# *meso*-Arylporphyrins as dienophiles in Diels–Alder reactions: a novel approach to the synthesis of chlorins, bacteriochlorins and naphthoporphyrins

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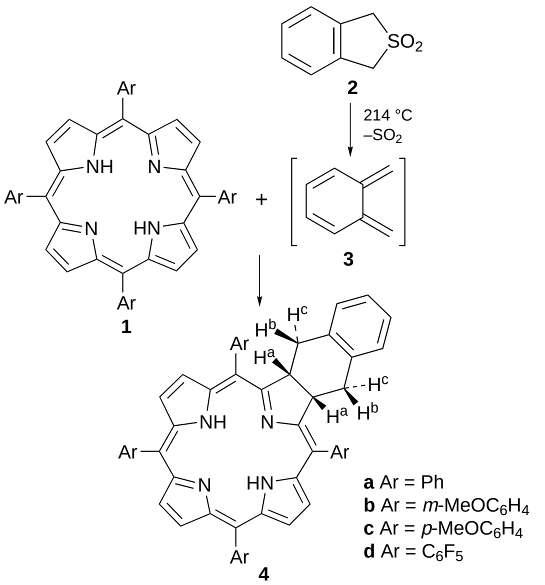
***meso*-Arylporphyrins participate, as dienophiles, in Diels–Alder reactions with *o*-benzoquinodimethane to yield novel chlorins, bacteriochlorins and naphtho[2,3-*b*]porphyrins.**

The use of porphyrin derivatives as photosensitizers for the photodynamic therapy (PDT) of malignant tumours received a boost with the authorisation, in several countries, of the clinical use of Photofrin, a complex mixture of porphyrins derived from haematoporphyrin.[1] In recent years, several studies related to PDT have been oriented to the search for single substances having strong absorption bands at the red end of the visible spectrum (the so-called second generation photosensitizers). This requirement is because of the greater tissue penetration of light with longer wavelengths.[2] Most of the second generation photosensitizers which have been studied are reduced porphyrins (mainly chlorins and bacteriochlorins) because of their strong absorptions near or above 700 nm.

A versatile route to the synthesis of chlorins is the Diels–Alder reaction of vinyl porphyrins with electron-deficient dienophiles.[3] Bacteriochlorins and isobacteriochlorins can also be prepared by the same type of reaction if a divinylporphyrin is used.[4] All previous studies involving Diels–Alder reactions with porphyrins have considered these macrocycles as the dienes. We now report that *meso*-arylporphyrins can also be used as dienophiles in Diels–Alder reactions.

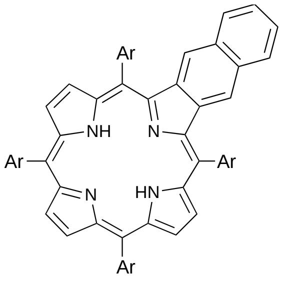
It is known that the peripheral double bonds of the porphyrin macrocycle are partially isolated from the macrocyclic conjugation pathway. The chemistry of these double bonds is, in some aspects, similar to the chemistry of normal alkenes, namely hydrogenation (to give chlorins and bacteriochlorins) and participation in pericyclic reactions (*e.g.* cheletropic reactions with carbenes[4*a*,5] and concerted reaction with $OsO_4$ to give β,β′-dihydroxychlorins[6]). These observations prompted us to investigate the possible participation of these peripheric double bonds in [4 + 2] cycloadditions, as the 2π electrons component, with very reactive dienes. In fact, we have found that porphyrins behave as dienophiles in the presence of *o*-benzoquinodimethane **3** (a highly reactive diene generated *in situ* by thermal extrusion of $SO_2$ from sulfone **2**) giving chlorins **4** (Scheme 1).†



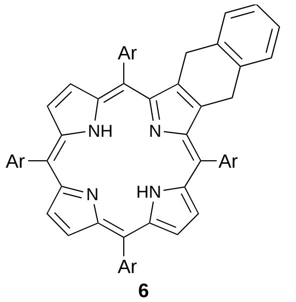
**Scheme 1**

After heating a solution of *meso*-tetraphenylporphyrin (TPP **1a**, 20 mg) and sulfone **2** (55 mg, 10 equiv.) in 1,2,4-trichlorobenzene (5 ml) at reflux for 7 h under a nitrogen atmosphere, the TLC of the reaction mixture revealed unchanged starting porphyrin and three new compounds. The product with higher $R_f$ and the unchanged starting porphyrin were separated from the other two products by column chromatography (silica); in this way two fractions were obtained. The products in each fraction were then separated by preparative TLC. The main product (26% yield), the one that runs immediately below TPP, was identified as the chlorin **4a**, on basis of its mass, $^1H$ and $^{13}C$ NMR and visible spectra.‡ Compound **4a** displays $C_2$ symmetric $^1H$ and $^{13}C$ NMR spectra. The two protons $H^c$ and the two protons $H^b$ appear as doublets of doublets, respectively, at δ 2.62 (*J* 8.3 and 14.2 Hz) and 2.80 (*J* 5.8 and 14.2 Hz). The two $H^a$ protons appear as a multiplet at δ 5.32. The $^{13}C$ NMR spectrum shows only 22 signals, which correspond to 'half' of the molecule. From these, two signals correspond to $sp^3$ carbons: δ 33.3 (benzylic carbons) and 48.0 (pyrroline carbons). The mass spectrum shows intense peaks at *m*/*z* 719 ($[M + H]^+$) and 718 ($[M]^+$), and one peak at *m*/*z* 614 (corresponding to TPP, formed by retro-Diels–Alder reaction). The visible spectrum of **4a** also confirms the chlorin-type structure ($\lambda_{max}$ 653 nm).

The product with higher $R_f$, the one runing slightly above TPP, was obtained in 20% yield; its mass spectrum (LSIMS) shows a base peak with *m*/*z* 715 and its visible spectrum shows a pronounced red shift of both Soret and Q bands ($\lambda_{max}$ 442, 525, 555, 606, 662 nm) relative to TPP, as expected for an extended conjugation of the porphyrin π-system. These data indicate that this compound is the naphtho[2,3-*b*]porphyrin **5a**,[7] formed by the autoxidation of chlorin **4a**. This compound was also obtained quantitatively by refluxing a $CHCl_3$ solution of chlorin **4a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The third product, the one with smaller $R_f$ obtained in 20% yield, shows a parent ion at *m*/*z* 717 ($[M + H]^+$) in its mass spectrum and a UV–VIS spectrum very similar to that of TPP.



**5**



**6**

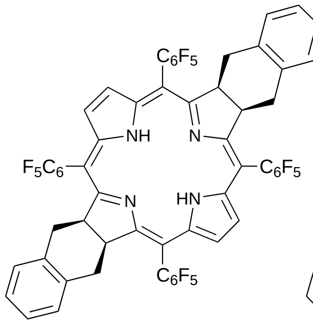
**a** Ar = Ph
**b** Ar = *m*-$MeOC_6H_4$
**c** Ar = *p*-$MeOC_6H_4$

These data are in agreement with structure **6a**, a likely intermediate in the oxidation of **4a** to the naphthoporphyrin **5a**.

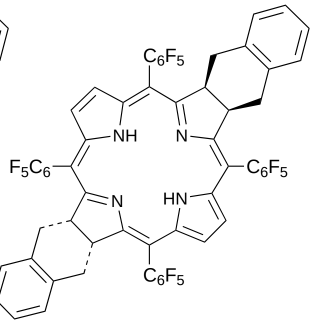
Similar results were obtained when porphyrins **1b** and **1c** were used. In both cases, the corresponding chlorins **4**, naphthoporphyrins **5** and porphyrins **6** could be isolated and characterized.

When *meso*-tetra(pentafluorophenyl)porphyrin **1d** was used as dienophile three products were also obtained, together with some unchanged **1d** (*ca.* 35%). The one with intermediate $R_f$ (silica) was identified as the chlorin **4d** on the basis of its $^1$H NMR, mass and electronic spectra.

The two other products show similar mass and electronic spectra, suggesting that they are diastereoisomers (**7**-*cis* and **7**-*trans*).§ Both compounds show the same parent ion at *m*/*z* 1183 (FAB$^+$) indicating the addition of two *o*-benzoquinodimethanes per molecule of porphyrin. From the electronic spectra of these 2 : 1 adducts ($\lambda_{max}$ 747 and 761 nm, Fig. 1), it is evident that they are bacteriochlorins (opposite bis-addition) and not isobacteriochlorins (adjacent bis-addition). The $^1$H NMR spectrum of the major isomer (the one with higher $R_f$) is also in agreement with structures **7**. The formation of these bacteriochlorins is in accord with other previous studies; Callot[5] observed opposite bis-addition of methoxycarbonylcarbene to TPP and Cavaleiro *et al.*[4b] have shown that in the Diels–Alder reactions of divinylporphyrins with dienophiles, the formation of bacteriochlorins is more thermodynamically favourable than the formation of isobacteriochlorins.



**7**-*cis*



**7**-*trans*

The addition to porphyrin **1d**, and not to the other ones, of two *o*-benzoquinodimethane species is not an unexpected result since it is known that *o*-quinodimethanes react more easily with electron-deficient dienophiles and, in this respect, porphyrin **1d** is much more 'electron-deficient' than porphyrins **1a**–**c**.

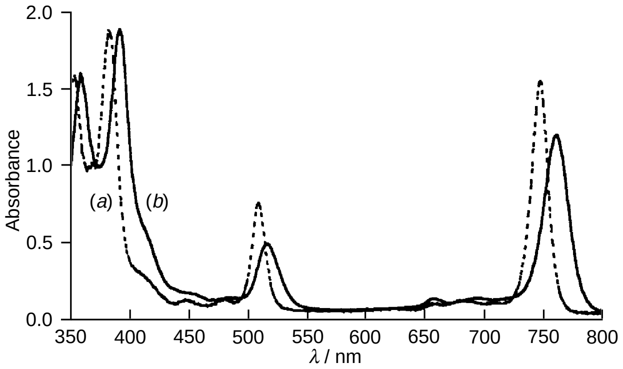


**Fig. 1** Electronic spectra of bacteriochlorins **7**: (*a*) main isomer, (*b*) minor isomer

This work was also extended to 5,15-disubstituted arylporphyrins. In this case it was found that 5,15-bis(*p*-methoxyphenyl)porphyrin also reacts with *o*-benzoquinodimethane **3** to yield the corresponding chlorin as the main product, which was characterized by $^1$H NMR, UV–VIS and mass spectral techniques.

Bacteriochlorins **7** (or other synthetic analogues), because of their strong absorption bands at 747 and 761 nm (Fig. 1) can be considered as potential new photosensitizers in PDT studies. Work is in progress in our laboratory to extend these studies to other *o*-quinodimethanes, especially certain heterocyclic ones, and to other porphyrins.

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## Footnotes

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† Our preliminary results from the reaction of TPP with heterocyclic *o*-quinodimethanes show that this type of reaction can be successfully applied to the syntheses of heterocyclic-fused chlorins.

‡ *Spectroscopic data* for **4a**: $^1$H NMR (300 MHz, CDCl$_3$): δ −1.59 (s, 2 H, NH), 2.62 (dd, 2 H, H$^c$, *J* 8.3 and 14.2), 2.80 (dd, 2 H, H$^b$, *J* 5.8 and 14.2), 5.32 (m, 2 H, H$^a$), 6.75 (m, 2 H), 6.99 (m, 2 H), 7.62–7.85 (m, 12 H), 7.99–8.30 (m, 10 H), 8.40 (m, 2 H), 8.56 (d, 2 H, *J* 5.0); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 33.3, 48.0, 112.6, 122.5, 124.0, 126.1, 126.8, 127.4, 127.6, 127.8, 128.3, 131.9, 132.2, 133.9, 134.3, 135.3, 138.9, 141.1, 142.0, 142.3, 152.5, 168.0; MS (FAB$^+$) 719 (M + H)$^+$, 718 (M)$^+$, 614 (TPP); $\lambda_{max}$(CHCl$_3$)/nm (log ε) 420 (5.27), 521 (4.12), 551 (3.99), 559 (3.76), 653 (4.36).

§ *Spectroscopic data* for the most abundant isomer **7**: $^1$H NMR (300 MHz, CDCl$_3$): δ −1.65 (s, 2 H, NH), 2.78–2.96 (m, 8 H, H$^b$ + H$^c$), 5.03 (m, 4 H, H$^a$), 6.85–6.94 (m, 8 H, C$_6$H$_4$), 8.00 (d, 4 H, β-H, *J* 1.1 Hz); $\lambda_{max}$(CHCl$_3$)/nm 747; MS (FAB$^+$) 1183 (M + H)$^+$.

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