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Regiospecific Synthesis of Oligomeric Porphyrins: Ether-bonded Porphyrin–Chlorins

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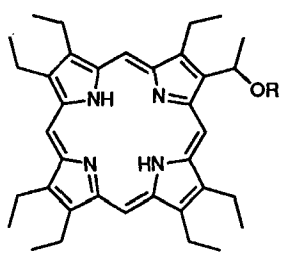
The dimeric porphyrin has been synthesized containing an ether bond between the macrocycles, one of which is a dihydro derivative of a chlorin type.

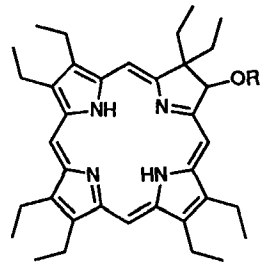
A relatively new and actively developing method for the diagnosis and treatment of cancer is based on the tendency of some dyes, mainly porphyrins, to selectively accumulate in tumour tissue. Subsequent illumination with light of a specific wavelength induces intense fluorescence of the accumulated substance. Red light initiates a chain of photophysical reactions, which is believed to include singlet oxygen generation,[1] thus leading to tumour necrosis. The method was named photodynamic therapy (PDT).[1,2] Oncologists now mainly use haematoporphyrin-based drugs, which are actually quite complex mixtures containing ether-bonded oligomeric porphyrins acting as anti-cancer components.[3–5]

The aim of this work was to synthesize oligomers containing both chlorin and porphyrin rings. Chlorins have two considerable spectral advantages in comparison with porphyrins: their major absorption band is bathochromically shifted, thus affording greater light penetration into the body tissue, and their extinction coefficient is greater than that of porphyrins. Thus, the marked affinity of oligomeric porphyrins for tumour tissue coupled with the spectral properties of chlorins open new and promising prospects for the design of new, effective photosensitizers for PDT.

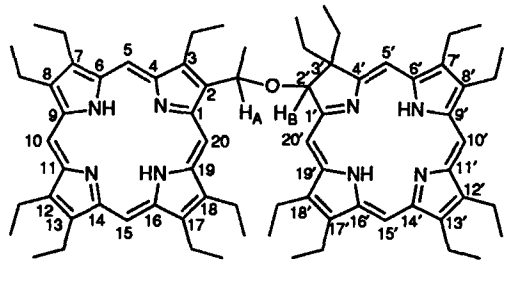
In this study, porphyrin–chlorin dimers are linked by a chain which is one carbon atom shorter than that of ether-bonded haematoporphyrin dimers. This shorter chain might cause considerable complications during the synthesis owing to steric hindrances. Indeed, it was not possible to synthesize the porphyrin–chlorin dimer by the known procedure *via* the bromo derivative **1b**.[6,7] (However, some time earlier a dimeric porphyrin was prepared using the bromo-activated intermediate **1b**.[8])



1a; R = H
b; R = Br
c; R = $COCF_3$



2a; R = H
b; R = $COCF_3$



3a,b

1a + 2b ⟶ 3a, b (63% : 3.4%)
1c + 2a ⟶ 3a, b (12% : 12%)

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A chlorin–porphyrin dimer was successfully synthesized by the trifluoroacetate procedure developed by the authors.[9] Octaethylchlorin **2a** was treated with trifluoroacetic anhydride to give the corresponding trifluoroacetate **2b**. After removal of the excess of anhydride, this relatively stable intermediate was coupled with α-hydroxyethylporphyrin **1a**. Silica gel chromatography and crystallization from hexane gave porphyrin–chlorins **3a,b** as two stable isomers with 63 and 3.4% yields, respectively.† Four optical isomers *RR'*, *SS'*, *RS'* and *SR'* could arise, thereby giving two pairs of diastereoisomers. When porphyrin trifluoroacetate **1c** was condensed with hydroxychlorin **2a**, the yield of the dimers obtained did not exceed 25% and the ratio of the **3a** and **b** components was 1:1.

The electronic absorption spectra are specific for porphyrin–chlorins and actually represent superpositions of chlorin and porphyrin spectra with λ_{max} of 650 and 500 nm, correspondingly. The major isomer **3a**, with a lower R_f, melts at 218–220 °C, *i.e.*, some 50 °C lower than the faster isomer.

In the ^{1}H NMR spectrum of the low R_f isomer **3a**, in contrast to that of the high R_f dimer **3b**, one of the porphyrin ethyl triplets is located in an unusually high magnetic field: δ − 1.3. By nuclear Overhauser enhancement, using the H_A and H_B protons as starting points,[10] we have assigned the signals from the meso-protons at C-20' in the chlorin and at C-20 in the porphyrin and shown that strong interaction takes place between these protons. These data indicate close sterical proximity between the porphyrin and chlorin rings in the molecule of the low R_f isomer **3a**.

In this study we have shown that a sterically hindered chlorin–porphyrin structure can be formed in relatively good yield in a coupling reaction of hydroxychlorin and α-hydroxyethylporphyrin with trifluoroacetate activation. This synthetic route to ether bond formation permits the synthesis of analogous dimeric and trimeric compounds.

† *Characterization data* for low R_f diastereoisomer **3a**: m.p. 218–220 °C, *m/z* 1085 ($M^+ + H$); λ_{max}/nm [10^{-3} (ε/mol^{-1} dm^3 cm^{-1})]: 392(220), 407(230), 499(26), 534(12), 569(7.8), 596(4.6), 624(7.6) and 644(48.2); fluorescence λ_{ex} 410 nm, λ_{em} 648 nm; ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 11.21 (s, H, meso-H), 10.29 (s, H, meso-H), 10.19, 10.17 (s, each 1H, meso-H), 9.70, 9.31, 8.88, 8.46 (s, each 1H, meso-H), 7.03 (s, H at C-2'), 6.85 [q, H, —OC*H*(CH$_3$)—], 3.0–4.3 (m, 30H, —C*H*$_2$CH$_3$), 2.80 (d, 3H, —OCH(C*H*$_3$)—), 0.7–2.3 (m, 42H, —CH$_2$C*H*$_3$), −1.30 (t, 3H, —CH$_2$C*H*$_3$), −2.69 (br s, 1H, N—H), −3.08 (br s, 1H, N—H), −3.45 (br s, 2H, N—H); satisfactory C, H, N analyses were obtained.

High R_f diastereoisomer **3b**: m.p. 267–268 °C; *m/z* 1086 ($M^+ + 2H$); λ_{max}/nm [10^{-3} (ε/mol^{-1} dm^3 cm^{-1})]: 404(370), 499(25), 537(10), 569(5.1), 595(3.0), 624(5.2) and 643(48.2); fluorescence λ_{ex} 400 nm, λ_{em} 640 nm; ^{1}H NMR δ_H (200 MHz, $CDCl_3$) 11.98 (s, H, meso-H), 10.17, 10.12, 10.08 (s, each 1H, meso-H), 9.78, (s, H, meso-H), 9.71, 9.70 (s, each 1H, meso-H), 8.40 (s, H, meso-H), 7.01 (s, H at C-2'), 6.97 [q, H, —OC*H*(CH$_3$)—], 3.5–4.6 (m, 30H, —C*H*$_2$CH$_3$), 1.2–2.1 (m, 39H, —CH$_2$C*H*$_3$), 0.38 (t, 3H, —CH$_2$C*H*$_3$), 0.20 (t, 3H,—CH$_2$C*H*$_3$), −2.40 (br s, 2H, N—H), −3.64 (br s, 2H, N—H).

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