Макрогетероциклы
http://macroheterocycles.isuct.ru

DOI: 10.6060/mhc160423z

New Pegylated Unsymmetrical *meso*–Arylporphyrins as Potential Photosensitizers

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Approaches to the synthesis of amphiphilic meso-arylporphyrins containing polyethylene oxide groups were elaborated. Two monopyrrole condensation methods – modified Adler method and synthesis in aqueous micellar medium were used to obtain the target compounds. Optimal conditions of the reactions and isolation of the products have been selected.

Keywords: *meso*-Arylporphyrins, monopyrrole condensation, spectral characteristics.

Новые ПЭГ–замещенные несимметричные *мезо*–арилпорфирины как потенциальные фотосенсибилизаторы

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Разработаны подходы к синтезу амфифильных мезо-арилпорфиринов, содержащих полиэтиленоксидные группы. Два метода монопиррольной конденсации – модифицированный метод Адлера и синтез в водно-мицеллярной среде были использованы для получения целевых соединений. Были подобраны оптимальные условия проведения реакций и выделения продуктов.

Ключевые слова: *мезо*-Арилпорфирины, монопропильная конденсация, спектральная характеристика.

Introduction

Natural and synthetic porphyrins and their metal complexes find an increasing application as photosensitizes (PS) for fluorescent diagnostics and photodynamic therapy (PDT) of malignant tumors.[1-3] Synthetic *meso*-arylporphyrins as analogues of natural PS are of additional interest as model compounds to studying of theoretical and instrumental aspects of PDT. Earlier it has been established that the amphiphilic character of porphyrins is one of the key factors affecting on the efficiency and intercellular localization of PS.[4,5] In this regard, synthesis and modification of hydroxyphenylporphyrins derivatives, structural analogs of the second generation PS – Foscan®, are actual. The amphiphilic polymer polyethyleneglycol (PEG) is widely exploited in medical purposes because its low toxicity, non-immunogenicity, solubility both in aqueous medium or in organic solvents, "invisibility" to the mononuclear phagocyte system and opsonizing proteins (immunoglobulins and complement factors).[3,6] Besides, introduction of the PEG residues at the PS molecule significantly increases its solubility under physiologic conditions. Hydroxyphenylporphyrins with higher alkyl substituents can be easily integrated into the model membrane structures (*e.g.*, micelles, liposomes).[7-9] Therefore the synthesis of amphiphilic unsymmetrically substituted hydroxyphenylporphyrins containing polyethylene oxide groups and higher alkyl residues is of practical interest for the development of effective medicines and diagnostic drugs.

Experimental

All chemicals were obtained commercially and used as received unless otherwise noted. Pyrrole was purified by vacuum

distillation; dichloromethane, hexane were dried by standard methods prior to use. Column chromatography was performed on silica gel G 60 (Merck Inc, 40-70 mesh). TLC was performed on pre-coated silica gel glass plates (silica gel 60, F-254, thickness 0.25 mm) by Merck Inc. 4-Hydroxybenzaldehyde, 3,4-dihydroxybenzaldehyde, triethyleneglycol monomethyl ether TEG), PEG M=550 monomethyl ether, mesylchloride, triethylamin were purchased from Sigma–Aldrich and used without further purification. UV-vis spectra were recorded on TermoSpectronic Helios Alpha spectrophotometer in quartz cells of 0.5 cm thickness. All reported NMR results were obtained using Bruker 300 MHz in DMSO-d_6. Mass-spectra were registered on «Ultraflex» (MALDI-TOF, matrix – DHB) or liquid chromatograph 1100 LCMSD (Agilent Technologies, USA) equipped with a mass spectrometric detector with chemical ionization at atmospheric pressure (APCI, APSI) and with UV-spectrophotometric detector (DAD).

1-(4-Methylsulfonyl)-3,6,9-trioxadecan, ***1***. Solution of TEG monomethyl ether (0.012 mol, 2.0 g) and triethylamine (0.18 mol, 18.20 g) in 50 ml of dry dichloromethane was cooled to 0 °C and stirred at argon flow. To these mixture, mesyl chloride (0.06 mol, 6.87 g) was added dropwise in 30 min, than the mixture was stirred at room temperature for 24 h. The residue was filtered, reaction mass was concentrated in vacuum. Product was isolated by column chromatography on silica gel G 60 (dichloromethane /methanol 20:1). Yield 2.32 g (79 %). R_f=0.4 (CH_2Cl_2:MeOH=20:1). ^{1}H NMR (DMSO-d_6) δ_H ppm: 4.48 (2H, m, -CH_2-OSO_2), 3.85 (2H, m, -CH_2CH_2-OSO_2), 3.73 (2H, m, -$CH_2OCH_2CH_2$-OSO_2), 3.68 (2H, m, -$CH_2CH_2OCH_2CH_2$-OSO_2), 3.61 (2H, m, $CH_3OCH_2CH_2$-), 3.51 (2H, m, $CH_3OCH_2CH_2$-), 3.42 (3H, s., CH_3O-), 3.35 (3H, s, CH_3SO_2-). ^{13}C NMR (DMSO-d_6) δ_c ppm: 37.19, 58.4, 68.55, 69.3, 70.4, 71.4.

PEG mesylate (M = 550 g/mol), ***2****,* was received according to the method described for compound **1** by interaction of PEG monomethyl ether of (Average mass 550 g/mol, 3.6 mmol, 2.0 g), triethylamine (0.064 mol, 6.54 g) and mesylchloride (0.025 mol, 2.87 g). Product was isolated by column chromatography on silica gel G 60 (dichloromethane /methanol 10:1). Yield 1.98 g (72 %). R_f=0.43 (CH_2Cl_2:MeOH=20:1). ^{1}H NMR (CD_3OD) δ_H ppm: 4.37 (2H, m, -CH_2-OSO_2), 3.77 (2H, m, -CH_2CH_2-OSO_2), 3.63 (44H, br.s, -$(CH_2CH_2O)_{11}CH_2CH_2$-OSO_2), 3.54 (4H, m, $CH_3OCH_2CH_2$-), 3.35 (3H, s, CH_3O-), 3.11 (3H, s, CH_3SO_2-). ^{13}C NMR (CD_3OD) δ_C ppm: 48.61, 48.32, 48.04, 47.76, 47.47, 47.19, 46.90, 70.25. IR ν cm^{-1}: 2867 (CH_3-O), 1466 (CH_3-), 1354 (R-SO_2-OR), 1307 (SO_2-CH_3), 774 ($(CH_2)_2$), 610 (C-S).

4-{2-[2-(2-Methoxyethoxy)-ethoxy]-ethoxy}benzaldehyde, ***3***. To the solution of *p*-hydroxybenzaldehyde (2.50 mmol, 0.30 g) in 15 ml of DMF mesylate **1** (3.72 mmol, 0.90 g) was added in presence of Cs_2CO_3 (2.5 mmol, 1.63 g), the mixture was stirred at 100 °C during 14 h. The target product was extracted and purified by column chromatography on silica gel G 60 (dichloromethane/ethylacetate 5:1). Yield 0.595 g (85 %). R_f=0.55 (ethylacetate). ^{1}H NMR (DMSO-d_6) δ_H ppm: 10.04 (1H, s, CHO), 8.42 (2H, m, Ar H2-6), 7.30 (2H, m, Ar H3-5), 4.40 (2H, m, $ArOCH_2CH_2$-), 3.96 (2H, m, $ArOCH_2CH_2$-), 3.79 (2H, m, -$CH_2O(CH_2)_2OCH_3$), 3.72-3.67 (4H, m, -$CH_2OCH_2CH_2OCH_3$), 3.61 (2H, m, -$CH_2CH_2OCH_3$), 3.40 (3H, s, OCH_3). MS (APCI) *m/z*: found 268.7 [M]$^+$, calcld 268.3.

Benzaldehyde PEG (M = 550 g/mol), ***4***, was received according to the method described above for compound **3** by interaction of *p*-hydroxybenzaldehyde (0.82 mmol, 0.10 g), mesylate **2** (0.82 mmol, 0.53 g) and Cs_2CO_3 (1.06 mmol, 0.35 g). The target product was extracted, washed by acidic water and purified by column chromatography on silica gel G 60 (dichloromethane:ethylacetate 2:1). Yield 0.36 g (80 %). R_f=0.45 (ethylacetate). ^{1}H NMR (DMSO-d_6) δ_H ppm: 9.85 (1H, s, CHO), 7.89 (2H, m, Ar H2-6), 7.14 (2H, m, Ar H3-5), 4.25 (2H, m., $ArOCH_2CH_2$-), 3.89 (2H, m, $ArOCH_2CH_2$-), 3.67 (40H, m, $ArOCH_2CH_2$-$(OCH_2CH_2)_{10}$-), 3.56 (4H, m, -$CH_2CH_2OCH_3$), 3.37 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ_C ppm: 22.48, 38.17, 42.61, 48.57, 48.29, 48.01, 47.72, 47.44, 47.15, 46.87, 57.89, 69.63, 114.84, 131.84, 169.24. IR ν cm^{-1}: 2872 (C-H of aldehyde group), 1678 (C=O of aldehyde group), 1601, 1578 (ar C-C), 1105 (CH_2-O-CH_2), 839 (ar C-H), 774 ($(CH_2)_2$). MS (APCI) *m/z*: found 663.5 [M]$^+$, calcld 664.8.

3,4-Di-{2-[2-(2-Methoxyethoxy)-ethoxy]-ethoxy}benzaldehyde, ***5***, was received according to the method described above for compound **3** by interaction of 3,4-dihydroxybenzaldehyde (8.2 mmol, 0.29 g), mesylate **1** (4.1 mmol, 1 g) and Cs_2CO_3 (2.6 mmol, 0.88 g). The target product was extracted, washed by acidic water and purified by column chromatography on silica gel G 60 (ethylacetate). Yield 0.622 g (70 %). R_f=0.65 (ethylacetate). ^{1}H NMR (DMSO-d_6) δ_H ppm: 9.77 (1H, s, CHO), 7.41 (1H, d, Ar H6, *J*=1.91 Hz), 7.37 (1H, m, Ar H2), 8.96 (1H, d, Ar H5, *J*=8.08 Hz), 4.18 (4H, m, $ArOCH_2CH_2$-), 3.86 (4H, m, $ArOCH_2CH_2$-), 3.69 (4H, m, $ArO(CH_2)_2OCH_2$-), 3.62-3.55 (8H, m, -$CH_2OCH_2CH_2OCH_3$), 3.50 (4H, m, -$CH_2CH_2OCH_3$), 3.32 (6H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ_C ppm: 30.35, 35.65, 48.56, 48.28, 48.00, 47.71, 47.43, 47.14, 46.86, 57.79, 68.75, 69.46, 70.09, 70.58, 71.68, 112.40, 126.38, 130.41, 149.26, 154.79, 163.56. IR ν cm^{-1}: 2876 (C-H of aldehyde group), 1687 (C=O of aldehyde group), 1601, 1591 (ar C-C), 1129, 1051 (CH_2-O-CH_2), 850 (ar C-H), 742 ($(CH_2)_2$). MS (APCI) *m/z*: found 431.2 [M+H]$^+$, calcld 430.5.

General procedure for modified Adler method (method 1). 4-Hydroxybenzaldehyde (1.5 mmol), substituted benzaldehydes **3-5** or *p*-alkyloxybenzaldehydes (0.5 mmol) were added to the mixture of propionic acid (8 ml), acetic acid (4 ml) and nitrobenzene (2 ml). The mixture was refluxed for 15 min. Then a solution of pyrrole (2 mmol) in nitrobenzene (2 ml) was added dropwise, and the mixture was refluxed for 2 h. The reaction mass was cooled, dissolved by solvent from which precipitation of porphyrin crystals occurs. The precipitate was filtered and dryed, than chromatographed on silica gel G60.

General procedure for the synthesis in aqueous micellar medium (method 2). Solution of 10 ml of 0.5 M SDS was stirred under argon in 10 min, then pyrrole (1 mmol) and substituted benzaldehydes (0.25 and 0.75 mmol) were added. After 10 min 100 µl of 3 % HCl was added dropwise, stirred for 30 minutes and oxidized with DDQ (1.3 mmol). Solutions of 2 M KOH (5 ml), 3 M KCl (15 ml) and 30 ml of water were added to the reaction mass. The reaction products were extracted with ethylacetate and chromatographed analogously to the procedure described above.

5-{4-2-[2-(2-Methoxyethoxy)-ethoxy]oxyphenyl}-10,15,20-tris(4-hydroxyphenyl)porphyrin, ***6****. Method 1.* Obtained from pyrrole (2 mmol, 0.14 g), benzaldehyde **3** (0.5 mmol, 0.134 g), *p*-hydroxybenzaldehyde (1.5 mmol, 0.184 g). Yield 53.6 mg (13 %). *Method 2.* Obtained from pyrrole (1 mmol, 0.07 g), benzaldehyde **3** (0.25 mmol, 0.067 g), *p*-hydroxybenzaldehyde (0.75 mmol, 0.092 g). Yield 16.5 mg (8 %). UV-Vis (ethylacetate) λ_{max} nm (lgε): 418.0 (5.63), 515.8 (4.29), 552.6 (3.99), 592.4 (3.81), 650.6 (3.67). ^{1}H NMR (DMSO-d_6) δ_H ppm: 9.00 (6 H, d, *J*=2.93 Hz, H2, H8, H12, H13, H17, H18), 8.96 (2H, d, *J*=4.77 Hz, H3, H7), 8.22 (2H, d, *J*=8.44 Hz, 2-H), 8.14 (6 H, d, *J*=24.94 Hz, 2-H), 7.48 (2H, d, *J*=8.92 Hz, 3-H), 7.35 (6H, d, *J*=8.25 Hz, 3-H), 4.47 (2H, m, -O-CH_2), 4.03 (2H, m, -O-CH_2CH_2), 3.83 (2H, m, $O(CH_2)_2OCH_2$), 3.75 (2H, m, $CH_3O(CH_2)_2OCH_2$-), 3.71 (2H, m, $CH_3OCH_2CH_2$), 3.62 (2H, m, CH_3O-CH_2), 3.39 (3H, s, CH_3O). ^{13}C NMR (DMSO-d_6) δ_C ppm: 158.35, 157.38, 135.47, 133.59, 131.86, 131.07, 130.52, 120.04, 119.32, 113.90, 112.95, 71.30, 70.01, 69.07, 67.39, 35.75, 30.75. MS (APCI) *m/z*: found 825.9 [M+H], calcld 824.9 ($C_{51}H_{44}N_4O_7$).

5,10,15,20-Tetrakis(4-hydroxyphenyl)porphyrin, monosubstituted by PEG residue (M-550), ***7****. Method 1.* Obtained from pyrrole (2 mmol, 0.14 g), benzaldehyde **4** (0.5 mmol, 0.334 g), *p*-hydroxybenzaldehyde (1.5 mmol, 0.184 g). Yield 72.6 mg (11 %). *Method 2.* Obtained from pyrrole (0.8 mmol, 0.054 g), benzaldehyde **4** (0.2 mmol, 0.145 g), *p*-hydroxybenzaldehyde (0.8 mmol, 0.073 g). Yield 29 mg (7 %). UV-Vis (ethylacetate) λ_{max} nm (band ratio): 420.4, 522.1, 555.3, 596.9, 652.0 (1:0.0473:0.0354:0.0139:0.0157). ^{1}H NMR (DMSO-d_6) δ_H ppm: 8.88 (8H, br.s, H2, H3, H7, H8, H12, H13, H17, H18), 8.22 (2H, d, *J*=8.44 Hz, 2-H), 8.06 (8H, m, 2-H), 7.24 (2H, m, 3-H), 7.16 (6H, m, 3-H), 4.10 (2H, m, -O-CH_2), 3.81

(4H, m, -O-$CH_2CH_2OCH_2$-), 3.60 (2H, m, -O-$(CH_2)_2OCH_2CH_2$-), 3.57 (40H, br.s, $CH_3(O(CH_2)_2)_{10}$-), 3.51 (4H, m, $CH_3OCH_2CH_2CH_2$-), 3.36 (3H, s, OCH_3). MS (APCI) (*m/z*): found 1046.0 $[M+H]^+$, 1089.1 $[M]^+$, 1134.1 $[M+H]^+$, 1178.2 $[M+H]^+$, 1222.2 $[M+H]^+$, 1266.3 $[M+H]^+$, 1310.3 $[M+H]^+$, 1354.4 [M+H]+, calcld. 1045.2 (PEG_8), 1089.2 (PEG_9), 1133.3 (PEG_{10}), 1177.3 (PEG_{11}), 1221.4 (PEG_{12}), 1265.4 (PEG_{13}), 1309.5 (PEG_{14}), 1353.5 (PEG_{15}) 1397.6 (PEG_{16}).

5-{4-2-[2-(2-Methoxyethoxy)-ethoxy]oxyphenyl}-10,15,20-tris(4-tetradecyloxyphenyl)porphyrin, ***8****. Method 1.* Obtained from pyrrole (2 mmol, 0.14 g), benzaldehyde 3 (0.5 mmol, 0.334 g), *p*-tetradecyloxybenzaldehyde (1.5 mmol, 0.47 g). Yield 91.1 mg (13 %). *Method 2.* Obtained from pyrrole (1 mmol, 0.070 g), benzaldehyde 3 (0.25 mmol, 0.067 g), *p*-tetradecyloxybenzaldehyde (0.75 mmol, 0.24 g). Yield 17.5 mg (5 %). UV-Vis (ethylacetate) λ_{max} nm (band ratio): 423.0, 520.0, 557.3, 593.1, 651.5 (1:0.0350 :0.0249:0.0101:0.0121). R_f=0.55 (dichloromethane:ethylacetate 5:1). ^{1}H NMR (DMSO-d_6) δ_H ppm: 8.48 (8H, br.s, H2, H3, H7, H8, H12, H13, H17, H18), 7.70 (8H, m, 2-H), 7.53 (8H, m, 3-H), 4.31 (2H, m, -O-CH_2CH_2O-), 4.23 (6H, m, -OCH_2-$(CH_2)_{14}CH_3$), 4.09 (2H, m, -OCH_2-CH_2-O-), 3.90 (2H, m, -$O(CH_2)_2OCH_2$-), 3.81 (2H, m, $CH_3O(CH_2)_2OCH_2$-), 3.76 (2H, m, $CH_3OCH_2CH_2$-), 3.63 (4H, m, $CH_3OCH_2CH_2$-), 3.44 (3H, s, CH_3O-), 2.02 (6H, m, -$OCH_2CH_2(CH_2)_{11}CH_3$), 1.68 (6H, m, -$O(CH_2)_2CH_2(CH_2)_{10}CH_3$), 1.32 (60H, br.s, -$O(CH_2)_3(CH_2)_{10}CH_3$), 0.92 (9H, m, -$O(CH_2)_{13}CH_3$). MS (APCI) *m/z*: found 1401.1 $[M+H]^+$, calcld. 1400.0.

5-{4-2-[2-(2-Methoxyethoxy)-ethoxy]oxyphenyl}-10,15,20-tris(4-hexadecyloxyphenyl)porphyrin, ***9****. Method 1.* Obtained from pyrrole (1.24 mmol, 0.083 g), benzaldehyde **3** (1.5 mmol, 0.31 g), *p*-hexadecyloxybenzaldehyde (0.93 mmol, 0.323 g). Yield 65 mg (14 %). *Method 2.* Obtained from pyrrole (1 mmol, 0.070 g), benzaldehyde **3** (0.25 mmol, 0.067 g), *p*-hexadecyloxybenzaldehyde (0.75 mmol, 0.26 g). Yield 21 mg (5.5 %). UV-Vis (ethylacetate) λ_{max} nm (band ratio): 420.3, 513.1, 550.0, 590.6, 651.2 (1:0.0368 :0.0280:0.0118:0.0162). ^{1}H NMR (DMSO-d_6) δ_H ppm: 8.9 (8H, br.s, H2, H3, H7, H8, H12, H13, H17, H18), 8.14 (8H, d, *J*=8.48 Hz, 2-H), 7.29 (8H, m, 3-H), 4.39 (2H, m, -O-CH_2CH_2O-), 4.23 (6H, m, -OCH_2-$(CH_2)_{14}CH_3$), 4.04 (2H, m, -OCH_2-CH_2-O-), 3.82 (2H, m, -$O(CH_2)_2OCH_2$-), 3.76 (2H, m, $CH_3O(CH_2)_2OCH_2$-), 3.63 (4H, m, $CH_3OCH_2CH_2$-), 3.45 (3H, s, CH_3O-), 1.99 (6H, m, -$OCH_2CH_2(CH_2)_{13}CH_3$), 1.64 (6H, m, -$O(CH_2)_2CH_2(CH_2)_{12}CH_3$), 1.32 (72H, br.s, -$O(CH_2)_3(CH_2)_{12}CH_3$), 0.92 (9H, m, -$O(CH_2)_{15}CH_3$). ^{13}C NMR ($CDCl_3$) δ_C ppm: 157.72, 134.35, 131.18, 130.68, 118.60, 113.45, 111.45, 76.20, 75.78, 75.35, 70.77, 69.72, 69.42, 68.67, 67.07, 66.44, 57.85, 30.70, 28.50, 25.01, 21.47, 12.89. MS (MALDI-TOF) (*m/z*): found 1498.5 $[M^+]$, calcld 1498.0.

5-{3,4-Di-2-[2-(2-methoxyethoxy)-ethoxy]oxyphenyl}-10,15,20-tris(4-hydroxyphenyl)porphyrin, ***10****. Method 1.* Obtained from pyrrole (5.46 mmol, 0.36 g), benzaldehyde **5** (1.36 mmol, 0.58 g), *p*-hydroxybenzaldehyde (4.1 mmol, 0.5 g). Yield 65 mg (10 %). *Method 2.* Obtained from pyrrole (1.78 mmol, 0.119 g), benzaldehyde **5** (0.44 mmol, 0.19 g), *p*-hydroxybenzaldehyde (1.3 mmol, 0.16 g). Yield 35 mg (8 %). UV-Vis (ethylacetate) λ_{max} nm (band ratio): 419.0, 520.1, 554.6, 595.0, 653.2 (1:0.0432:0.0337:0. 0162:0.0189). ^{1}H NMR (DMSO-d_6) δ_H ppm: 8.76 (8H, m, H2, H3, H7, H8, H12, H13, H17, H18), 8.15 (6H, m, 2-H), 7.86 (2H, m, 2-H), 7.33 (6H, m, 3-H),6.92 (1H, m, 3-H), 4.40 (4H, m, -O-CH_2), 4.00 (4H, m, -OCH_2CH_2), 3.82 (4H, m, -$O(CH_2)_2OCH_2$), 3.71 (8H, m, $CH_3O(CH_2)_2OCH_2CH_2$), 3.59 (4H, m, CH_3O-CH_2-), 3.37 (6H, s, CH_3O). MS (APCI) *m/z*: found 987.7$[M]^+$, calcld 987.1.

5-(4-Hydroxyphenyl)-10,15,20-tris(4-dodecyloxyphenyl) porphyrin, ***11****. Method 1.* Obtained from pyrrole (2 mmol, 0.14 g), *p*-hydroxybenzaldehyde (3.2 mmol, 0.178 g), *p*-dodecyloxybenzaldehyde (1.5 mmol, 0.44 g). Yield 77 mg (13 %). *Method 2.* Obtained from pyrrole (2.67 mmol, 0.18 g), *p*-hydroxybenzaldehyde (0.67 mmol, 0.081 g), *p*-dodecyloxybenzaldehyde (2 mmol, 0.58 g). Yield 47 mg (6 %). UV-Vis (dichloromethane) λ_{max} nm (lgε): 419.8 (5.72); 518.8 (4.31); 554.6 (4.06); 589.0 (3.86); 649.6 (3.75). R_f 0.45 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ_H ppm: 8.95-8.90 (8H, m, H2, H3, H7, H8, H12, H13, H17, H18), 8.1 (6H, d, *J*=8.44 Hz, 2-H), 8.01 (2H, d, *J*=8.25 Hz, 2-H), 7.28 (6H, m, 7.42, 3-H), 7.02 (2H, d, *J*=8.8 Hz, 3-H), 4.18-4.25 (6H, m, -$OCH_2(CH_2)_{10}CH_3$), 2.03-1.92 (6H, m, -$OCH_2CH_2(CH_2)_9CH_3$), 1.70-1.61 (6H, m, -$O(CH_2)_2CH_2(CH_2)_8CH_3$), 1.54-1.24 (48H, m, -$O(CH_2)_3(CH_2)_8CH_3$), 0.93-0.87 (9H, m, Alk$CH_3$), -2.90 (2H, br.s, NH). ^{13}C NMR ($CDCl_3$) δ_C ppm: 158.65, 157.15, 135.21, 133.66, 131.99, 131.54, 130.73, 128.40, 119.44, 114.45, 113.69, 112.54, 67.89, 67.59, 38.31, 31.51, 29.96, 29.24, 29.08, 28.94, 28.51, 25.82, 25.52, 23.36, 22.54, 22.28, 13.76, 10.67. MS MALDI-TOF *m/z*: found 1183.621; calcld 1183.690.

5-(4-Dodecyloxyphenyl)-10,15,20-tris(4-hydroxyphenyl)porphyrin, ***12****. Method 1.* Obtained from pyrrole (4 mmol, 0.27 g), *p*-hydroxybenzaldehyde (3 mmol, 0.36 g), *p*-dodecyloxybenzaldehyde (1 mmol, 0.29 g). Yield 101 mg (12 %). *Method 2.* Obtained from pyrrole (1 mmol, 0.07 g), *p*-hydroxybenzaldehyde (0.75 mmol, 0.36 g), *p*-dodecyloxybenzaldehyde (0.25 mmol, 0.07 g). Yield 18 mg (8.5 %). UV-Vis (ethylacetate) λ_{max} nm (lgε): 418.0 (5.98), 518.0 (5.35), 551.2 (4.01), 593.6 (3.82), 651.4 (3.46). ^{1}H NMR (DMSO-d_6) δ_H ppm: 8.96 (2H, d, *J*=4.77 Hz, H3, H7), 8.90 (6H, br.s, H2, H8, H12, H13, H17, H18), 8.13 (6H, d, *J*=8.44 Hz, 2-H), 8.05 (2H, d, *J*=8.25 Hz, 2-H), 7.32 (6H, d, *J*=8.62 Hz, 3-H), 7.5 (2H, d, *J*=8.80 Hz, 3-H), 4.29 (2H, m., -OCH_2), 2.07 (2H, m, -OCH_2CH_2), 1.66 (4H, m, -$O(CH_2)_2(CH_2)_2$), 1.4 (18H, m, -$(CH_2)_9CH_3$), 0.65 (3H, m, -CH_2CH_3). MS (APCI) *m/z*: found 848.1 [M+H], calcld 847.05.

5,10,15,20-Tetrakis{4-2-[2-(2-methoxy-ethoxy)-ethoxy] oxyphenylporphyrin, ***13****. Method 1.* Obtained from pyrrole (2 mmol, 0.14 g), benzaldehyde **3** (2 mmol, 0.36 g). Yield 0.19 g (30 %). *Method 2.* Obtained from pyrrole (0.5 mmol, 0.04 g), benzaldehyde **3** (0.5 mmol, 0.14 g). Yield 76 mg (21 %). UV-vis (ethylacetate) λ_{max} nm (band ratio): 420.1, 516.3, 554.2, 596.4, 650.0 (1:0.0483:0.0367:0.0124:0.0067). ^{1}H NMR (DMSO-d_6) δ_H ppm: 8.85 (8H, br.s, H2, H3, H7, H8, H12, H13, H17, H18), 8.12 (4H, d, *J*=7.87 Hz, 2-H), 7.90 (4H, d, *J*=8.83 Hz, 2-H), 7.39 (4H, d, *J*=8.92 Hz, 3-H), 7.13 (4H, d, *J*=8.00 Hz, 3-H),4.10 (8H, m, -O-CH_2), 3.81 (16H, m, -O-$CH_2CH_2OCH_2$-), 3.59 (8H, m, $CH_3O(CH_2)_2OCH_2$-), 3.51 (16H, m, $CH_3OCH_2CH_2$), 3.37 (12H, s, CH_3O). MS (APCI) *m/z*: found 1264.2 $[M+H]^+$, calcld 1263.5.

5,10,15,20-Tetrakis(3,4-dihydroxyphenyl)porphyrin, ***14****. Method 1.* Obtained from pyrrole (2 mmol, 0.14 g), *p*-3,4-dihydroxybenzaldehyde (2 mmol, 0.28 g). Yield 0.15 g (10 %). *Method 2.* Obtained from pyrrole (1 mmol, 0.07 g), *p*-3,4-dihydroxybenzaldehyde (1 mmol, 0.14 g). Yield 0.1 g (53 %). UV-Vis (ethylacetate) λ_{max} nm (band ratio): 419.6, 516.0, 553.20, 593.8, 651.0 (1:0.0857:0.0522: 0.0303,0.0256). R_f=0.66 (CH_2Cl_2:MeOH=15:1). ^{1}H NMR (DMSO-d_6) δ_H ppm: 9.02 (8H, d, *J*= 9.47 Hz, H2, H3, H7, H8, H12, H13, H17, H18), 7.61 (4H, s, 2-H), 7.45 (8H, d, *J*=9.86 Hz, 6-H). 7.17 (4H, d, *J*=7.98 Hz, 5-H), 3.40 (10H, br.s, OH). MS (APCI) *m/z*: found 743.7 [M+1], calcld 742.73.

5,10-Di-{4-2-[2-(2-methoxy-ethoxy)-ethoxy]oxyphenyl}-15,20-di-(4-hexadecyloxyphenyl)porphyrin, ***15****.* UV-vis (ethylacetate) λ_{max} nm (band ratio): 422.1, 455.0 (split Soret band), 519.3, 554.1, 592.0, 650.2 (1:0.0401:0.0295:0.0131:0.0213). ^{1}H NMR ($CDCl_3$) δ_H ppm: 8.88 (4H, d, H7, H8,H17, H18, *J*=5.24 Hz), 8.51 (4H, m, H2, H3, H12, H13), 8.13 (8H, d, *J*=8.53 Hz, 2-H), 7.52 (4H, t, 3-H), 7.31 (4H, m, 3-H), 4.42 (4H, m, -O-CH_2CH_2O-), 4.25 (4H, m, -OCH_2-$(CH_2)_{14}CH_3$), 4.07 (4H, m, -OCH_2-CH_2-O-), 3.89 (4H, m, -$O(CH_2)_2OCH_2$-), 3.81 (4H, m, $CH_3O(CH_2)_2OCH_2$-), 3.76 (4H, m, $CH_3OCH_2CH_2$-), 3.64 (4H, m, $CH_3OCH_2CH_2$-), 3.45 (6H, d, *J*=3.59 Hz, CH_3O-), 1.99 (4H, m, -$OCH_2CH_2(CH_2)_{13}CH_3$), 1.64 (4H, m, -$O(CH_2)_2CH_2(CH_2)_{12}CH_3$), 1.47 (4H, m, -$O(CH_2)_3CH_2(CH_2)_{11}CH_3$), 1.30 (44 H, br.s, -$O(CH_2)_4(CH_2)_{11}CH_3$), 0.90 (6H, m, -$O(CH_2)_{15}CH_3$). ^{13}C NMR ($CDCl_3$) δ_C ppm: 157.50, 157.14, 134.13, 133.36, 132.94, 118.42, 118.18, 111.24, 75.99, 75.58, 75.14, 70.54, 69.50, 69.31, 68.47, 66.86, 66.24, 57.63, 30.47, 28.27, 27.91, 24.78, 21.23, 12.67. MS MALDI-TOF (*m/z*): found 1421.357 $[M+H]^+$, calcld 1419.952.

5,15-Di-{4-2-[2-(2-methoxy-ethoxy)-ethoxy]oxyphenyl}-10,20-di-(4-hexadecyloxyphenyl)porphyrin, ***16****.* UV-Vis (ethylacetate) λ_{max} nm (band ratio): 421.0, 455.0 (split Soret band),

518.1, 558.3, 595.6, 652.0, 694.0 (aggregation band) (1:0.0790: 0.0580:0.0376:0.0273:0.1454). ^{1}H NMR ($CDCl_3$) δ_H ppm: 8.87 (4H, m, H7, H8, H17, H18), 8.48 (4H, m, H2, H3, H12, H13), 8.12 (8H, d, *J*=8.45 Hz, 2-H), 7.52 (2H, m, 3-H), 7.46 (2H, d, *J*=7.85 Hz, 3-H), 7.31 (2H, dd, *J*=7.26 Hz, 3-H), 7.08 (2H, t, $J_{1,2}$=7.33 Hz, 3-H), 4.46 (4H, m, -O-CH_2CH$_2$O-), 4.28 (4H, m, -OCH_2-(CH$_2$)$_{14}$CH$_3$), 4.08 (4H, m, -OCH$_2$-CH_2-O-), 3.89 (4H, m, -O(CH$_2$)$_2$OCH$_2$-), 3.81 (4H, m, CH$_3$O(CH$_2$)$_2$OCH$_2$-), 3.75 (4H, m, CH$_3$OCH$_2$CH$_2$-), 3.65 (4H, m, CH$_3$OCH_2CH$_2$-), 3.44 (6H, d, *J*=3.37 Hz, CH_3O), 2.30 (4H, m, -OCH$_2$CH_2(CH$_2$)$_{13}$CH$_3$), 2.02 (4H, m, -O(CH$_2$)$_2$CH_2(CH$_2$)$_{12}$CH$_3$), 1.66 (4H, m, -O(CH$_2$)$_3$CH_2(CH$_2$)$_{11}$CH$_3$), 1.29 (40H, m, -O(CH$_2$)$_4$(CH_2)$_{10}$CH$_2$CH$_3$), 1.20 (4H, t, $J_{1,2}$=7.52 Hz, -O(CH$_2$)$_{14}$CH_2CH$_3$), 0.90 (6H, m, -O(CH$_2$)$_{15}$CH_3).^{13}C NMR ($CDCl_3$) δ_C ppm: 144.92, 144.73, 138.82, 134.12, 127.44, 122.58, 118.18, 113.17, 111.35, 75.97, 75.55, 75.12, 70.53, 69.50, 69.21, 68.47, 68.31, 66.87, 57.61, 30.45, 29.16, 28.25, 27.90, 24.76, 21.22, 12.65, 8.14.

Results and Discussion

Heightened interest to the synthesis of unsymmetrically substituted amphiphilic porphyrins is due to their use in PDT, supramolecular chemistry,[10] biomimetic systems,[11,12] nonlinear optics.[13] As it was noted above, the modification of hydroxyphenyl porphyrins by oligo- and polyethylene glycol residues greatly increases their solubility in water and therefore expands biomedical scope of tetrapyrroles. In this context, the aim of this work was to develop the methods for obtaining of amphiphilic *meso*-hydroxyphenylporphyrins containing polyethylene oxide groups and higher alkyl residues.

Synthesis of amphiphilic derivatives of porphyrins is hindered and a little described in literature since it is accompanied by serious difficulties, among which it should be mentioned the need of carrying out reactions under mild conditions, the use of protecting groups, difficulties in chromatographic purification.[7] The method of monopyrrole condensation (MPC) remains demanded in the preparation not only the symmetrically, but also unsymmetrically substituted porphyrins. In this work we have shown that modern synthetic modifications of MPC method can be used to obtain long-chain mono- and trisubstituted amphiphilic *meso*-arylporphyrins.

It has been reported that PEG-containing porphyrins can be prepared by alkylation of the hydroxyl groups in the *meso*-substituted porphyrins by the action of methoxypolyethylene tosylates or mesylates.[14] We used an alternative strategy for the synthesis of such compounds – mixed aldehyde monopyrrole condensation using benzaldehydes functionalized by polyethylene oxide residues. To optimize the obtaining of target A_3B- and AB_3-*meso*-arylporphyrins two strategies of pyrrole and substituted benzaldehydes condensation were examined: in a mixture of organic solvents[15,16] and in an aqueous micellar medium.[16,17]

Earlier[16] we have shown the efficiency of the monopyrrole condensation method in a solvent mixture for the synthesis of 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin and its asymmetrically substituted analogs with higher alkyl substituents, worked out the methods of obtaining and picked up the conditions for isolation of such porphyrins. Previously the use of aqueous micellar medium allowed us to obtain not only the *meso*-tetrasubstituted porphyrins with polar groups, but also unsymmetrical amphiphilic porphyrins with higher alkyl substituents at the phenyl rings. These approaches were used to synthesize series of PEG-substituted porphyrins.

At the first stage we prepared oligo- and PEG-substituted benzaldehydes **3-5** using appropriate mesylates of monomethyl ethers of oligo- and PEG (Scheme 1). Yields of mesylates **1-2** were 75-80 %. A broad absorption band at 3446 cm^{-1} in the IR spectrum of the TEG (associated OH bond) greatly reduced in the IR spectrum of its mesylate **2**. Also signals of stretching vibrations of sulfogroup R-SO$_2$-R at 1176-1125 cm^{-1} appear in the IR spectrum of the compound **2**. Mesylates of monomethyl ethers of oligo- and PEG **1-2** were used for functionalization of 4-hydroxybenzaldehyde and 3,4-dihydroxybenzaldehyde (only **1**). The alkylation of hydroxyl groups was carried out in boiling DMF using cesium carbonate as a base. The individuality and structures of compounds **3-5** were confirmed by the methods of TLC, UV-vis and ^{1}H, ^{13}C NMR spectroscopy, MALDI-TOF mass-spectrometry. Yields of substituted benzaldehydes **3-5** were ranged from 70 to 80 %.

MPC in Aqueous-Micellar Medium

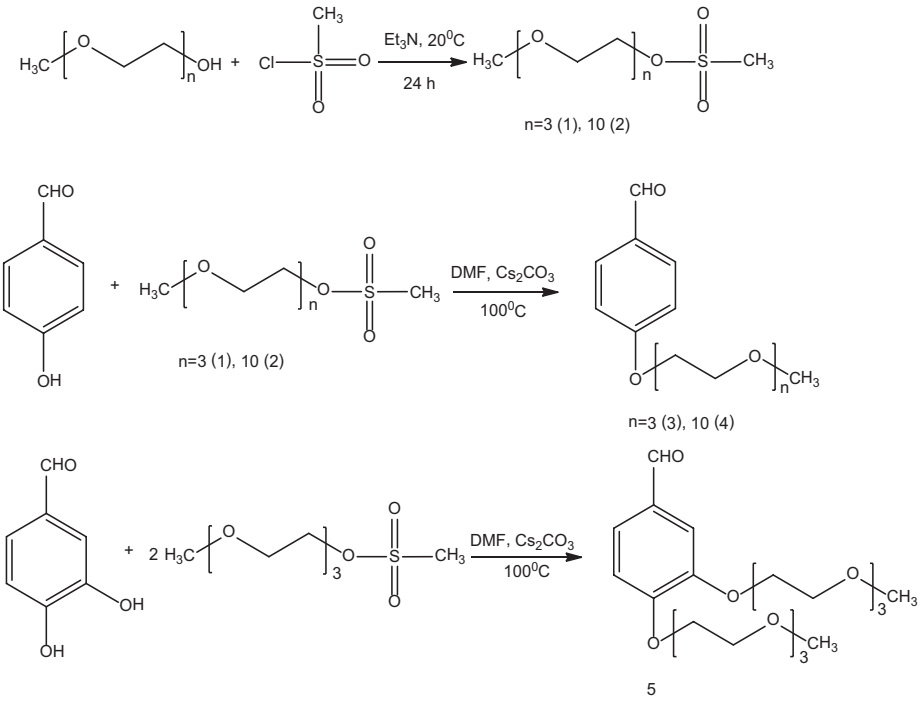
Pyrrole, benzaldehydes **3-5**, *p*-hydroxybenzaldehyde in ratio 4:1:3 were used for synthesis of oligo- and PEG-substituted *meso*-hydroxyphenylporphyrins according known approach[16] (Scheme 2). 3 % HCl was used as a catalyst, and DDQ – as an oxidant. The reaction time was 40 min for compound **6** and 3 h for compound **7**.

It should be noted that in this case the strict control is required to maintain p*H* in the range 4.5–5. The desired product was isolated by extraction into ethylacetate-water system with an addition of potassium chloride and alkali to convert sodium dodecyl sulfate (SDS) into insoluble potassium salt.

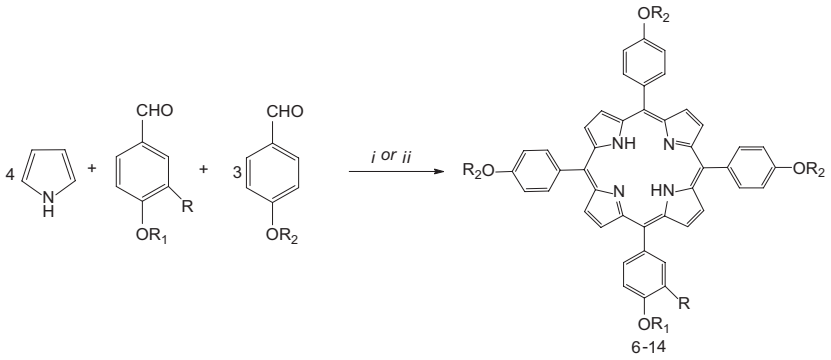
Column chromatography on silica gel was used for purification of porphyrins using as eluent mixture of dichloromethane:ethylacetate (2:1) for compound **6**, dichloromethane:hexane in the ratio 10:1 gradually increasing the polarity of the system to dichloromethane:methanol 10:1 for compound **10**, dichloromethane:ethylacetate in ratio 1:1 increasing polarity to the system ethylacetate:methanol 15:1 for compound **7**.

Table 1 shows the yields of target porphyrins **6-14**. Conclusions of the benzaldehyde structure influence on the yields of the MPC in aqueous-micellar medium were made based on the received data: in general, the more hydrophilic aldehyde (as in cases with compounds **6**, **10**, **12**, **14**), the yield was the higher, however; if an aldehyde (**13**) is too water-soluble or too hydrophobic (**8**, **9**, **11**), the formation of porphyrinogen apparently becomes unfavorable that reduces the porphyrin yields in these conditions.

The target substituted *meso*-hydroxyphenylporphyrins were prepared by mixed aldehyde monopyrrole condensation by modified Adler method[16] in the mixture of organic solvents nitrobenzenepropionic acid/acetic acid in volume ratio 1:2:1 (Scheme 2). Products of reaction were precipitated from hexane, filtered and chromatographed using column chromatography on silica gel in dichloromethane increasing the polarity of the eluent system to dichloromethane/ethylacetate 4:1. The yields of the products were 10-13 %, that is more than 2 times higher in Adler reported method for unsymmetrically substituted porphyrins.[18] So the efficiency



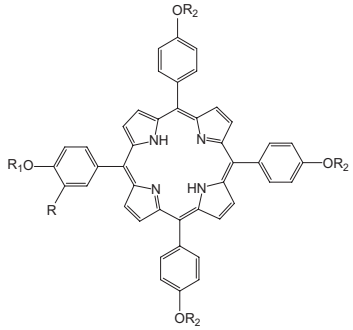
Scheme 1.



Reagents and conditions: *i* – 1) H_2O, SDS, HCl; 2) DDQ, 25°C; *ii* – C_2H_5COOH, CH_3COOH, $C_6H_5NO_2$, reflux.

Scheme 2.

Table 1. Structure and yields of target compounds **6-14**.



№	R	R_1	R_2	Yield 1*%	Yield 2*%
6	H	$(CH_2CH_2O)_3CH_3$	H	13	8
7	H	$(CH_2CH_2O)_{10}CH_3$	H	11	7
8	H	$(CH_2CH_2O)_3CH_3$	$C_{14}H_{29}$	13	5
9	H	$(CH_2CH_2O)_3CH_3$	$C_{16}H_{33}$	14.2	5.5
10	$O(CH_2CH_2O)_3CH_3$	$(CH_2CH_2O)_3CH_3$	H	10	8
11	H	OH	$C_{12}H_{25}$	13	6
12	H	$C_{12}H_{25}$	H	12	8.5
13	H	$(CH_2CH_2O)_3CH_3$	$(CH_2CH_2O)_3CH_3$	30	21
14	OH	H	H	10	53

1* – MPC by modified Adler method in mixture of organic solvents, 2* – MPC in aqueous-micellar medium.

of MPC method in the mixture of organic acids and nitrobenzene was shown for the synthesis of unsymmetrically oligo- and PEG-substituted amphiphilic porphyrins. The methods for the preparation of these compounds were developed and the conditions for their isolation were found. At chromatography purification of 5-{4-2-[2-(2-methoxyethoxy)-ethoxy] oxyphenyl}-10,15,20-tris(4-hexadecyloxyphenyl)porphyrin, **9**, the isomers 5,10-di-{4-2-[2-(2-methoxyethoxy)ethoxy]

Table 2. The parameters of UV-Vis spectra of tetraphenylporphyrins **6-16**.

Compound	Solvent	λ_{Soret}	λ_1	λ_2	λ_3	λ_4
6	EtOAc	418.0	515.8	552.6	592.4	650.6
7	EtOAc	420.4	522.1	555.3	596.9	652.0
8	EtOAc	423.0	520.0	557.3	593.1	651.5
9	EtOAc	420.3	513.1	550.0	590.6	651.2
10	EtOAc	419.0	520.1	554.6	595.0	653.2
11	CH_2Cl_2	419.8	518.8	554.6	589.0	649.6
12	EtOAc	418.0	518.0	551.2	593.6	651.4
13	EtOAc	420.1	516.3	554.2	596.4	650.0
14	EtOAc	419.6	516.0	553.2	593.8	651.0
15	EtOAc	422.1, 455.0	519.3	554.1	592.0	650.2
16	EtOAc	421.0, 455.0	518.1	558.3	595.6	652.0

oxyphenyl}-15,20-di-(4-hexadecyloxyphenyl)porphyrin, **15**, and 5,15-di-{4-2-[2-(2-methoxyethoxy)ethoxy] oxyphenyl}-10,20-di-(4-hexadecyloxyphenyl)porphyrin, **16**, were isolated with yields 5.5 and 2 %, consequently. The UV-Vis spectra of compounds **15** and **16** show a splitting of Soret band at 422.1/455.0 and 421.0/455.0 nm, consequently. We assume, that the splitting is due to the formation of supramolecular aggregates according to the literature data.[19] Also there are four band of low intensity in 497–592 nm region. The introducing of long-chain alkyl substituents leads to the small absorption bands shift to the red region (Table 2).

The structure of porphyrins **6-16** was confirmed by the methods of UV-Vis, IR, ^{1}H, ^{13}C NMR spectroscopy, MALDI-TOF mass-spectrometry.

Also symmetric porphyrins **13-14** were synthesized according to the approaches described above. The yields of compound **13** received by modified Adler method and in aqueous micellar medium were compared and are 30 and 21 %, respectively. For 5,10,15,20-tetrakis(3,4-dihydroxyphenyl)porphyrin, **14**, the yield in aqueous micellar medium was 53 %, practically in 5 times higher than in modified Adler method. In general, the yields of compounds **6-12** synthesized according to modified Adler method were higher than in the aqueous micellar medium (Table 1).

Conclusions

In this work the successful development of new asymmetric *meso*-aryl substituted porphyrins with oligo- and PEG-substituents synthesis has been demonstrated by two MPC methods – modified Adler and synthesis in aqueous micellar medium. The procedures for the preparation of these compounds were developed and the conditions for their isolation were found. We have shown that effectiveness of monopyrrole condensation largely depends on the amphiphility of target porphyrins: the most preferred method for preparation of hydrophobic porphyrin with long chain alkyl substituents and oligo- and PEG residues is modified Adler method, since the scheme of the synthesis and isolation conditions are considerably simplified. Porphyrins with oligo- and PEG residues and hydroxyl-group are expedient to obtain in aqueous micellar medium.

Acknowledgements. This work was supported by the Russian Science Foundation, project № 16-13-10092, and partially by Russian President Grant for the State Support of Leading Scientific Schools (number 7946.2016.11.).

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Received 27.04.2016
Accepted 14.06.2016