Modification of β-Octaethylporphyrin via Insertion of Amino and Azino Groups into meso–Positions

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The functionalization of Ni(II) β-octaethylporphyrin was performed by introducing various amino and azino groups into meso-positions. Amino, n-propylamino, and trifluoromethylacetylamino groups were used as electron donor substituents, while azino group was inserted as an electron acceptor. The azine fragment was inserted through formylation followed by reaction with hydrazine and then with aromatic aldehydes, and the corresponding azine derivatives of p-nitrophenylbenzaldehyde and methyl pyropheophorbide d were obtained. It was found that under the conditions of formylation of meso-(trifluoroacetamido)-β-octaethylporphyrin, the amide fragment was oxidized to form hydroxamic acid. As a result of substitution of meso-positions of β-octaethylporphyrin, new functionalized porphyrin derivatives with significantly altered electron-optical properties were obtained. In particular, the azine bridged conjugate of β-octaethylporphyrin with methyl pyropheophorbide d was synthesized, the electronic absorption spectrum of which contains bathochromically shifted long-wavelength bands. The resulting compounds could be of interest as potential photosensitizers, sensor dyes and biologically active compounds.

Keywords: Porphyrins, meso-functionalization, electron donors, electron acceptors, azines, electron absorption spectra.
Insertion of Amino and Azino Groups into \textit{meso}-Positions of Octaethylporphyrin

Porphyrins are a unique type of dyes whose electron optical properties can be easily tuned by introducing various substituents affecting the aromatic π-electron system of the tetrapyrrole macrocycle. As a result, porphyrins have found wide application in diverse fields as follows.

Porphyrin derivatives are used as sensor dyes, including in bioanalysis, photosensitizers in medicine, photocatalysis and photovoltaics. The greatest influence on the electronic system of porphyrins is exerted by donor and acceptor substituents at the \textit{meso}-position of the macrocycle. The highest efficiency of the organic dye sensitized solar cells was achieved using photosensitizers based on 5,15-diarylporphyrins substituted with azino groups.

There have been reported a lot of works devoted to studying similar systems based on synthetic \textit{meso}-unsubstituted \textit{meso}-arylporphyrins, including bis- and trisporphyrins. The effect of the insertion of electron donor and acceptor groups into the \textit{β}-positions of \textit{meso}-tetrarlylporphyrins was also investigated. At the same time, β-substituted porphyrins, as well as those containing no aryl groups in \textit{meso}-positions, have not been sufficiently studied yet. Therefore, in this work, β-octaethylporphyrin was selected as a substrate for the functionalization with electron donor amino and electron acceptor azino groups to study their influence on the electron absorption spectra. This synthetic porphyrin is often used as a model of natural porphyrins, in which β-positions are fully substituted and, as a rule, there are no \textit{meso}-substituents, except for annulated cycles.

**Experimental**

**General**

Reactions were carried out under argon atmosphere using commercially available reagents that were purchased and used as received. Heating reaction vessels was performed with oil bath. Silica gel 40/60 was used for column and flash chromatography.

Preparative thin layer chromatography (TLC) was performed using glass plates coated with 5–20 μm silica gel (5 mm thickness). 1H and 13C NMR spectra were recorded with a Bruker Avance III 600 MHz spectrometer at 303 K in CDCl$_3$. Chemical shifts are reported relative to signals of residual protons of solvents (CDCl$_3$ at 7.26 ppm). The assignment of the resonances in the 1H and 13C NMR spectra was achieved by the use of DEPT, COSY and HSQC techniques. The LDI-TOF mass spectra were obtained on a Ultraflex II mass spectrometer (Bruker Daltonics) in a positive ion mode using reflection mode (20 mV target voltage) without matrix. Electronic absorption spectra were recorded with U-2900 (Hitachi) spectrophotometer in quartz rectangular cells of 10 mm path length.

**Synthesis**

- β-Octaethylporphyrin (I) was obtained by monopyrrole condensation described by Johnson. Ni(II) complex of β-octaethylporphyrin was prepared according to procedure described by K. Smith. \textit{meso}-Nitrour β-octaethylporphyrin (2) was obtained by nitrating of β-octaethylporphyrin with NaNO$_2$ in trifluoroacetic acid as described by R. Bonnett.

\textit{meso}-octaethylporphyrin with tin dichloride in hydrochloric acid was used to obtain \textit{meso}-amino-β-octaethylporphyrin, which was converted to Ni(II) complex of \textit{meso}-amino-β-octaethylporphyrin (3).

**Ni(II) \textit{5-(n-propylamino)-2,3,7,8,12,13,17,18-octaethylporphyrin}** (4). 0.4 mL of glacial acetic acid and 1.3 mL of 1-propanal (18.2 mmol) were added to a solution of 55 mg (0.091 mmol) of \textit{β}-octaethylporphyrin, which was converted to Ni(II) complex with tin dichloride in hydrochloric acid. The reaction mixture was stirred for an hour at room temperature, then 1.14 g (18.2 mmol) of NaBH$_4$CN was added to the solution and the mixture was stirred for another 4 hours. Then the mixture was washed with saturated NaHCO$_3$ (2×30 mL) and water (3×30 mL), dried over anhydrous sodium sulfate and evaporated in vacuum. The residue was purified by the column chromatography with eluent CH$_2$Cl$_2$–n-hexane – triethyamine (3:5:0.01) yielding 15 mg (65 %) of the compound.

**Ni(II) \textit{5-(trifluoromethylacetyl)amino)-2,3,7,8,12,13,17,18-octaethylporphyrin}** (5). A solution of 20 mg (0.033 mmol) of \textit{meso}-amino-β-octaethylporphyrin (3) in 5 mL of CH$_2$Cl$_2$ and 184 μL (1.32 mmol) of triethylamine was cooled to 0 °C, and 11 μL of trifluoroacetic acid anhydride was added. The reaction mixture was stirred for 8 h at room temperature, then it was washed with water (5×20 mL), dried over anhydrous sodium sulfate and evaporated in vacuum. The residue was purified by the column chromatography with eluent CH$_2$Cl$_2$-n-hexane (1 : 1) yielding 15 mg (65 %) of the compound. 1H NMR (600 MHz, CDCl$_3$) δ ppm: 1.22 (2H, m, CH$_2$), 1.68 (6H, t, and CH$_2$), 3.15 (2H, m, CH$_2$), 3.73 (12H, m, CH$_2$), 4.94 (1H, t, CH$_2$), 9.07 (1H, s, 15-CH), 9.16 (2H, s, 4, 5-CH). UV-Vis (CH$_2$Cl$_2$)$_{λ_{max}}$ (\textit{A}$_{\max}$) nm: 419 (0.37), 457 (1.00), 546 (0.19), LDI TOF m/z: found 648.55, calc. for [M+H]$^+$ C$_{38}$H$_{38}$N$_7$Ni 648.36.

**General procedure of insertion of azine group into Ni(II) β-octaethylporphyrin.** Ni(II) \textit{5-(trifluoromethylacetyl)amino)-2,3,7,8,12,13,17,18-octaethylporphyrin} (5) (40 mg, 0.057 mmol) was dissolved in 15 mL of CH$_2$Cl$_2$, then Vilsmeyer reagent (freshly prepared from DMF (0.7 mL, 9.06 mmol) and POC(1) (0.7 mL, 7.51 mmol)) was added dropwise to the solution, and the reaction mixture was stirred for 1 hour at reflux. Then
the reaction mixture was washed with water (3×30 mL) to neutral pH and 0.5 mL of hydrazine hydrate (98 %, aq.) was added dropwise till the change of the color. The resulting solution was washed with water (3×30 mL) and dried over sodium sulfate and evaporated in vacuum. The residue was purified using preparative TLC with eluent CH<sub>2</sub>Cl<sub>2</sub>:EtOH = 100:4 yielding 24 mg (58 %) of the crude hydrazone, which was dissolved in 20 mL of CH<sub>2</sub>Cl<sub>2</sub> and 15 mg (0.1 mmol) of p-nitrobenzaldehyde was added. The reaction mixture was stirred for 96 hours at reflux, then the solvent was evaporated in vacuum and purified by preparative TLC, eluting with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 4:1 (R<sub>f</sub> = 0.39) and 4 mg (8 %) of compound 8 (R<sub>f</sub> = 0.18).

Ni(II) (1E,2E)-1-((15-(trifluoroacetylamino)-2,3,7,8,12,13,17,18-octaethylporphyrin-5-yl)methylene)-2-(4-nitrobenzylidene)hydrazine (6). 1H NMR (600 MHz, CDCl<sub>3</sub>, 303 K) δ ppm: 1.65 (24H, m, CH<sub>2</sub>), 3.75 (16H, m, CH<sub>2</sub>), 8.02 (2H, m, C<sub>H</sub>), 8.30 (2H, m, C<sub>H</sub>), 8.44 (1H, s, C<sub>H</sub>CH=N-N), 9.21 (2H, m, 15, 20-CH), 10.80 (1H, s, 5'-CH=N), UV-Vis (CH<sub>2</sub>Cl<sub>2</sub>) λ<sub>max</sub> (A<sub>rel</sub>) nm: 410 (1.00), 483 (0.18), 540 (0.02), 579 (0.07). LDI TOF m/z: found 877.62, calc. for [M+H]+ C<sub>46</sub>H<sub>50</sub>F<sub>3</sub>N<sub>10</sub>NiO<sub>3</sub> 877.33.

Ni(II) (1E,2E)-1-((10-(N-trifluoroacetyl(hydroxylamino))-2,3,7,8,12,13,17,18-octaethylporphyrin-5-yl)methylene)-2-(4-nitrobenzylidene)hydrazine (7). 1H NMR (600 MHz, CDCl<sub>3</sub>, 303 K) δ ppm: 1.63 (6H, m, CH<sub>2</sub>), 1.73 (18H, m, CH<sub>2</sub>), 1.75 (16H, m, CH<sub>2</sub>), 3.75 (16H, m, CH<sub>2</sub>), 8.01 (2H, m, C<sub>H</sub>), 8.31 (2H, m, C<sub>H</sub>), 8.44 (1H, s, C<sub>H</sub>CH=N-N), 9.21 (2H, m, 15, 20-CH), 10.80 (1H, s, 5'-CH=N), UV-Vis (CH<sub>2</sub>Cl<sub>2</sub>), λ<sub>max</sub> (A<sub>rel</sub>) nm: 410 (1.00), 504 (0.41), 576 (0.06), 653 (0.08). LDI TOF m/z: found 893.62, calc. for [M+H]+ C<sub>44</sub>H<sub>48</sub>F<sub>2</sub>N<sub>11</sub>NiO<sub>3</sub> 893.33.

Ni(II) (1E,2E)-1-((15-(trifluoroacetylamino)-2,3,7,8,12,13,17,18-octaethylporphyrin-5-yl)methylene)-2-((4-nitrobenzylidene)hydrazine (8). 1H NMR (600 MHz, CDCl<sub>3</sub>, 303 K) δ ppm: 1.70 (24H, m, CH<sub>2</sub>), 3.71 (16H, m, CH<sub>2</sub>), 8.04 (2H, m, C<sub>H</sub>), 8.31 (2H, m, C<sub>H</sub>), 8.48 (1H, s, C<sub>H</sub>CH=N-N), 9.21 (2H, m, 10, 20-CH), 10.78 (1H, s, 5'-CH=N), UV-Vis (CH<sub>2</sub>Cl<sub>2</sub>), λ<sub>max</sub> (A<sub>rel</sub>) nm: 412 (1.00), 488 (0.27), 544 (0.05), 581 (0.03), 625 (0.02). LDI TOF m/z: found 893.62, calc. for [M+H]+ C<sub>44</sub>H<sub>48</sub>F<sub>2</sub>N<sub>11</sub>NiO<sub>3</sub> 893.33.

Transformation of the meso-amino-group of β-octaethylporphyrin

The meso-amino-group of β-octaethylporphyrin (OEP) was subjected to the further transformations. First, the alkylation of the primary amino-group was carried out via one-pot two stage process: treatment of 3 with propanal in 1,2-dichloroethane containing trifluoroacetic acid as a catalyst led to the formation of the imino-group which was then reduced with sodium cyanoborohydride yielding n-propylamino substituted porphyrin 4 with 71 % yield. Alternatively, the acylation of the amino group was performed with trifluoroacetic anhydride and triethylamine in dichloromethane, resulting in the corresponding meso-trifluorooctaamidamo-β-octaethylporphyrin 5, which was isolated with 65 % yield (Scheme 2).

Emergence of the meso-amino group at the porphyrin macrocycle strongly perturbs π-electron system of the aromatic tetrapyrrrole macrocycle significantly affecting electron absorption spectrum: the Soret band of the meso-amino-β-octaethylporphyrin 3 was shifted for 27 nm towards longer wavelengths, while the Q-bands were broadened with decreasing intensity. The substitution of the hydrogen atom of the meso-amino group in 3 with a propyl group led to the even larger bathochromic shift of the main absorption band from 418 nm to 457 nm in 4 (Figure 1). An additional band at 416 nm appeared in the spectrum of 4. The trifluoroacetylation of the amino group decreased its donor ability and the spectrum of the acylated product 5 nearly approached that of NiOEP, but all the bands remained bathochromi-
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The Q-bands were generally less affected by the meso-amino groups compared to the Soret bands.

Synthesis of azines

The electron acceptor groups were planned to be inserted at the opposite to the amino-substituent meso-position in order to create push-pull type substitution pattern. Strong influence on the \( \pi \)-electron system can be exerted with electron acceptor possessing an extended \( \pi \)-conjugated system, and an azarine substituent can be regarded as such. Previously, aryl azines of porphyrinoids have been synthesized by the condensation of tetrapyrole hydrazones and arylaldehydes.\(^{[38]}\) In turn, hydrazones have been obtained via formylation followed by the reaction of the formylporphyrins with hydrazine.\(^{[39]}\) The trifluoroacylated amino derivative 5 was used as a starting material for the electron acceptor fragment insertion as the trifluoroacetyl played a role of a protective group for the reactive amino group. The Vilsmeier-Haack formylation of 5 with POCl\(_3\)/DMF\(^{[39–41]}\) was initially performed, and the so called intermediate “phosphorus complex” was then subjected to the reaction with hydrazine leading to the hydrazone, which was used in the next step without isolation. Finally, \( p \)-nitrobenzaldehyde was added to the reaction mixture containing the hydrazone and the condensation products of the three stage reaction were isolated. The main product 6 was the target \( p \)-nitrobenzalazine of the 5-(trifluoroacetylamino)-10-formylporphyrin isolated with 26% yield. Two additional products were formed, which were determined to be isomeric hydroxamic acids 7 and 8 with 8% and 16% yields, respectively (Scheme 3).

To the best of our knowledge, the transformation of amido group into hydroxamic acid derivative was observed for the first time without an oxidant, during the Vilsmeier-Haack formylation reaction. An oxidation of the amide to the hydroxamic acid possibly took place upon the action of the formylating complex POCl\(_3\)/DMF. That

![Scheme 2](image-url)  
**Scheme 2.** Transformations of the amino group of the meso-amino-\( \beta \)-octaethylporphyrin.

![Figure 1](image-url)  
**Figure 1.** UV-Vis absorption spectra of Ni(II) \( \beta \)-octaethylporphyrin (NiOEP) and the corresponding meso-amino-derivatives 3–5. Spectra were recorded in CH\(_2\)Cl\(_2\) at concentration of 10\(^{-5}\) M.

![Scheme 3](image-url)  
**Scheme 3.** Synthesis of meso-disubstituted \( \beta \)-octaethylporphyrin derivatives.
supports the fact of the formation of the mixture of 5,10- and 5,15-substituted porphyrin isomers of the hydroxamic acid 7, 8, while only the 5,15-substituted amide product 6 was formed. Weak but still donor amide group of 5 directs an electrophile to the opposite meso-position during the formylation reaction, leading to 6. However, a side reaction produced a partial transformation of 5 into an intermediate hydroxamic acid derivative, and since the hydroxamic group was practically not an electron donor, the formylating electrophile could attack any meso-position, leading to a statistical distribution of the 5,10- and 5,15-products 7 and 8, respectively.

Upon insertion of the azine substituent into 5 a new intense band at 483 nm has emerged in 6 and the slight bathochromic shift of the Soret band for 11 nm and 16 nm shift of Q-bands were observed (Figure 2). Comparing spectra of 6 and similar azine derivative of NiOEP and p-nitrobenzaldehyde (NiOEPCHNNCHC\textsubscript{6}H\textsubscript{4}NO\textsubscript{2})\textsuperscript{[38]} but without meso-amido substituent, one can see that the spectrum of 6 is bathochromically shifted relatively that of NiOEPCHNNCHC\textsubscript{6}H\textsubscript{4}NO\textsubscript{2}, and Q-bands are of relatively higher intensity. These differences are due to the influence of meso-trifluoroacetamido group. The main Soret and Q-bands of NiOEPCHNNCHC\textsubscript{6}H\textsubscript{4}NO\textsubscript{2} are very close in position to that of 5, though being of less intensity. Thus, the insertion of meso-trifluoroacetamido or the p-nitrobenzalazine group led to the almost identical bathochromic shifts of the main porphyrin absorption bands. However, azine group insertion led to the emergence of the additional band near 480 nm. Cooperative influence of both azine and amido groups additively shifted all the bands and notably increased the intensity of the 480 nm band. Hydroxamic acid derivative 8, which is similar to 6, possesses slightly different spectrum, which contains a new long wavelength band at 641 nm. The spectrum of 5,10-isomer of the hydroxamic acid derivative 7 is considerably different: a quite strong band at 504 nm and the longest wavelength band at 653 nm with appreciable intensity.

Further expansion of the π-electron system of the azine functionalized disubstituted β-octaethylporphyrin was achieved through the conjugation with another tetrapyrrole. Again, the same three step synthetic scheme was applied: formylation of 5 followed by treatment with hydrazine led to the hydrazone formation which was then reacted with methyl pyropheophorbide d (PPPd), containing formyl group at β-position of the tetrapyrrole ring resulting in formation of the azine bridged porphyrin-chlorin conjugate 9 with 18 % yield. In comparison with the reaction

![Figure 2](image-url). UV-Vis absorption spectra of trifluoroacylated amino derivative 5 and their azine derivatives 6–8, and p-nitrobenzalazine derivative of meso-formyl-β-octaethylporphyrin (NiOEPCHNNCHC\textsubscript{6}H\textsubscript{4}NO\textsubscript{2})\textsuperscript{[38]} for comparison. The spectra were recorded in CH\textsubscript{2}Cl\textsubscript{2} at concentration of 10⁻⁵ M.

![Scheme 4](image-url). Synthesis of the azine bridged conjugate 9 of meso-(trifluoroacetamido)-β-octaethylporphyrin with methyl pyropheophorbide d (PPPd).

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**Scheme 4.** Synthesis of the azine bridged conjugate 9 of meso-(trifluoroacetamido)-β-octaethylporphyrin with methyl pyropheophorbide d (PPPd).
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with p-nitrobenzaldehyde, which was used in 3-fold excess, considerably more valuable methyl pyropheophorbide d was used in the less excess of 1.5 eq., and this fact was possibly a cause of the lower yield.

The electron absorption spectrum of the azine bridged porphyrin-chlorin conjugate 9 significantly differs from that of the p-nitrobenzalazine derivative 6 due to presence of the chlorin chromophore (Figure 3). For comparison, the spectra of the p-bromobenzalazine derivative of methyl pyropheophorbide d (PPPdNNCHC6H4Br)38 and p-bromobenzalazine derivative of methyl pyropheophorbide d (PPPdNNCHC6H4Br)38 for comparison. Spectra were recorded in CH2Cl2 at concentration of 10^{-5} M.

Conclusions

The meso-functionalization of Ni(II) β-octaethylporphyrin was readily performed basing on the electrophilic substitution reactions (nitration and formylation) followed by nucleophilic addition, substitution as well as reduction. Unprecedented oxidation of the amide functionality was observed during the formylation process, which led to formation of hydroxamic acid derivatives of the porphyrin. meso-Substitution significantly altered electron absorption spectra of the porphyrin chromophore. meso-Propylamine group causes bathochromic shift of the Soret band for almost 40 nm. Insertion of two meso-substituents led even to greater spectral changes. Combination of trifluoroacetamid and azine groups strongly increased the absorption near 500 nm and considerably shifted the Q-band maxima to the red region up to 650 nm. The azine bridged conjugation of meso-trifluoroacetamidob -octaethylporphyrin with methyl pyropheophorbide d led to the substantial growth of the Q-band intensity as well as red-shifting Soret band. Thus, the meso-substitution with the electron donor and acceptor groups can be regarded as a powerful methodology of tuning the optical spectral properties of tetrapyrrole dyes. The resulting compounds could be of interest as potential photosensitizers, sensor dyes and biologically active compounds.

Acknowledgements. The reported study was funded by the Ministry of science and higher education of Russian Federation, agreement No 075-15-2021-983.

References

1. Paolese R., Nardis S., Monti D., Stefanelli M., Di Natale C. Chem. Rev. 2017, 117, 2517–2583, DOI: 10.1021/acs.chemrev.6b00361.
2. Papkovsky D.B., O’Riordan T.C. J. Fluoresc. 2005, 15, 569–584, DOI: 10.1007/s10895-005-2830-x.
3. Norvaïša K., Kielmann M., Senge M.O. ChemBioChem 2020, 21, 1793–1807, DOI: 10.1002/cbic.202000067.
4. Sternberg E.D., Dolphin D., Brückner C. Tetrahedron 1998, 54, 4151–4202, DOI: 10.1016/S0040-4020(98)00015-5.
5. Glowacka-Sobotta A., Wrotynski M., Kryjewski M., Sobotta L., Mielcarek J. J. Porphyrins Phthalocyanines 2019, 23, 1–10, DOI: 10.1142/s108842461850116x.
6. Ethirajan M., Chen Y., Joshi P., Pandey R.K. Chem. Soc. Rev. 2011, 40, 340–362, DOI: 10.1039/b915149b.
7. Zhong Y., Wang J., Zhang J., Peng T., Li R. Dalton Trans. 2017, 46, 8219–8228, DOI: 10.1039/c7dt01029j.
