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Novel barrelene-fused chlorins by Diels–Alder reactions

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Abstract

Novel chlorins with one or two fused barrelene moieties were prepared in moderate to good yields from the Diels–Alder reaction of *meso*-arylporphyrins with pentacene.

Keywords: porphyrins; chlorins; Diels–Alder reactions; barrelenes.

The importance of photodynamic therapy (PDT) in the treatment of neoplastic tumours is increasing. New photosensitizers are currently under intense photophysical and biological studies aiming to be approved as new drugs and, in parallel, a great effort is being put in the search for new synthetic routes to novel photosensitizers. Because of their unique photophysical properties, porphyrin derivatives are among the most studied and promising compounds for this purpose.[1]

Of the porphyrin-type compounds, the chlorins and bacteriochlorins are the most interesting ones for use in PDT. This is mainly due to their strong absorptions near or above 650 nm. New methods for the synthesis of these two types of compounds are being developed. Recently we have reported that porphyrins can be converted into chlorins, bacteriochlorins and isobacteriochlorins via Diels–Alder[2] and 1,3-dipolar[3] cycloaddition reactions. Here we report our results on the Diels–Alder reactions of *meso*-mono, *meso*-di and *meso*-tetraarylporphyrins with pentacene.[4] The products obtained are annelated barrelenes with interesting three-dimensional structures.

In our previous work dealing with Diels–Alder reactions with porphyrins we used a highly reactive and transient species, the *ortho*-benzoquinodimethane, as the diene.[2] In this work we used the commercially available polycyclic hydrocarbon pentacene as the diene. As dienophiles we used the *meso*-mono (**1a**),[5] *meso*-di (**1b**,**1c**) and *meso*-tetraarylporphyrins (**1d**–**1f**) (Scheme 1).

The reactions between these porphyrins and pentacene were all done in 1,2,4-trichlorobenzene, under a nitrogen atmosphere, at ca. 200°C, and the adducts **2a**–**2f** were obtained in moderate to good yields (Table 1). In each case, chlorins **2a**–**2f** were separated from the unconsumed starting porphyrin by column chromatography, recrystallised from dichloromethane/hexane and were then fully characterised by UV–vis, MS, ^{1}H and ^{13}C NMR and microanalysis.[6]

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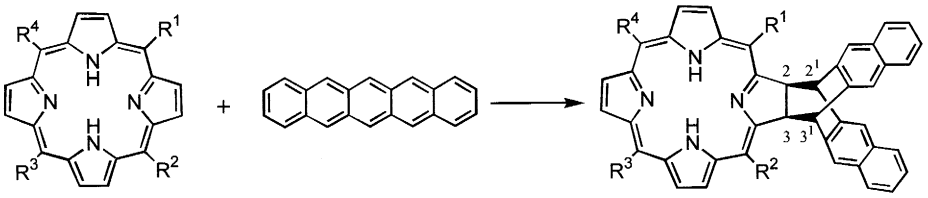


1 **2**

a, R^1= 3-$CH_3OC_6H_4$, R^2= R^3= R^4= H
b, R^1= R^3= 4-$CH_3OC_6H_4$, R^2=R^4=H
c, R^1= R^3= 3-$CH_3OC_6H_4$, R^2=R^4=H
d, R^1= R^2= R^3=R^4= C_6H_5
e, R^1= R^2= R^3=R^4= C_6F_5
f, R^1= R^2= R^3=R^4= 4-$CH_3OC_6H_4$

Scheme 1.

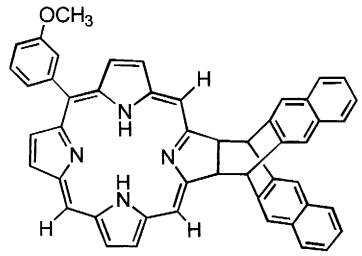
Table 1

Chlorin	**2a.1 + 2a.2**	**2b**	**2c**	**2d**	**2e**	**2f**
Yield (%) [a]	53	87	71	63	60	22
Recov. Start. Porph. (%)	35	12	12	55	74	69

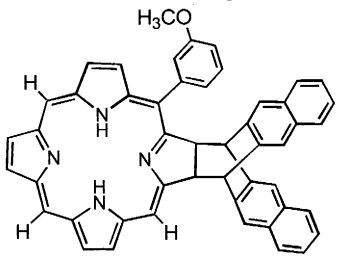
[a] Based on the consumed porphyrin

The visible spectra of adducts **2** confirm their chlorin-type structures (intense absorption bands at about 650 nm). The mass spectra (LSIMS) of all chlorins **2** show a signal corresponding to the $(M+H)^+$ ion and also a signal at *m/z* equivalent to the molecular weight of the corresponding porphyrin **1** (presumably formed by a retro-Diels–Alder cycloaddition reaction).

Because of the symmetry of the starting *meso*-di and tetraarylporphyrins used, only one chlorin was formed in each reaction. However, from the reaction of pentacene with porphyrin **1a** two regioisomeric chlorins **2a** were obtained in a proportion of ca. 7:3. These two chlorins were separated by preparative TLC and characterised. From their ^{1}H NMR spectra[7] we deduced the following structures:



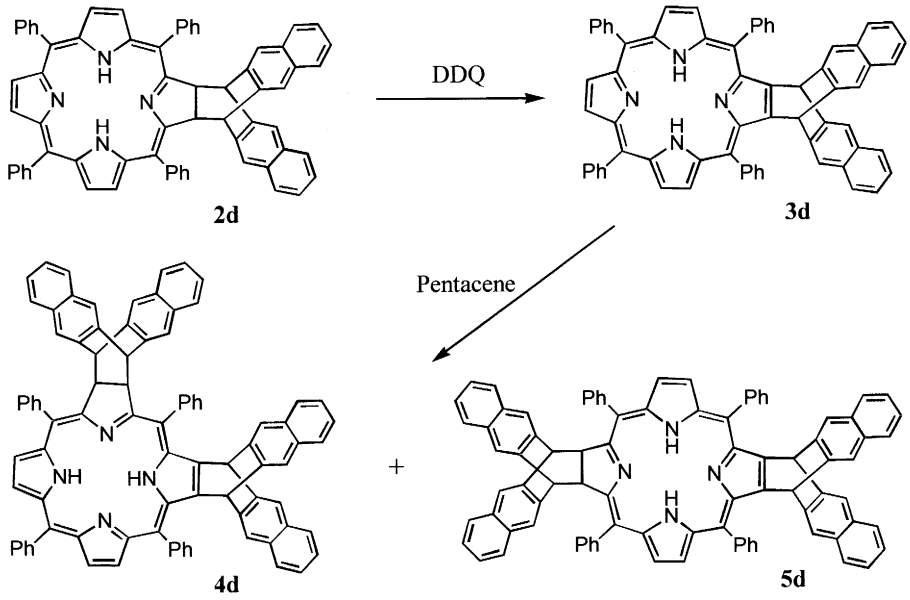
2a.1 (Main fraction)



2a.2 (Minor fraction)

Several attempts were tried to insert a second molecule of pentacene into the chlorins **2** in order to synthesise bacteriochlorins (or isobacteriochlorins). However, all attempts were unsuccessful, even with chlorins **2a** where the steric hindrance would be smaller. We decided then to oxidise chlorin **2d** to the corresponding porphyrin and then to use it as a precursor for bis-adducts of the chlorin type (Scheme 2). Chlorin **2d** was quantitatively converted into porphyrin **3d** by oxidation with DDQ.[8]

From the reaction of porphyrin **3d** with pentacene (12 equiv.) in refluxing 1,2,4-trichlorobenzene (17 h), two new chlorins were obtained in small amounts. These compounds, after chromatographic separation from the starting porphyrin (92% recovered), were characterised by UV–vis and MS. Both compounds show the expected molecular ion (*m/z*=1169) in their mass spectra and similar UV–vis spectra of the chlorin type: the isomer with higher R_f value has a strong absorption band at 657 nm while the



Scheme 2.

other has an absorption band at 654 nm. The two isomers were obtained in similar quantities which means that the barrelene moiety does not have a significant electronic or steric effect in this reaction to induce regioselectivity.

This work is currently being extended to other polycyclic hydrocarbons.

Acknowledgements

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3. Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S. *Chem. Commun.* **1999**, 1767–1768.
4. Part of this work has already been presented: Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. *XVIIIth European Colloquium on Heterocyclic Chemistry*, Abstract A-86, Rouen (France), 1998.
5. Porphyrin **1a** was obtained as a by-product during the synthesis of **1c** by the method of Bruce: Wang, Q. M.; Bruce, D. W. *Synlett* **1995**, 1267–1268.
6. As an example, the spectroscopic data for chlorin **2d**: ^{1}H NMR (300 MHz, $CDCl_3$, *J* Hz) δ: −2.07 (s, 2H, NH), 4.64 (s, 2H, H-2^1,3^1), 5.72 (s, 2H, H-2,3), 6.76 (dd, *J* 6.3 and *J* 3.3, 2H, H-naphth.), 7.02 (dd, *J* 6.3 and *J* 3.3, 2H, H-naphth.), 7.07 (s, 2H, H-naphth.), 7.33 (s, 2H, H-naphth.), 7.40 (dd, *J* 6.3 and *J* 3.3, 2H, H-naphth.), 7.64–7.68 (m, 6H, H-Ph), 7.75 (dd, *J* 6.3 and *J* 3.3, 2H, H-naphth.), 7.81 (d, *J* 7.5, 2H, H-Ph), 7.94 (t, *J* 7.5, 2H, H-Ph), 8.01–8.13 (m, 8H, H-Ph), 8.32–8.36 (m, 4H, H-β), 8.54–8.56 (m, 4H, H-Ph, H-β); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.5 (C-2^1,3^1), 55.0 (C-2,3), 112.6, 121.9, 122.2, 122.6, 123.9, 124.5, 125.4, 126.61, 126.64, 126.8, 127.6, 127.8, 128.0, 128.7, 131.5, 131.95, 132.02, 132.5, 133.9, 134.1, 135.3, 135.7, 138.2, 140.8, 141.7, 142.0, 142.7, 152.4, 164.2; MS (LSIMS): 893 $(M+H)^+$, 614 (TPP); UV–vis ($CHCl_3$), λ_{max}/nm (log ε): 652 (4.35), 598 (3.71), 548 (3.99), 521 (4.08), 422 (5.27); $C_{66}H_{44}N_4$1/2H_2O: calcd C 87.87, N 6.21, H 5.03; found C 87.72, N 6.25, H 5.27.

7. There is a significant difference in the spectra of these compounds: the *meso*-H of **2a.1** resonate at δ 9.20, 9.23 and 9.76 ppm while in **2a.2** they resonate at δ 9.32, 9.72 and 9.82 ppm.
8. Porphyrin **3d**: ^{1}H NMR (300 MHz, $CDCl_3$, *J* Hz) δ: −3.06 (s, 2H, NH), 5.00 (s, 2H, H-2^1,3^1), 7.32 (dd, *J* 6.2 and *J* 3.3, 4H, H-naphth.), 7.60 (s, 4H, H-naphth.), 7.69 (dd, *J* 6.2 and J 3.3, 4H, H-naphth.), 7.72–7.76 (m, 6H, H-Ph), 8.08–8.20 (m, 10H, H-Ph), 8.33–8.35 (m, 4H, H-Ph), 8.76–8.84 (m, 6H, H-β); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 50.1, 119.1, 120.1, 122.1, 125.6, 126.6, 127.0, 127.5, 127.6, 128.8, 131.7, 134.3, 134.5, 142.1, 142.9, 143.2; MS (LSIMS): 891 $(M+H)^+$; UV–vis ($CHCl_3$), λ_{max}/nm (log ε): 647 (3.53), 591 (3.76), 551 (3.77), 516 (4.32), 420 (5.58).