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Novel Synthesis of Hybrid Calixphyrin Macrocycles

Christophe Bucher,[†] Daniel Seidel,[†] Vincent Lynch,[†] Vladimír Král,[‡] and Jonathan L. Sessler*,[†]

Department of Chemistry and Biochemistry, Institute for Cellular and Molecular Biology, University of Texas at Austin, Austin, Texas 78712-1167, and Department of Analytical Chemistry, Technical University, 166 10 Prague 6, Czech Republic

sessler@mail.utexas.edu

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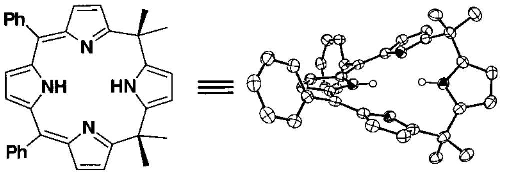
ABSTRACT



The reaction of benzaldehyde with excess pyrrole at room temperature in the absence of solvent affords a mixture of meso-substituted polypyrranes species. After separation by column chromatography, these may be used to prepare a range of calix[4]phyrin macrocycles by condensation with acetone under conditions of acid catalysis.

Porphyrinogens are important intermediates in porphyrin chemistry.[1] For instance, it is well-known that the Rothemund condensation between aldehydes and pyrrole affords inter alia unstable porphyrinogens[2] that are easily oxidized through a six-electron process to generate the corresponding porphyrins. Since the instability of the porphyrinogen-like intermediates is attributed primarily to the presence of hydrogen atoms in the meso-like positions, the use of different ketones has been employed in these reactions to produce stable porphyrinogen analogues, the so-called calix[4]pyrroles, which do not undergo autoxidation.[3] Intermediate between calix[4]pyrroles and porphyrins are porphomono-, di-, and trimethenes, species that we are terming calix[4]phyrins to highlight their presumed hybrid character. While the porphyrins are recognized as being cation coordinating ligands *par excellence*, the calixpyrroles have recently emerged as simple-to-make anion receptors. It is thus of interest to prepare and study calix[4]phyrins to ascertain whether they would react with cations, anions, or both. Currently, stable calix[4]phyrin species are without much precedence in the literature. As depicted in Figure 1, different

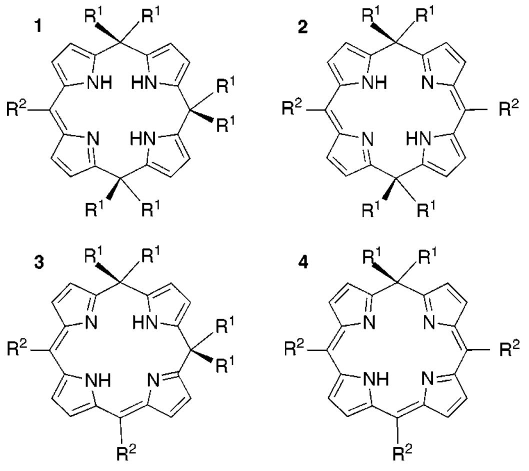


Figure 1. Hybrid calix[4]phyrin macrocycles.

[†] University of Texas at Austin.

[‡] Technical University, Prague.

(1) Smith, K. M. In *Porphyrins and Metalloporphyrins*; Elsevier: Amsterdam, 1975.

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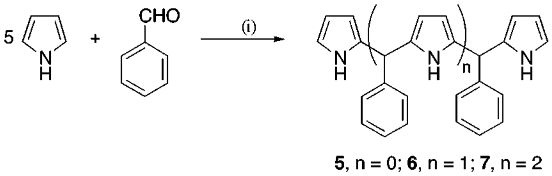
hybrids can be expected depending on the number of sp^3-hybridized meso carbon atoms (**1**, **2**, **3**, and **4**). Among them, we previously reported the synthesis of a macrocycle of type **2** (a porphodimethene) as the result of an acid-catalyzed condensation between mesityldipyrrylmethane and acetone.[4] Moreover, Floriani and co-workers have shown that derivatives of structural types **1** (porphomonomethene) and **2** could be obtained starting from *meso*-octaalkylated pophyrinogen analogues via multistep, albeit efficient, organic rearangements.[5] We report here a simple, new, two-step synthesis of calix[4]phyrin species of types **1**, **2**, **3**, and **4** that is predicated on the formation and isolation of appropriate di-, tri-, and tetrapyrrolic precursors.

The preparation of the requisite polypyrrolic precursors, the first step in the present two-step process, involves the reaction of an aldehyde with excess pyrrole at room temperature in the absence of solvent.

This affords both the well-known meso-substituted dipyrrylmethane derivatives that have been widely used as building blocks in porphyrin synthesis,[6] as well as higher tri- and tetrapyrrolic species. In accord with results reported very recently by Lee et al.,[7] we have been able to isolate these latter products from the acid-catalyzed (TFA) condensation between benzaldehyde and 5 equiv of pyrrole. This reaction process produces a complex mixture, containing, among other things, di-, tri-, and tetrapyrrane derivatives (**5**, **6**, and **7** obtained in 35, 12, and 4% yields, respectively), materials that could be separated readily by chromatography over silica gel using a hexane−dichloromethane mixture as the eluent (Scheme 1). Although **5** was found to be a stable colorless compound that decomposes very slowly, the tripyrrane and bilane[8] species **6** and **7** were found to be sensitive to light and moisture; they turn brown after being exposed to the air for a few days, even in the solid state. Thus, to avoid any degradation, these species were kept cold and stored in a dry atmosphere prior to use.

Scheme 1[a]



[a] (i) 2 h, room temperature, TFA.

With the above precursors in hand, attention turned to exploring their reactivity. It was found that by reacting **5** for 24 h with 2 equiv of pyrrole in acetone (as a presumed reactant as well as solvent) and in the presence of TFA (2 equiv), followed by DDQ oxidation and saturated Na_2CO_3 washing, a complex mixture was obtained from which **8** and **9** (Figure 2) could be isolated in ca. 5% yield each via column chromatography (silica gel; CH_2Cl_2/EtOAc, eluent).

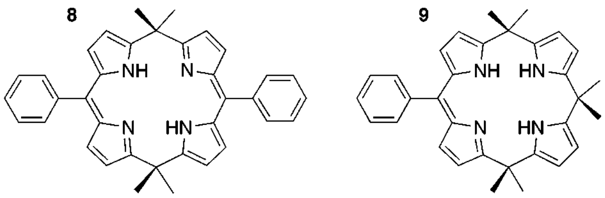


Figure 2. Calix[4]phyrin products obtained by reacting **5** with pyrrole in acetone in the presence of TFA.

X-ray quality single crystals were obtained from slow evaporation of MeOH/CH_2Cl_2 solutions of **8** and **9**. Whereas the diffraction-based structure of **8** proved coincident with that reported earlier,[4] that of the porphomonomethene[9] **9** confirmed the expectation that this system, containing as is it does three sp^3-hybridized meso carbon atoms, would exist in a highly distorted conformation (Figure 3).

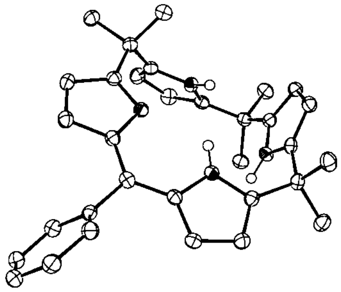


Figure 3. ORTEP[10] view of macrocycle **9**. Thermal ellipsoids are scaled to the 50% probability level.[17]

To synthesize a calix[4]phyrin of type **3** (Figure 1), a 5,-10-porphodimethene containing only two sp^3-hybridized meso carbon atoms, we used tripyrrane **6** as the critical precursor. In this case, the coupling reaction between the open chain polypyrrole, acetone, and pyrrole carried out under conditions identical to those used to prepare **8** and **9** above, afforded **10** in ca. 15% yield (Scheme 2). To the best of our knowledge, this dimethene-type calix[4]phyrin represents a new class of hybrid macrocycle that has not hitherto been reported in the literature.[11]

In contrast to what is observed in the spectrum of **8**, a species whose spectrum is characterized by one single

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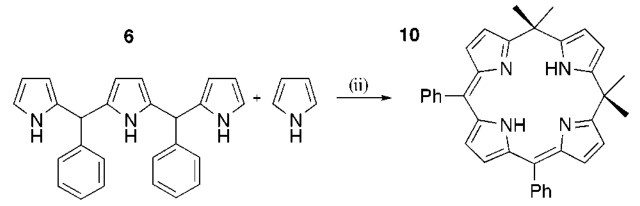
Scheme 2[a]



[a] (ii) (1) Acetone, 24 h, room temperature, TFA; (2) CH_2Cl_2, DDQ, 2 h, room temperature; (3) (Na_2CO_3) aq sat.

pyrrolic NH signal at 14.10 ppm, the ^1H NMR spectrum of **10** reveals the presence of two distinct NH signals at 10.70 and 13.06 ppm (500 MHz, $CDCl_3$). Moreover, as a consequence of proton exchange between the conjugated pyrrole NH moieties, only the equivalent β-hydrogen atoms of the unconjuguated pyrrolic subunits are seen to exhibit a ^4J (β H/NH) interaction ($\approx$3 Hz). As shown in an ORTEP perspective view (Figure 4), macrocycle **10** exhibits a nonplanar conformation but is much less distorted than **9**. The degree of deformation present in **10** may be described in terms of the twist angle between the two planes defined by the -(Me)$_2$**C**-**Py**-**C**(Me)$_2$- and -(Ph)**C**-**Py**-**C**(Ph)- subunits. The value of this angle is 49.9°, whereas the two remaining pyrrolic rings are seen to be twisted away from each other at an angle of 44.4°.

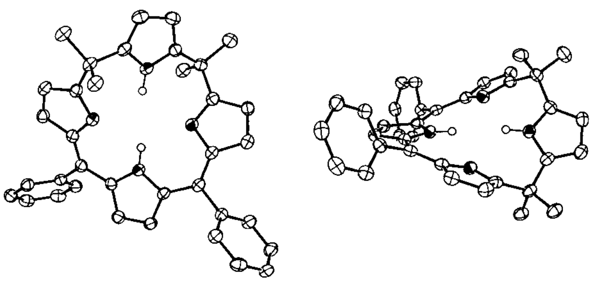


Figure 4. ORTEP perspective top and side views of **10**. Thermal ellipsoids are at the 50% probability level.[17]

Two different calix[4]phyrin type macrocyles containing only one sp^3-hybridized meso carbon atom can be found in litterature. These are isoporphyrin and phlorin (structures **4a** and **4b** in Figure 5, respectively). Phlorins are generally obtained from porphyrins by subjecting them to photochemical reduction (i.e., irradiation in the presence of a sacrificial donor).[12] By contrast, isoporphyrin has been obtained by rearrangement of porphyrin homologues with displacement of a pyrrolic NH hydrogen atom to one of the meso position.[13]

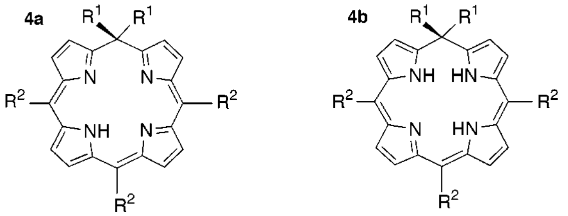


Figure 5. Calix[4]phyrin macrocycles containing only one sp^3-hybridized meso carbon atom.

Considering the great interest in these latter macrocyclic ligands, especially as regards their coordination chemistry, we have investigated a new synthetic methodology using the easily obtained β-unsubstituted bilane **7** as a potential starting material. By reacting **7** with acetone in the presence of TFA, followed by DDQ oxidation and washing with saturated aqueous Na_2CO_3, we obtained **11** as the main product in ca. 35% yield. Surprisingly, the mass spectrum of **11** was not in accordance with what would be expected for a type **4a** or type **4b** ligand, i.e., a species characterized by three sp^2-hybridized, meso-like positions.

Furthermore, both the ^1H and ^1H decoupled ^{13}C NMR spectra of **11** revealed unexpected signals at 2.96 (s, 1H) and 77.3 ppm in the ^1H and ^{13}C NMR spectra, respectively ($CDCl_3$, 500 MHz). Finally, the UV−visible spectra characteristics of **11** proved almost identical to those of **8**. This leads us to conclude that **11** is a calix[4]phyrin of type **2** (Figure 1), i.e., a system that contains only two sp^3-hybridized meso carbon atoms. Once this assumption was made, it was found that the various spectroscopic data, including those from ^{1}D NOEDIFF, ^{2}D COSY $^1H-^1H$, HMQC, and HMBC $^1H-^{13}C$ correlated NMR analyses, were in accord with those of the proposed dimethene structure **11** (Scheme 3).[14]

While the existence of the proposed *meso*-hydroxy substituent in **11** was established on the basis of the above NMR spectroscopic analyses, further proof of composition came from exchange studies. In particular, it was found that the addition of D_2O to a CD_3CN solution of **11** led to the disappearance of the signal located at 2.96 ppm that is ascribed to the hydroxyl proton, H(e) (Scheme 3). Consistent with this latter assignment, the HMBC $^1H-^{13}C$ correlation spectrum of **11** revealed no direct ^1J (C−H) interaction involving this particular signal. Further, when a long-range $^1H-^{13}C$ HMQC pulse sequence was used, a weak coupling was observed between the presumed H(e) resonance and the

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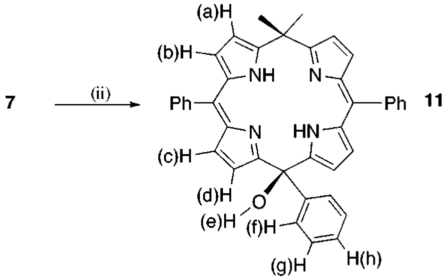
Scheme 3[a]



[a] (ii) (1) Acetone, 24 h, room temperature, TFA; (2) CH_2Cl_2, DDQ, 2 h, room temperature; (3) (Na_2CO_3) aq sat.

^{13}C NMR signal located at 77.3 ppm. By contrast, NOEDIFF experiments revealed a significant interaction between the presumptive hydroxyl signals H(e) and H(d) and H(f), respectively.

To date, attempts to obtain diffraction grade crystals of **11** have proved unsuccessful. Accordingly, the zinc(II) complex of **11** was prepared in an effort to obtain a crystalline derivative that, inter alia, would allow the structure of this novel macrocyclic system to be confirmed definitively. Toward this end, free-base **11** was stirred with an excess of zinc chloride in methanol in the presence of Et_3N for 2 h at room temperature. Black-green needles were then obtained by allowing the reaction mixture to undergo slow evaporation.

Surprisingly, the resulting X-ray diffraction structure of [(**12**)ZnCl] revealed that the reaction with, and complexation of, Zn(II) under aerobic conditions induced dehydration of the macrocycle, affording a calix[4]phyrin of type **4a** (Figure 5). While this kind of species has already been observed by Dolphin et al. as the result of controlled potential oxidation of *meso*-tetraphenylporphyrin,[15] to the best of our knowledge this is the first time such a tetrapyrrolic system has been characterized structurally. As depicted in Figure 6, the zinc center is pentacoordinate, being complexed by the four macrocyclic nitrogen atoms and one apical chloride ion. The metal ion is located at ca. 0.531(2) Å above the mean plane of the four nitrogen atoms, a distance that is higher than the ca. 0.19, 0.33, or 0.34 Å measured for $TPPZn{\cdot}H_2O$ $TpyPZn{\cdot}Py$, and $TPPZn{\cdot}ClO_4$, respectively.[16]

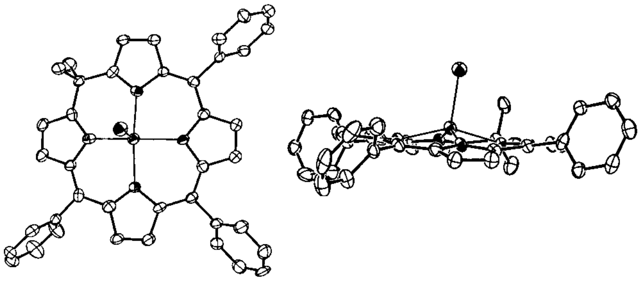


Figure 6. ORTEP top and side perspective views of [(**12**)ZnCl]. Thermal ellipsoids are at the 50% probability level.[17]

It is noteworthy that treatment of [(**12**)ZnCl] with sulfuric acid, an agent used widely to effect demetalation of porphyrin complexes, does not induce demetalation. While efforts are in progress to obtain the free-base form of **12** through alternate routes, the fact that this particular complex is so stable speaks to the chance that this and other systems will prove to be interesting and useful cation complexating agents. While the coordination chemistry of calix[4]phyrin derivatives of type **1** and **2** have already been investigated in part, type **3** hybrids, such as **10**, have not hitherto been reported and thus await detailed study. The potential use of these materials as new anion recognition agents is also noteworthy, and explorations along these latter lines are currently in progress.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE 9725339 to J.L.S.)

Supporting Information Available: Spectroscopic and analytical data for **8**−**11** and [(**12**)ZnCl]. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) All data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with Mo Kα radiation ($\lambda = 0.71073$ Å). The data were collected at −150° C using a Oxford Cryostream low-temperature device. Data reduction were performed using DENZO-SMN. The structure was solved by direct methods using SIR92 and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97. Definitions used for calculating $R(F)$, $R_w(F^2)$ and the goodness of fit, S, are given below. The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + (1.1(2) \times 10^{-6})F_c^2\, \lambda^3/(\sin 2\theta)]^{0.25}$, where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the *International Tables for X-ray Crystallography*, 1992; Tables of positional and thermal parameters, bond lengths and angles. X-ray experimental for **9**: $C_{32}H_{34}N_4$ $M = 474.6$, triclinic, space group $P{-}1$, $a = 10.3720(3)$, $b = 10.4900(3)$, $c = 13.2530(3)$ Å, and $\alpha = 79.655(2)$, $\beta = 77.5950(15)$, $\gamma = 65.6470(13)$ °. $V = 1276.26(6)$ Å^3, $Z = 2$, $\rho_c = 1.235$ g·cm^{-3}, $F(000) = 508$. A total of 324 frames of data were collected using ω scans with a scan range of 2.0° and a counting time of 42 s per frame. The function $\sum w(|F_o|^2 - |F_c|^2)^2$ was minimized, where $w = 1/[(\sigma(F_o))2 + (0.0509P)^2 + (0.3491P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.1122, with $R(F)$ equal to 0.0430, and a goodness of fit, $S, = 1.033$. X-ray experimental for **10**: $C_{36}H_{32}N_4$ $M = 520.66$, monoclinic, space group $P21/n$, $a = 8.8520(3)$, $b = 15.2620(6)$, $c = 20.6440(7)$ Å, $\beta = 102.279(2)$ °. $V = 2725.2(2)$ Å^3, $Z = 4$, $\rho_c = 1.269$ g·cm^{-3}, $F(000) = 1104$. A total of 156 frames of data were collected using ω scans with a scan range of 1.6° and a counting time of 83 s per frame. The function $\sum w(|F_o|^2 - |F_c|^2)^2$ was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0419P)^2 + (0.7526P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.107, with $R(F)$ equal to 0.0447 and a goodness of fit, $S, = 0.996$. X-ray experimental for [(**12**)ZnCl]: $C_{40}H_{29}ClN_4Zn$ $M = 666.49$, monoclinic, space group $P21/c$, $a = 20.4915(8)$, $b = 8.4301$ (3), $c = 18.9787(10)$ Å, and $\beta = 107.848(2)$°, $V = 3120.7(2)$ Å^3, $Z = 4$, $\rho_c = 1.419$ g·cm^{-3}, $F(000) = 1376$. A total of 643 frames of data were collected using ω scans with a scan range of 0.6° and a counting time of 271 s per frame. The transmission factors ranged from 0.8577 to 0.9826. The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to $1.2 \times U_{eq}$ of the attached atom ($1.5 \times U_{eq}$ for methyl hydrogen atoms). The function $\sum w(|F_o|^2 - |F_c|^2)^2$ was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0150P)^2 + (5.5000P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.1321, with $R(F)$ equal to 0.0859 and a goodness of fit, $S, = 1.273$.