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## Calixphyrins. Hybrid macrocycles at the structural crossroads between porphyrins and calixpyrroles\*

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**Abstract:** Calixphyrins are a class of hybrid molecules that lie at the structural crossroads between porphyrins and calixpyrroles. Porphyrins, long known for their versatile metal cation coordination chemistry, are macrocycles that contain only  $sp^2$ -hybridized bridging meso carbon atoms within their framework. Calix[n]pyrroles, on the other hand, are porphyrin analogs that contain pyrroles bridged exclusively by  $sp^3$  meso carbon centers, and in recent years have been shown to display remarkable anion-binding properties. Calix[n]phyrins bear analogy to both the porphyrins and calixpyrroles and are macrocyclic analogs that contain a mixture of  $sp^2$ - and  $sp^3$ -hybridized meso carbon bridges. This leads to partial interruptions in the conjugation pathway of the molecule, introduces novel structural features, and leads to interesting anion and cation recognition properties. It also allows for modular syntheses. In the present paper, the chemistry of calix[n]phyrins, still at an early stage of exploration, is reviewed.

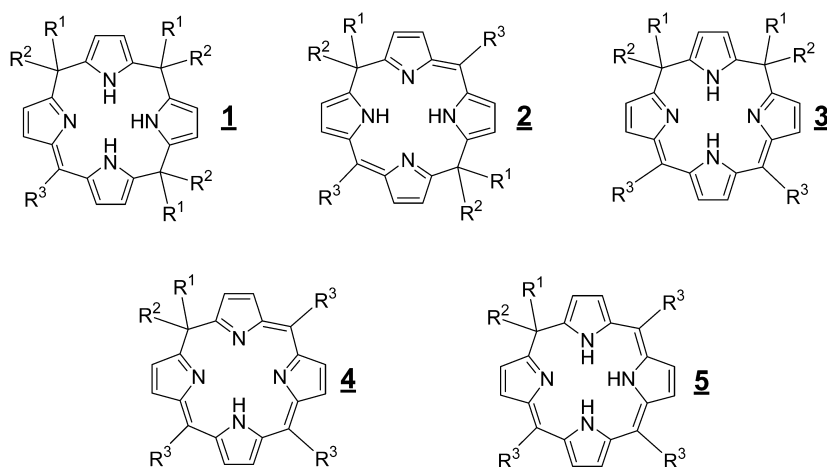
### INTRODUCTION

Calixphyrins encompass all porphyrin analogs that contain a mixture of  $sp^2$ - and  $sp^3$ -hybridized bridging meso carbon centers. In the case of hybrid systems containing four pyrroles, calix[4]phyrins, this definition encompasses systems with one, two, and three  $sp^2$ -hybridized bridging meso carbons. In contrast to calix[n]phyrins containing a greater number of pyrroles, such compounds have an established history and are known as porphomethenes **1** (one  $sp^2$ -hybridized meso carbon atom), porphodimethenes **2**, **3** (two  $sp^2$ -hybridized meso carbon atoms, arranged in either a “cis-” or “trans-like” (i.e., 5,10 or 5,15) fashion across the macrocycle), isoporphyrins **4** (three  $sp^2$ -hybridized meso carbon atoms, one NH hydrogen atom), and phlorins **5** (three  $sp^2$ -hybridized meso carbon atoms, three NH hydrogen atoms). This established history is underscored by the fact that several important calix[4]phyrin species are observed during classical porphyrin condensations involving pyrrole and an aldehyde. Here, initial condensation produces *inter alia* porphyrinogen, an octahydrocalixpyrrole [1,2]. This is then oxidized sequentially through a porphomethene and porphodimethene until a net 6 electron oxidation is achieved, leading to the formation of porphyrin [3,4].

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Historically, calix[4]pyrins have proved more difficult to isolate and study than porphyrins due to their relative conformational and electronic instability, something that abets oxidation to the corresponding porphyrin [1]. Initial proof of the formation of these species thus came from spectroscopic analyses carried out during studies of porphyrin formation or reduction. Many initial species were first isolated as metal complexes [5]. The factors influencing stability were then studied in terms of electronic and steric effects, allowing the evolution of stable nonmetalated species. Today, the field of free-base calix[n]pyrin chemistry is growing rapidly and is opening up new opportunities in the porphyrin analog area. The coordination and anion-binding properties of calix[n]pyrins, in particular, promise to be unique and different, while the structural features of these hybrid systems, containing as they do both  $sp^2$ - and  $sp^3$ -hybridized bridging meso carbon atoms within their frameworks, are sure to be of interest. This review will outline the historical origins of calix[n]pyrin chemistry while placing an emphasis on current, rapidly emerging developments in the area, including the introduction of new, modular syntheses that permit the preparation of higher-order calix[n]pyrin species.



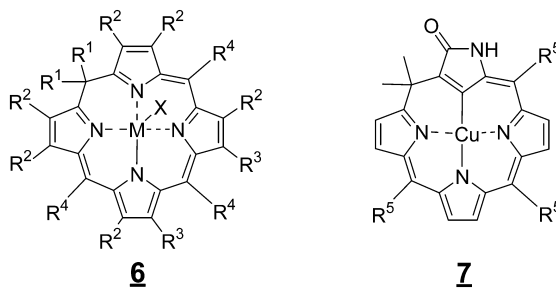
With the advent of higher-order, or expanded calix[n]pyrins, a need arises for a systematic nomenclature. Following the pattern set in the expanded porphyrin and calix[n]pyrrole areas [6], we propose a system based on distinguishing between the  $sp^2$  and  $sp^3$  meso carbon centers. For a calix[4]pyrin such as **2**, the systematic name, as proposed, would be calix[4]pyrin-(**1.1.1.1**). Starting with the highest order  $sp^2$  center, the molecule is named in the direction in which the nearest  $sp^2$  center lies. The bracketed number refers to the number of pyrroles in the macrocycle. Each individual bold and italicized number denotes the number of bridging meso centers between each pyrrole subunit. Bold numbers refer to  $sp^2$  centers, and italicized numbers refer to  $sp^3$  centers. This nomenclature, which will be elaborated on further in the section dealing with expanded calix[n]pyrins, will be used throughout the text. Common names for compounds with historical precedent will also be used.

## ISOPORPHYRINS

It is now known that isoporphyrins (**4**), a class of calix[4]pyrin-(**1.1.1.1**), are by-products of heme oxidation and intermediates in the biosynthesis of chlorophylls [7]. Initially, it was the discovery of phlorin (**5**) and the observation of its unexpected stability by Woodward [8] that led him to suggest that isoporphyrin could exist. The prescient nature of this prediction was subsequently demonstrated by Dolphin, who established that nucleophilic attack of methanol on the oxidized dication of Zn(II)TPP (TPP = tetraphenylporphyrin) leads to the formation of its unstable isoporphyrin derivative [9]. Isoporphyrins are obtained from the chemical oxidation of metalloporphyrins and are intermediates in electrophilic sub-

stitution reactions of porphyrins involving attack at the meso positions [10–20]. Additionally, they are products of electrochemical and photooxidation of the parent metalloporphyrin (containing either a transition or alkaline earth metal cation) [9,21–32]. Isoporphyrins have also been obtained as the result of protonation of neutral meso-substituted metalloporphyrins [33]. Apparently, the presence of the metal center reduces the reactivity of the pyrrole nitrogens while simultaneously increasing the susceptibility of the meso carbons towards electrophilic attack. Unfortunately, the resulting metalated isoporphyrins exist in cationic form and tend to revert to back to the parent porphyrin [7]. On the other hand, they can undergo further nucleophilic attack to produce the corresponding porphodimethene [34].

The first total synthesis of a stable isoporphyrin, at least with respect to unwanted conversion into a porphyrin, was obtained through a MacDonald condensation involving a dicarboxylic acid substituted dipyrromethane and a diformyl dipyrromethane in the presence of zinc acetate and *p*-TSA. This resulted in a Zn(II) isoporphyrin with two methyl groups at the  $sp^3$  meso position (**6**;  $R^1 = R^2 = \text{Me}$ ,  $R^3 = -(\text{CH}_2)_2\text{CO}_2\text{Me}$ ,  $R^4 = \text{H}$ ,  $X = \text{ClO}_4$ ), preventing oxidation to the corresponding porphyrin [7,35].



Recently, Furuta and Osuka reported the synthesis of an *N*-confused isoporphyrin system, **7**, obtained in 3% yield from the methanesulfonic acid-catalyzed cyclization of pyrrole, *p*-tolualdehyde, and acetone in a 4:3:1 molar ratio, followed by DDQ oxidation. The acetone group was found to be added in a *gem*-dimethyl fashion between the  $\alpha$ - and the  $\beta'$ -position of two pyrrole subunits; no other confused isomers were found. Due to the lower reactivity of acetone than tolualdehyde, at least when acting as an electrophile, it is thought that the *N*-confusion occurs in the final cyclization step. Crystal structures were obtained of the Ni(II) and Cu(II) complexes. These structures revealed the existence of dimers in the solid-state, formed through hydrogen-bonding interactions involving the outward-facing amide-like moiety present in the calixphyrin-type skeleton. Although the Ni(II) complex showed a typical ruffled structure, the Cu(II) was found to be relatively planar despite the presence of an  $sp^3$ -bridging meso carbon. System **7** thus afforded the first example of a structurally characterized organocopper(II) complex and demonstrated that complete  $\pi$ -conjugation is not a necessary prerequisite for the formation of a metal–carbon bond in a polypyrrolic system [36].

## PHLORIN

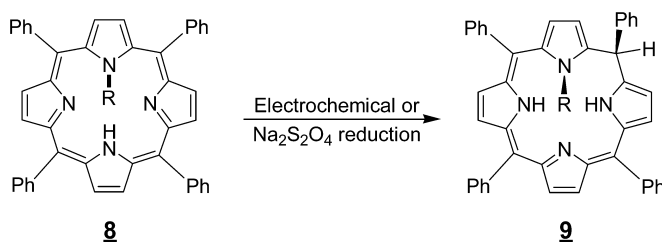
The study of phlorins (**5**), a different, more reduced, type of calix[4]phyrin-(1.1.1.1), dates back to the days of Woodward, who discovered this class of compounds during the course of his studies directed towards the total synthesis of chlorophyll a, [8] and to Mauzerall and his work on the photoreduction of porphyrins [37,38]. Phlorins are formed during nucleophilic attack on a meso position of porphyrin; many can also be obtained by electrochemical- or photo-reduction [39–41]. As a general rule, metal-free phlorins proved to be unstable and easily oxidized [39,42–44] except when bearing sterically hindered substituents at the meso positions. It was also found that a ZnTPP-derived phlorin (TPP = tetraphenylporphyrinato dianion) could be synthesized in its anionic form. In the presence of excess methanol, this latter species was found to rearrange to the corresponding ZnTPP-type chlorin

complex, the first phlorin to do so. Unfortunately, the low solubility and chemical lability of this latter species prevented proper characterization or future study [41,45–47]. The use of metalloporphyrins, and the increased electrophilic character they endowed, also permitted the use of nucleophiles in the addition-based formation of phlorins from porphyrins. In particular, Setsune *et al.* reported the formation of an air-sensitive rhodium-phlorin complex through attack of organolithium reagents upon rhodium(III) OEP (OEP = 2,3,7,8,12,13,17,18–octaethylporphyrin) [48]. Segawa and coworkers then described a direct nucleophilic addition of hydroxide ion on a nonoxidized porphyrin ring to afford an hydroxyphlorin [49]. Similarly, Sugimoto synthesized a neutral phlorin with trivalent gold from Au(III)TPP using  $\text{NaBH}_4$  in methanol; this provided a species that was stable for a relatively long period of time [50].

Without the activation induced by a coordinated electronegative metal cation in a high oxidation state, nucleophilic additions to the meso positions of porphyrins (to form the corresponding phlorin) generally require strong nucleophiles such as alkyl lithium derivatives [51]. In fact,  $\text{H}_2$ TPP reacts with *n*-BuLi in this fashion to yield the corresponding chlorin and phlorin congeners [51,52]. While stable in crystalline form, the phlorin produced in this manner readily decomposes in solution. The use of bulkier lithiating agents tended to lower the yield or give unwanted products [53]. Analogous alkylation reactions, involving the use of porphyrins not bearing substituents in the meso positions, have also been reported [54].

Historically, metal-free phlorins were difficult to isolate, and those that were stable showed strong *peri* interactions between peripheral meso and pyrrolic substituents [8,39,55–57]. Steric hindrance introduced by means of angular methyl groups [58,59], *N*(21),*N*(22) bridges [60–64], and the use of a tetra-*N*-substituted phlorin cation [65] resulted in stabilization. The use of *N*-methyl and *N*-phenyl substituted porphyrins as starting materials and treatment with reducing agents led to the formation of the corresponding phlorin; however, attempts to carry out further chemistry involving the pyrrolic nitrogen centers led to aromatization (i.e., loss of phlorin character) [66]. Smith showed that direct meso alkylation of *meso*-formylporphyrins results in substitution at the 15 position by way of a phlorin intermediate [67].

Callot has proposed possible alternative pathways to the formation of phlorin derivatives. He found that electrochemical or  $\text{Na}_2\text{S}_2\text{O}_4$ -based reduction of *N*-arylporphyrins gives stable phlorins that are epimeric to the phlorins obtained by tosylhydrazine or  $\text{NaBH}_4$  reduction of these same starting materials (Scheme 1). While the former species was found to bear a *syn* arrangement of the meso  $\text{sp}^3$  phenyl group with respect to the *N*-substituent, the products produced in the latter way possess an *anti* arrangement. Under cathodic conditions, it is thought that a radical anion is formed and that the meso carbon on the opposite face of the *N*-substituent is protonated, forcing the meso-phenyl substituent *syn* to the *N*-substituent. On the other hand, it is proposed that reducing agents effect reduction through hydride donation, a process that involves the irreversible donation of  $\text{H}^-$  to the porphyrin. In this case,



**Scheme 1** Reduction of *N*-arylporphyrins (**8**) to *N*-arylphlorin (**9**, *syn* isomer) [68].

steric factors that could hinder the approach of the reagent are expected to define the stereochemistry of the addition (i.e., *syn* or *anti*) [68].

## PORPHODIMETHENES AND PORPHOMETHENES

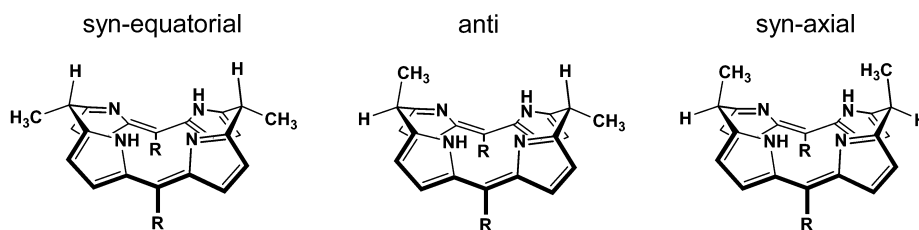
Porphomethenes {calix[4]pyrin-(1.1.1.1), **1**} as well as porphodimethenes {calix[4]pyrin-(1.1.1.1), **2** and calix[4]pyrin-(1.1.1.1), **3**} are known intermediates in the stepwise oxidation process leading to the production of porphyrin from porphyrinogen under many “normal” porphyrin-forming conditions [69,70]. Additionally, porphomethenes are the result of photoreduction [5]. The first air-stable porphodimethenes that were isolated and characterized were di- or trivalent metalated species bearing alkyl substituents at the meso positions [4,5,71–73]. Increasing steric hindrance results from the use of larger meso R substituents [74]. It is well known that relief of macrocyclic strain in overcrowded porphyrins can be achieved by converting to the corresponding porphodimethene; the larger the substituents, the more the strain is relieved by the conversion [75,76]. Although conjugation is lost, the relative energies of an overcrowded (and hence less than fully aromatic) porphyrin and the alternative porphodimethene are similar [77].

Initially, the only method to prepare porphodimethenes was via Buchler’s procedure that involves reductive alkylation at the meso position of porphyrin, an approach that was limited to the synthesis of symmetric metalated porphodimethenes [5,73,77,78]. Further, reductive alkylation was not effective on all types of metalated porphyrins or compatible with all types of *beta*-pyrrolic substituents. These limitations, in turn, made it hard to obtain a range of porphodimethenes and restricted the extent to which this class of compounds could be subject to in-depth study [74].

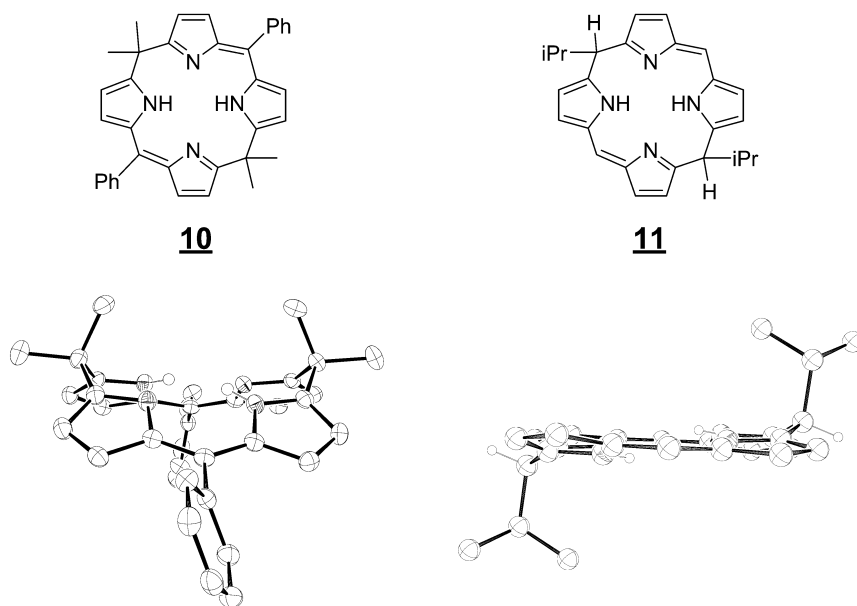
Today there are a number of alternative synthetic routes available that, taken in concert, have expanded greatly the range of metalated and nonmetalated porphodimethenes available for study [77]. These include 2+2 MacDonald-like condensation-based approaches [79], procedures based on acid-catalyzed condensations of oligo-calix[n]pyrroles with acetone [80–82], and strategies based on the condensation of sterically hindered aldehydes with pyrrole, an approach that precludes oxidation to the corresponding porphyrin [3,83].

Porphodimethenes, bearing alkyl groups at the meso  $sp^3$  centers are stable since, in contrast to species with hydrogens on these bridging atoms, they are able to resist oxidative dehydrogenation to the corresponding porphyrin. Within the context of this general statement, it has been found that the exact extent of resistance towards oxidation is dependent on the relative configuration of the  $sp^3$ -hybridized meso carbon atoms [78,84]. For instance, in the case of 5,15-porphodimethene species {i.e., calix[4]pyrins(1.1.1.1)} derived from unsymmetrical ketones, the most stable products are those in which the more bulky substituents adopt a *syn* diaxial configuration. As a general rule, this is the species wherein the substituents at the tetravalent centers are at a maximum distance from the macrocycle and steric hindrance is at a minimum.

Porphodimethenes with unsymmetrically substituted carbon atoms at the meso  $sp^3$  centers can exist in three isomeric forms: *syn* axial, *syn* equatorial, and *anti* (Scheme 2) [84]. As noted above, in the case of the 5,15-disubstituted porphodimethenes, the solid-state structure of **10** [85], as well as many metalated species [5,86–89], adopt the common “roof-like” appearance, with a bend occurring along the 5,15 axis. (Fig. 1). Alternatively, a flat geometry has been observed in the case of a *syn* axial bis-lithiated system, [90] while an *anti*-configuration in a free-base was seen in the case of a metal-free system containing bulky  $sp^3$  meso groups and octaethyl beta substituents; this “alternative” state structure of **11** [84] is also shown in Fig. 1. Interestingly, Ni(II) insertion of **11** resulted in complete conversion to a mixture of the *syn* axial and *anti* equatorial analogs. Moreover, heating **11** to reflux in glacial acetic acid for one hour resulted in complete isomerization to the *syn* axial conformation, proving that the conditions used for metal insertion result in ring opening and subsequent isomerization to the thermodynamically most stable *syn* axial isomer.



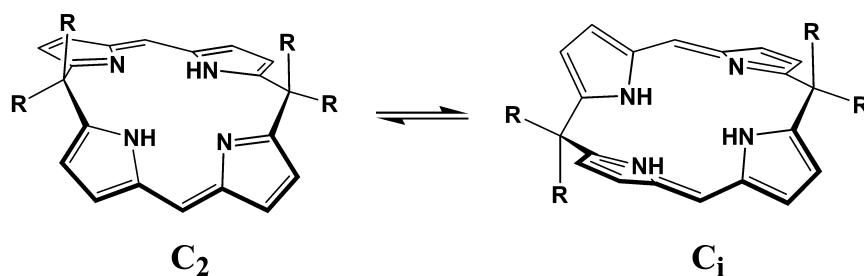
**Scheme 2** Schematic representation of the possible configurations for  $\alpha,\gamma$ -dimethyl- $\alpha,\gamma$ -dihydroporphyrins [84].



**Fig. 1** Drawing and side ORTEP views of **10** [85] and **11** [84].  $\beta$ -substituents (for **11**) and most hydrogen atoms have been omitted for clarity. Thermal ellipsoids are scaled to 40% probability level.

A very specific conformation is seen in the case of metalated systems containing axial ligands. In fact, for a variety of axial ligands, such as oxo-, chloro-, and nitrido-, the molecule is found to exhibit a *syn*-axial conformation with regard to the axial ligand [86–89,91]. For these complexes, the specific nature of the substituents on the  $sp^3$  meso carbon centers, as well as the geometry that the macrocycle assumes, were seen to influence stability toward oxidation.

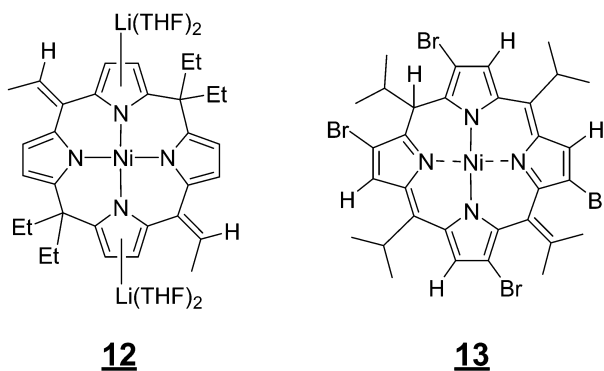
Temperature-dependent  $^1\text{H}$ - and  $^{13}\text{C}$ - NMR spectroscopy studies as well as *ab initio* calculations have been performed on calix[4]phyrins-(1.1.1.1) bearing perfluorophenyl substituents at the  $sp^2$ -hybridized meso carbon atom bridges and 2,2'-biphenyldiyl substituents at the  $sp^3$ -hybridized linking centers [82]. Interestingly, between  $-50$  and  $-100$  °C there is evidence for the existence of two chemically distinct conformations. The combination of experimental analyses and theory led to the conclusion that, although in the solid-state only one conformer is observed, in solution there is enough mobility in the  $sp^3$ -hybridized meso-like centers for them to adopt either a “*cis*” or “*trans*” relationship to one another. This results in structures with either  $C_2$  or  $C_1$  symmetry, respectively (Scheme 3). This is consistent with the alternate conformations seen in the solid-state being dependent on the electronic and



**Scheme 3** Proposed interconversion between  $C_2$  and  $C_i$  symmetry forms [82].

steric nature of the  $sp^3$  substituents. To the extent that such a conclusion is correct, it would stand to reason that minor variations in the choice of substituents could affect the symmetry of the species seen not only in solution but also in the solid-state.

Lately, several advances have been made in the field of metalated porphodimethene chemistry. Until recently, there was no method to prepare porphodimethenes bearing different meso substituents. Senge was able to circumvent this limitation by using organolithium and alkyl iodide reagents to successfully synthesize stable, mixed di, tri, and tetra- meso-substituted 5,15-disubstituted Ni(II) octaethylporphodimethenes [77]. Another recent advance is embodied in the preparation of *meso*-functionalized porphodimethenes. Floriani *et al.* were able to effect the stepwise deprotonation of Ni(II) tetraethylporphodimethene as well as the deprotonation of a dilithium hexaethylporphodimethene derivative to obtain the corresponding 5,15-disubstituted vinylidene products in metalated (**12**) and free-base forms [92,93]. Likewise, Smith and coworkers have synthesized calixphyrin-type products bearing exocyclic double bonds at the 5- and 5,15-positions (c.f., e.g., **13**) while carrying out octabrominations of Ni(II) and Cu(II) tetraisopropylporphyrin [94]. Meanwhile, Floriani has recently demonstrated the production of dianionic hexaethylporphodimethene precursors on large scale in the form of dilithium and Zr(IV) intermediates. This could potentially allow for additional transformations at the periphery of the molecule [95].



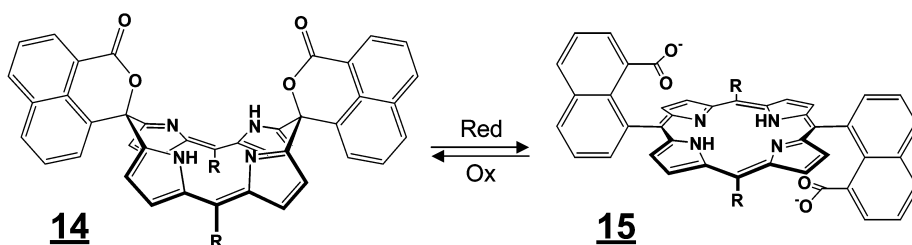
Current developments are also allowing for a diversification in the number and type of substituents available at the meso carbons. While studying the use of alkyl and aryl organolithium reagents to prepare regioselectively nona-, deca-, and undeca- and dodecasubstituted porphyrins, Senge was able to prepare 5,10- and 5,15-disubstituted metalated porphodimethenes containing a range of “mixed” meso substituents [96].

Proof for the formation of porphomethene and porphodimethene type intermediates during porphyrin synthesis has come from reacting bulky aldehydes with dipyrrolylmethanes. One example of a

stable nonmetalated porphodimethene isolated in this way has come from Do and Kim *et al.* [83]. These workers carried out a condensation between ferrocene carboxaldehyde and a dipyrrolylmethane. In this representative instance, enough steric hindrance was introduced upon macrocyclization to inhibit full, spontaneous oxidation to the porphyrin. Rather, under the reaction conditions employed, oxidation produces first an unstable porphomethene intermediate and then a stable 5,15-disubstituted porphodimethene of general structure **2** ( $R_1 = \text{H}$ ,  $R_2 = \text{ferrocenyl}$ ,  $R_3 = \text{H}$ ). This latter structure was isolable as a crystalline product and was resistant to typical chemical oxidants. Interestingly, irradiating a solution of this calixphyrin with visible light in the presence of acid under anaerobic conditions was found to effect the transformation to the porphyrin [83].

Recently, a 5,15-disubstituted porphodimethene {i.e., a calix[4]phyrin-(1.1.1.1)} was reported as the result of the first ever demonstrated reversible porphyrin-porphodimethene interconversion mediated by nucleophilic substituents proximal to the  $\text{sp}^3$  meso carbon centers. In this work, carried out by Scott and Harmjanz, a MacDonald-type 2+2 condensation between mesityldipyrromethane and acenaphthanequinone was carried out in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . Following DDQ oxidation, the air-stable *syn* and *anti* porphodimethenes were obtained [79]. Treatment of this product with KOH was found to result in ring opening and the formation of the respective porphyrin. While not germane to the present discussion *per se*, it is of interest to note that the  $\alpha,\alpha$  isomer of this porphyrinic product is soluble in  $\text{CHCl}_3$ , whereas its  $\alpha,\beta$  atropisomeric congener proved insoluble in organic solvents, possibly due to strong intermolecular hydrogen-bonding interactions involving the carboxylic acid groups.

This same research team also reported the synthesis of a very similar tetrapyrrolic skeleton bearing naphthoic acid meso-substituents in the 5 and 15 positions. In this case, a reversible, redox-controlled interconversion between the porphyrin and porphodimethene again unprecedented, was demonstrated; it was thought to proceed via a set of sequential intramolecular ring openings and closings at the meso position (Scheme 4) [97].



**Scheme 4** Schematic diagram of the porphyrin (**15**)-porphodimethene (**14**) conversion [97].

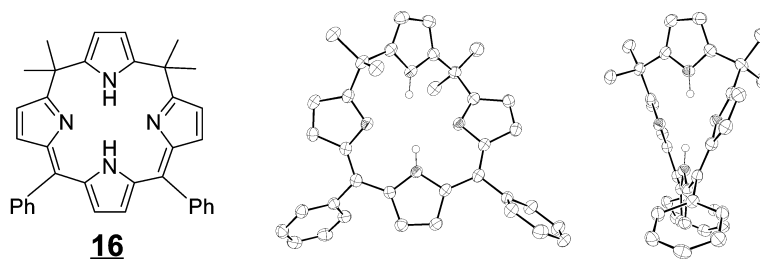
A different kind of porphodimethenes are the calix[4]phyrins-(1.1.1.1). Historically, references to these kinds of systems, bearing the disubstituted  $\text{sp}^3$ -hybridized meso-like bridges in the 5 and 10 positions, have been infrequent; presumably, this reflects their lower stability arising from their inherently lower resonance stabilization energy compared to their 5,15 congeners [98,99]. The first fully characterized free-base 5,10-disubstituted porphodimethene was obtained by Callot *et al.* and was isolated while these workers were seeking to optimize their method of producing phlorins via the direct alkylation of porphyrins [52]. Specifically, the initial success in obtaining phlorins in this way using *n*-BuLi [51] led them to consider the use of more sterically demanding bases. This, it was thought, would improve the phlorin to chlorin ratio. When *s*-BuLi was used in this way, no isolable phlorin product was obtained. On the other hand, the use of *t*-BuLi yielded, surprisingly, not the phlorin, but rather a 1% yield of chlorin and 5% yield of a 5,10-disubstituted porphodimethene. In this latter calix[4]phyrin-(1.1.1.1), the bulky *t*-butyl groups are arranged in an *anti* diaxial fashion. The solid-state structures of these porphodimethenes reveal a characteristic nonplanar tripyrrolic helical twisting that is most mani-



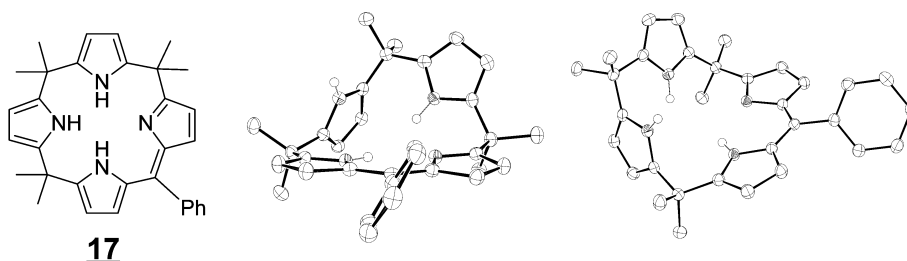
fest between the two planes defined by the isolated “calix”-type pyrrole, as exemplified in the solid-state structure of **16** (Fig. 2), an analog of Callot’s calix[4]phyrin-(1.1.1.1) that was recently prepared by the authors [85].

Porphomethenes {calix[4]phyrins-(1.1.1.1); **1**} are less common than porphodimethenes owing to their strained conformation, as illustrated in the solid-state X-ray structures of **17** (Fig. 3) [85] and the associated ease with which they may be “oxidized back” to the corresponding porphyrin species. Floriani *et al.* have developed a method that provides both metalated and metal-free porphomethenes and 5,15-disubstituted porphodimethenes on a large scale. It is predicated on a tin-assisted dealkylation of *meso*-octaethylporphyrinogen, followed by transmetalation to a lithium derivative and subsequent hydrolysis. This procedure is noteworthy because it provided the first examples of oxidatively stable porphomethene and porphodimethene derivatives bearing unsubstituted pyrroles and fully alkylated *meso* positions [90].

An important orthogonal development has been the discovery of reactions that allow for the preparation of multiple, mixed calixphyrin systems from single-step reactions that involve only a few simple reactants. Senge developed a method using sterically hindered starting materials that yields stable free-base porphomethenes, as well as 5,10- and 5,15-disubstituted porphodimethenes. Specifically, by reacting pivalaldehyde with aryl-substituted aldehydes and pyrrole, oxidation-resistant hydroporphyrins were obtained [100]. The main product of the reaction of pyrrole, pivalaldehyde, and 2,5-dimethoxybenzaldehyde (2,5-diMeO-Ph-CHO) was the porphomethene **1** ( $R_1 = \text{H}$ ,  $R_2 = t\text{-butyl}$ ,  $R_3 = 2,5\text{-diMeO-Ph}$ ). Additional test reactions were run under Lindsey conditions; these yielded the porphomethene product as well as the 5,15-disubstituted porphodimethene {i.e., a calix[4]phyrin-(1.1.1.1)} in addition to porphyrins. Using tolylaldehyde and Ag(I) oxide to help remove residual oxidant from the reaction mixture, a porphomethene {calix[4]phyrin-(1.1.1.1)}, as well as calix[4]phyrin-(1.1.1.1) and calix[4]phyrin-(1.1.1.1) species were obtained. All these hydroporphyrins proved resistant



**Fig. 2** Drawing, top and side ORTEP views of **16**. Most hydrogen atoms have been omitted for clarity. Thermal ellipsoids are scaled to 40% probability level [85].

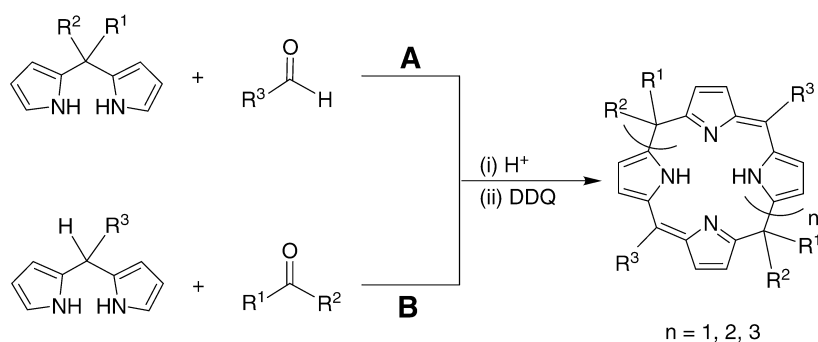


**Fig. 3** Drawing, top and side ORTEP views of **17**. Most hydrogen atoms have been omitted for clarity. Thermal ellipsoids are scaled to 40% probability level [85].

to oxidation when subject to treatment with DDQ, *p*-chloranil, Ag<sub>2</sub>O, MnO<sub>4</sub><sup>-</sup>, Ce(NH<sub>4</sub>)<sub>3</sub>NO<sub>3</sub>, and Br<sub>2</sub>. In fact, the resistance to oxidation displayed by these compounds proved so substantial that adding DBU, in an attempt to effect deprotonation and thereby facilitate oxidation, was found to result instead in ring opening [3].

Our own group has also been heavily involved in the development of modular methods for the synthesis of calix[4]phyrin derivatives. In particular, reacting a dipyrromethane unit (one sp<sup>3</sup>-hybridized bridging pro-meso carbon atom) with two molar equivalents of pyrrole in acetone, followed by DDQ oxidation, was found to yield a mixture of 5,15-disubstituted porphodimethene and porphomethene products (**10** and **17**). Starting with an appropriate tripyrrane (two sp<sup>3</sup>-hybridized pro-meso bridging atoms), the same conditions were found to yield a 5,10-porphodimethene which was shown to be highly distorted in the solid-state {i.e., **16** a calix[4]phyrin-(1.1.1.1)}. Starting with the bilane (tetrapyrane; three sp<sup>3</sup>-hybridized pro-meso carbon atoms) under analogous reaction conditions did not yield the corresponding phlorin or isoporphyrin. Rather, a 5,15-disubstituted porphodimethene {calix[4]phyrin-(1.1.1.1)} with a meso-hydroxy substituent was obtained. Reaction of this latter species with ZnCl<sub>2</sub> under aerobic conditions induced dehydration of the molecule to form a metalated isoporphyrin-type species **6** (R<sup>1</sup> = Me, R<sup>2</sup> = R<sup>3</sup> = H, R<sup>4</sup> = Ph). This species, characterized by X-ray analysis [85], is comparable to that initially observed by controlled potential oxidation of *meso*-TPP [9] or obtained by acid-catalyzed condensation of dipyrromethane precursors in the presence of zinc acetate [7,35].

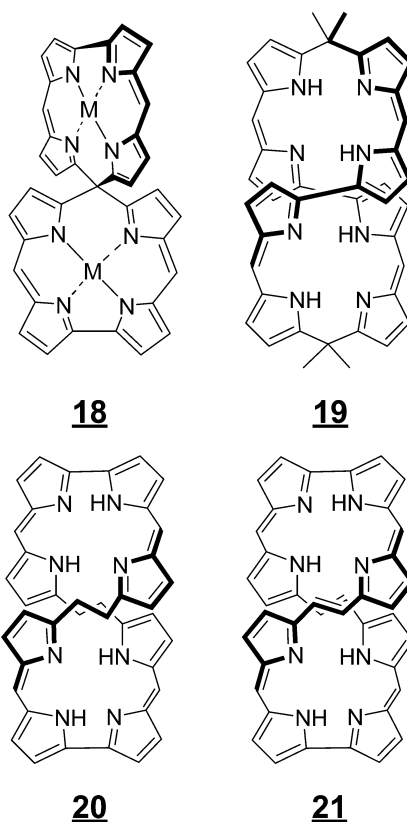
Sessler and Král and coworkers have also introduced an alternative synthetic methodology that involves switching the origin of the sp<sup>3</sup> and sp<sup>2</sup> centers. Specifically, by starting with a dialkyl-substituted dipyrrolylmethane and condensing it with an aldehyde, the sp<sup>3</sup>-hybridized centers get “built in” to the macrocyclic framework during the critical ring-forming step (Scheme 5, Pathway A). This “swap” allows for the incorporation of bulkier groups on the sp<sup>3</sup>-bridging carbons than the original methodology would allow (Scheme 5, Pathway B). For instance, pentamethylene, phenyl, and 2,2'-biphenyldiyl entities may either be appended off these centers or incorporated into them. Presumably, this greater ability to incorporate large substituents into hydroporphyrins when they are used as the electrophilic “partners” for oligopyrroles, reflects both the low reactivity of acetone and the steric encumbrance that would be inherent in using bulky oligopyrroles as reactants in such condensations [82].



**Scheme 5** Synthesis of calix[n]phyrins using dipyrrolylmethane precursors.

## EXPANDED CALIX[n]PHYRINS

The chemistry of higher-order or “expanded” calix[n]phyrins ( $n > 4$ ) is still in its infancy. While Smith has reported the synthesis of iso-oxopentaphyrin (obtained by oxidation of oxopentaphyrin) [101], only the Vogel group and our own have reported the preparation of purely pyrrole-derived expanded calix-



phyrins. Vogel's entry into this area came during attempts to synthesize a bimetallic nickel(II) complex of diketo-octaphyrin-(1.1.1.1.0.1.1.1.0). Instead of obtaining his desired product, Vogel and coworkers isolated the bis-nickel complex of the bicorrole **18**, a finding that raises the question of how the  $sp^3$ -bridging carbon atom (spiro center) influences the interactions between the two macrocyclic subunits [102]. Vogel has made further contributions to this area by demonstrating that a range of cyclo-octapyrroles (also known as octaphyrins) may be obtained from the MacDonald condensation of diformylbipyrrole with various dicarboxylic acid-substituted oligopyrroles under conditions that were expected to yield the tetrapyrrolic product, *trans*-corrphycene. While not extensively studied, larger materials, including a calix[12]phyrin-(1.0.1.1.1.0.1.1.1.0.1.1) analog, were also obtained. The octapyrrolic products obtained were all found to adopt a figure eight structure as illustrated by the line drawing of the calix[8]phyrin-(1.0.1.1.1.0.1.1) **19** [102].

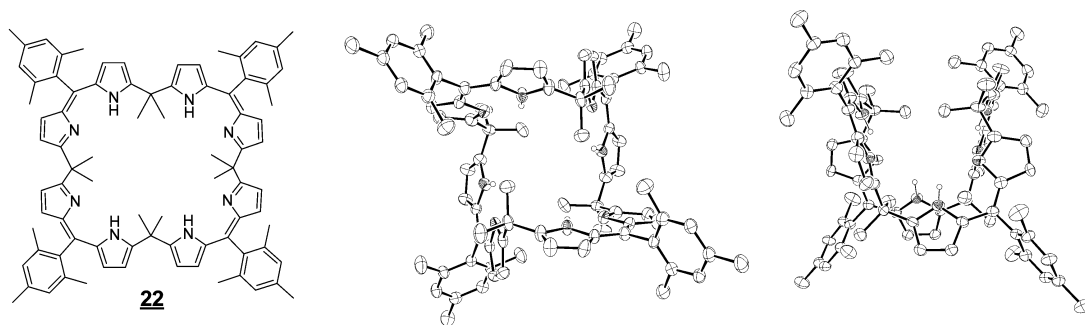
Vogel and coworkers also prepared a calix[8]phyrin-(1.0.1.2.1.0.1.2) species **20** that contains two bridging ethylene groups. (Here, the use of the digit 2 in italics is meant to denote the presence of the two atom  $sp^3$ -hybridized bridges.) They found that this calix[8]phyrin system could be oxidized to give the expanded porphyrin **21** with complete conjugation throughout the macrocycle. Interestingly, the conformations of the oxidized and nonoxidized forms of this octapyrrolic skeleton were found to be similar; apparently the conformation-defining influence of the apical bipyrrolic subunits dominates over that associated with a change in linking ethylene/ethene hybridization. Currently, these are the only free-base expanded calix[n]phyrin systems to incorporate *alpha*-linked oligopyrrolic subunits (e.g., bipyrrole) into their frameworks. The octapyrrolic species were found to form binuclear metal complexes with Pd(II) and Cu(II) [103].

In work very different from that of the Vogel group, we have recently found that the condensation of mesityldipyrromethane with acetone in the presence of a wide range of acid catalysts (e.g., TFA, MSA, etc.) at room temperature, followed by DDQ oxidation, produces not only the expected 5,15-disubstituted porphodimethene product but also the unprecedented higher-order calix[6]phyrin-(1.1.1.1.1.1) and calix[8]phyrin-(1.1.1.1.1.1.1.1) species (Scheme 5, Pathway B,  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{mesityl}$ ,  $n = 2$  and  $3$ , respectively) along with trace quantities of acyclic oligopyrroles. The total and relative yields of each product were found to be strongly dependent on the amount and type of catalyst. The X-ray structure of the calix[8]phyrin **22** (Fig. 4) reveals a distinct bowl-like conformation, with each pyrrole group oriented in a different direction than its neighbors [80].

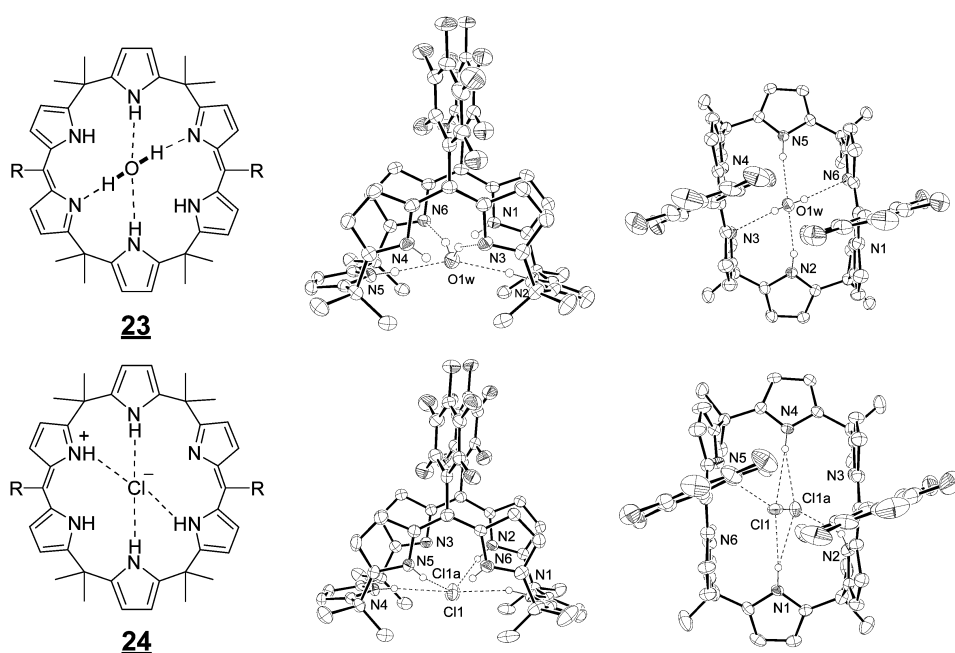
This structure leads us to infer that, as is true for typical 5,15-disubstituted porphodimethenes, with their roof-like structures enforced by the  $\text{sp}^3$ -hybridized bridging meso carbon atoms (*vide supra*), rather distorted structures will be the norm in higher-order calix[n]phyrin chemistry. This is likely to be especially true in systems such as **22** and its smaller homolog, a calix[6]phyrin-(1.1.1.1.1) species, that contain meso-like carbons with alternating hybridization [80]. Preliminary anion-binding studies of these “alternating” systems revealed a slight affinity for anions in the case of the calix[6]- and calix[8] products; however, the calix[4]phyrin-(1.1.1.1) was found to coordinate Cu(II) and Zn(II), and the calix[6]phyrin-(1.1.1.1.1) Co(III) and Ru(III), as judged from spectroscopic and mass spectrometric analysis.

In even more recent work, our group has found that condensing a *gem*-dimethyl-substituted tripyrrane with pentafluorobenzaldehyde followed by DDQ oxidation gave the calix[6]phyrin-(1.1.1.1.1.1) **23** as well as trace quantities of the calix[9]-(1.1.1.1.1.1.1.1.1) analog **25** (*vide infra*). Single crystal X-ray diffraction analysis of **23** revealed a semi-roof-like structure with apexes defined by the opposing  $\text{sp}^2$ -hybridized meso-like carbon centers (Fig. 5). The phenyl groups were found to be oriented in a *syn* fashion with respect to one another. All the pyrrole subunits were oriented in toward the cleft-like cavity and were found to be bound to a water molecule.

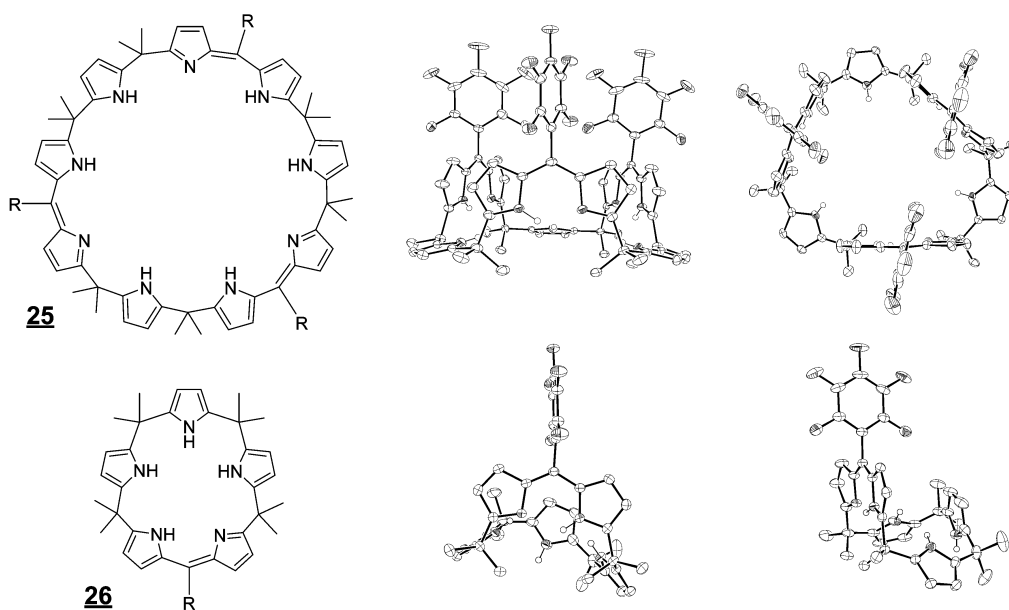
The alternating geometric arrangement of the  $\text{sp}^2$ - and  $\text{sp}^3$ -hybridized meso centers seen in the X-ray structure of **23** was found to be reflected in the resonance characteristics of each pyrrole subunit. In the original calix[6]phyrin-(1.1.1.1.1) discussed above, the macrocycle consists of four oxidized dipyrromethane units separated by  $\text{sp}^3$ -hybridized bridging carbon atoms. This causes the pyrroles along the ring to contain alternatively imine N- and amine NH-type heteroatoms in a ratio of 3:3. Calix[6]phyrin-(1.1.1.1.1) **23**, on the other hand, is comprised of two oxidized dipyrromethane units separated by a pyrrole that is, in turn, flanked by two “insulating”  $\text{sp}^3$ -hybridized tetrasubstituted bridging carbon centers. This results in a NH to N ratio of 4:2, as well as two calixpyrrole-like pyrroles with NH heteroatoms oriented in a fashion that makes them potentially suitable for anion-binding [81].



**Fig. 4** Drawing, top and side ORTEP views of **22**. Most hydrogen atoms have been omitted for clarity. Thermal ellipsoids are scaled to 40% probability level [80].



**Fig. 5** Drawing and ORTEP views of **23** and **24** (R = C<sub>6</sub>F<sub>5</sub>) showing the hetero atom labeling scheme. Hydrogen bonding interactions are indicated by dashed lines. Thermal ellipsoids are scaled to 40% probability level [81].



**Fig. 6** Drawing and ORTEP views of **25** [81] and **26** (R = C<sub>6</sub>F<sub>5</sub>). Thermal ellipsoids are scaled to 40% probability level.

Anion-binding studies revealed, surprisingly, that the unprotonated form of **23** displayed little affinity for anions (tested in the form of their tetrabutylammonium salts). As shown in Fig. 5, the mono-protonated form, however, was found to bind  $\text{Cl}^-$  in the solid-state (**24**). Anion recognition studies, carried out using the fully (doubly) protonated form revealed an affinity for  $\text{Br}^-$ ,  $\text{Cl}^-$ , and  $\text{I}^-$ ; however, perhaps as the result of competing equilibria, linear binding isotherms were seen only in the case of titration with iodide anion. In this instance, an effective binding constant of ca.  $10^8 \text{ M}^{-1}$  was derived for measurements carried out using an excess of sulfuric acid in acetone [81].

As noted above, the condensation used to produce **23** also produces the higher homolog, the [3+3] cyclization product **25** {calix[9]phyrin-(1.1.1.1.1.1.1.1)} [81]. Solid-state X-ray diffraction analysis revealed a structure similar to that of the calix[6]phyrin (Fig. 6) [81]. As yet, however, no anion recognition studies have been carried out with this potentially interesting system.

Our group has also succeeded in preparing the first-ever calix[5]phyrin-(1.1.1.1.1) **26** [104]. This product was obtained by reacting a *gem*-dimethyl-substituted pentapyrrane precursor with pentafluorobenzaldehyde under similar conditions to those used to obtain **23**. X-ray diffraction analysis revealed that, as expected, this system is highly distorted, with the phenyl group and adjacent dipyrromethane folded up over the tripyrrane (Fig. 6). Whether these interesting structural features will enhance or diminish the ability of this system to act as an anion-binding receptor is not currently known.

## CONCLUSION

In summary, calix[n]phyrins represent an old-but-new set of porphyrin analogs that, because of their unique structures and potential utility in supramolecular cation and anion recognition applications, are beginning to receive increasing attention. The fact that new synthetic methodologies have been put forward in recent years that make efficient syntheses of the metal-free forms possible will likely only serve to enhance the interest currently attendant to this class of compounds.

## ACKNOWLEDGMENTS

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