Synthesis of the First Expanded Carbaporphyrinoid by the "4 + 1" Approach

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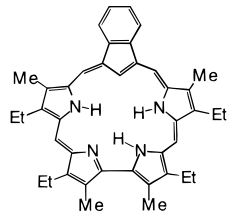
The sapphyrins (e.g., **1**), so-called because these compounds



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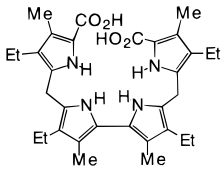

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are often isolated as intensely blue-colored crystals, were first observed by Woodward et al. as an unexpected byproduct from their early studies into the total synthesis of vitamin B_{12}.[1] These pentapyrrolic structures can be considered to be the first examples of the "expanded porphyrin" family, and this field of study subsequently grew by leaps and bounds.[2] The rational synthesis of sapphyrins and related furan and thiophene-containing species were subsequently investigated by Johnson et al.,[3] Woodward et al.,[1] and more recently by Sessler,[4] Latos-Grazynski,[5] and others.[6] The sapphyrins are members of a remarkable family of porphyrinoid structures that exhibit novel coordination chemistry and have potential utility in viral photoeradication[7] and as photosensitizers in photodynamic therapy (PDT).[8] In addition, protonated sapphyrins exhibit anion-binding properties that may give them suitable characteristics for other medicinal applications.[9] For these reasons, many related structures containing furan, thiophene[3,10] and selenophene[11] units have come under scrutiny, and this work has fueled the widespread interest in other expanded systems such as porphocyanines,[12] and others.[2]

Sapphyrins are usually prepared by the acid-catalyzed condensation of a tripyrrane dicarboxylic acid **2** with a bipyrroledicarboxaldehyde **3** (Scheme 1), which is essentially a "3 + 2" variation on the classic MacDonald condensation.[13] Recently, a "3 + 1" pathway has become widely used in the synthesis of "nonexpanded" porphyrinoids,[14,15] including novel aromatic systems such as oxybenziporphyrin **4**,[16] oxypyriporphyrin **5**,[17] and carbaporphyrins (e.g., **6**):[18] (Chart 1). The introduction of unusual subunits, such as carbocyclic rings in the case of **4** and **6**, is accomplished by the reaction of a tripyrrane **2** with a readily available aromatic dialdehyde. Given the spectacular success of the 3 + 1 methodology, we speculated that an analogous "4 +

Scheme 1

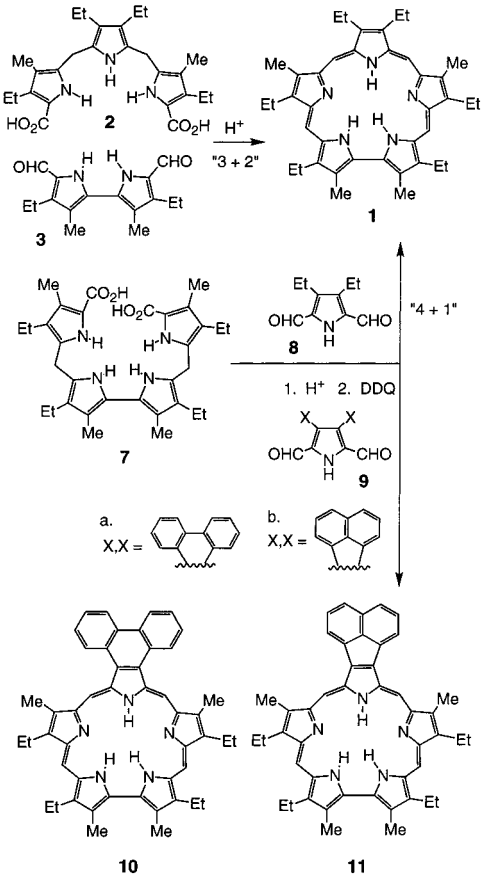
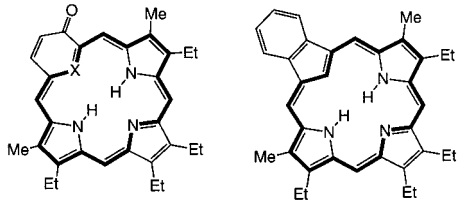


Chart 1



4 X = CH (Oxybenziporphyrin)
5 X = N (Oxypyriporphyrin)

6
Benzocarbaporphyrin

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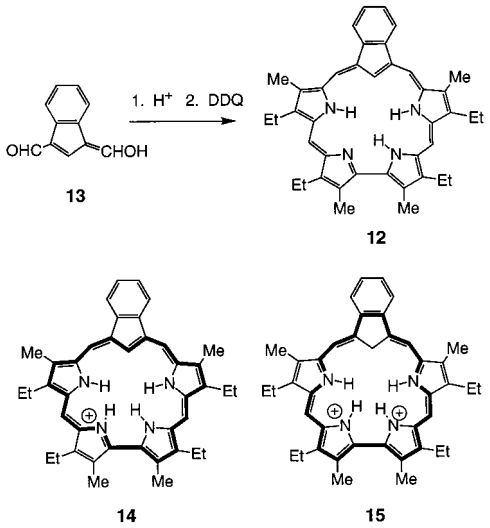
Scheme 2



1" approach might also yield fruit in the synthesis of expanded porphyrin systems related to the sapphyrins. Although in an early study by Woodward et al. decamethylsapphyrin was prepared by this route,[1] this chemistry had otherwise not been investigated. To test out whether the "4 + 1" reaction could be accomplished under the conditions applied to the "3 + 1" chemistry, sapphyrin **1** was synthesized from the known tetrapyrrole **7**[19] and pyrrole dialdehyde **8**.[14] Condensation of these reactants in the presence of TFA in dichloromethane, followed by neutralization with triethylamine and oxidation with DDQ, afforded sapphyrin **1** in 36% yield. Spurred by this success, the synthesis of related macrocyclic systems has been investigated.

Fused acenaphthylene rings induce large bathochromic shifts in the UV−vis spectra of porphyrins,[20] contrasting with the minimal influence of fused benzenoid aromatic systems such as phenanthrene,[21] and it was of some interest to see whether this was also the case in the sapphyrin series. Hence, phenanthropyrrole dicarboxaldehyde, **9a**, or acenaphthopyrrole dicarboxaldehyde, **9b**,[20] was condensed with **7** under the previously applied "4 + 1" conditions to give the related sapphyrins **10** and **11** in 33% and 16% yield, respectively (Scheme 1). As had been anticipated, the UV−vis absorptions for **11** were shifted to longer wavelengths than for the electronic spectra of both the free bases and dications of **10**. For instance, the UV−vis spectra of the dihydrochloride salt for **11** in chloroform shows a strong Soret band at 486 nm and weaker Q-bands at 647 and 710 nm, compared to values of 474, 639, and 697 nm, respectively, for **10**·2HCl. In addition, the absorption at 710 nm shows a substantially increased intensity compared to the longest wavelength band for the phenanthrosapphyrin, a trend that has also been observed for the acenaphthoporphyrins.[20]

Sapphyrins **1**, **10**, and **11** can be synthesized, in principle, by the usual "3 + 1" method, but the "4 + 1" protocol also allows the synthesis of further modified structures that would otherwise be inaccessible. This is illustrated by the synthesis of carbasapphyrin, **12**, (Scheme 2), the first example of an expanded porphyrin with a carbocyclic unit replacing one of the pyrrole rings. We recently demonstrated that diformylindene, **13**, was a superior precursor to benzocarbaporphyrin, **6**,[18a] and this suggested that the dialdehyde **13** could be used to prepare the sapphyrin analogue **12**. In this case, **13** condensed with tripyrrane, **7**, to yield a novel species that was isolated as the hydrochloride salt

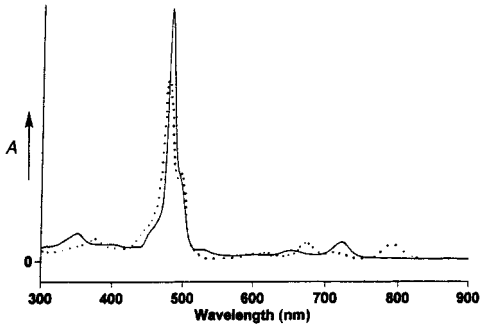


Figure 1. UV−vis spectrum of benzocarbasapphyrin **12**·HCl in chloroform (dotted line) and 5% TFA−chloroform (dication **15**, solid line).

14 in 18% yield after column chromatography and crystallization from chloroform−hexane. The identity of **14** was confirmed by proton NMR spectroscopy and mass spectrometry. The macrocycle showed a strong diatropic ring current by proton NMR, as would be expected for aromatic structures with pathways for 22π electron delocalization, with the internal CH appearing as a broad resonance near −8 ppm. The addition of a drop of TFA led to C protonation to give the dication **15**, a species that can be considered to be a bridged benzo[22]annulene. Although the delocalization pathways in **15** have to some extent been altered (as indicated by the 22π electron delocalization pathways highlighted in bold for structures **14** and **15**), this species retains a powerful macrocyclic ring current with the meso-protons downfield at 10.4 and 11.0 ppm while the internal NHs and CH_2 produced broadened upfield signals at +0.67, −0.56, and −3.75 ppm, respectively. The ease with which **14** undergoes C protonation contrasts to that of the carbaporphyrin **6** which only fully protonates on the internal carbon in 50% TFA−chloroform.[18a] This difference is undoubtedly due to the enhanced ability of the carbasapphyrin to allow charge delocalization.

The bright green monocation showed a fairly strong Soret band at 476 nm in chloroform, and the Q-bands were shifted to longer wavelengths with a moderately strong band appearing at 788 nm, a region of the electronic spectrum that is considered to be a window of opportunity in PDT[6] (Figure 1). Addition of 1% pyridine had little effect on the UV−vis spectrum, although 1% triethylamine appeared to partially deprotonate this system. Addition of the stronger base DBU (1%) afforded a slightly different spectrum that appears to correspond to the free base **12** with a Soret band at 470 nm ($\log \epsilon = 5.33$). This compares with a value of 450 nm for the free base form of the sapphyrin **1**. It is notable, however, that the intensity of this band is somewhat reduced compared to the absorptivity observed for the pentapyrrolic system **1**, paralleling the effects exhibited in the carbaporphyrin **6** compared to regular porphyrins. In 5% TFA−chloroform, the dication **15** displayed a strong Soret band at 482 nm ($\epsilon > 3.5 \times 10^5$) together with a weaker band at 722 nm (Figure 1).

These preliminary results suggest that the "4 + 1" approach will be a valuable route for the synthesis of novel expanded porphyrin structures. The straightforward synthesis of carbasapphyrins will also allow the chemical and physiological properties of this fascinating new system to be assessed. It is anticipated that this system will also allow anion binding to occur, and the expanded cavity should also enable novel coordination chemistry.

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Supporting Information Available: Experimental procedure for **14** and spectroscopic characterization of **1**, **10**, **11**, and **14** (14 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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