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Aromatic and Nonaromatic Pyriporphyrins†

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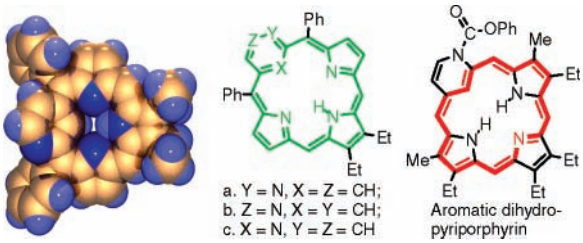
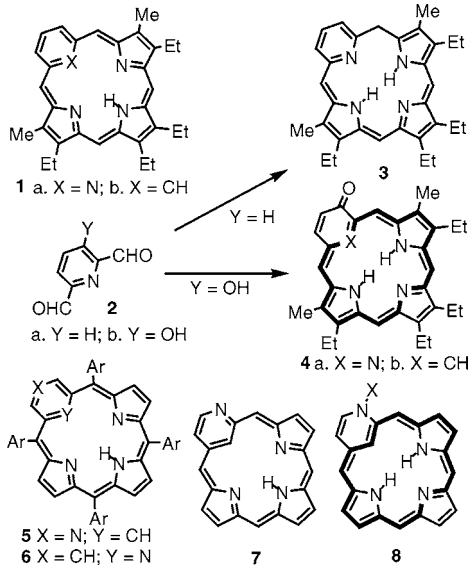
ABSTRACT



Pyriporphyrins with three different orientations for the pyridine moiety have been prepared using a '3 + 1' strategy. The nonaromatic pyriporphyrins are stable so long as phenyl substituents are present at the *meso*-positions adjacent to the pyridine ring. An aromatic dihydropyriporphyrin with an external CO_2Ph protective group has also been prepared from 2,4-pyridinedicarbaldehyde.

Pyridine analogues of the phthalocyanines were first described by Linstead in the 1950s,[1] but the porphyrin analogue "pyriporphyrin" **1a** eluded synthesis until very recently.[2−5] Reaction of 2,6-pyridinedicarbaldehyde with a tripyrrane in the presence of an acid catalyst was reported to give a labile dihydropyriporphyrin, but oxidation with DDQ or chloranil gave unstable oxophlorins or dimers instead of **1a** (Scheme 1).[2] In contrast, isophthalaldehyde reacted with tripyrranes under the same type of '3 + 1' conditions to give benziporphyrin **1b**,[6,7] while related hydroxydialdehydes gave excellent yields of the aromatic porphyrinoids **2a** and **2b**.[4,8] The '3 + 1' methodology[9] has been used to prepare many related macrocycles including azuliporphyrins[10] and benzocarbaporphyrins.[11] In recent studies, syntheses of tetraarylpyriporphyrins **5** and **6** were reported,[5,12] and the metalation

Scheme 1. Pyriporphyrins



of these systems has been investigated.[13] Although one-pot syntheses of tetraarylazuliporphyrins[14] and benziporphyrins[15] have been developed, these procedures could not be used in the synthesis of pyriporphyrins due to the poor reactivity

† Part 43 in the series Conjugated Macrocycles Related to the Porphyrins.

(1) Linstead, R. P. *J. Chem. Soc.* **1953**, 2873.
(2) Berlin, K.; Breitmaier, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 219.
(3) For the synthesis of related macrocycles, see: (a) Callot, H. J.; Schaeffer, E. *Tetrahedron* **1978**, *34*, 2295. (b) Carré, F. H.; Corriu, J. P.; Bolin, G.; Moreau J. J. E.; Vernhet, C. *Organometallics* **1993**, *12*, 2478. (c) Adams, K. R.; Bonnett, R.; Burke, P. J.; Salgado, A.; Vallés, M. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1769. (d) Liu, D.; Ferrence, G. M.; Lash, T. D. *J. Org. Chem.* **2004**, *69*, 6079. (e) Sim, E.-K.; Jeong, S.-D.; Yoon, D.-Hong, W. S.-J.; Kang, Y.; Lee, C.-H. *Org. Lett.* **2006**, *8*, 3355.
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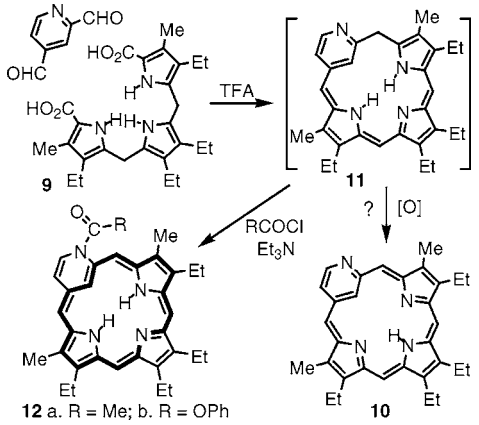
characteristics of the electron-deficient pyridine precursors.[5] Instead, multistep procedures were required to prepare macrocycles such as **5** and **6**.[5,12]

In our studies, we were particularly interested in the N-confused pyriporphyrin system **7**, which has not been investigated previously. This system could potentially form aromatic dihydropyriporphyrin derivatives **8** with chromophores similar to oxybenziporphyrin **4b**.[8] In addition, the presence of external nitrogen atoms may facilitate the formation of multicomponent molecular systems. In order to assess the possibility of synthesizing N-confused pyriporphyrins, tripyrrane **9** was reacted with 2,4-pyridinedicarbaldehyde[16] in the presence of trifluoroacetic acid using the '3 + 1' variant of the MacDonald condensation (Scheme 2).[9] The reaction solutions rapidly turned a dark green color

Scheme 2



that was consistent with macrocycle formation. However, attempts to oxidize the intermediate to **10** with DDQ or $FeCl_3$ gave complex mixtures, and column chromatography afforded a series of green bands that yielded no stable products. A dihydropyriporphyrin such as **11** is likely to be formed in the initial condensation reaction, but this species and its oxidation products appear to be highly unstable. However, no oxidation would be required if the aromatic tautomer of **11** could be trapped out as an acyl derivative **12**. This reaction was attempted by adding acetic anhydride and triethylamine. Small amounts of Ac_2O were not effective, but when a large excess of the reagent was used (>2 mL for 100 mg of **9**), a porphyrin-like product could be detected. However, attempts to acylate the crude reaction mixture with other reagents such as acetyl chloride, pivaloyl chloride, or benzoyl chloride failed to give more than trace amounts of the corresponding acyl derivatives. The crude Ac_2O-derived product showed a strong diatropic ring current with a CH resonance at −6 ppm and a strong Soret-type band at 426 nm in its UV−vis absorption spectrum. High-resolution EI mass spectrometry also gave a molecular ion at *m*/*z* 506.3050, which corresponded to the expected molecular formula for $C_{33}H_{38}N_4O$ (calculated mass 506.3046). Unfortunately, **12a** proved to be rather unstable and could not be fully purified. Phenyl chloroformate has been reported to be a superior reagent for derivatizing dihydropyridines[17] and for this reason was selected as an alternative reagent for stabilizing the porphyrinoid system. Reaction of the crude intermediate with a large excess of PhOCOCl and Et_3N generated the carbamate derivative **12b** as a major reaction product. Following chromatography on silica and recrystallization from chloroform−hexanes, the porphyrin analogue was obtained as dark purple crystals in 36% yield. The UV−vis spectrum for **12b** showed a Soret band at 420 nm and a series of Q-bands extending to 709 nm (Figure 1). Addition of TFA gave a

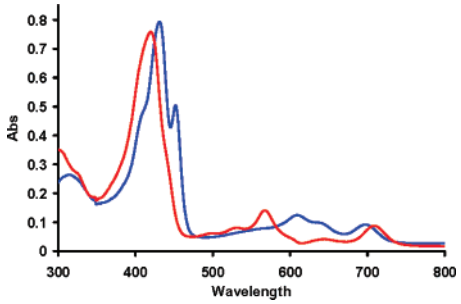


Figure 1. UV−vis spectra of pyriporphyrin **12b** in 1% Et_3N−$CHCl_3$ (red line) and trace TFA−$CHCl_3$ (blue line).

related cation **12b**H^+ that retained a porphyrin-like UV−vis spectrum with a Soret band at 431 nm. The proton NMR spectrum of **12b** in $CDCl_3$ confirmed that this system has highly diatropic characteristics, showing the internal CH upfield at −6.6 ppm and the external *meso*-protons as four 1H singlets in the downfield region between 8.5 and 9.6 ppm (Figure 2). Carbon-13 NMR and HRMS further confirmed the identity of this novel aromatic porphyrinoid structure.

The synthesis of pyriporphyrins presents a challenge not only due to the electron-withdrawing nature of the pyridine unit and the basicity of the nitrogen, which can also potentially interfere with macrocycle formation, but also because of their limited stability. The undesired reactivity of pyriporphyrins appears to be associated with the *meso*-carbons surrounding the pyridine unit, and *meso*-aryl substituents can

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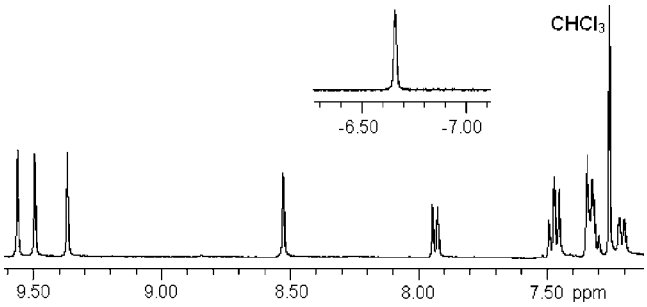
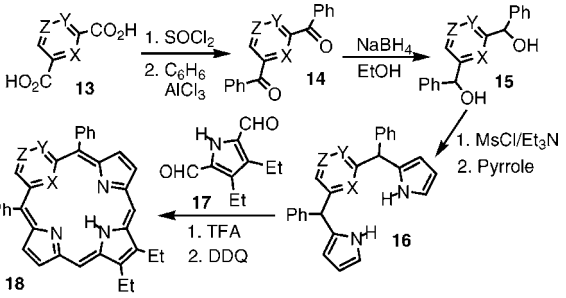


Figure 2. Partial 400 MHz ^{1}H NMR spectrum of pyriporphyrin **12b** in $CDCl_3$ showing the upfield and downfield regions.

protect these porphyrinoids from degradation processes. Although this consideration was beneficial in the synthesis of pyriporphyrins **5** and **6**,[5,12] those studies generated the required tripyrrane-type precursors from relatively expensive dibromopyridines. This approach also necessitated the use of very low-temperature metal−halogen exchange reactions.[12] The synthesis of **6** was particularly inefficient, requiring several additional steps, and the final ring closure step only occurred in 5.5% yield.[5] In our investigations, we have developed far more efficient syntheses of three isomeric nonaromatic pyriporphyrins starting with readily available pyridine dicarboxylic acids **13**. Treatment of **13** with excess thionyl chloride and catalytic DMF afforded the corresponding diacyl chlorides, and these reacted with benzene under Friedel−Crafts acylation conditions to give the corresponding diketones **14** in >70% yield. These were easily reduced with sodium borohydride in ethanol to give virtually quantitative yields of the corresponding dicarbinols **15**. At this stage, it was necessary to generate a tripyrrane-type intermediate **16**. Reaction of **15** or the corresponding acetate derivatives with pyrrole gave no reaction. However, Mysliborski and Latos-Grazynski had found that mesylate derivatives could be used to conduct this type of chemistry.[12] Reaction of **15a**−**c** with methane sulfonyl chloride and triethylamine at 0 °C, followed by condensation with 100 equiv of pyrrole at room temperature, gave the tripyrranes **16** in 23−43% yield. Although dialcohols **15a**−**c** and tripyrranes **16a**−**c** were obtained as mixtures of diastereomers, this was of little significance in these studies because the stereochemistry is lost in the subsequent chemistry.

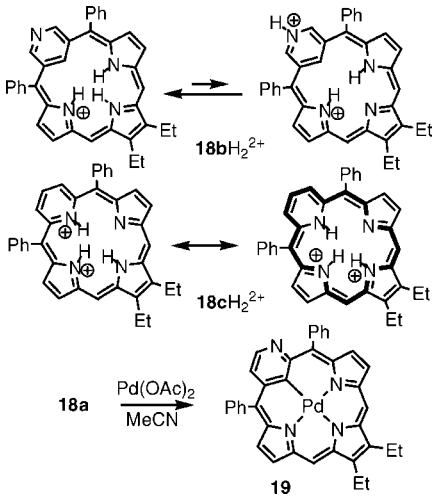
meso-Aryl tripyrranes often give poor yields in porphyrin syntheses because they can undergo fragmentation processes under acid-catalyzed conditions.[18] This can be overcome using mesityl groups that sterically hinder these side reactions.[5,19] However, in this case, the pyridine unit provides stabilization due to its electron-deficient characteristics, and this beneficial property is enhanced under acidic conditions due to protonation of the basic nitrogen atom. For this reason, we anticipated that these tripyrrane analogues could be used in '3 + 1' MacDonald-type reactions with readily available pyrrole dialdehydes.[20] In addition, the absence of substituents at the other two *meso*-positions was considered to not be crucial for stabilizing the pyriporphyrin systems. Hence, pyritripyrranes **16** were reacted with dialdehyde **17** in the presence of TFA in CH_2Cl_2 and oxidized with DDQ. Following workup, column chromatography on grade 3 basic alumina, and recrystallization, the three isomeric pyriporphyrins **18a**−**c** were isolated in 22−42% yield. N-Confused pyriporphyrins **18a** and **18b** showed no indication of a diatropic ring current, and the UV−vis spectra were similar to the spectrum reported for benziporphyrin **4a**. The proton NMR spectrum for **18a** showed the *meso*-protons at 5.84 and 5.88 ppm, while the more symmetrical isomer **18b** gave a 2H singlet at 6.32 ppm. The internal CH for **18a** gave a resonance at 8.98 ppm compared to 7.94 ppm for **18b**. Although there are minor differences, these results are not consistent with the presence of any macrocyclic ring currents. Addition of TFA afforded the related dications. Although external protonation on the pyridine nitrogen is possible, the proton NMR spectra indicate that internal protonation is favored for these compounds, as illustrated for **18b**H_2^{2+} in Scheme 4.[12]

Scheme 3



The molecular structure of **18a** was confirmed by X-ray crystallographic analysis (Figure 3). Difference Fourier maps clearly indicated the presence of electron density consistent with hydrogen atoms attached to the C(22) and N(24) atoms. The macrocycle adopts a saddled geometry with the 2-aza-benzi moiety tilted 30.7(1)° out of the N(23), N(24), N(25)

Scheme 4. Protonation and Metalation Reactions



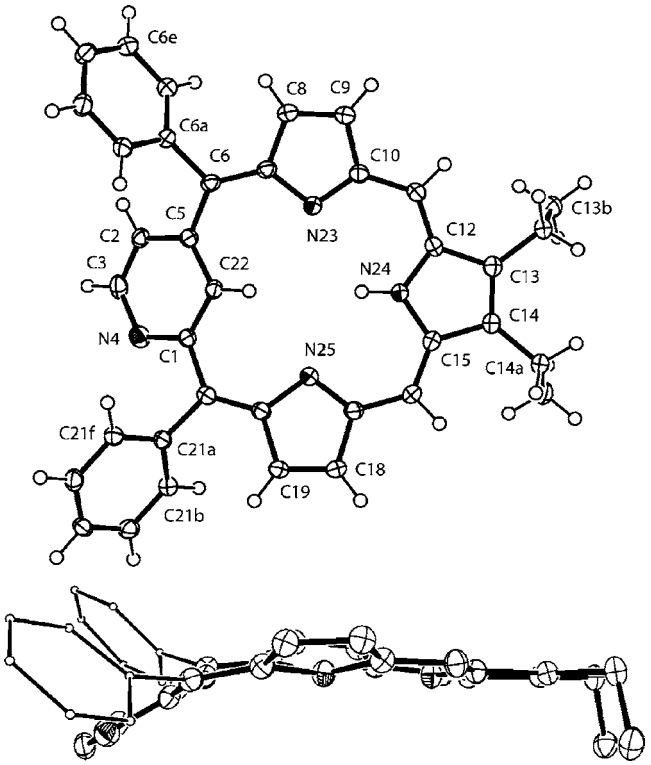


Figure 3. ORTEP III drawing (50% probability level, hydrogen atoms drawn arbitrarily small) of compound **18a** viewed (a) normal to and (b) edge on with the core N,N,N plane. Selected bond lengths (Å): C(1)−N(2) 1.367(2), N(2)−C(3) 1.345(2), C(3)−C(4) 1.376(2), C(4)−C(5) 1.384(2), C(5)−C(22) 1.398(2), C(22)−C(1) 1.397(2), C(5)−C(6) 1.479(2), C(1)−C(21) 1.479(2). Selected bond angles (deg): C(1)−N(2)−C(3) 117.2(2); N(2)−C(3)−C(4) 124.0(2), C(3)−C(4)−C(5) 119.1(2), C(4)−C(5)−C(22) 118.5(2), C(5)−C(22)−C(1) 119.3(2), C(22)−C(1)−N(2) 121.9(2).

plane. Close examination of the structure indicates this striking feature is attributable to contact between the 6 and 21 phenyl *ipso*-carbon atoms and the adjacent respective hydrogen atom attached to C(4) and N(2) lone pair of electrons. It is expected that such steric constraints are likely to prevent methylation and could even inhibit protonation of the 2-azabenzi nitrogen atom. The pyridine subunit possesses bond lengths and angles typical for an isolated pyridine π-system. The C(1)−C(21) and C(5)−C(6) distances, C(6) distances, both 1.479(2) Å, are typical for single-bond C(sp^2)−C(sp^2) interactions. These structural features corroborate that the pyridine ring retains unperturbed aromaticity and is electronically isolated from the macrocycle.

The free base form of pyriporphyrin **18c** also appears to be nonaromatic, and the proton NMR spectrum in $CDCl_3$ shows the *meso*-protons at 6.28, the pyridine protons at 7.94 (1H, t) and 8.14 (2H, d), and the internal NH at 10.0 ppm. However, in this case, addition of 1 drop of TFA showed a significant effect that was consistent with the resulting dication **18c**H_2^{2+} taking on aromatic character (Scheme 4). The *meso*-protons shift downfield to 7.61, while the internal NHs gave broad resonances at 6.1 (1H) and 9.6 ppm (2H). Although dications will give some deshielding, these shifts can only be explained by the presence of a weak diatropic ring current. Further support for this interpretation comes from the CH_2 resonances of the ethyl substituents, which shift downfield by 0.3 ppm on addition of acid, while virtually no shift occurs for these peaks in the NMR spectra of **18a** and **18b**. If one of the protonations for **18c**H_2^{2+} occurs on the pyridine nitrogen, this species can have a resonance contributor with an 18π-electron delocalization pathway that aids in charge delocalization (Scheme 4). Interestingly, pyriporphyrin **6** has been shown to have similar properties for the monoprotonated form but not for the dication.[5] Pyriporphyrin **18c** does show the formation of an intermediary monocation by UV−vis spectroscopy, but careful titration of TFA into an NMR tube only gave complex poorly resolved spectra until the dication had been fully generated.

Pyriporphyrins **18a** and **18b** have a carbaporphyrinoid core that may facilitate the formation of organometallic deriv atives.[21] In a preliminary study, **18a** was reacted with $Pd(OAc)_2$ in refluxing acetonitrile for 10 min. A nonpolar palladium complex was isolated by column chromatography, and following recrystallization from chloroform−hexanes, **19** was isolated in 57% yield. Hence, the new substitution pattern present in pyriporphyrins **18** appears to be compatible with metalation chemistry. Pd(II) complex **19** is nonaromatic but can be protonated with TFA on the external nitrogen to give a monocation, indicating that the *meso*-phenyl groups do not prevent protonation from occurring.

In conclusion, efficient syntheses of pyriporphyrins have been developed starting from pyridine dicarboxylic acids, and these show promise in formation of organometallic derivatives and supramolecular assemblies. This chemistry may also be applicable to the synthesis of other porphyrin analogue systems with other electron-deficient subunits. In addition, a dihydropyriporphyrin was trapped as a fully aromatic species that resembles carbaporphyrinoid systems such as oxybenziporphyrin.

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Supporting Information Available: Details of the X-ray crystallographic analysis, selected experimental procedures, and UV−vis, ^{1}H NMR, and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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