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On the Preparation of Nickel Porphyrins Bearing Two to Four Nitro Groups at β-Positions

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The preparation, isolation, and identification of dinitro, trinitro, and tetranitro metalloporphyrins bearing nitro groups on pyrrole rings—desirable intermediates that enable fundamental changes in the chemico-physical properties of the porphyrin core—are studied. All six possible dinitro-Ni-TPP isomers are formed; three are isolated as pure substances using column chromatography, while the remaining three are inseparable. All possible trinitro-Ni-TPP isomers are prepared and isolated, except for the 2,7,13 isomer. Attempts to synthesize tetranitro-Ni-TPP either through direct nitration of metalloporphyrin or via direct condensation of the nitropyrrole building blocks are unsuccessful. The molecular structures are unambiguously identified using 2D NMR experiments. Some experimental observations, though not all, are consistent with quantum chemical calculations performed on the geometry, energy, Fukui indices, dipole moments of nitroporphyrins, and the energy of nitration intermediates.

1. Introduction

Metalloporphyrins represent a unique and important class of substances, encompassing animal blood heme and plant chlorophyll, which are the basis of living processes. Scientists are, naturally, studying their properties in the hope of understanding the secrets of natural processes, or even improving and utilizing them for the benefit of humankind. These include photodynamic agents for disease treatment, catalysts for oxidation, selectors for sensors, light-harvesting systems for photovoltaics, agents enabling the estimation of absolute configuration, and many others.[1–7] As expected, specific applications of metalloporphyrins necessitate tailored functionalization. However, the chemistry of metalloporphyrins and porphyrins in general remains complex and is still the subject of extensive investigation. Most modifications have been performed at the *meso* positions, as these can be easily introduced via condensation of pyrrole with an appropriate aldehyde (usually an arylaldehyde). However, the aromatic ring of such *meso* aryl substituents is not coplanar, and therefore not conjugated, with the metalloporphyrin core, making their effect relatively weak.[8] Functionalization of the metalloporphyrin core at its β-positions (on the pyrrole units) would, in principle, yield substantially higher efficacy; however, such modifications remain comparatively rare.

A well-known efficient way to enable functionalization at the porphyrin β-positions is by introducing a nitro moiety through direct nitration of metalloporphyrins because nitration of the porphyrin free base typically places nitro groups on the *meso*-aryl rings.[9–19] Such β-nitroporphyrins play a significant role in the formation of complex derivatives through various transformations, including nucleophilic addition, nucleophilic substitution, and cycloaddition reactions.[9,20–27] Nitrometalloporphyrins have been widely used as precursors to aminoporphyrins,[26,28–30] which act as building blocks for porphyrin analogues of Tröger's base[31] and oligo-Tröger's base,[32] and also facilitate the conversion of the porphyrin core into a chlorin core.[33,34]

Although several β-nitroporphyrins have been synthesized in high yields through the direct nitration of porphyrin and metalloporphyrin derivatives,[33–38] only a few examples of β,β-dinitro- and β,β,β-trinitro- have been reported, while β,β,β,β-tetranitroporphyrins remain unreported. Additionally, these processes are often associated with low yields, poor selectivity, laborious isolation, and challenges in identifying their isomers, with crucial experimental details frequently omitted.

In this article, we provide a comprehensive summary of known (metallo)porphyrins with two or more nitro groups at the β-positions, comparing them with our own experimental findings. Through this comparison, we identified several discrepancies in the literature and outlined protocols for the preparation, isolation, and identification of nitroporphyrins. Additionally, we addressed limitations in current research and proposed strategic directions for future studies.

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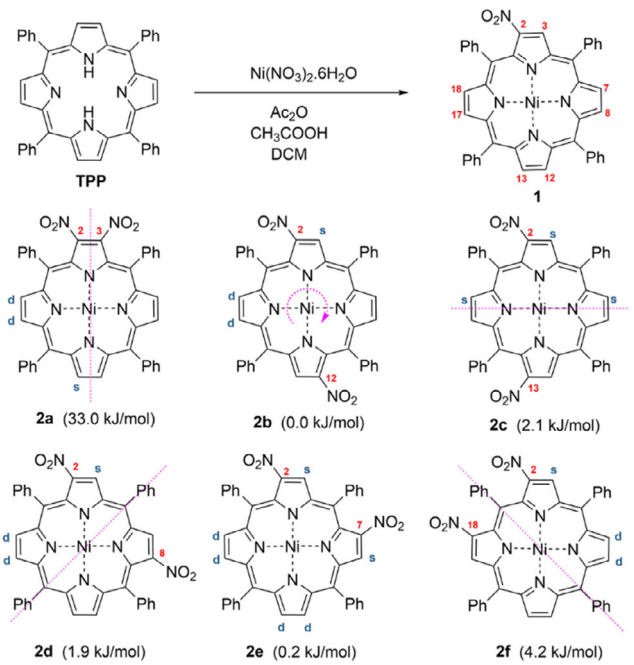
2. Results and Discussion

2.1. β,β-Dinitroporphyrins

The first β,β-dinitroporphyrins were reported by Dahal et al. in the nineties.[39–42] Based on their observations,[40] nitration of the copper complex of 5,10,15,20-tetraphenylporphyrin (Cu-TPP) with fuming nitric acid provided 2,12- and 2,13-dinitro-Cu-TPP isomers with an overall yield of 20%. When a higher amount of fuming nitric acid was used, then 2,7-, 2,8-, and 2,18-dinitro-Cu-TPP isomers were formed in the overall 20% yield (for the porphyrin core numbering see **Scheme 1**). The isomers were separated and identified by ^{1}H NMR spectroscopy (270 MHz) after demetallation. The molecular structure of 2,13-dinitro-TPP was confirmed by the single-crystal X-Ray diffraction (SCXRD).[42] It should be noted that the selectivity change upon the acid amount is surprising.

The formation of two dinitro-Ni-TPP isomers was observed as byproducts of nitro-Ni-TPP when TPP was treated with nitric acid.[43] One isomer was unambiguously assigned as 2,7-dinitro-Ni-TPP **2e** (6% yield) due to its unsymmetrical molecule, hence, the unique ^{1}H NMR spectrum. The next isomer was inaccurately assigned to the structure 2,8-dinitro-Ni-TPP **2 d** (3% yield) based on prior data and a comparison of the appearance and order of chemical shift; however, later corrected to the structure 2,18-dinitro-Ni-TPP **2f** by Mikus et al.[44]

Mikus et al. investigated the nitration of TPP complexes (Cu, Ni, Co) using a previously published methodology in search of other dinitro isomers. In the case of Ni-TPP, under nitric acid conditions, they successfully isolated and characterized nitro-Ni-TPP **1** (6% yield), and two major dinitro-Ni-TPP isomers, assigned based on correlation spectroscopy (COSY) and Nuclear Overhauser Effect Spectroscopy (NOESY) spectra as **2e** (22% yield) and **2f** (22% yield).[44] An additional mixture of other dinitro isomers (26% yield) was also isolated but not characterized. In addition, the authors stated that, for Cu-TPP, three dinitro isomers were isolated, and after demetallation, identified as 2,7-dinitro-TPP (15% yield), 2,18-dinitro-TPP (13% yield), and 2,13-dinitro-TPP (10% yield; the earlier wrong assignment as 2,8-dinitro-TPP was corrected by Mikus et al.).[45] They also reported that the nitration of tetrakis (3-methylphenyl) derivative of Cu-complex yielded similar results, i.e., 2,7-dinitro-Cu-TPP (22% yield), 2,18-dinitro-Cu-TPP (12% yield), 2,8-dinitro-Cu-TPP (5% yield), 2,12-dinitro-Cu-TPP (8% yield), and 2,13-dinitro-Cu-TPP (7% yield) were isolated; however, no elaboration regarding the elucidation of their molecular structures was provided.



Scheme 1. Preparation of all possible dinitro-Ni-TPP isomers; the calculated energy difference against the lowest for **2b** is given in the parentheses; the red numbers are the nomenclature numbering of the porphyrin core; the blue letters denote the multiplicity of the signal in ^{1}H NMR spectra (s for singlet, d for doublet); the violet dotted lines highlights the molecular symmetry.

2.2. Preparation of Dinitro-Ni-TPP Isomers 2a–f

For the preparation of dinitro-Ni-TPP **2** isomers, we chose direct nitration of TPP using two equivalents of nickel nitrate, acetic acid, and acetic anhydride in DCM at room temperature (Scheme 1), thus, nitration and metalation took place in a single reaction step. The reaction course was followed by thin-layer chromatography (TLC). At the beginning, the intensive spot of the starting TPP was followed by a less intense spot of Ni-TPP and the intense spot of nitro-Ni-TPP **1**. After an hour, the reaction mixture contained mostly nitro-Ni-TPP **1** with traces of dinitro-Ni-TPP isomers **2**. After overnight stirring, the starting TPP had disappeared completely, and most of the nitro-Ni-TPP **1** had converted to a mixture of dinitro-Ni-TPP isomers. At this point, the reaction was stopped, and the products were isolated using column chromatography on silica, where nitro-Ni-TPP **1** (8% yield) was isolated easily from the dinitro isomers **2**. Repeated chromatography of dinitro-Ni-TPP isomers **2** resulted in the isolation of previously never reported 2,3-dinitro-TPP **2a** (5% yield) followed by a mixture of three isomers **2b**, **2c**, and **2d** (29% total yield, in a 43:37:20 ratio), pure 2,7-dinitro-TPP **2e** (21% yield), and pure 2,18-dinitro-TPP **2f** (23% yield).

For the separation of the mixture of **2b**, **2c**, and **2d**, we applied high-performance liquid chromatography. On an analytical scale, it produced three overlapping peaks; however, on a preparative scale, only two odd-shaped peaks were observed. Surprisingly, each of the collected fractions contained all three isomers in various ratios (see ESI). This may be a consequence of the higher concentration during the preparative mode, so an aggregation of the isomers could happen. Additionally, we were also unable to find suitable conditions for the separation of the isomers after their reduction to the corresponding diamines. The challenging separation of dinitrometalloporphyrins is known from literature, where separation of individual isomers was reached only for tetrakis(3-methylphenyl) derivatives of Cu-TPP or for demetallated derivatives.[44]

It should be noted that the retention of nitroporphyrins follows the number of nitro groups above all; hence, we concluded that the interaction of nitro groups with silica is crucial for their

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Table 1. Characteristics of the studied dinitro-Ni-TPP isomers.

Experiment	2,3-dinitro **2a**	2,12-dinitro **2b**	2,13-dinitro **2c**	2,8-dinitro **2d**	2,7-dinitro **2e**	2,18-dinitro **2f**
Yield (rel)[a] (%)	5.1 (46)	12.4 (111)[b]	10.5 (94)[b]	5.7 (51)[b]	20.9 (94)	23.4 (210)
Retention factor R_f [c]	0.47	≈0.45	≈0.45	≈0.45	0.43	0.41
Calculated Dipole moment (D)	11.54	5.13	7.11	4.35	9.41	12.53
ΔE intermediate (kJ mol^{-1})	18.6	0.9	1.6	0.0	2.7 and 4.5[d]	7.8
Fukui index [e]	1.29	1.61	1.60	1.65	1.77 and 1.65[d]	1.78

[a]The preparative yield is followed by the relative yield in parentheses; that is the preparative yield divided by the total yield and by the statistically expected yield (if the reactivity of all positions would be equal then the yield of each isomer would be 14%, except 29% for **2e**). [b]The yield is calculated based on the molar content (from NMR spectrum) of the isomer in the isolated mixture of isomers **2b**, **2c,** and **2d**. [c]Solvent for elution was DCM/*n*-hexane 1:1; for nitro-Ni-TPP **1** is $R_f = 0.55$ and calculated dipole moment is 7.45 D. [d]The values are for positions 7 and 17, respectively. [e]The Fukui index at the carbon atoms of nitro-Ni-TPP **1**, which upon nitration gives the corresponding dinitro-Ni-TPP **2**.

separation. In the case of dinitro isomers **2**, their retention order follows the gain of their calculated dipole moments, excluding 2,3-dinitro-TPP **2a**, which has the weakest retention despite having the highest dipole moment (**Table 1**). We believe that the nitro groups in **2a** are so close to each other that they likely act as one stronger group rather than two separate groups. Thus, the retention depends on the number, accessibility, cooperativity, and probability of the interaction of nitro groups with silica.

2.3. Identification of Dinitro-Ni-TPP Isomers 2a–f

The unambiguous identification of each of the possible dinitro isomers is rather demanding, as demonstrated by a few corrections of the assignments in the literature (vide supra). The ^{1}H NMR signals of hydrogen atoms at the pyrrole rings and at the *ortho* positions of the phenyl moieties are the key for the isomers identification; hence, high-quality and resolution both 1D and 2D NMR spectra at a high field are required.

Considering all possible dinitro-Ni-TPP isomers **2a**−**f**, two are identified straightforwardly based on the ordinary ^{1}H NMR spectra due to their unique molecular symmetry; only 2,13-dinitro isomer **2c** has three singlets, and only 2,7-dinitro isomer **2e** has four doublets and two singlets. The remaining four dinitroisomers have one singlet and two doublets for the pyrrole hydrogen atoms; however, 2,3-dinitro **2a** and 2,12-dinitro **2b** have only two chemically inequivalent phenyl groups, while **2d** and **2f** have three.

We identified the isomer **2a** through the H12 singlet, which has only two strong correlations to C11 (identical with C14) and to C13 (identical with C12) in the heteronuclear multiple bond correlation (HMBC) spectrum; due to symmetry, the later correlation H12—C12 is observed both in the HMBC and heteronuclear single quantum coherence (HSQC). In contrast, the singlet of isomer **2b** has two strong correlations to C1 and C4, a very weak correlation to C2, and none to C3 (H3—C3 correlation is observed only in the HSQC spectrum).

The isomer **2f** was identified through the phenyl group on C20, which is surrounded by two nitro groups and no hydrogen, as a consequence there is no correlation between a pyrrole hydrogen atom and the hydrogen atoms at its *ortho* positions. In addition, the *ortho* protons of the phenyl group on C5 have nuclear overhauser effect (NOE) correlations to H3 and H7, and HMBC correlation to C5 (together with H3 and H7); the ^{1}H NMR spectrum was identical to the published one.[44] Unfortunately, we were unable to identify all ^{1}H and ^{13}C signals of the **2d** isomer due to its low content and unsuccessful separation; hence, the structure is also indirectly proved as the last possible configuration.

It is worth noting that dinitroisomers 2a-f have a specific color on the TLC plate. Isomer 2a is light green, the mixture of isomers 2b, 2c, and 2d is greenish, while 2e and 2f are brownish.

2.4. Formation Selectivity of Dinitro-Ni-TPP Isomers 2a–f

In an attempt to get a somewhat more sophisticated view of the observed selectivity, we performed two simple quantum chemical calculations. We assumed that nitration would take place via the attack by the NO_2^+ cation. First, we calculated the Fukui indices, which are expected to be highest at the most likely site of electrophilic attack.[46] Second, we calculated the energy of the expected intermediate (the σ-complex $[H\cdots C\cdots NO_2]^+$) for every possible reactive site, as there is the Hammond's postulate[47] saying the energy of a reaction intermediate is close to the energy of the associated activated complex (a transition state), which calculation is more demanding.

For the first step, the nitration of Ni-TPP to nitro-Ni-TPP **1**, the lowest energy was found for the intermediate on the pyrrole ring. The energy of the intermediate on the *para* and *meta* positions of the phenyl ring was 63 and 106 kJ mol^{-1} higher, respectively. The Fukui indices were 1.55e for the pyrrole position and 0.78e for the phenyl *para* positions. Both calculated parameters are in accordance with the observation.

For the second step, the nitration of nitro-Ni-TPP **1** to dinitro-Ni-TPP **2**, we calculated all possible intermediates and the Fukui indices for the introduction of the second nitro group into a β-position (Table 1). As would be expected, the intermediate of **2a** has the highest energy, which is in accord with a common assumption that the first nitro group deactivates the pyrrole against the next nitration. In light of this, the preparative yield of the **2a** isomer appears unexpectedly high compared to the yields of the other isomers. In addition, the Fukui index for carbon C3 is the lowest (a similar gain as for the phenyl *para* positions), thus, a very low yield of this isomer is expected. However, the

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experimental yield is comparable to **2d**, which has the lowest intermediate energy and a significant Fukui index on the carbon C8. Another ambiguity was found in the case of **2f**, which has the highest relative yield despite having a significantly higher energy of its intermediate than **2b**–**e**. In contrast, there is the highest Fukui index on the carbon C18. The yield of **2e** is not high since it could be formed by nitration at the positions C7 and C17. Obviously, there is no unambiguous relation between the observed yields and the calculations.

2.5. *β,β,β*-Trinitroporphyrins

There are four articles that mention β,β,β-trinitroporphyrin preparation; however, not all four possible isomers are described (**Scheme 2**), and their estimation may be ambiguous.[9,40,41,48]

In 1998, Dahal et al. observed the formation of only three trinitro-Cu-TPP isomers using an increased amount of fuming nitric acid.[40,41] The isomers were characterized using mass spectrometry (MS) and ^{1}H NMR spectroscopy as 2,13,17-, 2,8,12-, and 2,7,13-trinitro-Cu-TPP with an overall yield of 15%. The assignment was unambiguous for 2,8,12-trinitro-Cu-TPP as it was proven by SCXRD;[40] however, in our opinion, the assignment of the next two isomers on the basis of ^{1}H NMR spectra is insufficient and may be incorrect.

A review article on nitration of porphyrin systems[9] extracts the results of Ostrysz's Thesis[49,50] addressed the formation of trinitro isomers from Zn-TPP through fuming nitric acid, however, from the complex mixture only 2,13,17-trinitro-Zn-TPP was isolated (25% yield) and characterized, however, details of the assignment are not given. In a parallel study, the authors employed the nitration of Cu-TPP under the same conditions to obtain 2,13,17- (17% yield), 2,8,12- (2% yield), and 2,7,13-trinitro-Cu-TPP (9% yield). Unfortunately, no elaboration regarding the assignment was given.

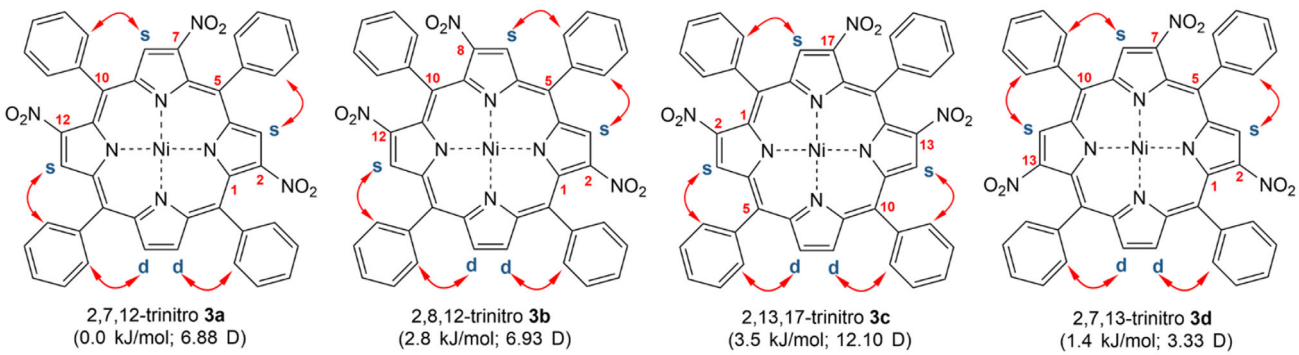
2.6. Preparation of Trinitro-Ni-TPP Isomers 3a–d

As our main goal was 2,7,12,17-tetranitroporphyrin, we started with the nitration of the 2,7-dinitro **2e** isomer, which is one of the possible precursors. The hydrate of copper(II) nitrate in a mixture of acetic anhydride and glacial acetic acid at room temperature was used, and the reaction course was followed by TLC. The use of copper(II) instead of nickel(II) nitrate usually produces a cleaner product. The starting isomer **2e** was consumed in five days, while only two greenish spots appeared, followed by a black insoluble material. The compounds were isolated by a repeated column chromatography and identified as 2,7,12-trinitro **3a** (13%) and 2,13,17-trinitro **3c** (11%). Surprisingly, no traces of the third possible 2,7,13-trinitro **3d** isomer were observed; the 2,8,12-trinitro **3b** isomer could not be formed from **2e**.

In the next approach, we started from Ni-TPP, thus, all four possible trinitro isomers **3a**–**d** (Scheme 2) could be formed. The treatment of Ni-TPP with 30% nitric acid was followed by TLC. After 5 min, the reaction mixture contained mostly nitro-Ni-TPP **1** followed by a trace of TPP as a consequence of demetallation. After 2 h, a small amount of dinitro-Ni-TPP **2** isomers appeared. Nitro-Ni-TPP **1** disappeared completely after overnight stirring, when dinitro-Ni-TPP isomers were followed by a significant amount of TPP. After 2 days, all dinitro-Ni-TPP **2** isomers were converted to a mixture of trinitro-Ni-TPP **3** isomers. The products were isolated by column chromatography, where TPP (the pink band) was easily isolated in the 16% yield from the trinitro isomers (the greenish bands). By a repeating column chromatography 2,7,12-trinitro **3a** (5% yield, $R_f = 0.25$), 2,8,12-trinitro **3b** (6% yield, $R_f = 0.18$) and 2,13,17-trinitro **3c** (5% yield, $R_f = 0.15$) were isolated, however, as in the previous experiments, no traces of 2,7,13-trinitro **3d** were observed.

2.7. Identification of Trinitro-Ni-TPP Isomers 3a–d

For the unambiguous identification of the trinitro **3** isomers, we recorded 2D NMR spectra such as DQF-COSY, TOCSY, NOESY and/or ROESY (if necessary also their 1D versions), HSQC, HMBC and LR HSQMBC, and by a careful analysis, we assigned the signals of all ^{1}H and ^{13}C nuclei of each isolated isomer. As it is obvious from the molecular structure, the ^{1}H NMR spectrum of each possible isomer should exhibit three singlets and two doublets for the pyrrole cores; hence, for the unambiguous assignment, the correlation experiments must be applied. In analogy to the identification of dinitroisomers (vide supra), HMBC correlations to the *meso*-carbon atoms can be used; however, uncertainty arises when



Scheme 2. The possible trinitroisomers of Ni-TPP; with the determinative NOE correlations; the calculated energy difference against the lowest for **3a** is given in the parentheses; the red numbers are the nomenclature numbering of the porphyrin core; the blue letters denote the multiplicity of the signal in ^{1}H NMR spectra (s for singlet, d for doublet).

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the expected $^{3}J_{CH}$ are small but $^{4}J_{CH}$ are significant. As a more reliable approach, we used the NOE between ^{1}H pyrrole signals and the signals of the *ortho* hydrogen atoms of the freely rotating phenyl groups, which is straightforward and unique for each isomer (Scheme 2). For example, no *ortho* hydrogen atom of **3a** has NOE both to the singlet and the doublet; however, two such hydrogen atoms are observed in the case of **3c**, etc.

It is worth comparing our results on Ni-TPP with the ones described on Cu-TPP.[9,40,41,49,50] In both cases, only three out of four possible trinitroisomers were formed, and the second, less retained isomer on a silica column has the 2,8, and 12 configuration (proven by SCXRD).[40] If we accept that the complexed metal ion has no massive effect on either nitration selectivity or separation order on a silica column, then it has to be considered that the previously published 2,13,17-trinitro-Cu-TPP should be 2,7,12-trinitro-Cu-TPP, and 2,7,13-trinitro-Cu-TPP should be 2,13,17-trinitro-Cu-TPP.

2.8. Formation Selectivity of Trinitro-Ni-TPP Isomers 3a–d

In both experiments, we observed no preferential formation of an isomer, however, In contrast, the 2,7,13-trinitro **3 d** isomer was not formed at all. We considered that four possible intermediates could be formed upon nitration of 2,7-dinitroisomer **2e**. Nitration at carbon C12 (4.6 kJ mol^{-1}, Fukui index 1.57) and C17 (1.0 kJ mol^{-1}, Fukui index 1.51) would produce 2,7,12-trinitro **3a**, nitration of the carbon C18 would yield 2,13,17-trinitro **3c** (0.0 kJ mol^{-1}, Fukui index 1.57), and nitration of the carbon C13 would give 2,7,13-trinitro **3d** (3.5 kJ mol^{-1}, Fukui index 1.48). These values align with the experimental yields, the lowest energy and the highest Fukui index are for **3c**, the formation of **3a** through nitration of the carbon C17 would be expected, and no formation of **3d** could be the consequence of the highest intermediate energy and the lowest Fukui index. However, isomer **3d** is not formed even if Ni-TPP is the starting substance; thus, all possible dinitro isomers are presented (vide supra). That would mean that even **2c** and **2d** cannot be converted to isomer **3d**. Our observation is probably in accord with nitration of Cu-TPP, which also gave only three trinitro isomers.[40,41,49]

2.9. β,β,β,β-Tetranitroporphyrins

2.9.1. Preparation of Tetranitro-TPP 4 via Nitration

First, we attempted to prepare the desired 2,7,12,17-tetranitroporphyrin **4a** via nitration of 2,7,12-trinitroporphyrin **3a**. Unfortunately, using either $Cu(NO_3)_2{\cdot}3H_2O$ or $Ni(NO_3)_2{\cdot}6H_2O$ led to the slow degradation of **3a** (during days), while no tetranitro compound was detected by MS analysis. Next, we tried direct nitration of the starting Ni-TPP by 25% nitric acid at room temperature, monitoring the reaction progress via TLC. During three days, the sequential formation, consumption, and degradation of nitro, dinitro, and trinitro derivatives were observed, as well as a new spot of a highly polar compound, which was isolated in only 0.2% yield. MS analysis of the isolated solid indicated the presence of tetranitro-Ni-TPP; however, the ^{1}H NMR spectrum revealed that it is a mixture of several substances with a modification also on the phenyl groups. We concluded that three nitro groups on the porphyrin core deactivated it for the next nitration, thus nitration of the phenyl groups took place.

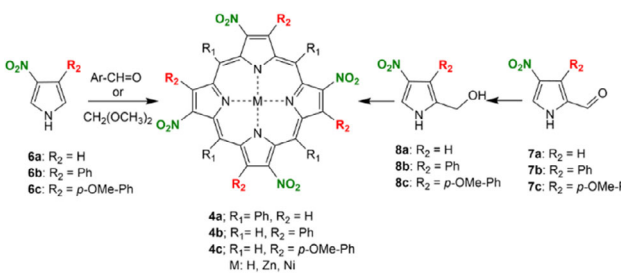
The negligible yield of a tetranitro-Ni-TPP isomer is in accordance with the observed decreasing net yield of the nitration; dinitro-Ni-TPP **2** (78%) and trinitro-Ni-TPP **3** (16% from TPP, 24% from **2e**) isomers. In addition, there is an obvious decrease in the approximate ratio of Fukui indexes for pyrrole and phenyl *para* position: it is 2.0 on Ni-TPP, about 1.3 on nitro-Ni-TPP **1**, 1.1 on dinitro-Ni-TPP **2e**, and 1.0 on trinitro-Ni-TPP **3a**, hence, nitration of a *para* phenyl position of **3a** could be expected. In contrast, calculations of intermediates as well as Fukui predict high selective formation of tetranitro **4a** (ΔE 0.0 kJ mol^{-1}) instead of nitration into *meta* (ΔE 69.3 kJ mol^{-1}) or *para* (ΔE 32.7 kJ mol^{-1}) position of the phenyl group in position 15. Nevertheless, based on our experimental results, we concluded that this approach is a dead end.

2.9.2. Preparation of Tetranitro-TPP 4 via Condensation

The successful preparation of β,β,β,β-tetranitroporphyrins was recently reported via condensation of appropriately substituted nitropyrroles (**Scheme 3**).[41,51] Albeit Masaret reported a high yield of tetranitro-TPP **4a** (72%) from the condensation of 3- nitropyrrole **6a** with benzaldehyde in DMF, catalyzed by TsOH,[51] we were unable to reproduce the preparation at all. Despite extensive variations in reaction conditions (acid amount, concentration, reaction time, and temperature), we observed only the formation of black insoluble material, with no traces of a tetranitro-TPP derivative (based on the MS analysis). Our observation aligns with Ono's work,[52] who described that condensation of nitropyrroles **6b**–**c** with aromatic aldehydes does not form the expected tetranitroporphyrins **4b**–**c**, due to low reactivity.

In contrast, Ono was successful in the condensation of nitropyrroles **6b**–**c** with dimethoxymethane, catalyzed via TsOH, where a mixture of four regioisomers was formed in 1% overall yield. To enhance yield and regioselectivity, the more reactive 2-hydroxymethylpyrroles **8b**–**c**, produced by reducing the 3-nitropyrroles **7b**–**c**, were used. Condensation of **8b**–**c** in THF, catalyzed by TsOH, yielded tetranitroporphyrins **4b** and **4c** in 5%–10%.[52]

Analogously, we tried the condensation of 2-hydroxymethyl-4-nitropyrrole **8a**, which we prepared by reducing of **7a**



Scheme 3. Synthetic routes attempt for the preparation of **β,β,β,β-**tetranitroporphyrin.

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(obtained via nitration of commercially available pyrrole-2-carboxaldehyde[53]). Unfortunately, despite many attempts and variations of the condensation reaction conditions (acid amount, concentration, reaction time, temperature, and solvents like DCM, THF, DMF), we detected no traces of tetranitroporphyrin **4a** (MS analysis).

3. Conclusion

Based on our research, we conclude that the preparation of β,β-dinitroporphyrins via direct nitration of metalloporphyrins is effective; however, its low selectivity and the demanding separation could be a serious complication. The analogous preparation of β,β,β-trinitroporphyrins results in significantly lower yields of all possible isomers, except for the 2,7,13-trinitro isomer. The identification of the possible isomers is not trivial and requires highly resolved 2D NOESY and HMBC NMR spectra recorded on high-field NMR machines.

The preparation of tetranitro porphyrins via common nitration is probably impossible, and the preparation via the condensation of nitropyrroles is uncertain. Thus, the preparation of β,β,β,β-tetranitroporphyrins remains challenging. As a possible approach to preparing porphyrin derivatives with a reactive moiety at each pyrrole ring, we suggest combining nitration and bromination steps, since bromine acts as a weak activating group for electrophilic attacks on aromatic systems.

We conclude that, although both the intermediate energy and Fukui indices correlate with the experimental results on reactivity and selectivity, such basic calculations alone are insufficient to predict the outcomes. More detailed modeling, including transition states, reaction pathways, and explicit solvent molecules, is needed.

4. Experimental Section

Preparation of β,β-Dinitro-Tetrakis(Phenyl)Nickel(II)Porphyrins 2

The substrate, TPP (1.01 g, 1.64 mmol), was dissolved in the mixture of DCM (1 L) and Ac_2O (67 mL). In a beaker, 0.52 g (1.79 mmol) of $Ni(NO_3)_2{\cdot}6H_2O$ was dissolved in 14 mL of AcOH, and the solution was poured into a dropping funnel to which 30 mL of DCM was then added and the mixture was gently shaken. The solution became clear and light green. The nitrate solution thus prepared was then slowly added to the reaction mixture at Room temperature. After the addition, the resulting mixture was left to stir overnight. The reaction mixture was washed with water (3×200 mL), brine (1×200 mL), and dried over Na_2SO_4. After filtration, it was evaporated to dryness to afford 0.95 g of the solid residue. The crude product was subjected to column chromatography (eluent: DCM/*n*-hexane-1:1 v/v) to give nitro-Ni-TPP **1** (97 mg, 8.2%, $R_f = 0.55$) and an impure mixture of dinitro-substituted compounds (991 mg). The dinitroisomers were separated by column chromatography on silica gel (DCM/*n*-hexane, 1:1 v/v, developed seven times), thus allowing isolation of: 2,3-dinitro-Ni-TPP **2a** (64 mg, 5.1%, $R_f = 0.47$); an inseparable mixture of dinitroisomers 2,12-dinitro-Ni-TPP **2b**, 2,13-dinitro-Ni-TPP **2c** and 2,8-dinitro-Ni-TPP **2 d** (358 mg, 28.7%, $R_f = 0.45$); 2,7-dinitro-Ni-TPP **2e** (261 mg, 20.9%, $R_f = 0.43$) and 2,18-dinitro-Ni-TPP **2f** (292 mg, 23.4%, $R_f = 0.41$).

Preparation of β,β,β-Trinitro-Tetraphenylporphyrins-Nickel(II) 3:

Method A: From 2,7-Dinitro- Tetraphenylporphyrins-Nickel(II) 2e

2,7-Dinitro-Ni-TPP **2e** (600 mg, 0.79 mmol) was dissolved in 200 mL DCM under argon atmosphere. Solution of $Cu(NO_3)_2.3H_2O$ (210 mg, 0.87 mmol) in Ac_2O (37 mL) and AcOH (9 mL) was added dropwise into the reaction mixture. The resulting mixture was stirred at room temperature for 5 days. The progress of the reaction was monitored by TLC (DCM/*n*-hexane 2:1 v/v). After the consumption of all starting materials, the reaction mixture was quenched by extraction with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude mixture was subjected to column chromatography using a mixture of DCM/*n*-hexane (1:1 to 3:2 v/v) as the eluent, thus allowing isolation of: 2,7,12-trinitro-Ni-TPP **3a** (80 mg, 13%, $R_f = 0.25$) and 2,13,17-trinitro-Ni-TPP **3c** (72 mg, 11%, $R_f = 0.15$).

Method B: From Ni-TPP

Metalation of porphyrin was performed by the known procedure based on our recent publication (see ESI).[34] Ni-TPP (3.28 g, 4.77 mmol) was dissolved in $CHCl_3$ (1.8 L) at room temperature under an argon atmosphere, and a solution of 30% HNO_3 (337 mL freshly prepared from 65% HNO_3) was added dropwise into the reaction. The process of reaction was monitored by TLC (DCM/*n*-hexane 2:1 v/v). After 3 days, all starting material was converted to trinitro-substituted isomers. The acidic layer was separated from the organic phase in a separatory funnel, then washed with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude mixture was subjected to column chromatography using a mixture of DCM/*n*-hexane (1:1 to 3:2 v/v) as the eluent thus allowing isolation of: 2,7,12-trinitro-Ni-TPP **3a** (167 mg, 5% $R_f = 0.25$), 2,8,12-trinitro-Ni-TPP **3b** (190 mg, 6%, $R_f = 0.18$) and 2,13,17-trinitro-Ni-TPP **3c** (165 mg, 5%, $R_f = 0.15$).

Quantum Chemical Calculations

To ensure the completeness of this study, high-level quantum chemical calculations were performed. Using the density functional theory M06/Def2SVPP hybrid functional with dispersion corrections and incorporating solvent effects, we characterized the structures of various porphyrin derivatives, ranging from mononitro- to tetranitro-Ni-TPP. In order to investigate the reactive center of porphyrins' nitration, the Fukui functions were calculated as well.[46] Since the focus of this study is on the preparation of the selected species, quantum chemical calculations were also carried out for protonated intermediates. All quantum chemical calculations were performed using the Gaussian16 program package (G16).[54] A detailed description of the calculation process can be found in the ESI.

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Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

Ameneh Tatar: conceptualization (equal); investigation (lead); writing—original draft (equal); writing—review & editing (lead). **Martin Havlík**: writing—review & editing (equal). **Tereza Navrátilová**: writing—review & editing (equal). **Tereza Uhlíková**: formal analysis (equal); writing—original draft (equal). **Michaela Drozdová**: writing—review & editing (equal). **Karolína Hricková**: writing—review & editing (equal). **Jan Hajduch**: writing—review & editing (equal).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: β-nitrometalloporphyrin · condensation · nitration · nitropyrrole · porphyrins

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