INTRODUCTION
INTRODUCTION

Porphyrin Nucleus

Porphyrs are highly coloured cyclic tetapyrrolic pigments formed by the linkage of four pyrrole rings through methene (–HC=) bridges, Fig.1. The basic structure of a tetapyrrole is four pyrrole rings. Porphyrs are 22 π electron systems whose main conjugation pathway contains 18 π electrons, which explains the aromatic nature from which the intense colour associated with the stems.

![Figure 1](image-url)

The porphyrs represent the most widespread of all the prosthetic groups found in nature. They mediate a spectrum of critical functions in a variety of biological systems ranging from electron transfer, oxygen transport, photosynthetic energy transduction and conversion of carbon dioxide into fuel. In addition, porphyrs in which the macrocycle is oxidized, i.e. cation radicals, are important intermediates in the catalytic cycles of heme proteins and in photosynthetic processes. These are appropriately termed as ‘pigments of life’. Common examples of important porphyrs include heme and cytochrome (with chelated iron), chlorophyll (with chelated magnesium), coenzyme B\textsubscript{12} (with chelated nickel). Thus, the parent form of these tetapyrrolic macrocycles has a common porphyrin nucleus shown in Fig.2. Relatively large photosensitizing molecules, mainly for intravenous administration, have been used for this purpose, (the first photosensitizer being porphyrin derivatives). A new method of inducing endogenous porphyrs, mainly protoporphyrin IX (PpIX), by
supplying a porphyrin precursor, 5-aminolevulinic acid (ALA), has been exploited clinically for the last 8 years.

Natural tetrapyrrolic macrocycles, in the form of metal complexes, play a vital role in certain biological processes, such as those concerned with respiration, drug detoxification, photosynthesis, and others. Porphyrin and chlorin derivatives are amongst the most important tetrapyrrolic macrocycles. The latter, in the free form, have the basic structures shown in Figure 1.

The porphyrin tetrapyrrolic structure was suggested for the first time in 1912 by Kuster, but at that time it was thought that such a ring would be extremely unstable.

The structure was definitively established in 1929 with the total synthesis of the iron complex of protoporphyrin-IX, known as heme (Fig.3), by Hans Fischer. The nomenclature initially put forward by Hans Fischer for this type of macrocycles, considered as being the classic nomenclature, is based on the numbering indicated in Fig. 2. The interpyrrolic positions are assigned as the meso-positions and are represented by the greek letters α, β, γ and δ. The pyrrolic carbons adjacent to the peripheral pyrrolic carbons, not adjacent to nitrogen atoms, are assigned as the β-pyrrolic positions and numbered from 1 to 8.
That nomenclature has limitations, and so it was necessary to have another system allowing the names standardization of all those macrocycles. The Commission on the Nomenclature of Biological Chemistry, in 1960, provided the 1-24 numbering scheme shown in Fig.2, which brought the assignment of a convenient number to all ring positions.\textsuperscript{[3]} However, due to its commodity, the classic nomenclature is still in use and it will be followed in this work.

**The Ubiquitous Porphyrin System**

Porphyrin is an ubiquitous molecule present in almost all living organisms in one form or other. The basic unit of porphyrin consists of four pyrrolic units linked by four methene bridges. It is an 18-electron system and hence exhibits aromaticity.\textsuperscript{[6]} There are also several porphyrin-like compounds, structures of some of which are given in Figure.4. The highly conjugated π system is the origin of the strong colour of these compounds and cause for their characteristic electronic and redox properties.

The porphyrin ring provides a vacant site at its center, ideally suited for metal incorporation. With very few exceptions the porphyrinato dianion acts as a tetradentate ligand with metal ions.\textsuperscript{[7]} Thus the minimum coordination number of the metal ion possible in a metalloporphyrin is four.

The extensive electronic delocalisation, which occurs in the porphyrinato ligand, leads to a substantial planarity of the macrocycle and an essentially square planar environment for the metal ion in four-coordinate complexes. Coordination number greater than four is also possible through ligation of suitable moieties either neutral or anionic. The five coordination complexes have generally a square-
pyramidal geometry with the single axial ligand occupying the apex of the square pyramid. The two ligands of the six-coordinate metalloporphyrins are found on the opposite sides of the porphyrinato plane yielding complexes with tetragonal/octahedral geometries.\[7\]

The Structure of Porphyrins and Metalloporphyrins

Understanding of the porphyrin system has advanced appreciably in recent years\[8\] determination of detailed structures for porphyrin and metalloporphyrin molecules by X-ray diffraction has contributed importantly to comprehension of the chemistry and the physical properties of porphyrin molecules. This account reviews some of these structural studies on porphyrins and discusses their implications.

Porphyrins are a class of tetapyrrole macrocycles with a skeleton as shown in Fig.5(5a). The phorphine (the parent compound) free base Fig.5(5b) has 11 double bonds and can be transformed into a metalloporphyrin 5c by replacement of the two inner pyrrole protons by a metal ion. One can also add two additional protons to the free base and obtain the porphyrin diacid species Fig.5(5d) (note that this is a doubly charged species). Protoporphyrin-IX Fig.6(6a) is one of the most abundant naturally
occurring porphyrins, while meso-tetraphenylporphyrine Fig.6(6b) is a synthetic porphyrin employed as a model for the naturally occurring porphyrins.

Three other compounds related to the porphine nucleus are especially important to the overall role played by the porphyrins in chemistry. Replacement of the α, β, γ, δ carbons by nitrogen and fusion of a benzene ring on the pyrroles gives us the well-known dye, phthalocyanine Fig.6(6c). (See ref 9 for an extensive review of phthalocyanines.) Two other important naturally occurring compounds related to aspects of the chemistry of porphyrins closely related to their acting as ligands in porphyrins are chlorophyll Fig.7(7a) and vitamin B₁₂ Fig.7(7b). A recent symposium on vitamin B₁₂ summarizes the structural work carried out in that system.[10]

Aspects of the chemistry of porphyrins closely related to their acting as ligands in coordination reactions are summarized in Scheme-I (Fig.8); we have approached the chemistry of the porphyrin from this viewpoint.[9,11] The chemistry of porphyrins from synthetic and reactivity aspects has recently been reviewed.[12,13]

The structural properties of the porphyrin molecule are necessary for understanding its physical properties, such as visible absorption spectra, solubility, and magnetic properties (magnetic susceptibility, nuclear and electron spin magnetic resonance). Knowledge of structure also clarifies chemical features such as the rates
and mechanism of metalloporphyrin formation and decomposition, ligand reactions at the metal center of the metalloporphyrins, substit-

**Figure.6**

6a. Protoporphyrin IX

6b. Meso-Tetraphenylporphyrin

6c. Phthalocyanine

**Figure.7**

7a. Chlorophyll

7b. Vitamin B₁₂
tution reactions on the ring system and oxidation-reduction reactions of the porphyrin and metalloporphyrin system. It is hoped that this review, by showing how structural data can be used in such systems, will assist in achieving broader understanding of the total chemical picture of porphyrin.

Table I lists the known crystallographic data on porphyrin and porphyrin-like molecules. Many of the compounds have been subjected to a complete X-ray diffraction analysis which yields the geometry of these compounds in the solid state; some compounds for which only the space group is known are also listed. It should be pointed out that X-ray diffraction gives information only about solid-state structures; although the bond distances are probably the same in solution, it is well known that bond angles and thus conformations of molecules are influenced by solid-state forces and may differ in the solid state and solutions.
**Table I : Crystal Structure Data for Porphyrins and Phthalocynines**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Space group</th>
<th>Cell constants</th>
<th>Z</th>
<th>a (Å)</th>
<th>b (Å)</th>
<th>c (Å)</th>
<th>α (°)</th>
<th>β (°)</th>
<th>γ (°)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ni phthalocyanine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>P21a</td>
<td>2</td>
<td>19.85</td>
<td>4.72</td>
<td>14.8</td>
<td>122.3</td>
<td>d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cu phthalocyanine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>P2da</td>
<td>2</td>
<td>19.85</td>
<td>4.79</td>
<td>14.6</td>
<td>122.6</td>
<td>f</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt phthalocyanine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>P2da</td>
<td>2</td>
<td>23.9</td>
<td>3.81</td>
<td>16.9</td>
<td>122.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Be phthalocyanine</td>
<td>P2da</td>
<td>2</td>
<td>21.2</td>
<td>4.84</td>
<td>14.7</td>
<td>122.3</td>
<td>g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co phthalocyanine</td>
<td>P2da</td>
<td>2</td>
<td>20.2</td>
<td>4.77</td>
<td>15.0</td>
<td>122.6</td>
<td>h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fe phthalocyanine</td>
<td>P21a</td>
<td>2</td>
<td>20.2</td>
<td>4.75</td>
<td>15.0</td>
<td>122.7</td>
<td>h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ptn phthalocyanine</td>
<td>P21a</td>
<td>2</td>
<td>20.2</td>
<td>3.78</td>
<td>15.1</td>
<td>122.8</td>
<td>h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ni-analog of phthalocyanine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>I2/a</td>
<td>4</td>
<td>23.5</td>
<td>6.61</td>
<td>21.9</td>
<td>122.7</td>
<td>h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrazenmmonoazoporphine</td>
<td>P21a</td>
<td>2</td>
<td>17.6</td>
<td>6.61</td>
<td>12.5</td>
<td>122.8</td>
<td>i</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrazenzporphine</td>
<td>P2da</td>
<td>2</td>
<td>17.2</td>
<td>4.72</td>
<td>12.2</td>
<td>122.5</td>
<td>j</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrazenz triazoporphine</td>
<td>P2da</td>
<td>2</td>
<td>19.85</td>
<td>31.3</td>
<td>14.8</td>
<td>122.3</td>
<td>k</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetramethylheteroporphrin</td>
<td>R3</td>
<td>6</td>
<td>31.3</td>
<td>12.12</td>
<td>19.6</td>
<td>122.7</td>
<td>l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porphine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>P2 1/a</td>
<td>4</td>
<td>12.36</td>
<td>10.42</td>
<td>10.27</td>
<td>122.8</td>
<td>m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetraphenylporphine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pi</td>
<td>1</td>
<td>6.44</td>
<td>19.2</td>
<td>14.7</td>
<td>122.5</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetraphenylporphine</td>
<td>P212121</td>
<td>4</td>
<td>12.0</td>
<td>15.12</td>
<td>13.94</td>
<td>122.3</td>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetraphenylporphine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>I42d</td>
<td>4</td>
<td>15.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetraphenylporphine&lt;sup&gt;a&lt;/sup&gt; diacid</td>
<td></td>
<td></td>
<td>16.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>122.1</td>
</tr>
<tr>
<td>(H4TPPZ-[FeCl3.Cl])</td>
<td>I4</td>
<td>2</td>
<td>16.45</td>
<td>19.26</td>
<td>106.1</td>
<td>99.1</td>
<td>101.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrapyrpyrrolepsin diacid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(H2TPyP&lt;sup&gt;a&lt;/sup&gt;·6HCl·H2O)</td>
<td>B2/b</td>
<td>4</td>
<td></td>
<td>14.31</td>
<td>13.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>q</td>
</tr>
<tr>
<td>(conventional cell)</td>
<td>12/m</td>
<td>4</td>
<td>19.89</td>
<td>19.26</td>
<td></td>
<td>98.6</td>
<td></td>
<td></td>
<td></td>
<td>q</td>
</tr>
<tr>
<td>Cu tetraphenylporphine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>I42d</td>
<td>4</td>
<td>18.99</td>
<td>15.04</td>
<td>13.88</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Cu tetrap-chlorotriphenylporphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>s</td>
</tr>
<tr>
<td>Pd tetraphenylporphine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>I2/d</td>
<td>4</td>
<td>15.75</td>
<td>14.31</td>
<td>14.6</td>
<td>102.8</td>
<td>r</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ni tetraphenylporphine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>I2/d</td>
<td>4</td>
<td>15.09</td>
<td>19.26</td>
<td>13.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Zn tetraphenylporphine</td>
<td>P212121</td>
<td>4</td>
<td>15.04</td>
<td>15.04</td>
<td></td>
<td>96.3</td>
<td></td>
<td></td>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Zn tetraphenylporphine</td>
<td>Pi</td>
<td>1</td>
<td>14.8</td>
<td>9.82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Zn tetraphenylporphine</td>
<td></td>
<td></td>
<td>6.03</td>
<td>8.64</td>
<td>11.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dihydrate</td>
<td>14/m</td>
<td>2</td>
<td>15.09</td>
<td>6.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Fe&lt;sup&gt;a&lt;/sup&gt;chlorotetraphenylporphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hydrate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>I4</td>
<td>2</td>
<td></td>
<td>17.2</td>
<td>12.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>98</td>
</tr>
<tr>
<td>VO tetraphenylporphine</td>
<td>P21/a</td>
<td>4</td>
<td>13.53</td>
<td>8.99</td>
<td>10.58</td>
<td>123</td>
<td>t</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoporphyrin I</td>
<td>P21/c</td>
<td>2</td>
<td>28.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>u</td>
</tr>
<tr>
<td>Ni etoporphyrin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>I4/amd</td>
<td>4</td>
<td>10.3</td>
<td>13.44</td>
<td>12.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>v</td>
</tr>
<tr>
<td>Ni etoporphyrin&lt;sup&gt;a&lt;/sup&gt; II</td>
<td>I4/amd</td>
<td>4</td>
<td>14.61</td>
<td>12.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>w</td>
</tr>
<tr>
<td>HemIn&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pi</td>
<td>2</td>
<td>14.68</td>
<td>19.5</td>
<td>13.57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Methoxymeron(III) mesoporphyrin</td>
<td></td>
<td></td>
<td>11.49</td>
<td>14.61</td>
<td>9.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>107.7</td>
</tr>
<tr>
<td>IX ester&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12/m</td>
<td>4</td>
<td>14.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>y</td>
</tr>
<tr>
<td>Ni-2-Diacetyldicoum-porphyrin</td>
<td></td>
<td></td>
<td>15.62</td>
<td>23.28</td>
<td>98.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>z</td>
</tr>
<tr>
<td>IX ester&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pi</td>
<td>2</td>
<td>13.2</td>
<td>24.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>86.4</td>
</tr>
<tr>
<td>FeC13-SAT-TPP</td>
<td></td>
<td>4</td>
<td>13.48</td>
<td>18.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>86.4</td>
</tr>
<tr>
<td>RhCOCI tetraphenylporphine</td>
<td>14</td>
<td>8.74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>86.4</td>
</tr>
<tr>
<td>CoCl tetraphenylporphine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>I4/m</td>
<td>2</td>
<td>13.41</td>
<td>17.3</td>
<td>12.45</td>
<td>116.</td>
<td></td>
<td></td>
<td></td>
<td>124.8</td>
</tr>
<tr>
<td>Rhphenylchlorotetraphenylporphy</td>
<td>2</td>
<td>17.11</td>
<td>13.48</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cc</td>
</tr>
<tr>
<td>rni</td>
<td>P21/a</td>
<td>2</td>
<td>13.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dd</td>
</tr>
<tr>
<td>Oxo-bis(tetraphenylporphine-iron(III))&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>15.12</td>
<td>13.09</td>
<td>14.09</td>
<td>105.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dd</td>
</tr>
<tr>
<td>Mg phthalocyanine/H2O</td>
<td>C2cb</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ee</td>
</tr>
<tr>
<td>2-pyridine</td>
<td>4</td>
<td>17.10</td>
<td>16.92</td>
<td>8.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ee</td>
</tr>
<tr>
<td>Au&lt;sup&gt;a&lt;/sup&gt; tetraphenylporphine [AuCl]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>P2dn</td>
<td>4</td>
<td>17.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ff</td>
</tr>
<tr>
<td>VO desoxyphosphorylionic-porphyrin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pi</td>
<td>4</td>
<td>17.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ff</td>
</tr>
<tr>
<td>CollI conoid complex&lt;sup&gt;a&lt;/sup&gt;</td>
<td>P21/a</td>
<td>1</td>
<td>124.86</td>
<td>13.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>gg</td>
</tr>
<tr>
<td>SnIV bisphthalocyanine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>c2/c</td>
<td>4</td>
<td>10.55</td>
<td>13.43</td>
<td>10.69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hh</td>
</tr>
<tr>
<td>p-Oxo-bis(pyrindinophthal-cyaninmanganoso(III) dimmer</td>
<td>P212121</td>
<td>8</td>
<td>11.10</td>
<td>50.74</td>
<td>16.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ii</td>
</tr>
<tr>
<td>N&lt;sup&gt;a&lt;/sup&gt; 1,8,13,13-pentamethyl-5-cyano-trans-corin</td>
<td>P212121</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>jj</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td></td>
<td>4</td>
<td>11.10</td>
<td>12.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INTRODUCTION


Bond Angles and Bond Distances

The bond distances of the porphine skeleton are quite invariant with respect to the porphyrin compound studied. The small differences one might expect due to substituent effects are usually smaller than the estimated errors of the bond parameters of the determined structures, thus not allowing any deductions to be made about variations in these parameters. The porphyrin usually has a fourfold axis of symmetry with respect to the bond distances and angles. A “best” set of these parameters is shown in Fig.9.

The one bond distance that does change appreciably is the metal-nitrogen bond distance of the metalloporphyrins. The distance can vary from 2.10 Å in the ferric porphyrins to 1.95 Å in the nickel porphyrins. The distance from the pyrrole nitrogen to the center of the ring is 2.05 Å. The trends in these bond distances are not completely understandable in terms of the usual additivities of bond parameters. Several observations can be made regarding the variations in the metal to pyrrole-nitrogen bond distances. The Metal(M) –Nitrogen(N) distance in the phthalocyanine compounds is about 0.05 Å smaller than in the metalloporphyrin. (In copper phthalocyanine the CuI11-N distance is 1.93 Å compared to 1.98 Å in copper tetraphenylporphine.) The macrocyclic nature of the porphyrin ligand might explain...
some of the metal-nitrogen bond distances in that the nitrogen-to-center-of-ring
distance is “fixed” and the macrocycle cannot easily expand and contract to “fit” the
metal ion of the metalloporphyrin. Thus the increase in the metal-nitrogen bond
distance from 1.96 Å

Figure. 9

"Best" Set Of Parameters For Porphyrin Skeleton

in nickel(II) porphyrins to 2.00 Å in palladium(II) porphyrins is somewhat smaller than
might be expected from the differences in their ionic radii of 0.72 and 0.86 Å,
respectively. This is also observed in the phthalocyanine compounds where in
copper phthalocyanine the Cu\(^{II}\)-N distance is 1.94 Å while the platinum
phthalocyanine has a Pt\(^{II}\)-N distance of 1.98 Å; the ionic radii of these two ions are
0.73 and 0.82 Å, respectively. The larger Fe\(^{III}\)-N distance (2.07 Å) in ferric high-spin
porphyrins arises from the antibonding d electrons of the ferric ion; the usual Fe\(^{III}\)-N
bond distance in high spin ammines is 2.30 Å. The contraction to the 2.07 Å value is
probably due to the charge on the pyrrole nitrogens in the metalloporphyrins.

The stability of the second-row divalent metalloporphyrins with respect to
metal ion displacement by acids is Ni\(^{II}\) > Cu\(^{II}\) > Zn\(^{II}\); the metal-nitrogen bond
distances in these metalloporphyrins are Ni-N, 1.96 Å; close to the carbon-carbon
distance in ethylene; thus Cu-N, 1.98 Å; Zn-N, 2.05 Å; this suggests that a shorter
bond distance indicates a more “stable” metalloporphyrin with respect to demetallization.

It is now well established that the porphyrin molecule is not completely rigid and its geometry can be greatly influenced by intramolecular crystal interactions. The porphyrins range from almost planar in porphine to very rufous in the tetraphenylporphine series. The tetraphenylporphine free base crystallizes in two different space groups with different conformations of the porphine skeleton in the two forms. The porphyrin in a “free” environment probably exists in a near-planar conformation with low energy barrier with respect to deviations from planarity; this condition makes for the conformational adaptability of the porphyrin skeleton to its surroundings. Because of the small amount of energy necessary to change the conformation of the porphyrin skeleton it is difficult, in general, to predict the structure of a porphyrin under various circumstances; that is, the detailed conformations of porphyrins in solution are not known because solvent-porphyrin interactions are not well enough understood to know the detailed effects they might have on the easily deformed porphyrin skeleton.

An interesting development from the accurate bond distances of the porphyrin skeleton as shown in Fig.9 is a correlation of the observed bond orders with interpretations of electronic structure. Structure Fig.10(10a) shows a resonance form of the porphyrin in which the “aromatic” ring current of the porphyrin is drawn around the outside of two pyrrole rings and around the inside of the other two; there are several other resonance forms of Fig.10(10a). From these one would predict the β-pyrrole-β-pyrrole distance (in any pyrrole ring) to be $1.37 \, \text{Å}$.\textsuperscript{[15]} The observed bond distance of $1.34 \, \text{Å}$ is very close to the carbon-carbon distance in ethylene; thus the β-pyrrole-β-pyrrole bond is nearly a pure double bond.

We have proposed another resonance form that is more consistent with the observed bond data for the porphyrin system; this is shown in Fig.10(10b) has the outer pyrrole bond as a double bond with the principal ring current now circulating around the 16-membered inner ring. There are two extra electrons in this ring, making it a 16-membered dianion. The conclusion that the main path of conjugation
is the inner 16-membered ring as in Fig.10(10b) has been substantiated by the detailed theoretical calculations of Kobayashi and Gouterman.\[16-18\]

A possible way to a more detailed understanding of porphyrin ring currents is through the nuclear magnetic resonance spectra of porphyrins. The effects of ring currents on the chemical shifts of substituent can these ring currents. Some experimental work on the NMR of porphyrins\[19-20\] and also some theoretical work on their interpretation\[21\] have been reported, but the work is complicated considerably by the concentration and solvent dependence of the chemical shifts. The best use of NMR in porphyrin chemistry, apart from the usual characterization of compounds, appears to be in studies of the details of the aggregates that porphyrins form, with attention both to thermodynamic stabilities and to structural details of the aggregate.\[22\] The large chemical shifts that the ring currents of the porphyrins produce are also being employed in the interpretation of the NMR spectra of porphyrin-containing proteins.\[23\] Gouterman,\[16\] Hush,\[24\] and Chen,\[25\] gave some theoretical interpretations of porphyrin properties, in their work.

**The Inner Hydrogen Problem**

X-Ray diffraction studies of porphyrin free bases have now definitely established that the inner pyrrole hydrogens are opposite to each other, as shown in Fig.11(11a), and not adjacent to each other, as in Fig.11(11b). The possibility of isomer Fig.11(11b) was raised by Rothemund.\[26\] Another possible structure is shown in Fig.11(11c) where the hydrogen atoms are now equally shared between two nitrogens. Various physiochemical techniques were used to probe this rather
sensitive problem of the position of the hydrogen atoms in porphyrin free bases.\textsuperscript{[27]} Low-temperature visible spectroscopy\textsuperscript{[28]} was interpreted in terms of the existence of the two isomers Fig.11(11a) and Fig.11(11b). Both IR and NMR studies were carried out without reaching any definitive conclusions. The IR and NMR studies did give evidence for rapid exchangeability of the inner pyrrole hydrogens. Some earlier studies concerned with the synthesis and properties of the N-methylated porphyrins\textsuperscript{[29]} Fig.11(11d) established that hydrogen bonding could not be important with respect to the electronic properties of the porphyrin molecule.

The visible spectra of a free base and a monomethylated free base of a porphyrin were indistinguishable.\textsuperscript{[30]} The X-ray studies on porphyrins definitely establish that the hydrogen positions are like those in Fig.11(11a). The triclinic form of tetraphenylporphine shows this most clearly,\textsuperscript{[31]} while the tetragonal forms of tetraphenylporphine\textsuperscript{[32]} and phorphine\textsuperscript{[33]} show this picture with the ambiguity of either a static or dynamic disorder of the hydrogen atoms which causes the X-ray diffraction experiment to see half-hydrogens on each nitrogen.

A refinement of the original Robertson phthalocyanine data\textsuperscript{[34a]} show that the hydrogens atoms take up positions as in Fig.11(11c). Hydrogens in these positions may be stabilized by an interaction with the meso nitrogens as shown in Fig.12(12a) (but see ref 34b for a contradictory and probably more accurate description of this system). This picture is also consistent with the distance between the hydrogen-bonded pyrrole nitrogens being 2.65 Å while the distance between the nonbonded pyrrole nitrogens is 0.11 Å greater.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure11}
\caption{Free base and mono-N-methylated porphyrin.}
\end{figure}
Geometry of Metals in Metalloporphyrins

The metalloporphyrins form a set of compounds in which the metal may be four-coordinate with a squareplanar geometry, five-coordinate with square-pyramidal geometry, six-coordinate with distorted octahedral geometry, or eight-coordinate to form a sandwich compound with square antiprism geometry. Most metallophthalocyanines and metalloporphyrins form square-planar coordination with the metal ion in the plane of the four pyrrole nitrogens as in Fig.12(12b). There are several five-coordinate metalloporphyrins with a geometry of a tetragonal pyramid Fig.12(12c). The high-spin ferric porphyrins assume this geometry with a=0.5 Å this has been carefully discussed by Hoard and his coworker.\textsuperscript{[34,35,36]} The prediction by Hoard that a low-spin iron (III) metalloporphyrin would have the iron in the plane of the pyrrole nitrogens has recently been verified by a structural analysis of the bisimidazoleiron(III) tetraphenylporphine complex.\textsuperscript{[37]} The magnesium ion in magnesium phthalocyanine hydrate is 0.495 Å out of the pyrrole nitrogen plane and bonded to a water in the apical position.\textsuperscript{[38]} The vanadium of the vanadyl-substituted etioporphyrin was also noted to be 0.48 Å out of the plane.\textsuperscript{[39]}

An interesting six-coordinate metalloporphyrin complex is the rhodium carbonyl tetraphenylporphine chloride that has the coordination shown in Fig. 12(12d).\textsuperscript{[40]} This is a prototype of the coordination that most of the metalloporphyrins assume in nature, as in the hemoprotein and cytochrome systems. If the metal is out of the porphyrin plane a seven coordinate species Fig.12(12e) is possible; this has not yet been observed in any metalloporphyrin complex. If the metal is out of the porphyrin plane a seven coordinate species Fig.12(12e) is possible; this has not yet been observed in any metalloporphyrin complex.

A very unusual complex is formed between two phthalocyanine rings and a stannic ion. The sandwich complex formed, Sn(Pc)\textsubscript{2}, has eight-coordination with a square-anti prismatic geometry as shown in Fig.13(13a).\textsuperscript{[41]} Two dimeric metalloporphyrin structures have now been determined in systems that have considerable chemical interest. The oxidation of phthalocyanine manganese(II) with oxygen in pyridine produces a compound that has been shown to be a manganese(III) phthalocyanine dimer with an oxo bridge connecting the two
manganese(III) phthalocyanines and a pyridine completing the octahedral coordination.\[42\] The two phthalocyanine rings are

![Figure 12](image1.png)

**H Positions in Phthalocyanine**

![Figure 13](image2.png)

**Square antiprism geometry of eight-coordinate tin phthalocyanine complex**

![Figure 13](image3.png)

**Manganese(III) Phthalocyanine dimer**

![Figure 13](image4.png)

**Possible seven-coordination metalloporphyrin**
staggered by 49° with respect to each other so that the phenyl groups on one ring are approximately between the phenyl groups on the other ring.

If one adds base (NaOH) to a solution of a ferric porphyrin or adds oxygen to a ferrous porphyrin a new species occurs that has now definitely been characterized as a μ-oxo-bis (porphyriniron (III)) dimer Fig.13(13c). The iron in this five-coordinate complex is 0.5 Å out of the pyrrole nitrogen plane toward the oxygen bridge. The porphyrin skeletons in this iron dimer are staggered. This compound shows interesting magnetic properties with an antiferromagnetic coupling between the iron ions resulting in a diamagnetic ground state at liquid helium temperatures and a magnetic moment at room temperature of 1.85 BM. This compares to the ferric tetraphenylporphine monomer that has a magnetic moment at room temperature of 5.87 BM and follows the Curie-Weiss law in the temperature range from 298 to 77°K.

The visible absorption spectra of the monomer and dimer species are quite different. It is hoped that a careful analysis of this system will lead to a better understanding of the electronic configuration of metalloporphyrins and of the way metal ions in complicated systems can interact via oxide and other ligand bridging groups. The interaction of two metal ions via an oxide bridge is well established in the literature, although the details of the interaction still are not well understood. We have also prepared a dimer of manganese(III) tetraphenylporphin.

**Porphyrin Diacids**

The porphyrin diacids that are formed in acidic solution present several interesting problems that were only recently solved by X-ray diffraction. The general geometry of the diacid complexes was unknown. The fact that some porphyrins, in particular, tetrapyridylporphine and tetraphenylporphine, existed in solution only as the free base and diacid but not as the monoacid species see Figure 13(13d) was unexplained. The fact that most porphyrin free bases are orange or red in solution while their diacid species are usually violet, except for the tetraphenyl- and tetrapyridylporphine diacid species which are green, can be interpreted in terms of the molecular structures of these diacid compounds. Both the tetraphenyl- and tetrapyridylporphine diacid species exhibit the remarkable nonplanar conformation of the porphyrin skeleton shown in Fig.14(14a).
The β-pyrrole carbon atoms are as much as 1.0 Å out of the “plane” of the four pyrrole nitrogen atoms. This highly nonplanar geometry arises from van der Waals and Coulombic repulsions of the four inner hydrogen atoms. The phenyl groups in most tetraphenylporphine compounds are almost perpendicular to the “mean plane” of the porphine ring; this does not allow any π interaction between the benzene π system and the extensive porphyrin π system.

The dihedral angle that the phenyl rings make with the porphyrin ring is required to be greater than 70° because of interactions between the phenyl hydrogens and the outer pyrrole hydrogens. In the diacid of tetraphenylporphine, the tilted porphine skeleton allows the phenyl group to rotate toward the porphine “plane,” making an angle of 21° with it; this now allows a strong interaction to occur between the phenyl and porphyrin π system with the resulting green color compared to the usual violet diacid species. All porphyrin diacids would be expected to have the geometry shown in Fig. 14(14a).
By now almost all metals and some semimetals have been incorporated into porphyrin cavity \(^{49}\). The essence of bonding between a central metal atom and the porphyrin ligand is to be found in the following two types of primary interactions \(\sigma\) and \(\pi\) coordination of nitrogen lone pairs directed towards the central metal atom and \(\pi\) interaction of metal \(\pi\) and/or \(d\pi\) orbitals with nitrogen \(\pi\) orbitals\(^{50}\). The appropriate symmetry-adapted linear combinations of ligands orbitals involved in the interaction are shown schematically in Fig.15.

The bonding of the central metal atom to the surrounding tetradeutate ligand is through interactions of \(dx^2-y^2\) - \(b_{1g}\); \(dxz, dyz\) - \(e_{g}\); \(dz^2\), \(s\) - \(a_{1g}\); \(px, py\) - \(e_{u}\) and \(pz\) - \(a_{2u}\) pairs. Each interaction may be spread out over several orbitals in the porphyrin system. In the \(\sigma\) system the porphyrin is clearly a donor to the metal while in the \(\pi\) system porphyrin has the appropriate orbitals to act both as \(\pi\) donor and as a \(\pi\) acceptor. The symmetry adapted linear combinations of porphyrin-ligand orbitals involved in the bonding with metal orbitals.

The most useful spectroscopic technique for the study of porphyrins/metalloporphyrins is the electronic absorption spectroscopy. The normal metalloporphyrin spectrum shows an intense B(Soret) band at 420nm and two weaker Q(\(\alpha,\beta\)) bands at \(\sim 550-600\)nm\(^{49,51}\). These spectral absorptions arises from \(\pi\)
- $\pi^*$ transitions of the aromatic porphyrin ligand. A typical spectrum of this (for Zn(II)) is given in Fig.14(14b). The widely accepted model to fit this spectrum, the four-orbit model, treats the porphyrin as a cyclic polyene and emphasizes the transition between the two highest filled bonding molecular orbital levels, $a_{1u}$, $a_{2u}$, and the lowest empty doubly degenerate antibonding molecular orbital levels, $e_g^*$. The schematic representation of the porphyrin HOMOs and LUMOs are shown in Fig.16(16a).

The allowed transitions, $a_{1u} \rightarrow e_g^*$, $a_{2u} \rightarrow e_g^*$, are assumed to be near degenerate in energy. As consequence, the states undergo configuration interaction and give rise to new states. The resulting spectrum shows a high energy band B in which the transition dipoles add (high intensity) and a low-energy band Q in which the transition dipoles nearly cancel (low intensity). The two Q bands are vibronic components of the same transition. The exact positions of the spectral maxima of MPs are related to a number of parameters including metal electronegativity and metalloporphyrin molecular structure. The overlap of filled metal d orbital with the porphyrin ligand orbitals can cause some shift in the absorption bands as compared to metal-free porphyrins.

Besides these absorptions some charge-transfer bands are also possible which can also shift the porphyrin $\pi-\pi^*$ transitions significantly. The synthetic metalloporphyrins have several functionalisation sites namely meso position, $\beta$ (pyrrole ring) position, central metal and also the inner nitrogens Fig.16(16b).

The common meso-substituted porphyrins are tetraphenyl porphyrin ($R = \text{phenyl}$) and ortho, meta or para substituted phenyl porphyrins. The important pyrrole substituted porphyrins includes octaethyl porphyrin ($R_1 = R_2 = \text{Ethyl}$) and etioporphyrin ($R_1 = \text{Ethyl}, R_2 = \text{Methyl}$).

**Synthetic Routes to Multiporphyrin Arrays**

The synthesis of suitable tetrapyrrolic macrocycles and assemblies of tetrapyrrolic macrocycles has proved to be problematic. Nature uses a myriad of biosynthetic pathways to make both the tetrapyrrolic macrocycles and the associated proteins and then to assemble them into arrays for energy- and electron-transfer interactions such as covalent thioether bonds, metal-ligand axial
coordination, hydrophobic or hydrophilic interactions, and hydrogen bonding. It is virtually impossible to synthetically reproduce the intricate and specific protein matrix. While some research groups have produced porphyrin-peptide conjugate assemblies as models for natural systems,\textsuperscript{[54-57]} many researchers interested in mimicking these systems have constructed artificial, generally covalently linked, tetrapyrrolic macrocyclic arrays. Thus, nature has created a huge impetus for the synthesis of a wide variety of multiporphyrin assemblies.

Largely as a consequence of this, tetrapyrrolic macrocycles have also been found to be of great interest in areas outside modeling and mimicking natural systems. Molecular sensing,\textsuperscript{[58]} medicine (photodynamic therapy,\textsuperscript{[59]} boron nuclear capture therapy,\textsuperscript{[60]} and DNA cleavage\textsuperscript{[61,62]}, and optical applications (data storage,\textsuperscript{[63]} nonlinear optics,\textsuperscript{[64]} electrochromism,\textsuperscript{[65]} and optical limiting\textsuperscript{[66]}) are just a few of the many areas that have inspired the synthesis of porphyrin assemblies. The development of tetrapyrrolic molecular materials with the potential to undergo controlled energy or electron transfer has led to the production of prototypical molecular-scale devices such as wires,\textsuperscript{[67,68]} logic devices, switches, and gates,\textsuperscript{[69]} essential for the miniaturization of electronic componentry and technology. The increasing importance of these applications provides a continuous stimulus for intensive research toward artificial porphyrin assemblies.
INTRODUCTION

Scheme 1. Condensation of pyrrole and arylaldehydes to form TAPs

Scheme 2. Mixed aldehyde condensation to give a mixture of products

Scheme 3. 2+2 Condensation of dipyrrylmethanes - The macDonald Method[89]

Scheme 4. 2+2 Condensation of a - free Dipyrrylmethanes with aldehydes.
Scheme 5. General synthesis scheme for porphyrin arrays formation.

**Scheme 6. Synthesis of Triporphyrin Cu-3 of Anton et al.[70]**

Scheme 6. Synthesis of Triporphyrin Cu-3 of Anton et al.[70]
General Synthetic Procedures

The driving force for the design of a porphyrin array is invariably from the requirements for specific array properties or functionality. This will lead the researcher to choose not only a particular porphyrin unit but also the type of linkage between units that will provide the desired properties and be easily incorporated into the synthetic strategy. Commonly the choice of linker will complement the functionality of the porphyrin unit. Therefore, any array synthetic strategy must take into account both the porphyrin functionalization and linkage implementation.

Procedures for the synthesis and functionalization of monomeric porphyrins have now progressed to the point that virtually any porphyrin can be made. Therefore, linker choice ultimately becomes one of availability of materials, researcher expertise, and ease of implementation. It is not the aim of this section to give a comprehensive insight into the vast multitude of porphyrin functionalization reactions; rather, a general summary is presented of both porphyrin and array formation strategies.

Porphyrin Formation

There has been a considerable volume of review literature published on the synthetic formation of porphyrins. What follows is a summary of the typical synthetic procedures used to form most of the porphyrins used in multiporphyrin assemblies.
A simple path to forming symmetrical synthetic porphyrins such as the TAPs is by the acid-catalyzed condensation reaction of pyrrole with a suitable aldehyde, followed by oxidation of the resulting porphyrinogen (Scheme 1). This procedure, originally developed by Rothemund and Menotti,[83] has been refined to generally give around 20% yields for TAPs.[84] Despite the modest yields, the relative simplicity of this method has made it well suited to large-scale preparation of TAPs (i.e., >1 g of porphyrin).

Higher yielding and milder reaction conditions have been developed by the Lindsey group.[85,86] Lindsey’s group subsequently developed higher reactant concentration conditions (0.1-0.3 mol L\(^{-1}\)) that were slightly lower yielding than before but more practical for larger scale preparations.[87] More recently, the group found that the addition of salts, such as sodium chloride, to the condensation reactions could increase (sometimes double) the yields.[88] The specific mechanism for this improvement in yields has not yet been determined.

Other variations on the Rothemund or Lindsey procedure have been published that employ hydroiodic acid, hydrochloric acid, p-toluenesulfonic acid (pTSA),[89] perchloric acid,[90] trichloroacetic acid (TCA),[91] montmorillonite clays,[92] or high-valent transition metals[93] as catalysts and/or oxidants. A preparation of meso-substituted porphyrins was published that employed no solvent or catalyst, reacting the pyrrole and aldehyde together in the gas phase (>200°C) while admitting oxygen as oxidant.[84] TPP was obtained in a 23% yield in this manner.

While easy to synthesize, these symmetrical porphyrins suffer in that there is no provision to be able to control the functionalization at individual meso positions, a severely limiting factor in the quest to form large covalently bonded arrays.

It is possible to synthesize unsymmetrically substituted porphyrins via mixed aldehyde condensations. If a mixture of two different aldehyde starting materials is employed in the Adler or Lindsey porphyrin syntheses, then a statistical mixture of products is obtained (Scheme 2). The desired porphyrin is then removed by extensive chromatography. The disadvantages here are that yields are lower by virtue of the statistical outcome of the reaction and the separation procedures can
be troublesome, particularly if the reactions are carried out on a significant scale.\textsuperscript{[95-97]}

Alternative approaches for synthesizing substituted porphyrins have been devised in which dipyrrolic starting materials are combined to form tetrapyroles. Dipyrromethenes, dipyrryl ketones, and dipyrrylmethanes (DPMs) have been used in these “2+2” synthetic methodologies. In 1960, MacDonald and co-workers published the first dipyrrylmethanbased porphyrin syntheses (Scheme 3).\textsuperscript{[89]} The condensations were catalyzed by acid and the intermediate tetrapyroles oxidized by exposure to air to give the desired porphyrins. In a variation of the Mac-Donald synthesis, “3+1” synthetic methodologies have been developed in which tripyrrolic species (or tripyrranes) are condensed with 2,5-diformylpyroles to form a cyclic tetrapyrole.\textsuperscript{[98]}
Alternative 2+2 methods involve the acid-catalyzed condensation of α-free dipyrrylmethanes with aldehydes to form porphyrinogens, which are then chemically oxidized to give porphyrins (Scheme 4).

Scheme 9. Synthesis of the Ru-Centered pentaporphyrin 13 of Sanders et al.[102]

This methodology is considerably more versatile for array formation, especially of larger assemblies as it is frequently higher yielding and produces more soluble products as well as allows control over substitution at the meso positions. There is however a trade off, the time and resources required to make the precursor...
dipyrrylmethane molecules. Nonetheless, since the development of efficient methods for the preparation of the required α-free dipyrrylmethanes,\textsuperscript{[99]} this methodology has been used extensively in the synthesis of a wide variety of porphyrins.

**Porphyrin Assembly Formation**

There are two fundamental strategies to porphyrin array construction. By far the majority of porphyrin assemblies have been made using strategy (A) (Scheme 5), in which the array is developed from the functionalization of the porphyrin monomer. In this case, either a linkage or porphyrin is generated as the array is constructed. The second strategy (B) is an increasingly popular method for array construction and involves the direct coupling of porphyrin moieties. In strategy (A) an array will be formed if the derivatized porphyrin (II) is either coupled with a second functionalized porphyrin to form the array linkage or if a new porphyrin is created from the functional group (X), for example, an aldehyde condensation with a pyrrole. The functionalization of the monomeric porphyrin can be achieved in two ways (Scheme 5). Starting with the monomeric porphyrin(I), it is possible to first functionalize it at either the β-pyrrolic or meso positions. Another approach is to introduce the functionalization during the porphyrin formation, via a number of alternative procedures, for example, statistical condensation using various aldehyde starting materials. Each functionalization method has advantages and disadvantages, for instance, statistical condensation is an inefficient way of forming functionalized monomeric precursors, giving low yields and requiring careful separation. In some instances however, it is still preferable to the alternative “2+2” and “3+1” strategies, which give excellent control over functionalization yet require lengthy syntheses of the precursor aldehydes and pyrroles. The direct functionalization of a preformed monomeric porphyrin is relatively straightforward but often limited by the small number of electrophilic aromatic substitution reactions that can be easily effected on the porphyrin nucleus. These are the most common methodologies used to form porphyrin arrays and cover the bulk of the literature examples on the synthesis of porphyrin arrays.
Scheme 10. Synthetic of the Amide-Linked Tetraporphyrin 18 of Dubowchik and Hamilton.\[71\]
Scheme 11. Synthesis of the "Radial" pentaporphyrin Zn-23 of Milgrom\textsuperscript{[72]}

Where Tol =  \[
\text{[tolyl]}
\]
Scheme 12. Synthesis of polymer 25 of Scamporrino and Vitalini\textsuperscript{[103]}

\[
\begin{array}{c}
\text{OMe} \\
\text{MeO} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{O} \\
\text{H} \\
\text{24} \\
\end{array} \xrightarrow{\text{Cl} \ (\text{CH}_2)_6 \text{Cl}} \xrightarrow{i \ 40\%} \begin{array}{c}
\text{OMe} \\
\text{MeO} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{O} \\
\text{O(\text{CH}_2)_6} \\
\text{25} \\
\end{array}
\]

Scheme 13. Synthesis of the Ether-Linked pentaporphyrin 28 of Norsten and Branda\textsuperscript{[105]}

\[
\begin{array}{c}
\text{ClCH}_2 \text{CO}_2\text{CH}_3 \\
\text{26} \\
\end{array} \xrightarrow{i} \begin{array}{c}
\text{CO}_2\text{CH}_3 \\
\text{27} \\
\end{array} \quad + \quad \begin{array}{c}
\text{H}_2\text{CO}_2\text{CO}_2\text{CH}_3 \\
\text{28} \\
\end{array}
\]
In a few yet steadily growing number of cases, strategy (B) has been employed to construct porphyrin arrays.\textsuperscript{[100]} By utilizing oxidative coupling via the unsubstituted meso-positions of monomeric porphyrins and continually cycling the products back into the reaction, very large arrays can be generated. This process is
quite clean experimentally, but by nature of the reaction only one type of linker is generated, namely, a direct carbon-carbon link between porphyrins.

Another issue that provides an extra layer of complexity is the incorporation of metalloporphyrins into the array. In many cases, metalloporphyrins have desirable characteristics which are important to the utility of a given porphyrin array. However, the stability of metalated porphyrins vary greatly, and this will dictate the time at which the metal should be inserted during the array synthesis. For example, strongly bound nickel and copper porphyrins will readily tolerate most conditions in forming an array from porphyrin I in Scheme 5. Nonetheless, some methodologies will simply fail
in the presence of these metals. It is often difficult to predict the success of a given reaction in the presence of different metalloporphyrins. In contrast, porphyrins containing the more labile zinc metal ion will not stand many of the array-forming reactions in Scheme 5. Therefore, the introduction of zinc into a porphyrin array will usually be the final step in the synthesis. Adding to this is the sensitivity of many linkers, which may not be compatible with the conditions necessary to achieve the metalloporphyrin. The combination of these problems will continue to challenge the imagination and skill of those involved in the synthesis of porphyrin arrays.

Scheme 18. Synthesis of Bispyro phenophorbidoporphyrin 45a of Zheng et al.[107]
**Porphyrons in Life Processes**

Metal complexes of porphyrins and related aromatic macrocycles are important prosthetic groups and form integral part of a wide variety of enzymes working as redox and rearrangement catalysts. Both the unique features of porphyrins mentioned earlier and controlled and cooperative interactions possible between porphyrins and the surrounding protein globule contribute substantially to the efficient functioning of these natural systems.

A large number of naturally occurring porphyrins have been isolated and characterised. Of these protoporphyrins are, by far, the most abundant and widely characterised ones. Protoporphyrin contains 4 methyl groups, two vinyl groups and two propionic acid groups. Fifteen different isomeric protoporphyrins differing in the sequence of substitution of the above groups in the eight available side chain positions are possible. Of these many possible forms, the protoporphyrin IX is the only form found in nature. It is found in hemoglobin myoglobin, heme enzymes and most of the cytochromes.\textsuperscript{[108]}

The chelate complex of protoporphyrin IX with Fe(II) is called protoheme or more simply heme; a similar complex with Fe(III) is called hemin or hematin. When
the fifth and sixth positions of Fe-atom are occupied the resulting structure is a hemochrome or hemochromogen. It is the heme moiety, which plays the crucial role in most dioxygen mediated life processes.

The various functions of heme proteins in the transport, storage and reactions with dioxygen are made possible essentially by different and selective interactions of diverse proteins with the heme groups. These differences derive from the axial ligands provided by ancillary groups of the protein and from the nature of the pockets on either side of the porphyrin. Both features create different environment about the heme so that the interaction of iron with dioxygen can achieve an extremely wide range of chemistries. Thus in blood, the tetrameric hemoglobin carries and shows cooperativity in binding of dioxygen. In the tissue, the structurally similar monomer myoglobin receives $O_2$ from hemoglobin and stores it for eventual reduction to water by cytochrome c oxidase in mitochondria.

Important porphyrin based natural systems are the heme enzymes, hemoglobin, myoglobin, the cytochromes and chlorophyll.

**Enzymes**

Enzymes are organic biocatalysts, which govern, initiate and control biological reactions, important for life processes. All known enzymes are proteins and some contain non-protein moieties termed prosthetic groups that are essential for the manifestation of catalytic activities. In a variety of natural enzymes, metalloporphyrins (especially the heme system) constitute these prosthetic groups, some of which are discussed in brief.

**Chlorophyll**

Chlorophyll is the major light absorbing pigment in most green cells. Chlorophyll is basically magnesium derivative of porphyrins and some slight structural changes in porphyrin moiety results in different classes of chlorophyll viz, chlorophyll a,b,c, or bacteriochlorophyll etc with slightly different photocatalytic properties. All of the chlorophylls absorb light very intensely, particularly at relatively long wave length regions. The light energy absorbed by a chlorophyll molecule become delocalized and spread through out the entire electronic structure of the excited molecule.
The photosynthetic pigments in the chloroplasts of plants consists of two functional units namely photosystem I and photosystem II.\textsuperscript{112} Photosystem I contains chlorophyll and β-carotene as well as a single molecule of P700, a specialized chlorophyll a which serves as an energy trap. Photosystem I absorbs light at longer wavelengths and it is not responsible for O\textsubscript{2} evolution. Photosystem II on the other hand, is activated by shorter wave lengths, 670 nm and below and is responsible for O\textsubscript{2} evolution. It has a characteristic reactive center namely P680 a specialized chlorophyll-protein complex. Although both photosystems contain chlorophyll a and chlorophyll b the ratio of chlorophyll a to b is higher in photosystem I than in photosystem II. The most significant difference between the photosystems, however, is the presence of large amounts of chlorophyll a-protein complexes absorbing at long wavelengths in photo system I and their absence in photosystem II. These two light systems, one absorbing in the region 680-720 nm (PS I) and the other at shorter wavelengths (PS II) must cooperate to yield maximal results in photosynthesis.

In addition to the above mentioned natural systems, some other macromolecules, structurally related to porphyrins are also involved in various biological processes. An example is the well known Vitamin B\textsubscript{12} which is a cobalt derivative of a 15-membered corrin ring.\textsuperscript{108} The controlled interaction between the porphyrin-like frame work and the surrounding proteins is expected to be the crucial factor in the specific functions of these biosystems also.

**Porphyrins and Metalloporphyrins: A General Outlook**

Metalloporphyrins in association with protein globule performs several important biochemical functions in nature. Hemoglobin, myoglobin, chlorophyll, cytochromes, catalase and paroxidases are well known examples, the chemistry of which relates principally to the redox property of corresponding metalloporphyrins and also their ability in transportation, storage and activation of molecular oxygen. Over the years a great deal of concerted efforts have brought to light substantial understanding of the structure-function relationship in these natural porphyrins.\textsuperscript{113-120}
Interests in metalloporphyrins are not confined only in the biological field as these compounds are equally important from chemical, industrial and technological point of view. During the last three decades synthetic porphyrins have been widely studied for various applications spanning the whole chemical and biological fields.\textsuperscript{121-128} Metalloporphyrins are widely and intensely investigated in the area of catalysis and also as models and mimics of enzymes like catalase, paroxidases, P450 cytochromes or as transmembrane electron transport agents.\textsuperscript{121-123} They have also been used as NMR image enhancement agents,\textsuperscript{126} nonlinear optical materials\textsuperscript{127} and DNA-binding or cleavage agents.\textsuperscript{125-128} Large numbers of patents have been lodged for the use of porphyrins as radio diagnostic agents and in photodynamic therapy (PDT), foodstuff antioxidants, semiconductors or electrochromic materials.\textsuperscript{121-124} Their applicability is so broad that they find a place even in beauty shops as body deodorants and stimulants of hair growth.\textsuperscript{121} Phorphyrin-type compounds constitute a major class of pharmacological agents under investigation for application in the early diagnosis and treatment of cancer by photodynamic therapy and a variety of other diseases. Two porphyrins derivatives, purified hematoporphyrin derivative and verteporfin, are FDA-approved for the photodynamic therapy treatment of melanoma, early and advanced stage cancer of the lung, digestive track, genitourinary track, and the wet form of age-related muscular degeneration, respectively. Both of these drugs are mixtures of compounds with limited specificity for tumor tissue. Although both drugs have been successfully used to treat several thousands of passions worldwide, skin photosensitivity is often and undesirable side effect in purified hemetoporphyrin derivative photodynamic therapy due to prolonged retention of this drugs in patients skin. This unwanted side effect has been minimized or illuminated with the use of second-generation photodynamic therapy photosensitizer currently undergoing clinical investigation.

The tetra aryl porphyrins (46) were the first easily prepared, easily purified porphyrines to be evaluated as photosensitizers. Tetra phenylporphyrine as a band I absorption maximum of 630nm and is an efficient generator of $^{1}$O$_{2}$ but has limited solubility. Sulphonation of tetra phenylporphyrine gives the tetrasulphonate(47) which
remains an excellent producer of $^1O_2$ has excellent water solubility and was once viewed as a promising photosensitizer for photodynamic therapy. Tetra phenylsulfonate is membrane permeable, displays lysosomal accumulation in cells, accumulates in tumors, and is effective both in vitro and \textit{in vivo}. However, clinical ambitions for tetra phenyl sulfonate ended after reported neurotoxicity in mice. Recent work with porphyrin derivatives suggest some novel approaches to porphyrin delivery. Dendrimeric porphyrin derivatives with a porphyrin ring as the dendrimer core (48) have been prepared. The porphyrin chromophor is buried inside a hydrophobic shell. While these molecules, can look protein–like, surface modifications of the dendrimer periphery have provided cationic and anionic surfaces photosensitizer in vitro. Tetra phenyl porphyrin derivatives bearing amino acids, for zinc porphyrins with up to 32 charged groups that have been touted as effective dc porphyrins with up to 32 charged groups that have been touted as effective peptides, or diamines (49) have demonstrated excellent surface recognition for potassium channels. This two different classis of porphyrin molecules suggest different ways of targeting porphyrin-base photosensitizers, which may be developed in the future.

Substituent changes in the meso positions of the porphyrins have little impact on the wave lengths of absorption of the porphyrin choromophore. While this allows tailoring of biological properties without a major change in absorption maximum, it
limits the absorption maxima of porphyrin molecules to the shorter wave length region of the biological window for photodynamic therapy. Longer-wave length-absorbing porphyrins have been prepared by substituting a chalcogen atom (S or Se) for an NH at the 21-position of the porphyrin ring. Such molecules are called core-modified porphyrins, and sulfonated analogues of the 21-thia and 21-selena porphyrins (50), (51) have been evaluated as photosensitizers for photodynamic therapy. The substitution of a chalcogen atom for N has little if any impact on singlet-oxygen generation. The sulphonated 21-thia and 21-selenaporphyrins, respectively are reported to be comparable to chlorine for efficacy in vivo with BFS1 sarcoma baring mice, and the 21-selenaporphyrin show no skin photosensitization in animals irradiated 24 h following injection. N-confused 21-thia core-modified porphyrins (52), (53) have band I absorption maxima near 730nm with value of $\varepsilon$ between $8 \times 10^3$ and $1.8 \times 10^4$ M$^{-1}$ cm$^{-1}$. However, their use as photosensitizers has yet to be reported.
Replacing a second core heteroatom with S or Se give 21, 23-core modified porphyrins with even longer wavelength band I absorption maxima (~ 695-700nm) sulphonated derivatives (54),(55) are easily prepared. In these two molecules the chalcogen atom substitution does impact singlet-oxygen generation with f(1O2) of 0.50 for (54) and 0.17 for (55). However, (56) is more effective than (50) invitro and also shows activity in vivo.

In the porphyrin series, analogues of (50) have been prepared that have allowed a limited structure-activity relationship to be developed. Molecules with two sulphonatoaryl substituents at the 5- and 10- position of the porphyrin core and with other substituents at the 15- and 20-position have shown optimal properties for both uptake and distribution. Studies with 21, 23-core modified porphyrins confirmed these observations with sulphonatoaryl groups at the 5- and 10-position relative to sulphonatoaryl substituents at all for meso positions. Compounds (56-61).With sulphonateophenyl substituents at the 5- and 10- position give 50% cell kill with for J cm⁻¹ of 590 to 800nm light at Concentrations of 0.64 to 7.9 mM with Colo-26 cells in vitro. In contrast, dithia porphyrin (56) give 50% cell kill at 30 mM and (47) gives 50% cell kill at 125 mM under identical conditions. Dithiaporphyrin (56) at 0.125 mg/kg is a comparable in efficacy to Photofrin at 2.5 mg/kg in BALB/c mice bearing Colo-26 tumors. Compounds (56) and (59) also shown greatly reduced skin photosensitization relative to Photofrin.

The photophyrical properties of (54-58) were little affected by hetero atom substitution in the core. All five compounds were efficient generators of singlet oxygen with Φ(1O2) in the range 0.55-0.78. The band I absorption maxima are all very similar including 21- thia porphyrin(60). Dithiaporphyrin (61) with two 4-dimethylaminophenyl substituents has a longer wavelength band I absorption maximum with a higher molar absorptivity than compound(56-60).

The sulfonic acid groups have very low pKa values and remain in the anionic form through out the physiological pH range. Replacing the sulphonato groups with carboxylic acid groups gives Core-modified (62) with two 4-fluorophenyl substituents at the 5- and 10- position and two carboxylic acid residues on substituents at the 15-
and 20- position gives 50% cell kill with 4J cm\(^{-2}\) 590-800 nm light at 0.43 µM with Colo-26 cells *in vitro*. Diphenyl derivative(18) was even more efficacious with 50% cell kill with 0.15 µM photosensitizer under identical conditions for irradiation. For comparison purposes, Photofrin gives 50% cell kill with 4J cm\(^{-2}\) of 590-800 nm light at 10 µM with Colo-26 cells, while the chlorin derivative gives 50% cell kill at 1 µM.

The carboxylic acid substituted core-modified porphyrins display an SAR similar to that of the sulfonated derivatives with respects to uptake and efficacy. Compound (63) with two carboxylic acid groups shows greater cellular uptake and greater efficacy than compounds (64-66) with one, three and four carboxylic acid groups, respectively, in R3230AC rat mammary adenocarcinoma cells. The meso-substituent
changes have essentially no impact on either band I absorption maxima or values of $f(\text{O}_2)$. However, the number of carboxylic acids has a significant impact on the n-
octanol/water partition coefficient (log p) with log p near 1.0 for (65,66), near 0.0 for (62), and > 3.5 for (63).
To attain a broader spectrum of indication, most desirable with reduced side effects, non-crost resistance, higher selectivity a range of alternative metal compound (68-88) are presently being clinically tested.

Ruthenium possesses several favorable prosperities suited to rational anticancer drug design, since certain ruthenium complexes reduce tumor growth by mechanisms involving interaction with DNA and RNA although non genomic targets also appear to be important, such as transferring which allows them to be selectively transported in to cancer cells. While most research has focused on Ru(III) and to a lesser extent Ru(IV) complexes, recent advances have been made using organometallic Ru(III) arine compounds(89-93) that show considerable promise for the treatment of cancer and metastatic.
REFERENCES:

31. See Table I, footnote n.
32. See Table I, footnote p.
33. See Table I, footnote m.
34. (a) See Table I, footnote aa; (b) B. F. Hoskins, S. A. Mason, and J. C. B. White, Chem. Commun., 554, 1969.
35. See Table I, footnote y.
37. J. L. Hoard, private Communication.
38. See Table I, footnote ee.
39. See Table I, footnote gg.
41. See Table I, footnote ii.
42. See Table I, footnote jj.
INTRODUCTION


46. See Table I, footnote q.


INTRODUCTION

In this review, the terms assembly and array are used interchangeably and refer to a system containing two or more porphyrins linked together by any means.
INTRODUCTION

INTRODUCTION