Studies Toward the Chemistry of N-Confused Porphyrins

by

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Date Apr. 14, 2003
Abstract

The objectives of this work were to study the chemistry of N-confused porphyrins, which is a porphyrin isomer with an inverted pyrrole ring, and to develop new photosensitizers based on N-confused porphyrins for photodynamic therapy (PDT).

Alkylation reactions of N-confused porphyrins were studied. N-confused tetraarylporphyrins reacted with CH$_3$I in the presence of Na$_2$CO$_3$ to yield N,N'-dimethylated N-confused porphyrin salts $103$ - $107$, which are mixtures of structural isomers. The structures of the major isomers (III) were determined by X-ray diffraction and NMR spectroscopic analyses. These N,N'-dimethylated N-confused tetraarylporphyrin salts can generate singlet oxygen when irradiated with light of the appropriate wavelengths and are potential photosensitizers for PDT.

The peripheral carbon-nitrogen double bonds of Ni(II) N-confused porphyrins are partially isolated from the 18 π conjugated aromatic system and reacted as dienophiles in Diels-Alder reactions with o-benzoquinodimethane yielding novel Ni(II) N-confused isoquinoporphyrins $133$ (a-c). Ni(II) N-confused tetraphenylisoquinoporphyrin, $133a$, was structurally characterized by X-ray diffraction analysis.
Reaction of Ni(II) N-confused tetrakis(p-tolyl)porphyrin with NaOCH₃ and DDQ resulted in the inner C(21) cyanide addition product 146. Minor product 145 was presumably formed by subsequent nucleophilic addition of CH₃O⁻ to 146 at C(3) followed by oxidation with DDQ. Structures of both complexes 145 and 146 were determined by X-ray diffraction analyses.

The Ni(III) complex of N-confused porphyrin inner C-oxide 153 was synthesized from oxidation of the precursor Ni(II) N-confused porphyrin using OsO₄. This Ni(III) complex has been structurally characterized.
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<th>Abbreviation</th>
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<td>AMD</td>
<td>age-related macular degeneration</td>
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<tr>
<td>Anal.</td>
<td>analytical</td>
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<tr>
<td>BPDMA</td>
<td>benzoporphyrin derivative monoacid ring A</td>
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<tr>
<td>br</td>
<td>broad (NMR)</td>
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<td>Calcd</td>
<td>calculated</td>
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<tr>
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<td>correlated spectroscopy</td>
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<td>doublet</td>
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<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theory</td>
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<tr>
<td>DMAD</td>
<td>dimethylacetylene dicarboxylate</td>
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<td>DPBF</td>
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<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TPP</td>
<td>meso-tetraphenylporphyrin</td>
</tr>
<tr>
<td>TTP</td>
<td>meso-tetra(p-tolyl)porphyrin</td>
</tr>
<tr>
<td>UV-vis</td>
<td>ultraviolet-visible</td>
</tr>
</tbody>
</table>
Nomenclature

Porphyrs and N-Confused Porphyrs

The parent porphyrin system is called porphine. The numbering of ring positions, including the nitrogens and the use of letters denoting individual rings, is shown below. Positions 1, 4, 6, 9, 11, 14, 16, and 19 are termed "α" positions, 2, 3, 7, 8, 12, 13, 17, and 18 are "β" positions and 5, 10, 15, and 20 are "meso" positions.

N-confused porphyrin is named as 2-aza-21-carbaporphyrin and the numbering is shown below.
Acknowledgements

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Chapter 1

Introduction
1.1 Porphyrin and Porphyrin Related Macrocycles

Porphyrons are aromatic tetrapyrrolic macrocycles consisting of four pyrrole units joined through four methine bridges (Figure 1.1).\(^1\) Although they have 22 \(\pi\)-electrons, only 18 of these \(\pi\)-electrons are involved in a cyclic delocalized pathway, which fulfills the requirement of Hückel's rule \((4n + 2, n = 4)\). X-ray diffraction analyses of both free base porphyrins and metalloporphyrins have shown the planarity of the porphyrin skeleton, which is a requirement for aromatic character.\(^2,3\) Signals for the \textit{meso}-H atoms of typical porphyrins in \(^1\)H NMR spectra appear at about 10 ppm, while signals for the two inner pyrrole protons are observed between -2 to -5 ppm, suggesting a strong ring current.\(^3\) Saturation of the two cross-conjugated double bonds at the \(\beta\) positions does not affect the aromaticity; consequently these two bonds are relatively reactive. Reduction of one of these double bonds leads to formation of a chlorin and a further one bond reduction leads to formation of either a bacteriochlorin or an isobacteriochlorin (Figure 1.1).\(^3\)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{porphyrin_chlorin_bacteriochlorin_isobacteriochlorin}
\caption{Porphyrin and porphyrin related macrocycles.}
\end{figure}
The four nitrogen atoms in a porphyrin are ideally arranged to chelate metal cations and thus readily form metal porphyrin complexes. Metalloporphyrins have been extensively studied, and most metals and some semimetals have been inserted into porphyrins, including all metals in the third to fifth row of the periodic table. Metalloporphyrins play important roles in a wide variety of biological processes, for example, iron complexes of protoporphyrin-IX, 1, and chlorophylls 2 (Figure 1.2). The Fe(II) complex of protoporphyrin-IX is the prosthetic group of hemoglobin and myoglobin. Both hemoglobin and myoglobin reversibly bind O₂. Hemoglobin transports O₂ in blood plasma and myoglobin stores O₂ in cellular tissues. The Fe(III) complex of protoporphyrin-IX forms the prosthetic group of catalases and peroxidases, which are essential components of the biological defense against oxygen toxicity by removing reactive intermediates such as superoxide (O₂⁻) and peroxide (O₂²⁻). Chlorophylls play a key role in the harvesting of light energy during photosynthesis.

![Figure 1.2 Protoporphyrin-IX 1 and chlorophylls 2.](image)
Porphyrrins have an intense absorption (molar extinction coefficient between 100,000 - 400,000 M$^{-1}$cm$^{-1}$) around 400 nm in the visible region, referred to as the Soret or B band.$^{3,6}$ Porphyrrins also have lower intensity absorption bands between 450 and 650 nm, called Q-bands.$^3$ Compared to those of porphyrrins, the Soret band of chlorins is weaker, whilst the lowest energy Q-band of chlorins is normally red-shifted about 20 - 30 nm and has a 10 times greater intensity (Figure 1.3).

![Figure 1.3 UV-vis spectra of a porphyrin and a chlorin (absorbance between 450 and 680 nm is shown with a 5 times greater intensity for clarity).]
1.2 Photodynamic Therapy (PDT)

Photodynamic therapy (PDT)\textsuperscript{7,8} is "a medical treatment which employs the combination of light and a drug to bring about a cytotoxic or modifying effect to cancerous or otherwise unwanted tissue".\textsuperscript{7} PDT employs the use of a photosensitizer. This photosensitizer can be excited by irradiation and transfers energy to a desired reactant. PDT is used to treat diseases which involve rapid cell growth, such as cancerous tissues or abnormal blood vessels.\textsuperscript{7} The first step involves intravenous administration of the photosensitizer which attaches to lipoproteins in the bloodstream. As rapidly dividing cells have more lipoproteins than normal cells, the photosensitizer concentrates in these tissues.\textsuperscript{7,8} The photosensitizer is then activated with a laser at a particular wavelength where the photosensitizer absorbs extensively compared to endogenous chromophores. Once activated, the photosensitizer converts triplet oxygen to singlet oxygen, which readily reacts with many cell components resulting in cell death.\textsuperscript{7,8}

Porphyrin and porphyrin related macrocycles have been extensively studied as potential PDT agents as they may absorb at ideal wavelengths for maximal therapeutic effect. At present, most photosensitizers in clinical trials for PDT are porphyrin related macrocycles.\textsuperscript{9}

1.2.1 Mechanism of Photosensitization

The process of photosensitization is shown in a modified Jablonski diagram (Figure 1.4).\textsuperscript{9-11} After absorption of light, the photosensitizer is converted from its ground singlet state ($S_0$) into excited singlet states ($S_n$). An excited singlet state molecule can lose energy via internal conversion ($S_m \rightarrow S_n + \text{heat}, m > n$) until it reaches the first excited singlet state ($S_1$), which normally has a very short lifetime ($\sim 10^{-6}$ s).\textsuperscript{9} The first excited singlet state ($S_1$) can return to the
ground singlet state ($S_0$) through either internal conversion or fluorescence. The first excited singlet state can also be transformed into an electronically excited triplet state ($T_1$) through a spin forbidden process, intersystem crossing ($S_1 \rightarrow T_1 + \text{heat}$). The triplet state can return to the ground singlet state through either phosphorescence or energy transfer. With phosphorescence being spin forbidden, the triplet state usually has a longer lifetime ($\sim 10^{-2}$ s) than that of an excited singlet state.

![Modified Jablonski diagram](image)


**Figure 1.4** Modified Jablonski diagram.$^9$-$^{11}$

The triplet state photosensitizer ($^3$ sensitizier) can undergo energy transfer *via* two types of reactions. It can abstract an electron or hydrogen atom from a substrate (Type I Reaction):$^9$-$^{11}$

$$^3\text{sensitizer} + \text{substrate} \rightarrow \text{sensitizer}^- + \text{substrate}^{+\text{ox}}$$

$$^3\text{sensitizer} + \text{RH} \rightarrow \text{sensitizerH}^- + \text{R}^-$$
The anionic photosensitizer can react with O\(_2\) to generate a superoxide anion (O\(_2^-\)).\(^{9-11}\)

\[
\text{sensitizer}^- + \text{O}_2 \rightarrow \text{sensitizer} + \text{O}_2^-
\]

The free substrate radical (R·) generated from hydrogen atom abstraction can react with O\(_2\) and ultimately produce hydroperoxides.\(^{9-11}\)

\[
\text{R}^- + \text{O}_2 \rightarrow \text{RO}_2^- \xrightarrow{\text{sensitizerH}^- \text{ (or other H donor)}} \text{RO}_2\text{H} + \text{sensitizer}
\]

Both superoxide anion and hydroperoxides are very reactive species and can react further with a variety of substrates.\(^{9-11}\)

The triplet state photosensitizer can also return to the ground state through reaction with triplet oxygen (\(^3\text{O}_2\)) giving singlet oxygen (\(^1\text{O}_2\)) (Type II Reaction).\(^{9-11}\) Singlet oxygen is a powerful oxidant which reacts with biological substrates in a variety of ways, for example (Scheme 1.1):\(^{10,11}\)

A. Addition to the diene systems in heterocycles to give endoperoxides.

B. Hydrogen abstraction and addition ("ene" reactions with compounds with allylic hydrogen atoms).

C. [2 + 2] addition to double bond followed by the cleavage of that bond.

D. Oxidation of sulfides to sulfoxides.
Scheme 1.1 Reactions of singlet oxygen with biological substrates.

These reactions result in destruction of biological substrates such as membranes, enzymes, proteins and nucleic acids. It is generally agreed that singlet oxygen is the key agent of cellular damage in PDT, although there is indication that the superoxide ion may also be involved in some aspects of PDT damage.
1.2.2 Desirable Properties of a PDT Drug

Ideally, a PDT drug, as drugs in general, should be easily and economically synthesized. Furthermore, a PDT drug should have strong absorption at wavelengths between 650 and 800 nm for the following reasons:

- The presence of endogenous chromophores such as hemoglobin results in very poor penetration of tissues by light at wavelengths below 650 nm.\(^7\)
- A compound which absorbs light above 800 nm may not have a large enough energy gap between its triplet state and ground state to generate singlet oxygen.\(^7\)

The criteria mentioned above are considered in this thesis work. Other desirable properties, such as high light toxicity,\(^7\) low dark toxicity,\(^7\) rapid clearance after injection,\(^7\) localizing specifically in tumours,\(^7\) and ease of formulation,\(^7\) are hard to control at the organic synthetic level.

1.3 From Porphyrins to Chlorins

As the lowest energy Q-band of chlorins is normally red-shifted 20-30 nm and has a 10 times greater absorption intensity compared to that of porphyrins, chlorins are better candidates as photosensitizers for PDT.\(^7\) Many methods have been developed to convert porphyrins to chlorins, for example, Diels-Alder reactions of porphyrins with \(\beta\)-vinyl groups as dienes,\(^7,12,13\) dihydroxylation with OsO\(_4\),\(^14\) cycloaddition reactions of porphyrins as dienophiles or dipolarophiles,\(^15,16\) diimide reductions\(^17\) and cyclopropanations with carbenes.\(^18\)
1.3.1 Diels-Alder Reactions of Porphyrins as Dienes

Porphyrins with β-vinyl groups can act as dienes and react with various dienophiles to yield the corresponding chlorins. For example, the benzoporphyrin derivative monoacid ring A (BPDMA, 4) was derived initially from the Diels-Alder reaction of protoporphyrin-IX dimethyl ester 3 with dimethylacetylene dicarboxylate (DMAD) (Scheme 1.2).\(^{7,12,13}\) BPDMA has been approved in more than 60 countries to treat age-related macular degeneration (AMD),\(^7\) the major cause of vision loss in people over the age of 60 in developed countries.

![Scheme 1.2 Synthesis of BPDMA, 4.](image-url)
1.3.2 Dihydroxylation of Porphyrins with OsO₄

Dihydroxychlorins can be obtained by oxidation of porphyrins with OsO₄. For example, *meso*-tetraphenylporphyrin (TPP, 5a) reacts with OsO₄ giving *meso*-tetraphenyl-2,3-*cis*-dihydroxy-2,3-chlorin, 6 (49 %) (Scheme 1.3).\(^{14}\)

![Scheme 1.3 Dihydroxylation of TPP with OsO₄.](image)

1.3.3 Cycloaddition Reactions of Porphyrins as Dienophiles or Dipolarophiles

Diels-Alder reactions of *meso*-tetraarylporphyrins 5 (a-d) as dienophiles with o-benzoquinodimethane, 8, were investigated by Cavaleiro et al.\(^{15}\) TPP, 5a, reacts with o-benzoquinodimethane, generated *in situ* from the sulfone 7, to yield chlorin 9a (26 %), naphtho[2,3-b]porphyrin, 10a (20 %), and compound 11a (20 %) (Scheme 1.4). Similar results are obtained when *meso*-tetraarylporphyrins 5 (b,c) are used.\(^{15}\)
Scheme 1.4 Diels-Alder reactions of tetraarylporphyrins 5 (a-c) with o-benzoquinodimethane.
When meso-tetrakis(pentafluorophenyl)porphyrin, 5d, is used, chlorin 9d (35 %) and two bacteriochlorin isomers 12 are obtained (Scheme 1.5). Porphyrin 5d is electron-deficient and o-benzoquinodimethane is known to react more easily with electron-deficient dienophiles, which might explain why there can be addition of two equivalents of o-benzoquinodimethane to porphyrin 5d.

Scheme 1.5 Diels-Alder reactions of meso-tetrakis(pentafluorophenyl)porphyrin, 5d, with o-benzoquinodimethane.
The 1,3-dipolar cycloaddition reaction of porphyrin 5d as dipolarophile with azomethine 13 (Scheme 1.6) yields chlorin 14 (61 %) and isobacteriochlorin 15 (11 %).\textsuperscript{16} There are four possible bis-adducts, \textit{cis} or \textit{trans} bacteriochlorins and isobacteriochlorin. The formation of bis-adducts in this reaction is regio- and stereoselective, yielding mainly \textit{trans}-isobacteriochlorin 15. Isobacteriochlorin 15 can also be obtained by the reaction of chlorin 14 with azomethine 13.

\textbf{Scheme 1.6} 1,3-Dipolar cycloaddition reaction of porphyrin 5d with azomethine 13.
1.4 N-Confused Porphyrins

1.4.1 Introduction

N-confused porphyrin (NCP) is a porphyrin isomer with an inverted pyrrole ring (Figure 1.5). Preparations of N-confused porphyrins were first independently reported by the groups of Furuta\textsuperscript{19} and Latos-Grażyński\textsuperscript{20} in 1994. In both cases, N-confused tetraarylporphyrins 16 (a,b) were obtained through acid catalyzed condensation of pyrrole and aryl aldehyde with a yield of about 5%.

![Porphyrin and N-confused porphyrin](image)

Figure 1.5 Porphyrin and N-confused porphyrins.

Similar to porphyrins, N-confused porphyrins have an 18 \( \pi \)-electron pathway and are aromatic (Figure 1.5). The \( ^1 \)H NMR spectrum of N-confused tetraphenylporphyrin (NCTPP, 16a) reveals characteristic high-field signals for the inner NHs and CH (at -2.5 and -5.1 ppm, respectively), as a result of the aromatic ring current\textsuperscript{19}.

The Soret band and Q-bands in the electronic absorption spectrum of NCTPP in CH\(_2\)Cl\(_2\) are broadened and red-shifted (\( \lambda_{\text{max}} = 438 \) and 725 nm, respectively), as compared to those of
TPP (419 and 647 nm),\textsuperscript{19} suggesting a potential application of NCPs as photosensitizers in PDT (Figure 1.6).

![UV-vis spectra of NCTPP and TPP](image)

**Figure 1.6** UV-vis spectra of NCTPP and TPP (absorbance between 484 and 800 nm is shown with a 5 times greater intensity for clarity).

As reported by Latos-Grażyński et al.,\textsuperscript{20} Ni(II) can be inserted into N-confused tetra(p-tolyl)porphyrin (NCTTP, 16b) under mild conditions to yield (NCTTP)Ni\textsuperscript{II}. The most notable feature of this complex is the coordination through the unprotonated inner carbon, suggested by the disappearance of the C(21)H proton resonance in the $^1$H NMR spectrum of (NCTTP)Ni\textsuperscript{II}.

N-confused porphyrins have been extensively studied since the first reports on their preparations.\textsuperscript{21-31} Many synthetic methods were developed.\textsuperscript{21-24} Different reactions of NCPs have been studied, including its alkylation reactions and coordination chemistry.\textsuperscript{25-29} Other porphyrin analogues with a CH in the inner macrocycle have been synthesized.\textsuperscript{30,31}
1.4.2 Structural Features of N-confused Porphyrins

The structure of NCTPP was determined by single crystal X-ray diffraction analysis (Figure 1.7). Crystals of NCTPP were obtained from a CH$_2$Cl$_2$/CH$_3$OH solution of NCTPP. Unlike TPP, the skeleton of NCTPP deviates from planarity. The confused pyrrole ring is tilted from the reference N(2)N(3)N(4) plane by 26.9°. Two adjacent and opposite pyrrole rings are tilted by 13.4°, 7.8°, and 5.8°, respectively. This deviation from planarity appears to result from mutual repulsion of the three inner hydrogen atoms.

![Image of ORTEP drawings of NCTPP](https://via.placeholder.com/150)

**Figure 1.7** ORTEP drawings of NCTPP (obtained from a CH$_2$Cl$_2$/CH$_3$OH solution) showing thermal ellipsoids at the 50 % probability level: top view (left) and side view (right). Solvent in both views and phenyl groups in the side view have been omitted for clarity.

The structures and electronic energies of hypothetical tautomers of N-confused porphyrins (Figure 1.8) were investigated by Szterenberg and Latos-Grażyński using density functional theory (DFT). Porphyrin was included to evaluate the relative stability of NCP with
respect to porphyrin. Tautomer $2\text{-NH-CPH}_2$ was suggested by Ghosh to promote the hypothetical carbene-like coordination of C(21) and to explain the unexpectedly labile inner C-H bond.\textsuperscript{33,34} The calculated total electronic energies are presented in Table 1.1. Tautomer $21\text{-CPH}_2$ in both solid state and CHCl$_3$ solution has been reported by the groups of Latos-Grażyński\textsuperscript{20} and Furuta,\textsuperscript{19} and is calculated to be the most stable tautomer.\textsuperscript{32} There is only a small calculated energy difference between $21\text{-CPH}_2$ and $21\text{-H-21-CPH}$ or $2\text{-NH-CPH}$, suggesting the possibility of equilibria with the less stable tautomers.\textsuperscript{32} The energy of $2\text{-NH-CPH}_2$ at 34.56 kcal/mol (B3LYP/6-31G**//B3LYP/6-31G) with respect to $21\text{-CPH}_2$ is high compared to that of either $21\text{-H-21-CPH}$ or $2\text{-NH-CPH}$, but is quite moderate considering its carbenic nature.\textsuperscript{32}

![Figure 1.8 Porphyrin and hypothetical tautomers of N-confused porphyrin.](image-url)
Table 1.1 Calculated relative electronic energies (kcal/mol) for porphyrin and hypothetical tautomers of N-confused porphyrin.

<table>
<thead>
<tr>
<th>macrocycle</th>
<th>B3LYP/3-21G//B3LYP/3-21G</th>
<th>B3LYP/6-31G//B3LYP/6-31G</th>
<th>B3LYP/6-31G**//B3LYP/6-31G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphyrin</td>
<td>-22.95</td>
<td>-21.08</td>
<td>-20.41</td>
</tr>
<tr>
<td>21-CPH₂</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>21-H-CPH</td>
<td>6.20</td>
<td>8.22</td>
<td>3.00</td>
</tr>
<tr>
<td>2-NH-CPH</td>
<td>3.39</td>
<td>4.56</td>
<td>4.56</td>
</tr>
<tr>
<td>2-NH-CPH₂</td>
<td>31.44</td>
<td>33.82</td>
<td>34.56</td>
</tr>
<tr>
<td>2-NH-21-H-CP</td>
<td>41.31</td>
<td>43.93</td>
<td>36.00</td>
</tr>
</tbody>
</table>

Calculations employing DFT on 2-NH-CPH and 2-NH-CPH₂ relative to 21-CPH₂ were carried out also by Ghosh et al.³⁵ and the results were similar to those described above.

The presence of a type 2-NH-CPH tautomer was first reported by Furuta et al.³⁶ A color difference of NCTPP in CHCl₃ (red) and DMF (green) was observed. The ¹H NMR spectra of NCTPP in CDCl₃ and DMF-d₇ were examined. The type 21-CPH₂ tautomer, predominant in CDCl₃, has signals at -4.99 and -2.41 (2H) ppm, respectively, for inner CH and NHs.¹⁹ On the other hand, the ¹H NMR spectrum of NCTPP in DMF-d₇ shows singlet signals at 0.76, 2.27, and 13.54 ppm, assigned to the inner CH, inner NH and outer NH, respectively, suggesting existence
of the type 2-NH-CPH tautomer, which should be stabilized by the hydrogen-bond between the peripheral NH and DMF.\textsuperscript{36} The structure of a type 2-NH-CPH tautomer was explicitly determined by X-ray diffraction analysis with a crystal obtained from a DMF-MeOH solution of NCTPP (Figure 1.9).\textsuperscript{36} The porphyrin skeleton is planar with four pyrrole rings tilted at 4.7°, 0.2°, 2.8°, and 0.9°, respectively, from the reference N(2)N(3)N(4) plane. The distance between the peripheral N of NCP and O of the associated DMF molecule is 3.101 Å, within hydrogen-bonding distances.

\textbf{Figure 1.9} ORTEP drawings of NCTPP obtained from DMF-MeOH showing thermal ellipsoids at the 50 % probability level: top view (up) and side view (down). For clarity, phenyl groups have been omitted in the side view.
1.4.3 Preparation of N-Confused Porphyrsns

N-confused porphyrins were initially synthesized from acid catalyzed condensation of pyrrole and aryl aldehyde, with Latos-Grażyński et al. using an excess of pyrrole and BF$_3$·Et$_2$O, and Furuta et al. using a 1:1 ratio of starting materials with HBr as a catalyst. In both cases, N-confused porphyrins were obtained in ~5 % yield.

Latos-Grażyński et al. suggested that two helical conformations of tetrapyrromethane differing only by a single 180° rotation of the terminal pyrrole are intermediates of this reaction (Scheme 1.7). Both intermediates are susceptible to electrophilic attack at either the α or β positions, and upon oxidation afford tetra(p-tolyl)porphyrin (TTP) or NCTTP, respectively.

![Scheme 1.7 Mechanism of NCTTP formation as suggested by Latos-Grażyński.](image)

The effects of the use of various acids as catalysts for the preparation of N-confused porphyrins by condensation of pyrrole and aryl aldehyde were studied by Lindsey et al. and it was found that the highest yield was obtained using methanesulfonic acid (MSA). For
example, a 1.5 L preparative scale reaction employing 10 mM of pyrrole and benzaldehyde and 7 mM of MSA affords NCTPP in the yield of 35 % (800 mg).\textsuperscript{21}

A lower yield was obtained using dipyrromethane 17 as starting material with toluene \textit{p}-sulfonic acid (\textit{p}-TsOH) as a catalyst (Scheme 1.8). NCTPP was obtained in 7 % yield.\textsuperscript{22}

\begin{center}
\textbf{Scheme 1.8} Synthesis of NCTPP from dipyrromethane 17.
\end{center}

The methods described above are simple but only useful for \(\beta\)-unsubstituted "symmetric" (excluding the asymmetric effect from the inverted pyrrole) \(N\)-confused tetraarylporphyrins (NCTAP). Other methods were developed to prepare \(\beta\)-substituted asymmetric \(N\)-confused porphyrins.\textsuperscript{23,24} For example, a MacDonald [2+2] synthesis was reported by Dolphin \textit{et al.} to generate \(N\)-confused porphyrin 18 (Scheme 1.9).\textsuperscript{23}

\begin{center}
\textbf{Scheme 1.9} MacDonald [2+2] synthesis of \(N\)-confused porphyrin 18.
\end{center}
Lash et al. reported that condensation of pyrrole 19 (a-c) with tripyrrane 20 yielded N-confused porphyrins 21 (a-c) (Scheme 1.10). The yield is high when the pyrrole contained a 5-alkyl substituent (28 - 47 %). This is an example of a [3 + 1] methodology.

Scheme 1.10 Synthesis of N-confused porphyrins 21 (a-c) by a [3 + 1] methodology.

A doubly N-confused porphyrin (N₂CP), 2-ethoxy-5,10,15,20-tetrapentafluorophenyl-3,7-diaza-21,22-dicarbaporphyrin, 23, can be prepared in ~2 % yield by condensation of perfluorobenzaldehyde and dipyrrromethane 22 in chloroform containing a trace of EtOH with BF₃·Et₂O as the acid catalyst followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 1.11).

Scheme 1.11 Synthesis of doubly N-confused porphyrin 23.
1.4.4 Reactivity of N-Confused Porphyrins

Unlike porphyrins, N-confused porphyrins have a peripheral nitrogen atom, which is less sterically hindered and much more nucleophilic than the inner nitrogen atoms in porphyrin, and consequently, the peripheral nitrogen atom can be easily methylated.\textsuperscript{25} The inner carbon atom in Ni(II) N-confused porphyrins is nucleophilic as well and can also be methylated.\textsuperscript{26}

N-confused porphyrins can act as either a di-anionic or tri-anionic ligand, while doubly N-confused porphyrins can act as a di-anionic, tri-anionic or tetra-anionic ligand (Figure 1.10).\textsuperscript{28} The peripheral nitrogen atom of NCP is protonated when NCP acts as a di-anionic ligand. A variety of N-confused porphyrin complexes have been prepared.\textsuperscript{27-29}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.10.png}
\caption{Multi-valence properties of NCP and N$_2$CP.}
\end{figure}
1.4.4.1 Alkylation of N-Confused Porphyrins

An outer N-methylated N-confused porphyrin, 2-aza-2-methyl-5,10,15,20-tetraphenyl-21-carpaporphyrin (N(2)-CH₃-NCTPP, 24) is obtained quantitatively by reaction of NCTPP with CH₃I (Scheme 1.12). The inner CH resonance at 0.43 ppm in the ¹H NMR spectrum of 24 shows that in 24 the aromaticity is preserved, though to a degree less than that of NCTPP, whose inner CH proton resonates at -5.1 ppm. The UV-vis spectrum of N(2)-CH₃-NCTPP is similar to that of a porphyrin, with the strongest absorption around 450 nm corresponding to the Soret band of a porphyrin, while the Q-band is red shifted to 710 nm. Compound N(2)-CH₃-NCTPP is readily metalated with Ni(OAc)₂·4H₂O at r. t. to yield (N(2)-CH₃-NCTPP)Ni⁺, 25.

Scheme 1.12 Synthesis of N(2)-CH₃CTPP 24 and its Ni(II) complex 25.

Methylation of (NCTPP)Ni⁺ was investigated by Latos-Grażyński et al. (Scheme 1.13). After 24 h, the product of reaction between (NCTPP)Ni⁺ and CH₃I (1:30 molar ratio) is predominantly the diamagnetic inner C-methylated N-confused porphyrin (C(21)-CH₃-NCTPP)Ni⁺, 26. Complete conversion to the dimethylated paramagnetic compound (N(2)-CH₃-C(21)-CH₃-NCTPP)Ni⁺I, 27, is observed after 7 days. Compound 27 can also be obtained quantitatively from the reaction of the Ni(II) N-confused porphyrin complex 25 with CH₃I.
Upon reaction of compound 26 with a 1% solution of HCl, a paramagnetic compound 28 is obtained. Demetalation of compounds 26 and 27 with conc. HCl yields N-confused porphyrins 29 and 30, respectively. The C-methylated N-confused porphyrins 29 and 30 preserve their coordination properties and can be remetalated to their parent N-confused metalloporphyrins. 

Scheme 1.13 Reactions of methylated (NCTPP)NiII.
It was proposed that CH$_3$I interacts directly with (NCTPP)Ni$^{II}$ (Scheme 1.14), and oxidative addition of the methyl cation to the substrate at C(21) takes place. The axially coordinated iodide is on the same side of the C-methyl group as the result of the sym-addition and thus the intermediate 32 is unstable due to the steric interaction. Dissociation of HI from the intermediate 32 results in the C-methylated compound 26.

![Scheme 1.14 Proposed mechanism for inner C-methylation of (NCTPP)Ni$^{II}$.

Compounds 27 and 28 have similar electronic absorption spectra, with broad absorptions around 730 nm (log$\varepsilon$ is 3.88 and 3.80, respectively), whilst compound 26 has only a weak absorption between 650 - 900 nm. Compounds 29 and 30 have strong absorptions at 740 nm (log$\varepsilon$ = 3.95) and 710 nm (log$\varepsilon$ = 4.25), respectively, and are thus potential photosensitizers for PDT.

The $^1$H NMR spectrum of compound 29 is similar to that of NCTPP, with the strongly upfield shifted C(21)H (-5.1 ppm) resonance being replaced by the resonance of C(21)-CH$_3$ (-4.84 ppm). The $^1$H NMR signal of C(21)-CH$_3$ in compound 30 appears at -1.40 ppm, suggesting weak aromaticity due to external N-methylation, as in the case of N(2)-CH$_3$-NCTPP,
24. The similarities of these $^1$H NMR spectra between compound 29 and NCTPP, or compound 30 and 24, respectively, suggest that inner C-methylation does not have a significant impact on the aromaticity nor the conjugation pathway.

The structure of compound 26 favors conjugation via the outer path at the inverted pyrrole unit, whilst compound 29 favors conjugation via the inner path at the inverted pyrrole unit (Scheme 1.13). Consequently, the $^1$H NMR signal of C(3)H in compound 29 appears at 7.11 ppm, compared to that in compound 26 at 9.90 ppm, as the result of a closer ring current.

The structures of compounds 26 and 27 were determined by X-ray crystallography (Figure 1.11). In both compounds, the planarity of the macrocycles is severely distorted. The dihedral angles between the pyrrole unit and the plane defined by N(22)N(23)N(24) are as follows: C(21) -42.2°, N(22) 15.4°, N(23) 3.1°, and N(24) 15.8° for compound 26, and C(21) -55.3°, N(22) 14.3°, N(23) 0.9°, and N(24) 14.4° for compound 27. The confused pyrrole of compound 26 coordinates to Ni(II) through sp$^3$-hybridized C(21) resulting in a pyramidal geometry, while the coordinating carbon in compound 27 preserves the planar trigonal geometry indicating sp$^2$ hybridization.
Figure 1.11 ORTEP drawings of compound 26 (left) and 27 (right) showing atomic labeling and thermal ellipsoids at 50 % probability. H atoms and solvent have been omitted for clarity.

(NCTPP)Ni\textsuperscript{II} reacts with CH\textsubscript{2}Br\textsubscript{2} to yield 2,21'-CH\textsubscript{2}-linked Ni(II) N-confused porphyrin dimer 33 (79 %) and 2,2'-linked dimer 34 (16 %) (Scheme 1.15).\textsuperscript{38} If CH\textsubscript{2}I\textsubscript{2} is used, only dimer 33 is formed.\textsuperscript{38}

Scheme 1.15 Synthesis of dimeric Ni(II) N-confused porphyrins 33 and 34.
1.4.4.2 Reactions of N-Confused Porphyrin Complexes

As mentioned before, NCTTP (section 1.4.1) and N(2)-CH₃-NCTPP, 24 (section 1.4.4.1), are readily metalated with Ni(OAc)₂·4H₂O at r. t. to yield Ni(II) complexes. The structure of (NCTTP)Ni²⁺ was determined by X-ray crystallography and the porphyrin skeleton is almost planar (Figure 1.12).

![Figure 1.12 ORTEP drawings of (NCTTP)Ni²⁺ showing thermal ellipsoids at 50 % probability: top view (left) and side view (right). p-Tolyl groups in side view have been omitted for clarity. The C(21) and N(2) atoms are disordered and not distinguishable in the X-ray structure.]

Reactions of Ni(II) dimethylated N-confused porphyrin 27 (X = Cl) with phenyl Grignard reagents, phenyllithium, and n-butyllithium were investigated by Chmielewski and Latos-Grażyński. Reaction of compound 27 (X = Cl) with PhMgBr at 203 K leads to the substitution of an axial chloride by the phenyl anion to give (N(2)-CH₃-C(21)-CH₃-NCTPP)Ni²⁺Ph, 35.
Compound 35 can also be obtained by the titration of compound 27 \((X = Cl)\) with phenyllithium, and a one-electron reduction of compound 35 with excess of phenyllithium gives \([\text{N}(2)-\text{CH}_3-\text{C}(21)-\text{CH}_3-\text{NCTPP})\text{Ni}^{\text{II}}\text{Ph}\] \(36\).\(^{27}\) Reaction of 27 with \(n\)-butyllithium yields a single species \([\text{N}(2)-\text{CH}_3-\text{C}(21)-\text{CH}_3-\text{NCTPP})\text{Ni}^{\text{II}}\text{Bu}]^{n-}\), 37 \((n = 1 \text{ or } 2)\), which is either one- or two-electron-reduced.\(^{27}\) The exact value of "\(n\)" can not be determined, though the authors favor the formation of two electron reduced species \((n = 2)\) for 37 based on its NMR spectra.\(^{27}\)

Reaction of doubly N-confused porphyrin 23 with Pd(OAc)\(_2\) in toluene results in Pd(II) complex 38, the inner C-arylated product (Scheme 1.16).\(^{28}\) A FAB peak at 1217.8 \(m/e\) suggests the addition of a tolyl group to the Pd-N\(_2\)CP complex. Signals corresponding to the tolyl protons were observed in the high-field region \((5.61 - 6.36 \text{ ppm})\) in the \(^1\)H NMR spectrum of compound 36, suggesting that the tolyl group is located in the porphyrin core. The methyl groups on the tolyl substituent were found to be at the para and meta positions in a 1:2 ratio. This complexation reaction does not proceed if either chloroform or benzene is used as the solvent. However, both C-phenyl and C-tolyl Pd-N\(_2\)CP complexes are obtained when a 1:1 benzene/toluene solution is used.\(^{28}\)

Scheme 1.16 C-arylation of doubly N-confused porphyrin 23.
The structure of compound 38 was explicitly determined by single crystal X-ray diffraction analysis (Figure 1.13). The arylation occurs on the inner carbon on the pyrrole without an ethoxy group. The tolyl-substituted inverted pyrrole ring is bent at 56.3° with respect to the mean plane defined by the four core nitrogen and carbon atoms, while the tolyl group stands almost vertically (88.6°) at the opposite side.

![Figure 1.13](image)

*Figure 1.13* An ORTEP drawing of complex 38. Solvents and pentafluorophenyl groups have been omitted for clarity.

The inner arylation reaction has not been observed in the reactions of N-confused porphyrins. When NCTTP and Pd(OAc)$_2$ are refluxed in chloroform, (NCTTP)Pd, 39, is obtained in 50% yield; if toluene is used as solvent, compound 39 and two red-colored products, 40a and 40b, are obtained in yields of 19%, 27%, and 36%, respectively (Scheme 1.17).
The structure of compound 39 was determined by X-ray crystallography, and the Pd ion is located in the porphyrin core in a square-planar fashion.\textsuperscript{29} The FAB mass spectra of both 40a and 40b have parent peaks at 1550 \textit{m}/\textit{e} suggesting they are dimeric species, (Pd-NCTTP)$_2$.\textsuperscript{29} In the $^1$H NMR spectra of complexes 40a and 40b, one set of inner proton (CH, NH) signals was observed at -4.40 and 0.09 ppm for 40a, while two sets of signals for inner protons were observed at -3.83 and 0.04 ppm and -3.28 and 0.51 ppm for 40b, suggesting the symmetrical and unsymmetrical structures of 40a and 40b, respectively.\textsuperscript{29} The unsymmetrical structure of 40b was elucidated by single crystal X-ray diffraction analysis.\textsuperscript{29} Because of the lack of the crystal structure of 40a, other isomeric structures which differ with respect to the coordinating nitrogen atoms can not be ruled out.\textsuperscript{29}

A tetra-Zn(II)-coordinated NCTPP dimer 41 is quantitatively obtained when NCTPP is treated with 2 equiv. of Zn(OAc)$_2$·2H$_2$O in CH$_2$Cl$_2$ at r. t. (Scheme 1.18).\textsuperscript{39} Removal of the acetate ligands of 41 by 1 % Et$_4$NOH aqueous solution leads to formation of dimer 42, of which
the molecular mass was determined by molecular ion peak at 1353 \textit{m/e} (FAB) as well as vapor pressure osmometry measurements at 1301 g/mol.\textsuperscript{39} The Zn dimer 42 can be further transformed into monomeric pyridine complex 43 by adding pyridine.\textsuperscript{39} The structures of complex 41 and 43 were determined by X-ray crystallography.\textsuperscript{39}

Scheme 1.18 Reactions of Zn complexes of NCTPP.

An inner and outer N-coordinated bis-Rh(I) N-confused porphyrin complex 44 is obtained from the reaction of N-confused porphyrin with [Rh(CO)\textsubscript{2}Cl\textsubscript{2}] (Scheme 1.19).\textsuperscript{40} The structure of complex 44 was explicitly demonstrated by single crystal X-ray diffraction
Both Rh(I) ions are located above the NCP plane and the geometry around the metal centers is close to square planar.

![Diagram of bis-Rh(I) N-confused porphyrin complex 44.](image)

Scheme 1.19 Synthesis of bis-Rh(I) N-confused porphyrin complex 44.

The Fe(II) complex (NCTPP)Fe^{II}Br, 45, can be obtained through the reaction of NCTPP with FeBr_2 in 85% yield, and the axial ligand Br^- can be changed to C_7H_7S^- through the reaction of complex 45 with NaSC_7H_7 in 78% yield (Scheme 1.20). The r.t. effective magnetic moment of 45 obtained by Evan's method is 4.85 \mu_B, close to the spin only value (\mu_{eff} = 4.90 \mu_B) of a high spin d^6 Fe(II) center with four unpaired electrons, while the effective magnetic moment of 46 is 2.77 \mu_B, suggesting an intermediate spin Fe(II) center with two unpaired electrons. Structures of 45 and 46 were determined by single crystal X-ray diffraction analyses. While the Fe···C(21) distances in 45 and 46, 2.361(10) and 2.398(3) Å, respectively, are comparable, the Fe···H(21) distance of 1.971 Å in 45 is much shorter than that of 46, 2.334 Å. Importantly, the C(21)-H(21)···Fe in 45 is within the bond distance of an agostic interaction between the iron and pyrrolic C(21)-H(21) bond. The iron center in 45 is relatively electron-deficient, as Br^- is less basic than C_7H_7S^-, resulting in the stronger three-center two-electron C(21)-H(21)···Fe interaction.
Stable NCP complexes with high oxidation state metals have been obtained, such as NCP complexes of Ni(III), Ag(III), Sb(V) and Cu(II).\textsuperscript{43-47}

One-electron oxidations of \((\text{NCTPP})\text{Ni}^{\text{II}}\) and \((\text{N}(2)-\text{CH}_3\text{-NCTPP})\text{Ni}^{\text{II}}\), \textbf{25}, result in formation of rare organonickel(III) derivatives 47 - 51 (Scheme 1.21).\textsuperscript{43} Oxidation of \((\text{NCTPP})\text{Ni}^{\text{III}}\) occurs without deprotonation of the outer nitrogen and the additional charge is compensated by an anionic ligand. The oxidation processes are chemically reversible, and \((\text{NCTPP})\text{Ni}^{\text{III}}\) or \((\text{N}(2)-\text{CH}_3\text{NCTPP})\text{Ni}^{\text{III}}\) is recovered after addition of typical reducing agents, e.g. sodium dithionite.\textsuperscript{43} EPR spectra of the one-electron oxidized species are heavily dependent on the axial group and the spin-Hamiltonian parameters in each case suggest a metal-centered oxidation rather than a cation radical formation.\textsuperscript{43} The localization of the one-electron oxidation on the nickel ion is supported by the observation of $^{61}\text{Ni}$ hyperfine splitting in the EPR spectra.\textsuperscript{43}
Scheme 1.21 Synthesis of organonickel(III) compounds.

A Ag(III) complex of N-confused porphyrin (NCTPP)Ag$^{III}$, 52, can be obtained through the reaction of Ag(I) trifluoroacetate and NCTPP, and this was the first example of an air-stable Ag(III) complex. Coordination of Ag(III) has a slightly distorted pseudo-square-planar geometry, shown by its X-ray structure (Figure 1.14). The Ag(III) oxidation state of the silver ion is supported by the following points:

- Absence of the counteranion indicates that the complex is neutral, and the outer nitrogen atom is deprotonated, as suggested by the $^1$H NMR spectrum.
- Complex 52 is diamagnetic, whilst the Ag(II) complex is paramagnetic.
Sb(V) N-confused porphyrins (NCTAP)Sb$^{\text{V}}$(OCH$_3$)$_2$ 53 (a,b) are prepared through the reactions of NCTAP and SbBr$_3$, followed by column chromatography with MeOH/CH$_2$Cl$_2$ as eluents (Scheme 1.22). Compounds 53 are neutral as NCPs act as a tri-anionic ligand, which is suggested by the singlet peaks of C(3)H protons observed in the $^1$H NMR spectra of 53a and 53b indicating no adjacent NH protons. The fact that there is no counteranion in the X-ray crystal structure of 53b also suggests that compounds 53 are neutral.
Scheme 1.22 Synthesis of (NCTAP)Sb(V)(OCH$_3$)$_2$ 53.

If 53 is refluxed in ethanol for 2 days, the axial group -OCH$_3$ is exchanged with -OCH$_2$CH$_3$ to give (NCTAP)Sb(V)(OCH$_2$CH$_3$)$_2$ 54 quantitatively.$^{45}$ Addition of acid speeds up the exchange process and an "S$_n$I-like" mechanism is proposed (Scheme 1.23).$^{45}$

Scheme 1.23 Axial group exchange of complexes 53 (a, b).
Reactions of Cu(OAc)$_2$ with NCTPP or N(2)-CH$_3$-NCTPP, 24, yield Cu(II) N-confused porphyrin 55 and 56, respectively (Scheme 1.24).$^{46}$ Titration of 55 and 56 with acid results in formation of new species, 57-X and 58-X ($X = \text{Cl, CF}_3\text{COO}$), respectively, which can also be generated through the reaction of CuCl$_2$ with NCTPP and 24, respectively.$^{46}$ Insertion of Cu(II) into dimethylated NCP 30 produces complex 59-X ($X = \text{Cl, I}$), which can also be obtained through the reaction of 56 with CH$_3$I (Scheme 1.25).$^{46}$ Those compounds represent the first examples of stable monomeric organometallic complexes of Cu(II).$^{46}$ The isotropic $^{14}$N EPR hyperfine pattern for 57-X and 58-X can be reproduced by a simulation assuming that all three inner nitrogen atoms are magnetically equivalent, indicating inner C(21) as the proton binding site.$^{46}$ The EPR spectrum of 59-X resembles those of 57-X and 58-X due to the structure similarities between them.$^{46}$

\[ \begin{array}{c}
\text{X} = \text{Cl, CF}_3\text{COO} \\
\text{CuCl}_2 \\
\text{57} \ R = \text{H} \\
\text{58} \ R = \text{CH}_3 \\
\text{HX, collidine} \\
\end{array} \]

![Scheme 1.24 Synthesis of Cu(II) N-confused porphyrin 55 - 58.](attachment://scheme_1.24.png)
Scheme 1.25 Syntheses of dimethylated Cu(II) N-confused porphyrin 59.

The Cu(II) complex can also be obtained through the metalation of N-confused calix[4]phyrin 60 (Scheme 1.26). Compound 60 is prepared in 3 % yield by the acid catalyzed condensation of aryl aldehyde, acetone and pyrrole. Metalation of 60 with NiCl₂ or Cu(OAc)₂ yields complex 61 and 62, respectively, suggesting that the π-conjugated system is not necessary to stabilize the organometallic compounds. Structures of both 61 and 62 were determined by single crystal X-ray diffraction analyses. The Ni(II) complex 61 has a ruffled structure, with four pyrrole rings tilting 20.55, 11.37, 14.63, and 0.00°, whilst the Cu(II) complex 62 has a near planar structure and the four pyrrole rings are tilted 6.69, 4.25, 2.91, and 4.70°. Both complexes form dimeric structures through hydrogen bonding between the peripheral amide groups. Although complex 62 is nearly planar in the solid state, differences between the EPR spectra of 62 in powder (gₓ = gᵧ = 2.031, g₂ = 2.139) and in DMF solution (gₓ = 2.01, gᵧ = 2.06, g₂ = 2.13) suggest a distortion from the square-planar form in DMF solution.
Diamagnetic Ag(III) and Cu(III) complexes of doubly N-confused porphyrin, 63 and 64, were prepared by Furuta et al. via the reaction of N₂CP 23 with AgOAc or Cu(OAc)₂ (Scheme 1.27). Both complexes have a square-planar tetracoordination, shown by their X-ray crystal structures.  


Scheme 1.27 Synthesis of N₂CP complexes 63 and 64.
As an aromatic system, an N-confused porphyrin undergoes electrophilic substitution. Nitration of NCTPP using either NaNO₂/HCl or 30% HNO₃ occurs on inner C(21) and the resulting nitro-substituted NCTPP 65 (Scheme 1.28) is severely distorted due to the repulsion in the core, with the confused pyrrole ring canting 42.4° from the porphyrin plane.⁴⁸,⁴⁹ Both nitronium (NO₂⁺) and nitrosonium (NO⁺) ions are plausible electrophiles, and electrophilic attack by nitrosonium ion followed by oxidation with O₂ in air is a candidate for the nitration process.⁴⁸

![Scheme 1.28 Nitration of NCTPP.](image)

When NCTPP is treated with 1 equiv. of N-bromosuccinimide (NBS), monobrominated NCTPP 66a is obtained in 90% yield, while 2 equiv. of NBS results to dibrominated NCTPP 67a (Scheme 1.29).⁴⁹ When either N-chlorosuccinimide (NCS) or N-iodosuccinimide (NIS) is used in place of NBS, the corresponding monohalogenated NCTPP 66b and 66c are formed, but the dihalogenated products are not obtained, presumably due to the low reactivity of NCS and the instability of the diiodo product.⁴⁹ Bromination of 66b, 66c, and 65 is achieved by treatment with 1 equiv. of NBS.⁴⁹
A new type of porphyrinoid, N-fused porphyrin (NFP) 68 with a fused tripentacyclic pyrrole ring in the macrocyclic core is spontaneously obtained from a pyridine solution of dibrominated N-confused porphyrin 67a in 91% yield (Scheme 1.30). Compounds 67 (b-d) undergo similar reactions. An inversion of the confused pyrrole ring is believed to precede the reaction. Compound 68 is aromatic, as it keeps the 18 π-electron pathway, and signals for the peripheral hydrogens are observed in the range of 7.55 - 8.96 ppm in the $^1$H NMR spectrum. The inner NH signal, expected to be highly shielded due to the ring current, appears at 8.38 ppm, as the result of strong hydrogen bonding overcoming ring current. Despite its crowded multi-ring structure, the porphyrinoid skeleton of 68 is almost planar, as revealed by its X-ray structure (Figure 1.15).
Scheme 1.30 Synthesis and reactions of N-fused porphyrins.

Compound 68 is unstable in basic media. Methoxy substituted N-confused porphyrin 69 is obtained in 72% yield when compound 68 is treated with NaOCH$_3$/CH$_3$OH for 30 min.$^{49}$ Debromination of compound 68 occurs when it is refluxed for 2 days in pyridine.$^{49}$ Presumably the hydrogen atom comes from the residual water in the solvent, as deuterium is introduced to NFP ring when D$_2$O is added to the pyridine solution.$^{49}$
Figure 1.15 ORTEP drawings of compound 68 showing atomic labeling and thermal ellipsoids at 50 % probability: top view (left) and side view (right). H atoms in both view and phenyl groups in the side view have been omitted for clarity.

NCTPP reacts with excess of pyrrole in refluxing DMF containing a catalytic amount of BF$_3$·OEt$_2$ to give a pentapyrrolic NCP 71 with a yield of 60 % (Scheme 1.31).$^{51}$ Compound 71 can also be obtained through BF$_3$·OEt$_2$ catalyzed condensation of benzaldehyde and excess pyrrole with a yield of 1.5 %.$^{51}$

Scheme 1.31 Synthesis of N-confused porphyrin 71.
1.4.4.4 Oxidative Degradation

It has been noticed that N-confused porphyrins are often unstable during the course of metalation with various transition metals such as Cu, Mn and Fe. The complexation reaction of N-confused porphyrins with Cu(II) under an aerobic atmosphere was investigated by Furuta et al. When NCTPP and Cu(OAc)$_2$ were refluxed in toluene for 24 h, a decomposing tripyrrolic complex 72 was obtained in 34% yield (Scheme 1.32). When the reaction was performed under rigorous anaerobic conditions, the inner core complex 55 was formed quantitatively (Scheme 1.24). Complex 72 can be demetalated with conc. H$_2$SO$_4$ giving a free tripyrrolic ligand 73 which can bind a variety of transition metals (Scheme 1.32).

Scheme 1.32 Reactions of tripyrrolic ligand 73.
The cleavage site of the meso-position, either 5-, 20- or both, was determined by using NCP 75 as the starting material (Scheme 1.33).\textsuperscript{52} The isolated tripyrrolic complex 76 preserves the pyridine unit and no other tripyrrolic derivative was observed in this reaction, indicating that the removal of the meso-phenyl group is regioselective at the 5- position.

![Scheme 1.33 Oxidative degradation of NCP 75.](image)

**Scheme 1.33** Oxidative degradation of NCP 75.

### 1.4.5 Other Porphyrin Analogues with a CH in the Inner Macrocycle

Carbaporphyrins are porphyrin analogues with one five-membered unsaturated all-carbon ring replacing one pyrrole ring. Carbaporphyrin 78 (a,b) can be prepared by condensation of hydroxyfulvenedialdehyde 77 (a,b) with tripyrrane 20 (Scheme 1.34).\textsuperscript{30,31} In the \(^1\)H NMR spectrum of compound 78a, the inner NH protons and CH proton have signals at -4.2 and -7.2 ppm, respectively, indicating a strong ring current and the overall aromaticity of carbaporphyrins.
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Scheme 1.34 Synthesis of carbaporphyrin 78 (a,b).

Benziporphyrin, a benzene containing porphyrin analogue, can be synthesized by acid catalyzed condensation of a tripyrrane dicarboxylic acid with isophthalaldehyde. NMR data suggest that benziporphyrin exists as a mixture of two tautomers 79 and 80 (Scheme 1.35). The system does not exhibit aromatic properties as a whole, as the conjugation discontinues in the benzene ring.

Scheme 1.35 Structures of the two tautomers for benziporphyrin.

Oxybenziporphyrin 82 was prepared by the reaction of tripyrrane dicarboxylic acid 20 and 5-formylsalicylaldehyde 81 (Scheme 1.36). It has the 18 π-electron pathway and is aromatic. The inner CH has a signal at -7.2 ppm in the 'H NMR spectrum for compound 82, indicating the presence of a macrocyclic ring current.
Compound 85, a tetraphenylthiaporphyrin bearing one inverted pyrrole, was obtained by Lee and Kim via the [3 + 1] condensation of pyrrole 83 and thiotripyrrane 84 (Scheme 1.37).\(^{57}\)

![Scheme 1.36 Synthesis of oxybenzoporphyrin 82.](image)

Compound 87, a tetraphenylthiaporphyrin bearing one inverted thiophene ring, can be synthesized through condensation of thiophene 86 with pyrrole and benzaldehyde (Scheme 1.38).\(^{58}\) The \(^1\)H NMR spectrum of 87 shows that inner CH and NH resonate at 4.76 and 5.81 ppm, respectively, suggesting weak overall aromaticity of compound 87.

![Scheme 1.37 Synthesis of compound 85.](image)
An aromatic isomer of 5,10,15,20-tetra(p-tolyl)-21,23-dithiaporphyrin with an inverted pyrrole ring, 5,10,15,20-tetra(p-tolyl)-2-aza-21-carba-22,24-dithiaporphyrin, 89, can be prepared by the reaction of 2,5-bis(p-tolylhydroxymethyl)thiophene, 88, with pyrrole (1:1 molar ratio) in dichloromethane, (Scheme 1.39).$^{59}$
A $[3 + 1]$ condensation of 2,5-bis(phenylhydroxymethyl)selenophene, 90, and 5,10-ditolyltripyrrin 91 produces 5,10-diphenyl-15,20-bis(p-tolyl)-2-aza-21-carba-22-selenaporphyrin, 92 (Scheme 1.40), which preserves aromaticity.\textsuperscript{60}

Scheme 1.40 Synthesis of compound 92.
1.5 Research Objectives and Thesis Preview

The objectives of this work are to explore the chemistry of N-confused porphyrins and develop new photosensitizers for PDT.

In the presence of Na$_2$CO$_3$, N-confused tetraarylporphyrins reacted with CH$_3$I to yield novel N,N'-dimethylated N-confused porphyrin salts, which are mixtures of structural isomers (Chapter 2). The structures of the major isomers were determined by X-ray diffraction or NMR spectroscopic analyses. These N,N'-dimethylated N-confused tetraarylporphyrin salts can generate singlet oxygen when irradiated, and therefore, are potential photosensitizers for PDT.

It was postulated that similar to chlorins, N-confused chlorins might have much greater absorption intensity than N-confused porphyrins in the Q-bands region, and thus are better candidates as photosensitizers for PDT. Diels-Alder reactions of N-confused tetraarylporphyrins as dienophiles, and dihydroxylation of N-confused porphyrins with OsO$_4$ were proposed to prepare N-confused chlorins.

In the Diels-Alder reactions of Ni(II) N-confused tetraarylporphyrins as dienophiles with o-benzoquinodimethane, cycloaddition occurred selectively on the peripheral carbon-nitrogen bond and Ni(II) N-confused isoquinoporphyrins were obtained, presumably through oxidation of corresponding N-confused chlorins, the initial cycloaddition product (Chapter 3). This reaction suggested that the peripheral carbon-nitrogen bond of Ni(II) NCPs has some iminium character and might be reactive towards nucleophiles.

Nucleophilic reactions of Ni(II) N-confused porphyrins with NaOCH$_3$ were then studied. In the reactions of (NCTTP)Ni$^{11}$ with NaOCH$_3$ and DDQ, inner C- cyanide addition to
(NCTTP)Ni$^{II}$ and subsequent electrophilic addition of CH$_3$O$^-$ were observed and the products were structurally characterized (Chapter 4).

In our studies involving the reactions of Ni(II) N-confused porphyrins with OsO$_4$, an unexpected product, a Ni(III) complex of N-confused porphyrin inner C-oxide, was obtained and structurally characterized (Chapter 5).
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References


Chapter 2

Alkylation of N-Confused Porphyrins
2.1 Introduction to Alkylation of Porphyrins and N-Confused Porphyrins

N-substituted porphyrins are of great importance to biological systems. They can be produced \textit{in vivo} from N-substitution of cytochrome P-450 enzymes or from reactions of hydrazines with hemoglobin and myoglobin and have been shown to be powerful inhibitors of the enzyme ferrochelatase, which is the terminal enzyme of the heme biosynthetic pathway. An N-substituted porphyrin, N-methyletioporphyrin I, was first reported by McEwen in 1936, and the synthesis and characterization of this compound were subsequently reported with its Zn(II) complex in 1946.

Many synthetic methods have been developed to prepare N-substituted porphyrins. For example, N,N'-dimethylated TPP 93 and 94 are obtained in the yield of 45 % when TPP and CH$_3$I are heated at 100 °C in a sealed tube with K$_2$CO$_3$ (Scheme 2.1). However, N-methylated TPP (N-CH$_3$TPP 95) is a stronger base than TPP and protonation occurs in the presence of AcOH, suppressing further methylation. Thus, when TPP is heated in chloroform at 65 - 70 °C in a sealed tube containing 7.5 % AcOH and 10 % CH$_3$I for 7 days, N-CH$_3$TPP is obtained as the major product (50 %) (Scheme 2.2). Other N-substituted porphyrins, including N-ethyl, N-vinyl, N-phenyl and N-benzyl porphyrins, have also been prepared.

\begin{center}
\textbf{Scheme 2.1} N-methylation of TPP with base.
\end{center}
Addition of a group to one of the central nitrogen atoms distorts the normally planar porphyrin skeleton. The X-ray crystal structure of N-methyl-5,10,15,20-tetrakis(p-bromophenyl)porphyrin, reported by Lavallee and Anderson, shows that the N-methyl substituted pyrrole ring deviates 27.7° from the plane defined by the three unsubstituted nitrogen atoms. X-ray crystal structures of other N-substituted porphyrins show similar deviations from planarity.

The $^1$H NMR spectrum of N-CH₃TPP shows a signal at -4.1 ppm for the inner methyl protons. Other N-substituted porphyrins exhibit similar upfield signals for the inner substituent groups in their respective $^1$H NMR spectra. These signals suggest that even though the porphyrin ring is severely distorted, N-substituted porphyrins preserve aromaticity.

N-substituted porphyrins have UV-vis absorptions with molar extinction coefficients of $10^5$ M⁻¹cm⁻¹ in the Soret region (400 - 500 nm) and $10^4$ M⁻¹cm⁻¹ in the Q-bands region (500 - 700 nm), and the bands are generally red-shifted about 10 nm compared to those of corresponding non-N-substituted porphyrins. The absorption intensities are similar to those of non-N-substituted porphyrins, indicating again that the high degree of aromaticity typical of nearly planar porphyrins is retained.
Alkylation of N-confused porphyrins was reviewed in section 1.4.4.1. In short, both outer N(2) and inner C(21) atoms can be alkylated and outer N(2)-methylated N-confused porphyrin 24, C(21)-methylated N-confused porphyrin 29, C(21),N(2)-dimethylated N-confused porphyrin 30, and their Ni(II) derivatives were prepared by Latos-Grażyński et al.\textsuperscript{7,8}

Other than the N(2) and C(21) atoms, the three inner nitrogen atoms in N-confused porphyrins might be expected to react similarly as the inner nitrogen atoms of porphyrins. Their susceptibility to alkylation in particular was studied in this thesis work. The resulting alkylated products are potential photosensitizers for PDT. These alkylated N-confused porphyrins may also be interesting for their possible novel coordination properties.

Another aspect of this investigation with alkylated N-confused porphyrins is the synthesis of intramolecular C,N-strapped N-confused porphyrins, which have novel structural properties. Intramolecular N-strapped porphyrins 97 have been prepared from their precursor 96 by Ishimaru et al. (Scheme 2.3).\textsuperscript{9} Signals for the N-CH\textsubscript{2} protons of 97 in the \textsuperscript{1}H NMR spectrum are observed upfield at -4.08 and -4.31 ppm, due to the ring current.\textsuperscript{9}

\begin{center}
\textbf{Scheme 2.3} Synthesis of N-strapped porphyrins 97.
\end{center}
As Ni(II) N-confused porphyrins have at least two nucleophilic centers, the N(2) located outside and the C(21) located inside of the porphyrin ring, intramolecular C,N-strapped Ni(II) N-confused porphyrins 98 may be readily synthesized (Scheme 2.4).

![Chemical structure](image)

**Scheme 2.4** Proposed synthesis of intramolecular C,N-strapped Ni(II) N-confused porphyrins.

### 2.2 Results and Discussion

#### 2.2.1 N-Confused Porphyrins

N-confused porphyrins were synthesized according to the procedure of Lindsey and coworkers via condensation of pyrrole and aryl aldehyde under catalysis of MSA (section 1.4.3) (Scheme 2.5).

![Chemical structure](image)

**Scheme 2.5** Synthesis of N-confused tetraarylporphyrins.
2.2.2 N,N'-Dimethylated N-Confused Porphyrins

Methylation of NCTPP with CH₃I in CH₂Cl₂ yields N(2)-CH₃-NCTPP, 24 (section 1.4.4.1). It is assumed that protonation of compound 24 by HI generated from the methylation reaction prevents subsequent inner N-methylation (Scheme 2.6). Therefore, addition of a base, such as Na₂CO₃, might neutralize the intermediate N(2)-CH₃-NCTPP-HI, 102, making the inner nitrogen atoms more nucleophilic towards methylation and resulting in N,N'-dimethylation. In fact, dimethylation of N-confused porphyrins was carried out in CH₂Cl₂ solution using CH₃I and Na₂CO₃ (Scheme 2.7), and addition of two methyl groups was confirmed by the low and high resolution LSIMS spectra of the products. For example, product 103 resulting from the reaction of CH₃I and NCTPP (C₄₆H₃₅N₄) has the molecular ion peak at 643.28623 m/e (HRLSIMS), and the molecular formula search results in C₄₆H₃₅N₄ (m/e Calcd 643.28617) for the molecular ion peak, as expected for the dimethylated product.

Scheme 2.6 Reactions of NCTPP with CH₃I without base.
Elemental analysis of 103 (C, 68.96; H, 4.76; N, 6.86; I, 15.82) agrees with the formation of iodide salts (Anal. Calcd for C₄₆H₃₄N₆·HI·1.5H₂O: C, 69.26; H, 4.80; N, 7.02; I, 15.91). Elemental analyses of 104 - 107 show similar results.

Each of the N,N'-dimethylated N-confused porphyrin salts 103 - 107 can consist of up to three structural isomers (I - III, Scheme 2.7), as there are three possible positions, N(22), N(23), and N(24), for inner N-methylation. ¹H NMR spectra data suggest that each of compounds 103 - 106 consists of two isomers, with the ratio of about 2:1 (Figure 2.1), while compound 107 has at least three isomers.
Each compound 103 - 107 showed only one spot on TLC plates (silica gel or alumina) with various developing solvents. Isolation attempts of the isomers by flash column chromatography using various developing solvents with different stationary phases, including silica gel (230 - 400 mesh), basic alumina, neutral alumina and acidic alumina, were not successful. Only the major isomers of compounds 103 - 106 were isolated by recrystallization with CH$_2$Cl$_2$/hexanes and structures of the major isomers were determined by X-ray diffraction and NMR spectroscopic analyses to be isomers III (Scheme 2.7).

Unlike the synthesis of N-methylated porphyrin, e.g. N-CH$_3$TPP, which requires heating at 65 - 70 °C in a sealed tube for 7 days, synthesis of dimethylated N-confused porphyrins was
performed at room temperature for 2 days. The inner CH resonance at 0.43 ppm in the $^1$H NMR spectrum of N(2)-CH$_3$-NCTPP shows that its ring current is weaker than that of NCTPP, of which the inner CH proton resonates at -5.1 ppm.\textsuperscript{7} Aromaticity is often associated with planarity and the weak ring current of N(2)-CH$_3$-NCTPP may indicate the distortion of planarity. N(2)-CH$_3$-NCTPP is the intermediate to N,N'-dimethylated N-confused porphyrins and the distortion of its planarity can make the inner nitrogen atoms less sterically hindered towards methylation, resulting in the rate increase of inner methylation.

In the presence of solid Na$_2$CO$_3$ (pK$_a$ value of the conjugate acid is 10.2),\textsuperscript{11} the final dimethylation products were iodide salts instead of the free base, suggesting that the basicity of N,N'-dimethylated N-confused porphyrin free base is similar to or stronger than that of Na$_2$CO$_3$. While significant differences of polarity are expected between the protonated form and free base of N,N'-dimethylated N-confused porphyrins, no change on TLC was observed when Et$_3$N (pK$_a$ value of the conjugate acid is 11.0)\textsuperscript{11} was added to a solution of N,N'-dimethylated N-confused porphyrin salt in CH$_2$Cl$_2$, suggesting again their strong basicity. For comparison, the pK$_a$ values of mono-protonated N-CH$_3$TPP and mono-protonated TPP in nitrobenzene are 5.6 and 4.4, respectively.\textsuperscript{1,12}

The cyclic $\pi$ conjugation is discontinued in the inverted pyrrole ring for N,N'-dimethylated N-confused porphyrin free base, while the cyclic delocalized pathway is retained in the protonated form (Scheme 2.8). In the cases of N-CH$_3$TPP or TPP, both the protonated form and free base retain their aromaticity (Scheme 2.9). Therefore, it is expected that the energy difference between the protonated form and the free base N,N'-dimethylated N-confused porphyrins is smaller than that of N-CH$_3$TPP or TPP, which explains the stronger basicity of N,N'-dimethylated N-confused porphyrins.
In an attempt to prepare neutral dimethylated N-confused porphyrins, the major isomers of 103 - 106 were washed with 0.1 % aqueous NaOH solution, and many spots were observed on TLC plates afterwards, suggesting that the dimethylated N-confused porphyrins are not stable in the presence of strong base. Isolation of the neutral dimethylated N-confused porphyrins was not successful.

Metalation of N-methylated porphyrins is faster than that of non-N-substituted porphyrins, as the planarity of N-methylated porphyrins is distorted and thus N-methylated
porphyrins are "predeformed" for complexation.\(^1\) Metalation reactions of Cd(II) and Zn(II) with N-methyletioporphyrin are about \(10^5\) times faster than that of etioporphyrin.\(^1,13\) NCTTP and N(2)-CH\(_3\)-NCTPP react with Ni(OAc)\(_2\)-4H\(_2\)O at room temperature to yield corresponding Ni(II) complexes.\(^7,14\) Therefore, it was expected that metalation of dimethylated N-confused porphyrins should readily proceed. However, when the dimethylated porphyrin salts were refluxed with Ni(OAc)\(_2\)-4H\(_2\)O or Zn(OAc)\(_2\) in CH\(_2\)Cl\(_2\)/CH\(_3\)OH (1:1) for 24 h, no reaction was observed.

### 2.2.2.1 Structural Determination by NMR Spectroscopy

The structure of 106-III (Figure 2.2), the major isomer of N,N'-dimethylated 2-aza-5,10,15,20-tetrakis(p-methoxyphenyl)-21-carbaporphyrin-HI, 106, was determined by NMR spectroscopic analyses (*\(^1\)H, \(^{13}\)C, selective NOE, HMQC and HMBC) (Figure 2.2, 2.3, 2.4 and 2.5). The \(^1\)H 3.81 ppm peak is assigned to H(25) based on the observed cross peak with the \(^{13}\)C 39.5 ppm peak using HMQC (Figure 2.4). Selective NOE experiments show correlations of H(25) (3.81 ppm) with H(43a) (8.40 ppm) and H(43b) (8.04 ppm), correlations of H(43a) with H(43b) and H(18) (7.56 ppm) and correlation of H(18) with H(17) (7.16 ppm), respectively. The N(2)-methyl group hinders rotation of the adjacent \(p\)-methoxyphenyl group. The rotation is slow and H(43a) and H(43b) can be distinguished by NMR spectroscopy. However, there is still some rotation, which results in H(43a) and H(43b) being interchangeable with their peaks broadened. The negative peak at 8.04 ppm, upon irradiation at 8.40 ppm, shows that the two hydrogens are interchangeable. The -1.47 ppm peak is assigned to the inner methyl group, as suggested by the chemical shift, and integration. The observed cross peaks of \(^{13}\)C 150.75 ppm with H(17) (7.16 ppm), H(18) (7.56 ppm) and H(26) (-1.47 ppm) in an HMBC experiment (Figure 2.5) clearly show that the inner methyl group is connected to the pyrrole unit containing H(17) and H(18).
Figure 2.2 $^1$H NMR spectra of 106-III in CD$_2$Cl$_2$ (400 MHz): (a) no irradiation; (b) upon irradiation at 3.81 ppm; (c) upon irradiation at 8.40 ppm; (d) upon irradiation at 7.56 ppm.
Figure 2.3 $^1$H NMR spectrum of 106-III in CD$_2$Cl$_2$ (400 MHz).

The $^1$H NMR signal of C(21)H in 106-III appears at -1.47 ppm, similar to that of N(2)-CH$_3$-NCTPP at 0.31 ppm, suggesting that inner N-methylation does not have a significant impact on the aromaticity.

The structures of 104-III and 105-III, the major isomers of compounds 104 and 105, respectively, were determined in a similar way by NMR spectroscopic analyses.

The N(2)-methyl group hinders rotation of the adjacent $p$-methoxyphenyl group in compound 106-III, as suggested by NMR spectra data. It is expected that the hindrance would be greater in the case of compounds 107, which have $m$-methoxyphenyl group adjacent to the N(2)-methyl group, resulting in atropisomers in addition to structural isomers, making
compounds 107 a more complicated mixture than compounds 103 - 106. Purification by recrystallization was not successful for compounds 107.

Figure 2.4 $^1$H, $^{13}$C HMQC spectrum of 106-III in CD$_2$Cl$_2$ (400 MHz).
Figure 2.5 Portion of the $^1$H, $^{13}$C HMBC spectrum of 106-III in CD$_2$Cl$_2$ (400 MHz).
2.2.2.2 Structural Determination by X-ray Diffraction Analysis

Compound 103-III is the major isomer of N,N'-dimethylated 2-aza-5,10,15,20-tetraphenyl-21-carbaporphyrin-HI, 103. The I⁻ was exchanged for CF₃SO₃⁺ in 103-III giving N(2)-CH₃-N(24)-CH₃-NCTPP-HCF₃SO₃, 108 (Figure 2.6). Crystals of 108 were obtained by solvent diffusion of hexanes into a CH₂Cl₂ solution of 108 and the structure of 108 was determined by X-ray crystallography, which confirms that the porphyrin is N,N'-dimethylated (Figure 2.7). Similar to N-methylated porphyrins, the planarity of 108 is severely distorted (Figure 2.8).

![Figure 2.6 Structure of 108.](image)

Selected bond lengths and angles of compound 108 are included in Table 2.1 and Table 2.2 (Selected bond lengths and angles of NCTPP obtained by Furuta et al.¹⁵ are included for comparison). Bond lengths of the regular pyrroles for 108 have the same pattern as of porphyrins: Cₐ - C₈ > Cₐ - N > C₈ - C₈. Changes of bond lengths in the inverted pyrrole from NCTPP to 108 is severe, -0.038, -0.046, and 0.034 Å, respectively for C(1)-N(2), C(3)-C(4), and C(1)-C(21), indicating that the change of N(2) from diagonal to trigonal changes the π-delocalization pattern.
Figure 2.7 An ORTEP drawing of 108 showing atomic labeling and thermal ellipsoids at the 50 % probability level (top view). H atoms have been removed for clarity.

Figure 2.8 An ORTEP drawing of 108 showing thermal ellipsoids at the 50 % probability level (side view). Phenyl groups, residual H₂O, counteranion and H atoms have been removed for clarity.
Table 2.1 Selected bond lengths (Å) for N(2)-CH₃-N(24)-CH₃-NCTPP and NCTPP.

<table>
<thead>
<tr>
<th>Bond Lengths (Å)</th>
<th>N(2)-CH₃-N(24)-CH₃-NCTPP</th>
<th>NCTPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(2)-C(25)</td>
<td>1.457(5)</td>
<td>N/A²</td>
</tr>
<tr>
<td>N(24)-C(26)</td>
<td>1.478(5)</td>
<td>N/A</td>
</tr>
<tr>
<td>C(1)-N(2)</td>
<td>1.405(5)</td>
<td>1.443</td>
</tr>
<tr>
<td>C(1)-C(20)</td>
<td>1.422(5)</td>
<td>1.436</td>
</tr>
<tr>
<td>C(1)-C(21)</td>
<td>1.389(5)</td>
<td>1.355</td>
</tr>
<tr>
<td>N(2)-C(3)</td>
<td>1.339(5)</td>
<td>1.336</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.408(5)</td>
<td>1.454</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.434(5)</td>
<td>1.410</td>
</tr>
<tr>
<td>C(4)-C(21)</td>
<td>1.391(5)</td>
<td>1.378</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.386(5)</td>
<td>1.366</td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.454(5)</td>
<td>1.441</td>
</tr>
<tr>
<td>C(6)-N(22)</td>
<td>1.386(5)</td>
<td>1.430</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.348(6)</td>
<td>1.352</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.447(5)</td>
<td>1.475</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.422(6)</td>
<td>1.411</td>
</tr>
<tr>
<td>C(9)-N(22)</td>
<td>1.361(5)</td>
<td>1.366</td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.388(5)</td>
<td>1.402</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.432(6)</td>
<td>1.439</td>
</tr>
<tr>
<td>C(11)-N(23)</td>
<td>1.391(5)</td>
<td>1.391</td>
</tr>
<tr>
<td>C(12)-C(13)</td>
<td>1.351(5)</td>
<td>1.325</td>
</tr>
<tr>
<td>C(13)-C(14)</td>
<td>1.439(5)</td>
<td>1.480</td>
</tr>
<tr>
<td>C(14)-C(15)</td>
<td>1.418(5)</td>
<td>1.403</td>
</tr>
</tbody>
</table>
Bond angles for C(25)-N(2)-C(1), C(25)-N(2)-C(3), C(26)-N(24)-C(16), and C(26)-N(24)-C(19) are in the range of 122 - 128° (Table 2.2), indicating that both substituted nitrogen atoms keep sp\(^2\) hybridization. Bond angles for both C(1)-N(2)-C(3) and C(16)-N(24)-C(19) are 108.5°, smaller than the optimum bond angle of 120° for sp\(^2\) hybridized atoms, and this deviation is the result of the strain from planar five-membered pyrrolic ring. N(24) atom is trigonal in both compound 108 and NCTPP, and the N(24) centered bond angles are very close in these two compounds with the difference been 0.1°, 3.6°, and 0.5° (Table 2.2), suggesting that changes of the π electron conjugation of the porphyrin skeleton due to inner N-methylation is small.
Table 2.2 Selected bond angles (°) for N(2)-CH$_3$-N(24)-CH$_3$-NCTPP and NCTPP.

<table>
<thead>
<tr>
<th>Bond Angles (°)</th>
<th>N(2)-CH$_3$-N(24)-CH$_3$-NCTPP</th>
<th>NCTPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(25)-N(2)-C(1)</td>
<td>127.2(4)</td>
<td>N/A*</td>
</tr>
<tr>
<td>C(25)-N(2)-C(3)</td>
<td>123.4(4)</td>
<td>N/A</td>
</tr>
<tr>
<td>C(1)-N(2)-C(3)</td>
<td>108.5(3)</td>
<td>103.5</td>
</tr>
<tr>
<td>C(26)-N(24)-C(16) / H(24)-N(24)-C(16)</td>
<td>122.6(3)</td>
<td>122.5</td>
</tr>
<tr>
<td>C(26)-N(24)-C(19) / H(24)-N(24)-C(19)</td>
<td>122.4(3)</td>
<td>126.0</td>
</tr>
<tr>
<td>C(16)-N(24)-C(19)</td>
<td>108.5(3)</td>
<td>109.0</td>
</tr>
</tbody>
</table>

* N/A stands for "Not Applicable".

### 2.2.2.3 Optical Absorption Spectra

N,N'-dimethylated porphyrin salts have strong absorptions around 475 nm and 800 nm, corresponding to the Soret and Q-bands of porphyrins, respectively (Figure 2.9). The long wavelength absorption around 800 nm is broad, with a molar extinction coefficient around 20,000 M$^{-1}$cm$^{-1}$, making the N,N'-dimethylated porphyrin salts good candidates as photosensitizers for PDT.

The absorption spectra of the salt mixture and the corresponding major isomer are almost identical (Figure 2.9), suggesting that the position of the inner N-methylation does not significantly affect the overall porphyrin π electron conjugation.
2.2.2.4 Generation of Singlet Oxygen

DPBF (1,3-diphenylisobenzofuran) was used to determine the ability of these N,N'-dimethylated N-confused porphyrin salts to generate singlet oxygen ($^1O_2$).\textsuperscript{16} DPBF reacts quickly with singlet oxygen (Scheme 2.10) and its absorption decay around 418 nm can be readily monitored.\textsuperscript{17} The reaction products of DPBF have no absorption in the visible region and do not quench singlet oxygen. A solution containing DPBF (~17 µM) and N,N'-dimethylated N-confused porphyrin salts (e.g. 104, ~13 µM) was irradiated with a halogen lamp using a filter (~700 nm) and monitored by UV-vis spectroscopy at 418 nm. Substantial decay of the UV-vis signal at 418 nm was observed confirming that N,N'-dimethylated N-confused porphyrin salts generate singlet oxygen (Figure 2.10). No change in UV-vis spectra was observed after a sample containing DPBF and an N,N'-dimethylated N-confused porphyrin salts was left in the dark for
10 min, and there is also no change in the UV-vis spectra after irradiating a solution containing only either DPBF or an N,N'-dimethylated N-confused porphyrin salts for 1 min.

![UV-vis spectra of DPBF and compound 104](image)

**Figure 2.10** UV-vis spectra of a solution of DPBF and compound 104 before and after irradiation (irradiation intervals at 20 s). The UV-vis spectrum of compound 104 is shown in the thicker line.

![Scheme 2.10](image)

**Scheme 2.10** Reactions of DPBF with \(^1\text{O}_2\).
2.2.3 C,N-Strapped N-Confused Porphyrins

Attempts to directly synthesize C,N-strapped N-confused porphyrin, using Ni(II) N-confused porphyrin and diiodooctane with AgBF$_4$, were not successful (Scheme 2.11). A mixture of products with molecular ion peaks at 1485 and 1498 m/e (LSIMS) was obtained.

![Scheme 2.11 Direct synthesis of C,N-strapped N-confused porphyrin.](image)

As outer N(2) of N-confused porphyrin can be selectively alkylated in the absence of a base$^7$ and inner C(21) can be alkylated after metalation,$^8$ a stepwise synthesis of the C,N-strapped Ni(II) N-confused porphyrins was designed (Scheme 2.12).
Scheme 2.12 Proposed synthesis of C,N-strapped N-confused porphyrins 116 and 111.

NCTPP was reacted with a large excess of alkyl diiodide (1:20 molar ratio) to avoid dimerization of N-confused porphyrin with an alkyl linkage. Iodoalkylated N-confused porphyrin 112 and 113 were obtained in the yields of 69% and 65%, respectively. Dimerization was not observed in these reactions.

Metalation of compounds 112 and 113 with Ni(OAc)$_2$·4H$_2$O readily proceeded at room temperature to give corresponding Ni(II) complexes 114 and 115 with yields of 92% and 95%, respectively.

When compound 115 was refluxed with AgBF$_4$ in freshly distilled CH$_3$CN/CH$_2$Cl$_2$ (1:1), a compound was obtained in 52% yield. An observed molecular ion peak of 781 m/e (LSIMS)
suggests that this paramagnetic compound is the C,N-strapped N-confused porphyrin 111. A similar result was obtained for compound 114.

The coordination environments of Ni(II) in complexes 111 and 116 are similar to that of paramagnetic dimethylated Ni(II) NCP 27 (section 1.4.4.1), thus it is expected that complex 111 and 116 are paramagnetic as well. Broad peaks were observed in the $^1$H NMR spectra of complexes 111 and 116, and their structures were not determined by NMR spectroscopy. Efforts to determine the structures of 111 and 116 by X-ray crystallography have yet to be successful.

2.2.3.1 Structural Determination of Ni(II) Iodooctylated N-Confused Porphyrin

Crystals of Ni(II) iodooctylated N-confused tetraphenylporphyrin 115 were obtained by solvent diffusion of hexanes into a CH$_2$Cl$_2$ solution of the complex, and the structure of 115 was determined by X-ray crystallography (Figure 2.11). The iodine atom was found to be disordered over two sites, with relative populations of 0.9 and 0.1 for the major and minor fragments, respectively. Only the major form is shown in Figure 2.11. Unlike planar (NCTPP)Ni$^{II}$, the porphyrin skeleton of complex 115 is slightly distorted from planarity (Figure 2.12).

The Ni-N(C) bond distances (Å) of complex 115 are: C(21) 1.904(3), N(22) 1.951(3), N(23) 1.975(2), and N(24) 1.934(3), close to that of (NCTPP)Ni$^{II}$ (1.955 or 1.963 Å). The bond angles of C(1)-N(2)-C(3), C(1)-N(2)-C(25) and C(3)-N(2)-C(25), are 107.7(3), 130.8(3), and 121.4(3)$^\circ$, respectively. The large bond angles of C(1)-N(2)-C(25) and C(3)-N(2)-C(25) indicates that N(2) atom is sp$^2$ hybridized.
Figure 2.11 An ORTEP drawing of 115 showing atomic labeling and thermal ellipsoids at the 50 % probability level (top view). H atoms have been removed for clarity.

Figure 2.12 An ORTEP drawing of 115 showing thermal ellipsoids at the 50 % probability level (side view). Phenyl groups and H atoms have been removed for clarity.
Chapter 2 Alkylation of N-Confused Porphyrins

The bond length of N(2)-C(3) in 115 is 1.311(4) Å, shorter than that of NCTPP (1.336 Å), in which the N(2)-C(3) is a partially isolated double bond. It is also shorter than those of the Cβ - Cβ bonds in 115 (1.345(5), 1.346(5), and 1.345(5) Å, respectively for C(7)-C(8), C(12)-C(13), and C(17)-C(18)). This can be explained by the resonance structures of the complex 115 (Scheme 2.13). Structure 115a, in which the N(2)-C(3) bond contains more of a single bond character, has no charge separation, however, the conjugation is not continued at the inverted pyrrole subunit. Structure 115b has a 18 π-electron pathway and should be reasonably stable. The N(2)-C(3) bond exhibit a double bond nature in structure 115b and the short bond length of N(2)-C(3) can be the result of structure 115b being a significant contributor to the resonance hybrid.

![Scheme 2.13 Resonance structures of the compound 115.](image-url)
2.3 Conclusions

N-confused tetraarylporphyrins react with CH$_3$I in the presence of Na$_2$CO$_3$ to yield N,N'-dimethylated N-confused porphyrin salts, which are mixtures of structural isomers. The structures of the major isomers are determined by X-ray diffraction and/or NMR spectroscopic analyses. These N,N'-dimethylated N-confused tetraarylporphyrin salts can generate singlet oxygen when irradiated and are potential photosensitizers for PDT.

Ni(II) iodoalkylated N-confused porphyrins were prepared as the intermediate to synthesize C,N-strapped N-confused porphyrins. Ni(II) iodooctylated N-confused tetraphenylporphyrin was structurally characterized.
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References


Chapter 3

Cycloaddition Reactions of N-Confused Porphyrrins
3.1 Cycloaddition Reactions

Cycloaddition reactions involve the reaction of two molecules resulting in the formation of a new ring.\(^1\) Many cycloaddition reactions are concerted: there is a single transition state, and therefore, no intermediate lies on the reaction path between reactants and the adduct.\(^1\) Two examples of cycloaddition reactions involving a concerted mechanism are the Diels-Alder reactions and the 1,3-dipolar cycloaddition reactions.

The Diels-Alder reaction is the addition of a diene to a dienophile, e.g. an alkene, to form a cyclohexene (Scheme 3.1).\(^1\) This is called a \([4 + 2]\) cycloaddition reaction as four \(\pi\) electrons from the diene and two \(\pi\) electrons from the dienophile are directly involved in the bonding change.

\[
\begin{array}{c}
\overset{\text{\[4 + 2\] cycloaddition}}{+} \\
\text{Diels-Alder reaction.}
\end{array}
\]

A 1,3-dipolar cycloaddition reaction is an addition reaction of a 1,3-dipole with a dipolarophile (Scheme 3.2).\(^1\) 1,3-Dipoles are isoelectronic with the allyl anion and have four \(\pi\) electrons. Each such dipole (Scheme 3.3) has at least one charge-separated resonance structure with opposite charges in a 1,3-relationship. The 1,3-dipolar cycloaddition reaction is analogous to the Diels-Alder reaction, as both are \([4 + 2]\) cycloaddition reactions.
While dienophiles and dipolarophiles are typically alkenes or alkynes, all that is essential is a $\pi$ bond. For example, different types of imines can act as dienophiles.² Bohlmann et al. found that the simple imine 118 reacted thermally with butadiene carboxylate 119 to afford a Diels-Alder type adduct 121 (Scheme 3.4).³ Only the conjugated ester 121, presumably formed by isomerization of the initial adduct 120, was isolated. In general, electron-deficient imines are the most reactive imine type dienophiles, particularly those of the N-sulfonyl, N-acyl, and iminium salt types.²
3.1.1 Cycloaddition Reactions of Porphyrins

Cycloaddition reactions of porphyrins have been extensively studied and porphyrins have been used as dienes, 1,3-dipoles, dipolarophiles and dienophiles.\textsuperscript{4-10}

Porphyrin 122, which has a $\beta$-fused 3-sulfolene on one of the pyrrole rings, acts as a porphodimethylidene precursor and can be used for a variety of Diels-Alder reactions. For example, it reacts with DMAD to yield the cycloaddition adduct 123 (Scheme 3.5).\textsuperscript{4}

Porphyrinic azomethine ylide 125 can be generated from the reaction of $\beta$-formyl porphyrin 124 with N-methylglycine and this ylide reacts with a range of dipolarophiles (Scheme 3.6).\textsuperscript{5,6} For example, reaction of porphyrin 125 with N-phenylmaleimide yields the
cycloaddition adduct 126 (61 %) and 127 (35 %). In the absence of a dipolarophile, intramolecular cycloaddition of 125 occurs to give porphyrin 128.

Scheme 3.6 Synthesis and reactions of porphyrin 125.

Diels-Alder reactions of porphyrins with β-vinyl groups as dienes, Diels-Alder reactions of porphyrins as dienophiles, and 1,3-dipolar cycloaddition reactions of porphyrins as dipolarophiles have been discussed in sections 1.3.1 and 1.3.3.

Similar to those of porphyrins, the peripheral C-C or C-N bonds of N-confused porphyrins are cross-conjugated and thus might react as alkenes or imines. Cycloaddition reactions of N-confused porphyrins as dienophiles or dipolarophiles were studied in this thesis.
work. This work demonstrates the reactivity of the cross-conjugated peripheral bonds of N-confused porphyrins and offers a simple method to modify N-confused porphyrins. Furthermore, the cycloaddition adducts are of interest as potential photosensitizers for PDT.

3.2 Results and Discussion

3.2.1 Ni(II) N-Confused Porphyrins

N-confused porphyrins were synthesized according to Lindsey's procedure\textsuperscript{11} via condensation of pyrrole and aryl aldehydes under catalysis of MSA (section 1.4.3). The condensation product mixture was passed through a silica gel column under vacuum to remove the less polar side product tetraarylporphyrin and some baseline impurities. The crude N-confused porphyrin product was used without further purification and reacted with Ni(OAc)\textsubscript{2}-4H\textsubscript{2}O to provide Ni(II) N-confused porphyrins 129 (a-e) with overall yield ranging from 6.4\% to 16\% (Scheme 3.7).\textsuperscript{12}

Metalation of N-confused porphyrins gave products that are much less polar than their free base counterparts. This decrease in polarity allowed for a cleaner gradient elution during column chromatographic purifications (silica gel, 230 - 400 mesh). The desired products came off the column with CH\textsubscript{2}Cl\textsubscript{2} (0.4 \% CH\textsubscript{3}OH in CH\textsubscript{2}Cl\textsubscript{2} was used for 129d and 129e), and the impurities normally co-eluted with the free base NCP as the polarity was increased to 1.2 \% CH\textsubscript{3}OH in CH\textsubscript{2}Cl\textsubscript{2}. The additional metalation step was more than offset by the resultant facile purification of the desired products.
3.2.2 Diels-Alder Reactions of Ni(II) N-confused Porphyrins

{o-Benzoquinodimethane, 8, was selected as the diene in the Diels-Alder reactions. Compound 8 is exceedingly reactive as a diene because cycloaddition re-establishes a benzenoid ring resulting in aromatic stabilization (Scheme 3.8).}

Scheme 3.8 Diels-Alder reaction of o-benzoquinodimethane 8.
o-Benzquinodimethane can be generated from sultine 130, which was synthesized from the reaction of sodium hydroxymethanesulfinate (rongalite) and α,α'-dibromo-o-xylene, 131, with a catalytic amount of tetrabutylammonium bromide (TBAB) (Scheme 3.9). Sultine 130 is an ideal precursor of o-benzquinodimethane because it decomposes smoothly around 80 °C and does not produce organic or inorganic byproducts except for gaseous sulfur dioxide.

![Scheme 3.9 Synthesis and reactions of sultine 130.](image)

No reaction was observed when NCTPP was refluxed with sultine 130 in benzene for two days (Scheme 3.10). However, when (NCTPP)NiII was used instead of NCTPP, Diels-Alder adducts were obtained (Scheme 3.11). The major product, which has a higher Rf value on silica gel than that of (NCTPP)NiII, was obtained in 23 % yield and identified as the N-confused isoquinoporphyin 133a based on its mass and NMR spectra (1H, 13C, selective NOE, COSY and 1H/15N HSQC) data (Figure 3.1, 3.2 and 3.3). Compound 133a was presumably formed by oxidation of the chlorin 132a. There is also a product with a higher Rf value than that of compound 133a with a parent ion observed at 879 m/e (LSIMS), presumably from the addition of two equivalents of o-benzquinodimethane to (NCTPP)NiII. However, the yield of this second compound was too low to allow characterization by NMR spectroscopy.
Scheme 3.10 Diels-Alder reaction of NCTPP with sultine 130.

Scheme 3.11 Diels-Alder reactions of Ni(II) N-confused porphyrins with sultine 130.

The parent ion of compound 133a is observed at 770 m/e (LSIMS), suggesting the addition of one o-benzoquinodimethane and the loss of four hydrogen atoms. This is corroborated by the formula search result of C_{52}H_{32}N_4Ni (m/e Calcd 770.19799) from the HRLSIMS result (770.19797 m/e). These results suggest that a four-electron oxidation occurred and 133a is either a Ni(II) N-confused naphthoporphyrin (Diels-Alder addition on a peripheral carbon-carbon bond) or a Ni(II) N-confused isoquinoporphyrin (addition on the peripheral carbon-nitrogen bond).
Attempts to synthesize Diels-Alder adducts of 129d and 129e with sultine 130 were not successful, probably because of the poor solubilities in either benzene or toluene.

3.2.2.1 Structural Determination by NMR Spectroscopy

Based on correlations shown in a COSY experiment (Figure 3.2), signals for the H^a/H^f protons of complex 133a appear as singlets at 6.91 and 8.57 ppm (see Scheme 3.11 for proton assignments) and signals for the H^b - H^e protons appear at 7.11, 7.27 (2H) and 7.46 ppm. The large difference in chemical shift between H^a and H^f protons in complex 133a suggests that the addition is on the peripheral carbon-nitrogen bond rather than on a peripheral carbon-carbon bond, as a nominal difference of chemical shift between H^a and H^f protons would be observed in the peripheral carbon-carbon bond addition product. A large chemical shift difference between H^a and H^f protons has also been observed in isoquinolinium salt 134 (Figure 3.4). Cycloaddition on the peripheral carbon-nitrogen bond is confirmed by the cross peak of ^1H 6.91 ppm with ^15N 17 ppm in a ^1H/^15N HSQC experiment of 133a (Figure 3.3), which indicates that H^a is either two or three bonds away from a nitrogen atom. Similar results were obtained for complex 133b and 133c. Thus, the combined solution NMR results suggest cycloaddition of o-benzoquinodimethane to Ni(II) N-confused porphyrins on the peripheral carbon-nitrogen bond giving N-confused isoquinoporphyrins.
Figure 3.1 $^1$H NMR spectrum of 133a in CD$_2$Cl$_2$ (400 MHz).
Figure 3.2 COSY spectrum of 133a in CD$_2$Cl$_2$ (400 MHz).
Figure 3.3 $^1$H/$^{15}$N HSQC spectrum of 133a (400 MHz, CD$_2$Cl$_2$).

Figure 3.4 $^1$H chemical shift (ppm) assignments of isoquinolinium iodide salt 134 in d$_6$-DMSO (300 MHz).
3.2.2.2 Structural Determination of Ni(II) N-Confused Tetraphenylisoquinoporphyrin by X-ray Diffraction Analysis

Crystals of compound 133a were obtained by solvent diffusion of hexanes into a CH$_2$Cl$_2$ solution of 133a and the structure of Ni(II) N-confused tetraphenylisoquinoporphyrin was determined by X-ray crystallography (Figure 3.5). However, the N(2) and C(3) atoms are disordered and not distinguishable in the X-ray crystal structure.

The X-ray crystal structure shows that the isoquino group is in the same plane with the linked pyrrole subunit. Deviation from planarity for the isoquinopyrrole unit is 0.066 Å. Unlike planar (NCTTP)Ni$^{11,12}$, the porphyrin skeleton of compound 133a is ruffled (Figure 3.6). The dihedral angles between the pyrrole planes of 133a and the plane defined by N(22)N(23)N(24) are as follows: C(21) 19.88°, N(22) 16.85°, N(23) -15.98°, N(24) -13.87°. The Ni-N(C) bond distances (Å) of 133a are: C(21) 1.904(2), N(22) 1.9239(18), N(23) 1.949(2), and N(24) 1.9276(18), which are shorter than that of (NCTTP)Ni$^{11}$ (1.955 or 1.963 Å),$^{12}$ and the shortened bond lengths are typical of the difference between planar Ni(II) porphyrins and ruffled Ni(II) porphyrins.$^{15}$

For complex 133a, there are three resonance structures with charge separation (133a-I, 133-II and 133a-III) and one resonance structure with no charge separation (133a-IV) (Scheme 3.12). Resonance structures with bonding differences outside of the isoquinopyrrole unit are omitted in Scheme 3.12 as the focus is on the bonds involving N(2) and C(3). Table 3.1 shows the bond lengths of N(2)-C(1), N(2)-C(3), N(2)-C(25), C(3)-C(4), and C(3)-C(32), as well as their bond orders in the charge separated resonance structures (133a-I, 133-II and 133a-III) and in structure 133a-IV. The charge separated resonance structures are the main contributors to the overall resonance hybrid of 133a, as indicated by the good match between the bond lengths and the bond orders derived from charge separated resonance structures.
Figure 3.5 An ORTEP drawing of compound 133a showing atomic labeling and thermal ellipsoids at the 50% probability level. Only one of two possible forms is shown.

Figure 3.6 An ORTEP drawing of 133a showing thermal ellipsoids at the 50% probability level (side view). Phenyl groups and H atoms have been removed for clarity.
**Table 3.1** Bond lengths (Å) and bond orders from selected resonance structures for selected bonds in complex 133a.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Bond order in 133a-I, 133-II and 133a-III</th>
<th>Bond order in 133a-IV</th>
<th>Bond length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(2)-C(1)</td>
<td>1</td>
<td>1</td>
<td>1.445(3)</td>
</tr>
<tr>
<td>N(2)-C(3)</td>
<td>4/3</td>
<td>1</td>
<td>1.389(3)</td>
</tr>
<tr>
<td>N(2)-C(25)</td>
<td>5/3</td>
<td>1</td>
<td>1.357(3)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1</td>
<td>2</td>
<td>1.452(3)</td>
</tr>
<tr>
<td>C(3)-C(32)</td>
<td>5/3</td>
<td>1</td>
<td>1.366(3)</td>
</tr>
</tbody>
</table>
3.2.2.3 Optical Absorption Spectra

Broad peaks at 438 and 628 nm, corresponding to the Soret and Q-bands of porphyrins respectively, were observed in the UV-vis spectrum for complex 133a (Figure 3.7). The intensity of the 628 nm peak (42000 M\(^{-1}\) cm\(^{-1}\)) is about 5 times larger than that of the Q-bands of (NCTPP)Ni\(^{II}\), 129a. The difference between the absorption spectra of 133a with (NCTPP)Ni\(^{II}\) reflects the changes in the conjugation pathway of 133a due to the fused isoquino group.

![UV-vis spectra of 133a and (NCTPP)Ni\(^{II}\), 129a.](image)

**Figure 3.7** UV-vis spectra of 133a and (NCTPP)Ni\(^{II}\), 129a.

3.2.2.4 Regioselectivity

The high selectivity of the peripheral carbon-nitrogen bond over the carbon-carbon bonds in the Diels-Alder reactions with o-benzoquinodimethane can be rationalized by the resonance contributions to the overall structure of Ni(II) N-confused porphyrins.\(^{16}\) Scheme 3.13 shows two such resonance structures. In canonical form II, the C=N is both "cross conjugated" and in the
iminium form which is known to be electron-deficient and an active dienophile.\textsuperscript{2} The reported X-ray structure of (NCTTP)Ni\textsuperscript{II} was disordered: the peripheral carbon-nitrogen bond could not be distinguished with the peripheral carbon-carbon bonds,\textsuperscript{12} and thus this X-ray structure is not very helpful in determining the importance of each resonance structure (I and II) to the overall resonance hybrid. Ni(II) N(2)-iodooctyl N-confused tetraphenylporphyrin 115 is isoelectronic with (NCTTP)Ni\textsuperscript{II} and its bond lengths (Figure 3.8) clearly demonstrate the uniqueness of the C=N\textsuperscript{+}R bond and confirm that it should be an effective dienophile (Section 2.2.3.1).

![Scheme 3.13 Two canonical forms for a Ni(II) N-confused porphyrin.](image)

![Figure 3.8 Peripheral bond lengths (Å) for compound 115.](image)
3.2.3 Demetalation of Ni(II) N-confused Isoquinoporphyrins

Demetalation of Ni(II) N-confused isoquinoporphyrin 133a occurred with 10 % TFA in CH₂Cl₂ giving a 63 % yield (Scheme 3.14). The product was confirmed to be 135 on the basis of its mass and NMR (¹H, and COSY) spectra.

![Scheme 3.14 Demetalation of Ni(II) N-confused isoquinoporphyrin 133a.](image)

3.2.3.1 Structural Determination of N-Confused Tetraphenylisoquinoporphyrin by X-ray Diffraction Analysis

Crystals of N-confused tetraphenylisoquinoporphyrin, 135, were obtained by solvent diffusion of hexanes into a CH₂Cl₂ solution of 135 and the structure of 135 was determined by X-ray crystallography (Figure 3.9). X-ray diffraction analysis indicates electron density equivalent to about two electrons in the porphyrin core. This electron density presumably comes from a hydrogen atom of 135 and nickel in an impurity, precursor 133a, present in about 3.8 % based on the electron density. This electron density is not shown in Figure 3.9 or 3.10. An X-ray structure report on 135 is not available because of the impurity.
Figure 3.9 An ORTEP drawing of compound 135 showing atomic labeling and thermal ellipsoids at the 50% probability level.

Figure 3.10 An ORTEP drawing of 135 showing thermal ellipsoids at the 50% probability level (side view). Phenyl groups and H atoms have been removed for clarity.
As shown in Figure 3.10, the isoquinoppyrrole unit is severely tilted from the porphyrin plane, presumably due to the steric repulsion between the isoquinoppyrrole group and the neighboring phenyl group.

### 3.2.3.2 Optical Absorption Spectra of N-Confused Tetraphenylisoquinoporphyrin

Optical absorption spectra of 135 and 133a are shown in Figure 3.11. Compared to that of 133a, the Q-bands of 135 are red-shifted about 50 nm to 678 nm, implying potential use as a photosensitizer for PDT.

![UV-vis spectra of 135 and Ni(II) complex 133a](image)

**Figure 3.11** UV-vis spectra of 135 and Ni(II) complex 133a.
3.2.4 Other Cycloaddition Reactions of N-confused Porphyrins

3.2.4.1 Diels-Alder Reactions of Non-Metalated N-Confused Porphyrins

A Diels-Alder reaction did not occur when NCTPP was refluxed with sultine 130 in benzene. However, similar to that of Ni(II) NCP, the peripheral carbon nitrogen bond of the protonated NCP is in iminium form (Figure 3.12) and thus protonated NCP may be expected to react faster than NCP in the Diels-Alder reaction with o-benzoquinodimethane.

![Figure 3.12 Structures of mono-protonated NCP and Ni(II) NCP.](image)

NCTPP was refluxed with sultine 130 in benzene with 5% acetic acid for 4 h. The major product and compound 135 are not distinguishable on TLC plates with various developing solvents. The parent ion peak of this product is observed at 715 \( m/e \), the same as observed for compound 135. However, purification of this compound was not successful.

3.2.4.2 Diels-Alder Reactions of Ni(II) N-Methylated N-confused Porphyrins

In an attempt to isolate the Diels-Alder adduct as a chlorin, Ni(II) N(2)-methylated N-confused tetra(p-tolyl)porphyrin\(^\text{17}\) was used as a dienophile. Formula search results of the major
product, 137 \((C_{57}H_{46}N_4O)\), based on its HRLSIMS spectrum \((860.30121 \, m/e)\) suggests the additions of one \(\sigma\)-benzoquinodimethane and one oxygen atom. The addition sites for the \(\sigma\)-benzoquinodimethane and oxygen were not determined as purification of 137 was not successful.

![Scheme 3.15 Attempted Diels-Alder reaction of complex 136.](image)

3.2.4.3 1,3-Dipolar Cycloaddition of Ni(II) N-Confused Porphyrins

1,3-Dipole 13\(^{10}\) was used to react with \((\text{NCTTP})\text{Ni}^{\text{II}}\), 129b, to obtain the 1,3-dipolar cycloaddition product (Scheme 3.16). The molecular ion peak of the major product 138 was observed at 782 \(m/e\) (LSIMS), suggesting the addition of one dipole 13 and the loss of two hydrogen atoms. Purification of 138 was not successful. A possible structure for 138 is shown in Scheme 3.16.
3.3 Conclusions

The peripheral carbon-nitrogen double bonds of Ni(II) N-confused porphyrins are partially isolated from the $18\pi$ conjugated aromatic system and react as dienophiles in Diels-Alder reactions with o-benzoquinodimethane yielding novel Ni(II) N-confused isoquinoporphyrins. Ni(II) N-confused tetraphenylisoquinoporphyrin has been structurally characterized.

As suggested by the mass spectra of the major products, Diels-Alder reactions of o-benzoquinodimethane with NCP in acid, Diels-Alder reactions of o-benzoquinodimethane with Ni(II) N(2)-methylated NCP, and 1,3-dipolar cycloaddition reaction of azomethine 13 with Ni(II) NCP do proceed, though purification of these cycloaddition adducts was not successful.
References


Chapter 4

Inner C- Cyanide Addition and Nucleophilic Addition Reactions to Ni(II) N-Confused Porphyrins
4.1 Introduction

Electrophilic substitution and nucleophilic addition reactions commonly occur in porphyrin chemistry.\textsuperscript{1} For electrophilic substitution reactions such as halogenation, formylation and nitrination reactions, metalloporphyrins are often used to avoid the deactivating effect which would occur upon protonation of inner pyrrolic nitrogen atoms.\textsuperscript{1} For instance, (TPP)Cu\textsuperscript{II}, 139, reacts with a large excess of Vilsmeier reagent (prepared by mixing DMF and POCl\textsubscript{3}) to give formylation product 140 in excellent yield (95\%) (Scheme 4.1).\textsuperscript{1,2} Porphyrins are also susceptible to attack by nucleophiles.\textsuperscript{1} For example, nucleophilic addition of butyllithium to TPP at low temperature produces a mixture of phlorin 141 (26\%) and chlorin 142 (18\%) (Scheme 4.2).\textsuperscript{3}

\begin{center}
\textbf{Scheme 4.1} Formylation of (TPP)Cu\textsuperscript{II} 139.
\end{center}
Some electrophilic and nucleophilic reactions of N-confused porphyrins were introduced in section 1.4.4.3. Additionally, as discussed in section 3.2.2.4, the peripheral carbon-nitrogen bond of Ni(II) N-confused porphyrins seems to have some iminium character. Thus, it was expected that, similar to iminium compounds, Ni(II) N-confused porphyrins might be reactive toward nucleophiles, and their reactions with NaOCH₃ were studied.

### 4.2 Results and Discussion

When (NCTTP)Ni⁺⁺ was added to a solution of NaOCH₃ in 1:1 CH₂Cl₂/CH₃OH, no reaction was observed. It was postulated that the addition product, N-confused chlorin 143, is not stable (Scheme 4.3). The reaction, however, might be driven toward a more stable product, 144, with the addition of an oxidant, e.g. DDQ, to convert the N-confused chlorin 143 to N-confused porphyrin 144.
Thus, to a 1:1 CH$_2$Cl$_2$/CH$_3$OH (70 mL) solution of NaOCH$_3$ (200 mg) were added (NCTTP)Ni$^{ll}$ (110 mg) and DDQ (400 mg). The solution was stirred at room temperature for 24 h and then washed with saturated aqueous NaHCO$_3$ solution. The solvent was removed in vacuo and the residue was subjected to column chromatography (silica gel, 230 - 400 mesh, 16 g). Using 1:1 CH$_2$Cl$_2$/hexanes, (NCTTP)Ni$^{ll}$ was eluted first; 3:1 CH$_2$Cl$_2$/hexanes eluted the first new compound, 145 (11.7 mg), and the second new compound, 146 (30.3 mg), was eluted with CH$_2$Cl$_2$.

However, based on the observed parent ion peak at 752 m/e (LSIMS), the major product 146 was not the product expected from simple nucleophilic addition of CH$_3$O$^-$. The formula search result of C$_{49}$H$_{36}$N$_5$Ni (m/e Calcd 752.23237) for 146 from the HRLSIMS result

**Scheme 4.3** Postulated reaction of (NCTTP)Ni$^{ll}$ with NaOCH$_3$ and DDQ.
(752.23242 \( m/e \)) suggested the addition of one carbon atom and one nitrogen atom to 
(NCTTP)Ni\(^{II}\) (C\(_{49}\)H\(_{36}\)N\(_{4}\)Ni). Similarly, compound 145 appeared to involve the addition of one methanol, one carbon atom, and one nitrogen atom to (NCTTP)Ni\(^{III}\) with the loss of two hydrogen atoms, also suggested by the formula search result of C\(_{50}\)H\(_{38}\)N\(_{5}\)ONi \((m/e \text{ Calcd 782.24294})\) based on its HRLSIMS result (782.24344 \( m/e \)).

4.2.1 Structural Determination by X-ray Diffraction Analyses

Full identification of the new complexes could only be obtained through crystal structure analyses. Crystals of complexes 145 and 146 were obtained by solvent diffusion of CH\(_{3}\)OH into CH\(_{2}\)Cl\(_{2}\) solutions of each complex, and the structures of complexes 145 and 146 were determined by X-ray diffraction analyses (Figure 4.1, 4.2 and 4.3). Cyanide addition had been found to occur in both complexes on the inner C(21) site. Additionally, the expected methoxy addition on the peripheral C(3) site was observed in complex 145, the minor product.

![Figure 4.1 Structures of complexes 145 and 146.](image)

The structure of complex 145 displayed disorder in the locations of the methoxy fragment. The structure has been refined to give 63 % occupancy with -OCH\(_{3}\) as shown in
Figure 4.2 and 37% occupancy with -OCH$_3$ attached to the C(3) which replaces N(2) of the major form. Figures 4.2 and 4.4 only show the major form.

**Figure 4.2** An ORTEP drawing of compound 145 showing atomic labeling and thermal ellipsoids at the 50% probability level. H atoms and the disorder of the OCH$_3$ fragment have been removed for clarity.
The porphyrin skeletons of complexes 145 and 146 are distorted from planarity (Figure 4.4 and 4.5). In the X-ray structure of complex 145, the dihedral angles between the pyrrole planes and the plane defined by N(22)N(23)N(24) are as follows: C(21) 39.52(13)°, N(22) -21.01(14)°, N(23) 12.77(13)°, and N(24) -20.56(16)°. For complex 146, the dihedral angles between the pyrrole planes and the plane defined by N(22)N(23)N(24) are as follows: C(21) 40.4(2)°, N(22) -21.0(3)°, N(23) 13.4(3)°, and N(24) -18.5(2)°. The degree of distortion for 145 and 146 is similar to that observed in the C(21)-methylated Ni(II) N-confused porphyrin 26 (Figure 1.11), in which the inverted pyrrole plane deviates from the N(22)N(23)N(24) plane by 42.2°.4
Figure 4.4 An ORTEP drawing of 145 showing thermal ellipsoids at the 50% probability level (side view). $p$-Tolyl groups, H atoms and the disorder of the OCH$_3$ fragment have been removed for clarity.

Figure 4.5 An ORTEP drawing of 146 showing thermal ellipsoids at the 50% probability level (side view). $p$-Tolyl groups, H atoms and solvent have been removed for clarity.
Chapter 4 Inner C- Cyanide Addition and Nucleophilic Addition Reactions

In the X-ray crystal structure of complex 145, the bond distances of N(2)-C(1), N(2)-C(3), and C(3)-C(4) are markedly shorter than those of C(21)-C(1) and C(21)-C(4) (Table 4.1), suggesting that the C(21) atom approaches sp$^3$ hybridization. The distance between Ni and C(26) is 2.429 Å, suggesting possible interaction between these two atoms. However, the bond lengths of C(26)-N(27) and C(21)-C(26) at 1.144(4) and 1.462(4) Å, respectively, and the bond angle of 178.3(3)° for C(21)-C(26)-C(27) are characteristic of N=C~C bonding, suggesting no bonding between Ni and C(26). These structural features were also observed in the structure of complex 146.

Table 4.1 Selected bond lengths for complexes 145 and 146.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Bond length in complex 145 (Å)</th>
<th>Bond length in complex 146 (Å)</th>
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<td>N(2)-C(1)</td>
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<td>1.363(6)</td>
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<tr>
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<tr>
<td>C(3)-C(4)</td>
<td>1.394(4)</td>
<td>1.396(6)</td>
</tr>
<tr>
<td>C(21)-C(1)</td>
<td>1.470(4)</td>
<td>1.468(6)</td>
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<tr>
<td>C(21)-C(4)</td>
<td>1.462(4)</td>
<td>1.442(6)</td>
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<tr>
<td>C(21)-C(25)</td>
<td>N/A$^a$</td>
<td>1.469(8)</td>
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<tr>
<td>C(21)-C(26)</td>
<td>1.462(4)</td>
<td>N/A</td>
</tr>
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<tr>
<td>Ni-N(24)</td>
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<td>1.953(3)</td>
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</table>

a: N/A stands for "Not Applicable".
4.2.2 NMR Spectra of the Cyanide Addition Products

In the $^1$H NMR spectra of 145 and 146, signals representative of the pyrrole protons, excluding C(3)H, are observed in the region of 8.29 - 8.51 ppm and 8.54 - 8.78 ppm, respectively (Figure 4.6, 4.7), and are downfield compared to those of (NCTTP)Ni$^{III}$, which are observed in the 7.65 - 8.12 ppm region. The 4.21 ppm peak in the $^1$H NMR spectrum of 145 was assigned to the OCH$_3$ protons. The 10.03 ppm peak observed in the spectrum of 146 was assigned to C(3)H proton and this signal was not located in the $^1$H NMR spectrum of 145, suggesting addition may have occurred at the C(3) position of complex 145.

Notably, the position of the C(3)H chemical shift for 146 is approximately 1.5 ppm downfield from the starting material, (NCTTP)Ni$^{III}$. A similar effect is observed in the case of inner C-methylated Ni(II) N-confused porphyrin (C(21)-CH$_3$-NCTPP)Ni$^{III}$, 26 (Scheme 1.12), and signal for the C(3)H of complex 26 is observed at 9.90 ppm.$^4$ Complexes 145 and 146 seem to favor the $\pi$ delocalization via the outer path C(1)-N(2)-C(3)-C(4) at the inverted pyrrole fragment, as C(21) atoms in both complexes approach sp$^3$ hybridization and inner conjugation C(1)-C(21)-C(4) is not possible (Figure 4.1). The downfield of C(3)H signal may be the result of a closer ring current.
Figure 4.6 $^1$H NMR spectrum of 145 in CD$_2$Cl$_2$ (400 MHz).

Figure 4.7 $^1$H NMR spectrum of 146 in CD$_2$Cl$_2$ (400 MHz).
4.2.3 Optical Absorption Spectra

The UV-vis spectra of complexes 145 and 146 both exhibit absorptions around 434 nm and 720 nm (Figure 4.8), corresponding to the Soret band and Q-bands of porphyrins, respectively. The single broad Q-bands of complexes 145 and 146 are much different from those of the starting material, (NCTTP)Ni^{II}, which exhibits three distinctive Q-bands, suggesting that inner cyanide addition changes the conjugation pathway. This change of conjugation pathway has also been suggested by the downfield C(3)H signal in the $^1$H NMR spectrum of 145, and is presumably caused by sp$^3$ hybridization of C(21).

![Figure 4.8 UV-vis spectra of complexes 145, 146, and (NCTTP)Ni^{II}.](image)

4.2.4 Reaction Mechanism

A possible mechanism for the generation of complexes 145 and 146 is shown in Scheme 4.4. Electrophilic addition of compound 148, the reduction product of DDQ, to the deprotonated
(NCTPP)Ni$^{II}$, 147, results in 149, which tautomerizes to 150. Elimination of 151 from 150 gives complex 146. Nucleophilic addition of CH$_3$O$^-$ to 146 at C(3) followed by protonation gives Ni(II) N-confused chlorin 152. Oxidation of 152 with DDQ results in complex 145.

Scheme 4.4 A possible mechanism for the generation of complexes 145 and 146.
The UV-vis spectra of (NCTTP)Ni\textsuperscript{II} in CH\textsubscript{2}Cl\textsubscript{2}/CH\textsubscript{3}OH (1:1) with and without NaOCH\textsubscript{3} are shown in Figure 4.9. The difference between the spectra suggests that (NCTTP)Ni\textsuperscript{II} is deprotonated in the presence of NaOCH\textsubscript{3}.

**Figure 4.9** UV-vis spectra of (NCTTP)Ni\textsuperscript{II} in CH\textsubscript{2}Cl\textsubscript{2}/CH\textsubscript{3}OH (1:1) with and without NaOCH\textsubscript{3}.
4.3 Conclusions

Reaction of (NCTTP)Ni^{II} with NaOCH₃ and DDQ resulted in the unexpected inner C-cyanide addition product 146. Subsequent nucleophilic addition of CH₃O⁻ to 146 followed by oxidation with DDQ gave complex 145. Structures of both complexes 145 and 146 were determined by X-ray diffraction analyses. The cyanide additions in both complexes are on the inner C(21) while the methoxy addition for 145 is on the peripheral C(3).

Complexes 145 and 146 seem to favor the π delocalization via the outer path C(1)-N(2)-C(3)-C(4) at the inverted pyrrole fragment as the result of sp³ hybridization of C(21). The resulting increase of the ring current effect in the inverted pyrrole fragment is demonstrated by the remarkable ¹H NMR chemical shift of C(3)H at 10.03 ppm for complex 146, while the signal for C(3)H of (NCTTP)Ni^{II} is observed at 8.56 ppm.

Electrophilic addition of compound 148, the reduction product of DDQ, to the deprotonated (NCTPP)Ni^{II}, was proposed as the critical step for the inner cyanide addition. The generality of the cyanide addition to other nucleophiles with DDQ and base is worthy of study in the future.
Chapter 4 Inner C- Cyanide Addition and Nucleophilic Addition Reactions

References


Chapter 5

$\text{Ni(III)}$ Complex of $N$-Confused Porphyrin

Inner C-Oxide
Chapter 5 Ni(III) Complex of N-Confused Porphyrin Inner C-Oxide

5.1 Introduction

Ni(III) tetrapyrrolic macrocycles have been intensively studied. Wolberg and Manassen reported on the generation of a Ni(III) porphyrin cation via electrochemical oxidation of Ni(II) tetraphenylporphyrin at 77 K. This reaction was re-examined by Dolphin et al. and it was observed that a Ni(II) porphyrin π cation radical is formed at room temperature and a low spin Ni(III) porphyrin is generated upon cooling to 77 K, showing intramolecular electron transfer. N-confused porphyrins can stabilize transition metals in high oxidation states and Ni(III) complexes were prepared by Chmielewski and Latos-Grażyński. Factor 430 (F430), a nickel tetrapyrrole, is the cofactor of methyl-coenzyme M reductase, which catalyzes the final steps of CO₂ conversion to methane by methanogenic Archaea, and a methyl-Ni(III) transient is suggested to be a key intermediate. Ni(III)-alkyl intermediates are also considered to be involved in the reactions of Ni(I) macrocycles with alkyl halides.

In our attempts to synthesize N-confused chlorins via dihydroxylation reactions of Ni(II) N-confused porphyrins with OsO₄, an unexpected product, a Ni(III) complex of N-confused porphyrin inner C-oxide, was obtained and structurally characterized.

5.2 Results and Discussion

A solution of the (NCTTP)Ni¹¹ complex, and OsO₄ in 15 % pyridine/CH₂Cl₂ (50 mL) was stirred at room temperature for 24 h and then filtered through a silica gel plug using 10 % CH₃OH in CH₂Cl₂. The solvent was removed in vacuo and the residue was separated on a silica gel column (230 - 400 mesh, 16 g). Compound 153 was eluted with 1.5 % CH₃OH in CH₂Cl₂ and was obtained in 42 % yield.
A molecular ion peak of 153 was observed at 742 m/e (LSIMS in the positive mode) and the molecular formula search resulted in C_{48}H_{36}N_{4}NiO (m/e Calcd 742.22421) based on the HRLSIMS result (742.22443 m/e), suggesting the addition of one oxygen atom to (NCTTP)Ni^{II} (C_{48}H_{36}N_{4}Ni). However, location of the oxygen atom could not be determined, as addition of oxygen to either N(2) or peripheral C-C bonds and dehydration of the dihydroxylation product are all possible.

Broad peaks were observed in the $^1$H NMR spectrum of 153 (Figure 5.1), suggesting that complex 153 is paramagnetic. Characterization of compound 153 with NMR spectroscopy was thus not successful.

Figure 5.1 $^1$H NMR spectrum of 153 in CD$_2$Cl$_2$ (400 MHz).
X-ray crystallography was relied upon to determine the structure of 153. After numerous unsuccessful attempts to grow crystals of 153 by solvent diffusion of hexanes or CH₃OH into a CH₂Cl₂ solution of 153, crystals of 153 were finally obtained by solvent diffusion of hexanes into a CH₂Cl₂/pyridine solution of 153. The structure of compound 153 was determined by single crystal X-ray diffraction analysis (Figure 5.2, 5.3).

Figure 5.2 An ORTEP drawing of compound 153 showing atomic labeling and thermal ellipsoids at 50 % probability. H atoms, solvent and the disorder of the O(1) atom have been removed for clarity.
The X-ray crystal structure of 153 shows that an oxygen atom has been added to C(21) and is coordinated to the center nickel ion as well. There is also an axial pyridine ligand \textit{trans} to the bridging oxygen atom. A counteranion was not detected. However, the nature of the nickel complex 153 was still not determined as the origin of the unpaired electrons that result in a paramagnetic compound can be from one of the following sources:

- A high spin Ni(II) ion (two unpaired electrons).
- A low spin Ni(II) ion with a porphyrin \( \pi \) cation radical (one unpaired electron).
- A Ni(III) ion (one unpaired electron for a low spin Ni(III) ion and three unpaired electrons for a high spin Ni(III) ion).

To determine the position of the unpaired electrons in complex 153, the EPR spectrum of 153 in toluene glass was taken at 130 K (Figure 5.4). The spectrum is similar to that observed for a Ni(III) complex of N-confused tetraphenylporphyrin containing an axial hydroxyl group (48a, Scheme 1.21).\(^7\) The g-factor \((g > 2.1)\) is indicative of the unpaired electron located on the metal center rather than in a porphyrin \( \pi \) cation radical \((g_{\text{c.c.}} \approx 2.002\) for porphyrin \( \pi \) cation radical).\(^3,7\)
Figure 5.4 EPR spectrum (X-band, 130 K, toluene) of complex 153.

Evan’s method\textsuperscript{14,15} was used to measure the room temperature effective magnetic moment ($\mu_{\text{eff}}$) of complex 153 in CD$_2$Cl$_2$, which was then used to determine the number of unpaired electrons in 153. A dilute CD$_2$Cl$_2$ solution of cyclohexane (reference) was placed in the NMR sample tube while the solvent containing a known concentration of complex 153 and cyclohexane was incorporated in an inner narrow-bore tube. The $^1$H NMR spectrum of cyclohexane in the two coaxial tubes exhibits a chemical shift difference (Figure 5.5) which was used to calculate the room temperature effective magnetic moment. The experimental result is 1.87 $\mu_B$, close to the spin-only value for a low spin d$^7$ Ni(III) center with one unpaired electron ($\mu_{\text{eff}} = (n(n+2))^{0.5} = 1.73 \mu_B$, $n = 1$). In comparison, a high spin Ni(II) ion would have $\mu_{\text{eff}} = 2.83 \mu_B$ ($n = 2$). The room temperature effective magnetic moment of complex 153 and its EPR spectrum lead to the conclusion that complex 153 is a Ni(III) complex of N-confused porphyrin inner C-oxide. This is corroborated by the parent ion peak of 153 at 741 m/e detected using LSIMS in the negative mode, together with the absence of the counteranion in the X-ray crystal structure. The corresponding Ni(II) complex would require protonation of either N(2) or O(1) to balance the charge, resulting in a parent ion peak observed at 742 m/e.
Figure 5.5 The $^1$H NMR (400 MHz, CD$_2$Cl$_2$) spectrum of cyclohexane showing the paramagnetic shift caused by complex 153 (6.9 x 10$^{-3}$ M). (A = cyclohexane in CD$_2$Cl$_2$, and B = cyclohexane peak shifted by complex 153).

5.2.1 X-ray Crystal Structure of Ni(III) N-Confused Porphyrin Inner C-Oxide

The X-ray crystal structure of complex 153 was found to contain a 6-coordinate nickel ion with an axial pyridine ligand. The nickel ion in complex 153 is bonded to both the oxygen atom and C(21). However, disorder was observed in the location of the O(1) atom. The structure was refined to give 64% occupancy with O(1) coordinated to the Ni and the C(21), as shown in Figure 5.2, and 36% occupancy with O(1) attached to the Ni and the N(23). The unit cell also contains one molecule of disordered CH$_2$Cl$_2$.

The planarity of the porphyrin skeleton of 153 is distorted (Figure 5.6), but not as severely as that of the C(21)-methylated Ni(II) N-confused porphyrin 26 (Figure 1.11), in which the inverted pyrrole plane deviates from the N(22)N(23)N(24) plane by 42.2°. For complex 153, the dihedral angles between the pyrrole planes and the plane defined by N(22)N(23)N(24) are as follows: C(21) 20.5(2)°, N(22) -17.61(7)°, N(23) 22.5(2)°, and N(24) -15.3(2)°.
Figure 5.6 An ORTEP drawing (side view) of compound 153 showing distortion from planarity (thermal ellipsoids at 50 % probability). Solvent, p-tolyl group, H atoms and the disorder of the O(1) atom have been removed for clarity.

The Ni-N bond distances (2.005 - 2.100 Å) in 153, listed in Table 5.1, are longer than those of the high spin Ni(II) complex of N(2),C(21)-dimethylated N-confused porphyrin 27 (section 1.4.4.1) (1.979 - 2.057 Å),\(^1\) contrary to what might be expected for the smaller Ni(III) ion.\(^1\) However, a similar elongation of Ni(III)-C bond lengths has also been observed in the case of [Ni\(^{III}\)(C\(_6\)Cl\(_5\))\(_4\)], of which the mean Ni-C distance is 2.007(8) Å.\(^1\)

The fact that the bond distances of N(2)-C(1), N(2)-C(3), and C(3)-C(4) are markedly shorter than those of C(21)-C(1) and C(21)-C(4) suggests that the C(21) atom approaches sp\(^3\) hybridization. The Ni-O(1)-C(21) ring distorts the octahedral coordination geometry of the central metal. While the pyridine ring is almost perpendicular to the N(22)N(23)N(24) plane with a dihedral angle of 83.3(2)°, the O-Ni-C(21) angle is only 39.19(16)°.
Table 5.1 Selected bond lengths (Å) for complex 153.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Bond length (Å)</th>
<th>Bond</th>
<th>Bond length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ni-C(21)</td>
<td>2.069(4)</td>
<td>N(2)-C(1)</td>
<td>1.393(5)</td>
</tr>
<tr>
<td>Ni-N(22)</td>
<td>2.088(3)</td>
<td>N(2)-C(3)</td>
<td>1.348(5)</td>
</tr>
<tr>
<td>Ni-N(23)</td>
<td>2.005(4)</td>
<td>C(3)-C(4)</td>
<td>1.409(5)</td>
</tr>
<tr>
<td>Ni-N(24)</td>
<td>2.100(3)</td>
<td>C(21)-C(1)</td>
<td>1.444(5)</td>
</tr>
<tr>
<td>Ni-N(25)</td>
<td>2.003(3)</td>
<td>C(21)-C(4)</td>
<td>1.427(5)</td>
</tr>
<tr>
<td>Ni-O(1)</td>
<td>2.037(4)</td>
<td>C(21)-O(1)</td>
<td>1.377(5)</td>
</tr>
</tbody>
</table>

Notably, complex 153 is structurally similar to an Fe(III) porphyrin N-oxide 154, which was proposed as an alternative candidate of compound I, 155, for the active intermediate of cytochrome P-450 (Figure 5.7). An Fe(III) porphyrin N-oxide 157 was prepared from oxidation of an Fe(III) porphyrin 156 (Scheme 5.1) and was structurally characterized by Groves and Watanabe. Octaethylporphyrin N-oxide, 159, can be prepared by oxidation of octaethylporphyrin with maleic peracid (Scheme 5.2). Metalations of 159 with Ni(OAc)₂ or Cu(OAc)₂ result in complexes 160 (a,b). The X-ray crystal structures of 159 and the Ni(II) porphyrin N-oxide 160a were reported by Balch et al. The nitrogen atom bonded to oxygen is not bonded to the metal ion in complex 157 and 160a.
Figure 5.7 Structures of Fe(III) porphyrin N-oxide 154, compound 1, 155.

Scheme 5.1 Synthesis of Fe(III) porphyrin N-oxide 157.

Scheme 5.2 Synthesis of porphyrin N-oxide 159 and metalloporphyrin N-oxide 160 (a,b).
5.2.2 Reaction Mechanism

Reactions at C(21) are not uncommon for N-confused porphyrin complexes. Methyllations of (NCTPP)Ni\textsuperscript{II} and Cu(II) N(2)-methylated NCP \textsuperscript{59} with CH\textsubscript{3}I at the C(21) position readily proceed at room temperature (Scheme 1.13, Scheme 1.25).\textsuperscript{8,16} Inner cyanide addition at C(21) was observed for (NCTTP)Ni\textsuperscript{II} in the presence of DDQ and NaOCH\textsubscript{3} (Chapter 4).

Three canonical forms for a Ni(II) N-confused porphyrin are shown in Scheme 5.3. The X-ray crystal structure of Ni(II) N(2)-iodooctyl N-confused tetraphenylporphyrin, \textsuperscript{115} (section 2.2.3.1), shows that its N(2)-C(3) bond length, 1.311(4) Å, is markedly shorter than those of peripheral C-C bonds, 1.345(5) or 1.346(5) Å. Complex \textsuperscript{115} is isoelectronic to Ni(II) N-confused porphyrins, and those bond lengths suggest that dipolar canonical forms II and III, which reserve the 18 \pi-electron pathway and have more double bond character for the N(2)-C(3) bond than canonical form I, are important contributors to the overall resonance hybrid.

\textbf{Scheme 5.3} Three canonical forms for a Ni(II) N-confused porphyrin.

In canonical form III, C(21) is negatively charged, which might explain why Ni(II) N-confused porphyrins readily methylate at C(21). Canonical form III could also be used to explain the susceptibility of C(21) towards oxidation. A possible mechanism for the oxidation of
(NCTTP)Ni\textsuperscript{II} with OsO\textsubscript{4} is shown in Scheme 5.4. Electrophilic addition of OsO\textsubscript{4} to (NCTTP)Ni\textsuperscript{II}, \textit{129b}, at C(21) results in intermediate 161. Rearrangement of 161 gives 162 and cleavage of the (C-)O-Os bond in 162 results in Ni(II) N-confused porphyrin C-oxide 163. One-electron oxidation of 163, followed by deprotonation and coordination of a pyridine gives Ni(III) N-confused porphyrin C-oxide 153. The coordination of pyridine to the nickel ion at earlier steps is also possible.
Scheme 5.4 A possible mechanism for the generation of complex 153.
5.2.3 Optical Absorption Spectra

The UV-vis spectrum of complex 153 displays a broad absorption at 380 nm (50,000 M$^{-1}$ cm$^{-1}$) with shoulder peaks at 428 nm and 470 nm (Figure 5.8). The absorption spectrum of 153 is much different from that of (NCTTP)Ni$^{II}$, suggesting a change of conjugation pathway after oxidation. Structure of 153 favors the outer C(1)-N(2)-C(3)-C(4) conjugation pathway as C(21) is sp$^3$ hybridized (Figure 5.9), while both inner C(1)-C(21)-C(4) and outer pathways are possible for (NCTTP)Ni$^{II}$. This change of conjugation pathway was also suggested for Ni(II) C(21)-methylated N-confused porphyrin 26 (section 1.4.4.1), and the UV-vis spectra of 26 and 153 are similar to each other.

![UV-vis spectra of 153 and (NCTTP)Ni$^{II}$](image-url)

**Figure 5.8** UV-vis spectra of 153 and (NCTTP)Ni$^{II}$. 
Figure 5.9 Structures of complexes 153 and 26 showing possible conjugation pathways.

5.3 Conclusion

A novel nickel complex of N-confused porphyrin inner C-oxide 153 was synthesized from the oxidation of the precursor Ni(II) N-confused porphyrin using OsO₄. This complex was characterized to be a Ni(III) complex based on its X-ray crystal structure, room temperature effective magnetic moment, and mass, NMR and EPR spectra.

Complex 153 was not the expected product, as dihydroxylation occurs for the reactions of Ni(II) porphyrins and OsO₄. However, reactions on C(21) are not uncommon for N-confused porphyrin complexes. In a dipole canonical form (III) of Ni(II) N-confused porphyrins (Scheme 5.3), the 18 π-electron pathway is reserved and C(21) is negatively charged. This canonical form could be used to explain the high reactivity of C(21) in NCP complexes.
References


Chapter 6

Experimental
6.1 Instrumentation and General Materials

All chemicals for syntheses were purchased from Sigma-Aldrich, fine chemicals, Across Chemicals, or Fisher Scientific. If necessary, chemicals were purified by published procedures.\(^1\) Deuterated solvents for NMR measurements were purchased from Cambridge Isotope Laboratories or Aldrich. The silica gel was 230 - 400 mesh (Silicycle). Activity III basic alumina was obtained by adding 6% water to activity I Brockman basic alumina, 60 - 325 mesh (Fisher). Analytical thin-layer chromatography was performed using pre-coated silica gel aluminum plates which contain a fluorescent indicator (GF 254 Merck).

The NMR spectra were recorded on a Bruker WH-400, a Bruker AV-400 or a Bruker AMX-500 in the solvents indicated and were referenced to residual solvent peaks. Elemental analyses were performed on a Carlo Erba Elemental Analyzer 1108. As N-confused porphyrins obtained are often hydroscopic, and $\text{H}_2\text{O}$ has been observed in the X-ray crystal structures of $\text{N},\text{N}'$-dimethylated N-confused porphyrin 108 and inner C(21)-cyano Ni(II) N-confused porphyrin 146, $\text{H}_2\text{O}$ was added to the formula in some cases to obtain acceptable elemental analysis results. The UV-vis spectra were measured with absorption in the range of 0.1 -1.0, on a Varian Cary 50 scan UV-visible spectrophotometer. Mass spectra were determined on a KRATOS Concept IIHQ hybrid mass spectrometer. X-ray crystallographic data were collected on a Rigaku/ADSC CCD. EPR spectrum was recorded on a Bruker ECS-106 spectrometer. Irradiations in the singlet oxygen test were carried with a 250 W Osram HLX 64655 arc lamp in an Oriel lamp housing (model 66184) and the light output passed through a filter: P70-700-S-Corion.
6.2 Experimental Data for Chapter 2

6.2.1 N-Confused Tetraarylporphyrins

General Procedure:

N-confused porphyrins were synthesized using a modification of the procedure of Lindsey and coworkers.\(^2\) To a solution of pyrrole (0.52 mL, 7.5 mmol) and arylaldehyde (7.5 mmol) in CH\(_2\)Cl\(_2\) (750 mL) was added methanesulfonic acid (MSA) (0.34 mL, 5.2 mmol). The mixture was stirred for 30 min after which DDQ (1.50 g, 6.6 mmol) was added. After 1 min, triethylamine (1.5 mL) was added. The crude reaction mixture was passed through a silica gel (14 \(\times\) 4.4 cm) column under vacuum and eluted with CH\(_2\)Cl\(_2\). 1.2 \% Methanol/CH\(_2\)Cl\(_2\) eluted the product with impurities. The fractions were collected and concentrated \textit{in vacuo} and then absorbed onto 7.5 g of activity III basic alumina. The absorbed sample was added to the top of a column with 150 g activity III basic alumina in 2:1 hexanes/CH\(_2\)Cl\(_2\). The polarity of the eluent was increased from 2:1 to 1:1 to 1:2 hexanes/CH\(_2\)Cl\(_2\), the N-confused porphyrins were eluted with 1:2 hexanes/CH\(_2\)Cl\(_2\) (in the case of compound 99 and 100, the polarity of the eluent was increased from CH\(_2\)Cl\(_2\) to 0.2 \% methanol/CH\(_2\)Cl\(_2\) to elute the product). The solvent was removed \textit{in vacuo} and the residue was triturated with CH\(_2\)Cl\(_2\)/hexanes to yield the product. Compound 16a, yield: 373 mg (32 \%); compound 16b, yield: 274 mg (22 \%); compound 99, yield: 259 mg (16 \%); compound 100, yield: 208 mg (15 \%); compound 101, yield: 316 mg (23 \%).

\textbf{2-Aza-5,10,15,20-tetraphenyl-21-carbaporphyrin (16a)}

\(R_f\) (silica-CH\(_2\)Cl\(_2\)/5 \% CH\(_3\)OH/2 \% Et\(_3\)N) 0.54; \(^1\)H-NMR (200 MHz, CD\(_2\)Cl\(_2\)) \(\delta = -3.88\) (s, 1H), -2.40 (br s, 2H), 7.69 - 7.94 (m, 12H), 8.12 - 8.26 (m, 4H), 8.31 - 8.45 (m, 4H), 8.53 -
Chapter 6 Experimental

8.66 (m, 4H), 8.78 (s, 1H), 8.94 (d, \(J = 4.9\) Hz, 1H), 9.01 (d, \(J = 4.9\) Hz, 1H); \(\lambda_{\text{max}}/\text{nm (log } \varepsilon)\)

438 (5.27), 542 (3.95), 582 (4.10), 726 (4.06); MS (EI) 614 (M\(^+\), 100 \%); HRMS (EI) \(m/e\) Calcd for C\(_{44}\)H\(_{30}\)N\(_4\): 614.24705, found 614.24691 (M\(^+\)); Anal. Calcd for C\(_{44}\)H\(_{30}\)N\(_4\) \(\cdot\)H\(_2\)O: C, 83.52; H, 5.10; N, 8.85. Found: C, 83.86; H, 4.77; N, 8.71. These data agree with the literature data.\(^3\)

2-Aza-5,10,15,20-tetrakis(p-tolyl)-21-carbaporphyrin (16b)

\(R_f\) (silica-CH\(_2\)Cl\(_2\)/5 \% CH\(_3\)OH/2 \% Et\(_3\)N) 0.51; \(^1\)H-NMR (400 MHz, CD\(_2\)Cl\(_2\) \(\delta = -5.00\) (s, 1H), -2.43 (br s, 2H), 2.67 (s, 3H), 2.69 (s, 6H), 2.70 (s, 3H), 7.52 - 7.78 (m, 8H), 7.98 - 8.13 (m, 4H), 8.16 - 8.30 (m, 4H), 8.51 - 8.61 (m, 3H), 8.63 (d, \(J = 4.9\) Hz, 1H), 8.70 (s, 1H), 8.93 (d, \(J = 4.9\) Hz, 1H); \(\lambda_{\text{max}}/\text{nm (log } \varepsilon)\) 440 (5.27), 542 (3.93), 586 (4.16), 732 (4.11); MS (LSIMS) 671 (MH\(^+\), 100 \%); Anal. Calcd for C\(_{48}\)H\(_{38}\)N\(_4\): C, 85.94; H, 5.71; N, 8.35. Found: C, 86.01; H, 5.52; N, 8.45. These data agree with the literature data.\(^4\)

2-Aza-5,10,15,20-tetrakis(p-methoxycarbonylphenyl)-21-carbaporphyrin (99)

\(R_f\) (silica-CH\(_2\)Cl\(_2\)/5 \% CH\(_3\)OH/2 \% Et\(_3\)N) 0.46; \(^1\)H-NMR (400 MHz, CD\(_2\)Cl\(_2\) \(\delta = -5.24\) (s, 1H), -2.56 (br s, 2H), 4.08 (d, 12H), 8.18 - 8.58 (m, 19H), 8.60 (d, \(J = 4.7\) Hz, 1H), 8.70 (s, 1H), 8.84(d, \(J = 4.7\) Hz, 1H), 8.94 (d, \(J = 4.7\) Hz, 1H); UV-vis (CH\(_2\)Cl\(_2\) \(\lambda_{\text{max}}/\text{nm (log } \varepsilon)\)) 444 (5.31), 544 (4.07), 586 (4.22), 728 (4.15); MS (LSIMS) 847 (MH\(^+\), 100 \%); HRMS (LSIMS) \(m/e\) Calcd for C\(_{52}\)H\(_{39}\)N\(_4\)O\(_8\): 847.27679, found 847.27667 (MH\(^+\)); Anal. Calcd for C\(_{52}\)H\(_{39}\)N\(_4\)O\(_8\): C, 73.75; H, 4.52; N, 6.62. Found: C, 73.95; H, 4.49; N, 6.72.

2-Aza-5,10,15,20-tetrakis(p-methoxyphenyl)-21-carbaporphyrin (100)

\(R_f\) (silica-CH\(_2\)Cl\(_2\)/5 \% CH\(_3\)OH/2 \% Et\(_3\)N) 0.38; \(^1\)H-NMR (400 MHz, CD\(_2\)Cl\(_2\) \(\delta = -4.92\) (s, 1H), -2.31 (br s, 2H), 4.04 (s, 3H), 4.07 (s, 6H), 4.09 (s, 3H), 7.25 - 7.49 (m, 8H), 8.00 -
8.13 (m, 4H), 8.25 (d, J = 8.6 Hz, 4H), 8.55 (d, J = 5.2 Hz, 3H), 8.61 (d, J = 4.7 Hz, 1H), 8.64 (s, 1H), 8.89 (d, J = 4.4 Hz, 1H), 8.97 (d, J = 4.7 Hz, 1H); UV-vis (CH₂Cl₂) λ_max/nm (log ε) 442 (5.38), 514 (sh), 548 (sh), 592 (4.32), 736 (4.24); MS (LSIMS) 735 (MH⁺, 100%); HRMS (LSIMS) m/e Calcd for C₄₈H₃₉N₄O₄: 735.29713, found 735.29721 (MH⁺); Anal. Calcd for C₄₈H₃₈N₄O₄: C, 78.45; H, 5.21; N, 7.62. Found: C, 78.11; H, 5.10; N, 7.71.

2-Aza-5,10,15,20-tetrakis(m-methoxyphenyl)-21-carbaporphyrin (101)

R_f (silica-CH₂Cl₂/5% CH₃OH/2% Et₃N) 0.50; ¹H-NMR (400 MHz, CD₂Cl₂) δ = -5.12 (s, 1H), -2.45 (br s, 2H), 3.98 (s, 6H), 4.02 (s, 3H), 4.06 (s, 3H), 7.22 - 7.45 (m, 4H), 7.58 - 7.82 (m, 8H), 7.82 - 8.00 (m, 4H), 8.55 - 8.66 (m, 3H), 8.68 (d, J = 4.7 Hz, 1H), 8.78 (s, 1H), 8.96 (d, J = 4.7 Hz, 1H), 9.05 (d, J = 5.2 Hz, 1H); UV-vis (CH₂Cl₂) λ_max/nm (log ε) 440 (5.34), 540 (4.06), 582 (4.13), 726 (4.11); MS (LSIMS) 735 (MH⁺, 100%); HRMS (LSIMS) m/e Calcd for C₄₈H₃₉N₄O₄: 735.29713, found 735.29827 (MH⁺); Anal. Calcd for C₄₈H₃₈N₄O₄: C, 78.45; H, 5.21; N, 7.62. Found: C, 78.44; H, 5.18; N, 7.71.

6.2.2 N,N'-Dimethylated N-Confused Porphyrins

General Procedure:

N-confused porphyrin (100 mg) was dissolved in a minimal amount of CH₂Cl₂ (about 10 mL). To this solution, CH₃I (8 mL) and Na₂CO₃ (250 mg) were added. The mixture was stirred for 2 days in the absence of light, and then filtered through Celite. The filtrate was evaporated to dryness in vacuo and the residue was triturated with CH₂Cl₂/hexanes to yield the products. Compounds 103, yield: 110 mg (88%); compounds 104, yield: 105 mg (85%); compounds 105, yield: 103 mg (87%); compounds 106, yield: 112 mg (92%); compounds 107, yield: 99 mg (82%).
N,N’-Dimethylated 2-aza-5,10,15,20-tetraphenyl-21-carbaporphyrin-I’ (103)

\[ R_f \text{ (silica-CH}_2\text{Cl}_2/5 \% \text{ CH}_3\text{OH/2 \% Et}_3\text{N}) 0.36; \quad ^1\text{H-NMR (400 MHz, CD}_2\text{Cl}_2) \delta = -1.62 \]
\[ (d, \ J = 1.4 \text{ Hz, 0.65H}), -1.57 (d, \ J = 1.5 \text{ Hz, 0.35H}), -1.48 (s, \ 3\times0.65H), -1.39 (s, \ 3\times0.35H), 3.62 \]
\[ (s, \ 3\times0.35H), 3.82 (s, \ 3\times0.65H), 7.18 - 8.54 (m, 27H); \text{UV-vis (CH}_2\text{Cl}_2) \lambda_{\text{max}}/\text{nm (log } \varepsilon ) 382 \text{ (sh),} \]
\[ 476 (4.85), 582 (3.79), 650 (3.73), 724 \text{ (sh),} 788 (4.39); \text{MS (LSIMS) 643 (M}^+ \text{, 100 %); HRMS (LSIMS) } m/e \text{ Calcd for } C_{46}\text{H}_{35}\text{N}_4: 643.28617, \text{ found 643.28623 (M}^+ \text{); Anal. Calcd for } C_{46}\text{H}_{35}\text{N}_4\text{-CF}_3\text{SO}_3: C, 68.96; \text{ H, 4.80; N, 7.02; I, 15.91. Found: C, 68.96; H, 4.76; N, 6.86; I, 15.82.} \]

2-Aza-2,24-dimethyl-5,10,15,20-tetraphenyl-21-carbaporphyrin-CF\textsubscript{3}SO\textsubscript{3}’ (108)

Compounds 103 (86 mg) were dissolved in 20 mL of CH\textsubscript{2}Cl\textsubscript{2}. Silver triflate (1.3 g) was added and the solution was stirred for 2 h. The mixture was passed through a silica gel column (14 g) and eluted with CH\textsubscript{2}Cl\textsubscript{2} under vacuum. CH\textsubscript{2}Cl\textsubscript{2} /1% CH\textsubscript{3}OH eluted the porphyrin triflate salts. The compounds were recrystallized three times with CH\textsubscript{2}Cl\textsubscript{2}/hexanes giving 108 (29 mg). Crystals of 108 were obtained by solvent diffusion of hexanes into a CH\textsubscript{2}Cl\textsubscript{2} solution of 108. \[ R_f \text{ (silica-CH}_2\text{Cl}_2/5 \% \text{ CH}_3\text{OH/2 \% Et}_3\text{N}) 0.36; \quad ^1\text{H-NMR (400 MHz, CD}_2\text{Cl}_2) \delta = -1.60 \text{ (s, 1H), -} \]
\[ 1.49 (s, \ 3H), 3.81 (s, \ 3H), 7.24 (d, \ J = 5.0 \text{ Hz, 1H}), 7.43 (s, \ 1H), 7.62 (d, \ J = 5.0 \text{ Hz, 1H}), 7.70 - \]
\[ 8.13 (m, 20H), 8.16 (d, \ J = 5.1 \text{ Hz, 1H}), 8.20 (d, \ J = 5.1 \text{ Hz, 1H}), 8.33 (d, \ J = 4.8 \text{ Hz, 1H}), 8.47 \]
\[ (d, \ J = 6.4 \text{ Hz, 1H}); ^{13}\text{C-NMR (100 MHz, CD}_2\text{Cl}_2) \delta = 35.47, 39.93, 98.91, 123.55, 124.13, \]
\[ 127.42, 128.06, 128.11, 128.64, 129.00, 129.50, 130.00, 130.23, 131.51, 131.70, 131.88, 132.97, \]
\[ 134.38, 134.93, 136.03, 136.16, 136.92, 137.24, 137.63, 138.70, 139.69, 139.86, 140.54, 141.16, \]
\[ 150.96; \text{UV-vis (CH}_2\text{Cl}_2) \lambda_{\text{max}}/\text{nm (log } \varepsilon ) 385 \text{ (sh),} \]
\[ 475 (4.85), 580 (3.74), 650 (3.67), 724 \text{ (sh),} 790 (4.41); \text{MS (LSIMS) 643 (M}^+ \text{, 100 %); Anal. Calcd for } C_{46}\text{H}_{35}\text{N}_4\text{-CF}_3\text{SO}_3\cdot1.5\text{H}_2\text{O: C, 68.85;} \]
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H, 4.67; N, 6.83; S, 3.91. Found: C, 68.99; H, 4.61; N, 6.78; S, 4.00.

N,N'-Dimethylated 2-aza-5,10,15,20-tetrakis(p-tolyl)-21-carbaporphyrin-I' (104)

\[ R_f (\text{silica-CH}_2\text{Cl}_2/5 \% \text{CH}_3\text{OH}/2 \% \text{Et}_2\text{N}) \] 0.36; \[ ^1\text{H-NMR (400 MHz, CD}_2\text{Cl}_2) \delta = -1.53 \] (d, \( J = 1.7 \text{ Hz}, 0.65\text{H})), -1.48 (s, 3\times0.65\text{H}), -1.45 (d, \( J = 1.7 \text{ Hz}, 0.35\text{H})), -1.34 (s, 3\times0.35\text{H}), 2.65 (m, 12\text{H}), 3.61 (s, 3\times0.35\text{H}), 3.81 (s, 3\times0.65\text{H}), 7.1 - 8.5 (m, 23\text{H}); UV-vis (CH\text{}_2\text{Cl}_2) \( \lambda_{\text{max}}/\text{nm} \) (log \( \varepsilon \)) 392 (sh), 478 (4.85), 588 (3.64), 646 (3.69), 798 (4.22); MS (LSIMS) 699 (M^+, 100%); HRMS (LSIMS) \( m/e \) Calcd for C\text{50H}\text{43N}\text{4}-I-0.5H\text{2O}: C, 71.85; H, 5.31; N, 6.70. Found: C, 71.85; H, 5.41; N, 6.70.

2-Aza-2,24-dimethyl-5,10,15,20-tetrakis(p-tolyl)-21-carbaporphyrin-I' (104-III)

Compounds 104 (109 mg ) were recrystallized three times with CH\text{2Cl}_2/hexanes to give the major isomer 104-III (34 mg). \[ R_f (\text{silica-CH}_2\text{Cl}_2/5 \% \text{CH}_3\text{OH}/2 \% \text{Et}_2\text{N}) \] 0.36; \[ ^1\text{H-NMR (400 MHz, CD}_2\text{Cl}_2) \delta = -1.55 \] (d, \( J = 1.7 \text{ Hz}, 1\text{H})), -1.49 (s, 3\text{H}), 2.63 (s, 6\text{H}), 2.66 (s, 6\text{H}), 3.82 (s, 3\text{H}), 7.22 (d, \( J = 5.2 \text{ Hz}, 1\text{H})), 7.33 (d, \( J = 1.3 \text{ Hz}, 1\text{H})), 7.51 - 8.05 (m, 17\text{H}), 8.15 (d, \( J = 5.2 \text{ Hz}, 1\text{H})), 8.18 (d, \( J = 5.2 \text{ Hz}, 1\text{H})), 8.29 (d, \( J = 4.7 \text{ Hz}, 1\text{H})), 8.34 (br s, 1\text{H}); \[ ^{13}\text{C-NMR (100 MHz, CD}_2\text{Cl}_2) \delta = 21.54, 21.56, 21.61, 21.83, 35.21, 39.72, 98.64, 114.12, 123.50, 123.96, 127.53, 128.60, 128.79, 128.89, 129.33, 130.01, 130.51, 130.68, 131.30, 131.60, 132.75, 134.25, 134.79, 135.06, 135.90, 136.85, 137.09, 137.45, 137.86, 137.89, 139.08, 139.76, 140.67, 141.30, 142.83, 147.10, 149.30, 150.88, 152.18, 160.56, 160.76; UV-vis (CH\text{2Cl}_2) \( \lambda_{\text{max}}/\text{nm} \) (log \( \varepsilon \)) 390 (sh), 435 (sh), 480 (4.78), 585 (3.54), 650 (3.56), 800 (4.26); MS (LSIMS) 699 (M^+, 100%); Anal. Calcd for C\text{50H}\text{43N}\text{4-I-0.5H\text{2O}}: C, 71.08; H, 5.37; N, 6.63; I, 15.02. Found: C, 71.05; H, 5.31; N, 6.58; I, 14.95.
N,N'-Dimethylated 2-aza-5,10,15,20-tetrakis(p-methoxycarbonylphenyl)-21-carbaporphyrin-1 (105)

\[ R_f (\text{silica-CH}_2\text{Cl}_2/5 \text{ % CH}_3\text{OH/2 % Et}_3\text{N}) 0.36; ^1\text{H-NMR (400 MHz, CD}_2\text{Cl}_2) \delta = -1.79 \text{ (m, 1H), -1.49 (m, 3H), 3.65 (s, 3x0.27H), 3.87 (s, 3x0.73H), 4.05 (m, 12H), 7.20 - 8.73 (m, 23H); UV-vis (CH}_2\text{Cl}_2 \lambda_{\text{max/nm (log e)}} 386 (sh), 478 (4.84), 576 (3.86), 652 (3.81), 726 (sh), 792 (4.24); MS (LSIMS) 875 (M^+, 100%); HRMS (LSIMS) m/e Calcd for C_{54}H_{43}N_4O_8: 875.30809, found 875.30815 (M^+); Anal. Calcd for C_{54}H_{43}N_4O_8I-2.5H_2O: C, 61.89; H, 4.62; N, 5.35. Found: C, 61.99; H, 4.42; N, 5.20. \]

2-Aza-2,24-dimethyl-5,10,15,20-tetrakis(p-methoxycarbonylphenyl)-21-carbaporphyrin-1 (105-III)

Compounds 105 (78.5 mg) were recrystallized three times with CH_2Cl_2/hexanes to give the major isomer 105-III (29 mg). \[ R_f (\text{silica-CH}_2\text{Cl}_2/5 \text{ % CH}_3\text{OH/2 % Et}_3\text{N}) 0.36; ^1\text{H-NMR (400 MHz, CDCl}_3) \delta = -1.45 \text{ (d, 4H), 3.91 (s, 3H), 4.06 (s, 12H), 7.19 (s, 1H), 7.52 (s, 2H), 7.82 - 8.85 (m, 20H); }^{13}\text{C-NMR (125 MHz, CD}_2\text{Cl}_2) \delta = 35.83, 40.50, 52.73, 52.78, 52.83, 52.94, 99.08, 114.20, 122.42, 123.95, 126.95, 128.01, 128.86, 129.15, 129.52, 129.59, 129.99, 130.27, 130.49, 130.76, 130.82, 130.89, 130.96, 131.18, 131.47, 131.55, 132.17, 132.81, 133.03, 134.28, 134.53, 135.19, 135.98, 136.06, 136.17, 137.05, 139.68, 139.90, 141.03, 143.82, 144.00, 144.46, 150.73, 160.48, 166.74, 167.02, 167.08; UV-vis (CH}_2\text{Cl}_2 \lambda_{\text{max/nm (log e)}} 385 (sh), 480 (4.83), 585 (3.67), 655 (3.16), 725 (sh), 790 (4.26); MS (LSIMS) 875 (M^+, 100%); Anal. Calcd for C_{54}H_{43}N_4O_8I-H_2O: C, 63.53; H, 4.44; N, 5.49; I, 12.43. Found: C, 63.26; H, 4.55; N, 5.48; I, 12.20. \]
N,N'-Dimethylated 2-aza-5,10,15,20-tetrakis(p-methoxyphenyl)-21-carbaporphyrin·I (106)

R_f (silica-CH_2Cl_2/5 % CH_3OH/2 % Et_3N) 0.36; ^1H-NMR (400 MHz, CD_2Cl_2) δ = -1.43 (s, 3×0.7H), -1.37 (d, J = 1.5 Hz, 1×0.7H), -1.22 (d, 4×0.3H), 3.60 (s, 3×0.3H), 3.82 (s, 3×0.7H), 4.00 - 4.14 (m, 12H), 7.07 - 8.50 (m, 23H); UV-vis (CH_2Cl_2) λ_max/nm (log ε) 436 (4.82), 486 (4.97), 592 (3.62), 662 (3.82), 818 (4.40); MS (LSIMS) 763 (M^+, 100 %); Anal. Calcd for C_{50}H_{43}N_4O_4·1.5H_2O: C, 65.43; H, 5.05; N, 6.10. Found: C, 65.67; H, 4.88; N, 5.98.

2-Aza-2,24-dimethyl-5,10,15,20-tetrakis(p-methoxyphenyl)-21-carbaporphyrin·I (106-III)

Compounds 106 (89 mg) were recrystallized three times with CH_2Cl_2/hexanes to give the major isomer 106-III (37 mg). R_f (silica-CH_2Cl_2/5 % CH_3OH/2 % Et_3N) 0.36; ^1H-NMR (500 MHz, CDCl_3) δ = -1.47 (s, 3H), -1.44 (s, 1H), 3.81 (s, 3H), 4.01 - 4.13 (m, 12H), 7.16 (d, J = 4.9 Hz, 1H), 7.19 (s, 1H), 7.28 (m, 4H), 7.38 (d, J = 8.6 Hz, 2H), 7.46 (m, 2H), 7.56 (d, J = 4.9 Hz, 1H), 7.75 (d, J = 4.7 Hz, 1H), 7.84 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 7.0 Hz, 2H), 8.04 (m, 3H), 8.11 (d, J = 5.1Hz, 1H), 8.14 (d, J = 4.6 Hz, 1H), 8.15 (d, J = 5.1 Hz, 1H), 8.40 (d, J = 6.4 Hz, 1H); ^13C-NMR (125 MHz, CD_2Cl_2) δ = 35.02, 39.48, 55.97, 56.04, 56.21, 56.38, 98.68, 113.27, 113.51, 113.64, 113.79, 113.97, 114.08, 115.24, 116.37, 122.90, 123.70, 127.73, 128.25, 129.77, 130.56, 130.60, 130.99, 131.19, 132.17, 132.37, 132.40, 133.37, 135.49, 135.93, 136.44, 136.52, 136.88, 137.24, 138.78, 139.19, 141.06, 146.55, 148.80, 150.75, 152.21, 160.39, 160.54, 160.94, 161.95, 163.24; UV-vis (CH_2Cl_2) λ_max/nm (log ε) 436 (4.78), 486 (4.91), 590 (3.56), 658 (3.74), 824 (4.37); MS (LSIMS) 763 (M^+, 100 %); HRMS (LSIMS) m/e Calcd for C_{50}H_{43}N_4O_4: 763.32843, found 763.32857 (M^+); Anal. Calcd for C_{50}H_{43}N_4O_4·I: C, 67.40; H, 4.87; N, 6.29; I, 14.25. Found: C, 67.11; H, 4.97; N, 6.16; I, 14.09.
N,N'-Dimethylated 2-aza-5,10,15,20-tetrakis(m-methoxyphenyl)-21-carbaporphyrin·I (107)

R_f (silica-CH\textsubscript{2}Cl\textsubscript{2}/5 % CH\textsubscript{3}OH/2 % Et\textsubscript{3}N) 0.36; \textsuperscript{1}H-NMR (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \( \delta = -1.61 \) (m, 1H), -1.48 (d, 3\times0.7H), -1.39 (s, 3\times0.3H), 3.68 (s, 3\times0.3H), 3.86 (s, 3\times0.7H), 3.95- 4.17 (m, 12H), 7.21 - 8.42 (m, 23H); UV-vis (CH\textsubscript{2}Cl\textsubscript{2}) \( \lambda_{\text{max}}/\text{nm (log } \epsilon) \) 378 (sh), 478 (4.95), 584 (3.81), 654 (3.74), 724 (sh), 788 (4.38); MS (LSIMS) 763 (M\textsuperscript{+}, 100 %); HRMS (LSIMS) \( m/e \) Calcd for C\textsubscript{50}H\textsubscript{43}N\textsubscript{4}O\textsubscript{4}: 763.32843, found 763.32854 (M\textsuperscript{+}); Anal. Calcd for C\textsubscript{50}H\textsubscript{43}N\textsubscript{4}O\textsubscript{4}\cdot0.5H\textsubscript{2}O: C, 66.74; H, 4.93; N, 6.23; I, 14.10. Found: C, 66.72; H, 4.93; N, 6.30; I, 13.97.

Singlet Oxygen Tests of N,N'-Dimethylated N-Confused Porphyrin Salts

A solution containing DPBF and an N,N'-dimethylated N-confused porphyrin salt (one of compounds 103 - 107 or the major isomer of 103 - 106) (OD = 0.8 - 1.0 at 418 nm, OD = -0.2 at irradiation wavelength) was prepared and the UV-vis spectra were measured. The solution was then irradiated with a halogen lamp (a 250 W Osram HLX 64655 arc lamp in an Oriel lamp housing, model 66184, at 30V) using a filter (\textasciitilde700 nm, P70-700-S-Corion) for four 20 second intervals (the UV cell is about 1 cm away from the filter) and UV-vis spectra were taken after each interval. Substantial decay of the signal around 418 nm was observed in all cases.\textsuperscript{5} No change in UV-vis spectra was observed after a sample containing DPBF and an N,N'-dimethylated N-confused porphyrin salt was left in the dark for 10 min, and there was also no change in UV-vis spectra after irradiating a solution containing only DPBF or an N,N'-dimethylated N-confused porphyrin salt for 1 min.
6.2.3 Synthesis towards C,N-Strapped N-Confused Porphyrins

6.2.3.1 Synthesis of Iodoalkylated N-Confused Porphyrins

A CHCl₃ solution (25 mL) of NCTPP (153 mg) and I(CH₂)₆I (1.76 g) was refluxed for three days under N₂, shielded from light. The reaction mixture was then chromatographed with silica gel (14 g) under vacuum and eluted with CH₂Cl₂/methanol. 0.8 % Methanol/CH₂Cl₂ eluted NCTPP with some impurities and 2 % methanol/CH₂Cl₂ eluted 112 (142 mg, 69 %).

2-Aza-2-iodohexyl-5,10,15,20-tetraphenyl-21-carbaporphyrin (112)

\[ R_f (\text{silica-CH}_2\text{Cl}_2/5 \% \text{CH}_3\text{OH}/2 \% \text{Et}_3\text{N}) 0.43; \] \[ ^1H-\text{NMR (300 MHz, CD}_2\text{Cl}_2) \delta = -2.90 \text{ (s, 1H), 0.62 (m, 2H), 0.89 (m, 2H), 1.19 (m, 2H), 1.36 (m, 2H), 2.87 (t, } J = 6.8 \text{ Hz, 2H), 4.01 (t, } J = 7.7 \text{ Hz, 2H), 7.59 (s, 1H), 7.70 - 8.42 \text{ (m, 24H), 8.67 (d, } J = 5.1 \text{ Hz, 1H), 8.85 (d, } J = 5.0 \text{ Hz, 1H); MS (LSIMS) 825 (M}^+, 100 \%); HRMS (LSIMS) m/e Calcd for C_{50}H_{42}N_{4}I: 825.24542, found 825.24554 (M}^+); \text{Anal Calcd for C}_{50}H_{42}N_{4}I-HI-2.5H_2O: C, 60.19; H, 4.75; N, 5.62. Found: C, 60.17; H, 4.40; N, 5.72.

6.2.3.2 Synthesis of Ni(II) Iodoalkylated N-Confused Porphyrins

N-confused porphyrin 112 (73 mg) and Ni(OAc)$_2$-4H₂O (0.36 g) were dissolved in CH₂Cl₂/CH₃OH (2:3) and the solution was stirred for 24 h. The solvent was then removed in vacuo, and the residue was separated with silica gel (12 g) column eluting with CH₂Cl₂ to give Ni(II) complex 114 (92 %). Ni(II) complex 115 was obtained similarly with a yield of 95 %.

2-Aza-2-iodohexyl-5,10,15,20-tetraphenyl-21-carbaporphyrinonickel(II) (114)

\[ R_f (\text{silica-CH}_2\text{Cl}_2/\text{hexanes 1:1}) 0.47; \] \[ ^1H-\text{NMR (400 MHz, CD}_2\text{Cl}_2) \delta = 0.96 \text{ (m, 2H), 1.21 (m, 2H), 1.67 (m, 4H), 3.10 (t, } J = 7.0 \text{ Hz, 2H), 3.80 (t, } J = 7.8 \text{ Hz, 2H), 7.56 - 7.69 \text{ (m, 12H),} \]
7.77 (d, J = 5.0 Hz, 1H), 7.80 - 7.97 (m, 12H), 8.09 (d, J = 5.1 Hz, 1H), 8.44 (s, 1H); $^{13}$C-NMR (100 MHz, CD$_2$Cl$_2$) δ = 7.12, 25.85, 30.15, 32.13, 33.61, 52.41, 127.20, 127.38, 127.46, 127.65, 127.80, 127.96, 128.27, 128.75, 130.20, 132.20, 132.34, 132.84, 133.51, 133.55, 133.80, 141.80, 152.44; UV-vis (CH$_2$Cl$_2$) $\lambda_{max}$/nm (log ε) 364 (4.68), 430 (4.98), 462 (sh), 562 (4.05), 718 (3.71), 786 (3.70); MS (LSIMS) 881 (M$^+$, 100 %).

2-Aza-2-iodooctyl-5,10,15,20-tetraphenyl-21-carbaporphyrinatonickeI(II) (115)

R$_f$(silica-CH$_2$Cl$_2$/hexanes 1:1) 0.20; $^1$H-NMR (400 MHz, CD$_2$Cl$_2$) δ = 0.95 (m, 2H), 1.14 (m, 4H), 1.32 (m, 2H), 1.68 (m, 4H), 3.48 (t, J = 6.7 Hz, 2H), 3.78 (t, J = 7.8 Hz, 2H), 7.55 - 7.68 (m, 12H), 7.75 - 7.98 (m, 13H), 8.09 (d, J = 5.1 Hz, 1H), 8.45 (s, 1H); $^{13}$C-NMR (100 MHz, CD$_2$Cl$_2$) δ = 26.79, 27.02, 28.96, 29.14, 32.26, 32.90, 45.60, 52.46, 117.51, 118.65, 122.03, 124.31, 126.13, 127.18, 127.38, 127.46, 127.65, 127.77, 127.95, 128.24, 128.70, 130.18, 131.34, 132.20, 132.33, 133.45, 133.52, 133.56, 133.80, 134.16, 139.71, 140.27, 141.83, 144.36, 146.24, 148.04, 149.47, 150.97, 152.52, 153.09; MS (LSIMS) 909 (M$^+$, 33 %), 818 (100 %).

6.2.3.3 Synthesis of C,N Strapped N-Confused Porphyrins

Compound 115 (63.1 mg) was refluxed with AgBF$_4$ (253 mg) in 150 mL fresh distilled CH$_3$CN/CH$_2$Cl$_2$ (1:1) for 24 h. The solvent was then removed in vacuo, and the residue was chromatographed with silica gel (12 g) eluting with 1.5 % methanol/CH$_2$Cl$_2$ to give complex 111 (28.3 mg, 52 %), MS (LSIMS) 781 (M$^+$, 100 %). Complex 116 was obtained similarly with a yield of 56 %, MS (LSIMS) 753 (M$^+$, 100 %).
6.3 Experimental Data for Chapter 3

6.3.1 Ni(II) N-Confused Porphyrins

To a solution of pyrrole (1.04 mL, 15 mmol) and arylaldehyde (15 mmol) in CH$_2$Cl$_2$ (750 mL) was added MSA (0.98 mL, 15 mmol). The mixture was stirred for 8 min after which DDQ (3.00 g, 13.2 mmol) was added. After 1 min, triethylamine (1.5 mL) was added. The crude reaction mixture was passed through a silica gel column (14 × 4.4 cm) under vacuum and eluted with CH$_2$Cl$_2$. CH$_2$Cl$_2$/1.2 % methanol eluted the product with impurities. The fractions were collected and dried in vacuo. The residue and Ni(OAc)$_2$·4H$_2$O (3.50 g) were dissolved in 500 mL CH$_2$Cl$_2$/CH$_3$OH (1:1) and the solution was stirred for 24 h. The solvent was then removed in vacuo, and the residue was purified with a silica gel column (12 × 4.4 cm) under vacuum eluting with CH$_2$Cl$_2$ (in the cases of 129d and 129e, 0.4 % methanol/CH$_2$Cl$_2$ eluted the product) to give the Ni(II) complex. Compound 129a, yield: 405 mg, (16 %); compound 129b, yield: 306 mg, (11 %); compound 129c, yield: 257 mg, (7.5 %); compound 129d, yield: 216 mg, (6.4 %); compound 129e, yield: 389 mg, (13 %).

2-Aza-5,10,15,20-tetraphenyl-21-carbaporphyrinonickel(II) (129a)

R$_f$ (silica-CH$_2$Cl$_2$/hexanes 3:1) 0.59; $^1$H-NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ = 7.56 - 7.64 (m, 9H), 7.65 - 7.71 (m, 3H), 7.77 - 7.86 (m, 6H), 7.86 - 7.95 (m, 6H), 8.06 (d, $J$ = 4.7 Hz, 1H), 8.09 (d, $J$ = 5.2 Hz, 1H), 8.57 (d, $J$ = 3.9 Hz, 1H), 10.24 (br s, 1H); UV-vis (CH$_2$Cl$_2$) $\lambda_{\text{max}}$/nm (log $\varepsilon$) 359 (sh), 426 (4.92), 596 (3.92), 718 (3.66), 788 (3.71); MS (LSIMS) 670 (M$^+$, 100%). These data agree with the literature data. 6
2-Aza-5,10,15,20-tetrakis(p-tolyl)-21-carbaporphyrinatonickel(II) (129b)

\[ \text{R}_f \ (\text{silica-CH}_2\text{Cl}_2/\text{hexanes 3:1}) \, 0.70; \ \text{'H-NMR (400 MHz, CD}_2\text{Cl}_2) \ \delta = 2.57 \ (d, \ 12\text{H}), \ 7.37-7.52 \ (m, \ 8\text{H}), \ 7.65-7.81 \ (m, \ 9\text{H}), \ 7.83 \ (d, \ J = 5.2 \text{ Hz, 1H}), \ 7.88 \ (d, \ J = 5.2 \text{ Hz, 1H}), \ 7.92 \ (d, \ J = 5.2 \text{ Hz, 1H}), \ 8.05 \ (d, \ J = 4.7 \text{ Hz, 1H}), \ 8.09 \ (d, \ J = 5.2 \text{ Hz, 1H}), \ 8.56 \ (d, \ J = 3.4 \text{ Hz, 1H}), \ 10.20 \ (\text{br s, 1H}); \ \text{UV-vis (CH}_2\text{Cl}_2) \ \lambda_{\text{max}}/\text{nm (log } \varepsilon) \ 362 \ (4.62), \ 428 \ (4.95), \ 598 \ (3.97), \ 720 \ (3.73), \ 792 \ (3.77); \ \text{MS (LSIMS) 726 (M}^+\text{, 100%); HRMS (LSIMS) } m/e \ \text{Calcd for C}_{48}\text{H}_{36}\text{N}_4\text{Ni: 726.22930, found 726.22923 (M}^+\text{); Anal. Calcd for C}_{48}\text{H}_{36}\text{N}_4\text{Ni-0.5H}_2\text{O: C, 78.28; H, 5.06; N, 7.61. Found: C, 78.00; H, 4.87; N, 7.41. These data agree with the literature data.}^4 \]

2-Aza-5,10,15,20-tetrakis(p-chlorophenyl)-21-carbaporphyrinatonickel(II) (129c)

\[ \text{R}_f \ (\text{silica-CH}_2\text{Cl}_2/\text{hexanes 3:1}) \, 0.75; \ \text{'H-NMR (400 MHz, CD}_2\text{Cl}_2) \ \delta = 7.56 - 7.95 \ (m, \ 20\text{H}), \ 8.04 \ (d, \ J = 4.9 \text{ Hz, 1H}), \ 8.07 \ (d, \ J = 5.7 \text{ Hz, 1H}), \ 8.56 \ (d, \ J = 3.8 \text{ Hz, 1H}), \ 10.17 \ (\text{br s, 1H}); \ \text{UV-vis (CH}_2\text{Cl}_2) \ \lambda_{\text{max}}/\text{nm (log } \varepsilon) \ 362 \ (\text{sh}), \ 426 \ (4.95), \ 600 \ (3.99), \ 720 \ (3.71), \ 792 \ (3.71); \ \text{MS (LSIMS) 809 (M}^+\text{, 100%).} \]

2-Aza-5,10,15,20-tetrakis(p-methoxycarbonylphenyl)-21-carbaporphyrinatonickel(II) (129d)

\[ \text{R}_f \ (\text{silica-CH}_2\text{Cl}_2/1 \ % \ \text{CH}_3\text{OH}) \, 0.22; \ \text{'H-NMR (400 MHz, CD}_2\text{Cl}_2) \ \delta = 4.02 \ (d, \ 12\text{H}), \ 7.77 \ (d, \ J = 4.9 \text{ Hz, 1H}), \ 7.81 \ (d, \ J = 4.9 \text{ Hz, 1H}), \ 7.85 - 8.10 \ (m, \ 12\text{H}), \ 8.22 - 8.39 \ (m, \ 8\text{H}), \ 8.56 \ (d, \ J = 3.8 \text{ Hz, 1H}), \ 10.19 \ (\text{br s, 1H}); \ \text{UV-vis (CH}_2\text{Cl}_2) \ \lambda_{\text{max}}/\text{nm (log } \varepsilon) \ 364 \ (4.52), \ 428 \ (4.88), \ 598 \ (3.90), \ 722 \ (3.60), \ 794 \ (3.62); \ \text{MS (LSIMS) 903 (M}^+\text{, 100%); HRMS (LSIMS) } m/e \ \text{Calcd for C}_{52}\text{H}_{37}\text{N}_4\text{O}_8\text{Ni: 903.19643, found 903.19619 (M}^+\text{); Anal. Calcd for C}_{52}\text{H}_{36}\text{N}_4\text{O}_8\text{Ni: C, 69.12; H, 4.02; N, 6.20. Found: C, 69.14; H, 4.06; N, 6.44.} \]
2-Aza-5,10,15,20-tetrakis(p-methoxyphenyl)-21-carbaporphyrinatonickeI(II) (129e)

R_f (silica-CH_2Cl_2/1 % CH_3OH) 0.68; ^1H-NMR (400 MHz, CD_2Cl_2) δ = 3.96 - 4.01 (m, 12H), 7.10 - 7.25 (m, 8H), 7.69 - 7.87 (m, 10H), 7.90 (d, J = 5.3 Hz, 1H), 7.93 (d, J = 5.3 Hz, 1H), 8.07 (d, J = 4.9 Hz, 1H), 8.10 (d, J = 4.9 Hz, 1H), 8.59 (d, J = 3.8 Hz, 1H), 10.22 (br s, 1H); UV-vis (CH_2Cl_2) λ_max/μm (log ε) 368 (4.59), 428 (4.94), 600 (3.99), 722 (3.80), 794 (3.85); MS (LSIMS) 791 (MH^+, 100%); HRMS (LSIMS) m/e Calcd for C_{48}H_{37}N_{4}O_{4}: 791.21679, found 791.21730 (MH^+); Anal. Calcd for C_{48}H_{36}N_{4}O_{4}Ni: C, 72.84; H, 4.58; N, 7.08. Found: C, 73.18; H, 4.51; N, 7.38.

6.3.2 Preparation of Sultine

A suspension of sodium hydroxymethanesulfinate (rongalite) (6.0 g, 40 mmol) was stirred with a solution of α,α'-dibromo-o-xylene (20 mmol) and TBAB (4 mmol) in DMF (40 mL) at 0 °C for 4 h. Water (300 mL) was then added and the precipitate was removed by filtration. The filtrate was extracted with ethyl ether and chromatographed on silica gel (16 g) with hexanes/CH_2Cl_2 (1:1) to yield sultine 130 2.31 g (69 %).

1,4-Dihydro-2,3-benzoxathiin 3-oxide (130)

^1H-NMR (400 MHz, CD_2Cl_2) δ= 3.56 (d, J = 15.6 Hz, 1H), 4.38 (d, J = 15.6 Hz, 1H), 4.96 (d, J = 13.7 Hz, 1H), 5.28 (d, J = 13.7 Hz, 1H), 7.20 - 7.31 (m, 2H), 7.33 - 7.45 (m, 2H); MS (LSIMS) 169 (MH^+, 100%). These data agree with the literature data.

6.3.3 Diels-Derer Reactions of Ni(II) N-Confused Porphyrins as Dienophiles

A solution of (NCTPP)Ni^{II} (129a, 100 mg) and sultine 130 (1.50 g) was refluxed in benzene (50 mL) for 2 days. The solvent was removed in vacuo and the residue was purified
with a silica gel column (14 g) using hexanes/CH$_2$Cl$_2$ (1:1). The product, 133a, which has a higher R$_f$ value than that of 129a, was obtained in 23 % yield. Complexes 133b and 133c were synthesized in a similar way with the yield of 25 % and 18 %, respectively.

**Ni(II) N-confused tetraphenylisoquinoporphyrin (133a)**

$R_f$ (silica-CH$_2$Cl$_2$/hexanes 2:1) 0.77; $^1$H-NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ = 6.91 (s, 1H), 7.11 (d, $J$ = 8.6 Hz, 1H), 7.27 (m, 2H), 7.46 (m, 1H), 7.55 - 8.05 (m, 20H), 8.22 (m, 2H), 8.29 (m, 3H), 8.36 (d, $J$ = 4.9 Hz, 1H), 8.57 (s, 1H); UV-vis (CH$_2$Cl$_2$) $\lambda_{max}$/nm (log $\varepsilon$) 438 (5.07), 628 (4.62); MS (LSIMS) 770 (M$^+$, 100%); HRMS (LSIMS) $m/e$ Calc'd for C$_{52}$H$_{32}$N$_4$Ni: 770.19799, found 770.19797 (M$^+$); Anal. Calc'd for C$_{52}$H$_{32}$N$_4$Ni-0.5H$_2$O: C, 80.02; H, 4.26; N, 7.18. Found: C, 79.88; H, 4.11; N, 6.95.

**Ni(II) N-confused tetrakis(p-tolyl)isoquinoporphyrin (133b)**

$R_f$ (silica-CH$_2$Cl$_2$/hexanes 2:1) 0.77; $^1$H-NMR (300 MHz, CD$_2$Cl$_2$) $\delta$ = 2.61 (s, 3H), 2.63 (s, 6H), 2.70 (s, 3H), 6.87 (s, 1H), 6.90 (s, 1H), 7.14 - 7.25 (m, 2H), 7.36 - 7.55 (m, 9H), 8.19 - 8.27 (m, 3H), 8.28 - 8.35 (m, 3H), 8.42 (s, 1H); UV-vis (CH$_2$Cl$_2$) $\lambda_{max}$/nm (log $\varepsilon$) 440 (5.07), 628 (4.75); MS (LSIMS) 827 (MH$^+$, 100%); HRMS (LSIMS) $m/e$ calc'd for C$_{56}$H$_{41}$N$_4$Ni: 827.26842, found 827.27036 (MH$^+$).

**Ni(II) N-confused tetrakis(p-chlorophenyl)isoquinoporphyrin (133c)**

$R_f$ (silica-CH$_2$Cl$_2$/hexanes 2:1) 0.44; $^1$H-NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ = 7.06 (s, 1H), 7.18 (d, $J$ = 8.6 Hz, 1H), 7.37 (m, 2H), 7.49 - 7.95 (m, 17H), 8.15 - 8.33 (m, 6H), 8.66 (s, 1H); MS (LSIMS) 908 (M$^+$ [C$_{52}$H$_{28}$Cl$_3$Cl$_{37}$CIN$_4$Ni], 100%); HRMS (LSIMS) $m/e$ Calc'd for C$_{52}$H$_{28}$Cl$_3$Cl$_{37}$CIN$_4$Ni: 908.03916, found 908.03956 (M$^+$).
6.3.4 Demetalation of Ni(II) N-Confused Tetraphenylisoquinoporphyrin

Complex 133a (40 mg) was dissolved in 10% TFA/CH$_2$Cl$_2$. After 24 h, the solution was washed with saturated aqueous Na$_2$CO$_3$ solution. The solvent was then removed in vacuo and the residue was purified on a silica gel column (12 g). CH$_2$Cl$_2$/4% CH$_3$OH/0.5% Et$_3$N eluted the product. This collection was concentrated and washed with aqueous NaCl solution. The solvent was removed in vacuo and the residue was triturated with CH$_2$Cl$_2$/hexanes to give demetalation product 135 24.6 mg (63%).

**N-confused tetraphenylisoquinoporphyrin 135**

$R_f$(silica-CH$_2$Cl$_2$/5% CH$_3$OH/2% Et$_3$N) 0.29; $^1$H-NMR (500 MHz, CD$_2$Cl$_2$) $\delta$ = 7.19 (s, 1H), 7.29 - 7.58 (m, 4H), 7.70 (s, 6H), 7.78 - 7.94 (m, 6H), 8.00 - 8.30 (m, 10H), 8.31 - 8.45 (m, 4H), 8.84 (s, 1H); MS (LSIMS) 715 (MH$^+$, 100%); HRMS (LSIMS) m/e Calcd for C$_{52}$H$_{35}$N$_4$: 715.28617, found 715.28614 (MH$^+$).

6.3.5 Diels-Alder Reactions of Ni(II) N(2)-Methylated N-Confused Porphyrins

A solution of Ni(II) N(2)-methylated N-confused tetra(p-tolyl)porphyrin (80 mg) and sultine 130 (1.50 g) was refluxed in benzene (60 mL) for 2 days. The solvent was removed in vacuo and the residue was subjected to column chromatography with a silica gel (14 g) using hexanes/CH$_2$Cl$_2$. Compound 137 was obtained with impurities. MS (LSIMS) 860 (100%); HRMS (LSIMS) m/e Calcd for C$_{52}$H$_{35}$N$_4$: 860.30121, m/e.

6.3.6 1,3-Dipolar Cycloaddition of Ni(II) N-Confused Porphyrins

A solution of (NCTPP)Ni$^{II}$ (129a, 50 mg), sarcosine (N-methylglycine, 0.70 g), paraformaldehyde (1.1 g) and DDQ (200 mg) was refluxed in toluene (70 mL) for 24 h. The
solvent was removed *in vacuo* and the residue was subjected to column chromatograph with silica gel (14 g) using 2 % CH$_2$OH/CH$_2$Cl$_2$. Compound 138 was obtained with impurities. MS (LSIMS) 782 (100%).

6.4 Experimental Data for Chapter 4

(NCTTP)Ni$^{II}$ (110 mg) and DDQ (400 mg) were added to a 1:1 CH$_2$Cl$_2$/CH$_3$OH (70 mL) solution of NaOCH$_3$ (200 mg). The solution was stirred for 24 h at r. t. and then washed with saturated aqueous NaHCO$_3$ solution for three times. The solvent was removed *in vacuo* and the residue was subjected to column chromatography (silica gel, 16 g). Using 1:1 CH$_2$Cl$_2$/hexanes. (NCTTP)Ni$^{II}$ was eluted first; 3:1 CH$_2$Cl$_2$/hexanes eluted the first new compound, 145 (11.7 mg, 9.9 %), and the second new compound, 146 (30.3 mg, 27 %), was eluted with CH$_2$Cl$_2$.

2-Aza-21-cyano-3-methoxy-5,10,15,20-tetrakis(p-tolyl)-21-carbaporphyrinatonickeII) (145)

R$_f$ (silica-CH$_2$Cl$_2$/hexanes 2:1) 0.63; $^1$H-NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ = 2.63 (m, 12H), 4.21 (s, 3H), 7.41 - 7.62 (m, 9H), 7.65 - 8.20 (m, 7H), 8.32 (d, $J$ = 4.8 Hz, 1H), 8.36 (s, 2H), 8.38 - 8.51 (m, 3H); $^{13}$C-NMR (100 MHz, CD$_2$Cl$_2$) $\delta$ = 21.57, 21.67, 57.72, 108.28, 123.02, 125.60, 126.28, 128.09, 128.18, 128.41, 128.88, 129.77, 131.75, 131.81, 132.55, 133.55, 133.86, 133.93, 135.50, 136.38, 137.19, 137.31, 137.76, 137.96, 138.31, 138.68, 138.80, 138.94, 146.64, 147.21, 148.60, 149.23, 155.29, 159.99, 164.85, 172.83; UV-vis (CH$_2$Cl$_2$) $\lambda_{max}$/nm (log $\varepsilon$) 434 (5.12), 716 (3.96); MS (LSIMS) 782 (MH$^+$, 100%); HRMS (LSIMS) m/e Calcd for C$_{50}$H$_{38}$N$_5$NiO: 782.24294, found 782.24344 (MH$^+$); Anal Calcd for C$_{50}$H$_{37}$N$_5$NiO-H$_2$O: C, 75.02; H, 4.91; N, 8.75. Found: C, 74.74; H, 4.68; N, 8.68.
2-Aza-21-cyano-5,10,15,20-tetrakis(p-tolyl)-21-carbaporphyrinonickel(II) (146)

\[ R_f (\text{silica-CH}_2\text{Cl}_2/\text{hexanes} \ 2:1) \ 0.37; \ ^1\text{H-NMR (400 MHz, CD}_2\text{Cl}_2) \ \delta = 2.66 (m, 12H), 7.56 (d, \ J = 7.7 \text{ Hz, 4H}), 7.63 (d, \ J = 7.7 \text{ Hz, 2H}), 7.69 (d, \ J = 7.5 \text{ Hz, 2H}), 7.78 - 8.32 (m, 8H), 8.56 (d, \ J = 4.8 \text{ Hz, 1H}), 8.58 - 8.66 (m, 3H), 8.73 (d, \ J = 5.0 \text{ Hz, 1H}), 8.76 (d, \ J = 5.0 \text{ Hz, 1H}), 10.03 (s, 1H); ^{13}\text{C-NMR (100 MHz, CD}_2\text{Cl}_2) \ \delta = 21.59, 106.75, 125.86, 127.50, 128.00, 128.13, 128.91, 129.40, 132.30, 133.01, 133.40, 133.71, 134.09, 134.27, 135.04, 135.57, 135.82, 136.86, 137.97, 139.04, 141.27, 147.80, 148.88, 149.25, 149.96, 154.63, 157.48, 158.15, 168.43; \ \text{UV-vis (CH}_2\text{Cl}_2) \ \lambda_{\text{max}}/\text{nm} (\log \varepsilon) \ 434 (5.14), 716 (3.65); \ \text{MS (LSIMS) 752 (MH}^+\text{, 100%); HRMS (LSIMS) m/e Calcd for C}_{49}\text{H}_{36}\text{N}_{5}\text{Ni-CH}_3\text{OH-0.5H}_2\text{O: C, 75.68; H, 5.08; N, 8.83. Found: C, 75.97; H, 4.76; N, 9.09.}

6.5 Experimental Data for Chapter 5

6.5.1 Synthesis of Ni(III) N-Confused Porphyrin Inner C-Oxide

A solution of the (NCTTP)Ni^{II} complex, 129b (130 mg), and OsO\textsubscript{4} (60 mg) in 15 % pyridine/CH\textsubscript{2}Cl\textsubscript{2} (50 mL) was stirred at r. t. for 24 h and then filtered through a silica gel plug using 10 % CH\textsubscript{3}OH in CH\textsubscript{2}Cl\textsubscript{2}. The solvent was removed in vacuo and the residue was subjected to column chromatography (silica gel, 16 g). Compound 153 was eluted with 1.5 % CH\textsubscript{3}OH in CH\textsubscript{2}Cl\textsubscript{2} and was obtained in a 42 % yield.

Ni(III) complex of N-confused porphyrin inner C-oxide 153

\[ R_f (\text{silica-CH}_2\text{Cl}_2/5\% \ \text{CH}_3\text{OH/2\% Et}_3\text{N}) \ 0.70; \ \text{UV-vis (CH}_2\text{Cl}_2) \ \lambda_{\text{max}}/\text{nm} (\log \varepsilon) \ 380 (4.70), 428 (sh), 470 (sh); \ \text{MS (LSIMS) 742 (MH}^+, 100\%); \ \text{HRMS (LSIMS) m/e Calcd for} \]
Chapter 6 Experimental

C₄₈H₃₆N₄NiO: 742.22421, found 742.22443 (MH⁺); MS (-LSIMS) 741 (M⁻, 100%); HRMS (-LSIMS) m/e Calcd for C₄₈H₃₅N₄NiO: 741.21639, found 741.21609 (M⁻); Anal. Calcd for C₄₈H₃₅N₄NiO.C₅H₅N: C, 77.47; H, 4.91; N, 8.52. Found: C, 77.36; H, 4.97; N, 8.61.

6.5.2 Measurement of Room Temperature Effective Magnetic Moment

A dilute CD₂Cl₂ solution of cyclohexane (reference) was placed in the NMR sample tube while the solvent containing complex 153 and cyclohexane was incorporated in an inner narrow-bore tube and held in place with a Teflon spacer. The ¹H NMR spectrum of cyclohexane in the two coaxial tubes exhibits a chemical shift difference, which was used to calculate the room temperature effective magnetic moment.⁸⁻¹¹

6.6 Crystal Data and Details of the Structure Determination
Table 6.1 Crystal data and details of the structure determination for 108.

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Table 6.1 Crystal data and details of the structure determination for 108 (continued).

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<td>No. Variables</td>
<td>544</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>10.69</td>
</tr>
<tr>
<td>Residuals (refined on ( F^2 ), all data): ( R; Rw )</td>
<td>0.122; 0.176</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>1.69</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.01</td>
</tr>
<tr>
<td>No. Observations ( (I&gt;2\sigma(I)) )</td>
<td>3078</td>
</tr>
<tr>
<td>Residuals (refined on ( F ), ( I&gt;2\sigma(I) )): ( R; Rw )</td>
<td>0.061; 0.074</td>
</tr>
<tr>
<td>Maximum peak in Final Diff. Map</td>
<td>0.60 ( e/\AA^3 )</td>
</tr>
<tr>
<td>Minimum peak in Final Diff. Map</td>
<td>-0.53 ( e/\AA^3 )</td>
</tr>
</tbody>
</table>
Table 6.2 Crystal data and details of the structure determination for 115.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>C_{52}H_{43}N_{4}NiI</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>909.54</td>
</tr>
<tr>
<td>Crystal Color, Habit</td>
<td>purple, needle</td>
</tr>
<tr>
<td>Crystal Dimensions</td>
<td>0.50 x 0.15 x 0.15 mm</td>
</tr>
<tr>
<td>Crystal System</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Lattice Type</td>
<td>Primitive</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td>a = 10.0178(8) Å</td>
</tr>
<tr>
<td></td>
<td>b = 14.2261(6) Å</td>
</tr>
<tr>
<td></td>
<td>c = 16.329(1) Å</td>
</tr>
<tr>
<td></td>
<td>α = 108.764(2)°</td>
</tr>
<tr>
<td></td>
<td>β = 94.009(2)°</td>
</tr>
<tr>
<td></td>
<td>γ = 109.291(3)°</td>
</tr>
<tr>
<td></td>
<td>V = 2038.9(2) Å³</td>
</tr>
<tr>
<td>Space group</td>
<td>Pt (#2)</td>
</tr>
<tr>
<td>Z value</td>
<td>2</td>
</tr>
<tr>
<td>D_{calc}</td>
<td>1.481 g/cm³</td>
</tr>
<tr>
<td>F_{000}</td>
<td>928.00</td>
</tr>
<tr>
<td>μ(MoKα)</td>
<td>12.76 cm⁻¹</td>
</tr>
<tr>
<td>Temperature</td>
<td>173 K</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Rigaku/ADSC CCD</td>
</tr>
<tr>
<td>Radiation</td>
<td>MoKα (λ = 0.71069 Å)</td>
</tr>
<tr>
<td></td>
<td>graphite monochromated</td>
</tr>
<tr>
<td>Detector Aperture</td>
<td>94 mm x 94 mm</td>
</tr>
<tr>
<td>Data Images</td>
<td>462 exposures @ 19.0 seconds</td>
</tr>
<tr>
<td>φ oscillation Range (χ = -90.0)</td>
<td>0.0 - 190.0°</td>
</tr>
</tbody>
</table>
Table 6.2 Crystal data and details of the structure determination for 115 (continued).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \omega ) oscillation Range ( (\chi = -90.0) )</td>
<td>-23.0 - 18.0°</td>
</tr>
<tr>
<td>Detector Position</td>
<td>40.30 mm</td>
</tr>
<tr>
<td>Detector Swing Angle</td>
<td>-10.52°</td>
</tr>
<tr>
<td>( 2\theta_{\text{max}} )</td>
<td>60.3°</td>
</tr>
<tr>
<td>No. of Reflections Measured</td>
<td>Total: 17463 Unique: 8533 (( R_{\text{int}} = 0.036 ))</td>
</tr>
<tr>
<td>Corrections</td>
<td>Lorentz-polarization Absorption/scaling/decay (trans. factors: 0.7367 - 1.0000)</td>
</tr>
<tr>
<td>Structure Solution</td>
<td>Patterson Methods (DIRDIF92 PATTY)</td>
</tr>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>( \Sigma w(F_o^2 - F_c^2)^2 )</td>
</tr>
<tr>
<td>p-factor</td>
<td>0.0000</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations ( (I&gt;0.00\sigma(I)) )</td>
<td>8533</td>
</tr>
<tr>
<td>No. Variables</td>
<td>527</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>16.19</td>
</tr>
<tr>
<td>Residuals (refined on ( F^2 ), all data): R; Rw</td>
<td>0.076; 0.134</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>1.69</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.01</td>
</tr>
<tr>
<td>No. Observations ( (I&gt;2\sigma(I)) )</td>
<td>6180</td>
</tr>
<tr>
<td>Residuals (refined on ( F ), ( I&gt;2\sigma(I) )): R; Rw</td>
<td>0.046; 0.062</td>
</tr>
<tr>
<td>Maximum peak in Final Diff. Map</td>
<td>1.02 ( e/\AA^3 )</td>
</tr>
<tr>
<td>Minimum peak in Final Diff. Map</td>
<td>-1.69 ( e/\AA^3 )</td>
</tr>
</tbody>
</table>
### Table 6.3 Crystal data and details of the structure determination for 133a.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empirical Formula</strong></td>
<td>C₅₂H₃₂N₄MI</td>
</tr>
<tr>
<td><strong>Formula Weight</strong></td>
<td>771.55</td>
</tr>
<tr>
<td><strong>Crystal Color, Habit</strong></td>
<td>dark, needle</td>
</tr>
<tr>
<td><strong>Crystal Dimensions</strong></td>
<td>0.50 x 0.15 x 0.05 mm</td>
</tr>
<tr>
<td><strong>Crystal System</strong></td>
<td>Monoclinic</td>
</tr>
<tr>
<td><strong>Lattice Type</strong></td>
<td>Primitive</td>
</tr>
<tr>
<td><strong>Lattice Parameters</strong></td>
<td>a = 13.2484(19) Å</td>
</tr>
<tr>
<td></td>
<td>b = 15.1197(17) Å</td>
</tr>
<tr>
<td></td>
<td>c = 19.255(3) Å</td>
</tr>
<tr>
<td></td>
<td>β = 110.821(3)°</td>
</tr>
<tr>
<td></td>
<td>V = 3605.1(9) Å</td>
</tr>
<tr>
<td><strong>Space group</strong></td>
<td>P2₁/c (#14)</td>
</tr>
<tr>
<td><strong>Z value</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>D&lt;sub&gt;calc&lt;/sub&gt;</strong></td>
<td>1.421 g/cm³</td>
</tr>
<tr>
<td><strong>F₀₀₀</strong></td>
<td>1600.00</td>
</tr>
<tr>
<td><strong>μ(MoKα)</strong></td>
<td>5.84 cm⁻¹</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>173 K</td>
</tr>
<tr>
<td><strong>Diffractometer</strong></td>
<td>Rigaku/ADSC CCD</td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td>MoKα (λ = 0.71069 Å)</td>
</tr>
<tr>
<td></td>
<td>graphite monochromated</td>
</tr>
<tr>
<td><strong>Detector Aperture</strong></td>
<td>94 mm x 94 mm</td>
</tr>
<tr>
<td><strong>Data Images</strong></td>
<td>460 exposures @ 49.0 seconds</td>
</tr>
<tr>
<td><strong>φ oscillation Range (χ = -90.0)</strong></td>
<td>0.0 - 190.0°</td>
</tr>
</tbody>
</table>
Table 6.3 Crystal data and details of the structure determination for 133a (continued).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\omega$ oscillation Range ($\chi = -90.0$)</td>
<td>-17.0 - 23.0°</td>
</tr>
<tr>
<td>Detector Position</td>
<td>38.10 mm</td>
</tr>
<tr>
<td>Detector Swing Angle</td>
<td>-5.59°</td>
</tr>
<tr>
<td>$2\theta_{\text{max}}$</td>
<td>55.7°</td>
</tr>
<tr>
<td>No. of Reflections Measured</td>
<td>Total: 33795</td>
</tr>
<tr>
<td></td>
<td>Unique: 8021 ($R_{\text{int}} = 0.085$)</td>
</tr>
<tr>
<td>Corrections</td>
<td>Lorentz-polarization</td>
</tr>
<tr>
<td></td>
<td>Absorption/scaling/decay</td>
</tr>
<tr>
<td></td>
<td>(trans. factors: 0.7875 - 1.0000)</td>
</tr>
<tr>
<td>Structure Solution</td>
<td>Direct Methods (SIR97)</td>
</tr>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>$\Sigma w(F_o^2 - F_c^2)^2$</td>
</tr>
<tr>
<td>p-factor</td>
<td>0.0000</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations ($I&gt;0.00\sigma(I)$)</td>
<td>7755</td>
</tr>
<tr>
<td>No. Variables</td>
<td>514</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>15.09</td>
</tr>
<tr>
<td>Residuals (refined on $F^2$, all data): $R$; $R_w$</td>
<td>0.076; 0.090</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>0.80</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.00</td>
</tr>
<tr>
<td>No. Observations ($I&gt;2\sigma(I)$)</td>
<td>4167</td>
</tr>
<tr>
<td>Residuals (refined on $F$, $I&gt;2\sigma(I)$): $R$; $R_w$</td>
<td>0.036; 0.039</td>
</tr>
<tr>
<td>Maximum peak in Final Diff. Map</td>
<td>$0.50 , e/\AA^3$</td>
</tr>
<tr>
<td>Minimum peak in Final Diff. Map</td>
<td>$-0.59 , e/\AA^3$</td>
</tr>
</tbody>
</table>
Table 6.4 Crystal data and details of the structure determination for 145.

<table>
<thead>
<tr>
<th>Empirical Formula</th>
<th>C$<em>{50}$H$</em>{37}$N$_5$NiO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula Weight</td>
<td>782.56</td>
</tr>
<tr>
<td>Crystal Color, Habit</td>
<td>Brown, platelet</td>
</tr>
<tr>
<td>Crystal Dimensions</td>
<td>0.20 x 0.20 x 0.10 mm</td>
</tr>
<tr>
<td>Crystal System</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Lattice Type</td>
<td>Primitive</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>9.8239(4) Å</td>
</tr>
<tr>
<td>b</td>
<td>12.7674(6) Å</td>
</tr>
<tr>
<td>c</td>
<td>15.3382(7) Å</td>
</tr>
<tr>
<td>α</td>
<td>82.788(8)°</td>
</tr>
<tr>
<td>β</td>
<td>81.698(7)°</td>
</tr>
<tr>
<td>γ</td>
<td>82.301(8)°</td>
</tr>
<tr>
<td>V</td>
<td>1875.39(15) Å$^3$</td>
</tr>
<tr>
<td>Space group</td>
<td>Pt (#2)</td>
</tr>
<tr>
<td>Z value</td>
<td>2</td>
</tr>
<tr>
<td>$D_{\text{calc}}$</td>
<td>1.388 g/cm$^3$</td>
</tr>
<tr>
<td>$F_{000}$</td>
<td>818.00</td>
</tr>
<tr>
<td>$\mu$(MoKα)</td>
<td>5.65 cm$^{-1}$</td>
</tr>
<tr>
<td>Temperature</td>
<td>173 K</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Rigaku/ADSC CCD</td>
</tr>
<tr>
<td>Radiation</td>
<td>MoKα ($\lambda = 0.71069$ Å)</td>
</tr>
<tr>
<td></td>
<td>graphite monochromated</td>
</tr>
<tr>
<td>Detector Aperture</td>
<td>94 mm x 94 mm</td>
</tr>
<tr>
<td>Data Images</td>
<td>460 exposures @ 47.0 seconds</td>
</tr>
<tr>
<td>$\phi$ oscillation Range ($\chi = -90.0$)</td>
<td>0.0 - 190.0°</td>
</tr>
</tbody>
</table>
Table 6.4 Crystal data and details of the structure determination for 145 (continued).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \omega ) oscillation Range (( \chi = -90.0 ))</td>
<td>-17.0 - 23.0°</td>
</tr>
<tr>
<td>Detector Position</td>
<td>38.79 mm</td>
</tr>
<tr>
<td>Detector Swing Angle</td>
<td>-5.54°</td>
</tr>
<tr>
<td>( 2\theta_{\text{max}} )</td>
<td>55.7°</td>
</tr>
<tr>
<td>No. of Reflections Measured</td>
<td>Total: 17139</td>
</tr>
<tr>
<td></td>
<td>Unique: 7723 (R&lt;sub&gt;int&lt;/sub&gt; = 0.066)</td>
</tr>
<tr>
<td>Corrections</td>
<td>Lorentz-polarization</td>
</tr>
<tr>
<td></td>
<td>Absorption/scaling/decay</td>
</tr>
<tr>
<td></td>
<td>(corr. factors: 0.7797 - 1.0000)</td>
</tr>
<tr>
<td>Structure Solution</td>
<td>Direct Methods (SIR97)</td>
</tr>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>( \Sigma w(Fo^2 - Fc^2)^2 )</td>
</tr>
<tr>
<td>p-factor</td>
<td>0.0000</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations (I&gt;0.00( \sigma(I) ))</td>
<td>7709</td>
</tr>
<tr>
<td>No. Variables</td>
<td>538</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>14.33</td>
</tr>
<tr>
<td>Residuals (refined on F^2, all data): R; Rw</td>
<td>0.088; 0.112</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>0.95</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.00</td>
</tr>
<tr>
<td>No. Observations (I&gt;2( \sigma(I) ))</td>
<td>5006</td>
</tr>
<tr>
<td>Residuals (refined on F, I&gt;2( \sigma(I) )): R; Rw</td>
<td>0.048; 0.099</td>
</tr>
<tr>
<td>Maximum peak in Final Diff. Map</td>
<td>0.31 ( e'/A^3 )</td>
</tr>
<tr>
<td>Minimum peak in Final Diff. Map</td>
<td>-0.54 ( e'/A^3 )</td>
</tr>
<tr>
<td>Empirical Formula</td>
<td>C₄₀H₃₅N₅Ni·0.5H₂O</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>761.55</td>
</tr>
<tr>
<td>Crystal Color, Habit</td>
<td>Dark, chip</td>
</tr>
<tr>
<td>Crystal Dimensions</td>
<td>0.15 x 0.15 x 0.10 mm</td>
</tr>
<tr>
<td>Crystal System</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Lattice Type</td>
<td>Primitive</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td>a = 9.7125(10) Å</td>
</tr>
<tr>
<td></td>
<td>b = 14.3732(15) Å</td>
</tr>
<tr>
<td></td>
<td>c = 14.0565(15) Å</td>
</tr>
<tr>
<td></td>
<td>α = 94.720(10)°</td>
</tr>
<tr>
<td></td>
<td>β = 77.440(10)°</td>
</tr>
<tr>
<td></td>
<td>γ = 76.150(10)°</td>
</tr>
<tr>
<td></td>
<td>V = 1840.9(4) Å³</td>
</tr>
<tr>
<td>Space group</td>
<td>Pt (#2)</td>
</tr>
<tr>
<td>Z value</td>
<td>2</td>
</tr>
<tr>
<td>D&lt;sub&gt;calc&lt;/sub&gt;</td>
<td>1.376 g/cm³</td>
</tr>
<tr>
<td>F&lt;sub&gt;000&lt;/sub&gt;</td>
<td>796.00</td>
</tr>
<tr>
<td>μ(MoKα)</td>
<td>5.73 cm⁻¹</td>
</tr>
<tr>
<td>Temperature</td>
<td>173 K</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Rigaku/ADSC CCD</td>
</tr>
<tr>
<td>Radiation</td>
<td>MoKα (λ = 0.71073 Å)</td>
</tr>
<tr>
<td></td>
<td>graphite monochromated</td>
</tr>
<tr>
<td>Detector Aperture</td>
<td>94 mm x 94 mm</td>
</tr>
<tr>
<td>Data Images</td>
<td>460 exposures @ 55.0 seconds</td>
</tr>
<tr>
<td>φ oscillation Range</td>
<td>0.0 - 190.0°</td>
</tr>
</tbody>
</table>
Table 6.5  Crystal data and details of the Structure determination for 146 (continued).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\omega$ oscillation Range ($\chi = -90.0$)</td>
<td>-17.0 - 23.0°</td>
</tr>
<tr>
<td>Detector Position</td>
<td>38.72 mm</td>
</tr>
<tr>
<td>Detector Swing Angle</td>
<td>-5.60°</td>
</tr>
<tr>
<td>$2\theta_{max}$</td>
<td>50.1°</td>
</tr>
<tr>
<td>No. of Reflections Measured</td>
<td>Total: 44912</td>
</tr>
<tr>
<td></td>
<td>Unique: 10104 ($R_{int} = 0.063$)</td>
</tr>
<tr>
<td>Corrections</td>
<td>Lorentz-polarization</td>
</tr>
<tr>
<td></td>
<td>Absorption/scaling/decay</td>
</tr>
<tr>
<td></td>
<td>(corr. factors: 0.4343 - 1.0000)</td>
</tr>
<tr>
<td>Structure Solution</td>
<td>Direct Methods</td>
</tr>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>$\Sigma w(Fo^2 - Fe^2)^2$</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations ($I&gt;$0.00$\sigma(I)$)</td>
<td>10104</td>
</tr>
<tr>
<td>No. Variables</td>
<td>509</td>
</tr>
<tr>
<td>Residuals (refined on $F^2$, all data): R; Rw</td>
<td>0.134; 0.160</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>0.96</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.00</td>
</tr>
<tr>
<td>No. Observations ($I&gt;$2$\sigma(I)$)</td>
<td>5521</td>
</tr>
<tr>
<td>Residuals (refined on F, $I&gt;$2$\sigma(I)$): R; Rw</td>
<td>0.064; 0.142</td>
</tr>
<tr>
<td>Maximum peak in Final Diff. Map</td>
<td>$0.58 , \varepsilon / \AA^3$</td>
</tr>
<tr>
<td>Minimum peak in Final Diff. Map</td>
<td>$-0.43 , \varepsilon / \AA^3$</td>
</tr>
<tr>
<td><strong>Table 6.6</strong> Crystal data and details of the structure determination for <strong>153</strong>.</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Empirical Formula</strong></td>
<td>$C_{53}H_{40}N_{5}NiO-CH_2Cl_2$</td>
</tr>
<tr>
<td><strong>Formula Weight</strong></td>
<td>906.56</td>
</tr>
<tr>
<td><strong>Crystal Color, Habit</strong></td>
<td>Green, platelet</td>
</tr>
<tr>
<td><strong>Crystal Dimensions</strong></td>
<td>0.35 x 0.30 x 0.03 mm</td>
</tr>
<tr>
<td><strong>Crystal System</strong></td>
<td>Monoclinic</td>
</tr>
<tr>
<td><strong>Lattice Type</strong></td>
<td>Primitive</td>
</tr>
</tbody>
</table>
| **Lattice Parameters** | $a = 21.2291(14) \, \text{Å}$  
$b = 8.6451(5) \, \text{Å}$  
$c = 25.7622(17) \, \text{Å}$  
$\beta = 93.004(3)^\circ$  
$V = 4721.6(5) \, \text{Å}^3$ |
| **Space group** | P2/a (#13) |
| **Z value** | 4 |
| **$D_{\text{calc}}$** | 1.275 g/cm$^3$ |
| **$F_{000}$** | 1884.00 |
| **$\mu$ (MoKα)** | 5.68 cm$^{-1}$ |
| **Temperature** | 173 K |
| **Diffractometer** | Rigaku/ADSC CCD |
| **Radiation** | MoKα ($\lambda = 0.71069 \, \text{Å}$)  
graphite monochromated |
| **Detector Aperture** | 94 mm x 94 mm |
| **Data Images** | 460 exposures @ 47.0 seconds |
| **$\phi$ oscillation Range ($\chi = -90.0$)** | 0.0 - 190.0° |
Table 6.6 Crystal data and details of the structure determination for 153 (continued).

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\omega$ oscillation Range ($\chi = -90.0$)</td>
<td>-17.0 - 23.0°</td>
</tr>
<tr>
<td>Detector Position</td>
<td>37.98 mm</td>
</tr>
<tr>
<td>Detector Swing Angle</td>
<td>-5.59°</td>
</tr>
<tr>
<td>$2\theta_{\text{max}}$</td>
<td>55.8°</td>
</tr>
<tr>
<td>No. of Reflections Measured</td>
<td>Total: 40883</td>
</tr>
<tr>
<td></td>
<td>Unique: 11220 ($R_{\text{int}} = 0.084$)</td>
</tr>
<tr>
<td>Corrections</td>
<td>Lorentz-polarization</td>
</tr>
<tr>
<td></td>
<td>Absorption/scaling/decay</td>
</tr>
<tr>
<td></td>
<td>(trans. factors: 0.7145 - 1.0000)</td>
</tr>
<tr>
<td>Structure Solution</td>
<td>Direct Methods (SIR97)</td>
</tr>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>$\Sigma w(F_o^2 - F_c^2)^2$</td>
</tr>
<tr>
<td>p-factor</td>
<td>0.0000</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations ($I&gt;0.00\sigma(I)$)</td>
<td>10590</td>
</tr>
<tr>
<td>No. Variables</td>
<td>587</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>18.04</td>
</tr>
<tr>
<td>Residuals (refined on $F^2$, all data): R; Rw</td>
<td>0.112; 0.209</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>0.94</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.00</td>
</tr>
<tr>
<td>No. Observations ($I&gt;2\sigma(I)$)</td>
<td>6256</td>
</tr>
<tr>
<td>Residuals (refined on $F$, $I&gt;2\sigma(I)$): R; Rw</td>
<td>0.071; 0.187</td>
</tr>
<tr>
<td>Maximum peak in Final Diff. Map</td>
<td>$0.98 , \epsilon / \AA^3$</td>
</tr>
<tr>
<td>Minimum peak in Final Diff. Map</td>
<td>$-0.77 , \epsilon / \AA^3$</td>
</tr>
</tbody>
</table>
References


Chapter 7

Summary and Future Work
Inner nitrogen atoms of N-confused porphyrins are reactive towards alkylation. N,N'-dimethylated N-confused porphyrin salts, which are mixtures of structural isomers, were obtained in the reactions of N-confused porphyrins with CH₃I in the presence of Na₂CO₃ (Chapter 2). These N,N'-dimethylated N-confused porphyrin salts have been shown to generate singlet oxygen when irradiated with light of the appropriate wavelengths and are potential photosensitizers for PDT.

Two dipolar canonical forms (Scheme 7.1) were proposed to explain the reactivity of Ni(II) N-confused porphyrins. Unlike canonical form I, canonical forms II and III reserve the 18 π-electron pathway and have more of a double bond character for the N(2)-C(3) bond. The importance of canonical forms II and III to the overall resonance hybrid is suggested by the X-ray crystal structure of Ni(II) N(2)-iodooctyl N-confused tetraphenylporphyrin, 115 (section 2.2.3.1), which is isoelectronic with Ni(II) N-confused porphyrins, as the N(2)-C(3) bond length of 115, 1.311(4) Å, is markedly shorter than those of the peripheral C-C bonds, 1.345(5) or 1.346(5) Å.

**Scheme 7.1** Three canonical forms for a Ni(II) N-confused porphyrin. The negative charge in canonical form II can also be located on other inner nitrogen atoms.
In canonical forms II and III, the peripheral C-N bond is both "cross conjugated" and in the iminium form, which is known to be electron-deficient and an active dienophile.\(^1\) Ni(II) N-confused porphyrins reacted selectively at the peripheral C-N bond with \(o\)-benzoquinodimethane giving novel Ni(II) N-confused isoquinoporphyrazins, presumably formed by oxidation of the initially formed Diels-Alder adducts (Chapter 3).

The canonical form III of Ni(II) N-confused porphyrins suggests that Ni(II) N-confused porphyrins are electrophiles at C(21). Inner C(21)-methylation has been observed by Latos-Grażyński et al.\(^2\) Inner C(21) cyanide addition and subsequent nucleophilic addition of \(\text{CH}_3\text{O}^-\) at C(3) followed by oxidation with DDQ were observed in reactions of (NCTPP)Ni\(^{11}\) with NaOCH\(_3\) and DDQ (Chapter 4). Electrophilic addition of the reduction product of DDQ to the deprotonated (NCTPP)Ni\(^{11}\) was proposed as the critical step for the inner cyanide addition.

A Ni(III) complex of N-confused porphyrin inner C-oxide was obtained in the reactions of Ni(II) N-confused porphyrins with OsO\(_4\), and the canonical form III of Ni(II) N-confused porphyrins can be used to explain the susceptibility of C(21) towards oxidation (Chapter 5).

In summary, N-confused porphyrins are involved in a variety of reactions, especially reactions involving the inner carbon and nitrogen atoms, as well as the peripheral C-N bond. These modified N-confused porphyrins can be potential photosensitizers for PDT, as well as interesting ligands with novel structural features.

### 7.2 Future Work

The canonical forms II and III of Ni(II) N-confused porphyrins suggest that the peripheral carbon-nitrogen bond of Ni(II) N-confused porphyrins has some iminium character and might be reactive towards nucleophiles. However, direct nucleophilic addition was not observed in the reactions of Ni(II) N-confused porphyrins with NaOCH\(_3\) and DDQ, presumably because of the
deprotonation of Ni(II) N-confused porphyrins in strong basic conditions. Therefore, nucleophilic addition of a less basic nucleophile, such as 166, to Ni(II) N-confused porphyrins, might be possible (Scheme 7.2).

Scheme 7.2 Proposed nucleophilic addition of an enolate to a Ni(II) N-confused porphyrin.

The mechanism proposed for the inner C- cyanide addition (section 4.2.1) suggests that the cyanide addition might be general to other nucleophiles. Thus, reaction of 148, the reduction product of DDQ, with an enolate, such as 166, may result in cyanide addition to the enolate (Scheme 7.3). This would be a useful method in organic synthesis as the cyanide group can be easily transformed to other functional groups, such as an amine, a carboxylic acid, or an aldehyde.
The Ni(III) complex of N-confused porphyrin inner C-oxide 153 is structurally similar to an Fe(III) porphyrin N-oxide 154, which was proposed as an alternative candidate of compound I, 155, for the active intermediate of cytochrome P-450 (Figure 5.7).\textsuperscript{3} It will be interesting to study the reactions of Fe(II) N-confused porphyrins\textsuperscript{4} with OsO\textsubscript{4}. The possible product, an Fe complex of N-confused porphyrin inner C-oxide, might have a high oxidation state for the iron ion and still be stable. It will also be interesting to see whether this Fe complex has any catalytic activity toward epoxidation or hydroxylation reactions.
References


