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A novel synthetic route to fused propenochlorin and benzochlorin photodynamic therapy probes

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Reaction of *meso*-(2-formylvinyl)octaethylporphyrin with $(CH_3)_3SiCN–Cu(OTf)_2$ produced unexpected 10^3-trimethylsiloxyl and 10^3-hydroxyl fused propenochlorins which, in H_2SO_4, underwent subsequent migration of the 8-ethyl group to the 10^3-position of the exocyclic benzene ring to form a novel benzochlorin.

Inspired by both the attractive features of photodynamic therapy (PDT) and the commercialization of Photofrin® and Visudyne,® considerable effort has been devoted to the development and study of so-called second generation photosensitizers.[1] For improved photosensitizers, a strong Q-band absorption in the red region of the visible spectrum is a highly desirable characteristic as this would enable treatment of deeply seated tumors. In this endeavour, several porphyrin-based compounds that exhibit high intensity Q-band absorbances, such as chlorins and bacteriochlorins, have been widely investigated. Among these experimental photosensitizers, benzochlorins, naphthochlorins, and pyridochlorins, which contain aromatic groups fused to porphyrin macrocycles, have attracted particular attention.[1] The formation of these fused-ring materials is very much dependent on the nature of the peripheral substituents present on the porphyrinic reactants.

In our recent studies with a series of alkyl ether analogs of pyropheophorbide-a, purpurin-18-*N*-alkylimide, and benzoporphyrin derivatives, we have shown that the overall lipophilicity plays an important role in altering PDT efficacy. In our continuing goal to establish generic structural requirements for effective photosensitizers we have extended our studies to include additional porphyrinic photosensitizers. In one such attempt, we recently reported an efficient regioselective synthesis of OEP-based free-base benzochlorins with variable lipophilicity.[2] This method was also found to be useful for the preparation of a variety of non-metallated fluorinated analogs which are otherwise difficult to synthesize (Scheme 1).

Our next step was to explore the utility of this approach for introducing functional groups into OEP-based benzochlorins that could be easily modified into a congeneric series of compounds. In recent years, cyanotrimethylsilane in combination with Cu(II) triflate has been frequently used for introducing cyano groups into a variety of aliphatic and aromatic systems.[2] We followed this approach for synthesizing a benzochlorin bearing a 10^3-cyano group on the fused benzene ring which could then be easily converted into a variety of substituents. Formylvinylporphyrin **1**, when reacted with Grignard reagents and trifluoromethyltrimethylsilane (Scheme 1) followed by treatment with H_2SO_4 produced benzochlorins **2** and **3**. However, to our surprise, when **1** was reacted with cyanotrimethylsilane–Cu(II) triflate a mixture of novel fused propenochlorins, **7** and **8**, was isolated in 31% and 45% yields respectively (instead of the expected product **6**). No acidic treatment for cyclization of the intermediate was required. A mechanism for the formation of **7** from porphyrin **1** is possibly due to the cyanide displacement (catalyzed by copper triflate) in intermediate **1a**, followed by a Woodward–Hoffman [1,6] electrocyclization as depicted in Scheme 2.

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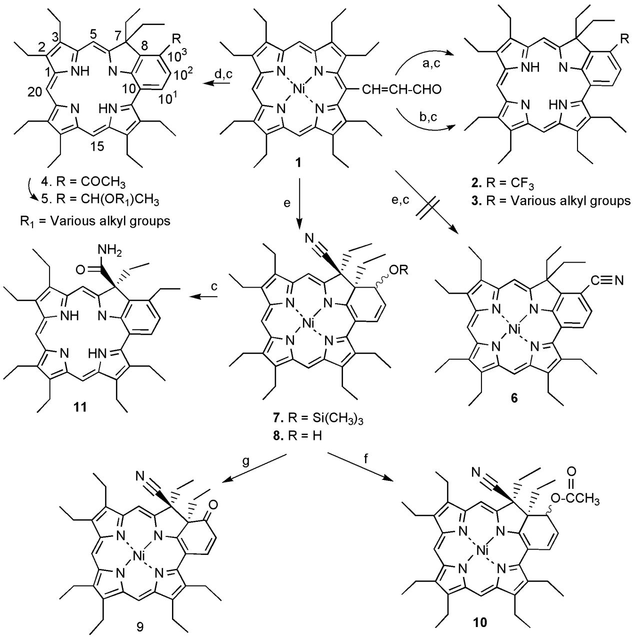
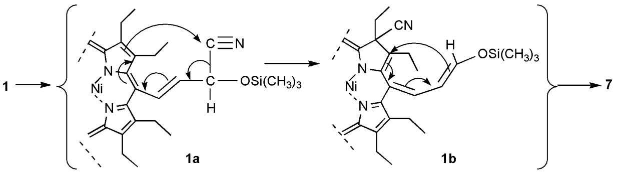


Scheme 1 *Reagents*: a. $(CH_3)_3SiCF_3$; b. alkylMgBr; c. H_2SO_4; d. ≡—MgCl; e. $(CH_3)_3SiCN–Cu(OTf)_2$; f. $(CH_3CO)_2O$–pyridine; g. TPAP–NMO

Reaction of **8** with TPAP–NMO produced fused ketopropenochlorin **9** while reaction of **8** with acetic anhydride in pyridine produced acetoxydihydrobenzochlorin **10** in quantitative yields. These reactions confirmed the presence of the hydroxy group in compound **8**. Our attempts to obtain suitable crystals of **7** and **8** for X-ray crystallographic studies were unsuccessful. However, crystals of **9** were obtained for an X-ray structural determination (Fig. 1).† For **9**, the presence of the cyano group at position-7 was first based upon its bond length [1.140(4) Å]. However, cyano and isocyano groups have similar CN bond lengths and the diffraction data were not sufficient to make the distinction between these choices. Based on HMBC experiments, the possibility of the isocyano group at position-7 was ruled out. In the HMBC spectrum of **8** (and **9**), a strong three bond interaction between the methylene protons at position-7 (δ 3.39 and 3.09 ppm) and cyano carbon (δ 119.86 ppm) was observed. The crystal structure revealed that the porphyrin macrocycle of ketopropenochlorin **9** exhibited a non-planar distortion that was mainly saddled[3] with a mean deviation of the 24 macrocyclic atoms from their least-squares plane of 0.283 Å. The average



Scheme 2 A possible mechanism for the formation of chlorin **7**.

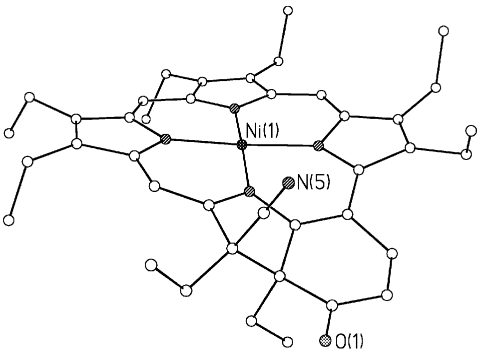


Fig. 1 The molecular structure of Ni(II) cyanochlorin **9**; hydrogens have been omitted for clarity.

Ni–N bond length was 1.935[6] Å (numbers in square brackets indicate deviations from the mean) which is within the normal range for Ni porphyrinoids.

Treatment of **7** and **8** (or a mixture of both) with concentrated sulfuric acid gave **11** in 40% yield. The structure of benzochlorin **11** was confirmed by X-ray crystallography (Fig. 2).‡ The porphyrin macrocycle demonstrated a lightly waved[3] nonplanar distortion with a mean deviation of the 24 macrocyclic atoms from their least-squares plane of 0.042 Å. There was a significant *m-str* in-plane distortion[3] (longitudinal stretching along the C^5–C^{15} axis) to the macrocycle which was apparent in the following data: interatomic distances: N^1–N^4 3.009(6) Å, N^2–N^3 3.082(7) Å, N^1–N^2 2.831(6) Å, N^3–N^4 2.794(6) Å, C^5–C^{15} 7.033(7) Å, C^{10}–C^{20} 6.615(7) Å; bond angles: C^4–C^5–C^6 124.4(5)°, C^{14}–C^{15}–C^{16} 124.9(5)°, C^9–C^{10}–C^{11} 131.3(5)°, C^{19}–C^{20}–C^1 129.0(5)°. This type of distortion is usually observed in mono-meso and 5,15-di-meso substituted free-base porphyrin crystal structures[4] with or without β-substituents. The structure of **11** closely resembles a mono meso 2,3,5,7,8,12,13,17,18-nonasubstituted free-base porphyrin, albeit differing somewhat in the vicinity of the reduced pyrrole ring. That being the case we expect the macrocyclic *m-str* distortion, as observed, for this structure. Metal ions attenuate *m-str* distortions in metalloporphyrins and **9** did not show appreciable *m-str* distortion. The crystal structures for **9** and **11** indicated racemic materials with relative stereochemistries as shown in Scheme 1.

The formation of benzochlorin **11** also demonstrated the presence of cyano groups in fused propenochlorins **7** and **8** (instead of isocyano groups). The ^{1}H NMR spectrum of **7** was very similar to that of **8** except the hydroxy group at position 10^3 (δ 2.39 ppm, 1H, d, J = 6.2 Hz) was replaced with a trimethylsiloxy group (δ 0.45 ppm, 9H, singlet). The ^{1}H and ^{13}C NMR resonances for **8**, **9** and **11** were assigned on the basis of their ^{1}H–^{1}H COSY, ROESY, HMQC and HMBC experiments. The high intensity Q-band absorbances observed for **8** ($\lambda_{\max}$ 630), **9** ($\lambda_{\max}$ 647), and **11** ($\lambda_{\max}$ 668 nm) demonstrated a trend wherein red-shifted $\lambda_{\max}$ values corresponded to increased levels of π electron conjugation with the chlorin macrocycles.

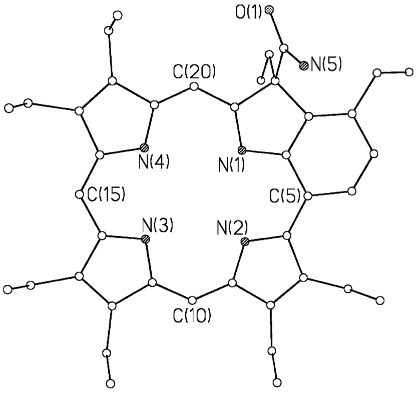


Fig. 2 The molecular structure of free-base amidochlorin **11**; hydrogens have been omitted for clarity.

Of the materials reported herein, chlorins **8–11** provide an excellent starting point from which a multitude of PDT probes can be prepared. These compounds have important properties required by photosensitizing agents (*i.e.* intense red absorbances high potential for tumor localization) and they bear sites ready for synthetic modification. The cyano, hydroxy, keto, aceto, and amido functional groups present provide avenues to make many additional photosenzitizers with a multitude of desired properties. Such compounds can be effectively designed and used as PDT probes with the goal of continuing to establish structural requirements for effective photosensitizers.

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Notes and references

† *Crystallographic data* for **9**: dark green plate-like prisms were grown from CH_2Cl_2–hexane ($C_{40}H_{45}N_5NiO$; M = 670.54). The selected crystal (0.25 × 0.25 × 0.15 mm) was monoclinic, space group $P2_1/c$, with cell dimensions a = 13.447(3), b = 20.780(4), c = 13.685(3) Å, β = 113.93(3)°, V = 3495.3(12) Å^3, and Z = 4. Data collection employed $\omega/2\theta$-scans on a CAD-4 computer-controlled diffractometer with a sealed tube source [λ(Cu Kα) = 1.54180 Å] at T = 293(2) K. Diffraction data were collected to 2θ = 150° ($\pm h,-k,\pm l$) affording 13788 total and 7187 unique reflections [R_{int} = 0.041, $T_{\min}$ = 0.77, $T_{\max}$ = 0.85, ρ_{calc} = 1.274 g cm^{-3}, μ = 1.093 mm^{-1}]. The structure was solved by direct methods and refined based on F^2 using all data by full matrix least-squares methods with 439 parameters (Bruker SHELXS-97, SHELXL-97). Hydrogen atom positions were generated by idealized geometry and refined with a riding model. Two ethyl groups were disordered with two sets of positions for each group; disordered atom sites were refined with isotropic thermal parameters. All other non-hydrogen atoms were refined with anisotropic thermal parameters. Final R factors were $R1$ = 0.053 (observed data) and w$R2$ = 0.162 (all data).

‡ *Crystallographic data* for **11**: dark green prisms were grown from CH_2Cl_2–hexane ($C_{40}H_{49}N_5O$; M = 615.84). The selected crystal (0.15 × 0.15 × 0.13 mm) was monoclinic, space group $C2/c$, with cell dimensions a = 19.084(4), b = 27.306(6), c = 15.113(3) Å, β = 116.21(3)°, V = 7066(2) Å^3, and Z = 8. Diffraction data were collected as for **9** ($\pm h,\pm k,-l$). A 2θ cutoff of 130° was applied to the data affording 12208 total and 6021 unique reflections [R_{int} = 0.097, $T_{\min}$ = 0.92, $T_{\max}$ = 0.94, ρ_{calc} = 1.158 g cm^{-3}, μ = 0.543 mm^{-1}]. The structure was solved and refined as for **9** with 436 parameters. All hydrogen atoms bonded to nitrogen were found on a difference map. Peripheral amino hydrogens were refined freely while core porphyrinic hydrogens were refined with a riding model. Core hydrogen positions were found in proximity to each of the 4 porphyrinic nitrogens; their occupancies were summed to 2.000(1) and refined as 4 free-variables with their thermal parameters refined as a single free variable. The remaining hydrogen atom positions were generated by idealized geometry and refined with a riding model. All non-hydrogen atoms were refined with anisotropic thermal parameters. Final R factors were $R1$ = 0.072 (observed data) and w$R2$ = 0.243 (all data).

CCDC 172740 (**9**) and 172741 (**11**). See http://www.rsc.org/suppdata/cc/b2/b202280j/ for crystallographic data in .cif format.

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