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The first example of Diels–Alder cycloaddition of *ortho*-xylylenes to *meso*-tetraarylporphyrins containing electron-deficient β,β-double bonds

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Abstract—β-Nitro-5,10,15,20-tetraphenylporphyrin and its zinc complex, or 2,7-dinitro-5,10,15,20-tetraphenylporphyrin, react with 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide in refluxing 1,2,4-trichlorobenzene, giving rise to chlorins, bacteriochlorins or isobacteriochlorins. The products obtained are attractive intermediates for further functionalization of porphyrins and may be of potential use as sensitizers in photodynamic therapy.

Recently, a number of investigations have focused on the synthesis and utilization of chlorins and bacteriochlorins. These compounds are referred to as second-generation photosensitizers[1] in antitumor photodynamic therapy (PDT),[2] due to their characteristic strong absorption bands shifted towards the red region of the visible spectrum. They absorb near or above 700 nm, which is medically desirable due to a greater tissue penetration afforded by light with longer wavelengths and lower energy.[3]

It is known that the peripheral β,β-double bonds of *meso*-tetraarylporphyrins can be regarded as units partially isolated from the macrocyclic conjugation pathway. In many reactions, they show a similar reactivity to normal double bonds, for example: a concerted oxidation reaction with OsO_4,[4] reduction,[5] and pericyclic additions of carbenes.[6] Thus, one possible route to the synthesis of chlorins and bacteriochlorins might involve the Diels–Alder cycloaddition reaction of the above-mentioned porphyrins with dienes. Examples of just such transformations have been reported by Cavaleiro and co-workers[7] and Smith and co-workers.[8] On the other hand, several papers were published concerning the synthesis of these types of compounds using vinyl-substituted porphyrins (as dienes) and electron-deficient dienophiles.[6c,9]

Taking into account this dichotomy of reactivity, porphyrins can be considered as very good substrate candidates for these transformations. Utilizing porphyrins as dienophiles, the [4+2]-cycloaddition of the 2π component in various *meso*-tetraarylporphyrins with highly active *ortho*-xylylenes yielded a mixture of the desired chlorins and products, which were a consequence of the subsequent oxidation. However, despite the relatively high reactivity of these dienes, the substrates need to be preheated at high temperature for several hours, and it is also worth mentioning that considerable amounts of unchanged starting porphyrins were recovered.[7]

Attractive chlorin systems can be synthesized by various methods (oxidation,[4] reduction,[5] addition of Br_2,[10] Diels–Alder reaction,[6c,7–9] 1,3-dipolar cycloaddition,[11] and cyclopropanation via carbene addition[6]). Some of the approaches involve total synthesis; however, in these cases the known representative examples are multi-step transformations (6–17 steps), with the total yields varying from 0.04% to 2.8% (see: Battersby et al.,[12] Jacobi et al.,[13] Lindsey et al.,[14] and Gryko and Gałęzowski[11b]).

Observations made regarding these approaches to chlorins include various difficulties and preparative inconveniences, for example: (1) the reactions are not regioselective, (2) several by-products can be formed

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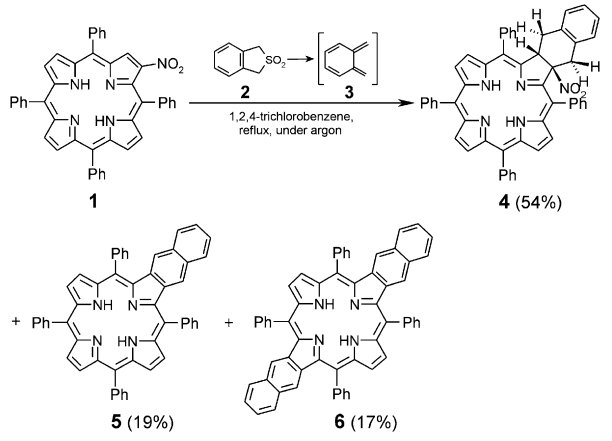
(i.e., in Diels–Alder reactions—bacteriochlorins which, during the process, could easily oxidize back to porphyrins), (3) chromatographic resolution of the products requires repeated chromatography or preparative TLC separation, (4) the yields are low and moderate, or strongly depend in some cases on the specific structure of the substrates. Therefore, due to the importance of these compounds, new synthetic approaches to chlorins and bacteriochlorins are being sought.

Our research was directed towards the synthesis of chlorin-type derivatives via substituted porphyrins containing electron-withdrawing groups at the β-position. The desired substrates for these transformations are easily available now, as an improved method for the preparation of this type of compounds [for example, 2-nitro-5,10,15,20-tetraphenylporphyrin (**1**) and 2,7-dinitro-5,10,15,20-tetraphenylporphyrin (**12**)], has recently been developed.[15] We hypothesized that the introduction of a substituent, such as NO_2, CN, and CO_2Et, to a β,β-double bond could increase the reactivity of the dienophile in the Diels–Alder reaction. Thus, the reactive diene (*ortho*-xylylene) on the one hand could enter into the [4+2]-cycloaddition with the reactive dienophile on the other.

Indeed, this is what we observed, and herein we report our preliminary studies on this type of cycloaddition. The precursor for the in situ generation of the *ortho*-xylylene was 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**2**). We found that heating a solution of β-nitro-*meso*-tetraphenylporphyrin (**1**) and sulfone **2** (ca. 10 equiv excess) in 1,2,4-trichlorobenzene (at reflux, under argon) gave some unchanged starting porphyrin ($R_f = 0.60$; $CHCl_3$/*n*-hexane—2:1) and three new compounds: chlorin **4** ($R_f = 0.51$; 54%), naphthoporphyrin **5** ($R_f = 0.85$; 19%), and bis-naphthoporphyrin **6** ($R_f = 0.91$; 17%).[16] The product **6** results from the double cycloaddition of *ortho*-xylylene to the β,β-double bonds of nitroporphyrin **1**, and the subsequent exhaustive aromatization of the system (via the elimination of HNO_2 and oxidation) (see Scheme 1).

The nitro group can be easily removed (if needed) from adduct **4**, because the 1,2-elimination of HNO_2 is a rather fast process. Usually, it occurs spontaneously, giving a conjugated structure, the porphyrinyl [22π]-electron system in the core ring.



Scheme 1.

The products were isolated via chromatography,[17] and identified on the basis of their MS, NMR, and UV–vis spectra.[18] In the ^1H NMR spectrum of chlorin **4**, the three groups of aliphatic protons appear as three multiplets at 5.22–5.30 ppm (1H), 2.70–2.84 ppm (2H), and 2.49–2.64 ppm (2H). Two β-protons, situated at the opposite side to the 'chlorin junction', appear as a singlet at 8.59 ppm, while the four other β-protons gave two AB-systems: 8.54/8.49 ppm ($J = 5.1$ Hz) and 8.53/8.48 ppm ($J = 5.1$ Hz). Finally, the spectrum revealed a characteristic broad singlet at ca. −0.90 ppm originating from the NH protons. The MS spectrum (ESI) revealed an intense M+H peak at $m/z = 764$ (100%), and the correct isotope pattern for this protonated molecular ion. The UV–vis spectrum of this adduct confirmed its chlorin-type structure with the observation of an absorption Q-band in the visible region ($\lambda = 647.0$ nm) (see Supplementary data).

The ^1H NMR spectrum of compound **5** showed only signals for aromatic protons.[18] In the UV–vis spectrum, absorption bands were found at $\lambda = 711.0$ nm and 662.0 nm, and in the MS analysis (ESI), a peak at $m/z = 715$ ($[M+H]^+$; 100%) was identified. The isotope pattern of this protonated molecular ion corresponded to the theoretical one, within experimental error limits.

Similarly, in the ^1H NMR spectrum of the last fully aromatic product, **6**, only the signals of aromatic protons were found [four β-protons, as a singlet at 8.70 ppm, and twelve naphtho-protons as multiplets at 7.81–8.08 (8H) and 7.40–7.54 ppm (4H)]. The diagnostic mass peak $m/z = 815$ (100%; M+H) confirmed the molecular weight of the proposed structure. On the basis of the ^1H NMR spectrum (singlet originating from the β-protons), and some earlier literature reports,[7a,c,8] a *trans* relationship for the naphtho rings is proposed.

The 2-nitro-*meso*-tetraphenylporphyrin zinc complex was less reactive. Its reaction, under similar conditions, with the above *ortho*-xylylene **3**, was also much less selective, giving a recovery of the substrate (47%), as well as five new products in relatively low yields (Fig. 1). Compounds **8**–**11** are the products of the subsequent reactions of chlorin **7**, which is formed in the first step of this process. The conversion of most of these intermediates into fully aromatic moieties is possible in situ. Indeed, a prolonged reaction time (up to 25 h), coupled with a decrease in the amount of the solvent, gave the desired transformations. However, product **8** was isolated in a low yield (ca. 10%), and a degradation of the reagents was mostly observed. These results probably explain why there are no reports concerning this particular type of [4+2]-cycloaddition of porphyrin complexes in the literature.

In attempts to further our investigations, we used 2,7-dinitro-*meso*-tetraphenylporphyrin **12** to obtain an isobacteriochlorin. It was found that in the reaction of

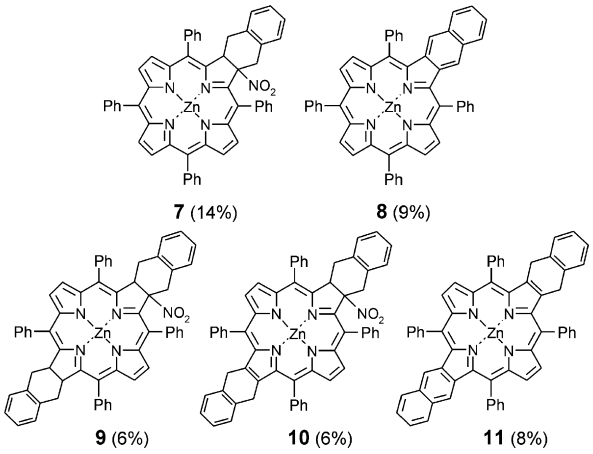


Figure 1.

porphyrin **12** with sulfone **2**, the formation of a mixture of products were observed, and some of the starting porphyrin was recovered (29%). One of the isolated compounds exhibited an MS peak at $m/z = 815$ ($[M+H]^+$; without NO_2 groups in the structure). This indicated that the bis-cycloaddition process occurred in conjunction with the elimination of HNO_2. The formation of the molecule obtained $M = 814$ (compound **13**) is only possible through the double cycloaddition of *ortho*-xylylene to the neighboring β,β-double bonds (substituted with NO_2 groups), to give isobacteriochlorin, and spontaneous elimination of two HNO_2 molecules, followed by subsequent exhaustive aromatization. Thus, *thanks to the presence of two electron-withdrawing groups at positions 2- and 7-, the bis-cycloaddition leads to isobacteriochlorin-like products, which to date has not been observed in this type of processes.*[7a,c,8] However, in this reaction, several other porphyrin derivatives were formed, as observed in TLC analysis. From this mixture, we could isolate and identify an additional fraction of two isomeric chlorins (**14/15**; one spot on TLC), each bearing two NO_2 groups in the structure, as well as two nitronaphthoporphyrins (**16/17**), formed therefrom (after elimination of HNO_2 and subsequent oxidative aromatization) (see Fig. 2).

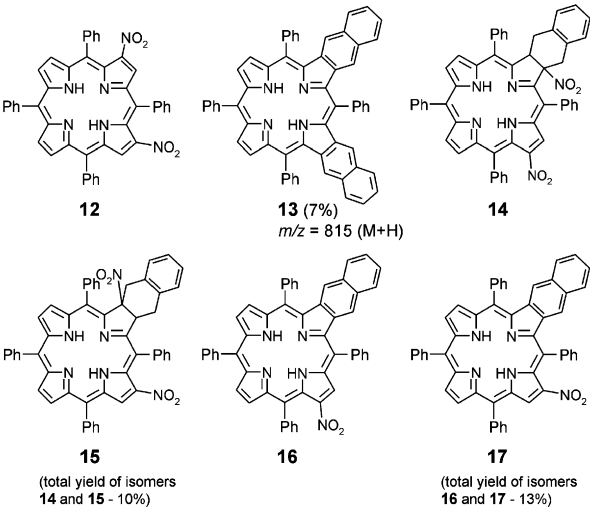


Figure 2.

The structures of these two pairs of isomers, indicated respectively by only one molecular ion in MS, were proposed on the basis of careful inspection of their ^1H NMR spectra. In each of the spectra of isomer mixtures, two isolated and considerably deshielded singlets, originating from the protons adjacent to the NO_2 group, were found.

The ability to access chlorins, bacteriochlorins, and isobacteriochlorins (and compounds obtained therefrom) is of great importance due to the biological activity of these systems as second-generation photosensitizers for PDT.

A convenient synthetic improvement, involving the Diels–Alder cycloaddition of *ortho*-xylylenes to the electron-deficient β,β-double bonds (in porphyrins), enhanced the reactivity of the system as compared to the previously reported reactions. When applying the 2,7-dinitroporphyrin derivative to this reaction, our finding allows the synthesis of very attractive isobacteriochlorin-type systems.

The products obtained are also versatile intermediates for further functionalization of porphyrins. Currently, we are exploring other possibilities of this type of cycloaddition with electron-releasing substituents (the so-called Diels–Alder reaction with inverse electron demand). The present approach may well receive future attention in the synthesis of chlorins, as well as in the area of porphyrin skeleton modifications.

Supplementary data

Supplementary data (copies of spectra of selected compounds—^1H NMR for compounds **4**, **5**, and **8**; MS for compounds **4**, **5**, **6**, and **13**; UV–vis for compounds **4**, **5**, **6**, and **8**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.006.

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16. *Typical procedure*. To a solution of 2-nitro-5,10,15,20-tetraphenylporphyrin (**1**; 28.8 mg, 0.044 mmol) in 1,2,4-trichlorobenzene (2 mL) 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**2**; 64 mg, 0.38 mmol) was added, and the reaction mixture was heated to reflux in a light-shielded flask for ca. 7 h (under argon; TLC monitoring, eluent: $CHCl_3$/*n*-hexane, 2:1). After completion, the mixture was cooled to room temperature and chromatographed, using initially *n*-hexane as an eluent (ca. 100–150 mL; to remove 1,2,4-trichlorobenzene), and then $CHCl_3$/*n*-hexane (2:1), to give two fractions (each containing two compounds). The first fraction (less polar) was chromatographed by preparative TLC ($CHCl_3$/*n*-hexane; 2:1) to give naphthoporphyrin **5** (19%) and bis-naphthoporphyrin **6** (17%). The second fraction was rechromatographed on a short column ($CHCl_3$/*n*-hexane, 2:1) to give some unchanged starting porphyrin (**1**; $R_f = 0.60$) and chlorin **4** (54%).
17. Column chromatography: silica gel, 230–400 mesh (Kieselgel 60); preparative TLC chromatography: Kieselgel 60 F–254; Merck AG; eluent: $CHCl_3$/*n*-hexane, 2:1.
18. *Data for the products of the reaction of 2-nitro-5,10,15,20-tetraphenylporphyrin* (**1**) *with 1,3-dihydrobenzo-[c]thiophene 2,2-dioxide* (**2**):
Compound **4**: mp >300 °C. $R_f = 0.51$ ($CHCl_3$/*n*-hexane, 2:1). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta_H = 8.59$ (s, 2H, H^β-pyrrole), 8.54 and 8.49 (AB-system, $J = 5.1$ Hz, 2H, H^β-pyrrole), 8.53 and 8.48 (AB-system, $J = 5.1$ Hz, 2H, H^β-pyrrole), 8.26–7.97 (m, 8H, H-Ph), 7.89–7.67 (m, 12H, H-Ph), 6.89–6.83 (m, 2H, H-Ar), 6.77–6.70 (m, 2H, H-Ar), 5.30–5.22 (m, 1H, CH), 2.84–2.70 (m, 2H, CH_2), 2.64–2.49 (m, 2H, CH_2), −0.90 (br s, 2H, 2 × NH). UV–vis ($CHCl_3$): $\lambda_{max} = 647.0$, 600.5, 550.0, 449.5 (Soret band), 375.0 nm. MS (ESI), *m*/*z* (% rel intensity): 766 (12), 765 (54), and 764 (100) [isotope $(M+H)^+$], 719 (12), 663 (2), 615 (3), 495 (2), 391 (3). HR-MS ($C_{52}H_{38}N_5O_2$, $[M+H]^+$): calcd—764.3026; found—764.2982.
Compound **5**: This compound has been already described in the earlier literature (e.g., Ref. 7a); however, the detailed spectroscopic data were not reported therein. Mp >300 °C. $R_f = 0.85$ ($CHCl_3$/*n*-hexane, 2:1). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta_H = 8.84$ (d, $J = 5.0$ Hz, 2H, H^β-pyrrole), 8.75 (d, $J = 5.0$ Hz, 2H, H^β-pyrrole), 8.65 (s, 2H, H^β-pyrrole), 8.26–8.17 (m, 8H, H-Ph), 8.08–7.82 (m, 4H, H-Ar), 7.80–7.63 (m, 12H, H-Ph), 7.56–7.39 (m, 2H, H-Ar), −2,33 (s, 2H, 2 × NH). UV–vis ($CHCl_3$): λ_{max} ($\lg\varepsilon$) = 711.0 (3.41), 662.0 (3.04), 606.0 (3.20), 559.5 (3.30), 525.5 (3.75), 442.0 (4.73, Soret band). MS (ESI), *m*/*z* (% rel intensity): 717 (8), 716 (53), 715 (100) [isotope $(M+H)^+$].
Compound **6**: mp >300 °C. $R_f = 0.91$ ($CHCl_3$/*n*-hexane, 2:1). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta_H = 8.70$ (s, 4H, H^β-pyrrole), 8.27–8.19 (m, 8H, H-Ph), 8.08–7.81 (m, 8H, H-Ar), 7.78–7.62 (m, 12H, H-Ph), 7.54–7.40 (m, 4H, H-Ar), −2.29 (br s, 2H, 2 × NH). UV–vis ($CHCl_3$): $\lambda_{max} = 708.5$, 641.0, 562.5, 526.0, 452.0 nm (Soret band). MS (ESI), *m*/*z* (% rel intensity): 818 (19), 817 (23), 816 (73), and 815 (100) [isotope $(M+H)^+$], 715 (5), 663 (4), 607 (2), 551 (2), 495 (5), 439 (4), 383 (2), 327 (3). HR-MS ($C_{60}H_{39}N_4$, $[M+H]^+$): calcd—815.3175; found—815.3235.