Synthesis of a pyridine-fused porphyrinoid: oxopyridochlorin[†]

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The treatment of 3,5-dibenzoylporphyrins with ammonium acetate provided novel oxopyridochlorins as the first examples of pyridine-fused porphyrinoids, which displayed absorption bands reaching into the near IR region and an ability to sensitize singlet oxygen effectively.

The introduction of fused π -conjugated segments into porphyrins is expected to create a variety of conjugated porphyrin systems that could exhibit unique optical and electrochemical properties.¹ This is a reflection of the flexible electronic properties of porphyrins that respond to such perturbations. As an interesting example, the fusion of a benzene ring to the periphery of the 3,4,5-positions of porphyrins causes disruption to the cyclic electronic conjugation of the porphyrin, hence forming benzochlorins that exhibit considerably perturbed optical properties.² Various benzochlorins have been studied as photosensitizers for photodynamic therapy (PDT) owing to their red-shifted absorption bands (670-680 nm), which is favorable for better photoexcitation with light penetrating tissues. More preferably, the pigment should be absorbent in the near infrared region of 750-900 nm, which is called the "therapeutic window" due to the minimum absorbance of biological tissue in this range.

In this Communication, we wish to report the synthesis of novel pyridine-fused porphyrins, oxopyridoporphyrins **3**. This work was motivated by our recent finding that zinc(II) dehydropurpurin **1Zn** was efficiently prepared from *meso*-bromoporphyrin under palladium catalysis, and was converted into 3,5-dibenzoylporphyrin **2Zn** by photochemical oxidative cleavage of the outer C=C double bond.³ Oxopyridoporphyrins **3** are, to the best of our knowledge, the first examples of pyridine-fused porphyrins. Interestingly, oxopyridochlorins **3** exhibit absorption bands in the therapeutic window that are further red-shifted upon protonation.

The treatment of 3,5-dibenzoylporphyrin 2Zn with ammonium acetate at 130 °C in toluene/AcOH for 2 d furnished oxopyridochlorin 3Zn in 60% yield (Scheme 1). The parent

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mass ion peak of **3Zn** was observed at m/z = 1142.5698 (calc. for $C_{76}H_{80}N_5OZn = 1142.5649 [M + H]^+$ in its high resolution electrospray ionization time-of-flight mass spectrum. The ¹³C NMR spectrum displayed a distinct signal at 191.17 ppm, indicating the presence of a carbonyl group. The ¹H NMR spectrum exhibited six doublet signals due to the six pyrrolic β -protons. Compared with other non-fused porphyrins, such as 2Zn, these outer β -protons appear in a substantially upfield-shifted region between 7.99 and 7.47 ppm. This finding indicates weak aromaticity in 3Zn, because the fused pyridine moiety tends to retain its local aromaticity. Such decreased ring currents in porphyrinic macrocycles have also been observed in the ¹H NMR spectra of benzochlorins.³ In a similar manner, Ni-pyridochlorin and the free base, 3Ni and **3H**, were also synthesized in 65 and 40% yield, respectively. The inner NH protons of 3H were observed in a particularly down-field region at 7.34 and 7.08 ppm, again indicating a weakened diatropic ring current.

Final structural elucidation was accomplished by single crystal X-ray diffraction analyses,‡ which showed the presence of pyridine and carbonyl moieties in **3Zn**, **3H** and **3Ni** (Fig. 1). While **3Zn** and **3H** display relatively planar structures characterized by mean-plane deviations of 0.145 and 0.099 Å, **3Ni** shows a more distorted saddle-like structure with a mean-plane deviation of 0.412 Å. The dihedral angles of the phenyl substituents with respect to the pyridine moiety are 38.6 and 31.6° for **3Ni**, which are smaller than those of **3Zn**



Scheme 1 The synthesis of oxopyridochlorins 3Zn, 3H and 3Ni. Reaction conditions: (a) air, light; (b) HCl; (c) Ni(acac)₂; (d) NH₄OAc, toluene/AcOH, 130 °C, 2 d.; (e) NaBH₄, CH₂Cl₂/MeOH; (f) air.

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Fig. 1 X-Ray crystal structures of oxopyridochlorin. Top and side views of (a) **3Zn**, (b) **3Ni**, and (c) **3H**. 3,5-Di-*tert*-butyl groups and hydrogen atoms are omitted for clarity.

(60.8 and 45.5 or 58.1°; one phenyl group is slightly disordered) and **3H** (60.2 and 39.0°), suggesting that the distorted structure of **3Ni** leads to the mitigation of steric hindrance among the peripheral groups. In addition, a distinct bond length alternation is observed among C–C and C–N bonds in the X-ray crystal structures of **3Zn**, **3H** and **3Ni**, in line with the observed weakened aromaticity.

A plausible mechanism for the formation of 3 is shown in Scheme 2. Cyclization of a dihydropyridine moiety, A, followed by the elimination of water, gives cationic species B, and the subsequent nucleophilic attack of water furnishes pyridine moiety C. Finally, aerobic oxidation of the hydroxyl



Scheme 2 A plausible mechanism for the formation of oxopyridochlorins.

group occurs to form an oxopyridoporphyrin. A similar spontaneous oxidation has been reported for a benzochlorin.^{2g} In our case, **3Zn** can be reduced with NaBH₄ quantitatively to afford **4Zn**, which is oxidized back to **3Zn** upon standing in the air for 4–5 h.

Fig. 2(a) shows the UV/vis absorption spectra of **2Zn**, **3Zn**, **3H** and **3Ni** measured in CH₂Cl₂. While the absorption spectrum of **2Zn** has the typical features of porphyrins, involving a sharp Soret band at 433 nm, and Q-bands at 558 and 599 nm, those of oxopyridochlorins are strikingly altered. The metal complexes **3Zn** and **3Ni** exhibit split Soret bands at 403 and 477 nm, 405 and 480 nm, and structured Q-bands at 753 and 767 nm, respectively. Free base **3H** shows a narrowly split Soret band at 414 and 448 nm, and differently structured Q-bands at 690 and 785 nm. Interestingly, the absorption spectra of our oxopyridoporphyrins cover over 800 nm, deeply entering the therapeutic window. The absorption spectrum of **4Zn** shows a Soret band at 449 nm, and Q-bands at 638 and 696 nm, which indicates the importance of the carbonyl group in the red-shifted absorption spectra of **3**.

Since pyridochlorins **3** bear an external basic nitrogen site, protonation at this site would be expected to change their electronic structure. To investigate this possibility, we examined the effects of protonation on the absorption spectrum of **3Ni** with acids, including TFA, aqueous HCl and methanesulfonic acid (MSA). As shown in Fig. 2(b), protonation caused changes in the intensities of the split Soret band and a distinct red shift of the Q-bands.

The electrochemical properties of our oxopyridochlorins were also examined by cyclic voltammetry $(0.1 \text{ M Bu}_4\text{NPF}_6 \text{ as})$



Fig. 2 (a) The UV/vis absorption spectra of 2Zn (red), 3Zn (blue), 3H (violet) and 3Ni (green) in CH₂Cl₂. (b) Changes in the UV/vis absorption spectra of 3Ni in CH₂Cl₂ with no acid (red), TFA (blue), HCl (green) and MSA (violet).

the electrolyte, glassy carbon and Ag/AgClO₄ as the working and reference electrodes, respectively, relative to internal ferrocene/ferrocenium, in CH₂Cl₂). One-electron oxidation and reduction waves were observed at 0.43 and -1.55 V for **2Zn**, and 0.36 and -1.21 V for **3Zn**, which leads to estimations of the HOMO–LUMO gap as 1.98 and 1.57 eV, respectively, in accordance with their absorption spectra. Similar measurements revealed the one-electron oxidation and reduction potentials of **3Ni** as being 0.51 and -1.18 V.

Finally, the ability to sensitize the generation of singlet oxygen was examined by means of the photooxidation of 1,3-diphenylisobenzofuran (DPBF)⁴ using a xenon lump equipped with a light filter (>490 nm). Photoirradiation of a toluene solution of **3Zn** or **3H** containing DPBF caused clear absorption spectral changes associated with DPBF oxidation, which were monitored by the absorbance changes at 416 nm. Oxopyridochlorins **3Zn** and **3H** were found to be considerably robust under these irradiation conditions. The quantum yields of singlet oxygen formation for **3Zn** and **3H** in toluene were determined to be 0.79 and 0.52, respectively, compared to a reference value (0.73) for tetraphenylporphyrin (TPP).⁵

In summary, oxopyridochlorins, new pyridine-fused porphyrins, have been synthesized efficiently from dibenzoylporphyrins. These oxopyridochlorins displayed weakened diatropic ring currents as a consequence of their fused pyridine moiety, as well as their absorption spectra tailing in the near infrared region, entering significantly the therapeutic window. Interestingly, protonation of the nitrogen atom in the fused pyridine ring causes substantial changes in their UV/vis absorption spectra, thus underscoring the effectiveness of the peripheral and conjugated coordination site for controlling the whole porphyrinic π -system by external stimuli. The use of these pigments for photodynamic therapy is encouraged because of their abilities to sensitize the generation of singlet oxygen, despite their low-lying excited states. Moreover, the red-shift observed in the presence of a Brønsted acid is very interesting for photodynamic therapy applications, since it is well known that solid tumors develop regions of acidic interstitial pH.

Notes and references

‡ Crystal data for **3Zn**·2(methanol): C₇₈H₈₇N₅O₃Zn, M = 1207.90, triclinic, space group *P*-1 (no. 2), a = 10.549(15), b = 16.88(3), c = 20.16(3) Å, $\alpha = 87.34(6)$, $\beta = 85.64(6)$, $\gamma = 74.93(6)^\circ$, V = 3455(9) Å³, T = 123(2) K, Z = 2, $D_c = 1.161$ g cm⁻³, $R_1 = 0.0675$ for 11 672 observed reflections with [$I > 2\sigma(I)$] and w $R_2 = 0.2001$ for all 14 994 unique reflections, GOF = 1.050. CCDC 707383.†

Crystal data for **3H**·(methanol): $C_{77}H_{85}N_5O_2$, M = 1112.50, monoclinic, space group $P_{2_1/c}$ (no. 14), a = 19.251(5), b = 20.011(6), c = 18.977(7) Å, $\alpha = 90$, $\beta = 111.030(11)$, $\gamma = 90^{\circ}$, V = 6824(4) Å³, T = 123(2) K, Z = 4, $D_c = 1.124$ g cm⁻³, $R_1 = 0.0952$ for 11 302 observed reflections with $[I > 2\sigma(I)]$ and $wR_2 = 0.3085$ for all 48 936 unique reflections, GOF = 1.034. Some unassigned electron density due to severely disordered solvent was removed using the utility SQUEEZE in the PLATON software package.⁶ CCDC 707381.[†]

Crystal data for **3Ni**-3(dichloroethane): $C_{82}H_{91}Cl_6N_5NiO$, M = 1434.01, triclinic, space group *P*-1 (no .2), a = 14.341(5), b = 15.957(6), c = 17.625(5) Å, $\alpha = 73.134(11)$, $\beta = 82.737(12)$, $\gamma = 69.420(11)^{\circ}$, V = 3864(2) Å³, T = 123(2) K, Z = 2, $D_c = 1.232$ g cm⁻³, $R_1 = 0.0941$ for 13165 observed reflections with $[I > 2\sigma(I)]$ and $wR_2 = 0.2782$ for all 29611 unique reflections, GOF = 1.048. CCDC 707382.†

For 3Zn and 3Ni, some disorder features were found in certain substituents and solvent molecules, and appropriately restrained (see ESI†).

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