Research Article

A Synthetic Approach of New Trans-Substituted Hydroxylporphyrins

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The synthesis of new trans A2B2-substituted porphyrins bearing oxygenic substituent (methoxy, acetoxy, hydroxy) at the periphery of the ring are described. All of the synthesized products were characterized by 1H-N.M.R., 13C-N.M.R., and H.R.M.S. Electrochemical studies revealed two one-electron oxidations and two reductions. In addition, the X-ray structure of one methoxy-derivative was determined.

1. Introduction

In the last years porphyrin derivatives have been developed or are under development for use as photosensitizers for photoelectronic materials such as sensors [1] and photosensitized solar cells [2]. Because of their interesting optical properties, porphyrin molecules have been investigated as artificial light harvesting antennae. Carbon-based donor-acceptor hybrid materials have been reported where, in many cases, the porphyrin molecule is covalently attached [3, 4]. Among the great diversity of porphyrins with a specific pattern of substituents, trans-substituted porphyrins with functional groups at the periphery of the ring act as precursors for supermolecular structures.

During the past decades a great effort has been directed towards the synthesis of porphyrins [5, 6]. Porphyrins with nearly all sorts of substituents at the periphery of the 18π-electron system are now accessible. The synthetic procedures followed were mainly based on the Adler-Longo reaction of the condensation of pyrrole with various aldehydes.

In the field of trans-substituted porphyrins an attractive route for the synthesis of these key structural components found in a wide range of model systems [7] was developed by Lindsey’s group [8–10]. The synthetic approach of Lindsey’s group was based on the convenient preparation of 5-substituted dipyrromethanes [8]. Condensation of a dipyrromethane with an aldehyde in a MacDonald-type synthesis has been used for the preparation of a wide range of trans A2B2 type meso-substituted porphyrins [8, 11, 12].

Based on this method we tried to explore the possibility of the synthesis of meso-substituted trans hydroxyporphyrins due to the ability of the hydroxy group to link substructures over the porphyrin plane. Hydroxyporphyrins can act as precursors for the synthesis of porphyrin dimers serving as host molecules [13]. Furthermore a series of hydroxyporphyrins has been tested as photosensitizers in photodynamic therapy (PDT) [14, 15]. For their synthesis the methoxy- or acetoxy-derivatives were prepared first.

2. Experimental

2.1. Measurements. 1H-N.M.R. and 13C-N.M.R. spectra were recorded on a Bruker AMX-500 MHz N.M.R. spectrometer using chloroform-D3 as a solvent. Resonances in the 1H-N.M.R were referenced versus the residual proton signal of the solvent.
Absorption spectra were collected on a Perkin-Elmer Lambda 6 grating spectrophotometer. Cyclic voltammetry experiments were performed in an AUTOLAB PGSTAT20. MS spectra were recorded on Bruker MALDI TOF/TOF ultraflextreme.

X-ray diffraction measurements were conducted on a STOE IPDS II diffractometer using graphite-monochromatized Mo Kr radiation. A dark blue crystal with approximate dimensions 0.50 x 0.40 x 0.14 mm was mounted on a capillary. Intensity data were recorded using 2θ scan (2θ max = 46.5, 1°/min). The structure was solved by direct methods and refined on F2 values using SHELX [16]. All nonhydrogen atoms were refined anisotropically; all of the hydrogen atoms were introduced at calculated positions as riding on bonded atoms and were refined isotropically.

2.2. Synthesis of Porphyrinic Compounds. The preparation of 5-mesityl dipyrromethane was based on previously published procedures [8].

2.2.1. 5,15 Dimesityl-10,20 Bis(3-Methoxyphenyl)Porphyrin 1. 3.8 mmol (1 gr) of 5-mesityl dipyrromethane and 3.8 mmol of 3-methoxybenzaldehyde were dissolved in 400 mL of CH2Cl2 (A.C.S. grade) under argon atmosphere. 7.12 mmol of 3-methoxybenzaldehyde were dissolved in 400 mL of CH2Cl2 (A.C.S. grade) under argon atmosphere. The solution was pale brown. The solvent was removed under reduced pressure and the solid was dissolved in 50 mL of toluene, heating at reflux for 1 hour, after the addition of 0.38 mmol of DDQ. After cooling at room temperature the solvent was removed and the solid was purified by a column chromatography. A column of Al2O3 was performed with CH2Cl2 as eluent (yield 22%).

MS: [M]+ 758.3631,
UV-Visible: λmax (toluene, 5.3 × 10−5 M)/(logε/M−1 cm−1): 401 (sh, 4.79), 419 (Soret, 5.54), 482 (sh, 3.84), 513 (Q, 4.28), 550 (Q, 3.90), 591 (Q, 3.92), 647 (Q, 3.72),

1H-N.M.R. (500 MHz, CDCl3, 300 K) δ = 8.86 (d, 4H, J = 4.6 Hz, pyrrole); 7.71 (d, 4H, J = 4.6 Hz, pyrrole). Phenyl Group: δ = 7.84 (m, 4H, 2,6-ph); 7.66 (tr, 2H, J = 8 Hz, 3-ph); 7.35 (dd, 2H, J = 8 Hz, 4-ph); 4.02 (s, 6H, −OCH3). Mesityl Group: δ = 7.31 (s, 4H, 3,5-mes); 1.88 (s, 12H, 2,6-mes); 2.66 (s, 6H, 4-mes); −2.60 (s, 2H, N-pyrrole).

2.2.2. 5,15 Dimesityl-10,20 Bis(2-Methoxyphenyl)Porphyrin 2. The standard procedure described above was followed obtaining 0.38 gr of 2 as a mixture of the two atropisomers (yield 26%):

MS: [M]+ 758.3630,
UV-Visible: λmax (toluene, 6.2 × 10−5 M)/(logε/M−1 cm−1): 401 (sh, 4.78), 419 (Soret, 5.55), 482 (sh, 3.87), 515 (Q, 4.30), 550 (Q, 3.91), 591 (Q, 3.91), and 647 (Q, 3.76),

1H-N.M.R. (500 MHz, CDCl3, 300 K) δ = 8.73 (d, 4H, J = 4.6 Hz, pyrrole); 8.65 (d, 4H, J = 4.6 Hz, pyrrole). Phenyl Group: δ = 8.03 (d, 2H, J = 7.2 Hz, 6-ph); 7.82 (tr, 2H, J = 7.6 Hz, 4-ph); 7.36 (dd, 4H, J = 8.5 Hz, 3,5-ph); 3.63 (s, 6H, −OCH3). Mesityl Group: δ = 7.29 (s, 4H, 3,5-mes); 1.87 (s, 12H, 2,6-mes); (a) 1.89 (s, 6H); (b) 1.86 (s, 6H); (b) 2.65 (s, 6H, 4-mes); −2.51 (s, 2H, N-pyrrole).

(a) α, β atropisomer,
(b) α, a atropisomer.

2.2.3. 5,15 Dimesityl-10,20 Bis(4-Acetoxyphenyl)Porphyrin 3. The procedure described for 1 was followed. The product was obtained after repeat washings with cold ethanol and recrystallization from CH2Cl2/Hexane/EtOH (10/1/5 v/v/v) at −5°C overnight (yield 27%): UV-Visible: λmax (toluene, 1.6 × 10−4 M)/(logε/M−1 cm−1): 399 (sh, 4.85), 418 (Soret, 5.48), 480 (sh, 3.98), 513 (Q, 4.36), 549 (Q, 4.04), 591 (Q, 4.02), and 647 (Q, 3.92),

1H-N.M.R. (500 MHz, CDCl3, 300 K) δ = 8.85 (d, 4H, J = 4.5 Hz, pyrrole); 7.83 (d, 4H, J = 4.5 Hz, pyrrole). Phenyl Group: δ = 8.25 (d, 4H, J = 8 Hz, 2,6-ph); 7.52 (d, 4H, J = 8.5 Hz, 3,5-ph); 2.52 (s, 6H, −OCOCCH3). Mesityl Group: δ = 7.32 (s, 4H, 3,5-mes); 2.67 (s, 6H, 4-mes); 1.89 (s, 12H, 2,6-mes); −2.51 (s, 2H, N-pyrrole).

2.2.4. 5,15 Dimesityl-10,20 Bis(4-Methoxyphenyl)Porphyrin 4. The standard procedure described above was followed (yield 26%): UV-Visible (CH2Cl2): λmax (toluene, 2 × 10−4 M)/(logε/M−1 cm−1): 420 (5.67), 516 (4.27), 552 (3.95), 592 (3.75), and 649 (3.71),

1H-N.M.R. (500 MHz, CDCl3, 300 K) δ = 8.85 (d, 4H, J = 5 Hz, pyrrole); 8.71 (d, 4H, J = 4.5 Hz, pyrrole). Phenyl Group: δ = 8.16 (d, 4H, J = 7.5 Hz, 2,6-ph); δ = 7.30 (m, 4H, 3-ph); δ = 4.10 (s, 6H, −OCH3). Mesityl Group: δ = 7.30 (s, 4H, 3,5-mes); 2.65 (s, 6H, 4-mes); 1.87 (s, 12H, 2,6-mes); −2.56 (s, 2H, N-pyrrole).

2.2.5. 5,15 Dimesityl-10,20 Bis(3-Hydroxyphenyl)Porphyrin 5. 0.079 mmol (0.06 gr) of porphyrin 1 was dissolved in 8 mL of dry CH2Cl2 under Ar atmosphere. The solution was cooled at −78°C and BBr3 (1.85 mmol) was added dropwise under vigorous stirring. The reaction mixture was allowed to stand at r.t. for 5 hours. Aqueous saturate NaHCO3 was added carefully and the organic layer was washed with saturate NaCl solution and dried over MgSO4. After the removal of the solvent the product was chromatographed on SiO2 column (2 cm × 4 cm). With CH2Cl2/EtOH (100/0.2 v/v), traces of unreacted porphyrin were eluted while the product was
obtained with CH\textsubscript{2}Cl\textsubscript{2}/EtOH (100/5 v/v) as eluents (yield 85\%):  

MS: [M+H]\textsuperscript{+} 731.3399,  
UV-Visible: \(\lambda_{\text{max}}\) (toluene, 4.2 \times 10\textsuperscript{-5} M)/(log \varepsilon/ M\textsuperscript{-1} cm\textsuperscript{-1}): 402 (sh, 4.80), 420 (Soret, 5.54), 480 (sh, 3.98), 515 (Q, 4.29), 552 (Q, 4.06), 593 (Q, 3.95), and 650 (Q, 3.89),  
\(1\text{H}-\text{N.M.R.}\) (500 MHz, CDCl\textsubscript{3}, 300 K) \(\delta\) = 8.86 (d, 4H, \(J = 4.5\text{ Hz}, \text{pyrrole}\)); 8.71 (d, 4H, \(J = 4.5\text{ Hz}, \text{pyrrole}\)). Phenyl Group: \(\delta\) = 7.82 (d, 2H, \(J = 7.8\text{ Hz, 6-ph}\)); 7.70 (s, 2H, 2-ph); 7.60 (tr, 2H, \(J = 8\text{ Hz, 5-ph}\)); 7.25 (d, 2H, \(J = 7\text{ Hz, 4-ph}\)); 5.45 (s br, 2H, OH). Mesityl Group: \(\delta\) = 7.26 (s, 4H, 3,5-mes); 2.66 (s, 6H, 4-mes); 1.79 (s, 12H, 2,6-mes); –2.60 (s, 2H, N-pyrrole).

added and the organic layer was washed with sat. NaCl solution. After being dried over MgSO\textsubscript{4}, the solvent was removed giving 0.165 gr of 7 (yield 90\%).

MS: [M+H]\textsuperscript{+} 731.3399,  
UV-Visible: \(\lambda_{\text{max}}\) (toluene, 6.2 \times 10\textsuperscript{-5} M)/(log \varepsilon/ M\textsuperscript{-1} cm\textsuperscript{-1}): 402 (sh, 4.60), 420 (Soret, 5.30), 478 (sh, 3.79), 515 (Q, 4.04), 550 (Q, 3.84), 592 (Q, 3.76), and 650 (Q, 3.71),  
\(1\text{H}-\text{N.M.R.}\) (500 MHz, CDCl\textsubscript{3}, 300 K) \(\delta\) = 8.85 (d, 4H, \(J = 4.5\text{ Hz, pyrrole}\)); 8.67 (d, 4H, \(J = 4.5\text{ Hz, pyrrole}\)). Phenyl Group: \(\delta\) = 8.03 (d, 4H, \(J = 6.5\text{ Hz, 2,6-ph}\)); 7.19 (d, 4H, \(J = 6\text{ Hz, 3,5-ph}\)). Mesityl Group: \(\delta\) = 7.38 (s, 4H, 3,5-mes); 2.61 (s, 6H, 4-mes); 1.82 (s, 12H, 2,6-mes); –2.60 (s, 2H, N-pyrrole).

### 3. Results and Discussion

Following Lindsey’s methodology, trans-methoxyporphyrins 1, 2 and 4 were synthesized as precursors for 5 and 6 while for compound 7 the precursors were 3 and 4 (Scheme 1).

The choice of acetoxy- or methoxy- as protecting groups was based on published results for the formation of a dipyrrole product from an attempted synthesis of arylporphyrins with o-acetoxycinnamaldehyde [17].

Compound 2 is a mixture of atropisomers that proved to be inseparable despite our repeated efforts for chromatographic separation. Compounds 5 and 6 were obtained by cleavage of the methyl ether by BB\textsubscript{3} (Scheme 1), while 7 is obtained by alkaline hydrolysis of the ester group or alternative by cleavage of the methoxy group. The two isomers of compound 6 (Scheme 2) in contrast to these of 2 are easily separated by silica gel chromatography. 6\alpha\beta is eluted with CH\textsubscript{2}Cl\textsubscript{2}/Hexane (6/4 v/v) while the more polar 6\alpha\alpha is eluted with 0.5% EtOH/CH\textsubscript{2}Cl\textsubscript{2}.

The two isomers (Scheme 2) were characterized by \(1\text{H}-\text{N.M.R.}\) spectroscopy. A characteristic feature is that in 6\alpha\beta the o-Me of the mesityl group appears as a singlet while in 6\alpha\alpha the o-Me group gives two separate singlets, while no other remarkable spectroscopic difference was observed for the two isomers. In 2 since it is a mixture of the two isomers its N.M.R. spectrum shows these three groups of peaks. For derivatives 3 and 1 the o-H and m-H are equivalent giving one

<table>
<thead>
<tr>
<th>Compound</th>
<th>(E_{1/2\text{oX}}) (V versus SCE)</th>
<th>(E_{1/2\text{red}}) (V versus SCE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>0.96; 1.40</td>
<td>–1.34; –1.68</td>
</tr>
<tr>
<td>Compound 2</td>
<td>0.94; 1.36</td>
<td>–1.34; –1.71</td>
</tr>
<tr>
<td>Compound 4</td>
<td>0.92; 1.37</td>
<td>–1.33; –1.66</td>
</tr>
</tbody>
</table>

\((\text{a})\) Redox potentials were determined by cyclic voltammetry at room temperature in dry and deoxygenated CH\textsubscript{2}Cl\textsubscript{2} containing 0.1 M of tetraethylammonium hexafluorophosphate as supporting electrolyte and a solute concentration in the range of 1.5 \times 10\textsuperscript{-3} M. A Saturated Calomel Electrode (SCE) was used as reference. Under these conditions, the reversible oxidation of ferrocene was \(E_{1/2\text{Fe}}\) = +0.47 V. The error on the reported potentials is ±0.01 V.

### Method 1

The procedure was the same as for compound 5 and compound 4.

### Method 2

0.25 mmol (0.2 gr) of porphyrin 3 were added in 10 mL of THF. 7.38 mmol KOH were dissolved in 5 mL of EtOH and the resulting alcoholic solution was added dropwise. The solution was stirred for 30 min at room temperature and then refluxed for a further 2 hours. After cooling at room temperature the solution was acidified by carefully adding glacial acetic acid. 15 mL of CH\textsubscript{2}Cl\textsubscript{2} were
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Scheme 1: Reaction scheme.

Scheme 2: 6aa and 6af atropoisomers.
signal for each group. The hydrolysis product 5 the o-H are
no longer equivalent resonating at 7.82 ppm and 7.70 ppm.
Characteristic in the $^{13}$C-N.M.R. is the signal at 170 ppm for
the carbonyl carbon of 3 and at 56 ppm of $-\text{OCH}_3$ group
for 1 and 2 that disappears in the $^{13}$C-N.M.R. spectra of the
hydrolysis products. Similar characteristic I.R. peaks for 3
at 1763 cm$^{-1}$ for $\nu$(C=O) str. no longer exist in 7 while
they are also observed two new peaks, one at 1162 cm$^{-1}$ and
another one at 1200 cm$^{-1}$ for (C–O) stretching vibrations.
In methoxy derivatives two bands, one at 1050 cm$^{-1}$ for
(C–O–C) sym. str. and one at 1282 cm$^{-1}$ for (C–O–C) asym. str.,
are observed.

For all of the methoxy derivatives electrochemical studies
were performed by cyclic voltammetry. The redox potentials
measured are the typical ones for meso-substituted porphyrins [18] that exhibited two one-electron reversible oxidations and two one-electron reversible reductions (Table 1).

The structure of derivative 4 is centrosymmetric (Table 2) and the asymmetric unit contains half of the porphyrin molecule and one water solvate molecule, which was found disordered and refined over three positions with occupation factors summing one (Figure 1).

The rather large values of dihedral angles formed between the porphyrin C$_{20}$N$_{4}$ mean plane, the mesityl phenyl ring (84.72$^\circ$), and the methoxophenyl ring (65.12$^\circ$) indicate that there is no twist distortion of the porphyrin skeleton, together with the small average absolute displacement of the C$_{m}$ atom (0.032 Å) from the porphyrin core. The displacement of the two $-\text{OCH}_3$ groups is 0.643 Å alternative from the porphyrin plane.

In conclusion in this work we have reported the preparation of new porphyrinic complexes bearing the appropriate groups in order to functionalize specific sides
of the aromatic macrocycle. The formed complexes are
fully characterized. The formation and the properties of
macromolecule structures with the formed complexes as
precursors will be published elsewhere.

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References


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