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Porphyrins in Diels–Alder reactions. Improvements on the synthesis of barrelene-fused chlorins using microwave irradiation

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Abstract—The microwave irradiation technique was applied to the Diels–Alder reaction of tetrakis(pentafluorophenyl)porphyrin with pentacene and naphthacene. Both reactions proceed within minutes to afford the corresponding monoadducts in 83% and 23% yield, respectively. When compared with the yields obtained under classical heating (22% and no reaction, respectively), this represents an impressive improvement of these reactions. Bisadducts (bacteriochlorins and isobacteriochlorins) are also obtained in the reaction with pentacene; these compounds are not formed under classical heating.

In the last few years intensive work has been done in the study of cycloaddition reactions with porphyrins[1] and, more recently, with corroles.[2] We have found that porphyrins react with dienes such as *ortho*-benzoquinodimethane or pentacene, under thermal conditions, to give mainly the corresponding Diels–Alder monoadducts (chlorins).[3,4] Such reduced porphyrins are especially important since their long-wavelength absorption bands ($\lambda_{max} \cong 650$ nm) make them potential photosensitizers for the photodynamic therapy (PDT) of cancer.[5]

It is well-known that cycloaddition reactions with porphyrins can be used as a simple and easy strategy to produce chlorins and other reduced porphyrins. However this method presents some experimental limitations: long reaction times and sometimes low yields. These limitations are directly associated with the comparatively low reactivity of the porphyrins. Higher yields are obtained when porphyrins with *meso* withdrawing groups (pentafluorophenyl group, for instance) are used.

Microwave-assisted organic synthesis (MAOS) has been used with great success to improve several difficult cycloaddition reactions.[6] It has been postulated that the short reaction times associated with microwave activation avoids the decomposition of the reagents and the products and prevents the polymerization of the diene or dienophile, giving rise to significant improvements in the reaction yields. In order to evaluate the benefits of microwave irradiation in the synthesis of barrelene-fused chlorins, we decided to explore the application of this technique in the Diels–Alder reaction of tetrakis(pentafluorophenyl)porphyrin with pentacene and naphthacene. Under classical heating conditions porphyrin **1** reacts with pentacene to give chlorin **2** in very low yield (22%, after 8 h at 200 °C);[4] with naphthacene no reaction is observed.

Our first experiment was carried out in 1,2-dichlorobenzene (DCB) and 3 equiv of pentacene were used. The reaction was performed in a single mode microwave cavity using sealed vessel conditions at 200 °C during 30 min. Under these conditions chlorin **2** was isolated in 64% yield. This represents a significant increase of the reaction yield and a shortening of the reaction time (Scheme 1).

Since the dielectric loss of the solvent is an important factor for the efficient absorption of microwave energy,[6] we tried to increase the reaction yield by using two different solvent systems with higher loss tangents ($\tan\delta$): 1-methyl-2-pyrrolidone (NMP: $\tan\delta = 0.275$)

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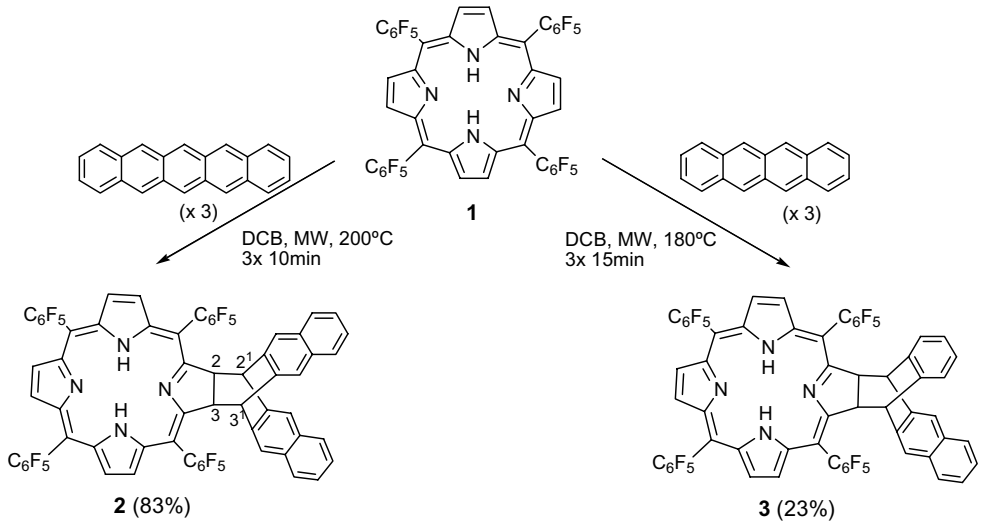


Scheme 1.

and DCB ($\tan\delta = 0.280$), doped with an ionic liquid (1-butyl-3-methyl-imidazolium hexafluorophosphate).[7] Unfortunately none of these experiments gave better results. We have also tried to perform the reaction under solvent-free 'dry-media' conditions using graphite as solid support.[8] However, the porphyrin has shown to be very sensitive to these experimental conditions and most part of the starting material was destroyed.

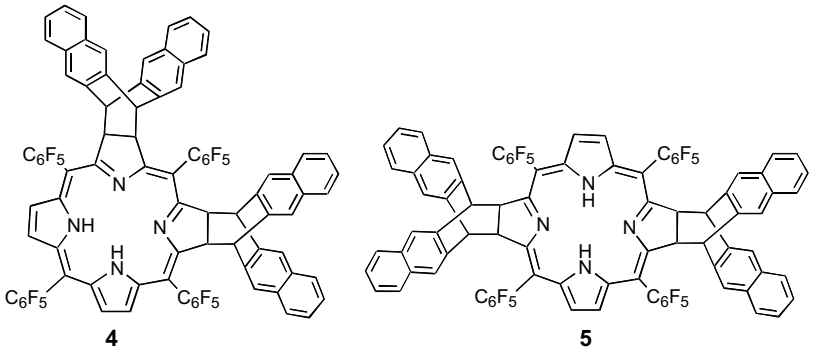
Attempts to increase the reaction yield by using higher temperatures failed. This is due to the retro-Diels–Alder process at temperatures above 200 °C. To confirm this a sample of chlorin **2** was submitted to microwave heating in DCB: heating at 200 °C for 10 min leads to the formation of a small amount of the starting porphyrin **1** while irradiation at 250 °C for 10 min leads to the complete regeneration of the porphyrin **1**. This was also confirmed by differential scanning calorimetry (DSC) experiments in the solid state.

We also tried to favour the formation of chlorin **2** by using a very concentrated reaction mixture. In fact, when we added 3 equiv of pentacene to 0.1 and 0.2 M solutions of porphyrin **1** in DCB, and irradiated the resulting mixtures with microwaves at 200 °C for 20 min, chlorin **2** was obtained in 66% and 77% yield, respectively. Furthermore, in both cases, a small amount of bisadducts **4** and **5** was also isolated; this contrasts with the results obtained by conventional heating where no bisaddition was observed.[4]

An even higher yield of chlorin **2** was obtained when the reaction was performed by adding the pentacene in small portions (3×1 equiv).[9] In this case the chlorin **2** was isolated in 83% yield (bisadducts were also formed) after purification by column chromatography (Scheme 1).[10]

The UV–vis and the ^{1}H NMR spectra of the bisadducts show them to be mixtures of the two positional isomers isobacteriochlorin **4** and bacteriochlorin **5**. These two compounds could not be separated by preparative TLC but were separated by preparative HPLC.[11] The first fraction was identified as **4** (major compound)[12] and the other as **5**. Both the ^{1}H NMR spectrum and the HPLC chromatogram of compound **4** shows that it is a pure compound and not a mixture of the possible 'cis' and 'trans' isomers. The HPLC chromatogram of compound **5** also shows it to be a single isomer. This means that the addition of the second dienophile molecule is not site-selective but is completely stereoselective.

The UV–vis spectra of compounds **4** and **5** (Fig. 1) are typical of isobacteriochlorins and bacteriochlorins, respectively.[13]



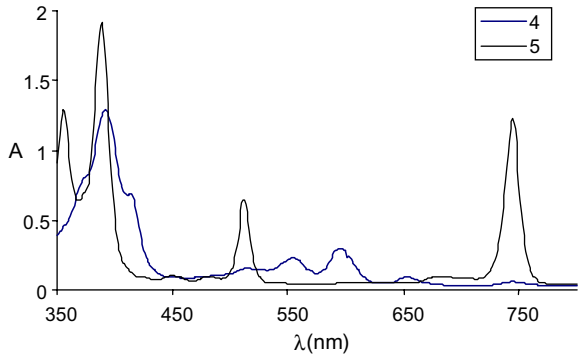


Figure 1.

In order to promote the formation of compounds **4** and **5**, we carried out the reaction of a 0.2 M solution of the monocycloadduct **2** in DCB with 3 equiv of pentacene (irradiation at 200 °C for 20 min). After the usual chromatographic separation, a mixture of compounds **4** and **5** was isolated in 7% yield. Unchanged chlorin **2** (65%) and regenerated porphyrin **1** (16%, formed by retro-Diels–Alder reaction) were also recovered. Although the bisadducts are obtained in low yields, this is also a significant improvement since such compounds are not available from conventional heating conditions.

The reaction with naphthacene was also performed by adding small portions of this reagent (3 × 1 equiv) to a solution of porphyrin **1** in DCB and irradiating it for 45 min (total time) at 180 °C. Under these conditions, a ca. 3:2 mixture of chlorins **3a** and **3b** was isolated in 23% yield. This reaction was carried out at a lower temperature because we observed retro-Diels–Alder reaction at temperatures above 180 °C. Chlorins **3a** and **3b** were separated by HPLC[11] and characterized by UV–vis, MS and ^{1}H NMR.[14]

In conclusion, microwave irradiation was successfully applied to the Diels–Alder reaction of porphyrin **1** with pentacene to yield chlorin **2** in higher yield and in a shorter period of time when compared with the same reaction under traditional heating. This new method also allowed the formation of the bisadducts **4** and **5**. The reaction with naphthacene gave chlorins **3a** and **3b**, which could not be obtained by the conventional heating method. Further microwave-assisted cycloaddition reactions of porphyrins with other cycloaddition partners are currently being evaluated in our laboratories.

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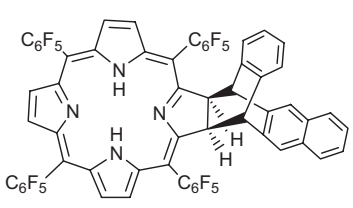
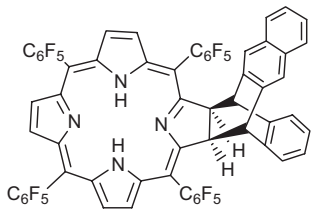
9. All microwave experiments were performed using a CEM Disover unit. Typical procedure: pentacene (0.01 mmol) was added to a microwave vessel containing a solution of *meso*-tetrakis(pentafluorophenyl)porphyrin **1** (0.01 mmol) in 50 μL of DCB. A Teflon-coated magnetic stirrer bar was added and the vessel was sealed under a nitrogen atmosphere. The resulting mixture was irradiated for 10 min at 200 °C. A second portion of pentacene (0.01 mmol) was added to the reaction mixture and it was irradiated under similar conditions. A third portion of pentacene (0.01 mmol) was added to the reaction mixture and the irradiation was continued for an additional 10 min at 200 °C. After cooling, the mixture was purified by flash chromatography on silica gel. The DCB was eluted with cyclohexane and then the unchanged porphyrin **1**, the chlorin **2** and the bisadducts were successively eluted with a 4:1 mixture of cyclohexane–dichloromethane.
10. Spectroscopic data for chlorin **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ −2.08 (s, 2H, NH), 4.78 (br s, 2H, H-2^1, H-3^1), 5.51 (br s, 2H, H-2, H-3), 6.76 (dd, 2H, J = 6.2 and 3.2 Hz, H-naphth.), 7.02 (dd, 2H, J = 6.2 and 3.2 Hz, H-naphth.), 7.12 (br s, 2H, H-naphth.), 7.50 (dd, 2H, J = 6.2 and 3.2 Hz, H-naphth.), 7.63 (br s, 2H, H-naphth.), 7.87 (dd,



3a



3b

2H, $J = 6.2$ and 3.2 Hz, H-naphth.), 8.35 (s, 2H, H-12, H-13), 8.39 (d, 2H, $J = 5.0$ Hz, H-β), 8.63 (d, 2H, $J = 5.0$ Hz, H-β). ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.4, 55.5, 96.7, 106.2, 122.3, 122.9, 123.0, 123.8, 124.9, 126.2, 127.1, 127.7, 128.0, 130.3, 131.1, 131.7, 132.2, 132.6, 135.2, 136.2, 140.2, 152.6, 166.6. $C_{66}H_{24}N_4F_{20}$: calcd C, 63.27; H, 1.93; N, 4.47. Found: C, 62.87; H, 2.15; N, 4.39. UV–vis ($CHCl_3$) λ_{max} ($\log \varepsilon$): 410 (5.47), 507 (4.40), 603 (3.88), 658 (4.87) nm. MS FAB$^+$ *m/z*: 1253 $(M+H)^+$, 975 $[(M-\text{pentacene})+H]^+$.

11. The separation of the two bisadducts **4** and **5** and the two chlorins **3a** and **3b** by HPLC was performed using a Waters Spherisorb S10 ODS2 column equipped with a Chrom A Scope/Barspec detector. A methanol–dichloromethane mixture (4:1) with 2% NEt_3 was used as mobile phase for the separation of the bisadducts and methanol for chlorins. The mobile phase flow rate was 0.7 mL/min. Chromatograms were recorded at 389 nm for all compounds.
12. Data for bisadduct **4**: ^1H NMR (300 MHz, $CDCl_3$): δ 3.41 (s, 2H, NH), 4.11 (d, 2H, $J = 2.7$ Hz), 4.32 (d, 2H, $J = 2.7$ Hz), 4.61 (dd, 2H, $J = 9.0$ and 2.7 Hz), 4.73 (dd, 2H, $J = 9.0$ and 2.7 Hz), 6.98–7.04 and 7.22–7.50 (2m, 24H, H-naphth.), 7.79–7.82 (m, 4H, H-β). UV–vis ($CHCl_3$) λ_{max}: 391 (100%), 514 (13), 553 (18), 595 (24), 653 (7) nm. MS FAB$^+$ *m/z*: 1531 $(M+H)^+$, 1253 $[(M-\text{pentacene})+H]^+$, 975 $[(M-2\times\text{pentacene})+H]^+$.
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14. Data for chlorin **3a**: ^1H NMR (300 MHz, $CDCl_3$): δ −2.04 (s, 2H, NH), 4.67 (br s, 2H, H-2^1, H-3^1), 5.42 (br s, 2H, H-2, 3), 6.11 (dd, 2H, $J = 5.5$ and 3.1 Hz, H-benz.), 6.62–6.63 (m, 2H, H-benz.), 7.50 (dd, 2H, $J = 6.2$ and 3.2 Hz, H-naphth.), 7.60 (br s, 2H, H-naphth.), 7.87 (dd, 2H, $J = 6.1$ and 3.3 Hz, H-naphth.), 8.39–8.41 and 8.65–8.66 (2m, 6H, H-β). MS FAB$^+$ *m/z*: 1203 $(M+H)^+$, 1202 $(M)^{+\cdot}$, 975 $[(M-\text{naphthacene})+H]^+$. UV–vis ($CH_2Cl_2$) λ_{max}: 409 (100), 506 (11), 657 (25) nm.
    Data for chlorin **3b**: ^1H NMR (300 MHz, $CDCl_3$): δ −2.11 (s, 2H, NH), 4.63 (br s, 2H, H-2^1, H-3^1), 5.45 (br s, 2H, H-2, 3), 6.76 (dd, 2H, $J = 6.3$ and 3.2 Hz, H-naphth.), 7.01 (dd, 2H, $J = 6.2$ and 3.3 Hz, H-naphth.), 7.08 (br s, 2H, H-naphth.), 7.20–7.24 (m, 4H, H-benz.), 8.35 (s, 2H, H-β), 8.38–8.40 and 8.62–8.64 (2m, 4H, H-β). MS FAB$^+$ *m/z*: 1203 $(M+H)^+$, 1202 $(M)^{+\cdot}$, 975 $[(M-\text{naphthacene})+H]^+$. UV–vis ($CH_2Cl_2$) λ_{max}: 409 (100), 506 (11), 656 (27) nm.