Adding to the confusion! Synthesis and metalation of pyrazole analogues of the porphyrins†

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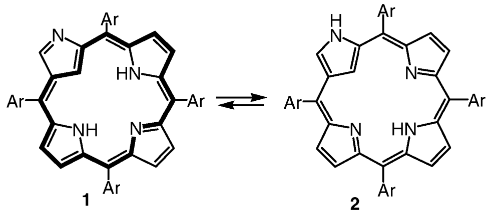
N-substituted pyrazole dialdehydes are shown to react with a tripyrrane under '3 + 1' conditions to give aza-analogues of the N-confused porphyrins; these novel porphyrinoids show borderline aromatic properties and readily afford organometallic derivatives with Ni(OAc)$_2$ and Pd(OAc)$_2$.

N-confused porphyrins (NCPs) were first isolated in 1994 as by-products in Rothemund-type syntheses of *meso*-tetraarylporphyrins.[1–3] This system, which contains an inverted pyrrole subunit, was at the time only the second example of a porphyrin isomer, and showed important characteristics that immediately attracted the interests of porphyrin chemists.[4,5] These properties included long wavelength absorptions that could lead to applications in photodynamic therapy, and the ability to generate organometallic derivatives.[5,6] Not only can NCPs act as dianionic and trianionic ligands, but they also afford coordination complexes at the external nitrogen that allow the formation of supramolecular systems.[6,7] NCPs are commonly isolated as the fully conjugated tautomer **1**, but this species is only slightly more stable than the less aromatic cross-conjugated form **2** which is favored in polar aprotic solvents.[8] NCPs also exhibit unusual reactivity and can allow the confused pyrrole ring to rotate to form N-fused porphyrins.[6] Given the intensity with which NCPs have been investigated, it is somewhat surprising that pyrazole analogues that extend the "confused" aspect of these porphyrinoid macrocycles have not been reported previously. In this communication, we report the first examples of porphyrin analogues of this type, and the formation of stable organometallic derivatives.

Syntheses of pyrazole-containing expanded porphyrins have been conducted previously, but these studies only gave partially conjugated macrocycles.[9,10] Recently, Brückner and coworkers synthesized Schiff's base complexes **3** that incorporate the pyrazole moiety.[10] Although this important new study has provided an anionic binding system that resembles the texaphyrins, attempts to synthesize fully conjugated macrocycles of this type have so far been unsuccessful. In our studies, we have made extensive use of a '3 + 1' variant on the MacDonald condensation, where an aromatic dialdehyde is condensed with a tripyrrane to afford structurally diverse analogues of the porphyrins.[11–13] This methodology has allowed the synthesis of carbaporphyrins and related systems, and has been applied by others to the synthesis of triazole-containing porphyrin analogues **4a**.[14,15] In addition, an alternative strategy has allowed the synthesis of imidazole analogues **4b**.[16] Pyrazoledialdehyde **5a** was previously investigated as a potential precursor to a pyrazole containing porphyrin analogue, but failed to give any isolatable porphyrinoid products.[17] As the presence of substituents often aids in the generation of macrocyclic products, we speculated that N-substituted pyrazoledialdehydes might allow the synthesis of pyrazole-containing porphyrinoids. 1-Phenyl-3,5-pyrazole-dicarbaldehyde (**5b**) was condensed with tripyrrane dicarboxylic acid (**6**) in the presence of 1% TFA in dichloromethane for 16 h (Scheme 1). In this method, an oxidation step is required to generate the fully conjugated product. However, attempts to oxidize the crude product with DDQ led to complete decomposition. In related work, we have found that dilute aqueous solutions of ferric chloride can be used as a mild oxidant[3b,18] and may give superior yields of conjugated porphyrinoid macrocycles. This transformation is usually carried out by vigorously shaking the reaction solution in a separatory funnel with 0.1% aqueous FeCl$_3$. Prolonged shaking (*ca.* 10 min) again gave only decomposition, but shorter exposure times failed to oxidize the intermediate. Extraction and column chromatography on grade 3 basic alumina, eluting with CH$_2$Cl$_2$, gave a blue fraction that corresponded to the phlorin analogue **7a**. This species was reasonably stable and could be recrystallized from chloroform-methanol to give the macrocyclic product in 40% yield. The reaction was repeated with *N*-methylpyrazoledialdehyde **5c**, and prior to oxidation an unstable phlorin product **7b** could be observed by proton NMR spectroscopy. However, in this case oxidation with 0.2% ferric chloride solution for 7–8 min, and column



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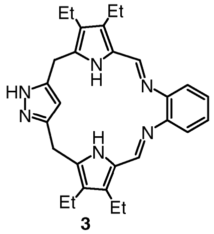

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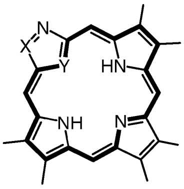

4a X = Y = N
4b X = CH; Y = N

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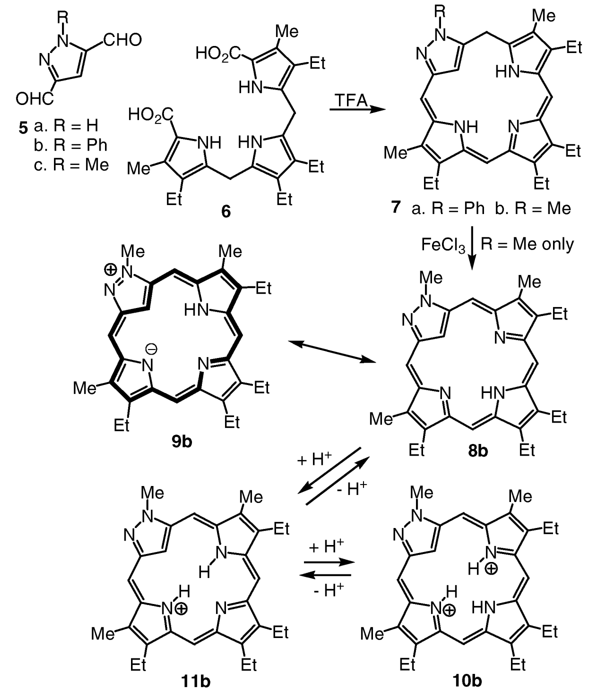


Scheme 1 Synthesis and protonation of 3-azaNCPs.

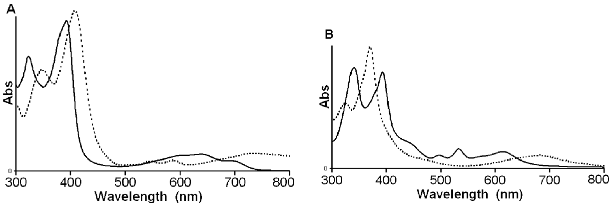


Fig. 1 (A) UV-vis spectra of **8b** in 1% Et_3N–$CHCl_3$ (bold line; free base) and 1% TFA–$CHCl_3$ (dotted line; dication **10b**). (B) UV-vis spectra of nickel(II) complex **12b** in $CHCl_3$ (bold line) and 5% TFA–$CHCl_3$ (dotted line; cation **15b**).

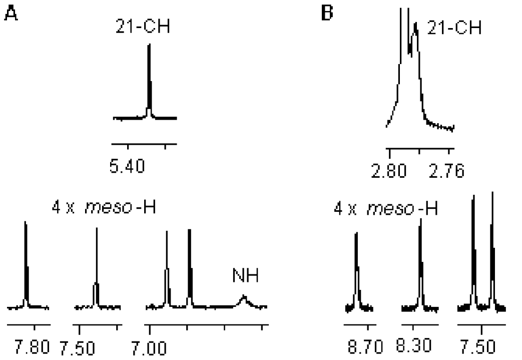
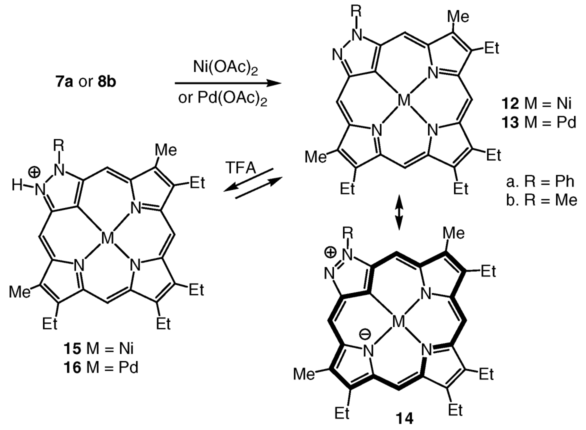


Fig. 2 400 MHz proton NMR spectra of pyrazole-porphyrin analogue **8b**. (A) Downfield region in $CDCl_3$. (B) Partial NMR spectrum of dication **10b** in TFA–$CDCl_3$ showing downfield shifts of the *meso*-protons and a pronounced upfield shift of the 21-CH resonance.

chromatography on grade 3 basic alumina, gave the fully conjugated pyrazole-containing porphyrin analogue **8b** in 21% yield. The UV-vis absorption spectrum for **8b** (Fig. 1A) shows a Soret-like band at 393 nm and broad absorptions through the visible region. Titration with TFA gave complex results that showed the presence of several species but in excess TFA a stronger Soret band could be observed at 408 nm. The proton NMR spectrum of **8b** in $CDCl_3$ was also insightful showing a series of 1H singlets for the *meso*-protons at 6.89, 6.95, 7.45 and 7.82 ppm (Fig. 2A). These values are nowhere near as far downfield as those seen for true porphyrins (*ca.* 10 ppm), but the shifts are consistent with a system that has a degree of diatropic character. This interpretation is reinforced by the presence of a relatively upfield NH resonance at 6.75 ppm and the presence of a 1H singlet for the internal CH at 5.34 ppm. The aliphatic region shows the methyl resonances at 2.5 ppm slightly downfield from values seen for nonaromatic porphyrinoids but again much less deshielded than the values for fully aromatic porphyrinoid systems (*ca.* 3.5 ppm).[19] The aromatic character of **8b** is attributed to dipolar canonical form **9b**, although this contributor is not very favored due to the requirement for charge separation and the placement of a positive charge next to a nitrogen atom. Addition of a drop of TFA gave the diprotonated species **10b** where the *meso*-protons were shifted downfield to values between 7.4 and 8.8 ppm (Fig. 2B). The resonances for the two methyl groups were also shifted downfield to approx. 2.8 ppm. Although these shifts might be attributable in part to the positive charges, these results suggest that the dication has significantly increased diatropic characteristics compared to the free base and the presence of a 1H singlet for the internal CH at 2.77–2.79 ppm confirms the presence of a diatropic ring current. The increased diatropicity is due to the greater favorability of resonance forms like **8b** that now aid in charge delocalization. Addition of trace amounts of TFA (1–2 eq.) gave poor quality spectra but a species could be observed where the *meso*-protons were shifted downfield to 7.8–9.1 ppm and the internal CH gave a signal at 0.3 ppm. This observation is consistent with the formation of a monoprotonated species **11b** with a slightly increased diatropic ring current.

The 2-phenylphlorin analogue **7a** and the 2-methyl-3-azaNCP **8b** both reacted with nickel(II) acetate in refluxing DMF to give the fully conjugated nickel(II) derivatives **12** in 43–45% yield (Scheme 2). Similarly, **7a** and **8b** reacted with palladium(II) acetate in refluxing acetonitrile to give the corresponding palladium(II) organometallic complexes **13** in 59–61%. The Ni(II) complexes gave green colored solutions that produced very different UV-vis spectra from the red-brown solutions of the Pd(II) derivatives. Addition of TFA to these solutions gave rise to protonated species with simplified UV-vis absorptions. The proton NMR data for the Pd(II) and Ni(II) derivatives of both the phenyl and methyl series showed similar downfield shifts for the external protons and the *meso*-resonances were observed between 7.38 and 8.02 ppm. Nevertheless, these stable derivatives show significant downfield shifts compared to the parent porphyrinoid **8b**, again derived in part from a dipolar resonance contributors **14**. Addition of TFA to the NMR solution led to the formation of protonated species **15** and **16** that showed no sign of macrocyclic aromaticity. The *meso*-proton resonances in the nickel series **15** showed up at 6.4–6.9 ppm, while the protonated palladium complexes **16** showed these resonances further upfield at



Scheme 2 Metalation of pyrazole-containing NCP analogues.

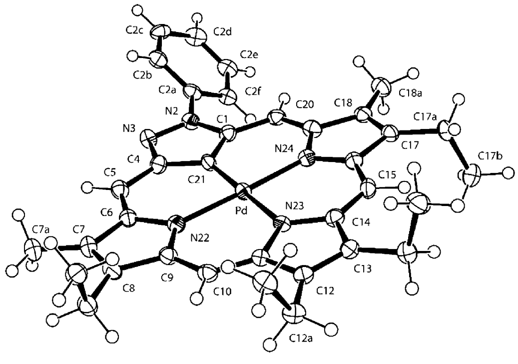


Fig. 3 ORTEP III drawing (50% probability level, hydrogen atoms drawn arbitrarily small) of compound **13a**. Selected bond lengths (Å): C(1)–N(2) 1.384(6), N(2)–N(3) 1.344(5), N(3)–C(4) 1.377(6), C(4)–C(21) 1.405(6), C(21)–C(1) 1.383(6), Pd–C(21) 1.946(5), Pd–N(22) 2.018(4), Pd–N(23) 2.038(4), Pd–N(24) 2.011(4). Selected bond angles (°): C(1)–N(2)–N(3) 111.5(4), N(2)–N(3)–C(4) 104.3(4), N(3)–C(4)–C(21) 112.3(4), C(4)–C(21)–C(1) 103.7(4), C(21)–C(1)–N(2) 108.2(4), C(21)–Pd–N(22) 88.9(2), C(21)–Pd–N(23) 179.9 (2), C(21)–Pd–N(24) 89.4(2), N(22)–Pd–N(24) 178.1(2).

6.18–6.63 ppm. The associated shifts to the substituents were consistent with the formation of a nonaromatic species and the pyrrolic methyls shifted upfield by 0.4–0.6 ppm. These results are to be expected if the aromatic characteristics of the nonprotonated metallo-derivatives derive from the electron-donating pyrazole (*i.e.*, from contributors **14**) because the protonated species would have to place two positive charges directly next to one another if this type of interaction still played a role.

The X-ray crystal structure of palladium complex **13b** has also been obtained (Fig. 3),‡ and this not only confirms the presence of a "confused" pyrazole but also demonstrates that the macrocycle is quite planar as evidenced by the 0.073 Å rms distance the framework atoms lie from the plane defined by C(21), N(22), N(23), and N(24). In fact, only N(3) (0.1541 Å), C5 (0.1715 Å), and C7 (0.1787 Å) deviate more than 0.15 Å and 18 of the 25 framework atoms deviate less than 0.03 Å from this plane. The structure exhibits framework bond distances consistent with a generally localized π-bonding model, so the planarity is primarily dictated by constraints of palladium atom binding, namely the Pd(II) size, square-planar coordination, and optimal Pd–N and Pd–C bond lengths. The metal coordination environment of **13a** is quite similar to a previously characterized palladium(II) azuliporphyrin, although the 1.946(5) Å Pd–C distance is slightly shorter than the 1.980(3) Å value for the earlier example.[20]

In conclusion, the first fully conjugated porphyrinoid systems with pyrazole subunits have been synthesized and the nature of the N-substituent has been shown to be crucial for the stabilization of this species. In addition, these diazacarbaporphyrinoids readily form stable organometallic derivatives and in this respect parallel the properties of the N-confused porphyrins.

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Notes and references

‡ *Crystal data* **13a**: $C_{35}H_{35}N_5Pd$, M = 632.08, monoclinic, a = 11.922(2), b = 16.776(3), c = 14.465(3) Å, β = 102.546(3)°, U = 2824.0(9) Å, T = 100 K, space group $P2_1/n$ (no. 14), Z = 4, 27 503 reflections measured, 8558 unique (R_{int} = 0.100), R_1 = 0.0721 [$I > 2\sigma(I)$], wR_2 = 0.1397 (all data).†

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