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Reaction of *meso*-tetraarylporphyrins with pyrazine *ortho*-quinodimethanes

Shengxian Zhao, Maria G. P. M. S. Neves, Augusto C. Tomé, Artur M. S. Silva, José A. S. Cavaleiro,* Maria R. M. Domingues and A. J. Ferrer Correia

Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal

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Abstract—Novel π-extended porphyrins were obtained from the Diels–Alder reaction of *meso*-tetraarylporphyrins with a pyrazine *o*-quinodimethane derivative.

Porphyrin functionalization has become the current focus of research due to its applications in diverse fields such as materials, supramolecular chemistry, biomimetic models for photosynthesis, catalysis and medicinal applications.[1]

Over the past years, we have shown that peripheral double bond(s) of a porphyrin macrocycle can participate in Diels–Alder reactions,[2] 1,3-dipolar cycloadditions[3] and other electrocyclic reactions[4] yielding novel chlorins, bacteriochlorins and isobacteriochlorins. Some of these compounds show excellent spectroscopic properties to be used in medicinal assessments related with photodynamic therapy of cancer cells.

Based on our previous results of the Diels–Alder reaction of *meso*-tetraarylporphyrins with *o*-benzoquinodimethane,[2a] we have studied the reaction of *meso*-tetraarylporphyrins **1a**–**c** with a pyrazine *o*-quinodimethane derivative. In these reactions, the expected chlorins or bacteriochlorins were not obtained but instead the novel π-extended porphyrins **3**–**6** have been isolated (Scheme 1).

The pyrazine *o*-quinodimethane was generated in situ from the corresponding 2,3-bis(bromomethyl)pyrazine derivative **2** in the presence of porphyrins **1a**–**c**.[5] In the reaction with **1a**, a TLC of the reaction mixture revealed the presence of starting porphyrin and four new compounds (Scheme 1). This mixture was separated by column chromatography (silica gel) into three fractions. The first fraction contained the starting porphyrin **1a** (3.5 mg, 18%). The second one was shown to be a mixture of the monoaddition compounds **3a** and **4a**, which were then separated by preparative TLC.[6,7] The third fraction was also a mixture of two compounds which, after being separated by preparative TLC, were identified as the bisaddition compounds **5a** and **6a**.[8,9] The structures of the new compounds were deduced from their UV–vis, ^{1}H and ^{13}C NMR and mass spectra. The main product (**3a**) has a C_2 symmetry. It is very clear from its ^{1}H and ^{13}C NMR spectra that there are no sp^3 carbons (and the corresponding protons) ruling out the structure of a chlorin. In the ^{1}H NMR spectrum, the singlet at δ 8.29 ppm corresponds to the two quinoxaline protons, the singlet at δ 8.76 ppm corresponds to two β-pyrrolic protons H-12 and H-13. Finally, the two doublets at δ 8.95 (J = 5.1 Hz) and 9.04 ppm (J = 5.1 Hz) correspond to the four β-pyrrolic protons H-7, H-8, H-17 and H-18. The ^{13}C NMR spectrum shows only 14 signals, which correspond to 'half' of the molecule [the carbons of the C_6F_5 groups appear as small signals (m, δ 114.9–148.2) due to the coupling with the fluorine atoms and to the long relaxation times]. The FAB mass spectrum of **3a** shows a peak at m/z 1127 ([M+H]$^+$) and its UV–vis spectrum shows a pronounced red shift of both Soret and Q bands relatively to **1a**, as expected for a porphyrin with an extended conjugation of the π-system.

Keywords: Diels–Alder reactions; Porphyrins and analogues; Pyrazines; Quinoxalines.
* Corresponding author. Tel.: +351 234 370 717; fax: +351 234 370 084; e-mail: jcavaleiro@dq.ua.pt

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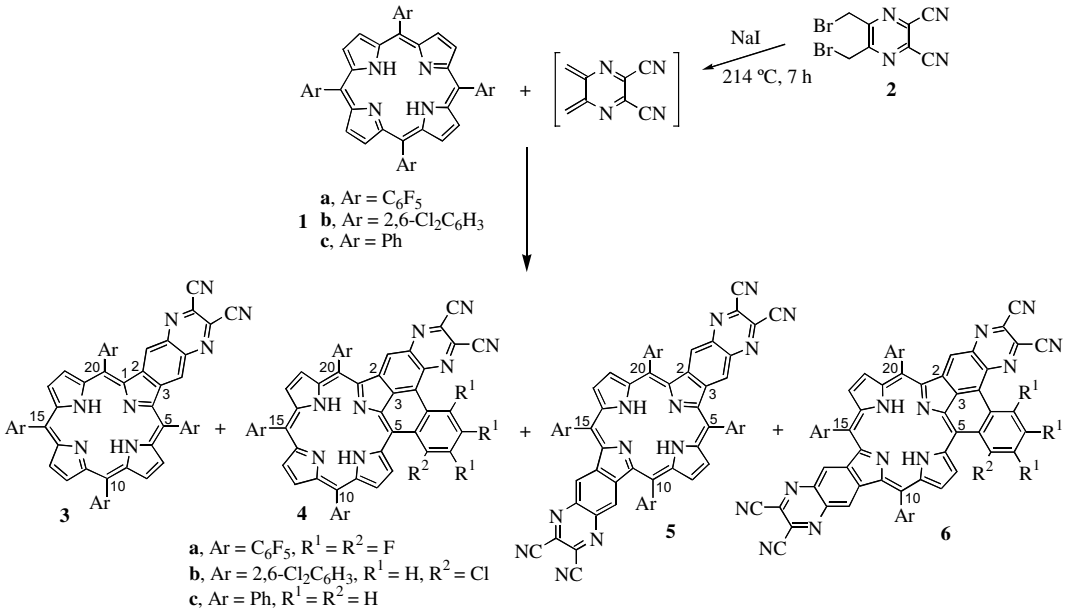

Scheme 1.

Compound **4a** has an interesting structure, resulting from a cyclization reaction between the β-fused quinoxaline ring and the adjacent *meso*-aryl group. Its mass spectrum shows a peak at *m*/*z* 1107 ($[M+H]^+$), which means that HF has been eliminated from **3a**. The ^1H NMR spectrum shows two signals at δ −1.49 and −1.20 ppm corresponding to the NH protons and one singlet at δ 8.47 ppm corresponding to the quinoxaline proton. The β-pyrrolic protons H-12 and H-13 appear as an AB spin system at δ 8.68 (J = 5.0 Hz), while the protons H-17 and H-18 appear as two doublets at δ 8.83 (J = 5.0 Hz) and 8.94 ppm (J = 5.0 Hz). The β-pyrrolic proton H-8 appears as a doublet at δ 8.79 ppm (J = 5.0 Hz) and, surprisingly, H-7 appears as a double doublet at δ 9.47 ppm (J = 5.0 Hz and 11.2 Hz); this signal splitting is due to the through-space coupling with the *ortho*-fluorine atom of the adjacent *meso*-aryl group.[10] The UV–vis spectrum of **4a** shows a pronounced red shift of both Soret and Q bands relatively to **3a**.

The mass spectrum of **5a** shows a peak at *m*/*z* 1279 ($[M+H]^+$), which indicates that it comes from a bisaddition process. Its ^1H NMR spectrum shows only three singlets: one at δ −2.42 ppm corresponding to the NH protons, one at δ 8.27 ppm corresponding to the four equivalent quinoxaline protons and another one at δ 8.96 ppm corresponding to the four β-pyrrolic protons. It is evident from this ^1H NMR spectrum that **5a** resulted from a site specific bisaddition to opposite pyrrolic rings and not to adjacent pyrrolic rings. The mass spectrum of compound **6a** shows a peak at *m*/*z* 1259 ($[M+H]^+$). Its ^1H NMR spectrum shows that the β-pyrrolic proton H-7 appears as a double doublet of doublets at δ 9.48 ppm due to the coupling with NH (J = 1.7 Hz, long-range coupling), H-8 (J = 5.0 Hz) and with *ortho*-fluorine atoms of the fused *meso*-aryl group at position 5 (J = 10.4 Hz), while H-8 appears at δ 8.72 ppm as a broad doublet due to the small coupling with NH (responsible for the broadening of the signal) and with H-7. Protons H-17 and H-18 appear as an AB spin system (δ 8.898 and 8.899 ppm, J = 4.8 Hz). This compound has an absorption band at 744 nm in its UV–vis spectrum.

Quite similar results were obtained when we used porphyrin **1b**. In this case, the formation of compounds **4b** and **6b** resulted from the elimination of HCl from **3b** and **5b**, respectively. Since porphyrin **1c** is much less reactive as a dienophile than **1a** and **b**, and since there is no halogen atoms at the *meso*-phenyl groups, we expected to obtain only the monoaddition product **3c**. However, surprisingly, together with **3c** (3% yield), a reasonable amount of **4c** (16% yield) was also formed. In this case, since the formation of **4c** could not result from the elimination of HX, possibly it was formed by an oxidative coupling reaction. Attempted formation of **4c** by refluxing **3c** in chloroform in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was unsuccessful. Also refluxing **3a**, **b** and **c** in 1,2,4-trichlorobenzene did not afford the corresponding derivatives **4**. These experiments seem to indicate that the coupling process must occur before the aromatization of the Diels–Alder adduct.

Other π-extended porphyrin systems, resulting from the oxidative cyclization of *meso*-aryl groups with a pyrrolic β-position[11,12] or from Bergman cyclization of porphyrinic-enediynes,[13,14] were recently described.

The ESI-MS spectra of all new porphyrins showed the $[M+H]^+$ ion, except the bisadducts **5a** and **6a** which showed the $[M+2H]^+$ ions as the most abundant ones, respectively at *m*/*z* 1280 and 1260. The observation of these $[M+2H]^+$ ions as has been already observed in FAB-MS spectra of dimeric and fluorinated porphy-

rins.[15,16] The formation of the $[M+2H]^+$ in these two cases could be due to the presence of fluorine atoms and additional nitrogen atoms. Studies of the fragmentation of each $[M+H]^+$ and $[M+2H]^+$ ions by ESI-MS/MS show that compounds **3a**–**6a** display very similar spectra. While **3a** and **4a** show loss of one to five HF molecules, **5a** and **6a** show loss of one to four HF molecules. Loss of one $C_6F_5\cdot$ and combined loss of $C_6F_5\cdot$ with one to four (for **3a** and **4a**) or one to three (for **5a** and **6a**) HF molecules is also observed. The ESI-MS/MS spectra of porphyrins **3b** to **6b** show a similar fragmentation pathway, namely successive loss of one to four HCl molecules, loss of one 2,6-$Cl_2C_6H_3\cdot$ and combined loss of 2,6-$Cl_2C_6H_3\cdot$ with one to three HCl molecules. ESI-MS/MS spectra of **3c** and **4c** showed loss of one and two $C_6H_5\cdot$.

In conclusion, the Diels–Alder reaction of *meso*-tetraarylporphyrins with the pyrazine *o*-quinodimethane affords mainly the oxidized compounds **3a**–**c** instead of the expected chlorin adducts. The bisaddition is site specific, occurring in opposite pyrrolic rings and leads to compounds **5** and **6**. The novel polycyclic products **4a**–**c**, **6a** and **b** result from coupling reactions between the β-fused quinoxaline ring and one adjacent *meso*-aryl group. These π-extended porphyrin derivatives show absorption bands at wavelengths higher than 700 nm, an important feature for their potential use as photosensitizers in the photodynamic therapy (PDT) of tumours.

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5. *Typical experiment*: a 1,2,4-trichlorobenzene (6 mL) solution of *meso*–tetrakis(pentafluorophenyl)porphyrin **1a** (20 mg), 2,3-bis(bromomethyl)pyrazine derivative **2** (65 mg, 10 equiv) and sodium iodide (92 mg, 30 equiv) was heated at reflux (214 °C) for 7 h. A TLC of the reaction mixture revealed some starting porphyrin and four new compounds. The reaction mixture was diluted with $CHCl_3$ (50 mL), washed with an aqueous solution of $Na_2S_2O_3$ (3×10 mL) and then it was dried (Na_2SO_4). The resulting mixture was separated by column chromatography (silica gel) using a gradient of petroleum ether/chloroform as eluent.
6. Compound **3a**: 34% yield, mp > 300 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −2.62 (s, 2H, NH), 8.29 (s, 2H, quino-H), 8.76 (s, 2H, β-H), 8.95 (d, 2H, β-H, J = 5.1 Hz), 9.04 (d, 2H, β-H, J = 5.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 100.7, 105.7, 113.4, 123.6, 128.0, 128.5, 130.9, 134.7, 138.2, 139.1, 139.7, 145.2, 148.4, 155.7. UV–vis ($CHCl_3$) λ_{max} ($\log\varepsilon$) 379 (4.71), 425 (5.32), 525 (4.20), 564 (4.20), 608 (3.97), 662 (3.95) nm. FAB-MS *m/z* 1127 $(M+H)^+$. Anal. Calcd for $C_{52}H_{10}F_{20}N_8$: C, 55.43; H, 0.89; N, 9.95. Found: C, 55.13; H, 0.89; N, 10.09.
7. Compound **4a**: 3% yield, mp > 300 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −1.49 and −1.20 (2s, 2H, NH), 8.47 (s, 1H, quino-H), 8.68 (AB, 2H, β-H, J = 5.0 Hz), 8.79 (d, 1H, β-H, J = 5.0 Hz), 8.83 (d, 1H, β-H, J = 5.0 Hz), 8.94 (d, 1H, β-H, J = 5.0 Hz), 9.47 (dd, 1H, β-H, J = 5.0 and 11.2 Hz). UV–vis ($CHCl_3$) λ_{max} 388, 439, 482, 651, 707 nm. FAB-MS *m/z* 1107 $(M+H)^+$. HRMS (FAB) calcd for $C_{52}H_{10}F_{10}N_8$ $(M+H)^+$: 1107.0725. Found 1107.0728.
8. Compound **5a**: 6% yield, mp > 300 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −2.42 (s, 2H, NH), 8.27 (s, 4H, quino-H), 8.96 (s, 4H, β-H); UV–vis ($CHCl_3$) λ_{max} ($\log\varepsilon$) 368 (4.70), 379 (4.70), 424 (5.28), 459 (5.17), 542 (4.20), 585 (4.79), 635 (4.21), 695 (4.47) nm. FAB-MS *m/z* 1279 $(M+H)^+$.
9. Compound **6a**: 1% yield, mp > 300 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −1.42 and −1.03 (2s, 2H, NH), 8.26 (s, 1H, quino-H), 8.35 (s, 1H, quino-H), 8.52 (s, 1H, quino-H), 8.72 (br d, 1H, H-8, J = 5.0 Hz), 8.898 and 8.899 (AB, 2H, H-17 and H-18, J = 4.8 Hz), 9.48 (ddd, 1H, H-7, J = 1.7, 5.0 and 10.4 Hz). UV–vis ($CHCl_3$) λ_{max} 379, 440, 497, 575, 676, 744 nm. MS (FAB) *m/z* 1259 $(M+H)^+$. HRMS (FAB) calcd for $C_{60}H_{10}F_{19}N_{12}$ $(M+H)^+$: 1259.0848. Found 1259.0845.
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