A *meso*-unsubstituted N-confused porphyrin prepared by rational synthesis

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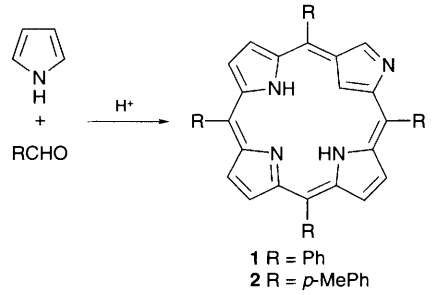
Condensation of a tetraalkyl-α,α-dipyrromethane dialdehyde in a MacDonald-type [2+2]-condensation with a trialkyl-α,β-dipyrromethane gives a heptaalkyl N-confused porphyrin.

In 1994 two novel isomers of porphine, the so called 'N-confused porphyrins' or 'carbaporphyrins' were independently isolated and characterized by Furuta and co-workers[1] in Japan and Latos–Grazynsky and co-workers[2] in Poland. These N-confused *meso*-tetraphenylporphyrins (**1** and **2**) were isolated in low yields (5–7% and *ca.* 5%, respectively) as byproducts of modified preparations of *meso*-tetraarylporphyrins as originally developed by Rothemund[3] and improved by Adler *et al.*[4] and then Lindsey *et al.*[5] (Scheme 1). N-Confused porphyrins have aroused interest[6] and following Vogel's porphycenes,[7] they were only the second example of a porphin isomer to become known.[8] Their optical spectra compared to those of *meso*-tetraphenylporphyrin are red-shifted, which makes them potential candidates for applications such as photodynamic therapy (PDT).[9] Interestingly, they form Ni^{II} complexes in which the inner carbon has lost a proton, forming a carbon–metal bond.[2,10] One other derivative of **2** has been recently reported.[11]

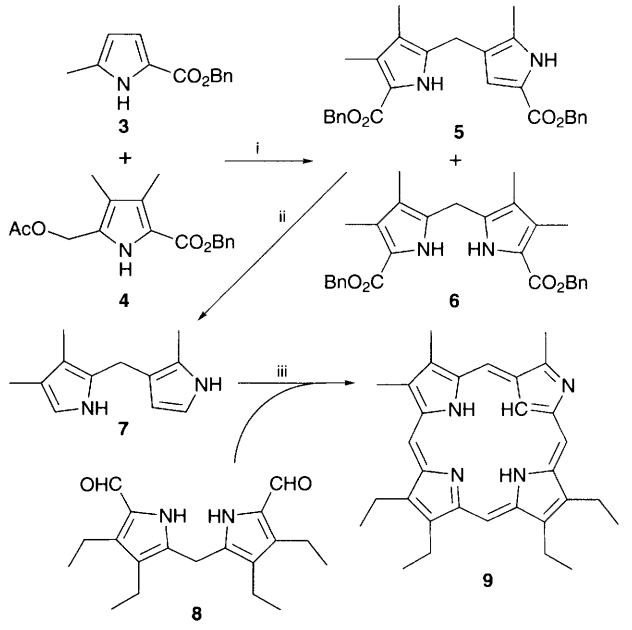
The majority of porphyrin syntheses are directed towards the preparation of porphyrins unsubstituted at the *meso*-positions with all eight β-positions alkyl-substituted in analogy to naturally occuring porphyrins.[12] Such syntheses start with pyrrolic precursors fully β-substituted, preventing any serendipitous formation of N-confused porphyrins. We report here on the rational synthesis of a *meso*-unsubstituted, heptaalkyl β-substituted N-confused porphyrin **9**.‡

We choose the α,β-dipyrromethane **7** as the key intermediate as it has, as the result of the α-to-β pyrrole linkage, the N-confused unit already locked in place.[13] Most important, **7** is set up for a conventional MacDonald-type [2+2] condensation,[15] *i.e.* the acid catalysed condensation of an α,α'-unsubstituted dipyrromethane with an α,α'-dipyrromethane dialdehyde. Compound **7** was accessible by reaction of acetoxymethylpyrrole **4** with the β-unsubstituted pyrrole **3**, followed by debenzylation and acid catalysed decarboxylation of the primary condensation product **5**.§,[15] The directing effect of the electron-withdrawing ester functionality in **3** prevented the formation of the other possible isomer of **5**. Symmetric dipyrromethane **6**, formed as a side product during the condensation of **3** and **4**, was readily separated by silica gel chromatography.

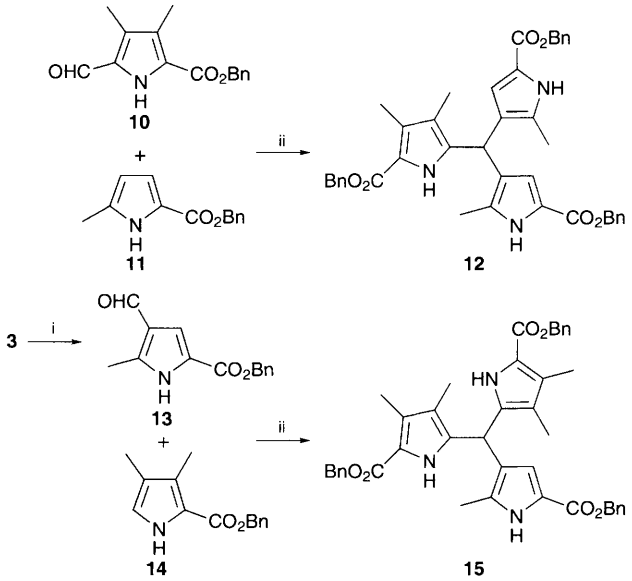


Scheme 1

An alternative synthesis of the α,β-dipyrromethane **7** could result from the reduction of the corresponding α,β-dipyrromethene, which we hoped would be accessible from the acid catalysed condensation of the α-pyrrole aldehyde **10** with the β-



Scheme 2 *Reagents and conditions*: i, aq. HOAc, 100 °C; ii, 1 bar H_2 over 10% Pd–C in THF–trace Et_3N; iii, HCl–HOAc (40:3), room temp., 2–3 d, then evaporation to dryness by a stream of air followed by preparative thin layer chromatography (silica gel, 7% MeOH–CH_2Cl_2)



Scheme 3 *Reagents and conditions*: i, $POCl_3$–DMF, 0 °C → reflux, then NaOAc–H_2O, reflux; ii, 45% HBr in HOAc, MeOH

free pyrrole **11**, or from the β-pyrrole aldehyde **13** and α-free pyrrole **14**.[16] Numerous attempts to prepare the α,β-dipyrromethene failed, instead the main products were the tripyrrolic compounds **12** and **15**. The formation of these tripyrrolic compounds is in accord with reports in the literature, however, these reports also described the cleavage of these compounds to give the desired dipyrromethene and a pyrrolic unit.[17] This did not occur in our hands.

The acid catalysed condensation¶ of **7**, prepared *in situ*, and dialdehyde **8**,[18] followed by air oxidation, yielded, after purification by preparative thin layer chromatography, a green pigment in reasonable yield (25%). The product was identified as the heptaalkyl N-confused porphyrin **9**.‖ Small amounts (≤5%) of octaethylporphyrin from the self-condensation of **8** were also found in the reaction mixture.

The electronic spectrum of **9** (Fig. 1) is porphyrin-like with a Soret band at 416 nm (free base) and four characteristic etio-type Q-bands at 516, 552, 614 and 678 nm. The previously reported N-confused tetraarylporphyrins (**1** and **2**) show a phyllo-type spectrum. An unusually strong band in the short wavelength region is also observed in the spectrum of **9**. In analogy to **1**, **9** can be monoprotonated with 1 equiv. of TFA. The optical spectrum bathochromically shifts (24 nm) and the Soret-band splits. Upon protonation of **9** with a large excess of acid the split Soret band is maintained and shifted towards longer wavelengths and the Q-bands undergo a further bathochromic shift (24 nm) (Fig. 1). The free base and the diprotonated form fluoresce at 683 (MeOH) and 724 nm (MeOH–HCl), respectively.

The mass spectrum (+LSIMS, thioglycerol matrix) exhibits only one strong signal with *m/z* 465, corresponding to the expected mass for MH^+. The ^1H NMR spectrum, like the optical spectrum, shows that **9** is aromatic with a ring current similar to regular octaalkylporphyrins. The highest field resonance at δ −6.12 (not exchangeable with D_2O) is assigned to the inner β-H (21-CH) which is about 1 ppm higher than the corresponding signals for **1** and **2**.[1,2] The inner NH protons of **9** are observed at ambient temperature at δ −3.58 ($CDCl_3$) compared to those of octaethylporphyrin, **1** and **2** at δ −3.72, −2.5 and −2.56 and −2.67 (24-H and 22-H of **2**), respectively. At −50 °C the tautomeric exchange of the non-equivalent NH protons slows down, and two broad signals of equal intensity at δ −3.9 and −4.1 ($CDCl_3$) were observed. The four *meso*-protons are observed as four singlets in the low field aromatic region of the spectrum (δ 9.55, 9.69, 9.71 and 10.05), and the alkyl substituents show chemical shifts typical for other β-alkyl porphyrins.

Protonation of **9** with 1 equiv. of TFA in $CDCl_3$ caused the appearance of an additional broadened signal at δ 13.5 in the ^1H NMR. This chemical shift is characteristic of protons attached to the outer periphery of porphyrins, thus, it was concluded that the outer nitrogen (N-2) was the first nitrogen to be protonated. The addition of several equivalents of TFA was neccessary to protonate the inner nitrogen, clearly visible in the ^1H NMR spectrum ($CDCl_3$, −50 °C) by the splitting of the high field signals into four peaks (δ −0.32, −0.53 and −1.57 for NHs, and δ 4.58 for 21-CH) of equal intensity.

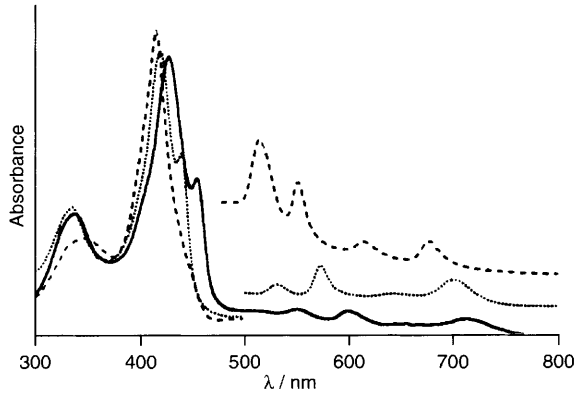


Fig. 1 Optical spectrum of **9** in CH_2Cl_2–trace pyridine (dashed trace); monoprotonated in CH_2Cl_2–1 equiv. TFA (dotted trace); diprotonated in CH_2Cl_2–excess TFA (solid trace)

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Footnotes

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‡ Formal nomenclature: 2-aza-21-carba-12,13,17,18-tetraethyl-3,7,8-trimethylporphyrin.

§ *Selected spectroscopic data* for **5**: ^1H NMR (200 MHz, $CDCl_3$, 20 °C): δ 1.94 (s, 3 H), 2.14 (s, 3 H), 2.25 (s, 3 H), 3.65 (s 2 H), 5.25 (s, 4 H), 6.88 (s, 1 H), 7.25–7.42 (m, 10 H), 8.42 (s, 1 H) and 9.08 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ 8.76, 10.78, 11.32, 22.96, 65.36, 65.84, 116.64, 116.81, 117.94, 120.05, 127.91, 128.13, 128.48, 128.54, 131.21, 132.65, 136.26, 136.72, 160.84 and 161.52; HRMS (EI): *m/z* 456.2051 (found for M^+), calculated for $C_{28}H_{28}N_2O_4$: 456.2049. Satisfactory elemental analysis was obtained.

¶ The formation of porphyrins using the MacDonald [2 + 2] method frequently requires the use of special and carefully controlled conditions unique to a particular system. This was especially true in the present case.

‖ *Selected spectroscopic data* for **9**: ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ −6.12 (s, 1 H), −3.58 (br s, 2 H), 1.82 (m, 12 H), 3.48 (s, 3 H), 3.49 (s, 3 H), 3.59 (s, 3 H), 3.87 (m, 4 H), 3.99 (m, 4 H), 9.55 (s, 1 H), 9.69 (s, 1 H), 9.71 (s, 1 H), 10.05 (s, 1 H); HRMS (FAB): *m/z* 465.3025 (found for MH^+), calculated for $C_{31}H_{37}N_4$: 465.3018; UV–VIS λ_{max} nm (ε × 10^{-3}) (CH_2Cl_2–trace pyridine): 352 (11.8), 416 (25.6), 516 (3.3), 552 (2.2), 614 (1.2) and 678 (1.1); (CH_2Cl_2–1 equiv. TFA): 336 (11.4), 420 (24.8), 440 (16.0), 530 (2.7), 572 (4.5), 702 (3.1); (CH_2Cl_2–1% TFA): 340 (10.5), 428 (23.5), 456 (13.6), 550 (2.7), 600 (2.5) and 714 (1.9).

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