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–порфиринонов 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-тетрафенилпорфирна (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 °С 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. These systems are present in well-known biological materials (e.g. chlorophyll, heme, vitamin B12) [3]. 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) [4], molecular-based multi-bit memory storage [5], electron-donor parts in artificial photosynthetic models [6], etc. For example, from this process, the hydophobic 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 NO2 groups) was achieved by the direct electrophilic nitrination of the system.

Experimental

1H 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 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 [7]: 5,10,15,20-tetrakis(3-fluorophenyl)porphyrin (1a, 37%), 5,10,15,20-tetrakis(3-bromo-phenyl)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 [8]).

They have already been described in the previous literature: [1a-c,9] Herein, their 1H NMR data were given for more detailed characterization.

5,10,15,20-Tetrakis(3-fluorophenyl)porphyrin (1a). 1H NMR (CDCl3, 400 MHz) δ ppm: 8.86 (s, 8H, H-Fl), 8.02 (d, J = 7.2 Hz, 4H, H-6 of C6H4F), 7.95 (d, J = 9.2 Hz, 4H, H-2 of C6H4F), 7.73 (apparent q, J2 = 7.9 Hz, 1H, H-5 of C6H4F), 7.52 (apparent td, "J" = ca 8.0 Hz, J2 = 2.0 Hz, 4H, H-4 of C6H4F), -2.91 (s, 2H, 2×NH).

5,10,15,20-Tetrakis(3-bromophenyl)porphyrin (1b). 1H NMR (CDCl3, 400 MHz) δ ppm: 8.86 (s, 8H, H-Br), 8.38 (s, 4H, H-2 of C6H4Br), 8.16 (d, J = 7.6 Hz, 4H, H-6 of C6H4Br), 7.95 (d, J = ca 8.0 Hz, 4H, H-4 of C6H4Br), 7.64 (apparent t, J1 = 7.6 Hz, 4H, H-5 of C6H4Br), -2.92 (s, 2H, 2×NH).

5,10,15,20-Tetrakis(3-iodophenyl)porphyrin (1c). 1H NMR (CDCl3, 400 MHz) δ ppm: 8.86 (s, 8H, H-I), 8.59 (s, 4H, H-2 of C6H4I), 8.19 (d, J = 7.2 Hz, 4H, H-6 of C6H4I), 8.15 (d, J = 8.0 Hz, 4H, H-4 of C6H4I), 7.50 (apparent t, J = 7.6 Hz, 4H, H-5 of C6H4I), -2.92 (s, 2H, 2×NH).

Nitrination 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 CHCl3 (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; 0.18 ml, 39 mmol) in CHCl3 (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 MgSO4/Na2CO3. After evaporating the solvent, the products were isolated by column chromatography (eluent: a gradient mixture of CHCl3/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) resulted in the analytically pure sample of 3a (for its full characterization).

5-(3-Fluoro-4-nitrophenyl)10,15,20-tris(3-fluorophenyl)porphyrin (2a). 1H NMR (CDCl3, 400 MHz) δ ppm: 8.91 (d, J = 4.8 Hz, 2H, H-Fl-pyrophe), 8.87 (s, 4H, H-Fl-pyrophe), 8.87 (d, J = 4.8 Hz, 2H, H-Fl-pyrophe), 8.48 (apparent t, J = 8.1 Hz, 1H, H-5 of C6H5(NO2)F), 8.17 (d, J = 7.4 Hz, 1H, H-6 of C6H5(NO2)F), 8.00 (d, J = 7.5 Hz, 3H, H-6 of C6H5F), 7.93 (d, J = 9.2 Hz, 3H, H-2 of C6H5F), 7.74 (apparent q, J1 = 4.7 Hz, 2H, H-4 of C6H5F), 7.54 (apparent td, "J" = ca 8.4 Hz, J2 = 2.5 Hz, 3H, H-4 of C6H5F), -2.87 (s, 2H, 2×NH). UV-vis (CHCl3) λmax nm (log e): 647.5 (3.19), 594 (3.26), 551.5 (3.36), 515 (3.77), 418.5 (5.05, Soret), 369 (4.03), m/z (FD): 734 (7), 733 (21), 732 (57), 731 (100) [isotope M+]; HR-MS (FD) found: 731.1938, C44H25N5O2F4 (M+) requires 731.1944.
Nitrations of 5,10,15,20-tetakis(3-bromophenyl)porphyrin (1b). 5,10,15,20-Tetakis(3-bromophenyl)porphyrin (1b; 100 mg, 0.107 mmol) was dissolved in CHCl₃ (46 ml), and the solution was stirred under argon and cooled to 0–5 °C. To this mixture, yellow nitric acid (1.52 g) dissolved in 0.1 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 MgSO₄/Na₂CO₃. After evaporating the solvent, the products were isolated by column chromatography (eluent: a gradient mixture of CHCl₃/n-hexane – 1:1; 2:1, 3:1, CHCl₃) 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-tetakis(3-bromophenyl)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 F₂₅₄, 2 mm), and they were fully characterized.

Nitration of 5,10,15,20-tetrakis(3-iodophenyl)porphyrin (1c). 5-(3-Iodo-4-nitrophenyl)-10,15,20-tris(3-iodophenyl)porphyrin (1b) 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.


d= 7.4 Hz, 2H, H₆-phenyl), 8.87 (s, 4H, H₅-phenyl), 8.80 (d, J = 4.7 Hz, 2H, H₆-pyrrrole), 8.70 (s, 1H, H-2 of C₆H₄(NO₂)Br), 8.37 (s, 3H, H-2 of C₆H₂(3-Br), 8.31 and 8.28 (AB, J = ca 8.6 Hz, 6H, H-6 and H-5 of C₆H(NO₂)Br), 8.15 (d, J = 7.0 Hz, 2H, H-6 of C₆H₄Br), 7.98 (d, J = 7.4 Hz, 2H, H-4 of C₆H₄Br), 7.66 (apparent t, J = 7.7 Hz, 2H, H-5 of C₆H₄Br), -2.90 (s, 2H, 2×NH). UV-vis (CHCl₃), 645.5 (3.46), 590 (3.74), 552 (3.87), 515 (4.00), 423 (5.21, Soret). m/z (APPI(+)-photospray) (%): 1025 (10), 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 theoretical and experimental isotope patterns for the [M⁺H]⁺ ion (C₄₄H₂₅N₆O₄Br₄) – found to be identical within the experimental error limits.
Results and Discussion

According to Kruper et al.\textsuperscript{[16]} method direct nitration of meso-tetraphenylporphyrin occurs in the para-position of the meso-phenyl ring.\textsuperscript{[10]} Many of its derivatives (3-Me, 3-Cl, 3-OMe) react similarly.\textsuperscript{[10a,11]} Manipulation of the reaction conditions offers the possibility of the introduction the NO₂ functionality to other Ph-units. In some papers published by us and by another groups the introduction of two, three, or even four NO₂ substituents was demonstrated,\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[11c,13]} In this paper, the investigations were undertaken towards the influence of halogenes 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-tetra(3-fluorophenyl)porphyrin (1a), meso-tetra(3-bromophenyl)porphyrin (1b), meso-tetra(3-iodophenyl)porphyrin (1c), and meso-tetra(2,6-dichlorophenyl)porphyrin (7). The nitration of meso-tetra(3-chlorophenyl)porphyrin, a compound of very similar structure to the above systems, was studied earlier by chance.\textsuperscript{[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 HNO₃, in CHCl₃, ca 9 min) we observed the formation of five products. The mononitro- and tetrinitro-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-nitropheno)-15,20-bis(3-fluorophenyl)-
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 (2b + 4b, 22 %), which was accompanied with mononitro- (2b, 7 %), trinitro- (5b, 10 %), and tetrinitro-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 tetrinitro-substituted (6c, 2 %). A larger amount of HNO₃ 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 ¹H 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. In this work, we included to the study another chloro-substituted moiety, 5,10,15,20-tetrakis(2,6-dichlorophenyl)-porphyrin (7). 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).

Scheme 1.
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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References


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