Giant Porphyrinoids: From Figure Eights to Nanomolecular Cavities

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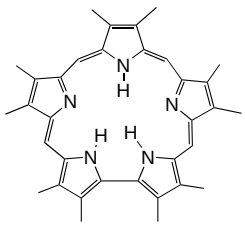
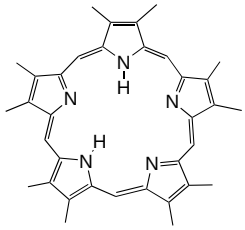
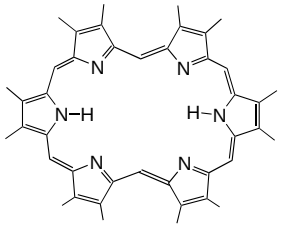
Expanded porphyrinoids with five or more conjugated pyrrolic rings have been known for well over 35 years.[1] Sapphyrin (**1**) and its analogues, pentapyrrolic structures with four carbon bridges, were originally discovered by accident during R. B. Woodward's investigations into the total synthesis of Vitamin B_{12}.[1, 2] These macrocyclic systems were further studied by Woodward and Johnson and later, in more detail, by other workers. Further examples of penta- and hexapyrrolic structures were described during the 1970's, 1980's, and early 1990's, including analogues of pentaphyrin (**2a**),[3] hexaphyrin (**2b**),[4] and rubyrin (**3**).[5] The early studies



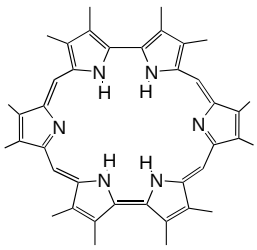
1 sapphyrin



2a pentaphyrin



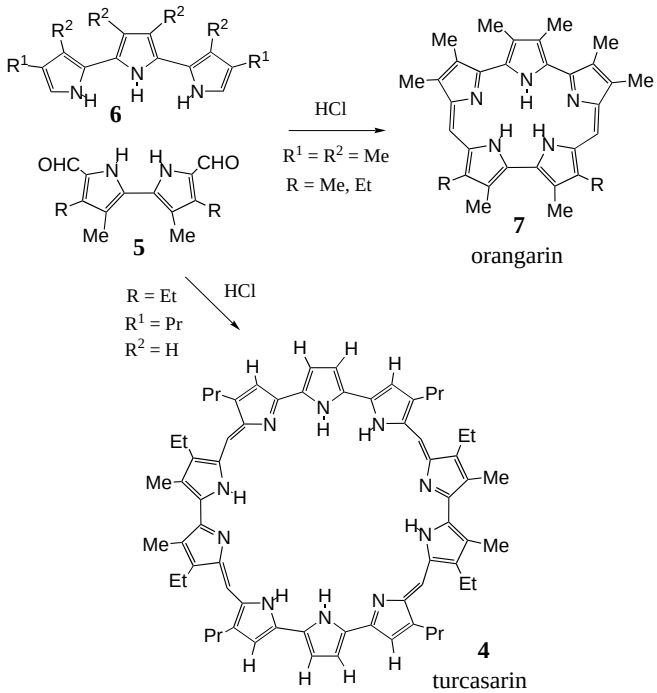
2b hexaphyrin



3 rubyrin

in this area mostly focused upon the aromatic characteristics of these conjugated oligopyrroles and to a lesser extent on their metallation chemistry.[1a, b] However, more recent observations, most notably by Sessler and co-workers,[1d, 2c] have discerned many additional intriguing properties for these systems, including selective anion binding. In addition, the unique properties of the expanded porphyrins have led to potential biomedical applications.[1b, d]

Perhaps surprisingly, no larger oligopyrrolic structures were described in the literature until 1994 when Sessler and coworkers reported the synthesis of a decapyrrolic macrocycle **4**, named turcasarin for the deep turquoise color that it exhibits in solution.[6] The synthesis of **4** made use of a "MacDonald-type" condensation,[7, 8] where a bipyrrole dialdehyde **5** is condensed with a terpyrrole **6** in the presence of an acid catalyst (Scheme 1). Interestingly, hexamethylterpyrrole underwent a "3+2" condensation with **5** to give the



Scheme 1. Sessler's synthesis of turcasarin **4**.

nonaromatic pentapyrrolic system of orangarin (**7**) as the exclusive macrocyclic product,[9] while the dialkylterpyrrole with $R^1 = Pr$, $R^2 = H$ underwent a "3+2+3+2" condensation to afford decapyrrolic turcasarin (**4**) instead.[6] This demonstrates that the peripheral substituents exert a critical influence on these cyclizations and may, under certain circumstances, facilitate the formation of higher order systems. The NMR data for **4** was consistent with a nonaromatic

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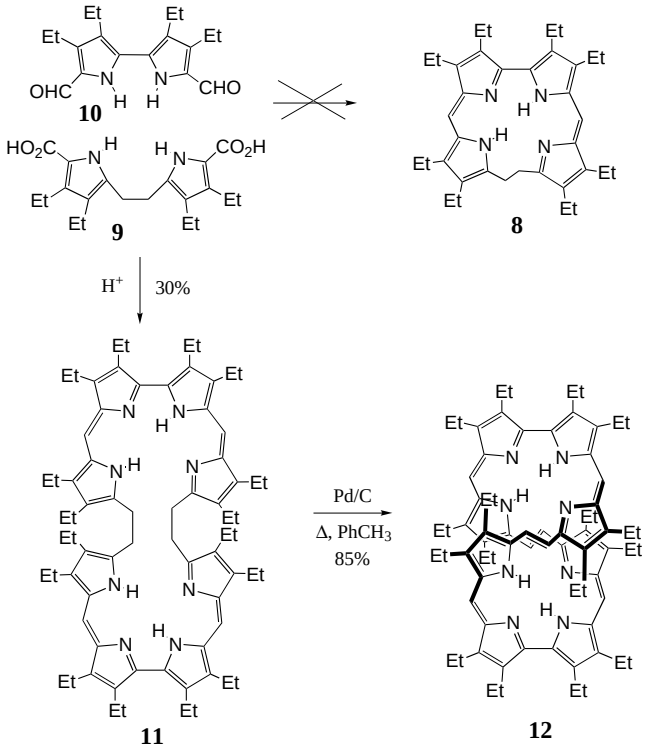
fully conjugated macrocycle that possesses C_2 symmetry and exists in a twisted "figure eight" conformation. This analysis was confirmed in the solid state for the tetrahydrochloride $[H_4(\mathbf{4})]^{4+}\,4Cl^-$ by X-ray crystallography. The point of "ribbon crossing" for the figure eight structure showed a separation between the pyrrolic units of 3.268 Å. The presence of two "hemipentaphyrin" cavities indicated that this structure might be able to form bimetallic complexes and some evidence for the generation of a bis-uranyl chelate was noted.[6] The figure eight conformations are also chiral and interconvert slowly on the NMR timescale, suggesting the possibility of isolating conformational enantiomers for this system.[6] While these possibilities have so far been little explored, a dioxaturcasarin has recently been prepared.[1d]

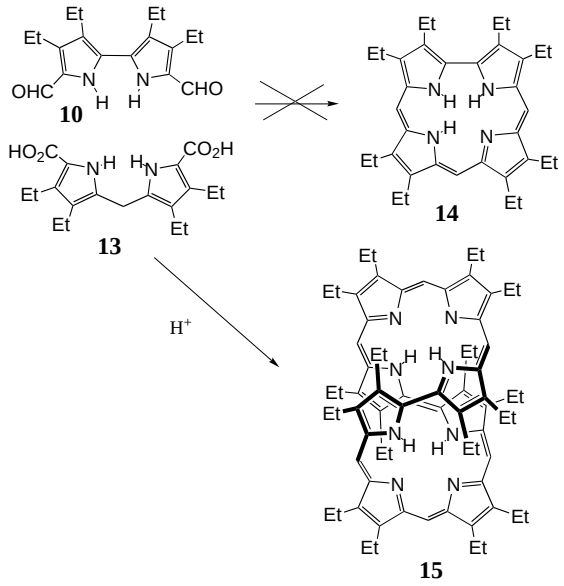
In relation to their exploration of porphyrin isomers,[10] Vogel and co-workers attempted to prepare a dihydrocorrphycene **8** by a MacDonald "2+2" condensation of 1,2-di(2-pyrrolyl)ethane (**9**) with a bipyrroledialdehyde **10** (Scheme 2).



Scheme 2. Vogel's synthesis of [36]octaphyrin-(2.1.0.1.2.1.0.1) **12**.

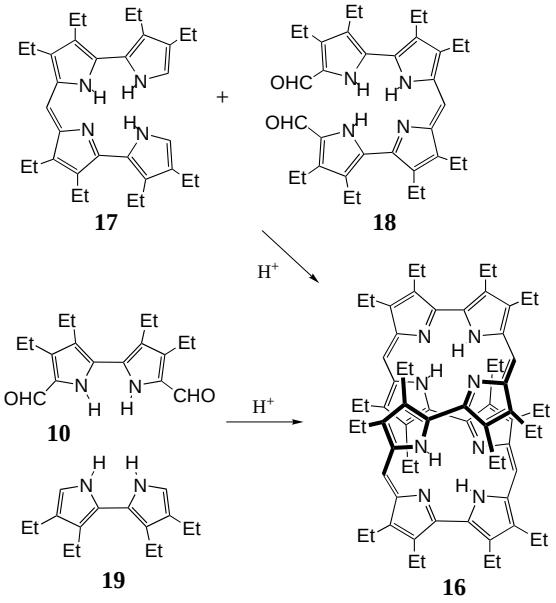
Instead of isolating the expected tetrapyrrole **8**, an octapyrrolic "2+2+2+2" condensation product **11** was obtained.[11] Dehydrogenation with Pd/C in refluxing toluene afforded the fully conjugated albeit nonaromatic [36]octaphyrin **12** (Scheme 2) in 85% yield. The NMR spectra for **11** and **12** indicated the presence of diastereotopic CH_2 groups and figure eight conformations were postulated for these structures. This was confirmed for **12** by X-ray crystallography. The barrier to conformational racemization for **12** must be high as the ethyl substituents remained diastereotopic by proton NMR spectroscopy even at 378 K.

In related studies,[11] acid-catalyzed condensation of **13** with **10** failed to give corrole (**14**), the "2+2" condensation product, but instead generated the "2+2+2+2" product [34]octaphyrin **15** (Scheme 3). Again this system favors a



Scheme 3. Vogel's synthesis of [34]octaphyrin-(1.1.1.0.1.1.1.0) **15**.

figure eight conformation as demonstrated by NMR spectroscopy and X-ray crystallography. A third octapyrrolic system **16** was prepared[12] by the "4+4" condensation of tetrapyrrole **17** with the related dialdehyde **18** in the presence of TFA, although better yields were subsequently obtained by treating bipyrrole **19** with **10** (Scheme 4). X-ray crystallography indicates that [32]octaphyrin **16** also exists as a figure eight structure, although this system appears to be far more dynamic and the barrier to racemization is predicted to be relatively low.[12]



Scheme 4. Vogel's syntheses of [32]octaphyrin-(1.0.1.0.1.0.1.0) **16**.

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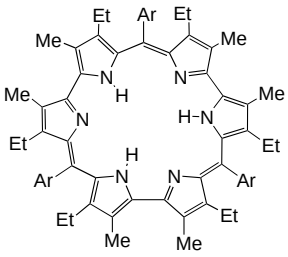
Octaphyrins **12**, **15**, and **16**, together with the tetrahydrooctaphyrin **11**, potentially provide two porphyrin-sized cavities for metal complexation. This offers the possibility of forming mononuclear, homobinuclear, and heterobinuclear metal complexes. This potential has recently been exploited in the preparation of all three categories of metal chelates for **16**, while nickel(II), palladium(II), and copper(II) homobinuclear complexes of **12** have also been synthesized.[13, 14] Although the full details of this work have as yet not been published, the electrochemical properties of these metallooctaphyrins have been examined.[13]

All of the octaphyrins described above, together with turcasarin (**4**), exist in chiral figure eight conformations and the possibility exists that these might be separated into the individual enantiomers. This has recently been accomplished for **12** and the related tetrahydrooctaphyrin **11**.[14] Octaphyrin **12** was easily resolved by HPLC on a chiral column and the individual enantiomers characterized by circular dichroism. The enantiomers of **12** proved to be optically stable at room temperature and no racemization was observed in *n*-hexane even after several hours at 60 °C. The derivative **11** was also resolved by HPLC at 15 °C, although racemization occurred at room temperature. Nonetheless, even in this case the barrier to racemization was shown to be > 85 kJ mol^{-1}.[14] In addition to these exciting developments, the Pd-Pd complex of **11** and the Pd-Pd and Cu-Cu chelates of **12** have also been resolved. These results point the way to potential applications for these novel chiral molecules as catalysts for asymmetric syntheses.

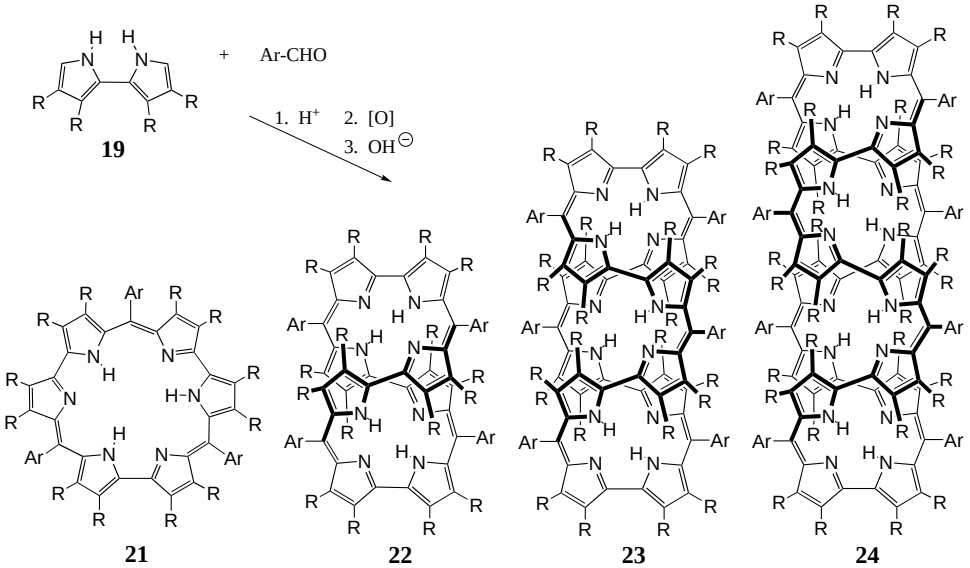
The assembly of four or more components by the MacDonald condensation can potentially be applied to condensations involving other pyrrolic building blocks such as 1,2-di(2-pyrrolyl)ethanes, dipyrrolylketones, dipyrrolylsulfides, and 2,2-di(2-pyrrolyl)propanes.[15] Although the resulting pyrrolic macrocycles may not be fully conjugated, this approach has led to the generation of a dodecapyrrolic system by cross-condensation of a bipyrroledialdehyde with a 2,2-di(2-pyrrolyl)propane.[15]

The Rothemund reaction provides the most straightforward method for porphyrin synthesis[16] in that a simple pyrrole is condensed with an aldehyde to generate the porphyrin macrocycle. Within the last years, this chemistry has been shown to generate other macrocyclic species such as N-confused porphyrins,[17] corroles,[18] sapphyrins,[19] and hexaphyrins.[20] Sessler and co-workers demonstrated that a tetraalkylbipyrrole underwent a Rothemund-type condensation to produce the hexapyrrolic system rosarin (**20**) in excellent yields.[21] As was the case for the MacDonald syntheses described above, the nature of the substituents of bipyrrole and aldehyde might be expected to influence the structures of the resulting macrocyclic products. Although the formation of a tetrapyrrolic product is disallowed due to steric constraints, the generation of higher cyclic oligomers of the rosarin type is clearly a possibility.



20, Ar = Ph, *o*-$NO_2C_6H_4$, *p*-$NO_2C_6H_4$, *p*-$H_3COC_6H_4$

In an important new study, Setsune et al. report[22] the synthesis of octa-, dodeca- and hexadecacyclopyrroles by exploiting this aspect of the Rothemund chemistry (Scheme 5). Reaction of tetraethylbipyrrole **19** with benzaldehyde in the presence of 0.25 equivalents of trifluoroacetic acid in dichloromethane at room temperature, followed by oxidation with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), afforded the rosarin **21a** in 60% yield together with a new purple compound corresponding to octaphyrin **22a**. X-ray analysis of **22a** indicated that the *meso*-phenyl substituents caused the ring system to be highly distorted from planarity. In order to further exaggerate this effect, the chemistry was repeated using 2,6-dichlorobenzaldehyde but in this case a third blue-colored macrocyclic product was isolated. The yield of rosarin was much reduced (17% **21b**), while octaphyrin **22b** and the new species dodecaphyrin **23b** were isolated in 19% and 5% yield, respectively. Reaction in the presence of zinc acetate produced the dodecaphyrin in 6% yield together with a second blue compound that was



a, Ar = Ph; **b**, Ar = 2,6-$Cl_2C_6H_3$

Scheme 5. Setsune's synthesis of octaphyrins **22**, dodecaphyrins **23**, and hexadecaphyrins **24**. R = Et.

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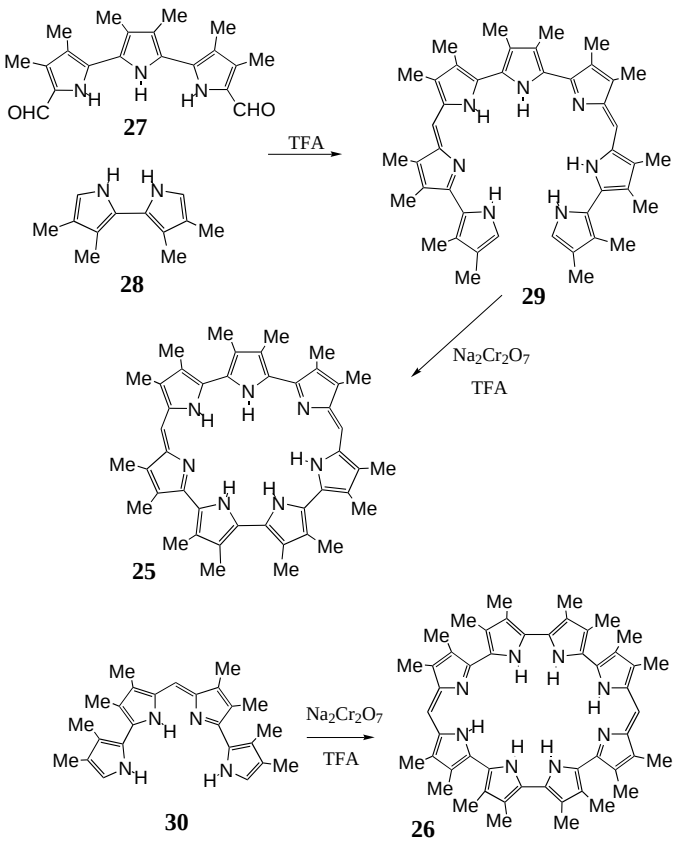
identified as hexadecaphyrin **24b** (9%).[22] These represent the largest cyclopyrrolic macrocycles described to date and the simplicity of this methodology, together with the accessibility of the bipyrrolic precursors, makes these compounds readily available for further study. Clearly, the steric bulk of the aryl substituents provides a means by which the ratio of macrocyclic products can be manipulated. The influence of the zinc acetate in directing the chemistry is also intriguing, if somewhat difficult to explain. X-ray crystallography for **23b** shows that the decapyrrolic system takes on a chiral zigzag conformation that is analogous to the figure eight structures observed previously for the octaphyrins.

The fact that macrocycles with 8, 12, or 16 pyrrole subunits can be generated by this chemistry, while 10 and 14 membered systems are not observed, may indicate that there is a preference for the alignment of four individual pyrrole rings and this structural consideration presumably guides macrocylic ring formation. The crystal structure for **23b** differs from those of Vogel's octaphyrins in that there is a greater degree of distortion from planarity and the separation between the "upper" and "lower" strands corresponds to approx. 5 Å, while the length of the entire π-conjugated structure is 9.9 Å.[22] Molecular models for the larger hexadecaphyrin **24b** suggest that the cylindrical cavity of this system has a diameter of approximately 1 nm.[22] These new systems may be able to act as hosts in molecular recognition studies and anion binding, and could potentially form complexes with three or more transition metal ions.

McMurry coupling has been extensively utilized in the preparation of porphyrin analogues[10] with CH=CH connections, but this methodology has not been applied to macrocycles with more than six pyrrole subunits. Nonetheless, this approach has been used to synthesize conjugated macrocycles with six five-membered ring subunits,[23–25] in particular, thiophene-containing systems. Wittig chemistry has also been applied to the synthesis of larger ring systems built up from furan and thiophene rings.[1d] These approaches, particularly the former, may provide alternative routes to new porphyrinoid giants in the future.

Oxidiative couplings have recently become widely applied in the synthesis of porphyrinoid systems such as sapphyrins,[26] corroles,[27] and expanded corroles.[28] In a new study, Sessler et al. report[29] the synthesis of [28]heptaphyrin **25** and [32]octaphyrin **26** (Scheme 6). Previous attempts to synthesize macrocycles with quaterpyrrole subunits from preformed quaterpyrroles had failed, and a strategy to generate this moiety by coupling bipyrrole units was explored. Acid catalyzed condensation of terpyrrole dialdehyde **27** with bipyrrole **28** afforded the open-chain heptapyrrole **29** and subsequent cyclization with sodium dichromate in TFA afforded heptaphyrin **25** in an overall 43% yield. Similarly, tetrapyrrole **30** reacted under these conditions to give octaphyrin **26** in 16% yield.[29] These systems contain a far greater number of direct pyrrole–pyrrole linkages relative to the previously discussed porphyrinoids, and for this reason can be considered to be "contracted" expanded porphyrins.[29] This greatly alters the conformations of these macrocycles. Although they are both nonaromatic compounds, heptaphyrin **25** is fairly planar and forms an open cavity. In the



Scheme 6. Sessler's Cr^{VI} oxidative cyclization methodology for the synthesis of [28]heptaphyrin-(1.0.0.1.0.0.0) **25** and [32]octaphyrin-(1.0.0.0.1.0.0.0) **26**.

diprotonated form $[H_2(\mathbf{25})]^{2+}$, it can accommodate a sulfate counterion (observed by X-ray crystallography) and hence this system shows some promise for anion binding. X-ray diffraction analysis of octaphyrin **26** was carried out on the dihydrochloride $[H_2(\mathbf{26})]^{2+}2Cl^-$ and, while this system greatly deviates from planarity, it also encloses a large cavity and can bind to two chloride anions.[29] These more open structures are unlikely to form metal complexes of the type observed for Vogel's octaphyrins, but nonetheless appear to be better suited for anion binding studies. The Cr^{VI} oxidative coupling methodology also appears to be well suited for the synthesis of expanded porphyrinoids and complements the MacDonald and Rothemund routes to related systems.

Now that efficient synthetic methodologies are available to these nonaromatic cyclo-oligopyrroles, research is likely to focus on their physical and chemical properties. There is clearly a great deal of promise in selective anion binding, molecular recognition and catalysis. In addition, now that resolutions of chiral octaphyrins and their bimetallic chelates have been achieved, applications in asymmetric catalysis and enantioselective binding can be contemplated.

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