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Dihydropyracyloporphyrins

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ABSTRACT

A pyrrole ethyl ester with a fused dihydropyracylene unit was prepared by reacting 5-nitro-1,2-dihydropyracylene with ethyl isocyanoacetate in the presence of a phosphazene base. Cleavage of the ester moiety, followed by reaction with an acetoxymethylpyrrole and acetic acid in refluxing ethanol, afforded a tripyrrane, and subsequent '3 + 1' condensation with a pyrrole dialdehyde gave a dihydropyracyloporphyrin. Cyclotetramerization of the dihydropyracylopyrrole with benzaldehyde and $BF_3{\cdot}Et_2O$ gave a sterically crowded tetrakis(dihydropyracylo)-porphyrin and the reduced five-membered rings proved to be an excellent NMR probe for conformational mobility. The new porphyrins and their nickel(II) complexes also showed potentially valuable highly red shifted UV–vis spectra.

Introduction

Extension of the porphyrin chromophore can lead to substantial bathochromic shifts to major electronic absorptions, although these effects are highly structure dependent [1–4]. Although the shifts due to fused phenanthrene rings are quite modest [5], acenaphthylene-fused porphyrins (e.g. **1**, Fig. 1) have highly modified UV–vis spectra [6–8]. Monoacenaphthoporphyrin **1** gave multiple Soret bands and a strong Q absorption at 658 nm [6], while *opp*-diacenaphthoporphyrins **2** showed the long wavelength absorption at 692 nm [6]. *meso*-Tetraaryltetraacenaphthoporphyrins (e.g. **3a**) gave even larger shifts, showing the Soret band at an unusually long wavelength value of 556 nm [7,8]. The related *meso*-tetrakis(phenylethynyl)porphyrin **3b** further extended the conjugation and this resulted in a Soret band at 604 nm; the lead complex of **3b** gave an even longer wavelength Soret band at 642 nm [8]. Similar effects have been noted for expanded porphyrinoids [9] and carbaporphyrinoid systems [10]. There is considerable interest in the synthesis of porphyrins with long wavelength absorptions (λ_{max} > 650 nm) for potential applications. Acenaphthoporphyrins have shown promise as photosensitizers in photodynamic therapy (PDT) [11], as well as in the treatment of leismaniasis [12]. Band gap engineering of tetraacenaphthoporphyrins has also been accomplished by introducing naphthalene diimide subunits [13]. In order to extend these studies, we were interested in the possibility of introducing related pyracylene subunits into porphyrin structures.

Results and discussion

Unlike acenaphthylene (**4**), pyracylene (**5**) is unstable and has a degree of antiaromatic character due to the presence of 12π electron delocalization pathways (Fig. 1) [14]. However, pyracene (**6**), a reduced form of pyracylene, is easily obtained by treating bis(bromomethyl)acenaphthene **7** with phenyllithium (Scheme 1) [15]. In the original procedure, biphenyl, which is formed as a byproduct, was removed by fractional sublimation. However, we found that biphenyl could easily be removed by steam distillation leaving behind pure pyracene in quantitative yields. Oxidation with DDQ in refluxing chloroform afforded 1,2-dihydropyracylene (**8**) but further dehydrogenation to give **5** was unsuccessful. Due to the inaccessibility and instability of pyracylene, we elected to continue the investigations with **8** and potentially introduce dehydrogenated structures at a later stage. The Barton-Zard reaction has been used to prepare pyrroles from nitroalkenes [16] and this methodology has been applied to the preparation of *c*-annulated pyrroles from nitroaromatic compounds [17]. Dihydropyracylene **8** was nitrated with nitryl chloride in carbon tetrachloride to give nitro derivative **9** in 33% yield. Subsequent condensation with ethyl isocyanoacetate in the presence of phosphazene base **10**[17b] afforded dihydropyracylopyrrole **11** in 47% yield. This novel pyrrole displayed low solubility but NMR data could be obtained in $CDCl_3$ at 50 °C or in DMSO d_6. In $CDCl_3$, the aromatic protons of the naphthalene subunit were observed between 8.03 and 7.63 ppm, while the ethylene unit gave an AB quartet at 3.5 ppm. The pyrrole C—H could be identified at 7.18 ppm and the N—H gave rise to a broad peak at 8.9 ppm. In DMSO d_6, the NH resonance shifted downfield to 11.7 ppm due to strong

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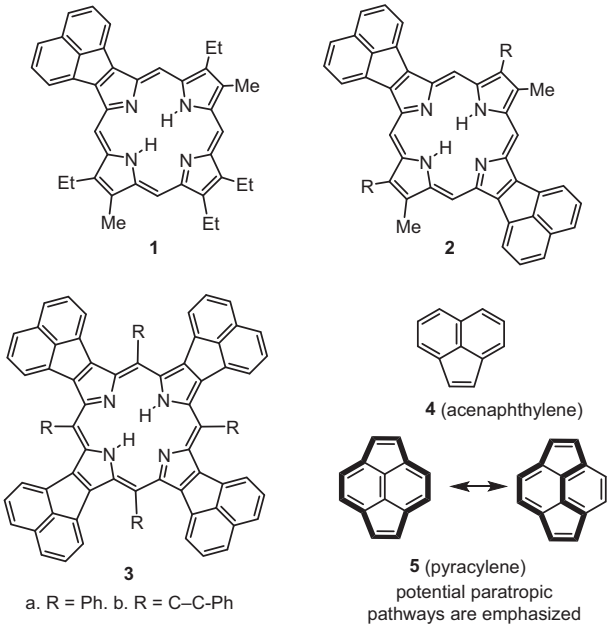
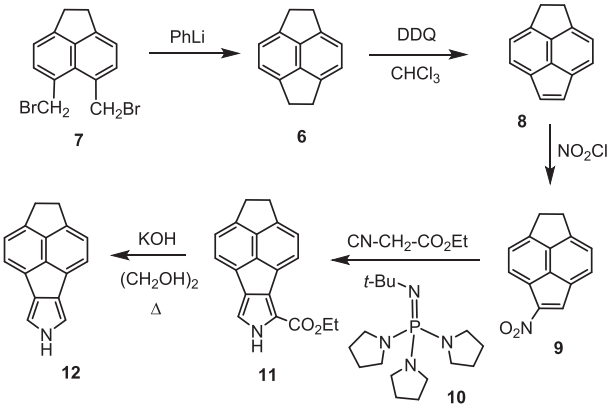


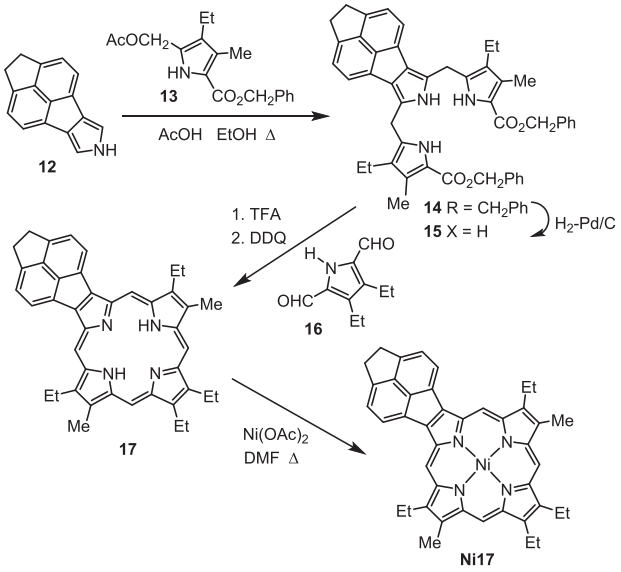
Fig. 1. Structures of acenaphthoporphyrins, acenaphthylene and pyracylene.



Scheme 1. Synthesis of pyracylopyrroles.

hydrogen bonding interactions. The ethyl ester unit of **11** was cleaved with potassium hydroxide in ethylene glycol at 200 °C. Under these conditions, the initially formed carboxylate ion decarboxyated to afford α-unsubstituted pyrrole **12**. The NMR spectrum for **12** in $CDCl_3$ showed the presence of a plane of symmetry, and the pyrrole CH's gave a 2H doublet (J = 2.4 Hz) at 7.01 ppm. The ethylene unit gave a 4H singlet at 3.45 ppm, while the naphthalene protons afforded doublets (J = 6.9 Hz) at 7.55 and 7.29 ppm. The EI MS for ethyl ester **11** gives a molecular ion at m/z 289 and a base peak at m/z 243 corresponding to loss of ethanol. Pyrrole **12** is more robust to EI MS analysis and gives a strong molecular ion at m/z 217, as well as a smaller fragment ion at m/z 189 that is associated with loss of ethylene. Loss of ethylene can also be seen in the EI MS for **11**, but in this case it corresponds to a very minor pathway.

The '3 + 1′ variant of the MacDonald condensation has been widely applied to the synthesis of porphyrins with fused aromatic rings [18,19], including acenaphthoporphyrins such as **1** [6]. In this synthetic approach, a tripyrrolic intermediate (tripyrrane) is required. Dihydropyracylopyrrole **12** was reacted with 2 equiv. of acetoxymethylpyrrole **13** and acetic acid in refluxing ethanol to give the required tripyrrane **14** in 62% yield (Scheme 2). The proton



Scheme 2. Synthesis of a dihydropyracyloporphyrin.

NMR spectrum of **14** in $CDCl_3$ showed the methylene bridges as broadened resonances at 3.71 ppm, while the methylene component for the benzyl esters gave a broad, anomalously upfield peak at 4.42 ppm. This behavior is typical of tripyrrane dibenzyl esters and has been attributed to the structures taking on a helical conformation in solution [20]. In DMSO d_6, the helical conformation is disrupted due to hydrogen bonding interactions and the bridge-CH_2 and ester CH_2 units now give conventional 4H singlets at 4.06 and 5.27 ppm, respectively. Hydrogenolysis of the benzyl ester protective groups of **14** over 10% Pd/C afforded the related dicarboxylic acid **15**. Subsequent condensation of **15** with pyrrole dialdehyde **16** in the presence of trifluoroacetic acid (TFA), followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), gave dihydropyracyloporphyrin **17** in 33% yield. The UV–vis spectrum for **17** in chloroform gave similar results to acenaphthoporphyrin **1**, showing multiple absorptions in the Soret region between 387 and 457 nm (Fig. 2). Notably, the Q bands were red shifted appearing at 529, 571, 596 and 657 nm. Addition of 5 equiv of TFA led to the formation of dication $\mathbf{17}H_2^{2+}$ and this

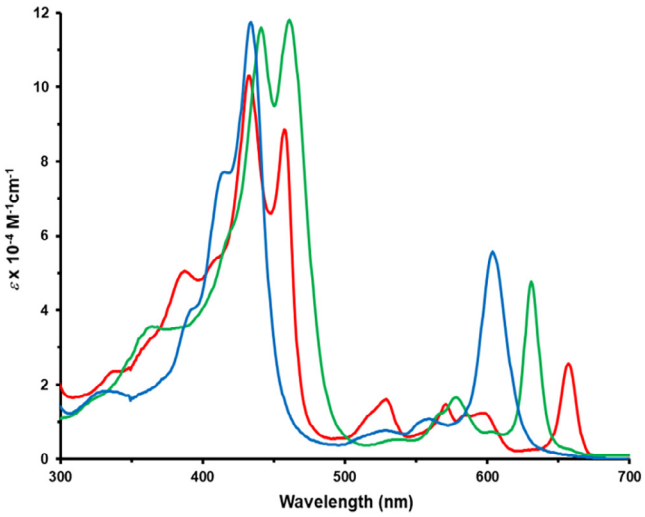


Fig. 2. UV–vis spectrum of porphyrin **17** in 1% Et_3N-$CHCl_3$ (red line), dication $\mathbf{17}H_2^{2+}$ in 0.5% TFA-$CHCl_3$ (green line) and **Ni17** in $CHCl_3$ (blue line).

showed two Soret bands at 441 and 461 nm and a long wavelength Q band at 631 nm. Further changes were noted when additional TFA was added but these were ascribed to hydrogen bonding interactions rather than the formation of further protonated species. Due to the low solubility of **17**, NMR spectra were obtained for dication **17**H_2^{2+} in TFA-$CDCl_3$. The proton NMR spectrum for **17**H_2^{2+} was consistent with an aromatic porphyrin system, showing the external *meso*-protons as two downfield 2H singlets at 10.66 and 11.17 ppm, while the internal NH resonances appeared upfield between −3.69 and −3.88 ppm. Reaction of **17** with nickel(II) acetate in refluxing DMF gave the corresponding nickel complex **Ni17**. The proton NMR spectrum for **Ni17** showed the *meso*-protons as two 2H singlets at 10.14 and 9.68 ppm, while the methyl substituents resonated at 3.46 ppm. This compares to values of 10.50, 10.01 and 3.62 ppm for **17**, which is highly insoluble, and the results indicate that the diatropicity for the macrocycle decreases in the nickel complex but increases upon protonation. The UV–vis spectrum of **Ni17** showed a Soret band at 434 nm and a strong absorption at 604 nm (Fig. 2).

Reaction of dihydropyracylopyrrole **12** with benzaldehyde in the presence of boron trifluoride etherate, followed by oxidation with DDQ, gave tetraphenyl-tetrakis(dihydropyracylo)porphyrin in 41% yield (Scheme 3). The porphyrin proved to be rather insoluble in organic solvents and was primarily characterized in its more soluble protonated form **18**H_2^{2+}. The phenyl substituents gave multiplets at 9.96 (*ortho*), 8.15 (*para*) and 8.15 (*meta*) ppm, while the embedded naphthalene units gave two doublets at 7.17 and 6.15 ppm. The resonance at 6.15 is atypically upfield but this can be explained because the naphthalene protons closer to the macrocycle fall into the shielding zone for the phenyl substituents. The NH protons appeared near 0 ppm, suggesting that this highly crowded system has significantly reduced diatropicity compared to regular porphyrins. Interestingly, the ethylene units no longer give rise to a singlet but instead afford a 16H multiplet at 3.33–3.35 ppm (Fig. 3). Although good quality NMR data could not be obtained for the free base form, this unit gave a similar multiplet for this species as well. Tetraacenaphthoporphyrins **3a** have been shown to have a deeply saddled conformations [2,21] and this would also be expected for **18** (Fig. 4). If there is a significant barrier to inversion for the saddle conformation, the two faces of the five-membered rings would fall into different chemical environments and the ethylene unit would become the observed AA'BB' system. In fact, this unit provides a unique NMR probe into the conformational mobility for these systems and demonstrates that inversion does not occur on the NMR time scale. Nevertheless, the carbon-13 NMR spectrum of **18**H_2^{2+} in TFA-$CDCl_3$ shows the presence of 14 carbon resonances and thereby demonstrates that the structure possesses the expected elements of symmetry. The UV–vis spectrum of **18** in 1% Et_3N-$CHCl_3$ gave a Soret band at 557 nm and Q bands at 634 and 700 nm (Fig. 5). In 1% TFA-$CHCl_3$, dication **18**H_2^{2+} produced a Soret band at 591 nm and a weaker absorption at 705 nm. The Soret band for **18** is only bathochromically shifted by 1 nm compared to tetraacenaphthoporphyrin **3a**. However, the related dication gives a Soret band that has been bathochromically shifted by 26 nm, indicating that the presence of the additional five-membered rings has a significant influence on these chromophores.

Reaction of **18** with nickel(II) acetate in refluxing chloroform–methanol gave the related nickel(II) complex **Ni18**. The metal complex was also rather insoluble, but its proton NMR spectrum could be obtained in $CDCl_3$ at 50 °C. The spectrum indicates that some conformational changes have occurred as the inner naphthalene protons are further shielded giving a doublet at 5.72 ppm. Furthermore, the ethylene units afforded a 16H singlet (Fig. 3),

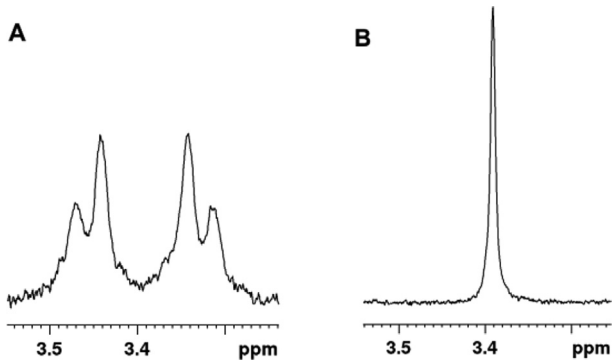


Fig. 3. Proton NMR resonances for the CH_2CH_2 unit in tetrakis(dihydropyracylo)-porphyrin dication (**18**H_2^{2+}) (A) and the related nickel(II) complex **Ni18** (B). In the spectrum for **18**H_2^{2+}, the saddle conformation is frozen in place and the ethylene unit appears as an AA'BB' system. However, this situation no longer applies to **Ni18** and the chemically equivalent ethylene protons give rise to a 16H singlet.

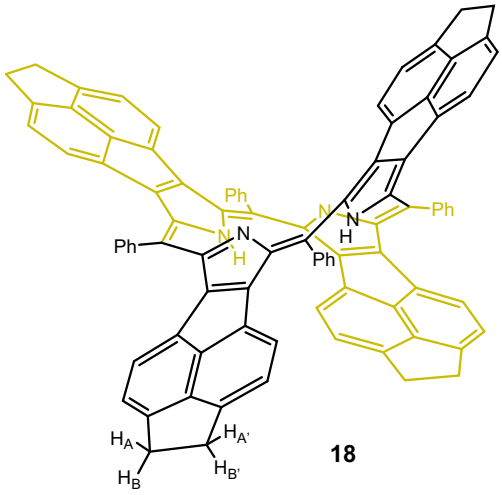
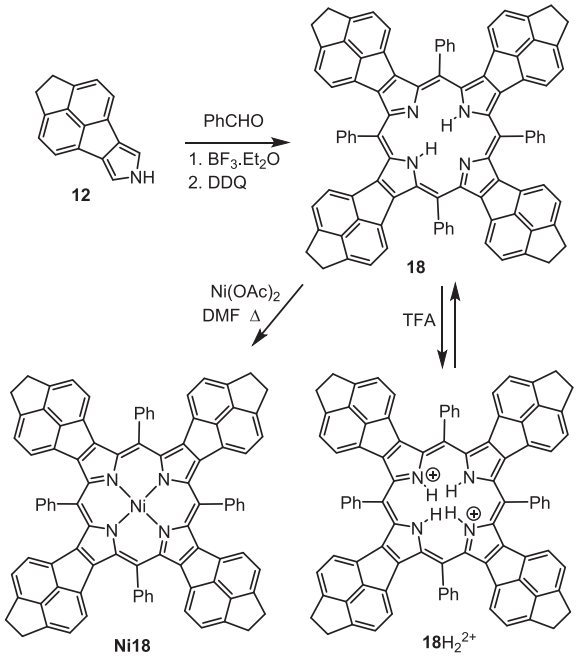


Fig. 4. Proposed saddle conformation for porphyrin **18**.



Scheme 3. Tetraphenyl-dihydropyracyloporphyrin.

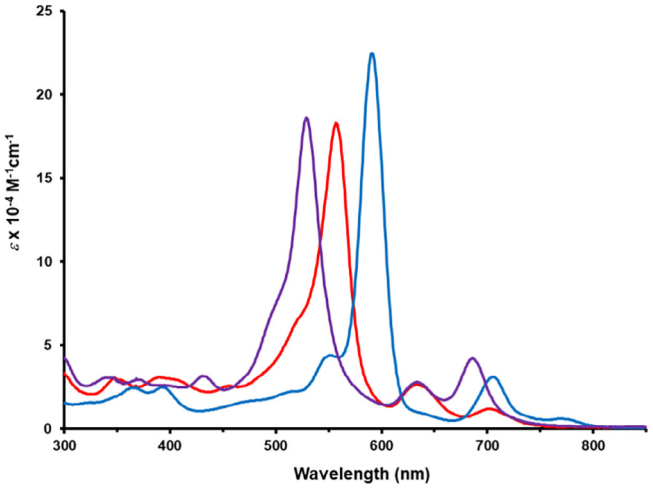


Fig. 5. UV–vis spectra of **18** in 1% Et_3N-$CHCl_3$ (red line), **18**H_2^{2+} in 1% TFA-$CHCl_3$ (blue line) and **Ni18** in $CHCl_3$ (purple line).

demonstrating that the macrocycle is no longer conformational locked. The UV–vis spectrum of Ni**18** gave a Soret band at 529 nm and weaker Q bands at 634 and 686 nm (Fig. 5). These bands are shifted to longer wavelength by 1–4 nm compared to the nickel(II) complex of **3a**, demonstrating that the five-membered rings have a much smaller influence on the UV–vis spectra for the nickel complex than the related porphyrin dication.

Attempts to dehydrogenate dihydropyracyloporphyrins **17** and **18**, or their nickel complexes **Ni17** and **Ni18**, by refluxing the samples with DDQ in chloroform or toluene did not result in the formation of the related fully conjugated pyracyloporphyrins. Although the limited solubility of dihydropyracyloporphyrins **17** and **18** may be a factor, an alternative strategy may be required to access these potentially antiaromatic porphyrinoids.

Conclusions

A dihydropyracylopyrrole ethyl ester has been prepare by reacting 5-nitro-1,2-dihydropyracylene with ethyl isocyanoacetate in the presence of a non-nucleophilic phosphazene base. Following cleavage of the ester moiety, this intermediate was reacted with two equivalents of an acetoxymethylpyrrole to form a tripyrrane and following deprotection of the terminal ester protective groups, '3 + 1′ condensation with a pyrrole dialdehyde afforded a dihydropyracyloporphyrin. The annulated porphyrin and the related nickel(II) complex gave strongly red shifted UV–vis spectra. The dihydropyracylopyrrole also reacted with benzaldehyde and BF_3-Et_2O to give a tetrakis(dihydropyracylo)porphyrin and this system gave a highly red shifted Soret band at 557 nm. The ethylene units of the dihydropyracylene moieties acted as a probe for conformational mobility in these systems. Although the fully annelated porphyrin was effectively frozen into a saddle-type conformation on the NMR time scale, the related nickel(II) complex did not exhibit conformational restriction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Experimental procedures and selected ^{1}H NMR, ^{1}H-^{1}H COSY, HSQC, DEPT-135, ^{13}C NMR, and UV-Vis spectra are provided. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152662.

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