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Synthesis and Structure Elucidation of β,β,β-Trinitro-*meso*-tetraphenylporphyrin Derivatives

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The preparation, chromatographic isolation, and structure elucidation of β,β,β-substituted isomers of trinitro-5,10,15,20-tetraphenylporphyrin complexes are described. meso-Tetraphenylporphyrin (m-TPP) chelates (Cu^{II} and Zn^{II}) in the reaction with nitric acid (yellow fuming HNO_3) in $CHCl_3$ resulted in the formation of a mixture of nitroderivatives with combined yields of ca 50%. This nitration (under optimized conditions: 1–2 min, r.t.) can be carried out selectively to give mainly β,β,β-trinitro-compounds in the yield of up to 30-40%. From the above mixtures of seven possible regioisomers to form, two or three of them were usually isolated for which the structures were assigned on the basis of ^1H NMR spectra including HSQC and HMBC measurements. These types of products are attractive starting materials for synthesis of potential anticancer PDT agents of unique structure that are practically not available by any other alternative method.

Keywords: Porphyrins, complexes, β-nitration, electrophilic aromatic substitution, nitric acid, 2D NMR, HSQC and HMBC measurements.

Синтез и определение структуры производных β,β,β-тринитро-*мезо*-тетрафенилпорфирина

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Описано получение, хроматографическое выделение и выяснение структуры β,β,β-замещенных изомеров тринитро-5,10,15,20-тетрафенилпорфириновых комплексов. Хелаты мезо-тетрафенилпорфирина (м-ТФП) (Cu^{II} и Zn^{II}) в реакции с азотной кислотой (желтая дымящая HNO_3) в $CHCl_3$ приводят к образованию смеси нитропроизводных с совокупными выходами около 50%. Такое нитрование (в оптимизированных условиях: 1–2 мин, комнатная температура) можно проводить избирательно с получением преимущественно β,β,β-тринитросоединений с выходом до 30–40%. Из вышеуказанных смесей семи возможных региоизомеров обычно выделяли два или три из них, для которых структуры определялись на основе спектров ^1H ЯМР, включая HSQC и HMBC. Полученные соединения являются ценным исходным материалом для синтеза перспективных противораковых агентов ФДТ уникальной структуры, практически недоступных другими альтернативными методами.

Ключевые слова: Порфирины, комплексы, β-нитрование, электрофильное ароматическое замещение, азотная кислота, 2D ЯМР, измерения HSQC и HMBC.

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Introduction

The porphyrin system is present in well-known biological materials (*e.g.*, chlorophyll, heme, vitamin B_{12}). A number of porphyrin derivatives are of significant importance due to their potential use in many fields of chemistry, medicine, pharmacology, and new materials.[1] Thus, they are intensively studied in recent years. The investigations focused on the utilization of porphyrins as sensitizers in photodynamic cancer therapy (PDT),[2-5] molecular-based multi-bit memory storage,[6] bis-faced substituted building blocks,[7] electron-donor parts in artificial photosynthetic models,[8-10] *etc*. The desired precursors for the synthesis of these compounds can be isolated from naturally occurring substances or prepared *via* selective derivatization of the easily available simple laboratory-made moieties (*e.g.*, well-known *meso*-tetraphenylporphyrin, *m*-TPP). In both cases the above precursors are convenient intermediates for porphyrinic macrocycles possessing a high degree of complexity.

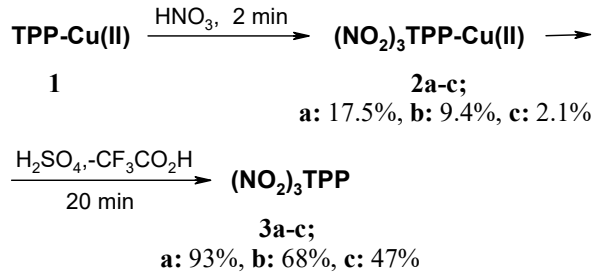
We present herein a synthesis of a series of such intermediates, namely trinitro-substituted *meso*-tetraarylporphyrins that could be used in this area. β,β,β-Trinitro-*meso*-tetraarylporphyrin derivatives seems to be very attractive substrates for functionalization *via* nucleophilic substitution of hydrogen.[11-13] For review concerning this substitution – see [14]. Each NO_2 group should allow introduction of a new substituent, thus leading to multi-substituted moieties. We have already attempted to obtain such porphyrins, however from the preparative point of view, it was rather unsuccessful.[15] On the other hand, there is a single report in the literature concerning synthesis of the above trinitro compounds. Dahal *et al.*[16] prepared three various trisubstituted isomers when treated Cu(II)-complex of *m*-TPP with fuming nitric acid. The ratios were not determined for these products and no assignment of the structures to individual isomers (except one case) was made. Moreover, the overall yield of the mixture obtained was equal to only 15%, the isomers were not separated at this stage, and not analysed.

Results and Discussion

Copper complexes of β,β,β-trinitro-5,10,15,20-tetraphenylporphyrins

We needed multisubstituted β-nitroporphyrins (particularly trinitro-) for our ongoing research. Thus, we have undertaken study to elaborate the procedures for preparation the above-mentioned derivatives, in conjunction with elucidation of their structures. This could allow application in the modification of porphyrin ring at the β-positions and using in the synthesis of more complex porphyrinoids. Initially, many experiments were carried out to find the optimized conditions. The reaction of (*meso*-tetraphenylporphyrinato)copper(II) (**1**) with fuming yellow nitric acid in chloroform during 2 minutes gave the highest yield (Scheme 1).

The post-reaction mixtures were monitored by MS spectrometry. Always the desired intensive molecular ion peak at *m/z* = 810 originating from β,β,β-trinitroderivative(s)



Scheme 1.

was detected. HR-MS measurements confirmed the elemental composition of the product (one or more isomers). TLC analysis showed three spots, thus, at least three β,β,β-trinitro porphyrin chelates were formed. Their isolation from the mixture was somewhat troublesome. However, double column chromatography and final purification on preparative TLC plates, led to the following compounds: 3,7,12-trinitro- (**2a**, 17.5%), 2,7,13-trinitro- (**2b**, 9.4%), and 2,8,12-trinitro- (**2c**, 2.1%). The overall yield was two times higher as compared to that described in the literature.[16] In fact, it had to be even better as the purification required quadruple chromatography.

The structure of the obtained products was an open question. Previously, only one isomer was fully identified, (2,8,12-trinitro-5,10,15,20-tetraphenylporphyrinato)copper(II) (**2c**) – *via* its demetallation and spectroscopic characterization of the respective free-base porphyrin including X-ray analysis. This compound was misnamed in the original paper as 3,7,13-trinitro-isomer. Some data for other products were also described.[16]

Herein, we have undertaken the studies to determine the mutual orientation of the nitro groups in the products obtained. The direct elucidation of the structure of all products could be possible on the basis of X-ray analysis. However, despite several attempts, a crystallization of these isomers to give the desired crystals failed. On the other hand, paramagnetic properties of the molecules **2a-c** due to containing copper cation in the core ring do not allow to measure readable ^{1}H NMR spectra.

These complexes were demetallated (in a mixture of concentrated H_2SO_4 and CF_3COOH) and structures of free base porphyrins obtained **3a-c** were investigated using nuclear magnetic resonance methods. Harsh conditions affect the yields of the reactions (especially in the case of transformation **2c** → **3c**). Removing of metal cation was accompanied with partial degradation that is possible herein as the β-polynitro-substituted porphyrins are relatively unstable.[17]

Theoretically, the nitration of porphyrins (and their metal complexes) at the β-positions could give up to seven trinitro-isomers (see Figure 1). One can suppose that isomers in which two nitro groups occupy β-positions in the same pyrrole ring can be excluded from this list (2,3,7-; 2,3,8-; 2,3,12-); their formation due to electronic effects is rather unlikely. Indeed, it was a case. The NMR investigations confirmed this hypothesis. A meticulous analysis of the spectra performed for demetallated products **3a-c** has become very helpful in the correct assignment of the structures **2a-c**. Nevertheless, elucidation of the above structures

was not a trivial problem. The diagnostic signals of the free base nitroporphyrins in ^{1}H NMR spectra appear in the region of *ca* 8.80-9.10 ppm. They are originating from β-protons. The substitution pattern of three NO_2 groups influences the signals shape and the differentiation in chemical shifts of the corresponding β-pyrrolic protons.

In the spectrum of the first isomer three singlets originating from β-protons were found at: 9.09 ppm (1H), 8.94 ppm (1H), and 8.86 ppm (1H). There are also two doublets (as AB system) situated very close to each other, 8.89 and 8.87 ppm, J = 5.3 Hz ($\Delta\delta$ = 0.02 ppm) – obviously from two protons of the same unsubstituted pyrrole ring. In the definitive assignment of the ^{1}H NMR spectra to the respective isomers very useful was taking into account the spectrum of mononitro derivative **5** (Figure 2). This compound is known and its ^{1}H NMR data were described in the literature.[*e.g.*11,18-22] We present here data obtained on the basis of our own measurements and observations, and some selected chemical shifts from the previous papers.[22]

In this case the signals of two β-protons from the opposite site to that substituted with NO_2 group (marked with a red arc) appear in the spectrum as a singlet (δ = 8.72 ppm; for comparison in *m*-TPP δ = 8.78 ppm). This indicated that influence of the NO_2 group on the chemical shifts of these protons is very small, or even there is not any effect. Thus, the first spectrum of our products (see data above) is originating from 3,7,12- (**3a**) or 2,7,13-isomer (**3b**) (Figure 1). In both cases two NO_2 groups are situated symmetrically to AB-protons of unsubstituted pyrrole ring; the third NO_2 group is 'far away' and doesn't generate observable effect on the chemical shifts.

To the second isomer of these two above-mentioned compounds we can initially assign the spectrum in which the broad singlet (δ = 8.90 ppm) originating from the two neighbouring H-β protons is present. Such protons, although non-equivalent, often give one signal in the spectrum. This may concern compound **3b** which was obtained from complex **2b** (M = Cu; Figure 1). The analysis shows that in these two isomers the orientation of nitro groups in two pyrrole rings in respect to the neighbouring unsubstituted one is symmetrical – because they do not differentiate (or differentiate very weak) chemical shifts of H-17 and H-18. Such a situation one can find in two isomers only: 3,7,12- or 2,7,13- (from the four possible that were listed in Figure 1).

To assign the structure to the corresponding compounds the chemical shifts of H-8 β-protons were compared. They should be deshielded due to proximity with three NO_2 groups. This influence in 3,7,12- pattern is larger (due to shorter distance from H-8 to the nitro groups) as compared to 2,7,13- one. Thus, the corresponding H-8 signal of the first isomer should be the most shifted downfield. It was a case in the spectrum of compound which was formed with 17.5% yield (chemical shift in free-base derivative $\delta_{H\text{-}8}$ = 9.09 ppm). This was assigned with number **3a** (free-base) and **2a** (as Cu-complex; first band from the column chromatography). The second isomer ought to be 2,7,13-substituted: **2b** (Cu-complex, 9.4%; band 2) and **3b** (free-base, $\delta_{H\text{-}8}$ = 8.93 ppm). Interestingly, the latter $\delta_{H\text{-}8}$ is not the most moved downfield chemical shift. It is not surprising because there is another β-proton herein (H-3) that is moved away from the two nitro groups by two-bonds and five-bonds, while in the first case this distance was larger (two/six or two/seven bonds; marked with yellow and blue/red colour in Figure 3). These two neighbouring NO_2 groups practically determine the chemical shift of H-8. The influence of the third group on proton H-8 in both isomers is rather small (see earlier analysis and Figure 2).

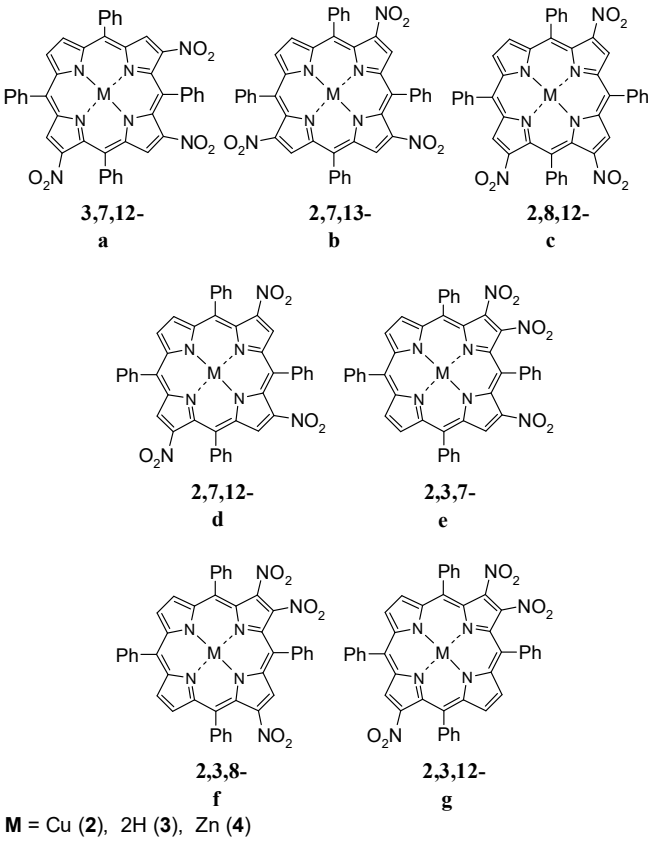


Figure 1. The possible regioisomers of β,β,β-trinitrotetraphenylporphyrins.

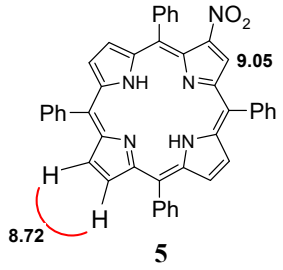


Figure 2. Selected chemical shifts of mononitro derivative **5**.

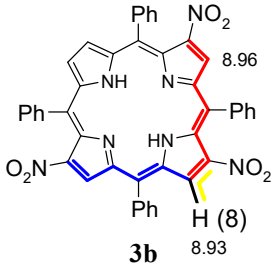
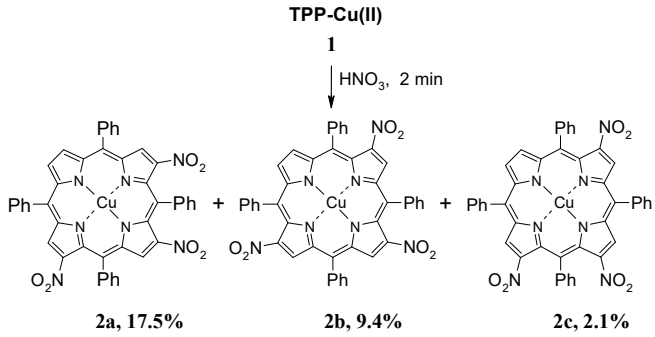


Figure 3. Spectral analysis of the isomer **3b.**

The last isomer must be generally non-symmetrical. It reflects in considerably large difference between chemical shifts of protons from the unsubstituted pyrrole ring (δ = 8.95/8.88, Δδ = 0.07 ppm). They appear as AB system (*J* = 5.2 Hz). The question is whether is this isomer 2,8,12- or 2,7,12- from the two remaining possible compounds. Fortunately, one isomer (of these two) has been described earlier in the literature and its structure was determined by X-ray analysis.[16] It was 2,8,12-isomer. We found that the product obtained in our experiment has the consistent data (MS, ^{1}H NMR, and UV-vis) with those described in the literature (despite some mistakes made in paper [16]). Thus, we confirmed the 2,8,12-trinitro pattern for **2c** (and **3c**). Now, we can draw the reaction scheme (Scheme 2).



Scheme 2.

The above analysis was done using simple ^{1}H NMR spectra. Subsequently, we have undertaken the attempts to confirm independently these structures. The studies involved two–dimensional correlation measurements. In heteronuclear 2D-experiments HSQC (correlations ^{1}H–^{13}C *via* one-bond) we found five expected correlations in the spectral region of H$^\beta$-protons (see Experimental). It was observed for three demetallated isomers **3a**, **3b**, and **3c**.

In the next step, two-dimensional HMBC spectra were analysed (^{1}H–^{13}C correlation *via* three bonds; and weaker – *via* five bonds). One could expect that these long distance heteronuclear correlations should confirm the structures of isomers. Theoretically, in the analysed systems even seven-bond correlation signals ^{1}H–^{13}C could be observed for each H$^\beta$-proton. In our case, for H-8 proton (compound **3b**) there are two carbon atoms three-bonds away from H-8 and two carbon atoms moved away by five bonds (see the arcs along the core ring in Figure 4a). Additionally, three other correlations (along the core ring) *via* 5 bonds might be expected (the respective carbons are indicated by red and blue circles in Figure 4b). However, the most diagnostic correlations could be that between two different protons and the same carbon atom. It is possible herein. Moreover, even correlation between three different β-protons from one side and one particular C-atom can also be observed. In fact, we found the spectra were greatly simplified. In all the above isomers each proton usually correlated with two, three, maximum with four carbon atoms.

In the spectrum of 3,7,12-trinitro isomer (**3a**) ^{1}H–^{13}C correlation of every H$^\beta$-proton with various non-repeating carbon atoms were observed (see Experimental). Very interesting were the correlations between β-protons of AB system (in unsubstituted pyrrole ring) and two carbon atoms of δ = 131.7 ppm and δ = 131.5 ppm. Identical correlations have been already observed in HSQC experiment *via* one bond [8.89/8.87 (AB system) – 131.5/131.7 ppm], originating from H-17/C-17 and H-18/C-18 pairs of atoms. In HMBC spectrum the above correlation(s) are consequence of H-17/C-18 and H-18/C-17 relationships (the only possibility). In this case, it must be a correlation *via* five bonds (indicated in Figure 5a within the pyrrole ring with blue and red colour). This is the only explanation of this effect in HSQC and HMBC spectra.

In 2,7,13-isomer (**3b**) one can observe for each H$^\beta$-proton correlation with 3-4 different carbon atoms (see Figure 4, colour arcs, circles, and arrows). In this case, there are interesting strong correlations of H-8 and H-12 neighbouring two NO_2 groups with the same quaternary carbon atom (δ = 149.5 ppm). It must be the C-10 (substituted with Ph, marked in Figure 5b). It is three bonds away from each of these protons.

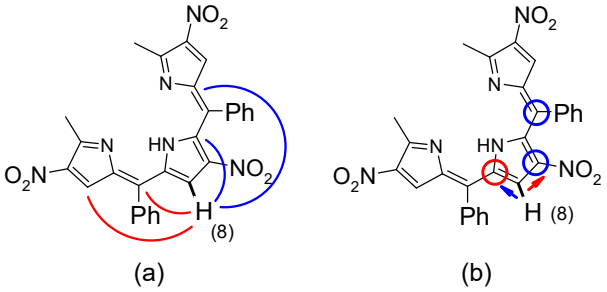


Figure 4. Selected HMBC-correlations in compound **3b**: (a) correlations *via* three-bonds and five-bonds; (b) five-bond correlations involving pyrrole ring (the arrows indicate the beginning of the five-bond way around pyrrole ring from the proton H-8 to the corresponding carbon atoms marked with the same colour).

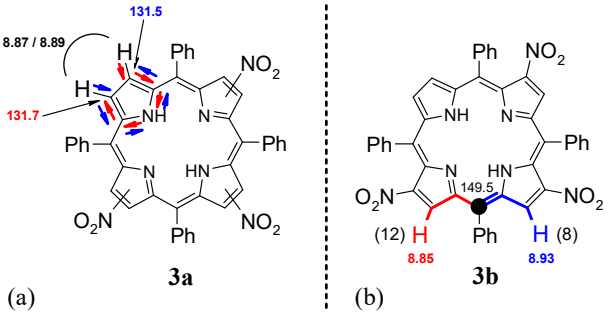


Figure 5. (a) HMBC measurements for H-17/C-18 and H-18/C-17 correlations in product **3a**. (b) strong three-bond HMBC-correlations of H-8 and H-12 protons with carbon C-10 in product **3b**.

The HMBC spectrum of the last isomer (2,8,12-, **3c**) did not display correlations between the various β-protons neighbouring the NO_2 groups and the same, one particular carbon atoms. We found the following correlations δ(^{1}H)–δ(^{13}C) in this case: 9.04/(130.0, 132.8) (*via* three bonds), 9.04/139.8 (*via* five bonds), (8.95/8.88, AB system)/(141.0, 142.0), 8.95/142.6 (*via* five bonds), 8.93/(145.9, 148.0) (*via* three bonds), 8.84/(145.2, 149.8) (*via* three bonds). The only β-protons that correlate to the same two carbon atoms

are protons of AB system. The reason is that there are at least four possible carbon atoms meeting this criterium (in various combinations: *via* three bonds, five bonds, and even *via* seven bonds). However, these correlations are not crucial for the structure determination of this isomer.

The above discussed HMBC spectra did not provide new relevant informations to confirm the structures of isomers, however all the observed correlations are in agreement with the data and conclusions we found from our earlier measurements.

At the end of this discussion we would like to add that the fourth possible trinitro-isomer, substituted with one NO_2 group in three different pyrrole rings (**2d**) was not observed during the nitration. How can this be explained? It seems that the formation of all isomers, as well as the mutual orientation of NO_2 groups, are governed by electronic effects. The key-intermediate for the formation of product **2d** (as well as for some other trinitro-isomers) must be 2,7-dinitro-5,10,15,20-tetraphenylporphyrinate. It comes from the analysis of the target products, and it is also in accordance with our previous observations concerning synthesis of dinitro-isomers. 2,7-Dinitro-5,10,15,20-tetraphenylporphyrinates were always the main products in the mixture of dinitrated derivatives.[23-26]

The mechanistic considerations, when studying the resonance structures of this 2,7-dinitro moiety, suggest the lower electron density at the position(s), the consequences of which gives the electrophilic substitution leading to 2,7,12-product. These crucial resonance structures that influenced the absence of the last possible trinitro-isomer **2d** are presented in Figure 6. One can see there the positive charge localized in the rings in which substitution should take place to give the desired 2,7,12-substitution pattern. The positions of the expected electrophilic attack are indicated by colour circles. Unfortunately, in two structures these positions are occupied by positive charge, thus disfavouring the reaction.

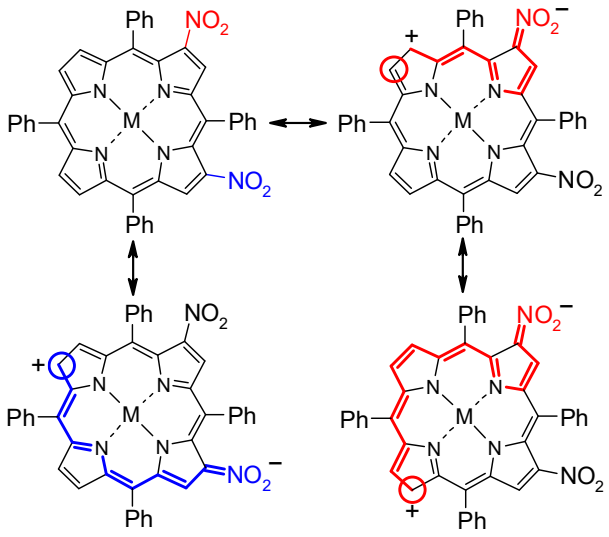
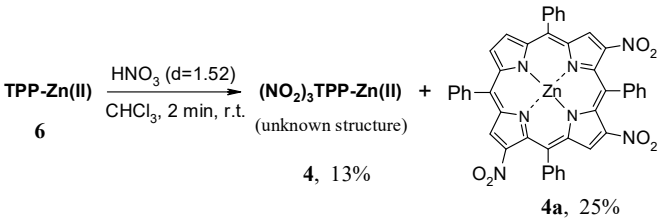


Figure 6. Crucial resonance structures of the key-intermediate (2,7-dinitro-5,10,15,20-tetraphenylporphyrinate) for the formation of product **2d**. Positions in which substitution ensures the formation of the desired product were indicated by colour circles.

Zinc complexes of β,β,β-trinitro-5,10,15,20-tetraphenylporphyrin isomers

Nitration of zinc complex of 5,10,15,20-tetraphenylporphyrin (**6**) (yellow fuming nitric acid in $CHCl_3$, 2 min) led to isolation of two trinitro-isomers (Scheme 3). The structure of the minor isomer (yield 13%) has not been determined, while the major one (yield 25%) turned out to be 3,7,12-trinitro-substituted derivative (**4a**). We found in its ^{1}H NMR spectrum AB system at δ = 8.86 ppm and 8.78 ppm (J = 4.8 Hz; β-protons of unsubstituted pyrrole ring) and two singlets: 9.00 ppm (1H) and 8.76 ppm (2H). The second one, originating from two protons, is only an apparent singlet.

These data are not sufficient to propose the structure of the above isomer. The substitution pattern was determined in a cross-experiment. When 3,7,12-trinitroporphyrin (previously obtained from copper complex) was treated with hydrate of zinc acetate $Zn(OAc)_2{\times}2H_2O$, it gave the same compound [the same R_f on TLC: R_f = 0.27, $CHCl_3$/MeOH (100:1); and the same chemical shifts in ^{1}H NMR spectrum]. Thus, this major isomer has the structure **4a**.



Scheme 3.

Experimental

General

^{1}H NMR spectra were recorded with a Varian GEMINI-200 and Varian MR-400 spectrometers, operating at 200 MHz and 400 MHz, respectively. Coupling constants J are expressed in hertz [Hz]. UV-vis spectra were measured with a Beckman DU-68 and Metertech SP-8001 spectrophotometers. Mass spectra were measured with a GCT Premier (Waters, FD-TOF) spectrometer (FD method) and MARINER (PerSeptive Biosystems, ESI-TOF) spectrometer (ESI method); *m/z* intensity values for peaks are given as % of relative intensity. Molecular formulas of new compounds were confirmed by HR-MS (ESI and FD), and by comparing the isotope molecular patterns (theoretical and experimental). TLC analysis was performed on aluminium foil plates pre-coated with silica gel (60 F-254, Merck AG); UV-vis lamp: 254/366 nm.

All the reactions were carried out in light-shielded flasks equipped with a septum. Starting porphyrinates were obtained according to known procedures described in the previous literature.[12,29,30] All the products were isolated by column chromatography (silica gel, 230-400 mesh; Merck AG). Some trinitro-isomers were rechromatographed on preparative TLC plates (silica gel, 60 F-254, 2 mm and 0.5 mm; Merck AG).

Synthesis

Copper(II) β,β,β-trinitro-5,10,15,20-tetraphenylporphyrinates. Nitration of (meso-tetraphenylporphyrinato)copper(II) with nitric acid. To a stirred solution of (*meso*-tetraphenylporphyrinato)copper(II) (**1**; 300 mg, 0.444 mmol) in $CHCl_3$ (300 mL) at room temperature, a fuming yellow nitric acid (density 1.52 g/mL, Fluka; 6 mL) was added dropwise *via* syringe during *ca* 2 min. Then, the mixture was poured into aqueous solution of 5% KOH (200 mL), and shaken carefully in a separatory funnel. The separated organic layer was washed with water (3×100 mL), and dried with anhydrous $MgSO_4/Na_2CO_3$. After evaporating the solvent, the residue was subjected to column chromatography (eluent: $CHCl_3$/*n*-hexane – from 1:1 to 2:1) to give two fractions: (a) a mixture of isomers **2a**, **2b**, and **2c** (three spots originating from three β,β,β-trinitro-substituted porphyrinates were detected by TLC); (b) some amounts of the fraction consisting of dinitro-isomers and other products. Trinitroporphyrinates of copper(II) were identified in the first fraction by MS method. In the spectrum the intensive ion *m/z* = 810 was observed (with characteristic isotope pattern). Molecular formula of these compounds was confirmed by HR-MS (ESI); calcd. for $C_{44}H_{25}N_7O_6Cu$ (M^+): 810.1162, found: 810.1171.

The mixture of isomers **2a-c** was subjected to preparative TLC to separate them (eluent: $CHCl_3$/*n*-hexane, 2:1). Yields of the respective trinitroporphyrinates: a) (3,7,12-trinitro-5,10,15,20-tetraphenylporphyrinato)copper(II) (**2a**) – 63.0 mg, 17.5%; b) (2,7,13-trinitro-5,10,15,20-tetraphenylporphyrinato)copper(II) (**2b**) – 33.9 mg, 9.4%; c) (2,8,12-trinitro-5,10,15,20-tetraphenylporphyrinato)copper(II) (**2c**) – 7.5 mg, 2.1%.

*(3,7,12-Trinitro-5,10,15,20-tetraphenylporphyrinato)copper(II) (**2a**).* R_f = 0.66 [$CHCl_3$/*n*-hexane (2:1)]. m.p. > 300 °C. UV-vis ($CHCl_3$) λ_{max} (log ε) nm: 613 (3.94), 601 (3.98), 571 (4.01), 446.5 (5.21, Soret band), 332 (4.31). MS (ESI) *m/z* (% rel. int.): 814 (11), 813 (35), 812 (66), 811 (61), 810 (100) [isotope M^+ and $(M+H)^+$]. HR-MS (ESI) – see above.

*(2,7,13-Trinitro-5,10,15,20-tetraphenylporphyrinato)copper(II) (**2b**).* R_f = 0.61 [$CHCl_3$/*n*-hexane (2:1)]. m.p. > 300 °C. UV-vis ($CHCl_3$) λ_{max} (log ε) nm: 615.5 (4.10), 570 (4.13), 444.5 (5.29, Soret band), 325.5 (4.39). MS (ESI) *m/z* (% rel. int.): 814 (12), 813 (39), 812 (70), 811 (66), 810 (100) [isotope M^+ and $(M+H)^+$]. HR-MS (ESI) – see above.

*(2,8,12-Trinitro-5,10,15,20-tetraphenylporphyrinato)copper(II) (**2c**).* R_f = 0.55 [$CHCl_3$/*n*-hexane (2:1)]. m.p. > 300 °C. UV-vis ($CHCl_3$) λ_{max} (log ε) nm: 614.5 (3.99), 574.5 (4.14), 450.5 (5.18, Soret band), 336.5 (4.38). MS (ESI) *m/z* (% rel. int.): 814 (11), 813 (35), 812 (67), 811 (62), 810 (100) [isotope M^+ and $(M+H)^+$]. HR-MS (ESI) – see above.

Demetallation of copper(II) β,β,β-trinitro-5,10,15,20-tetraphenylporphyrinates. In a round-bottomed flask (20 mL), to the corresponding β,β,β-trinitroporphyrinate (**2a**, **2b**, **2c**; 50 mg, 0.062 mmol) concentrated H_2SO_4 (95%; 1.6 mL) was added followed by dropwise addition of TFA (8 mL). The mixture was stirred under argon at room temperature during *ca* 20 min. Then, it was poured into water (10 mL) and extracted with $CHCl_3$ (3×10 mL). The combined organic layers were washed with water (3×15 mL) and dried over anhydrous $MgSO_4/Na_2CO_3$. The solvent was evaporated to dryness, and the residue was subjected to column chromatography using a mixture of $CHCl_3$/*n*-hexane (2:1) as eluent. Yields of the respective free-base porphyrins obtained in three different reactions: a) 3,7,12-trinitro-5,10,15,20-tetraphenylporphyrin (**3a**) – 43.5 mg, 93%; b) 2,7,13-trinitro-5,10,15,20-tetraphenylporphyrin (**3b**) – 31.6 mg, 68%; c) 2,8,12-trinitro-5,10,15,20-tetraphenylporphyrin (**3c**) – 22.0 mg, 47%.

*3,7,12-Trinitro-5,10,15,20-tetraphenylporphyrin (**3a**).* R_f = = 0.27 [$CHCl_3$/*n*-hexane (2:1)]. m.p. > 300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 9.09 (s, 1H, H^β-pyrrole), 8.94 (s, 1H, H^β-pyrrole), 8.89 and 8.87 (AB, *J* = 5.3 Hz, 2H, H^β-pyrrole), 8.86 (s, 1H, H^β-pyrrole), 8.31-8.15 (m, 8H, H-Ph), 7.92-7.72 (m, 12H, H-Ph), -1.98 (broad s, 2H, 2×NH). NMR-HSQC ($CDCl_3$, 400 MHz / 100 MHz) δ_H ppm (diagnostic ^{1}H–^{13}C correlations): 9.09/124.7, 8.94/133.1, 8.89/131.5, 8.87/131.7, 8.86/133.4. NMR-HMBC ($CDCl_3$, 400 MHz /100 MHz) δ_H ppm (diagnostic ^{1}H–^{13}C correlations *via* three bonds): 9.09/(128.8, 132.6), 8.94/(146.5, 147.8), 8.89/(146.6, 149.0), 8.89/131.7 (*via* five bonds), 8.87/(146.6, 149.0), 8.87/131.5 (*via* five bonds), 8.86/(146.6, 149.0). UV-vis ($CHCl_3$) λ_{max} (log ε) nm: 709.5 (3.94), 600.5 (3.83), 550.5 (3.98), 450.5 (5.23, Soret band). MS (FD) *m/z* (% rel. int.): 752 (3), 751 (15), 750 (49), 749 (100) [isotope M^+]. HR-MS (FD) calcd. for $C_{44}H_{27}N_7O_6$ (M^+): 749.2023, found: 749.2035.

*2,7,13-Trinitro-5,10,15,20-tetraphenylporphyrin (**3b**).* R_f = = 0.19 [$CHCl_3$/*n*-hexane (2:1)]. m.p. > 300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 8.96 (s, 1H, H^β-pyrrole), 8.93 (s, 1H, H^β-pyrrole), 8.90 (broad s, originating from AB system, 2H, H^β-pyrrole), 8.85 (s, 1H, H^β-pyrrole), 8.34-8.16 (m, 8H, H-Ph), 7.90-7.68 (m, 12H, H-Ph), -2.11 (broad s, 2H, 2×NH). NMR-HSQC ($CDCl_3$, 400 MHz / 100 MHz) δ_H ppm (diagnostic ^{1}H–^{13}C correlations): 8.96/125.5, 8.93/132.9, 8.90/*ca* 130.4, 8.85/133.1. NMR-HMBC ($CDCl_3$, 400 MHz / 100 MHz) δ_H ppm (diagnostic ^{1}H–^{13}C correlations *via* three bonds): 8.96/(130.2, 134.0), 8.93/(144.7, 149.5), 8.90/(*ca* 130.4, *ca* 140.8), 8.85/(145.5, 149.6). UV-vis ($CHCl_3$) λ_{max} (log ε) nm: 707 (3.89), 602 (3.82), 552 (3.89), 452.5 (5.12, Soret band). MS (FD) *m/z* (% rel. int.): 752 (3), 751 (17), 750 (55), 749 (100) [isotope M^+]. HR-MS (FD) calcd. for $C_{44}H_{27}N_7O_6$ (M^+): 749.2023, found: 749.2015.

*2,8,12-Trinitro-5,10,15,20-tetraphenylporphyrin (**3c**).* R_f = = 0.22 [$CHCl_3$/*n*-hexane (2:1)]. m.p. > 300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 9.04 (s, 1H, H^β-pyrrole), 8.95 and 8.88 (AB, *J* = 5.2 Hz, 2H, H^β-pyrrole), 8.93 (s, 1H, H^β-pyrrole), 8.84 (s, 1H, H^β-pyrrole), 8.34-8.18 (m, 8H, H-Ph), 7.92-7.66 (m, 12H, H-Ph), -2.12 (broad s, 2H, 2×NH). NMR-HSQC ($CDCl_3$, 400 MHz / 100 MHz) δ_H ppm (diagnostic ^{1}H–^{13}C correlations): 9.04/125.1, 8.95/131.0, 8.93/132.8, 8.88/130.9, 8.84/133.0. NMR-HMBC ($CDCl_3$, 400 MHz / 100 MHz) δ_H ppm (diagnostic ^{1}H–^{13}C correlations): 9.04/(130.0, 132.8) (*via* three bonds), 9.04/139.8 (*via* five bonds), 8.95/(141.0, 142.0) (*via* three bonds), 8.95/(130.9, 142.6) (*via* five bonds), 8.93/(145.9, 148.0) (*via* three bonds), 8.88/(141.0, 142.0) (*via* three bonds), 8.88/130.9 (*via* five bonds), 8.84/(145.2, 149.8) (*via* three bonds). UV-vis ($CHCl_3$) λ_{max} (log ε) nm: 705.5 (4.59), 599.5 (4.48), 550 (4.56), 452 (5.84, Soret band). MS (FD) *m/z* (% rel. int.): 752 (4), 751 (17), 750 (55), 749 (100) [isotope M^+]. HR-MS (FD) calcd. for $C_{44}H_{27}N_7O_6$ (M^+): 749.2023, found: 749.2037. This compound was fully-characterized and described in the literature.[16] Its spectral data (despite some mistakes in paper [16]) are in agreement with those reported therein.

Nitration of (meso-tetraphenylporphyrinato)zinc(II) with nitric acid. In a round-bottomed flask (250 mL), to a stirred solution of (*meso*-tetraphenylporphyrinato)zinc(II) (**6**; 100 mg, 0.148 mmol) in $CHCl_3$ (100 mL) at room temperature, a fuming yellow nitric acid (density 1.52 g/mL, Fluka; 2 mL) was added dropwise *via* syringe during *ca* 2 min. Then, the mixture was poured into aqueous solution of 5% KOH (100 mL), and shaken carefully in a separatory funnel. The separated organic layer was washed with water (3×100 mL), and dried with anhydrous $MgSO_4/Na_2CO_3$. After evaporating the solvent, the residue was subjected to column chromatography (eluent: $CHCl_3$/MeOH – 250:1) to give two fractions containing one product each. They were rechromatographed on preparative TLC plates (silica gel, 60 F-254, 2 mm; eluent: $CHCl_3$/MeOH – 250:1). Yields of the respective trinitroporphyrinates: a) isomer of unknown structure (**4**) – 15.5 mg, 13%; b) (3,7,12-trinitro-5,10,15,20-tetraphenylporphyrinato)zinc(II) (**4a**) – 29.9 mg, 25%.

*(3,7,12-Trinitro-5,10,15,20-tetraphenylporphyrinato)zinc(II) (**4a**).* R_f = 0.27 [$CHCl_3$/MeOH (100:1)]. m.p. > 300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 9.07 and 9.05 (AB, *J* = 5.2 Hz, 2H, H^β-pyrrole), 9.04 (s, 1H, H^β-pyrrole), 8.81 (broad s, 2H, H^β-

pyrrole), 8.18-8.03 (m, 8H, H-Ph), 7.87-7.60 (m, 12H, H-Ph). UV-vis ($CHCl_3$) λ_{max} (log ε) nm: 624 (4.34), 577 (4.37), 448 (5.56, Soret band), 335 (4.72), 269 (4.95). MS (ESI), *m/z* (% rel. int.): 817 (16), 816 (34), 815 (62), 814 (51), 813 (84), 812 (69), 811 (100) [isotope M^+ and $(M+H)^+$]. HR-MS (ESI) calcd. for $C_{44}H_{25}N_7O_6Zn$ (M^+): 811.1158, found: 811.1153.

Product ***4***. R_f = 0.25 [$CHCl_3$/MeOH (100:1)]. m.p. > 300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ppm: 9.00 (s, 1H, H^β-pyrrole), 8.86 and 8.78 (AB, *J* = 4.8 Hz, 2H, H^β-pyrrole), 8.76 (s, 2H, H^β-pyrrole), 8.18-8.04 (m, 8H, H-Ph), 7.84-7.60 (m, 12H, H-Ph). UV-vis ($CHCl_3$) λ_{max} (log ε) nm: 619.5 (4.33), 574 (4.41), 448 (5.53, Soret band). MS (ESI), *m/z* (% rel. int.): 817 (10), 816 (26), 815 (57), 814 (47), 813 (78), 812 (57), 811 (100) [isotope M^+ and $(M+H)^+$]. HR-MS (ESI) calcd. for $C_{44}H_{25}N_7O_6Zn$ (M^+): 811.1158, found: 811.1153.

Final remarks: 1) The structure of compound **4a** was additionally confirmed by demetallation of product **2a** and complexation of free-base with $Zn(OAc)_2{\times}2H_2O$. The properties of both products **4a** and the obtained complex were identical. 2) Zinc-complexation of 3,7,12-trinitro-5,10,15,20-tetraphenylporphyrin (**3a**) was carried out according to literature reports;[12,30] yield – quantitative.

Conclusions

Treatment of copper(II) and zinc(II) *meso*-TPP complexes with yellow fuming HNO_3 in $CHCl_3$ resulted in the formation of a mixture of nitroderivatives with combined yields of *ca* 50%. Further purification and separation of these mixtures led to two or three major products. The detailed analysis of simple ^{1}H NMR spectra allowed to establish substitution pattern of NO_2 groups in the three obtained isomers of copper(II) and one isomer of zinc(II) complexes of β,β,β-trinitro-5,10,15,20-tetraphenylporphyrin. In the case of Cu^{II} chelates, elucidation of the structures of free-base porphyrins determined at the same time the structures of porphyrinates.

All the above nitro derivatives are very valuable materials for their further transformations into more complex systems substituted at the β-positions. Probably they can react with various carbanions (in the neighbouring position to each NO_2 group),[12,14] thus giving up to six times β-derivatized porphyrins. This approach is particularly effective. It leads to multi-substituted products including two steps only. Such compounds are practically not available by other methods. The studies concerning the above mentioned functionalization will be published soon.

The interest in nitroporphyrins is increasing. The investigations concerning synthesis of β-nitro-, *meso*-nitro-, and *meso*-nitroaryl-porphyrins are constantly undertaken.[*e.g.* 27] In the recent past all the methods used to date for this nitration were thoroughly reviewed.[28]

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