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 photo-electronic 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 hydroxylporphyrins 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 ultraflxxtreme.

X-ray diffraction measurements were conducted on a STOE IPDS II diffractometer using graphite-monochromatized MoKα radiation. A dark blue crystal with approximate dimensions 0.50 × 0.40 × 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 Porphyrin 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 (0.86 gr) of DDQ were added and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was filtered through a column of Al₂O₃ (6 cm × 8 cm) using CH₂Cl₂ as eluent until the color 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 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: λ_{max} (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).

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%):

- UV-Visible: λ_{max} (toluene, 2 × 10⁻⁴ 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).

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: λ_{max} (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).

2.2.4. 5,15 Dimesityl-10,20 Bis(4-Hydroxyphenyl)Porphyrin 4. The standard procedure described above was followed (yield 26%):

- UV-Visible: (CH₂Cl₂): λ_{max} (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).

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 BB₃ (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 CH₂Cl₂/EtOH (100/5 v/v) as eluents (yield 85%):

MS: [M+H]+ 731.3399,
UV-Visible: \( \lambda_{\text{max}} \) (toluene, 4.2 × 10⁻⁵ M)/(log ε/ M⁻¹ cm⁻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),

\(^1\)H-N.M.R. (500 MHz, CDCl₃, 300 K) \( \delta \) = 8.86 (d, 4H, J = 4.5 Hz, pyrrole); 8.71 (d, 4H, J = 4.5 Hz, pyrrole). *Phenyl Group*: \( \delta \) = 7.82 (d, 2H, J = 7.8 Hz, 6-ph); 7.70 (s, 2H, 2-ph); 7.60 (tr, 2H, \( J = 8 \) Hz, 5-ph); 7.25 (d, 2H, \( J = 7 \) 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).

2.2.6. 5,15 Dimesityl-10,20 Bis(2-Hydroxyphenyl)Porphyrin 6.
The procedure was the same as for compound 5. Compound 6 is a mixture of two atropisomers that were separated by column chromatography on SiO₂ (5 cm × 2 cm). The \( \alpha \beta \) (Ri: 0.95 in CH₂Cl₂) is eluted with CH₂Cl₂/Hexane (6/4 v/v) and \( \alpha \alpha \) (Ri: 0.25 in CH₂Cl₂) is eluted with 0.5% EtOH/CH₂Cl₂.

MS: [M+H]+ 731.3398,
UV-Visible: \( \lambda_{\text{max}} \) (toluene, 3.4 × 10⁻⁵ M)/(log ε/ M⁻¹ cm⁻¹): 402 (sh, 4.78), 420 (Soret, 5.55), 480 (sh, 3.83), 515 (Q, 4.32), 552 (Q, 3.99), 593 (Q, 3.92), and 650 (Q, 3.86),

\( 6\alpha\alpha \): \(^1\)H-N.M.R. (500 MHz, CDCl₃, 300 K) \( \delta \) = 8.84 (d, 4H, \( J = 4.5 \) Hz, pyrrole); 8.74 (d, 4H, \( J = 4.5 \) Hz, pyrrole). *Phenyl Group*: \( \delta \) = 8.0 (ddd, 2H, \( J = 7 \) Hz, 6-ph); 7.73 (tr, 2H, \( J = 8 \) Hz, 4-ph); 7.37 (d, 2H, \( J = 8.5 \) Hz, 5-ph); 7.34 (dd, 2H, \( J = 8 \) Hz, 3-ph); 5.37 (s br, 2H, \( J = 5 \) Hz, -OH). *Mesityl Group*: \( \delta \) = 7.31 (s, 4H, 3.5-mes); 2.65 (s, 6H, 4-mes); 1.85 (s, 12H, 2,6-mes); –2.59 (s, 2H, N-pyrrole).

\( 6\alpha\beta \): \(^1\)H-N.M.R. (500 MHz, CDCl₃, 300 K) \( \delta \) = 8.85 (d, 4H, \( J = 4.5 \) Hz, pyrrole); 8.74 (d, 4H, \( J = 4.5 \) Hz, pyrrole). *Phenyl Group*: \( \delta \) = 8.03 (dd, 2H, \( J = 7 \) Hz, 6-ph); 7.71 (tr, 2H, \( J = 7.5 \) Hz, 4-ph); 7.37 (d, 2H, \( J = 8 \) Hz, 5-ph); 7.34 (d, 2H, \( J = 8 \) Hz, 3-ph); 5.32 (s br, 2H, –OH). *Mesityl Group*: \( \delta \) = 7.30 (s, 4H, 3.5-mes); 2.65 (s, 6H, 4-mes); 1.88 (s, 6H); 1.83 (s, 6H); –2.58 (s, 2H, N-pyrrole).

2.2.7. 5,15 Dimesityl-10,20 Bis(4-Hydroxyphenyl)Porphyrin 7
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 CH₂Cl₂ were added and the organic layer was washed with sat. NaCl solution. After being dried over MgSO₄, the solvent was removed giving 0.165 gr of 7 (yield 90%).

MS: [M+H]+ 731.3399,
UV-Visible: \( \lambda_{\text{max}} \) (toluene, 6.2 × 10⁻⁵ M)/(log ε/ M⁻¹ cm⁻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),

\(^1\)H-N.M.R. (500 MHz, CDCl₃, 300 K) \( \delta \) = 8.85 (d, 4H, \( J = 4.5 \) Hz, pyrrole); 8.67 (d, 4H, \( J = 4.5 \) Hz, pyrrole). *Phenyl Group*: \( \delta \) = 8.03 (d, 4H, \( J = 6 \) Hz, 4-ph); 7.19 (d, 4H, \( J = 6 \) 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, \( \textit{trans} \)-methoxyxoporphyrins 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 \( \textit{a}-\)acetoxybenzaldehyde [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 BBr₃ (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 CH₂Cl₂/Hexane (6/4 v/v) while the more polar \( 6\alpha\alpha \) is eluted with 0.5% EtOH/CH₂Cl₂.

The two isomers (Scheme 2) were characterized by \(^1\)H-N.M.R. spectroscopy. A characteristic feature is that in \( 6\alpha\beta \) the \( \textit{o}-\)Me of the mesityl group appears as a singlet while in \( 6\alpha\alpha \) the \( \textit{o}-\)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 \( \textit{o}-\)H and \( m\)-H are equivalent giving one
Scheme 1: Reaction scheme.

Scheme 2: 6αα and 6αβ 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 −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 ν(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 methoxyl derives two bands, one at 1050 cm$^{-1}$ [ν(C−O−C) sym. str.] and one at 1282 cm$^{-1}$ [ν(C−O−C) asym. str.], are observed.

For all of the methoxyl 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°), and the methoxypheynyl ring (65.12°) 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 −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

![Figure 1: Partially labeled plot of 4 with ellipsoids drawn at 30% thermal probability. Hydrogen atoms have been omitted for clarity. Primed atoms are generated by symmetry operation: (′)-x, -y, -z.](image)

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

[1] Y. Xu, Z. Liu, X. Zhang, et al., “A graphene hybrid material covalently functionalized with porphyrin: synthesis and optical limiting property,” *Advanced Materials*, vol. 21, no. 12, pp. 1275–1279, 2009.

[2] C. M. Drain, A. Varotto, and I. Radivojevic, “Self-organized porphyrinic materials,” *Chemical Reviews*, vol. 109, no. 5, pp. 1630–1658, 2009.

[3] G. Pagona, A. S. D. Sandanayaka, Y. Araki, et al., “Covalent functionalization of carbon nanohorns with porphyrins: nanohybrid formation and photoinduced electron and energy transfer,” *Advanced Functional Materials*, vol. 17, no. 10, pp. 1705–1711, 2007.

[4] G. Pagona, A. S. D. Sandanayaka, T. Hasobe, et al., “Characterization and photovoltaic properties of nanostructured thin film composed of carbon nanohorns covalently functionalized with porphyrins,” *Journal of Physical Chemistry C*, vol. 112, no. 40, pp. 15735–15741, 2008.

[5] J. S. Lindsey, in *The Porphyrin Handbook*, K. M. Kadish, K. M. Smith, and R. Guillard, Eds., vol. 1, pp. 45–118, Academic Press, Boston, Mass, USA, 2000.

### Table 2: Crystallographic data for 4 2H$_2$O.

| Property        | Value |
|-----------------|-------|
| Formula         | C$_{52}$H$_{50}$N$_{4}$O$_{4}$ |
| Fw              | 794.96 |
| Space group     | P2$_1$/c |
| a (Å)           | 17.288(4) |
| b (Å)           | 8.2587(17) |
| c (Å)           | 17.829(4) |
| α (°)           | 90 |
| β (°)           | 106.15(3) |
| γ (°)           | 90 |
| V (Å$^3$)       | 2445.1(9) |
| Z               | 2 |
| T (°C)          | 25 |
| Radiation       | Mo K |
| g$_{calc}$ (g cm$^{-3}$) | 1.080 |
| μ (mm$^{-1}$)   | 0.069 |
| Reflections with I > 2σ(I) | 2338 |
| R$_{1}$         | 0.0723 |
| wR$_{2}^{a}$    | 0.1890 |

$w = 1/([σ^{2}(F_{o}^{2}) + (αP)^{2} + bP]$ and $P = \max(F_{o}^{2}, 0) + 2F_{c}^{2})/3$. 

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[6] J. W. Buchler, in *The Porphyrins*, D. Dolphin, Ed., vol. 1, pp. 389–483, Academic Press, London, UK, 1978.

[7] J. S. Lindsey, *Metalloporphyrin—Catalyzed Oxidations*, Kluwer Academic Publishers, Dodrecht, The Netherlands, 1994.

[8] B. J. Littler, Y. Cirimghi, and J. S. Lindsey, “Investigation of conditions giving minimal scrambling in the synthesis of trans-porphyrins from dipyrromethanes and aldehydes,” *The Journal of Organic Chemistry*, vol. 64, no. 8, pp. 2864–2872, 1999.

[9] B. J. Littler, M. A. Miller, C.-H. Hung, et al., “Refined synthesis of 5-substituted dipyrromethanes,” *The Journal of Organic Chemistry*, vol. 64, no. 4, pp. 1391–1396, 1999.

[10] P. D. Rao, B. J. Littler, G. R. Geier, and J. S. Lindsey, “Efficient synthesis of monoacyl dipyrromethanes and their use in the preparation of sterically unhindered trans-porphyrins,” *The Journal of Organic Chemistry*, vol. 65, no. 4, pp. 1084–1092, 2000.

[11] D. T. Gryko and M. Tasior, “Simple route to meso-substituted trans-A2B2-porphyrins bearing pyridyl units,” *Tetrahedron Letters*, vol. 44, no. 16, pp. 3317–3321, 2003.

[12] K. Ladomenou, G. Charalambidis, and A. G. Coutsolelos, “A strategic approach for the synthesis of new porphyrin rings, attractive for heme model purpose,” *Tetrahedron*, vol. 63, no. 13, pp. 2882–2887, 2007.

[13] K. Tashiro, T. Aida, J.-Y. Zheng, et al., “A cyclic dimer of metalloporphyrin forms a highly stable inclusion complex with C60,” *Journal of the American Chemical Society*, vol. 121, no. 40, pp. 9477–9478, 1999.

[14] J. A. Lacey, D. Phillips, L. R. Milgrom, G. Yahioglu, and R. D. Rees, “Photophysical studies of some 5,10,15,20-tetraarylporphyrinatozinc(II) complexes as potential lead compounds for photodynamic therapy,” *Photochemistry and Photobiology*, vol. 67, no. 1, pp. 97–100, 1998.

[15] D. A. James, D. P. Arnold, and P. G. Parsons, “Potency and selective toxicity of tetra(hydroxyphenyl)porphyrins in human melanoma cells, with and without exposure to red light,” *Photochemistry and Photobiology*, vol. 59, no. 4, pp. 441–447, 1994.

[16] G. M. Sheldrick, “A short history of SHELX,” *Acta Crystallographica Section A*, vol. 64, no. 1, pp. 112–122, 2007.

[17] J. A. S. Cavaleiro, M. D. F. P. N. Condesso, M. M. Olmstead, D. E. Oram, K. M. Snow, and K. M. Smith, “An anomalous dipyrrole product from attempted synthesis of a tetraarylporphyrin,” *The Journal of Organic Chemistry*, vol. 53, no. 25, pp. 5847–5849, 1988.

[18] K. M. Kadish, E. Van Caemelbecke, and R. Royal, in *The Porphyrin Handbook*, K. M. Kadish, K. M. Smith, and R. Guilard, Eds., vol. 8, chapter 55, pp. 1–97, Academic Press, San Diego, Calif, USA, 2000.