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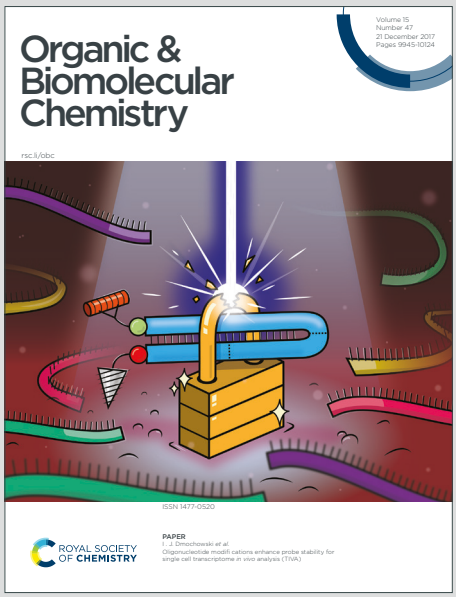

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Synthesis of 2-bromo- and 2-phenyl-neo-confused porphyrins

Arwa S. Almejbel and Timothy D. Lash*

ABSTRACT

Neo-confused porphyrins (neo-CPs), porphyrin isomers with a 1,3-connected pyrrolic subunit, are aromatic structures with a CNNN coordination core. Previously, examples of neo-CPs with fused benzo units or electron-withdrawing ester substituents have been described. In this paper, two new examples of neo-CPs are reported that lack a fused aromatic unit or an ester moiety, but instead have a bromo or phenyl substituent on the neo-confused ring. Acid-catalyzed condensation of suitably substituted 1,2'-dipyrrylmethane dialdehydes with a 2,2'-dipyrrylmethane, followed by oxidation with aqueous ferric chloride solutions, afforded the neo-CPs in 40-45% yield. These porphyrin analogues had slightly reduced diatropic ring currents and slowly decomposed in solution. The related palladium(II) and nickel(II) complexes proved to be very unstable, even though the diatropicity of the macrocycle was enhanced. This study shows that stabilizing substituents are necessary for investigations into this class of porphyrinoids. Attempts to prepare imidazole versions of neo-CPs were unsuccessful.

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† Electronic supplementary information (ESI) available: selected UV-Vis, ^{1}H NMR, ^{1}H-^{1}H COSY, HSQC, DEPT-135, ^{13}C NMR, and mass spectra.

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INTRODUCTION

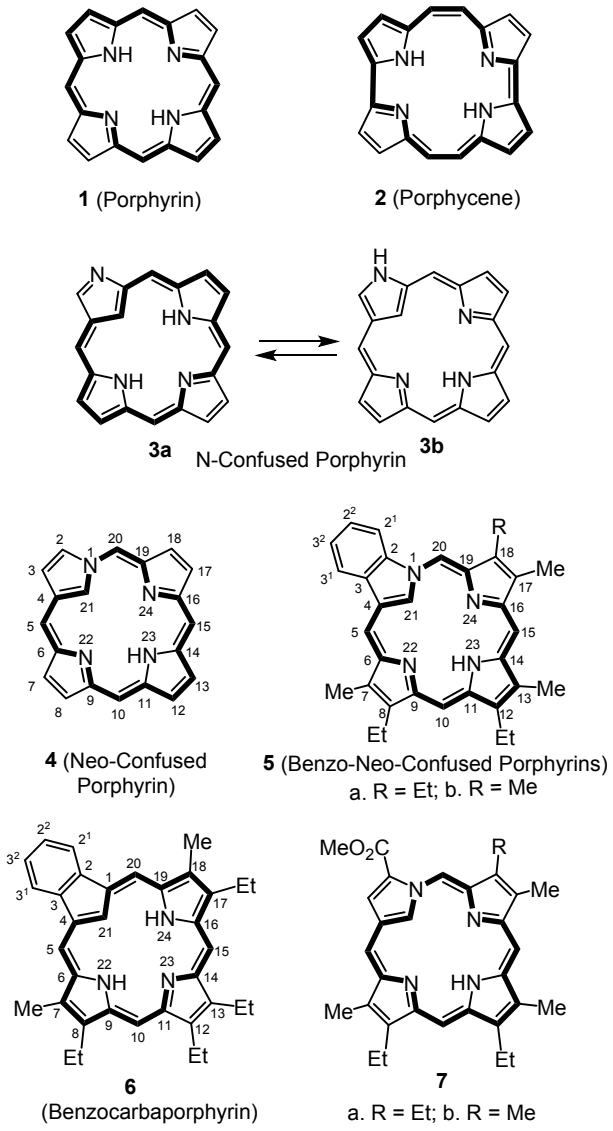

Figure 1. Porphyrin isomers and analogues.

Porphyrins **1** are one of the most studied families of organic compounds and have many important biological functions.[1] Synthetic porphyrins are being investigated for numerous applications that include the development of sensors,[2] optical materials,[3] catalysts[4] and photosensitizers in photodynamic therapy (PDT).[5] The importance of this macrocyclic system has led to investigations into related structures, including expanded porphyrins,[6] contracted porphyrins,[7] core modified porphyrins[8] and porphyrin isomers.[9]

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The first example of a porphyrin isomer, porphycene **2** (Figure 1), was reported in 1986 by Vogel and coworkers.[10] In porphycene,[11] the four pyrrolic subunits are linked by two ethylene bridges and two direct connections rather than the four single carbon bridges found in true porphyrins. Nevertheless, both porphyrin and porphycene use a total of four methine carbons and four pyrrole units to construct these macrocyclic systems. Porphycenes retain strongly aromatic characteristics and readily form metalated derivatives, but also show comparatively strong absorptions at longer wavelengths.[11,12] Several other examples of porphyrin isomers were subsequently discovered with inward facing nitrogen atoms.[12] An alternative class of porphyrin isomers, the so-called N-confused porphyrins (NCPs, **3**), were reported in 1994,[13,14] although structures of this type had been proposed at a far earlier point in time.[15] NCPs have a "confused" pyrrolic subunit that places its nitrogen atom on the macrocyclic periphery. This results in a carbon atom being placed within the macrocyclic core, and NCPs can be considered to be carbaporphyrinoid systems.[16] There are two thermodynamically accessible NCP tautomers, **3a** and **3b**, although the more aromatic form **3a** is favored in relatively nonpolar solvents such as chloroform.[17] NCPs exhibit long wavelength absorptions and have been investigated as potential photosensitizers for PDT applications.[18] In addition, NCPs readily form metalated derivatives, including organometallic complexes.[19] Examples of porphyrin isomers with two inverted pyrrole subunits, doubly N-confused porphyrins or N_2CPs, have also been reported.[20]

Another category of porphyrin isomer was discovered more recently in which the nitrogen atom of a pyrrole subunit is directly attached to a methine bridge.[21-23] Porphyrin isomers of this type were termed "neo-confused porphyrins", or neo-CPs (**4**, Figure 1), and were initially prepared as benzo-fused derivatives such as **5**.[21,23] Benzo-neo-confused porphyrins have electronic absorption spectra that are surprisingly similar to regular porphyrins, showing a strong Soret band at 407 nm and four smaller Q bands between 503 and 615 nm. Nevertheless, the diatropic ring current in benzo-neo-CPs is significantly reduced[21,23,24] compared to porphyrins or benzocarbaporphyrins (e.g. **6**).[25] The NMR spectrum for **6** in $CDCl_3$ showed the internal CH and NH protons at highly upfield values of -6.74 and -4.0 ppm, respectively, while the external *meso*-protons were strongly deshielded giving rise to two 2H singlets at 9.82 and 10.10 ppm.[25] In contrast,

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the internal CH and NH resonances for **5** were observed at -0.74 and -0.33 ppm, while the *meso*-protons gave rise to four 1H singlets at 8.91, 8.96, 9.68 and 9.99.[21,24] It is worth noting that the most downfield *meso*-proton is deshielded, in part, because it is connected to a nitrogen atom. Even so, the difference in chemical shifts between the most upfield and downfield proton resonances (Δδ) is 10.73 ppm, while **6** had a Δδ value of almost 17 ppm (Δδ values can be quite diagnostic in assessing global aromaticity in macrocyclic systems of this type).[21,23,24] NICS calculations were used to confirm these observations[26,27] and while the NICS(0) value for benzo-neo-confused porphyrin of -12.21 ppm showed that the system has a significant degree of magnetic aromaticity, benzocarbaporphyrin gave a larger negative value of -14.43 ppm. Neo-confused porphyrin **5** gave a slightly reduced negative NICS(0) value of -11.41 ppm.[26]

Following the initial report, examples of neo-confused porphyrins **7** with an electron-withdrawing methyl ester unit attached to the neo-confused ring were reported.[24,28] These porphyrinoids were also stable aromatic compounds with porphyrin-like characteristics. The Δδ value for methyl ester **7a** was 9.34 ppm, although this result is slightly exaggerated because one of the *meso*-protons is deshielded by its proximity to the ester moiety, but the results still indicated that neo-confused porphyrin esters **7** have reduced diatropicity compared to **5**. Both neo-CPs **7** and benzo-neo-CPs **5** acted as dianionic ligands and afforded stable nickel(II) and palladium(II) derivatives.[21,24] In an attempt to prepare a neo-confused porphyrin **8a** without any substituents on the neo-confused ring,[24] 1,2'-dipyrrylmethane dialdehyde **9a** was condensed with a dipyrrylmethane dicarboxylic acid **10** under MacDonald "2 + 2" reaction conditions (Scheme 1).[29] However, no porphyrin-like products could be isolated.[24] It was unclear whether the expected neo-confused porphyrin product was too unstable to isolate or whether the unsubstituted pyrrole ring failed to facilitate cyclization. In order to extend these observations, the synthesis of related neo-CPs lacking fused benzo-units or electron-withdrawing substituents was investigated. Two new examples of neo-NCPs are described but these compounds proved to be less stable than the previously described structures. Nevertheless, these neo-CPs continued to exhibit significant macrocyclic diatropicity.

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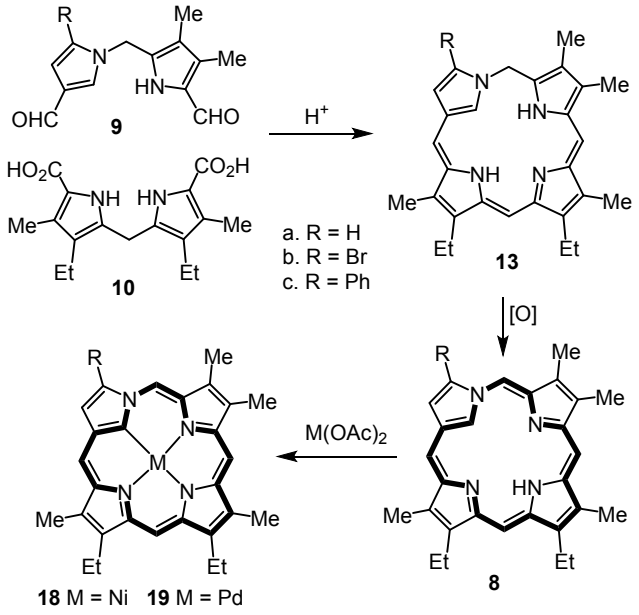
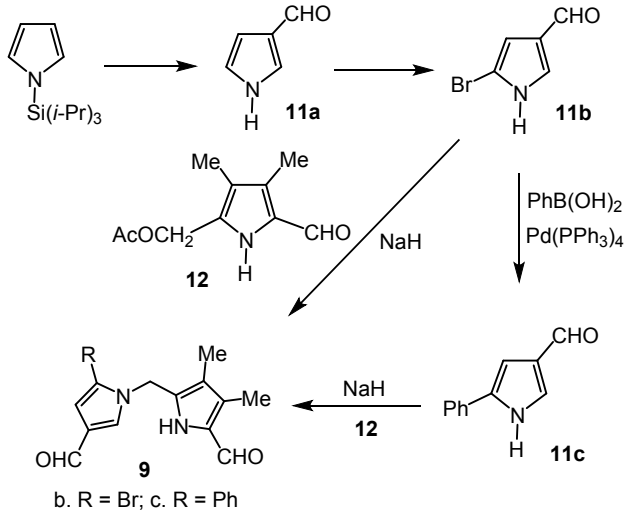


Scheme 1. Synthesis and metalation of neo-confused porphyrins.

RESULTS AND DISCUSSION



Scheme 2. Synthesis of pyrrole-3-carbaldehydes and 1,2'dipyrrylmethane dialdehydes.

Initially, 2-bromo-neo-CP **8b** was targeted for synthesis. The required precursor to the neo-confused ring, 5-bromopyrrole-3-carbaldehyde (**11b**), was prepared from *N*-tri-isopropylsilylpyrrole (Scheme 2).[30]

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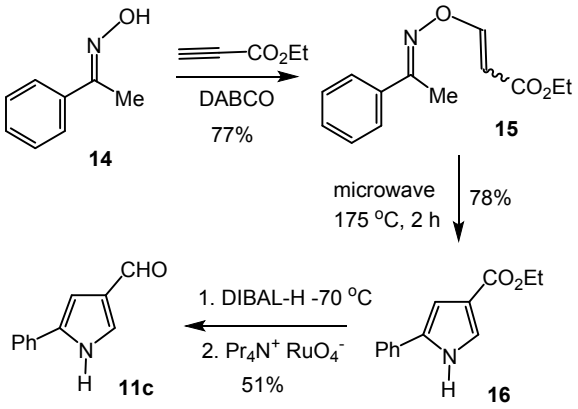
Vilsmeier formylation, followed by cleavage of the silyl group with aqueous sodium hydroxide, gave pyrrole-3-carbaldehyde (**11a**) and subsequent bromination with *N*-bromosuccinimide afforded the required bromopyrrole (Scheme 2).[31] Treatment with sodium hydride and subsequent reaction with acetoxymethylpyrrole aldehyde **12** gave dipyrrylmethane **9b**. Initially, THF was used as the solvent for this chemistry, but very poor yields of **9b** were obtained. However, after numerous trials, a 74% yield of the dipyrrolic product was obtained when the reaction was performed in DMF at 30 °C. Acid catalyzed condensation of dialdehyde **9b** with dipyrrylmethane **10**, followed by oxidation of the intermediary phlorin **13b** with ferric chloride, gave neo-confused porphyrin **8b** in 45% yield (Scheme 1).



Scheme 3. Synthesis of 5-phenylpyrrole-3-carbaldehyde.

In parallel work, 5-phenylpyrrole-3-carbaldehyde (**9c**) was required as a precursor to 2-phenyl-neo-CP **8c**. This pyrrole can be obtained by $Pd(Ph_3)_4$-catalyzed Suzuki-Miyaura coupling of **8b** with phenylboronic acid.[31] Alternatively, **9c** can be prepared in 4 steps from oxime **14** by adapting procedures reported by Ngwerume and Camp (Scheme 3).[32] Reaction of *E*-acetophenone oxime **14**[32] with ethyl propiolate and 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded a 9:1 mixture of *E* and *Z*-isomers of acrylate **15**. Thermal rearrangement and cyclization was accomplished under microwave conditions to give ethyl 5-phenylpyrrole-3-carboxylate (**16**). This chemistry was very sensitive to temperature. In our hands, no significant reaction was observed after 45 min at 170 °C. However, at 180 °C extensive decomposition took place. The best results were obtained when the reaction was carried out at 175 °C for 2 h and **16** was isolated

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in 78% yield. Reduction of the ester moiety with DIBAL-H at -70 °C, followed by oxidation of the resulting carbinol with tetrapropylammonium perruthenate, furnished the required aldehyde **9c**.[31] Treatment of **9c** with sodium hydride and reaction with acetoxymethylpyrrole **12**[24] in DMF at 30 °C, gave dipyrrylmethane dialdehyde **9c** in 75% yield (Scheme 2). Condensation of **9c** with dipyrrylmethane **10** in the presence of *p*-toluenesulfonic acid, followed by oxidation with aqueous ferric chloride, afforded 2-phenyl-neo-CP **8c** in 40% yield (Scheme 1).

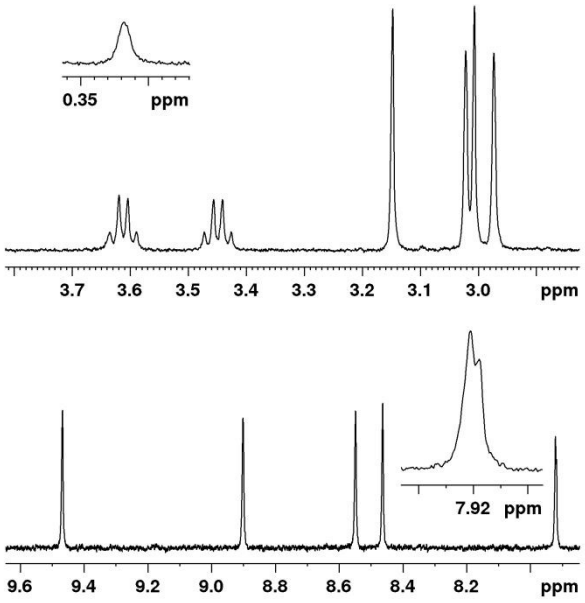

Figure 2. Partial 500 MHz proton NMR spectrum of bromo-neo-confused porphyrin **8b** in $CDCl_3$.

The proton NMR spectra of **8b** and **8c** demonstrated that these porphyrin analogues possessed significant diatropic character (Figure 2). Neo-confused porphyrin **8b** in $CDCl_3$ gave four 1H singlets for the *meso*-protons at 8.46, 8.54, 8.90 and 9.45 ppm (the latter corresponding to the methine unit connected to the nitrogen atom). In addition, the internal CH was shifted upfield to between 0.21 and 0.32 ppm. The outer pyrrolic CH gave a resonance at 7.92 ppm; in some spectra, a poorly resolved doublet was observed due to transannular coupling with the internal CH. Phenyl-neo-CP **8c** gave the *meso*-resonances at 8.55, 8.65, 9.12 and 9.42 ppm, while the external 3-H and internal 21-H peaks appeared at 7.96 and 0.88 ppm, respectively. The results suggest that **8b** and **8c** have comparable aromatic ring currents, although the diatropicity is

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slightly reduced compared to neo-CPs **5** and **7**. In the carbon-13 NMR spectrum for **8b**, the *meso*-protons appeared at 93.5 (15-CH), 94.1 (10-CH), 110.3 (20-CH) and 113.0 (20-CH), and the internal CH resonance showed up at 118.7 ppm. Addition of TFA to solutions of **8b** or **8c** resulted in the formation of the corresponding dications **8**H_2^{2+}, and these showed enhanced diamagnetic ring currents. For instance, the proton NMR spectrum of **8b**H_2^{2+} in $CDCl_3$ (Figure 3) gave four downfield 1H singlets for the *meso*-protons at 9.09 (15-H), 9.17 (10-H), 9.73 (20-H) and 10.12 (5-H) ppm, while the external pyrrolic proton (3-H) produced a resonance at 7.77 ppm and the internal 21-H peak shifted upfield to -2.20 ppm. Hence, the Δδ value for **8b**H_2^{2+} increased to 12.32 ppm, compared to Δδ = 9.2 ppm for the free base form. 2-Phenyl-neo-CP dication **8c**H_2^{2+} gave a similar Δδ value of 12.77 ppm.

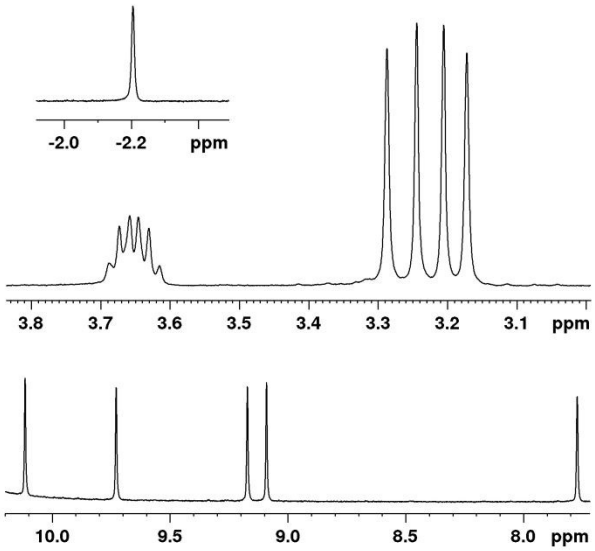

Figure 3. Partial 500 MHz proton NMR spectrum of neo-confused porphyrin dication **8b**H_2^{2+} in TFA-$CDCl_3$.

The UV-vis spectra for **8b** and **8c** were porphyrin-like in appearance. Bromo-neo-confused porphyrin **8b** gave a Soret band at 394 nm and smaller Q bands at 509, 544, 564 and 614 nm (Figure 4). The equivalent absorptions in **8c** appeared at 398, 510, 544, 565 and 614 nm. The corresponding dications **8**H_2^{2+} in 1% TFA-$CHCl_3$ produced modified chromophores. **8b**H_2^{2+} gave a broad split Soret band near 400 nm, together with a broad absorption at 665 nm (Figure 4).

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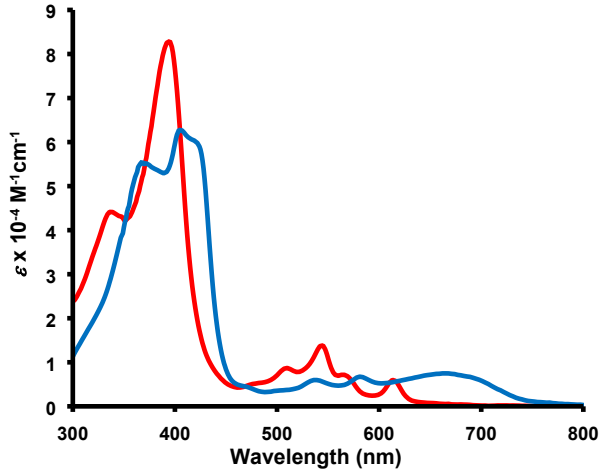

Figure 4. UV-vis spectra of bromo-neo-CP **8b** in 1% Et_3N-$CHCl_3$ (red line) and 1% TFA-$CHCl_3$ (dication **8b**H_2^{2+}, blue line).

Although good yields of **8b** and **8c** were obtained, the stability of these derivatives appeared to be substantially reduced compared to **5** and **7**. In the dark, solutions of **8b** and **8c** showed little sign of degradation after several hours. However, when dilute solutions were exposed to ambient levels of light in the laboratory (fluorescent lights, not sunlight) the samples underwent substantial decomposition. This is illustrated for phenyl-neo-CP in Figure 5. After 20 minutes exposure to light, the intensity of the Soret band was reduced by nearly 50% and the Q bands become less well defined. Bromo-neo-CP did not decompose as quickly but significant changes to the UV-vis spectra were still observed over a similar time frame (see ESI section).

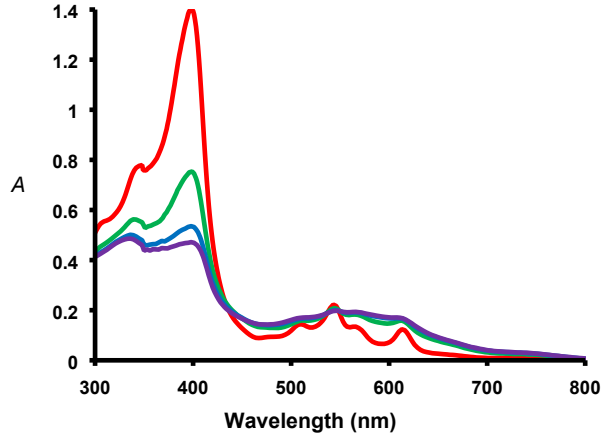

Figure 5. UV-vis spectrum of phenyl-neo-CP **8c** in 1% Et_3N-$CHCl_3$ after 0 min (red), 20 min (green), 40 min (blue) and 60 min (purple) exposure to ambient lighting in the laboratory.

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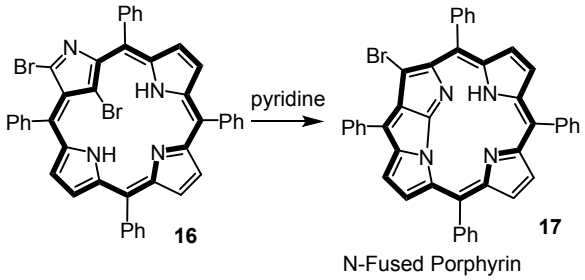

Scheme 4. Conversion of a dibromo-NCP into an N-fused porphyrin.

Bromo-N-confused porphyrins such as **16** undergo inversion of the confused pyrrolic subunit and cyclization in the presence of pyridine to produce N-fused porphyrins **17** (Scheme 4).[33] We contemplated that a similar transformation might also be possible for neo-confused porphyrins. However, all attempts to further brominate **8b** at position 21 lead to decomposition and this prevented any further investigations into the preparation of neo-fused porphyrins. Attempts to prepare organometallic derivatives of **8b** and **8c** were also problematic. Both of the neo-confused porphyrins reacted with nickel(II) acetate or palladium(II) acetate to afford the related metalated porphyrinoids **18** and **19** (Scheme 1). However, unlike the metal complexes of **5** and **7**, these species proved to be very unstable in solution. The nickel and palladium complexes of **8b** were isolated in reasonably pure form but decomposed before carbon-13 NMR data could be obtained. The proton NMR spectrum of nickel(II) complex **18b** in $CDCl_3$ showed the *meso*-protons at 8.56, 8.88, 8.97 and 9.48 ppm, while the equivalent resonances for palladium(II) derivative **19b** appeared at 8.65, 8.94, 9.08 and 9.58 ppm. The results suggest that the diatropic ring current for **19b** is slightly larger than for **18b**, and that both metalloporphyrinoids are more diatropic than neo-CP **8b**. Nevertheless, the increased diatropicity coincides with drastically reduced stability for these complexes. The UV-vis spectra for **18b** and **19b** (Figure 6) show similarities to previously described nickel(II) and palladium(II) complexes of neo-confused porphyrins.[24] Nickel complex **18b** gave Soret band at 383 nm and several broad poorly resolved absorptions that extended up to 700 nm. Palladium derivative **19b** afforded several absorptions in the Soret region (i.e. near 400 nm) and a series of Q-like bands at 499, 532, 603 and 644 nm.

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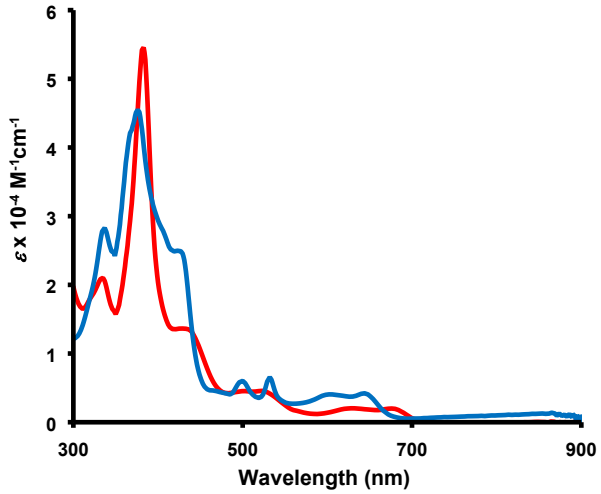
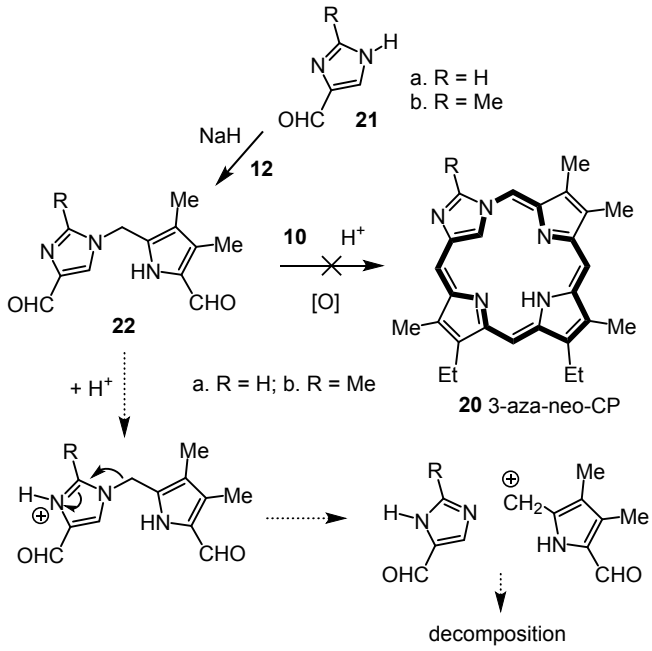


Figure 6. UV-vis spectra of metalated neo-confused porphyrins in chloroform: Ni(II) complex **18b** (red line) and Pd(II) complex **19b** (blue line).



Scheme 5. Attempted synthesis of 3-aza-neo-confused porphyrins.

The formation of related macrocyclic ring systems was also considered. Specifically, the synthesis of imidazole analogues of neo-CPs **20** was attempted (Scheme 5). Imidazole-4-carbaldehyde (**21a**) was reacted with sodium hydride and condensed with acetoxymethylpyrrole **12** in THF to give 1-(2-

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pyrrolylmethyl)imidazole **22a** in 60% yield. 2-Methylimidazole carbaldehyde **19b**[34] similarly afforded the related pyrrolylmethylimidazole **22b** in 51% yield. However, all attempts to react these intermediates with dipyrrylmethane **10** failed to give any macrocyclic products. It may be that aza-neo-CPs **20** are too unstable to isolate. However, another possibility is that **22a** and **22b** fragment rapidly under the acid-catalyzed conditions that are required for MacDonald-type condensations and this circumvents macrocycle formation. Alternative routes to 3-aza-neo-CPs will be investigated in the future.

CONCLUSIONS

Neo-confused porphyrins are an interesting class of porphyrin isomers that exhibit reduced stability compared to porphyrins and N-confused porphyrins. Structures with fused benzo-units or electron-withdrawing ester moieties are robust compounds that easily form organometallic derivatives. However, in the absence of these structural units, neo-CPs have more limited stability and while the formation of organometallic species can still be accomplished, the nickel(II) and palladium(II) complexes are very unstable in solution. Neo-confused porphyrins of this type, together with their metalated derivatives, exhibit global aromatic properties, and have strong diamagnetic ring currents, even though the stability of the system has been undermined. These observations suggest that further exploration of neo-confused porphyrins should be directed towards structures with fused aromatic rings and/or electron-withdrawing substituents.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded using a 400 or 500 MHz NMR spectrometer and were run at 302 K unless otherwise indicated. ^{1}H NMR values are reported as chemical shifts δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak) and coupling constant (*J*). Chemical shifts are reported in parts per

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million (ppm) relative to $CDCl_3$ (^1H residual $CHCl_3$ δ 7.26, ^{13}C $CDCl_3$ triplet δ 77.23) or DMSO-d_6 (^1H residual DMSO-d_5 pentet δ 2.49, ^{13}C DMSO-d_6 heptet δ 39.7), and coupling constants were taken directly from the spectra. NMR assignments were made with the aid of ^1H-^1H COSY, HSQC, DEPT-135, and NOE difference proton NMR spectroscopy. 2D experiments were performed by using standard software. High-resolution mass spectra (HRMS) were obtained by using a double focusing magnetic sector instrument. ^1H and ^{13}C NMR spectra for all new compounds are reported in Supporting Information.

Ethyl 5-phenylpyrrole-3-carboxylate (**16**). Acetophenone oxime **14** (2.00 g, 14.8 mmol) and 1,4-diazabicyclo[2.2.2]octane (180 mg) were dissolved in dichloromethane (40 mL) and cooled to -10 °C. A mixture of ethyl propiolate (1.4 mL, 1.35 g, 1.38 mmol) in dichloromethane (15 mL) was added dropwise over 10 min while maintaining the temperature at -10 °C. The reaction was warmed to room temperature and stirred for 20 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with 10% ethyl acetate-petroleum ether (60-90) to give a mixture of *E*- and *Z*-isomers of ethyl 3-(1-phenylethylideneamino-oxy)acrylate in a ratio of 9:1 (2.449 g, 10.7 mmol, 77%) as a colorless oil. *E*-isomer (major): ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, t, J = 7.1 Hz), 2.36 (3H, s), 4.20 (2H, q, J = 7.1 Hz), 5.68 (1H, d, J = 12.5 Hz), 7.38-7.44 (3H, m), 7.68-7.71 (2H, m), 8.08 (1H, d, J = 12.5 Hz). *Z*-isomer (minor): ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (3H, t, J = 7.2 Hz), 2.47 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 4.93 (1H, d, J = 7.4 Hz), 7.39-7.45 (3H, m), 7.48 (1H, d, J = 7.4 Hz), 7.67-7.70 (2H, m). A solution of the foregoing oil (300 mg, 1.30 mmol) in toluene (7.5 mL) was heated to 175 °C for 2 h under microwave irradiation. The solvent was evaporated under reduced pressure and the residue purified on silica gel, eluting with 25% ethyl acetate-petroleum ether (60-

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90), to give the pyrrole ester (216 mg, 1.00 mmol, 78%) as a pale orange oil. A sample crystallized from chloroform-hexanes to give an off-white solid, mp 152-153 ^{o}C (lit.[35] mp 149-151 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.32 (2H, q, J = 7.1 Hz, OCH_2), 6.92 (1H, dd, J = 1.6, 2.7 Hz, 4-H), 7.24-7.27 (1H, m, *p*-H), 7.37-7.40 (2H, m, 2 x *m*-H), 7.47 (1H, dd, J = 1.6, 3.0 Hz, 2-H), 7.48-7.50 (2H, m, 2 x *o*-H), 8.87 (1H, br s, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7 (CH_3), 60.1 (OCH_2), 106.9 (4-CH), 118.4, 124.31, 124.33 (2 x *o*-CH and 2-CH), 127.3 (p-CH), 129.2 (m-CH), 132.0, 133.2, 165.2 (C=O).

2-Bromo-3',4'-dimethyl-1,2'-dipyrrylmethane-4,5'-dicarbaldehyde (**9b**). Sodium hydride (60% in mineral oil, 48 mg, 1.2 mmol) was added to a solution of 5-bromopyrrole-3-carbaldehyde (144 mg, 0.827 mmol) in DMF (30 mL) and the mixture was stirred for 30 min at room temperature. A solution of acetoxymethylpyrrole aldehyde **12** (171 mg, 0.875 mmol) in DMF (15 mL) was added dropwise over 10 min, and the mixture stirred for 18 h at 30 ˚C. The mixture was then diluted with ether and washed with water. The aqueous phase was back extracted with ether (x3) and the combined organic layers dried over sodium sulfate. After suction filtration, the solvent was evaporated down under reduced pressure. Recrystallization from ethanol gave the dipyrrylmethane (190 mg, 0.615 mmol, 74%) as a pale brown solid, mp 196-198˚ C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (3H, s, 3'-Me), 2.28 (3H, s, 4'-Me), 5.10 (2H, s, bridge-CH_2), 6.68 (1H, d, J = 2.0 Hz, 4-H), 7.24 (1H, d, J = 2.0 Hz, 2-H), 9.57 (1H, s), 9.59 (1H, s) (2 x CHO), 9.83 (1H, br s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.7 (3'Me), 9.0 (4'-Me), 44.1 (bridge-CH_2), 105.9, 111.1 (4-CH), 120.6, 127.1, 129.1 (2-CH), 129.6, 130.4, 132.3, 177.8 (CHO), 184.4 (CHO). HRMS (EI) *m/z*: M^+ calcd for $C_{13}H_{13}BrN_2O_2$ 308.0160, found 308.0168.

2-Phenyl-3',4'-dimethyl-1,2'-dipyrrylmethane-4,5'-dicarbaldehyde (**9c**). Sodium hydride (60% in mineral oil, 44 mg, 1.1 mmol) was added to a solution of 5-phenyl-3-pyrrolecarbaldehyde

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(147 mg, 0.858 mmol) in DMF (27.5 mL) and the mixture stirred for 30 min at room temperature. A solution of acetoxymethylpyrrole aldehyde **12** (156 mg, 0.80 mmol) in DMF (13.8 mL) was added dropwise over 10 min, and the mixture was stirred for 18 h at 30 ˚C. The mixture was then diluted with ether and washed with water. The aqueous phase was back extracted with ether (x3) and the combined organic layers dried over sodium sulfate. After suction filtration, the solvent was evaporated down under reduced pressure. Recrystallization from ethanol gave the dipyrrylmethane (185 mg, 0.604 mmol, 75%) as a brown solid, mp 202-204 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$, 50 ^{o}C) δ 1.81 (3H, s, 3'-Me), 2.23 (3H, s, 4'-Me), 5.05 (2H, s, bridge-CH_2), 6.67 (1H, d, J = 1.85 Hz, 4-H), 7.28 (1H, d, J = 1.85 Hz, 2-H), 7.31-7.34 (2H, m, 2 x *o*-H), 7.41-7.45 (3H, m, *m*- & *p*-H), 8.67 (1H, br s, NH), 9.55 (1H, s), 9.76 (1H, s) (2 x CHO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.3 (3'Me), 8.8 (4'-Me), 43.6 (CH_2), 109.0 (4-CH), 126.9, 128.8 (2 x *o*-CH), 129.1 (2-CH), 129.3, 129.5, 129.6, 130.9, 131.5, 131.7, 137.2, 177.4 (CHO), 185.4 (CHO). HRMS (ESI) *m/z*: M^+ calcd for $C_{19}H_{18}N_2O_2$ 306.1368, found 306.1378.

1(5-Formyl-3',4'-dimethyl-2-pyrrolylmethyl)imidazole-4-carbaldehyde (**22a**). Sodium hydride (60% in mineral oil, 26 mg, 0.65 mmol) was added to a solution of formyl imidazole (87 mg, 0.90 mmol) in THF (16 mL) and the mixture was stirred for 30 min at room temperature. A solution of acetoxymethylpyrrole aldehyde **12** (92 mg, 0.47 mmol) in THF (8 mL) was added dropwise over 10 min, and the mixture was stirred for 18 h at 30 ˚C. The mixture was then diluted with ether and washed with water. The aqueous phase was back extracted with ether (x3) and the combined organic layers dried over sodium sulfate. After suction filtration, the solvent was evaporated under reduced pressure. Recrystallization from ethanol gave the dialdehyde (66 mg, 0.28 mmol, 60%) as a brown solid, mp 198-200 ˚C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.96 (3H, s, 3-Me), 2.18 (3H, s, 4-Me), 5.21 (2H, s, bridge-CH_2), 7.90 (1H, d, J = 1.2 Hz, imidazole-2-H),

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7.99 (1H, d, J = 1.2 Hz, imidazole-5-H), 9.57 (1H, s, imidazole-CHO), 9.67 (1H, s, pyrrole-CHO), 11.83 (1H, br s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 8.1 (3'-Me), 8.8 (4'-Me), 41.3 (CH_2), 119.0, 127.3 (imidazole-5-CH), 129.1, 131.3, 139.6 (imidazole-2-CH), 141.7, 178.1 (pyrrole-CHO), 185.4 (imidazole-CHO). HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{14}N_3O_2$ 232.1086, found 232.1081.

1(5-Formyl-3',4'-dimethyl-2-pyrrolylmethyl)-2-methylimidazole-4-carbaldehyde (**22b**). Sodium hydride (60% in mineral oil, 48 mg, 1.2 mmol) was added to a solution of 4(5)-formyl-2-methylimidazole (104 mg, 0.944 mmol) in THF (21.5 mL) and the mixture was stirred for 30 min at room temperature. A solution of acetoxymethylpyrrole aldehyde **12** (122 mg, 0.625 mmol) in THF (11 mL) was added dropwise over 10 min, and the mixture was stirred for 18 h at 30˚C. The mixture was then diluted with ether and washed with water. The aqueous phase was back extracted with ether (x3) and the combined organic layers dried over sodium sulfate. After suction filtration, the solvent was evaporated under reduced pressure. Recrystallization from ethanol gave the dialdehyde (78 mg, 0.32 mmol, 52%) as a brown solid, mp 200-202 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.96 (3H, s, 3'-Me), 2.26 (3H, s, 4'-Me), 2.43 (3H, s, imidazole-Me), 5.11 (2H, s, bridge-CH_2), 7.46 (1H, s), 9.49 (1H, s, pyrrole-CHO), 9.66 (1H, s, imidazole-CHO), 11.19 (1H, br s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.7 (3'-Me), 9.1 (4'-Me), 13.4 (imidazole-Me), 42.0 (CH_2), 120.5, 126.3 (imidazole-5-CH), 129.8, 130.4, 140.4, 147.2, 178.1 (pyrrole-CHO), 185.6 (imidazole-CHO). HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{15}N_3O_2Na$ 268.1062, found 268.1065.

2-Bromo-8,12-diethyl-7,13,17,18-tetramethyl-1-aza-21-carba-1*H*,23*H*-porphyrin (**8b**). *p*-Toluenesulfonic acid (56 mg) in methanol (6 mL) was added dropwise to a stirred mixture of dialdehyde **9b** (31 mg, 0.10 mmol) and dipyrrylmethane dicarboxylic acid **10** (32 mg, 0.10 mmol) in dichloromethane (50 mL) and methanol (6 mL). The resulting mixture was stirred for 16 h at

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room temperature. The solution was stirred vigorously with a 0.2% aqueous ferric chloride solution for 1 h to oxidize the phlorin intermediate. The organic phase was separated, and the aqueous solution back extracted with dichloromethane. The combined organic solutions were washed with water and 5% aqueous sodium bicarbonate solution, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on grade 3 alumina eluting with 3:1 hexanes-dichloromethane. The product was collected as a pink-purple fraction. Recrystallization from chloroform-hexanes gave the neo-confused porphyrin **8b** (20.4 mg, 0.0407 mmol, 41%) as a purple powder, mp >300 ˚C. UV-vis (1% Et_3N-$CHCl_3$): λ_{max}/nm (log ε) 337 (4.64), 394 (4.92), 476 (sh, 3.70), 509 (3.94), 544 (4.14), 564 (3.86), 614 (3.78). UV-vis (1% TFA-$CHCl_3$): λ_{max}/nm (log ε) 368 (4.74), 405 (4.80), 422 (sh, 4.78), 538 (3.78), 581 (3.83), 665 (3.87). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.21 (1H, br s, 21-H), 1.58 (3H, t, *J* = 7.7 Hz), 1.65 (3H, t, *J* = 7.7 Hz) (2 x CH_2CH_3), 2.97 (3H, s, 17 -Me), 3.009 (3H, s), 3.014 (3H, s) (7,18-Me), 3.15 (3H, s, 13-Me), 3.45 (2H, q, *J* = 7.7 Hz, 8-CH_2), 3.61 (2H, q, *J* = 7.7 Hz, 12-CH_2), 7.92 (1H, s,[34] 3-H), 8.46 (1H, s, 15-H), 8.54 (1H, s, 10-H), 8.90 (1H, s, 5-H), 9.45 (1H, s, 20-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.01, 11.02, 11.04, 11.1 (7,13,17,18-Me), 16.7, 16.8 (2 x CH_2CH_3), 19.3 (2 x CH_2), 93.5 (15-CH), 94.1 (10-CH), 109.1, 110.3 (20-CH), 113.0 (5-CH), 118.7 (21-CH), 119.8 (3-CH), 122.9, 135.0, 135.6, 140.2, 141.0, 141.8, 141.9, 143.3, 144.5. ^{1}H NMR (500 MHz, TFA-$CDCl_3$, dication **8b**H_2^{2+}) δ -2.20 (1H, s, 21-H), 1.55 (3H, t, *J* = 7.7 Hz), 1.59 (3H, t, *J* = 7.7 Hz) (2 x CH_2CH_3), 3.17 (3H, s), 3.20 (3H, s) (17,18-Me), 3.24 (3H, s, 13-Me), 3.29 (3H, s, 7-Me), 3.61-3.69 (4H, overlapping quartets, 8,12-CH_2), 7.77 (1H, s, 3-H), 9.09 (1H, s, 15-H), 9.17 (1H, s, 10-H), 9.73 (1H, s, 20-H), 10.12 (1H, s, 5-H). ^{13}C NMR (125 MHz, TFA-$CDCl_3$, dication **36a**H_2^{2+}) δ 11.0, 11.3, 11.4, 11.8 (7,13,17,18-Me), 15.7 (2 x CH_2CH_3), 19.4 (CH_2), 19.7 (CH_2), 94.8 (15-CH), 96.4 (10-CH), 109.0 (21-CH), 111.1, 113.7 (5-CH), 117.7 (3-CH), 119.0 (20-CH), 126.3, 133.1,

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137.0, 140.2, 142.4, 142.7, 144.4, 146.3, 147.8, 148.0, 151.0, 154.7. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{30}BrN_4$ 501.1654, found 501.1652.

2-Phenyl-8,12-diethyl-7,13,17,18-tetramethyl-1-aza-21-carba-1*H*,23*H*-porphyrin (**8c**). *p*-Toluenesulfonic acid (56 mg) in methanol (6 mL) was added dropwise to a stirred mixture of dialdehyde **9c** (29 mg, 0.94 mmol) and dipyrrylmethane dicarboxylic acid **10** (30 mg, 0.94 mmol) in dichloromethane (50 mL) and methanol (6 mL). The mixture was stirred for 16 h at room temperature, a 0.2% aqueous ferric chloride solution was added, and the resulting biphasic mixture was vigorously stirred for 1 h. The organic phase was separated, and the aqueous solution back extracted with dichloromethane. The combined organic solutions were washed with water and 5% aqueous sodium bicarbonate solution, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on grade 3 alumina eluting with 3:1 hexanes-dichloromethane, and the product was collected as a pink-purple fraction. Recrystallization from chloroform-hexane gave the neo-confused porphyrin **8c** (19.5 mg, 0.039 mmol, 41%) as a purple powder, mp >300 ˚C. UV-vis (1% Et_3N-$CHCl_3$): λ_{max}/nm (log ε) 348 (4.64), 398 (4.91), 478 (sh, 3.72), 510 (3.92), 544 (4.09), 565 (4.64), 614 (3.81). UV-vis (1% TFA-$CHCl_3$): λ_{max}/nm (log ε) 382 (4.88), 415 (4.78), 538 (3.84), 582 (3.84), 671 (3.84). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73 (1H, br s, NH), 0.88 (1H, br s, 21-CH), 1.62 (3H, t, *J* = 7.7 Hz), 1.68 (3H, t, *J* = 7.7 Hz) (2 x CH_2CH_3), 2.89 (3H, s, 18-Me), 2.99 (3H, s, 17-Me), 3.07 (3H, s, 7-Me), 3.19 (3H, s, 13-Me), 3.51 (2H, q, *J* = 7.7 Hz, 8-CH_2), 3.66 (2H, q, *J* = 7.7 Hz, 12-CH_2), 7.64 (1H, t, *J* = 7.4 Hz, *p*-H), 7.73 (2H, t, *J* = 7.5 Hz, 2 x *m*-H), 7.96 (1H, s, 3-H), 7.99 (2H, d, *J* = 7.5 Hz, 2 x *o*-H), 8.55 (1H, s, 15-H), 8.65 (1H, s, 10-H), 9.12 (1H, s, 5-H), 9.42 (1H, s, 20-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.0 (13-Me), 11.1 (7,18-Me), 11.2 (17-Me), 16.8 (CH_2CH_3), 17.1 (CH_2CH_3), 19.4 (12-CH_2), 19.5 (8-CH_2), 92.8 (15-CH), 93.9 (10-CH), 111.6 (20-CH), 114.2 (5-CH), 117.8 (3-CH), 120.1 (21-CH), 122.9, 128.5

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(*p*-CH), 129.1 (2 x *m*-CH), 131.5 (2 x *o*-CH), 132.5, 133.8, 135.4, 139.5, 139.9, 140.7, 141.2, 141.7, 142.4, 143.3, 144.2, 154.0, 160.1, 161.5. ^{1}H NMR (500 MHz, TFA-$CDCl_3$, dication **36a**H_2^{2+}) δ -2.78 (1H, s, 21-H), 1.59 (3H, t, *J* = 7.7 Hz), 1.64 (3H, t, *J* = 7.7 Hz) (2 x CH_2CH_3), 3.15 (3H, s, 18-Me), 3.20 (3H, s, 17-Me), 3.28 (3H, s, 13-Me), 3.33 (3H, s, 7-Me), 3.67-3.77 (4H, m, 2 x CH_2CH_3), 7.75-7.80 (5H, m, Ph), 7.84 (1H, s, 3-H), 9.26 (1H, s, 15-H), 9.34 (1H, s, 10-H), 9.93 (1H, s, 20-H), 9.99 (1H, s, 5-H). ^{13}C NMR (125 MHz, TFA-$CDCl_3$, dication **36a**H_2^{2+}): δ 10.9 (17-Me), 11.3 (13-Me), 11.4 (7-Me), 11.7 (18-Me), 15.7 (2 x CH_2CH_3), 19.5 (CH_2), 19.8 (CH_2), 94.6 (15-CH), 96.1 (10-CH), 108.1 (21-CH), 114.6 (20-CH), 115.2 (3-CH), 119.9, 126.3, 128.7, 129.8 (2 x *m*-CH), 130.7 (*p*-CH), 132.1 (2 x *o*-CH), 133.0, 136.8, 140.2, 141.04, 142.4, 142.8, 146.1, 147.0, 147.7, 149.8, 149.9, 153.6. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{35}N_4$ 499.2862, found 499.2857.

[2-Bromo-8,12-diethyl-7,13,17,18-tetramethyl-1-aza-21-carba-1*H*,23*H*-porphyrinato]nickel(II) (**18b**). Neo-confused porphyrin **8b** (15.0 mg, 0.030 mmol) was dissolved in pyridine (15 mL) along with nickel(II) acetate (15.0 mg) and the mixture was stirred under reflux for 1 h. The mixture was diluted with dichloromethane, washed with water and the aqueous solution back extracted with dichloromethane. The combined organic solutions were evaporated under reduced pressure. The residue was purified by column chromatography on grade 3 alumina eluting with 3:1 hexanes-dichloromethane to give the nickel neo-confused porphyrin (10.0 mg, 0.0179 mmol, 60%) as a brown powder, mp >300 ˚C. UV-vis ($CHCl_3$): λ_{max}/nm (log ε) 334 (4.32), 383 (4.74), 432 (sh, 4.13), 523 (3.66), 631 (3.31), 675 (3.30). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (3H, t, *J* = 7.7 Hz), 1.65 (3H, t, *J* = 7.7 Hz) (2 x CH_2CH_3), 2.88 (3H, s), 2.92 (3H, s), 3.00 (3H, s), 3.09 (3H, s) (7,13,17,18-Me), 3.53-3.59 (4H, m, 2 x CH_2CH_3), 7.92 (1H, s, 3-H), 8.56 (1H, s, 15-H), 8.88 (1H, s, 10-H), 8.97 (1H, s, 5-H), 9.48 (1H, s, 20-H). ^{13}C NMR (partial data derived from

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HSQC and DEPT-135 spectra) δ 10.7, 10.8, 10.90, 10.95, 16.9, 17.0, 19.2 (CH_2), 19.3 (CH_2), 94.4 (15-CH), 96.9 (10-CH), 109.7 (20-CH), 112.4 (5-CH), 123.4 (3-CH). HRMS (ESI) *m/z*: M^+ calcd for $C_{28}H_{27}BrN_4Ni$ 556.0773, found 556.0772.

[2-Bromo-8,12-diethyl-7,13,17,18-tetramethyl-1-aza-21-carba-1*H*,23*H*-porphyrinato]palladium(II) (**19b**). Neo-confused porphyrin **8b** (10.0 mg, 0.019 mmol) was dissolved in acetonitrile (10 mL) along with palladium(II) acetate (10.0 mg) under reflux conditions for 1 h. The mixture was diluted with dichloromethane and washed with water. The organic solution was evaporated under reduced pressure and the residue was purified by column chromatography on grade 3 alumina eluting with 3:1 hexanes-dichloromethane to give the palladium neo-confused porphyrin (4.8 mg, 0.0079 mmol, 40%) as a green solid, mp >300 ˚C. UV-vis ($CHCl_3$): λ_{max}/nm (log ε) 336 (4.45), 377 (4.66), 426 (sh, 4.40), 499 (3.78), 532 (3.82), 603 (3.61), 644 (3.62). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (3H, t, *J* = 7.7 Hz), 1.68 (3H, t, *J* = 7.7 Hz) (2 x CH_2CH_3), 2.98 (3H, s, 17-Me), 3.00 (3H, s, 18-Me), 3.09 (3H, s, 13-Me), 3.14 (3H, s, 7-Me) 3.57-3.65 (4H, m, 2 x CH_2CH_3), 7.90 (1H, s, 3-H), 8.65 (1H, s, 15-H), 8.94 (1H, s, 10-H), 9.08 (1H, s, 5-H), 9.52 (1H, s, 20-H). ^{13}C NMR (partial data derived from the HSQC spectrum) δ 95.1 (15-CH), 97.9 (10.CH), 111.4 (20-CH), 114.8 (5-CH), 123.0 (3-CH). HRMS (ESI) *m/z*: M^+ calcd for $C_{28}H_{27}{}^{79}BrN_4{}^{108}Pd$ 606.0458, found 606.0480.

Conflicts of Interest

There are no conflicts to declare.

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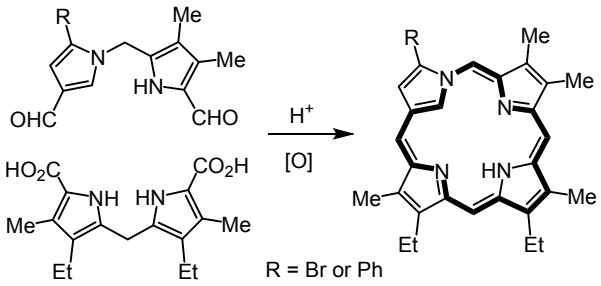
Graphical Abstract



New examples of neo-confused porphyrins are reported. These retain global diatropic characteristics but are relatively unstable in solution.