On Selective Derivatization of meso-Tetraarylporphyrins (A Microreview)

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Abstract

The studies on selective derivatization in one or two aromatic rings of meso-tetraarylporphyrin systems (and their zinc and copper complexes) using (a) selective nitrations, (b) Vicarious Nucleophilic Substitution of Hydrogen (VNS), and (e) alkylation of the above intermediates with alkyl halides, are reported.

The stepwise selective nitrations of meso-aryl substituted porphyrins with fuming yellow nitric acid ($d = 1.53$) at the temperature $0^\circ C$ to $20^\circ C$ results in the formation of 5-(4-nitroaryl)-10,15,20-triarylporphyrins, 5,10-bis(4-nitroaryl)-15,20-diarylporphyrins or trinitro- and tetrinitro- derivatives, respectively, in good or reasonable yield.

The above intermediates, after simple transformation to their copper or zinc complexes, react with carbanions bearing leaving groups at the carbanionic center, according to VNS scheme. This reaction can be also realized at low temperature ($-30^\circ C$ to $-40^\circ C$) without complexation of the parent nitroporphyrins. Alkylation of the products obtained with alkyl halides or alkyl halides bearing multiple bonds in the carbon chain led to useful compounds for further functionalization.

The reactions described above give new opportunities for the peripheral functionalization of porphyrins.

1. Introduction – Porphyrins and Photodynamic Theraphy

Many porphyrin derivatives are widely used as photosensitizers in Photodynamic Theraphy (PDT) [1,2]. PDT is a treatment modality using photosensitising drugs and light to kill neoplastic cells. This simple technique was evaluated in multiple clinical trials with promising results [3-5]. The clinical use of PDT requires the presence of a photosensitising agent, oxygen, and light of a specific wavelength, which matches the absorption characteristic of the photosensitizer. Then, the photosensitizer is activated by the appropriate wavelength of light, and the energy is transferred through inter system crossing (ISC) to molecular oxygen. This forms a
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toxic, short-lived species (singlet oxygen, $^1\text{O}_2$), which is thought to mediate cellular
death.

In oncology, the development of PDT has great potential to become an integral
part of cancer treatment in the future. This is relatively new technique, and is based
on the administration of tumor-localizing photosensitizers and their subsequent
activation by visible light to destroy cancer cells. However, their mode of action is
still not clear. It has been known that human serum albumin (HSA) binding affinity
to various photosensitizers plays an important role in their biodistribution within the
tumor stroma [6,7], and the distribution of porphyrins among serum proteins is
dependent upon their chemical structure [8]. Unsymmetrical, functionalized
porphyrins have also been covalently incorporated into polymer backbones [9] and
are known to serve as useful synthetic precursors to monoxygenase and allosteric
enzyme model systems [10,11].

Of particular interest is the preparation of newer photosensitizers, which would
allow greater depth of tissue penetration. In spite of numerous studies in this field,
new methods for synthesis and derivatization of hydrophilic, lipophilic and
amphiphilic porphyrins, especially unsymmetrical ones, are continuously sought. In
light of this knowledge, the selective derivatization of easily available TPP (and
derivatives), is of significant importance due to their products’ potential use in the
field of Photodynamic Therapy.

2. Derivatization of Tetraarylporphyrins

2.1. Nitration

The selective nitration of tetraarylporphyrins can be a key step in the reaction
sequence of the transformation of the hydrophobic moieties into the lipophilic
compounds. The latter, as such, being insoluble in the physiological milieu, may be
considered as potential PDT agents. The nitro group, lending the possibility for
further transformations [12-18], is one of the most versatile substituents for this
purpose.

Direct nitration of tetraarylporphyrins and their metal complexes usually occurs
in the $\beta$-positions in pyrrole units [19-23]. In 1989 Kruper et al. [24] described
the selective mono-nitration in para-position of one phenyl ring of TPP. Similar results
were obtained by other groups [25-28].

Scheme 1

![Scheme 1](image)

On the other hand, the direct synthesis of porphyrins, substituted with
electrophilic aryl rings in positions meso-, by the Rothemund synthesis [29] (and its cross-condensation modifications [30]), from the corresponding aldehyde(s) and pyrrole, is an extremely difficult task (yields < 3%) [31,32]. It is improbable that the synthesis of porphyrins, substituted by the nitro groups in two meso-aryl rings, can be effectively realized by this way.

Krupor et al. [24] investigated the possibility of the electrophilic introduction of the next nitro group to another phenyl (aryl) ring. However, this was practically limited to one case of electron-enriched meta-tolyl substituent only, with the use of inconvenient, expensive and dangerous red fuming nitric acid (containing 12-24% of N₂O₄). Moreover, they unfortunately obtained in this reaction a mixture of two different dinitro-compounds: 5,10-bis(3-methyl-4-nitrophenyl)-15,20-bis (3-methylphenyl) porphyrin and 5,15-bis(3-methyl-4-nitrophenyl)-10,20-bis (3-methylphenyl) porphyrin.

Later, it was found that the selective nitration of meso-tetraarylporphyrins in two neighbouring aromatic rings could be realized with the use of fuming yellow nitric acid (d = 1.53) when the temperature is manipulated [33]. Hence, well-known and readily available TPP [34,35] (and other tetraarylporphyrins), with a variety of aromatic ring substituents, each containing different kind of electron-drawing properties (e.g. hydrogen, methyl, methoxy, and chlorine), are candidates for the following reaction: when nitrated with HNO₃ at 0°C to r.t., selective substitution occurs in two neighbouring aromatic rings of meso-tetraarylporphyrins to give the desired products 4 with satisfactory yields (30-83%). The following diagram demonstrates the general character of this process (Scheme 2).

**Scheme 2**

\[
\begin{align*}
\text{Ar} = \text{Ph (a); } m-\text{Tol (b); } m-\text{Cl-}C₆H₄ (c); m-\text{OMe-}C₆H₄ (d) \\
\end{align*}
\]

In some cases [for TPP and meso-tetrakis(3-chlorophenyl)porphyrin], small amounts of mono-nitration products, of type 2, were observed (5-20%) [33b]. Prolonging the reaction time usually allows the exhaustive conversion of the mononitro- and dinitro-compounds, 2 and 4, into the higher nitro-substituted products with moderate yields [24,27].

In the case of the electron-withdrawing substituent, -Cl, the nitration proved somewhat troublesome, and formation of all of the four possible products was
observed (mono-, di-, tri-, and tetra-nitro; e.g. 5 - 8, Fig. 1). Moderate amounts of tri-nitratated and tetra-nitratated derivatives of this type were also found for meso-tetrakis(3-methoxyphenyl)porphyrin and meso-tetrakis(2-methoxyphenyl)porphyrin [33,36].

Figure 1

Taking into account the wide range of synthetic possibilities offered by conversion of the nitro group (reduction to nitroso- and amino- groups, further functionalization via diazotisation, substitution of hydrogen in position ortho- [37], many types of cyclizations [14-18], etc.) the presented method probably can receive much attention in the area of porphyrin skeleton modification.

Example 1: Nitration of meso-Tetraphenylporphyrin

TPP (1a; 50 mg, 0.08 mmole) was dissolved in a dry CHCl₃ (15 mL) and the solution was stirred under argon and cooled to ca 2°C. To this mixture nitric acid (314 mg, 0.2 mL, d = 1.53) was added via syringe. After 2 hours, the next portion of HNO₃ (0.2 mL) was added. The reaction was left for 1 h, and the mixture was allowed to warm to room temperature. Then, the next portion of HNO₃ (0.2 mL) was added and it was left for 20 h (overnight) at room temperature. The reaction mixture was washed with water (5 x 20 mL) and dried with MgSO₄/Na₂CO₃.

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residue was chromatographed (silica gel 200-300 mesh; Merck AG) using n-hexane/CHCl₃ mixture as eluent (from 1:1 to 1:4) to give: 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (2) [24] – 3 mg (6%) and 5,10-bis(4-nitrophenyl)-15,20-diphenylporphyrin (4a) – 24 mg (42%).

(4a): – M.p. >300°C. – ¹H NMR (CDCl₃, 200 MHz; Varian GEMINI-200): 8.92 (d, J = 4.9 Hz, 2 H, H⁻⁻pyrrole), 8.89 (s, 2 H, H⁻pyrrole), 8.79 (s, 2 H, H⁻pyrrole), 8.75 (d, J = 4.9 Hz, 2 H, H⁻pyrrole), 8.62 & 8.38 (AA'XX', 8 H, H-Ar(NO₂)), 8.26–8.18 (m, 4 H, H-Ar), 7.84–7.72 (m, 6 H, H-Ar), -2.77 (s, 2 H, 2 x NH). – UV-VIS (CHCl₃; Perkin Elmer UV spectrometer Lambda 20), λmax (λg): 646 (3.60), 591 (3.82), 553 (3.99), 517 (4.30), 420.5 nm (5.48, Soret). – MS (EI; AMD 604 Intectra GmbH), m/z (% rel. int.): 707 (3), 706 (8), 705 (37) & 704 (72) [isotopic M⁺], 675 (5), 674 (12), 659 (7), 658 (7), 644 (8), 612 (5), 536 (4), 535 (4), 505 (2), 429 (4), 352 (6, doubly charged ion M⁺⁺), 281 (16), 207 (45), 77 (50), 57 (31), 55 (33), 44 (100); HR-MS (ESI) calcd. for C₄₄H₃₂N₄O₄ (M+H) – 705.2250, found – 705.2220.

2.2. Derivatization via Substitution of Hydrogen in Nitro-metalloporphyrins

An excellent tool for the selective derivatization of nitroaromatic compounds is the reaction of Vicarious Nucleophilic Substitution of Hydrogen in Nitro (VNS) [37]. Among other nitroaromatics, porphyrins should also enter this process. The VNS reaction involves addition of a carbanion, bearing a leaving group (X = Cl, Br, OPh, SP, etc.) at the carbanionic center, to a nitroarene (or other electrophilic aromatic or heteroaromatic compound) followed by base induced β-elimination of HX, and protonation as a final step. This leads to the substitution of hydrogen product (Scheme 3).
Scheme 3

As model compounds to investigate the possibility of VNS in porphyrin systems easily available meso-tetraphenylporphyrin (TPP, 1) [34,35] and its derivatives (2, 14-16) were selected (Fig. 2). However, it is well known that the VNS reaction proceeds very smoothly and with high yield in electrophilic aromatic compounds where free OH or NH-acidic groups are "blocked" (e.g. with Me, CH₂Ph, THP, etc. [38,39]). Due to this reason, compounds 1 and 2 could not react with carbanion of chloromethyl para-tolyl sulphone ClCH₂SO₂Tol (the standard nucleophile for this reaction), thus supporting this hypothesis.

Figure 2

Afterwards, it was found that the meso-tetraphenylporphyrin heterocyclic system alone (the compound without any additional activating substituents, e.g. NO₂) is not active enough to enter the above reaction. This was confirmed by the use of the TPP derivative 15 in which the free NH-positions were protected with methyl groups. As a result of the reaction of 15 with the carbanion of ClCH₂SO₂Tol, the formation of the expected VNS product was detected in the post-reaction mixture by ¹H NMR, in small amounts only.
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The N,N,N-trialkyl porphyrinium salt 16 [40], being of higher electrophilicity, should react with nucleophiles smoothly. In this case, the addition takes place probably at position α- of pyrrole ring, and due to lack of hydrogen in this position the further VNS reaction was not observed. Finally, the degradation (ring opening) of the macrocyclic moiety, under the reaction conditions, occurred, and no defined products were isolated [41]. Hence, in all investigated instances of the compounds 1, 2, 14 - 16, the VNS reaction was unsuccessful.

On the other hand, transformation of the two NH-centers in the macrocyclic ring into the metal complex, where the central metal cation (copper, zinc) is playing the role of a very convenient protective group for this reaction, allows the substitution of hydrogen in 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin derivatives with good yield [28,41].

The use of Cu-complex, due to the paramagnetic effect of the copper cation involved, caused difficulty in following the reaction sequence by NMR technique, and full characterization could be finally given for the demetallated products. Most of the examples demonstrating the possibility of VNS reaction were done with the use of a zinc complex (Scheme 4) – very easy obtainable from the corresponding 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (2) with almost quantitative yield [41,42].

Scheme 4

\[
\begin{align*}
\text{NO}_2 & + \text{Ph} \rightarrow \text{Ph} \\
\text{Cu} \quad \text{Zn} & \quad \text{M} = \text{Cu} \quad \text{M} = \text{Zn} \\
\text{Ph} \quad \text{Ph} & \quad \text{Ph} \\
\text{Cl}, \text{OC}_2 \text{H}_4 \text{Cl} & \quad \text{SO}_2 \text{Ph}, \text{F} \\
\text{SO}_2 \text{Ph}, \text{CN}, \text{SPh}, \text{SO}_2 \text{Ph}, \text{SO}_2 \text{NM} & \quad \text{SO}_2 \text{Bu} \\
\text{H}, \text{Me}, \text{Ph} & \quad \text{CF}_3 \text{CO}_2 \text{H} \\
\text{H}_2 \text{SO}_4 & \quad \text{H}_2 \text{O} \\
\text{reflux} & \quad \text{reflux} \quad \text{reflux} \\
\text{ca 10 h, 92%} & \quad \text{ca 4 h, quantitatively} \quad \text{ca 4 h, quantitatively} \\
\text{[41]} & \quad \text{[41]} & \quad \text{[41]}
\end{align*}
\]

Thus, nitro-porphyrin complexes (17,18) react in the presence of i-BuOK with carbanions, bearing leaving groups at the carbanionic center (10°), in DMSO, DMF or in liquid ammonia, giving in most cases, good yields of the desired products (Scheme 4). The substitution takes place selectively in the phenyl ring in the ortho-position to NO₂. The use of heterogeneous system, namely powdered NaOH in DMSO at room temperature (X = Cl, Y = SO₂Tol, R = H, M = Zn), also gave a
satisfactory yield of the corresponding para-toluenesulphonylmethyl derivative (20, 71%). In the case of rather poor leaving groups, such as X = OAr or F [44], the conversion in the NaOH/DMSO system was moderate or low (5-51%). For the carbamion bearing poor leaving group X = STol (Scheme 5), a similar yield of the desired product 22 was obtained (29%) (this was only observed in the t-BuOK / liquid ammonia reaction system).

Scheme 5

By this way, a series of new TPP derivatives, substituted with α-functionalized alkyl groups, e.g. arylsulphonylmethyl-, cyanomethyl-, N,N-dimethyl-sulphonamide, etc., was synthesized. Some of the products give opportunities for further transformations and can be easily converted into other derivatives, e.g., the 5-(3-cyanomethyl-4-nitrophenyl)-derivative to carboxylic acid and its esters.

Reactions with tertiary carbonanions were unsuccessful due to steric hindrances. Bulky carbonanions of low nucleophilicity, e.g. α-phenyl-(chloromethyl)phenyl sulphone (X = Cl, Y = SO_2Ph, R = Ph), did not give any product. Better results were obtained for α-chloroethyl para-tolyl sulphone (10: X = Cl, Y = SO_2Tol, R = Me), under the conditions described earlier in the literature for tertiary carbonanions (t-BuOK/DMF, 40°C [45]). The desired product, in this case, was isolated in 50% yield [28].

The VNS in [5,10-bis(4-nitrophenyl)-15,20-diphenylporphyrinato]zinc(II) allows the introduction of two α-functionalized substituents in two different phenyl rings (Fig. 3). However, the zinc complex of the product (23a) is relatively unstable; hence, in the applied reaction conditions, it underwent partial decomposition to 23b. This was investigated by UV-VIS and MS method.

Figure 3
Example 2: Vicarious Nucleophilic Substitution - \{[2-Nitro-3-(10,15,20-
triphenylporphyrinato-5-yl)-phenyl]acetoniirile\}zinc(II) (22)

\[
\text{t-BuOK/DMSO system:} \quad \text{A solution of [5-(4-nitropheny1)-10,15,20-
triphenylporphyrinato]zinc(II) (18; 108 mg, 0.15 mmol) and a para-
chlorophenoxyacetoniirile (50 mg, 0.30 mmol) in DMSO (1.5 mL) was added}
dropwise via syringe to a stirred solution of t-BuOK (112 mg, 1.0 mmol) in
anhydrous DMSO (3.5 mL, under argon) at room temp. during ca 10 min. After
additional 20 min of stirring the mixture was poured into 3% HCl with ice (50 mL).
The precipitate was filtered, washed with water, and then dissolved in CHCl\textsubscript{3}. After
drying with anhydrous Na\textsubscript{2}SO\textsubscript{4} and evaporation of the solvent the product was
isolated by column chromatography (silica gel 200-300 mesh, Merck AG; eluent:
CHCl\textsubscript{3}); yield \(\sim 75\) mg, 66%.

- M.p. >300°C. \(\text{\textsuperscript{1}H\ NMR (CDCl\textsubscript{3}, 200 MHz; Varian GEMINI-200):} \text{9.03 (d, } J = \text{4.7 Hz, 2H, H}\textsubscript{3}-\text{pyrrole), 8.99 (s, 4H, H}\textsubscript{4}-\text{pyrrole), 8.83 (d, } J = \text{4.7 Hz, 2H, H}\textsubscript{3}-\text{pyrrole), 8.60 (d, } J = \text{8.8 Hz, 1H, H-Ar(NO}\textsubscript{2}), 8.58 (s, 1H, H-Ar(NO}\textsubscript{2}), 8.43 (dd, } J = \text{8.8,1.4 Hz, 1H, H-Ar(NO}\textsubscript{2}), 8.29-8.21 (m, 6H, H-Ph), 7.83-7.74 (m, 9H, H-Ph),
4.50 (s, 2H, CH\textsubscript{2}CN). \text{\textsuperscript{2}UV-VIS (CH\textsubscript{2}Cl\textsubscript{2}; Perkin Elmer UV spectrometer Lambda 20), } \lambda_{\text{max}} \text{(lgs): 591 (3.77), 549 (4.23), 5.12 (3.72), 420 (5.41, Soret), 351 (4.03), 302 nm (4.14). \text{\textsuperscript{3}MS (EI; Shimadzu GC MS-QD 5050A), } m/z \text{(rel. int.): 764 (42), 762 (70), 760 (100) [isotopic M\textsuperscript{+}], 719 (47), 636 (12), 380 (7), 299 (12), 149 (10), 91 (10); HR-MS calcd. for C}_{48}H_{32}N_{4}O_{7}Zn_{1} - 760.1565, \text{found - 760.1566.}}

2.3. Nucleophilic Substitution of Hydrogen in Nitro-substituted meso-Tetraarylpor-
phyrins – Unprotected at NH-Centers in the Core Ring

Porphyrins behave as very weak acids with two NH groups capable of losing
protons. Alkali metal alkoxides allow spectroscopic observation even of the di-N-
anion in these systems. Both pK\textsubscript{a} values for these compounds have been estimated to
be of the order of ca 16 [46]. Hence, under the strongly basic conditions of the VNS
reaction (t-BuOK/DMSO, r.t. [28,41]), the porphyrin macrocycle should exist in the
$N$-anionic form (25). On the other hand, it is well-known that the VNS substitution takes place in the electron-impoverished ortho- position to the NO$_2$ group in the nitroaryl moiety. However, the electronic nature of the nitrophenyl ring can be greatly affected by conjugation with a neighbouring negatively charged porphyrin core ring.

Usually, the [18π]-electron aromatic porphyrin system and meso-substituted aryl rings remain in mutually orthogonal planes, thus impeding the conjugation. Nevertheless, the lack of success when attempting the VNS reaction in unprotected 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (2) [28] might be explained simply by the possibility of conjugation due to the free-rotation around the meso- C-C bond. This should result in coplanarity of these rings. In consequences, the negative charge can be delocalized onto the six-membered ring, as well as the NO$_2$ group (resonance structure 26), thus increasing the electron density therein and deactivating the ring toward carbanion addition.

**Figure 4**

At low temperature, the above discussed free-rotation should be suppressed, and all four meso-aryl rings should still remain in vertical planes to the central core ring, thus limiting the conjugation. This gives an opportunity for the VNS reaction. The resonance structure 25 may predominate; hence, the nitroaryl moiety can be regarded as an isolated system, to allow the nucleophilic addition.

This could indeed be the case, as in $t$-BuOK/THF at -30°C to -40°C or $t$-BuOK/DMF at 0°C, the unprotected nitroporphyrins (2, 4a) react according to the VNS scheme to give the desired products in good yield (51-89%) [47]. By this route, the introduction of arylsulphonyl-methyl, $N,N$-dimethyl sulphonamidomethyl, and cyanomethyl substituents was realized. For applications involving total porphyrin derivatives synthesis, this procedure allows avoidance of two (complexation/decomplexation) steps.
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Scheme 6

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{NH} & \quad \text{NH} \\
\text{NO}_2 & \quad \text{H} \\
Y & \quad \text{CH} \\
X & \quad \text{H} \\
Z & \quad \text{Y} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\[Y = \text{SO}_2\text{Tol}, \text{SO}_2\text{Ph}, \text{CN}, \text{SO}_2\text{NMMe}_2 \]
\[X = \text{Cl, Br, O-C}_6\text{H}_4\text{Cl} \]

2: \( Z = \text{H} \)
4a: \( Z = \text{NO}_2 \)

\[ \Sigma (27\text{a-f}) = 61-86\% \]

In the reactions of 5,10-bis(4-nitrophenyl)-15,20-diphenylporphyrin (4a, \( Z = \text{NO}_2 \)) the substitution takes place in one or in two meso-nitrophenyl rings to give a mixture of products with reasonable or moderate yields (27+28; ca 30-57%). However, the mono-substituted products predominate.

The control of this process by the reaction conditions is probably general in nature, and can be applied for other similar nucleophilic reactions in porphyrin systems.

Example 3: \( N,N'\text{-Dimethyl-C-[2-nitro-5-(10,15,20-triphenylporphyrin-5-yl)phenyl]-methanesulphonamide} (27e) \)

A solution of 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (2: 132 mg, 0.20 mmol) and \( N,N'\text{-dimethyl (chloromethane)sulphonamide (ClCH}_2\text{SO}_2\text{NMMe}_2) (47 mg, 0.30 mmol) in THF (1.5 mL) was added dropwise via syringe to a stirred solution of \( \text{t-BuOK} (112 mg, 1.0 mmol) in anhydrous THF (4 mL, under argon) at -30^\circ\text{C during ca 10 min. After additional 40 min of stirring at this temperature the mixture was poured into a 3% HCl with ice (50 mL). The precipitate was filtered, washed with water, and then dissolved in CHCl}_3. After drying with anhydrous Na\text{SO}_4 and evaporation of the solvent, the porphyrin 27e was isolated by column chromatography (silica gel 200-300 mesh, Merck AG; eluent: CHCl}_3); yield -- 139 mg (89%).
27c

- M.p. >300°C. - $^1$H NMR (CDCl$_3$, 200 MHz; Varian GEMINI-200): 8.93 (d, $J$ = 4.9 Hz, 2H, 1st-pyrrole), 8.86 (s, 4H, H$_6$-pyrrole), 8.83 (d, $J$ = 4.9 Hz, 2H, H$_8$-pyrrole), 8.51 (d, $J$ = 1.4 Hz, 1H, H-Ar(NO$_2$)), 8.46 (part of AB, $J$ = 8.4 Hz, 1H, H-Ar(NO$_2$)), 8.38 (part of AB coupled with another proton, $J$ = 8.4,1.4 Hz, 1H, H-Ar(NO$_2$)), 8.26-8.17 (m, 6H, H-Phe), 7.83-7.70 (m, 9H, H-Phe), 5.03 (s, 2H, CH$_2$), 2.95 (s, 6H, N(CH$_3$)$_2$), -2.80 (s, 2H, 2 x NH). - UV-VIS (CHCl$_3$; Beckman DU-68), $\lambda_{max}$ (lgE): 653 (3.70), 591 (3.83), 553 (4.02), 516 (4.33), 420 nm (5.64, Soret). - MS (El; AMD 604 Intectra GmbH), m/z (% rel. int.): 782 (7), 781 (18), and 780 (34) [isotopic M$^+$.], 721 (14), 676 (3), 675 (3), 656 (2), 655 (3), 628 (4), 627 (3), 626 (3), 369 (8), 295 (14), 281 (9), 221 (24), 121 (100), 91 (29), 73 (26), 57 (35), 55 (28), 44 (40), 40 (48); HR-MS calcd. for C$_{47}$H$_{38}$N$_6$O$_4$S$_1$ - 780.2519, found - 780.2526.

2.4. Alkylation of the TPP Derivatives ortho-Disubstituted in One Aryl Ring

Thanks to the possibility of the direct introduction of cyanomethyl- or arylsulphonylmethyl- group into the para-nitrophenyl substituent of 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (2), this process has become an attractive method for the synthesis of meso-tetraarylporphyrin derivatives possessing a high degree of complexity in one phenyl ring. Among others, the value of this approach is connected with the possibility of alkylating these intermediates [48], as they are bearing methylene hydrogens of high acidity and could effectively be deprotonated under basic conditions. When treated with alkyl halides the carbamions formed undergo transformations to precursors of many heterocyclic compounds, tethered through a carbon atom at meso-position of porphyrin skeleton.

These types of alkylation products, after single or multistep transformations, or direct cyclizations in various conditions, lead to other heterocyclic moieties [17,49-52]. The preparation of various intermediates in $\tau$-BuOK/DMF or CH$_2$CN system, with the use of alkyl halides and alkyl halides bearing double and triple bonds in the carbon chains, are exemplified in Scheme I.
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Scheme 7

The yields of the alkylated products varied from 20% to 83%. All of them present the possibility for synthesis of new porphyrins substituted in the meso-position with more complicated heterocyclic systems, e.g. indoles [17,38,49,52], quinolines (and their N-oxides) [38,49,50], and naphthyridines [51]. They might also serve as reactants for many other valuable processes, e.g. simple functionalization of multiple bonds, cycloaddition, metathesis [53], etc., leading to biologically active porphyrins, such as PDT agents [1-3].

Example 4: {5/-4-Nitro-3-[1-(toluene-4-sulphonyl)-hexyl]-phenyl-/10,15,20-
triphenylporphyrinato}zinc(II) (29ad)

In a round-bottom flask (10 mL), the solution of {5/-4-nitro-3-(toluene-4-
sulphonyl)methyl)-phenyl]-10,15,20-triphenylporphyrinato}zinc(II) (20; 86 mg, 0.096 mmol) in DMF (2.5 mL) was cooled to 0°C. Then, t-BuOK (45 mg, 0.40 mmol) was added in a one portion and the mixture was stirred for 15 min under argon. To this mixture, the 1-iodopentane (79 mg, 0.40 mmol) in DMF (1 mL) was added at 0°C. The reaction was continued at this temp. for ca 3 h until completion (TLC monitoring; CHCl₃/n-hexane – 3:1). The mixture was poured onto water with
ice (40 mL), the product was extracted with CHCl₃ (3 x 10 mL), and the organic layer was washed with H₂O (2 x 20 mL). After drying over MgSO₄ and evaporation of the solvent the crude product was purified by column chromatography (silica gel 200-300 mesh, Merck AG) using CH₂Cl₂/n-hexane mixture (1:1) as eluent. Yield of pure deep-purple solid of \( \{5\text{-}4\text{-}nitro\text{-}3\text{-}[1\text{-}(toluene\text{-}4\text{-}sulphonyl)\text{-}hexyl]\text{-}phenyl\text{-}10\text{-}15\text{-}20\text{-}tri(phenyl)porphyrinato\} \text{zinc(II)} \) (29% d) - 77 mg (83%).

- M, p, >300°C. – IR (neat, cm⁻¹): Perkin Elmer 1600 FTIR spectrometer: 3103, 3055 & 3021 (CH₃stret); 2956, 2921 & 2850 (CH₂, CH₃); 1597; 1524 & 1340 (NO₂); 1320 & 1147 (SO₂). – ¹H NMR (CDCl₃, 200 MHz; Varian GEMINI-200): 9.11 (d, \( J = 4.8 \) Hz, 1H, H²-pyrrole), 9.02-8.95 (m, 3 lines, 6H, H³-pyrrole), 8.77 (d, \( J = 4.6 \) Hz, 1H, H⁴-pyrrole), 8.66 (d, \( J = 1.7 \) Hz, 1H, H-Ar(NO₂)), 8.30 (part of AB coupled with another proton, \( J = 8.3,1.7 \) Hz, 1H, H-Ar(NO₂)), 8.28-8.19 (m, 6H, H-Ph), 8.18 (part of AB, \( J = 8.3 \) Hz, 1H, H-Ar(NO₂)), 7.83-7.73 (m, 9H, H-Ph), 7.70 (apparent d, \( J = 8.2 \) Hz, 2H, H-Tol), 7.33 (apparent d, \( J = 8.2 \) Hz, 2H, H-Tol), 5.69 (dd, \( J = 10.8,4.2 \) Hz, 1H, CH(SO₂Tol)), 2.50-2.38 (m, 2H, CH₂), 2.41 (s, 3H, CH₃-Tol), 1.37-1.22 (m, 6H, 3 x CH₃). 0.85 (t, \( J = 6.9 \) Hz, 3H, CH₂). – UV-VIS (CHCl₃; Beckman DU-68), \( \lambda_{\text{max}} \) (λg): 596.5 (3.56), 556 (4.09), 518 (3.38), 423.5 (5.39, Soret), 356 (3.90), 333 nm (4.10). – LSIMS(+), AMD 604 Intectra GmbH; /m/z (rel. int.): 961 (2), 960 (3, M+H), 959 (3), 958 (3), 803 (2), 601 (2), 523 (2), 395 (7), 369 (3), 307 (12), 154 (100). – Elemental analysis calcd. for C₇₅H₇₅N₅S₅O₂Zn (961.46): C • 71.21, H • 4.72, N • 7.28. Found: C • 70.75, H • 5.26, N • 6.32.

3. Conclusions

The ability to access new types of porphyrin derivatives is of great importance due to biological activity of these systems. The studies on selective derivatization of meso-tetraarylporphyrins using (a) selective nitration, (b) Vicarious Nucleophilic Substitution of Hydrogen (VNS), and (c) alkylation of the above intermediates with alkyl halides, were described.

The tandem nitration / nucleophilic substitution of hydrogen methodology can be a new tool in this field. Taking into account a wide range of synthetic possibilities offered by the NO₂ group, these useful approaches might receive much attention in the area of porphyrins skeleton modification – especially in their peripheral functionalization.

It was also shown that the central metal cation in porphyrin complexes can play a role as a very labile and convenient protective group for the VNS process in every conditions, and it can be easily removed after the reaction, if needed. The VNS can be also realized (at low temperature) without complexation of the porphyrin skeleton. These approaches were exemplified by preparation of many new porphyrin derivatives. Their subsequent alkylation (especially with alkyl halides bearing multiple bonds in the carbon chains) leads to useful intermediates for further functionalization. Some of the compounds presented herein could reveal potential anti-cancer activity [54].
On Selective Derivatization of meso-Tetraarylporphyrins (A Microreview)

حوالاشتقاقات الانتقالية لـ ميزو- الپورفورین رباعی - اریل
(meso- Tetraarylporphyrin)

ستانیسلوف اوستروفیسکی

ملخص

لقد تم تقديم الدراسات الخاصة بالإشتقاقات الانتقالية لـ ميزو - الپورفورین رباعی اریل في
واحدة أو اثنين من الحلقات العضوية إضافة إلى بعض معقاداتها.

يتم الاشتقاق بواسطة ثلاثة طرق مختلفة لقد تم مناقشة هذه الطرق ومقارنتها وتقديمها.

References

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On Selective Derivatization of meso-Tetraarylporphyrins (A Microreview)


