

Combinatorial Synthesis and Characterization of New Asymmetric Porphyrins as Potential Photosensitizers in Photodynamic Therapy

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A photosensitizer must perform an increased absorbance in the red-region of the spectrum, associated with increased molar absorption coefficients and fluorescence quantum yields. The purpose of this work was the obtaining of new photosensitizers based on hydroxy- and methoxy-phenyl substituted porphyrins, because hydroxyphenyl groups confer some degree of hydrophilicity.

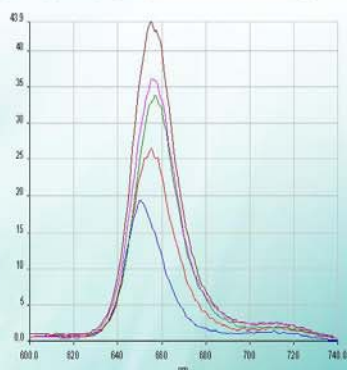
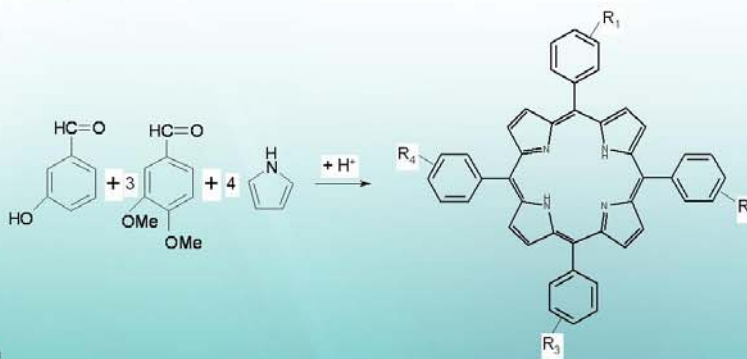


Fig. 1. Fluorescence emission spectra of the new asymmetric porphyrins (1)-red line; (3)-green; (4)-brown; (5)-violet; in comparison with TPP-blue, at the same concentration, $1.11 \cdot 10^{-6}$ M, in THF.

In the emission spectra, these four porphyrins display a supplementary red-shifted band in the range of 720 nm (with a maximum at acidic pH values), that indicates them to be considered future potential photosensitizers for PDT. The relative fluorescence quantum yields (Φ_f), with values between 0.14-0.26, calculated in comparison with meso-tetraphenylporphyrine, recommend further trials for these compounds.



- R1=R2=R3=3, 4-di MeO; R4=3-OH (1); 5-(3-hydroxyphenyl)-10, 15, 20-tri(3,4-dimethoxyphenyl)porphyrin
- R1=R2=R3=R4= 3, 4-di MeO (2); 5,10,15,20-tetrakis(3,4-dimethoxyphenyl)porphyrin
- R1=R2= 3, 4-di MeO; R3=R4= 3-OH (cis) (3); 5,10-di(3-hydroxyphenyl)-15,20-di(3,4-dimethoxyphenyl)porphyrin (cis)
- R1=R3=3, 4-di MeO; R2=R4=3-OH (trans) (4); 5,15-di(3-hydroxyphenyl)-10,20-di(3,4-dimethoxyphenyl)porphyrin (trans)
- R1=R2=R3=3-OH; R4=3, 4-di MeO (5); 5,10,15-tri(3-hydroxyphenyl)-20-(3,4-dimethoxyphenyl)porphyrin
- R1=R2=R3=R4=3-OH (6); 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin

$$\Phi_{\text{sample}} = \Phi_{\text{ref}} \left(\frac{F_{\text{sample}}}{F_{\text{ref}}} \left(\frac{A_{\text{ref}}}{A_{\text{sample}}} \right) \left(\frac{n_{\text{sample}}^2}{n_{\text{ref}}^2} \right) \right)$$

The purple product, isolated from polypyrrolic side-reaction compounds, was subjected to HPLC on polar column using as eluent acetone/hexane 1/1 and it was found to be a mixture of six possible porphyrin compounds (1-6). The same result was obtained by TLC. Silica gel column chromatography of the mixture, using as eluent chloroform/dichloroethane/ethylc ether solution of ratio 5/5/1 enabled separation of the six purified porphyrins in order of increasing polarity. The new porphyrinic compounds were comparatively characterized with respect to their aggregation properties and equilibrium coexisting species under the influence of different solvent-systems and pH conditions.

Table 1. Physico-chemical characteristics of porphyrins 1 – 6

Porphyrin	TLC, R _f	HPLC, R _T [min]	UV-vis, CHCl ₃ λ _{max} (log ε)	¹ H-NMR (CDCl ₃ , 200MHz), δ, ppm	¹³ C-NMR (CDCl ₃ , 100MHz), δ, ppm
(1)	0.60	3.973	422.49 (5.33); 517.71 (3.95); 553.88 (3.70); 591.61 (3.48); 648.74 (3.31)	-2.81 (brs, 2H, NH), 2.53-2.74 (s, 1H, OH), 3.99-4.18 (d, 18H, OCH ₃), 7.25-7.27 (d, 4H, <i>m</i> -Ph), 7.75-7.77 (d, 8H, <i>o</i> -Ph), 7.96 (s, 1H, <i>p</i> -Ph), 8.91 (s, 8H, β-Pyr)	148.85, 147.05, 134.73, 131.12, 130.00, 127.34, 126.75, 119.86, 118.23, 110.22, 109.41, 108.76, 56.08, 55.94
(2)	0.66	3.560	421.27 (5.49); 518.86 (4.57); 556.38 (4.31); 592.81 (4.05); 649.91 (4.00)	-2.70 (brs, 2H, NH), 3.96-4.08 (d, 24H, OCH ₃), 7.10-7.27 (d, 4H, <i>m</i> -Ph), 7.68-7.71 (d, 4H, <i>o</i> -Ph), 7.78 (s, 4H, <i>o</i> -Ph), 8.90 (s, 8H, β-Pyr)	149.33, 148.90, 147.08, 134.70, 132.03, 131.20, 127.65, 127.41, 120.95, 118.25, 109.45, 56.14
(3)	0.54	4.573	423.89 (5.15); 517.28 (4.21); 553.55 (4.05); 590.31 (3.91); 649.38 (3.85)	-2.75 (brs, 2H, NH), 2.62-2.73 (dd, 2H, OH), 4.15 (s, 12H, OCH ₃), 7.20-7.24 (d, 4H, <i>m</i> -Ph), 7.51-7.54 (d, 2H, <i>p</i> -Ph), 7.72-7.77 (t, 8H, <i>o</i> -Ph), 8.91 (s, 8H, β-Pyr)	154.01, 148.87, 147.06, 143.55, 134.73, 131.10, 127.40, 121.88, 119.89, 118.27, 114.75, 109.45, 56.12
(4)	0.45	5.373	422.75 (5.38); 518.07 (4.05); 554.70 (3.70); 592.09 (3.48); 649.29 (3.48)	-2.80 (brs, 2H, NH), 2.71 (brs, 2H, OH), 4.10-4.13 (d, 12H, OCH ₃), 7.11-7.23 (m, 4H, <i>m</i> -Ph), 7.40-7.53 (m, 2H, <i>p</i> -Ph), 7.60-7.75 (m, 8H, <i>o</i> -Ph), 8.85-8.89 (d, 8H, β-Pyr typical for <i>trans</i> -A ₂ B ₂)	154.07, 149.29, 148.87, 147.05, 143.44, 134.68, 132.05, 131.07, 129.62, 127.86, 127.45, 121.89, 120.94, 118.27, 114.77, 109.42, 56.10
(5)	0.35	6.427	421.75 (5.47); 518.11 (4.24); 554.46 (3.91); 591.90 (3.70); 649.22 (3.61)	-2.79 (brs, 2H, NH), 2.64-2.68 (d, 3H, OH), 3.93-4.10 (d, 6H, OCH ₃), 7.07-7.22 (dd, 4H, <i>m</i> -Ph), 7.73-7.75 (d, 8H, <i>o</i> -Ph), 7.97 (brs, 3H, <i>p</i> -Ph), 8.64-8.89 (dd, 8H, β-Pyr typical for A ₂ B)	
(6)	0.29	7.23	421.50 (5.47); 517.87 (4.26); 554.20 (3.91); 591.70 (3.70); 649.05 (3.61)	-2.78 (brs, 2H, NH), 2.91 (brs, 4H, OH), 7.20-7.95 (m, 16H, <i>o</i> -Ph, <i>m</i> -Ph and <i>p</i> -Ph), 8.90 (d, 8H, β-Pyr)	

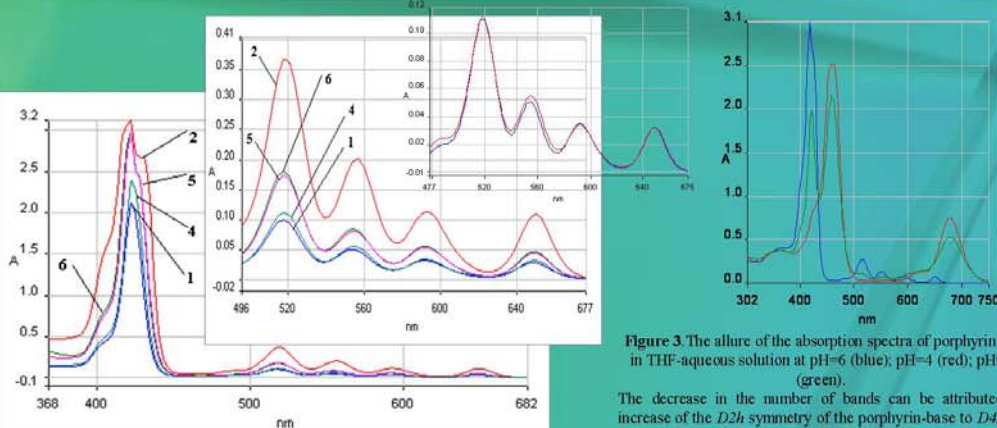


Fig. 2. Overlapped UV-Vis spectra of synthesized porphyrins (detail: Q - bands and *cis* and *trans* Q - bands)

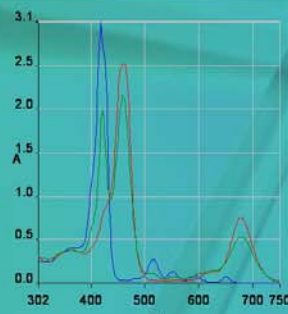


Figure 3. The allure of the absorption spectra of porphyrin (5) in THF-aqueous solution at pH=6 (blue); pH=4 (red); pH=3 (green). The decrease in the number of bands can be attributed to increase of the *D_{2h}* symmetry of the porphyrin-base to *D_{4h}* by protonation, and generation of the dication species. It is clear that the interval in which the porphyrin is monodispersed is limited by the ionic strength too.

With increasing acidity to pH=4 and lower, two additional protons are bond to the nitrogen atoms in the center of porphyrin ring, so that the partial positive charge is induced in the central part of the molecule. A high ionic strength causes a decrease of the monomer absorption Soret band situated around 420 nm, eventually reducing it to a pronounced shoulder. The curve (red) from Fig. (3) shows a Soret band unresolved and broadened. These changes in spectral allure might be attributed to the dication generations, and are associated with a significant increase of the intensity of the Q1 band, which is forbidden otherwise, as can be seen in Fig. (3), curve-red line.

The most important feature is that, in acidic media, the Q bands are reducing to only one. The Q1 band is also bathochromic shifted from 649 nm (pH=5) to 680 nm. Upon increased ionic strength of the solution, a clear tendency toward resolution is noticed by the splitting of the Soret band into two individual Lorentzian bands located around 420 nm and 460 nm, respectively (Fig. (3), curve-green) as the result of a tendency to form aggregates. The band centered around 420 nm can be unequivocally assigned to the monomer.