$), 7.70 (part B of A_2B, $|J|$ = 8.3 Hz, 4H, H-4 of $C_6H_3Cl_2$), -2.52 (s, 2H, 2×NH).

*Nitration of 5,10,15,20-tetrakis(3-fluorophenyl)porphyrin (**1a**).* 5,10,15,20-Tetrakis(3-fluorophenyl)porphyrin (**1a**; 80 mg, 0.12 mmol) was dissolved in $CHCl_3$ (24 ml), and the solution was stirred under argon and cooled to 0-5°C. To this mixture, yellow nitric acid (*d* = 1.52 g/ml; 0.8 ml, 19.30 mmol) in $CHCl_3$ (4 ml) was added in one portion (*via* syringe). The reaction was continued for 10 min, then the mixture was poured onto water (40 ml). The organic layer was separated, washed with water (3×40 ml), and dried with $MgSO_4/Na_2CO_3$. After evaporating the solvent, the products were isolated by column chromatography (eluent: a gradient mixture of $CHCl_3$/*n*-hexane – 1:1, 2:1, 3:1) to give: 5-(3-fluoro-4-nitrophenyl)-10,15,20-tris(3-fluorophenyl)porphyrin (**2a**; 29.9 mg, 34 %), mixture of 5,10-bis(3-fluoro-4-nitrophenyl)-15,20-bis- (3-fluorophenyl)porphyrin and 5,15-bis(3-fluoro-4-nitrophenyl)-10,20-bis(3-fluorophenyl)porphyrin (**3a** and **4a**; 8.4 mg, 9 %), 5,10,15-tris(3-fluoro-4-nitrophenyl)-20-(3-fluorophenyl) porphyrin (**5a**; 7.9 mg, 8 %), and 5,10,15,20-tetrakis(3-fluoro-4-nitrophenyl)porphyrin (**6a**; 15.6 mg, 15 %).

Several times repeated column chromatography of the mixture of 5,10-bis(3-fluoro-4-nitrophenyl)-15,20-bis(3-fluorophenyl)-porphyrin (**3a**) and 5,15-bis (3-fluoro-4-nitrophenyl)-10,20-bis(3-fluorophenyl)porphyrin (**4a**) gave small amounts of the analytically pure sample of **3a** (for its full characterization).

*5-(3-Fluoro-4-nitrophenyl)-10,15,20-tris(3-fluorophenyl)-porphyrin (**2a**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.91 (d, *J* = 4.8 Hz, 2H, H$^\beta$-pyrrole), 8.87 (s, 4H, H$^\beta$-pyrrole), 8.79 (d, *J* = 4.8 Hz, 2H, H$^\beta$-pyrrole), 8.48 (apparent t, *J* = 8.1 Hz, 1H, H-5 of $C_6H_3(NO_2)$ F), 8.17 (d, $J_{H\text{-}F}$ = 11.3 Hz, 1H, H-2 of $C_6H_3(NO_2)$ F), 8.17 (d, *J* = 7.4 Hz 1H, H-6 of $C_6H_3(NO_2)$ F), 8.00 (d, *J* = 7.5 Hz, 3H, H-6 of C_6H_4F), 7.93 (d, $J_{H\text{-}F}$ = 9.2 Hz, 3H, H-2 of C_6H_4F), 7.74 (apparent q, $J_1+J_2+J_3$ = 21.7 Hz, 3H, H-5 of C_6H_4F), 7.54 (apparent td, "J_1" = *ca* 8.4 Hz, J_2 = 2.5 Hz, 3H, H-4 of C_6H_4F), -2.87 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 647.5 (3.19), 594 (3.26), 551.5 (3.36), 515 (3.77), 418.5 (5.03, Soret), 369 (4.03). *m/z* (FD) (%): 734 (7), 733 (21), 732 (57), 731 (100) [isotope M^+]. HR-MS (FD) found: 731.1938. $C_{44}H_{25}N_5O_2F_4$ (M^+) requires 731.1944.

*5,10-Bis(3-fluoro-4-nitrophenyl)-15,20-bis(3-fluorophenyl) porphyrin (**3a**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.93 (d, *J* = 4.7 Hz, 2H, H$^\beta$-pyrrole), 8.89 (s, 2H, H$^\beta$-pyrrole), 8.85 (s, 2H, H$^\beta$-pyrrole), 8.81 (d, *J* = 4.7 Hz, 2H, H$^\beta$-pyrrole), 8.49 (apparent t, *J* = 8.0 Hz, 2H, H-5 of $C_6H_3(NO_2)$ F), 8.17 (d, $J_{H\text{-}F}$ = 10.7 Hz, 2H, H-2 of $C_6H_3(NO_2)$F), 8.17 (d, *J* = 7.9 Hz, 2H, H-6 of $C_6H_3(NO_2)$F), 7.99 (d, *J* = 7.5 Hz, 2H, H-6 of C_6H_4F), 7.93 (d, $J_{H\text{-}F}$ = 9.1 Hz, 2H, H-2 of C_6H_4F), 7.79-7.69 (m, 2H, H-5 of C_6H_4F), 7.55 (apparent td, "J_1" = *ca* 8.6 Hz, J_2 = 2.1 Hz, 2H, H-4 of C_6H_4F), -2.88 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 646.5 (3.19), 591.5 (3.62), 555.5 (3.75), 514 (4.09), 420 (5.29, Soret). *m/z* (ESI) (%): 779 (23), 778 (50), 777 (100) [isotope $(M+H)^+$].

*5,10,15-Tris(3-fluoro-4-nitrophenyl)-20-(3-fluorophenyl)-porphyrin (**5a**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.89 (s, 4H, H$^\beta$-pyrrole), 8.86 (d, *J* = 4.5 Hz, 2H, H$^\beta$-pyrrole), 8.83 (d, *J* = 4.5 Hz, 2H, H$^\beta$-pyrrole), 8.51 (apparent t, *J* = 7.9 Hz, 3H, H-5 of $C_6H_3(NO_2)$F), 8.17 (d, $J_{H\text{-}F}$ = 10.6 Hz, 3H, H-2 of $C_6H_3(NO_2)$F), 8.16 (d, *J* = 8.1 Hz, 3H, H-6 of $C_6H_3(NO_2)$F), 7.73 (d, *J* = 7.5 Hz, 1H, H-6 of C_6H_4F), 7.62 (apparent d, "*J*" = *ca* 9.1 Hz, 1H, H-2 of C_6H_4F), 7.51 (apparent q, $J_1+J_2+J_3$ = 21.4 Hz, 1H, H-5 of C_6H_4F), 7.33 (apparent td, "J_1" = *ca* 8.3 Hz, J_2 = 1.8 Hz, 1H, H-4 of C_6H_4F), -2.91 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 589 (3.39), 549 (4.03), 513.5 (3.39), 422 (5.21, Soret). *m/z* (ESI) (%): 825 (9), 824 (22), 823 (55), 822 (100) [isotope $(M+H)^+$].

*5,10,15,20-Tetrakis(3-fluoro-4-nitrophenyl)porphyrin (**6a**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.86 (s, 8H, H$^\beta$-pyrrole),

8.54-8.46 (m, 4H, H-5 of $C_6H_3(NO_2)F$), 8.23-8.11 (m, 8H, H-2 and H-6 of $C_6H_3(NO_2)F$), -2.84 (s, 2H, 2×NH). *m/z* (ESI) (%): 869 (21), 868 (62), 867 (100) [isotope $(M+H)^+$].

*Nitration of 5,10,15,20-tetrakis(3-bromophenyl)porphyrin (**1b**).* 5,10,15,20-Tetrakis(3-bromophenyl)porphyrin (**1b**; 100 mg, 0.107 mmol) was dissolved in $CHCl_3$ (46 ml), and the solution was stirred under argon and cooled to 0-5 ˚C. To this mixture, yellow nitric acid (*d* = 1.52 g/ml; 0.8 ml, 19.30 mmol) was added dropwise *via* syringe during *ca* 5 min. The reaction was continued for 30 min, then the mixture was poured onto water (30 ml). The organic layer was separated, washed with water (3×40 ml), and dried with $MgSO_4/Na_2CO_3$. After evaporating the solvent, the products were isolated by column chromatography (eluent: a gradient mixture of $CHCl_3$/*n*-hexane – 1:1, 2:1, 3:1, $CHCl_3$) to give: 5-(3-bromo-4-nitrophenyl)-10,15,20-tris(3-bromophenyl)porphyrin (**2b**; 7.5 mg, 7 %), mixture of 5,10-bis(3-bromo-4-nitrophenyl)-15,20-bis(3-bromophenyl)porphyrin and 5,15-bis(3-bromo-4-nitrophenyl)-10,20-bis(3-bromophenyl)porphyrin (**3b** and **4b**; 24.5 mg, 22 %), 5,10,15-tris(3-bromo-4-nitrophenyl)-20-(3-bromophenyl)-porphyrin (**5b**; 11.7 mg, 10 %), and 5,10,15,20-tetrakis (3-bromo-4-nitrophenyl)porphyrin (**6b**; 8.5 mg, 7 %).

From the mixture of 5,10-bis(3-bromo-4-nitrophenyl)-15,20-bis(3-bromophenyl)porphyrin (**3b**) and 5,15-bis(3-bromo-4-nitrophenyl)-10,20-bis(3-bromophenyl)porphyrin (**4b**) small amounts of the analytically pure samples of both products were isolated, *via* repeated chromatography on preparative TLC plates (silica gel 60 F_{254}, 2 mm), and they were fully characterized.

When the reaction time was shortened to 8 min, 5-(3-bromo-4-nitrophenyl)-10,15,20-tris(3-bromophenyl)porphyrin (**2b**) was obtained as the main product (67 %). Additionally, small amounts of 5,10-bis(3-bromo-4-nitrophenyl)-15,20-bis(3-bromophenyl)-porphyrin (**3b**; 3 %) were isolated.

*5-(3-Bromo-4-nitrophenyl)-10,15,20-tris(3-bromophenyl)-porphyrin (**2b**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.91 (d, *J* = 4.7 Hz, 2H, H$^\beta$-pyrrole), 8.87 (s, 4H, H$^\beta$-pyrrole), 8.80 (d, *J* = 4.7 Hz, 2H, H$^\beta$-pyrrole), *ca* 8.60 (s, 1H, H-2 of $C_6H_3(NO_2)Br$), 8.37 (s, 3H, H-2 of C_6H_4Br), 8.31 and 8.28 (AB, *J* = 8.0 Hz, 2H, H-6 and H-5 of $C_6H_3(NO_2)Br$), 8.15 (d, *J* = 7.6 Hz, 3H, H-6 of C_6H_4Br), 7.97 (d, *J* = 8.0 Hz, 3H, H-4 of C_6H_4Br), 7.65 (apparent t, *J* = 7.7 Hz, 3H, H-5 of C_6H_4Br), -2.90 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 645.5 (3.42), 589 (3.51), 551 (3.57), 516 (3.87), 420 (5.10, Soret). *m/z* (APPI(+)-photospray) (%): 982 (3), 981 (9), 980 (23), 979 (31), 978 (64), 977 (46), 976 (100), 975 (34), 974 (66), 973 (9), 972 (15) [isotope $(M+H)^+$]. HR-MS (ESI) found: 971.8862. $C_{44}H_{26}N_5O_2Br_4$ (M+H) requires 971.8820.

*5,10-Bis(3-bromo-4-nitrophenyl)-15,20-bis(3-bromophenyl)-porphyrin (**3b**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.93 (d, *J* = 4.7 Hz, 2H, H$^\beta$-pyrrole), 8.89 (s, 2H, H$^\beta$-pyrrole), 8.86 (s, 2H, H$^\beta$-pyrrole), 8.82 (d, *J* = 4.7 Hz, 2H, H$^\beta$-pyrrole), 8.62 (s, 2H, H-2 of $C_6H_3(NO_2)Br$), 8.37 (s, 2H, H-2 of C_6H_4Br), 8.30 and 8.29 (AB, *J* = 8.5 Hz, 4H, H-6 and H-5 of $C_6H_3(NO_2)Br$), 8.15 (d, *J* = 7.2 Hz, 2H, H-6 of C_6H_4Br), 7.98 (d, *J* = 8.4 Hz, 2H, H-4 of C_6H_4Br), 7.66 (apparent t, *J* = 7.8 Hz, 2H, H-5 of C_6H_4Br), -2.90 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 646.5 (3.36), 591 (3.74), 551.5 (3.82), 516 (4.23), 422.5 (5.45, Soret). *m/z* (APPI(+)-photospray) (%): 1026 (11), 1025 (28), 1024 (39), 1023 (78), 1022 (55), 1021 (100), 1020 (41), 1019 (73), 1018 (11), 1017 (20) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $(M+H)^+$ ion ($C_{44}H_{25}N_6O_4Br_4$) – found to be identical within the experimental error limits. *m/z* (FD) (%): 1025 (11), 1024 (24), 1023 (41), 1022 (77), 1021 (50), 1020 (100), 1019 (41), 1018 (67), 1017 (7), 1016 (15) [isotope M^+]. HR-MS (FD) found: 1015.8265. $C_{44}H_{24}N_6O_4Br_4$ (M^+) requires 1015.8292.

*5,15-Bis(3-bromo-4-nitrophenyl)-10,20-bis(3-bromophenyl)-porphyrin (**4b**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.92 (d, *J* = 4.6 Hz, 4H, H$^\beta$-pyrrole), 8.82 (d, *J* = 4.6 Hz, 4H, H$^\beta$-pyrrole), 8.62 (s, 2H, H-2 of $C_6H_3(NO_2)Br$), 8.37 (s, 2H, H-2 of C_6H_4Br), 8.31 and 8.28 (AB, *J* = 8.6 Hz, 4H, H-6 and H-5 of $C_6H_3(NO_2)Br$), 8.15 (d, *J* = 7.0 Hz, 2H, H-6 of C_6H_4Br), 7.98 (d, *J* = 7.4 Hz, 2H, H-4 of C_6H_4Br), 7.66 (apparent t, *J* = 7.7 Hz, 2H, H-5 of C_6H_4Br), -2.90 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 645.5 (3.46), 590 (3.77), 552 (3.87), 515.5 (4.27), 421 (5.52, Soret). *m/z* (FD) (%): 1025 (5), 1024 (31), 1023 (18), 1022 (65), 1021 (32), 1020 (100), 1019 (23), 1018 (53), 1017 (6), 1016 (24) [isotope M^+]. The molecular formula was confirmed by comparing the theore tical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{44}H_{24}N_6O_4Br_4$) – found to be identical within the experimental error limits.

*5,10,15-Tris(3-bromo-4-nitrophenyl)-20-(3-bromophenyl)-porphyrin (**5b**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.94 (d, *J* = 4.7 Hz, 2H, H$^\beta$-pyrrole), 8.87 (s, 4H, H$^\beta$-pyrrole), 8.84 (d, *J* = 4.7 Hz, 2H, H$^\beta$-pyrrole), 8.61 (s, 3H, H-2 of $C_6H_3(NO_2)Br$), 8.37 (s, 1H, H-2 of C_6H_4Br), 8.31 and 8.30 (AB, *J* = *ca* 8.6 Hz, 6H, H-6 and H-5 of $C_6H_3(NO_2)Br$), 8.15 (d, *J* = 7.2 Hz, 1H, H-6 of C_6H_4Br), 8.00 (d, *J* = 8.0 Hz, 1H, H-4 of C_6H_4Br), 7.68 (apparent t, *J* = 7.8 Hz, 1H, H-5 of C_6H_4Br), -2.91 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 645.5 (3.03), 590 (3.52), 550 (3.55), 515.5 (4.00), 423 (5.21, Soret). *m/z* (APPI(+)-photospray) (%): 1071 (11), 1070 (26), 1069 (38), 1068 (78), 1067 (52), 1066 (100), 1065 (35), 1064 (66), 1063 (11), 1062 (18) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theore tical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{44}H_{24}N_7O_6Br_4$) – found to be identical within the experimental error limits.

*5,10,15,20-Tetrakis(3-bromo-4-nitrophenyl)porphyrin (**6b**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.88 (s, 8H, H$^\beta$-pyrrole), 8.60 (s, 4H, H-2 of $C_6H_3(NO_2)Br$), 8.30 and 8.29 (AB, *J* = *ca* 9.0 Hz, 8H, H-6 and H-5 of $C_6H_3(NO_2)Br$), -2.93 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 644.5 (3.43), 590 (3.84), 551 (3.93), 516 (4.31), 422.5 (5.50, Soret). *m/z* (APPI(–)-photospray) (%): 1114 (14), 1113 (29), 1112 (41), 1111 (77), 1110 (65), 1109 (100), 1108 (46), 1107 (64), 1105 (16) [isotope $(M-H)^-$]. The molecular formula was confirmed by comparing the theore tical and experimental isotope patterns for the $[M-H]^-$ ion ($C_{44}H_{21}N_8O_8Br_4$) – found to be identical within the experimental error limits.

*Nitration of 5,10,15,20-tetrakis(3-iodophenyl)porphyrin (**1c**).* The reaction was carried out according to the procedure applied for **1b** (**1c**: 80 mg, 0.072 mmol; $CHCl_3$: 40 ml; HNO_3: 0.8 ml, 19.30 mmol; 0-5 ˚C; reaction time: 30 min; TLC monitoring). The products were isolated by column chromatography using a gradient mixture of $CHCl_3$/*n*-hexane (2:1; 3:1; 4:1) to give: 5-(3-iodo-4-nitrophenyl)-10,15,20-tris(3-iodophenyl)porphyrin (**2c**; 26 mg, 31 %), mixture of 5,10-bis(3-iodo-4-nitrophenyl)-15,20-bis-(3-iodophenyl)porphyrin and 5,15-bis(3-iodo-4-nitrophenyl)-10,20-bis(3-iodophenyl)porphyrin (**3c** and **4c**; 20.9 mg, 24 %), 5,10,15-tris(3-iodo-4-nitrophenyl)-20-(3-iodophenyl)porphyrin (**5c**; 4.5 mg, 5 %), and 5,10,15,20-tetrakis(3-iodo-4-nitrophenyl) porphyrin (**6c**; 1.9 mg, 2 %).

From the mixture of 5,10-bis(3-iodo-4-nitrophenyl)-15,20-bis 3-iodophenyl)porphyrin (**3c**) and 5,15-bis(3-iodo-4-nitrophenyl)-10,20-bis(3-iodophenyl)porphyrin (**4c**) small amounts of the analytically pure samples of both products were isolated, *via* repeated chromatography on preparative TLC plates (silica gel 60 F_{254}, 2 mm), and they were fully characterized.

A larger amount of HNO_3 added (1.2 ml, 28.95 mmol) allow to increase the yield of a mixture of dinitrated products (**3c** and **4c**, 46 %).

A larger amount of HNO_3 added (1.2 ml, 28.95 mmol) and additional slight prolonging the reaction time (up to 35 min) afforded 5,10,15,20-tetrakis(3-iodo-4-nitrophenyl)porphyrin (**6c**), as a main product (18 %).

*5-(3-Iodo-4-nitrophenyl)-10,15,20-tris(3-iodophenyl)-porphyrin (**2c**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.93 (s, 1H, H-2 of $C_6H_3(NO_2)I$), 8.91 (d, *J* = 4.8 Hz, 2H, H$^\beta$-pyrrole), 8.87 (s, 4H, H$^\beta$-pyrrole), 8.80 (d, *J* = 4.8 Hz, 2H, H$^\beta$-pyrrole), 8.58 (s, 3H, H-2 of C_6H_4I), 8.34 and 8.29 (AB, *J* = 8.4 Hz, 2H, H-6 and H-5 of $C_6H_3(NO_2)I$), 8.23-8.12 (m, 6H, H-4 and H-6 of C_6H_4I), 7.52

(apparent t, J = 7.6 Hz, 3H, H-5 of C_6H_4I), -2.90 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 646.5 (3.42), 591 (3.68), 556 (3.83), 516.5 (4.13), 421 (5.41, Soret). *m/z* (APPI(+)-photospray) (%): 1167 (3), 1166 (16), 1165 (58), 1164 (100) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theore tical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{44}H_{26}N_5O_2I_4$) – found to be identical within the experimental error limits.

*5,10-Bis(3-iodo-4-nitrophenyl)-15,20-bis(3-iodophenyl)-porphyrin (**3c**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.95–8.80 (m, 10H) [4×H$^\beta$-pyrrole, 2×H-2 of $C_6H_3(NO_2)I$; inside: 8.89 and 8.85 (2×s, 2×2H$^\beta$-pyrrole)], 8.58 (s, 2H, H-2 of C_6H_4I), 8.34 and 8.30 (AB, J = 8.0 Hz, 4H, H-6 and H-5 of $C_6H_3(NO_2)I$), 8.21-8.15 (m, 4H, H-4 and H-6 of C_6H_4I), 7.54 (apparent t, "J" = *ca* 8.0 Hz, 2H, H-5 of C_6H_4I), -2.90 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 648 (2.91), 591 (3.26), 553.5 (3.37), 517 (3.74), 423.5 (4.98, Soret). *m/z* (APPI(+)-photospray) (%): 1212 (3), 1211 (15), 1210 (54), 1209 (100) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{44}H_{25}N_6O_4I_4$) – found to be identical within the experimental error limits.

*5,15-Bis(3-iodo-4-nitrophenyl)-10,20-bis(3-iodophenyl)-porphyrin (**4c**);* this was contaminated with other nitroporphyrins. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.94-8.89 (m, 6H, 4×H$^\beta$-pyrrole and 2×H-2 of $C_6H_3(NO_2)I$), 8.82 (d, J = *ca* 4.6 Hz, 4H, H$^\beta$-pyrrole), 8.58 (s, 2H, H-2 of C_6H_4I), 8.34 and 8.29 (AB, J = *ca* 8.5 Hz, 4H, H-6 and H-5 of $C_6H_3(NO_2)I$), 8.21-8.15 (m, 4H, H-4 and H-6 of C_6H_4I), 7.58-7.53 (m, 2H, H-5 of C_6H_4I), -2.90 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 646.5 (3.93), 591 (4.15), 555.5 (4.30), 517.5 (4.58), 422 (5.79, Soret).

*5,10,15-Tris(3-iodo-4-nitrophenyl)-20-(3-iodophenyl)-porphyrin (**5c**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.94 (d, J = *ca* 5.0 Hz, 2H, H$^\beta$-pyrrole), 8.92 (s, 3H, H-2 of $C_6H_3(NO_2)I$), 8.87 (s, 4H, H$^\beta$-pyrrole), 8.83 (d, J = *ca* 5.0 Hz, 2H, H$^\beta$-pyrrole), 8.58 (s, 1H, H-2 of C_6H_4I), 8.34 and 8.30 (AB, J = *ca* 8.0 Hz, 6H, H-6 and H-5 of $C_6H_3(NO_2)I$), 8.22-8.15 (m, 2H, H-4 and H-6 of C_6H_4I), 7.58-7.50 (m, 1H, H-5 of C_6H_4I), -2.91 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 648.5 (4.02), 590.5 (4.10), 556 (4.25), 517.5 (4.56), 422 (5.78, Soret). *m/z* (APPI(+)-photospray) (%): 1257 (3), 1256 (13), 1255 (51), 1254 (100) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theore tical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{44}H_{24}N_7O_6I_4$) – found to be identical within the experimental error limits.

*5,10,15,20-Tetrakis(3-iodo-4-nitrophenyl)porphyrin (**6c**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.91 (s, 4H, H-2 of $C_6H_3(NO_2)$ I), 8.89 (s, 8H, H$^\beta$-pyrrole), 8.32 and 8.31 (AB, J = *ca* 8.0 Hz, 8H, H-6 and H-5 of $C_6H_3(NO_2)I$), -2.92 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 651 (3.99), 591.5 (4.04), 556 (4.19), 517 (4.37), 424 (5.48, Soret). *m/z* (APPI(+)-photospray) (%): 1303 (14), 1302 (18), 1301 (26), 1300 (63), 1299 (100) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theore tical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{44}H_{23}N_8O_8I_4$) – found to be identical within the experimental error limits.

*Nitration of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin (**7**).* 5,10,15,20-Tetrakis(2,6-dichlorophenyl)porphyrin (**7**; 90 mg, 0.10 mmol) was dissolved in $CHCl_3$ (9 ml). To this mixture, yellow nitric acid (d = 1.52 g/ml; 1.8 ml, 43.4 mmol) was added *via* syringe and it was left with stirring for 6 min at room temperature. Then, the reaction mixture was poured onto water (20 ml). The organic layer was separated, washed with water (5×20 ml) and dried with $MgSO_4/Na_2CO_3$. After evaporating the solvent, the products were isolated by column chromatography (eluent: $CHCl_3$/*n*-hexane – 2:1) to give: 5-(2,6-dichloro-3-nitrophenyl)-10,15,20-tris(2,6-dichlorophenyl)-porphyrin (**8**; 16.8 mg, 18 %) and 5,10-bis(2,6-dichloro-3-nitrophenyl)-15,20-bis(2,6-dichlorophenyl)porphyrin (**9**; 13.7 mg, 14 %). They were partially contaminated with other nitroporphyrin products.

*5-(2,6-Dichloro-3-nitrophenyl)-10,15,20-tris(2,6-dichlorophenyl)porphyrin (**8**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.86-8.52 (m, H$^\beta$-pyrrole), 8.36-8.22 and 8.04-7.82 (m, H-$C_6H_2(NO_2)Cl_2$ and H-$C_6H_3Cl_2$), NH - undetected. *m/z* (APPI(+)-photospray) (%): 942 (10), 941 (17), 940 (37), 939 (37), 938 (76), 937 (53), 936 (100), 935 (55), 934 (91), 933 (65), 932 (62) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theore tical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{44}H_{22}N_5O_2Cl_8$) – found to be identical within the experimental error limits.

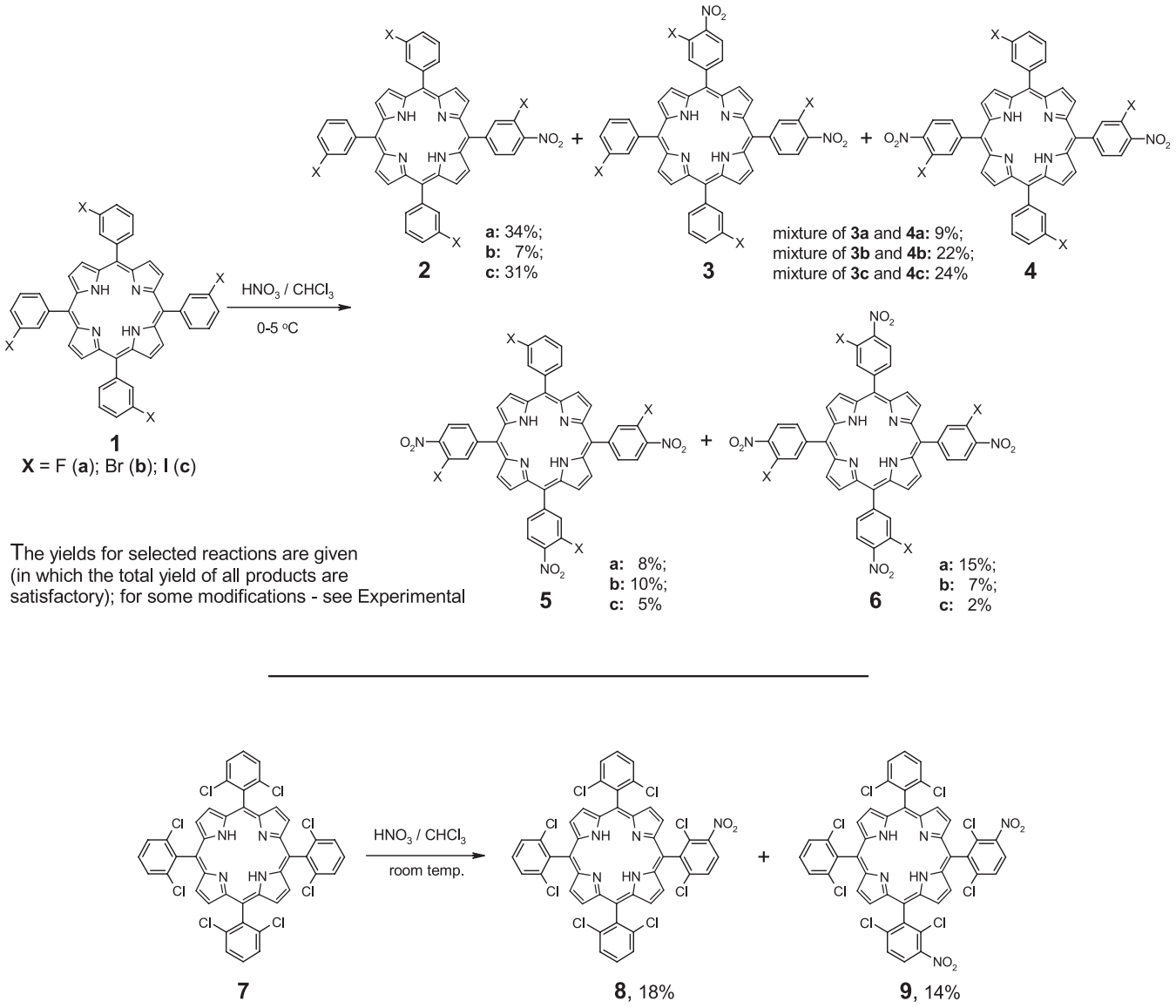
*5,10-Bis(2,6-dichloro-3-nitrophenyl)-15,20-bis(2,6-dichlorophenyl)porphyrin (**9**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.82-8.74 and 8.59-8.54 (2×m, H$^\beta$-pyrrole), 8.36-8.26, 8.04-7.98, and 7.93-7.87 (3×m, H-$C_6H_2(NO_2)Cl_2$ and H-$C_6H_3Cl_2$); inside: 8.34 and 8.31 (AB, J = 8.4 Hz, H-4 and H-5 of $C_6H_2(NO_2)Cl_2$), -2.47 (s, 2H, 2×NH). UV-vis ($CHCl_3$) λ_{max} nm (log ε): 647 (2.54), 589.5 (2.59), 545.5 (2.84), 517.5 (3.07), 419 (4.41, Soret). *m/z* (APPI(+)-photospray) (%): 986 (14), 985 (33), 984 (35), 983 (73), 982 (48), 981 (100), 980 (41), 979 (83), 978 (17), 977 (30) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theore tical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{44}H_{21}N_6O_4Cl_8$) – found to be identical within the experimental error limits.

Results and Discussion

According to Kruper *et al.*'s[10a] method direct nitration of *meso*-tetraphenylporphyrin occurs in the *para*-position of the *meso*-phenyl ring.[10] Many its derivatives (3-Me, 3-Cl, 3-OMe) react similarly.[10a,11] Manipulation of the reaction conditions offers the possibility of the introduction the NO_2 functionality to other Ph-units. In some papers published by us and by another groups the introduction of two, three, or even four NO_2 substituents was demonstrated,[10a,11,12] thus giving highly substituted derivatives on one or more of the *meso*-aryl rings. In this work, we used for this purpose (as substrates) readily available halo-substituted *m*-TPP derivatives.[7–9]

All these compounds (substrates and products) are also involved in another our ongoing project. They are very good models for calculations the ^{1}H NMR substituent increments in *meso*-tetraarylporphyrin systems.[11c,13] In this paper, the investigations were undertaken towards the influence of halogens on the above derivatization, which enable determining the desired increments. Thus, we describe the nitration of a series of various halo-substituted *meso*-tetraphenylporphyrin derivatives: *meso*-tetrakis(3-fluorophenyl)porphyrin (**1a**), *meso*-tetrakis(3-bromophenyl) porphyrin (**1b**), *meso*-tetrakis(3-iodophenyl)porphyrin (**1c**), and *meso*-tetrakis(2,6-dichlorophenyl)porphyrin (**7**). The nitration of *meso*-tetrakis(3-chlorophenyl)porphyrin, a compound of very similar structure to the above systems, was studied earlier by chance.[11a-b] The nitro group introduced, which lends the possibility for further transformations, is one of the most versatile substituents for the preparation of various highly decorated porphyrins.

In the reaction of **1a** with the use of fuming yellow nitric acid (d = 1.52; 0÷5 °C, large excess of HNO_3, in $CHCl_3$, *ca* 9 min) we observed the formation of five products. The mononitro- and tetranitro-compound were the major derivatives (34 % of **2a** and 15 % of **6a**, respectively). Additionally, a mixture of double nitrated moieties (**3a** + **4a**, 9 %) and trinitrated one (**5a**, 8 %) were isolated. Several times repeated column chromatography of the mixture **3a** and **4a** gave small amounts of the analytically pure sample of 5,10-bis(3-fluoro-4-nitrophenyl)-15,20-bis(3-fluorophenyl)-



Scheme 1.

porphyrin (**3a**) for its full characterization.

A quite different distribution of the products and lower yields were observed for *meso*-tetrakis(3-bromophenyl)-porphyrin (**1b**). In this case, the nitration led mainly to a mixture of dinitrated porphyrins (**3b** + **4b**, 22 %), which was accompanied with mononitro- (**2b**, 7 %), trinitro- (**5b**, 10 %), and tetranitro-product (**6b**, 7 %). Again, the rechromatography of the mixture of dinitro-porphyrins (on preparative TLC plates) allowed us to isolate **3b** and **4b** in a pure form and fully characterize.

On the other hand, the reaction under similar conditions within a short interval of time (8 min) gave predominantly 5-(3-bromo-4-nitrophenyl)-10,15,20-tris(3-bromophenyl)-porphyrin (**2b**) in a good yield (67 %).

Similarly, the nitration of *meso*-tetrakis(3-iodophenyl)-porphyrin (**1c**) produced a mixture of all the possible products in reasonable total yield: mononitro- (**2c**, 31 %), dinitro- (**3c** + **4c**, 24 %), trinitro- (**5c**, 5 %), and tetranitro-substituted (**6c**, 2 %). A larger amount of HNO_3 added allows us to increase the yield of a mixture of dinitrated products (**3c** + **4c**, up to 46 %), while additional slight prolonging the reaction time afforded mainly 5,10,15,20-tetrakis(3-iodo-4-nitrophenyl)-porphyrin (**6c**), however with moderate yield (18 %).

The above substrates and products are porphyrins of 3-halo-substitution in *meso*-aryl rings. They were chosen herein due to our ^{1}H NMR interests. Such substitution pattern in these systems allows to determine the previously discussed parameters for all the positions in the *meso*-phenyl ring. As it was mentioned at the beginning of this chapter, the nitration of 3-chloro-derivative has been described earlier.[11a,11b] In this work, we included to the study another chloro-substituted moiety, 5,10,15,20-tetrakis(2,6-dichlorophenyl)-porphyrin (**7**).[7,9] Thus, we extended the list of various halo/nitro-substituted *meso*-tetraphenylporphyrin derivatives obtained. In the latter, two *ortho*-/*para*- directed -Cl atoms should result in the nitration in position 3-. Indeed, it was a case. The above reaction led to a mixture of nitrocompounds, from which the mononitro-substituted and *cis*-like dinitrosubstituted products were isolated (**8**, **9**; 18 % and 14 %, respectively).

Conclusions

The ability to access new types of porphyrin derivatives is of great importance due to their biological activity. In this paper, we demonstrated the preparation of *meso*-tetraarylporphyrins, bearing up to ten functional groups (halogens and nitro-substituents, in *meso*-aryl moieties), by tandem cyclocondensation/electrophilic nitration reactions in these systems. The nitro-haloporphyrins synthesized could be precursors for further functionalization, for example, to give derivatives of higher hydrophilicity. Syntheses of such compounds are sought due to their solubility in physiological milieu and characteristic strong absorption bands shifted to the red region of visible spectrum; hence, they may be of potential use as the sensitizers in photodynamic therapy.

Preparation of porphyrins,[12] substituted with electrophilic highly functionalized aryl rings in *meso*-positions , by the Rothemund synthesis[14] (and its cross-condensation modifications[15]), from the corresponding aldehydes and pyrrole, is an extremely difficult task (yields below 3 %),[16] or even impossible.

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