# Synthesis, Characterization, and Electrochemical Studies of New $\pi$ -Extended Metalloporphyrins

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A doubly fused porphyrin has been synthesized by two successive cyclization reactions. The first *meso*-phenyl group was fused by an intramolecular Cadogan reaction leading to an enamine-functionalized porphyrin. After Vilsmeier–Haack formylation of the nickel enaminoporphyrin, an intramolecular Friedel–Crafts reaction followed by dehydration of the intermediate alcohol afforded the doubly fused aromatic nickel porphyrin, which could be demetalated. The free base

and the copper and palladium porphyrins show extremely high absorbances in the 700–800 nm range. The palladium complex was a good catalyst for the oxidation of cholesterol with singlet oxygen, which makes this chromophore a potential candidate for photodynamic therapy.

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#### Introduction

The synthesis of extended aromatics or  $\pi$ -conjugated molecules is a very active field of research.<sup>[1]</sup> Molecules of this type are expected to be used in materials science due to their unusual electronic properties. Among these aromatics, porphyrin tapes, described by Tsuda and Osuka, are the most spectacular achievement in this research area.<sup>[2]</sup>

In the particular case of porphyrins, extension of the aromatic core might also be useful for medical applications like photodynamic therapy, for which sensitizers that absorb preferentially in the 650–900 nm range are desired.<sup>[3]</sup> Several synthetic strategies might be envisaged. One of the most promising approaches is the fusion of the *meso*-aryl group to the aromatic core of the porphyrin. Compounds in which benzene, naphthalene, anthracene, pyrene, and azulene have been fused across the *meso* and  $\beta$  positions or with a porphyrinic pyrrole have been synthesized.<sup>[4,5]</sup> Various fused heterocycles (e.g., pyridine, imidazole, pyrrole) have also been described.<sup>[6]</sup> Herein the synthesis, characterization, and electrochemical study of a doubly fused (naphthalene and quinoline) extended porphyrin are reported.

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### **Results and Discussion**

Starting from the easily available nickel 2-nitro-*meso*tetraphenylporphyrin Ni-1, the green nickel porphyrin Ni-2 was obtained by reaction with triethyl phosphite.<sup>[7a]</sup> The Ni-2 porphyrin is functionalized with an enamine that connects the porphyrin aromatic core to a neighboring *meso*-phenyl group. Formylation of the enamine under Vilsmeier–Haack conditions led to the enamino aldehyde Ni-3. This nickel porphyrin is now fitted with an external chelating site, which allows the coordination of metal ions (see Scheme 1). This compound and various analogues have been used to build porphyrin dimers connected by divalent metal ions.<sup>[6a]</sup> Strong electronic coupling through the connecting metal ions was observed in these compounds, as in similar porphyrin oligomers published previously.<sup>[8]</sup>



Scheme 1. Synthesis of enamino aldehyde Ni-3.

It is also well known that under acidic conditions, the nickel 2-formylporphyrin Ni-4 leads to cyclized species like the ketone Ni-5 (see Scheme 2).<sup>[4a,4b]</sup>





Scheme 2. Cyclization of formylporphyrin Ni-4.

This prompted us to try to cyclize the enamino aldehyde Ni-3 under acidic conditions. Under the experimental conditions used to cyclize Ni-4 (room temperature, trifluoro-acetic acid), no reaction occurred. However, by using more drastic conditions (10 equiv. *p*-toluenesulfonic acid in refluxing chlorobenzene), complete conversion of the starting material took place after 1 h (Scheme 3).



Scheme 3. Cyclization of enamino aldehyde Ni-3.

However, instead of a ketone or methylene linkage between the β-pyrrolic position and the neighboring mesophenyl group (expected after dismutation of an intermediate alcohol), two major products were isolated and characterized after chromatography of the reaction mixture. The first compound to elute from the column proved to be Ni-2 (isolated in 28% yield), which was clearly the product of acid-catalyzed thermal decarbonylation of Ni-3. Decarbonylation of aromatic aldehydes (and especially of porphyrinic aldehydes) is a known reaction, but generally requires much more drastic conditions.<sup>[9]</sup> The second major product was the doubly fused Ni-6 (52% yield). This compound was obtained after dehydration of the intermediate alcohol. This pathway was highly favored in this cyclization reaction because the dehydration resulted in the aromatization of the fused pentacyclic entity (this cannot occur if only one fused *meso*-phenyl group is involved). To avoid decarbonylation, the experimental conditions were improved by decreasing the number of acid equivalents and/or lowering the reaction temperature. By using only 2 equiv. of *p*-toluenesulfonic acid in refluxing chlorobenzene (5 h were then required to obtain a 95% conversion) Ni-6 was isolated in 60% yield. This yield was further improved by lowering the reaction temperature (48 h in toluene at reflux in the presence of 2 equiv. of *p*-toluenesulfonic acid). Under these conditions, Ni-6 was obtained in a satisfactory 72% yield. Even under these relatively mild conditions, decarbonylation was still observed (Ni-2 was isolated in 8% yield). The doubly fused nature of Ni-6 could be easily deduced from the <sup>1</sup>H NMR and HRMS spectra ( $m/z = 693.1534 \, [M + H]^+$ ). In the case

of singly fused *meso*-tetraarylporphyrins, a set of four inequivalent coupled protons are generally observed in addition to the usual *meso*-phenyl signals. Sometimes, the neighboring pyrrole protons are also highly deshielded due to the steric hindrance of the cyclized phenyl. The <sup>1</sup>H NMR spectrum (300 MHz in CDCl<sub>3</sub> at 45 °C) of Ni-6 revealed two sets of four inequivalent and coupled phenyl protons in addition to one aromatic proton appearing as a broad singlet at low field ( $\delta = 8.98$  ppm, attributed to the isolated naphthyl proton). Three sets of doublets (two at low field and one at higher field) were observed for the six remaining pyrrolic protons. Ni-6 was demetalated by following the standard procedure for removing the nickel ion (sulfuric acid in trifluoroacetic acid, see Scheme 4).



Scheme 4. Demetalation of nickel porphyrin Ni-6.

The free base H<sub>2</sub>-**6** was characterized by the usual spectroscopic techniques. The <sup>1</sup>H NMR signals were satisfactorily assigned after a variable-temperature study (between 25 and 75 °C). The  $\beta$ -pyrrolic protons were broad at room temperature due to N–H proton exchange between the different protonation sites of the molecule (four pyrrolic and one pyridine nitrogen atoms). An X-ray structure of suitable crystals confirmed the doubly fused nature of the compound (see Figure 1).



Figure 1. X-ray crystal structure of the free base  $H_2$ -6. Top and side views showing the ruffled nature of the porphyrin macrocycle and the flat pentacyclic part.

The unit cell contains two molecules of the free base H<sub>2</sub>-6 and four benzene molecules (solvent used for the crystallization). The inner pyrrolic N-H hydrogen atoms of the porphyrin are located (at least in the solid state, not in solution) on the two opposite pyrroles not involved in the fused pentacyclic aromatic system. The porphyrin core itself is ruffled. In contrast, the pentacyclic fused aromatic (naphthalene-pyrrole-quinoline) appears to be almost flat. The fused quinoline and naphthalene groups cannot be distinguished, each group half-occupying the positions in the Xray structure. The *peri* interactions between the fused naphthyl (or quinolyl) and the neighboring pyrroles are the cause of the ruffled nature of the macrocycle. The two hydrogen atoms ( $\beta$ -pyrrolic and naphthyl or  $\beta$ -pyrrolic and quinolyl) are in close proximity (d = 2.11 and 2.13 Å, respectively). The  $\beta$ - $\beta'$  pyrrolic C-C bonds are also markedly different in this porphyrin. Whereas the three isolated pyrroles present bond lengths (1.358, 1.349, and 1.361 Å) in accordance with the bond length found in porphyrin bases, the  $\beta$ - $\beta'$  pyrrolic C-C bond of the fourth pyrrole fused to the naphthyl and quinolyl groups is significantly longer (1.445 Å). In the Xray structures of chlorines, these bond lengths are close to 1.36 Å for the normal pyrroles and 1.52 Å for the reduced  $\beta$ - $\beta'$  bond.<sup>[10]</sup> In this porphyrin, one of the  $\beta$ - $\beta'$  pyrrolic C-C bonds seems to have lost part of its double bond (or aromatic) character.

This loss together with the extension of the conjugation might explain in part the unusual electronic spectra of the porphyrin free base and the metal complexes (see Figure 2). Typical of simple *meso*-tetraarylporphyrins is a very intense Soret band in the 400–500 nm area with extinction coefficients usually much greater than  $10^5 \text{ M}^{-1} \text{ cm}^{-1}$ . In our case, the Soret band is split into at least two bands between 400 and 470 nm (with extinction coefficients well below  $10^5 \text{ M}^{-1} \text{ cm}^{-1}$ ).



Figure 2. Electronic spectra of the free base  $H_2$ -6 (normal line) and of the palladium complex Pd-6 (bold line).

The lowest-energy band of the free base was found at 751 nm. Moreover, the same band was observed at wavelengths higher than 700 nm (with very large extinction coefficients) for the nickel ( $\lambda = 734$  nm,  $\varepsilon = 36000$  m<sup>-1</sup> cm<sup>-1</sup>), the copper ( $\lambda = 732$  nm,  $\varepsilon = 42000$  m<sup>-1</sup> cm<sup>-1</sup>), and the palladium complexes ( $\lambda = 710$  nm,  $\varepsilon = 43000$  m<sup>-1</sup> cm<sup>-1</sup>). These absorp-



tion bands are ideally located for photodynamic studies, for which the therapeutic window starts from approximately 650 up to 900 nm. To check if these compounds might be useful as sensitizers, their ability to oxidize cholesterol was verified under irradiation.<sup>[11]</sup> The efficiency of the newly obtained sensitizers was compared with the well-known tetraphenylporphyrin (H<sub>2</sub>TPP) and all the results are summarized in Table 1 (see the Supporting Information for details).

Table 1. Photochemical oxidation of cholesterol: efficiency of different sensitizers,  $^{\left[ a\right] }$ 

Sensitizer <sup>[a]</sup>	$\lambda_{\max}$ [nm], $\varepsilon$ [M <sup>-1</sup> cm <sup>-1</sup> ]	Turnover number	
H <sub>2</sub> TPP	648, 3400	16	
H <sub>2</sub> -6	751, 17500	11.5	
Ni-6	734, 36000	0	
Cu-6	732, 42000	5	
Pd-6	710, 43000	52	

[a] Experimental conditions: benzene (20 mL), cholesterol ( $2 \times 10^{-3}$  M), sensitizer ( $10^{-5}$  M), 4 h irradiation (400 W slide projector,  $\lambda > 510$  nm), cholesterol/sensitizer = 200.

Because these metalloporphyrins have an external basic site (the nitrogen atom of the fused quinoline), their electronic spectra were expected to change in the presence of acid. This was indeed observed, as is shown in Figure 3 for the nickel complex Ni-6. After the addition of a drop of trifluoroacetic acid, the spectrum was shifted to the NIR.



Figure 3. Electronic spectra of the nickel porphyrin Ni-6 before (normal line) and after the addition of trifluoroacetic acid (bold line).

The electrochemistry of these molecules was studied by cyclic (CV) and rotating disk voltammetry (RDV). The electrochemistry of metalloporphyrins is well established and for simple metalloporphyrins like the one used in our studies (nonelectroactive metal ions), two reversible oxidation and two reduction waves are usually described.<sup>[12]</sup> As expected, two well-resolved reversible one-electron reductions were observed for all of the compounds (see Table 2 for all potential values). The RDV studies showed two oxidation steps, with amplitudes similar to those measured in the reductions (see the Supporting Information). However, the first oxidation step was spread out over the potential axis. Wave analyses for Ni-6, Cu-6, and Pd-6 RDV studies dem-

onstrated that these spread-out waves correspond to the overlap of two waves of equal amplitude. Assuming a oneelectron transfer for each reduction step, these spread-out oxidation steps involve two 0.5 electron steps.

Table 2. Cyclic voltammetry data for M-6.[a]

Species	$\vec{E_{\rm red2}}$	$\vec{E_{\rm red1}}$	$\vec{E}_{ox1}$	$E_{\rm ox2}^{\circ}$	$\vec{E}_{ox3}$	$E_{\rm pa}$
H <sub>2</sub> -6	-1.46	-1.11	+0.53		+0.83	
	(60)	(60)	(110)		(60)	
Ni-6	-1.60	-1.20	+0.42	+0.58	+1.21	
	(60)	(70)	(75)	(75)	$E_{\rm pa}$	
Pd-6	-1.58	-1.18	+0.44	+0.68	+1.03	+1.15
	(60)	(60)	(60)	(60)	$E_{\rm pa}$	$E_{\rm pa}$
Cu-6	-1.55	-1.17	+0.38	+0.61	+0.81	+1.09
	(60)	(60)	(60)	(60)	(60)	$E_{\rm pa}$

[a] Potentials are given in Volt vs. the ferrocene/ferrocenium couple used as an internal standard. Values indicated in parentheses correspond to the peak potential differences ( $\Delta E_{\rm p} = E_{\rm pa} - E_{\rm pc}$  in mV). See the Exp. Sect. for details of the conditions.

Cyclic voltammetry experiments confirmed the RDV results. Two well-resolved, reversible, one-electron reduction waves were observed for all compounds, which were, as expected for large aromatic molecules, separated by approximately 400 mV. The "first" oxidation is clearly split into two steps for the nickel, palladium, and copper porphyrins (see Figure 4).



Figure 4. Cyclic voltammograms ( $v = 100 \text{ mV s}^{-1}$ ) of the free base H<sub>2</sub>-6 and of the nickel complex Ni-6 in the presence of ferrocene.

Similar behavior has been observed for other  $\pi$ -extended diketoporphyrins.<sup>[13]</sup> After being generated at the anode, the porphyrinic radical cation associates strongly with the remaining neutral molecule to give a dimeric radical cationic species, which is then oxidized at a different and more anodic potential. Similar electrochemical results have been described for other large flat aromatic molecules (eilatin, for example) or even for their metal complexes.<sup>[14]</sup> Association between an electron-poor radical cation and an "electron-

rich" neutral molecule should be highly favored if the two species are large flat aromatics. In the case of Pd-6 and Cu-6, an additional third nonreversible oxidation step was observed at +1.15 and 1.09 V, respectively.

#### Conclusions

A doubly fused porphyrin has been synthesized. Starting from the cheapest metalloporphyrin (nickel meso-tetraphenylporphyrin), new chromophores were obtained in a few steps in good yields. Successive nitration (95% yield), Cadogan cyclization (75% yield), Vilsmeier-Haack formylation (90% yield), and Friedel-Crafts cyclization (72% yield) of the nickel porphyrin gave these new chromophores in very good overall yields. The reaction sequence is composed of well-known and widely used reactions that all use very cheap reagents. The nickel complex could be easily demetalated. Based on the preparation of the copper and palladium complexes, it seems that the porphyrin free base might be complexed to many other metal ions. All of these compounds showed high absorbances in the therapeutic window and some of them were able to generate singlet oxygen efficiently, which makes these sensitizers good candidates for photodynamic therapy.

Owing to their large flat aromatic pentacyclic substructure, which is similar to some other natural alkaloids (cryptolepine), these compounds might also be potential intercalators of DNA bases or G-Quadruplex stabilizing ligands and therefore potential inhibitors of telomerases.<sup>[15]</sup>

Finally, the presence of the pyridine might be used to complex metal ions or metal complexes at this nitrogen coordinating site. Because this pyridine is fused to the aromatic core of the porphyrin one might expect substantial interactions between the metal ions located inside and outside of the porphyrin ring.

### **Experimental Section**

**General Procedures:** The known starting compounds nickel enaminoporphyrin **2** and nickel enamino aldehyde **3** were prepared according to our previously published procedures.<sup>[7a]</sup> Chromatographic separations were performed by using Merck 9385 silica gel or Merck 1097 alumina.

Nickel Porphyrin 6: A degassed solution of nickel enamino aldehyde 3 (127 mg, 178 µmol) and *p*-toluenesulfonic acid (79 mg, 415 µmol) in toluene (45 mL) was heated at reflux under argon for 48 h. After cooling, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was then washed with water and dried with sodium sulfate. After evaporation of the solvent, the residue was added to a chromatography column [silica gel, eluent: from cyclohexane/ dichloromethane (1:1) to dichloromethane/ethyl acetate (3:1)]. After separation and crystallization (dichloromethane/methanol), nickel enamine 2 and nickel porphyrin 6 were obtained in 8 (10 mg, 14 µmol) and 72% (89 mg, 128 µmol) yields, respectively; m.p. >260 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 45 °C):  $\delta$  = 8.63 and 8.09 (2 d, *J* = 5 Hz, 2 H, pyrrole), 8.61 and 8.10 (2 d, *J* = 5 Hz, 2 H, pyrrole), 8.61 and 8.10 (2 d, *J* = 5 Hz, 2 H, pyrrole), 8.98 (s, 1)



H, H<sub>naphth</sub>), 8.53, 8.13, 7.72, and 7.54 (4 m, 4 H, H<sub>naphth</sub>), 8.68, 8.45, 7.74, and 7.73 (4 m, 4 H, H<sub>quin</sub>), 7.78–7.83 (m, 4 H, H<sub>ortho</sub>), 7.57–7.63 (m, 6 H, H<sub>meta+para</sub>) ppm. UV/Vis (CH<sub>2</sub>Cl<sub>2</sub>):  $\lambda_{max}$  ( $\varepsilon$ ) = 401 (57000), 469 (85000), 668 (20000), 696 (24000), 734 (36000 m<sup>-1</sup> cm<sup>-1</sup>) nm. HRMS: calcd. for C<sub>45</sub>H<sub>25</sub>N<sub>5</sub>Ni + H<sup>+</sup> 694.1536; found 694.1534.

Free Base H<sub>2</sub>-6: A solution of nickel porphyrin 6 (305 mg, 439 µmol) in a mixture of trifluoroacetic acid and sulfuric acid (25 and 12 mL, respectively) was stirred at room temperature for 2 h. Then the reaction mixture was poured onto ice and after addition of dichloromethane (100 mL), the aqueous phase was neutralized with sodium hydrogen carbonate. The organic phase was dried and after crystallization (dichloromethane/methanol) the green freebase H<sub>2</sub>-6 was obtained in 95% yield (266 mg, 417 µmol); m.p. >260 °C.<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 50 °C):  $\delta$  = 8.43 and 7.80 (2 d,  $J \approx 5$  Hz, 2 H, pyrrole), 8.42 and 7.79 (2 d,  $J \approx 5$  Hz, 2 H, pyrrole), 7.47 and 7.41 (2 d, J = 4.5 Hz, 2 H, pyrrole), 9.46 (s, 1 H, H<sub>naphth</sub>), 8.82, 8.34, 7.82, and 7.65 (4 m, 4 H, H<sub>naphth</sub>), 8.97, 8.67, 7.86, and 7.86 (4 m, 4 H, H<sub>quin</sub>), 7.80-7.88 (m, 4 H, H<sub>ortho</sub>), 7.59–7.67 (m, 6 H, H\_meta+para) ppm. UV/Vis (CH<sub>2</sub>Cl<sub>2</sub>):  $\lambda_{max}$  ( $\varepsilon$ ) = 398 (61000), 443 (52000), 505 (14500), 679 (19500), 751  $(17500 \text{ m}^{-1} \text{ cm}^{-1})$ . HRMS: calcd. for C<sub>45</sub>H<sub>27</sub>N<sub>5</sub> + H<sup>+</sup> 638.2339; found 638.2331.

The copper and palladium complexes were obtained in almost quantitative yields by using standard porphyrin metalation procedures [with  $Cu(OAc)_2$  in chloroform/methanol mixtures at reflux and with  $Pd(acac)_2$  in toluene or chlorobenzene at reflux].

**Cu-6:** M.p. >260 °C. UV/Vis (CH<sub>2</sub>Cl<sub>2</sub>):  $\lambda_{max}$  ( $\varepsilon$ ) = 401 (62000), 467 (73000), 665 (21000), 699 (27000), 732 (42000 m<sup>-1</sup> cm<sup>-1</sup>). HRMS: calcd. for C<sub>45</sub>H<sub>25</sub>N<sub>5</sub>Cu + H<sup>+</sup> 699.1479; found 699.1474.

**Pd-6:** M.p. >260 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 45 °C): *δ* = 8.82 and 8.14 (2 d, *J* = 4.8 Hz, 2 H, pyrrole), 8.76 and 8.13 (2 d, *J* = 4.8 Hz, 2 H, pyrrole), 7.96 and 7.92 (2 d, *J* = 4.8 Hz, 2 H, pyrrole), 9.09 (s, 1 H, H<sub>naphth</sub>), 8.76, 8.23, 7.81, and 7.64 (4 m, 4 H, H<sub>naphth</sub>), 8.89, 8.57, 7.83, and 7.82 (4 m, 4 H, H<sub>quin</sub>), 7.88–7.93 (m, 4 H, H<sub>ortho</sub>), 7.65–7.75 (m, 6 H, H<sub>meta</sub> and H<sub>para</sub>) ppm. UV/Vis (CH<sub>2</sub>Cl<sub>2</sub>):  $\lambda_{max}$  ( $\varepsilon$ ) = 402 (50000), 467 (72000), 647 (18000), 681 (27000), 710 (43000 m<sup>-1</sup> cm<sup>-1</sup>). HRMS: calcd. for C<sub>45</sub>H<sub>25</sub>N<sub>5</sub>Pd + H<sup>+</sup> 742.1218; found 742.1195.

**Electrochemical Studies:** Dichloromethane was purchased spectroscopic grade from Merck, dried with molecular sieves (4 Å), and stored under argon prior to use. NBu<sub>4</sub>PF<sub>6</sub> was purchased electrochemical grade from Fluka and used as received. The electrochemical experiments were carried out at room temperature in dichloromethane containing 0.1  $\times$  NBu<sub>4</sub>PF<sub>6</sub> in a classical three-electrode cell by cyclic voltammetry (CV) or rotating disk voltammetry (RDV). The working electrode was a glassy carbon disk (3 mm in diameter), the auxiliary electrode a Pt wire, and the pseudo-reference electrode a Pt wire. All potentials are given vs. Fc/Fc<sup>+</sup> used as an internal standard and are uncorrected from the ohmic drop.

**Crystal Data for Compound H<sub>2</sub>-6:**  $C_{57}H_{39}N_5$ ,  $C_{45}H_{27}N_5 \cdot 2C_6H_6$ , M = 793.98, triclinic, space group  $P\bar{1}$ , a = 10.8368(10), b = 11.6205(10), c = 18.234(2) Å,  $a = 107.42(2)^\circ$ ,  $\beta = 95.33(2)^\circ$ ,  $\gamma = 107.32(2)^\circ$ , V = 2049.3(3) Å<sup>3</sup>, Z = 2, and D = 1.29 g cm<sup>-3</sup>. A total of 11945 reflections were collected from a green crystal of dimensions  $0.20 \times 0.12 \times 0.08$  mm<sup>3</sup> using a KappaCCD diffractometer, graphite-monochromated Mo- $K_a$  irradiation,  $1.19 < \theta < 30.07^\circ$ , and a of temperature 173 K. A total of 6427 unique reflections having  $I > 2\sigma(I)$  were used to determine and refine the structure. Final results: R = 0.0694, wR2 = 0.1907, GOF = 0.984, and final largest difference peak: 0.274 e Å<sup>-3</sup>.

CCDC-741936 contains the supplementary crystallographic data for  $H_2$ -6. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data\_request/cif.

**Supporting Information** (see also the footnote on the first page of this article): Experimental details for cholesterol photochemical oxidation, <sup>1</sup>H NMR and electronic spectra, RDV and CV experiments, unit cell view of the crystal structure of  $H_2$ -6.

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