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Synthesis of a Tetraazulene Porphodimethene Analogue†

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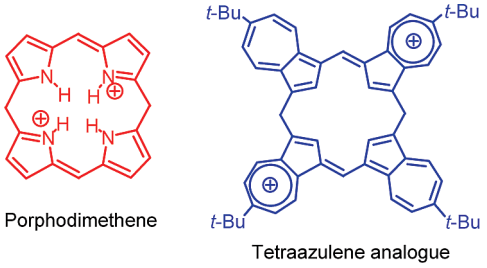
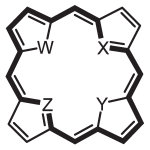


Substituted calix[4]azulenes were prepared by reacting 6-alkylazulenes with paraformaldehyde in the presence of florisil. Hydride abstraction of a calix[4]azulene with Ph_3CPF_6 afforded a tetraazulene analogue of the porphodimethenes.

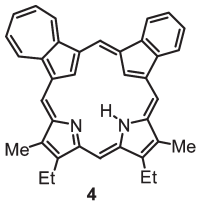
The aromatic characteristics of porphyrins (**1**) are commonly attributed to the presence of [18]annulene substructures (emphasized in bold) within the macrocycle.[1,2] However, the system has a total of 26π electrons and other models have been invoked to explain the aromaticity and diatropic properties of these structurally unique natural products.[3,4] To gain a further understanding of porphyrinoid aromaticity, as well as to explore the chemistry of related macrocyclic systems, conjugated macrocycles related to carbaporphyrins **2** have been synthesized.[5,6] Carbaporphyrins show fully aromatic characteristics and their proton NMR spectra commonly show the interior CH resonance upfield near −7 ppm.[7] These structures also show remarkable chemical properties, including the ability to form organometallic derivatives[8] and to undergo selective oxidation reactions.[9,10] The data demonstrate that the replacement of one pyrrole moiety with a cyclopentadiene or indene unit does not greatly diminish the aromatic properties of the system. In principle, 2, 3, or even 4 of the nitrogens could be replaced by carbons to give bridged annulene structures that could give further insights into the nature of porphyrinoid aromaticity.[11] The hydrocarbon porphyrin analogue "quatyrin" (**3**) is the ultimate goal of these studies, but a synthesis of this "Holy Grail" has not yet been achieved.[11] Nevertheless, a series of dicarbaporphyrinoids have been synthesized with azulene and indene subunits.[11−15] Dicarbaporphyrins with opposite carbocyclic subunits have proven to be somewhat unstable,[11,12] but recent reports on the synthesis of adjacent dicarbaporphyrinoid systems have shown that structures like **4** and **5** are quite robust and show significant diatropic properties.[14,15]

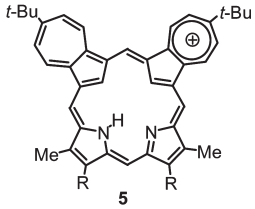


1 Porphyrin
W = Y = NH; X = Z = N

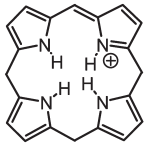
2 Carbaporphyrin
W = Y = NH; X = CH; Z = N

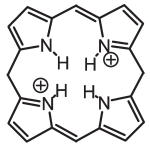
3 Quatyrin
W = Y = CH_2; X = Z = CH

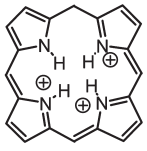


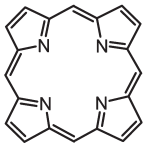


Selected Conjugated Tetrapyrrolic Macrocycles


6 Porphomethene


7 Porphodimethene


8 Isoporphyrin


9 Didehydroporphyrin

Many partially or fully conjugated systems are known that share the same tetrapyrrolic framework as porphyrins but

† Part 53 in the series Conjugated Macrocycles Related to the Porphyrins.

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(10) Carbaporphyrin ketals have also been shown to be promising agents in the treatment of leishmaniasis. See: Morganthaler, J. B.; Peters, S. J.; Cedeño, D. L.; Constantino, M. H.; Edwards, K. A.; Kamowski, E. M.; Passini, J. C.; Butkus, B. E.; Young, A. M.; Lash, T. D.; Jones, M. A. *Bioorg. Med. Chem.* **2008**, *16*, 7033–7038.
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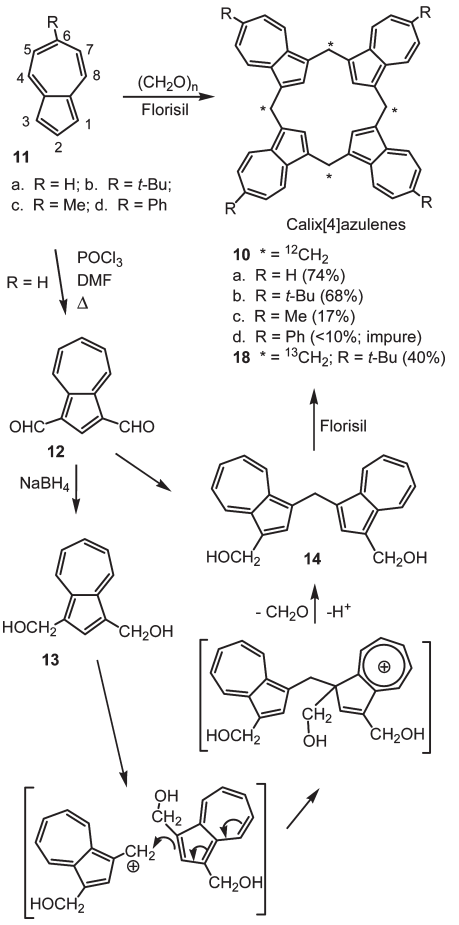
are nonaromatic. These include porphomethenes **6**, porphodimethenes **7**,[16] phlorins,[17] isophlorins,[18] isoporphyrins **8**,[19] and the formally antiaromatic didehydroporphyrins **9**.[20] Although initial interests in hydroporphyrins like **6** and **7** primarily related to their intermediacy in porphyrin syntheses,[21] *gem*-disubstituted derivatives have been widely studied in recent years for molecular recognition and anion binding studies.[22] It is worth noting that these systems are generally more stable in their protonated forms. Some years ago we reported a synthesis of calix[4]azulene **10a**, a nonconjugated macrocycle that shares the same carbon skeleton of quatyrin.[23] Although the formation of a quatyrin-like system from **10a** is unlikely, the preparation of structures resembling **6**−**8** is far more plausible. In this report, we further explore the synthesis of calixazulenes and their conversion into hydroporphyrin analogues.

The synthesis of porphyrins commonly relies on the ability of pyrroles to undergo electrophilic substitution at the α-positions and thereby generate the required carbon−carbon bonds to form the macrocycle.[21] Azulene (**11a**) also readily undergoes electrophilic substitution at the equivalent 1,3-positions and this property can be used to synthesize porphyrin analogue systems.[12,24−29] This principle was used to generate tripyrrane analogues that could be used in the synthesis of azuliporphyrins and related systems.[12,24,25] In addition, a one-pot synthesis of tetraarylazuliporphyrins was developed where mixtures of azulene, pyrrole, and arylaldehydes could be condensed in the presence of $BF_3 \cdot Et_2O$, followed by oxidation with DDQ, to directly afford the azuliporphyrins.[26−28] However, initial attempts to prepare calix[4]azulene **10a** from azulene proved to be difficult due to poor yields and problems encountered in purification.[23] Reaction of **11a** with paraformaldehyde in the presence of acid catalysts gave moderate yields of impure **10a** that was contaminated with the related calix[5]azulene, and attempts to purify the product by column chromatography on silica or alumina led to extensive degradation.[23] During the course of these investigations, stepwise routes to **10a** were considered. Azulene reacts with phosphorus oxychloride and DMF at 80 °C to give dialdehyde **12**,[30] and this was reduced with sodium borohydride in an attempt to form dicarbinol **13**. However, these reductions gave diazulene dialcohol **14** as the major product. This result was unexpected but can be rationalized by the mechanism shown in Scheme 1. Following initial reduction to give **13**, the formation of a carbocation species could be envisaged and subsequent *ipso*-substitution onto a second dicarbinol and elimination of formaldehyde would give the bridged diazulene **14**. Although this product could be identified by NMR spectroscopy, it could not be isolated in pure form. Attempts to purify **14** by chromatography on alumina or silica again led to decomposition and immediate color changes (blue to pink) were evident. Due to these difficulties, alternative materials for carrying out chromatographic purifications were explored. Florisil proved to give remarkable results, although this magnesium silicate did not allow us to isolate

SCHEME 1



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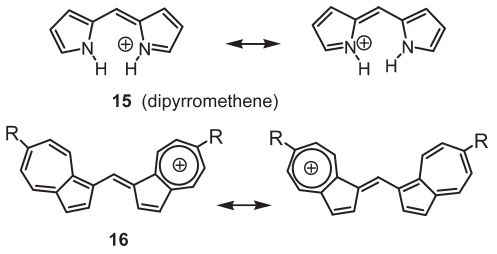
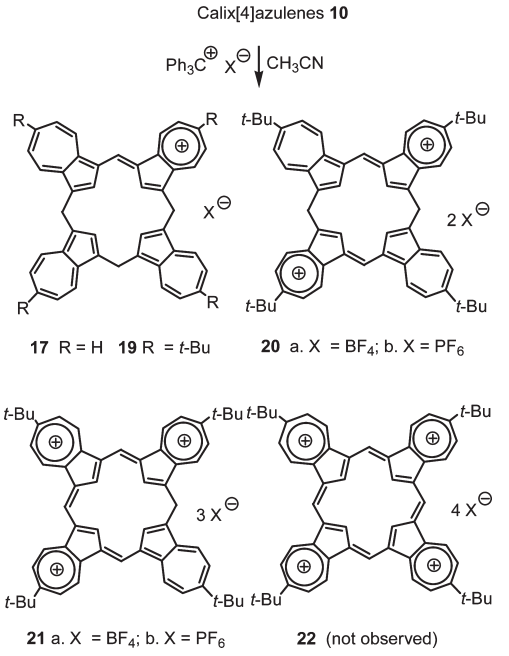
SCHEME 2



dialcohol **14**. Instead, when crude **14** was loaded onto a florisil column and eluted with dichloromethane, pure calix[4]azulene was collected as the only product. It was this observation that led us to use florisil as a catalyst for the formation of **10a**. When azulene was stirred with 4 equiv of paraformaldehyde and florisil in dichloromethane, and the catalyst was removed by suction filtration, calix[4]azulene was obtained in pure form in 74% yield.[23] Unfortunately, these conditions failed to give macrocyclic products with other aldehydes and ketones.[23]

The conjugated units in hydroporphyrins such as **6** and **7** contain dipyrromethene components **15** (Scheme 2) that are stabilized in their protonated forms by charge delocalization. Similar azulene-containing conjugated systems **16** can be obtained by treating di- or triazulenylmethanes with triphenylcarbenium hexafluorophosphate.[31] This type of conjugated diazulene system is also a component of the recently described porphyrin analogue *adj*-diazuliporphyrin **5**.[15] In an attempt to prepare conjugated tetraazulenes, **10a** was treated with 1 equiv of Ph_3CBF_4 in acetonitrile. The original calixazulene and the resulting product were both rather insoluble, and while the proton NMR data for the product were consistent with the formation of **17a** further investigations proved to be impractical. In other studies, we have found that the presence of *tert*-butyl substituents aids in increasing the solubility of azuliporphyrin systems as well as stabilizing tropylium-type characteristics.[15,25,28,32] With this in mind, the reaction of 6-substituted azulenes **11b**−**d** with paraformaldehyde was investigated. 6-*tert*-Butylazulene (**11b**)[25,31] reacted with 4 equiv of paraformaldehyde in the presence of florisil to give the tetra-*tert*-butylcalixazulene **10b** in 68% yield. The same conditions were used with 6-methylcalixazulene (**11c**),[33] but in this case poorer yields of **10c** were obtained. Following recrystallization from toluene, **10c** was isolated in 17% yield. The poorer results in this case can be attributed to the acidity of the methyl substituent, which can lead to side reactions.[33] However, 6-phenylazulene (**11d**)[25] gave very poor results and complex mixtures were formed that appeared to contain **10d**, a related calix[5]azulene, and other possibly oligomeric species. It is not clear why 6-phenylazulene no longer allows selective formation of the calix[4]azulene under the solid phase conditions. Nevertheless, we also investigated the synthesis of ^{13}C-labeled calix[4]azulene **18** from $(^{13}CH_2O)_n$. However, as 4 equiv of paraformaldehyde was used in the original syntheses,

SCHEME 3



we sought to modify the conditions so that less of the labeled precursor was required. By extending the reaction time from 90 min to 6 h, we were able to form the labeled calixazulene in 40% yield by reacting 6-*tert*-butylazulene with 1.2 equiv of ^{13}C-labeled paraformaldehyde. Therefore, a fairly efficient route to labeled calixazulenes is available.

Attempts to oxidize calixazulene **10a** or **10b** with DDQ gave no identifiable products. However, hydride abstraction with Ph_3CBF_4 or Ph_3CPF_6 gave more useful results. Both reagents could be used to generate conjugated tetraazulenes, but the best results were usually obtained with the hexafluorophosphate. In principle, the tetra-*tert*-butylcalixazulene could form porphomethene analogue **19**, porphodimethene analogue **20**, isoporphyrin analogue **21**, or didehydroporphyrin analogue **22** (Scheme 3). Unfortunately, many of the reactions gave mixtures of products. Reaction of **10b** with 1 equiv of the carbenium reagent gave samples that contained **19** but this system could not be isolated in pure form. Reactions with 5 equiv of the reagent at room temperature in acetonitrile gave the porphodimethene analogue **20** and this could be isolated by precipitation with ether. However, when **10b** was heated with the carbenium reagent, impure isoporphyrin analogue **21** was formed but again this product could not be purified. None of the results were consistent with the formation of tetracation **22**, but this system is likely to be antiaromatic and therefore unstable. Finally, all attempts to form conjugated tetraazulenes from tetramethylcalix[4]azulene **10c** were unsuccessful and complex mixtures were generated in reactions with the carbenium reagents. This is not particularly surprising as the methyl substituent is likely to deprotonate following hydride abstraction.

The porphodimethene analogue **20** gave deep blue solutions in acetonitrile and the UV−vis spectrum showed a strong absorption (molar absorptivity ca. 10^5) at 616 nm (Figure 1). This spectrum is bathochromically shifted compared to porphodimethenes **7**, which show a similarly strong

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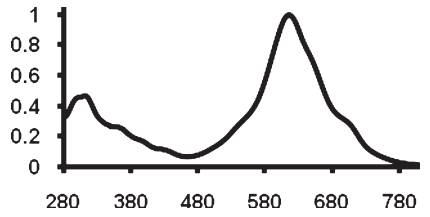

FIGURE 1. The UV−vis spectrum of **20b** in acetonitrile.

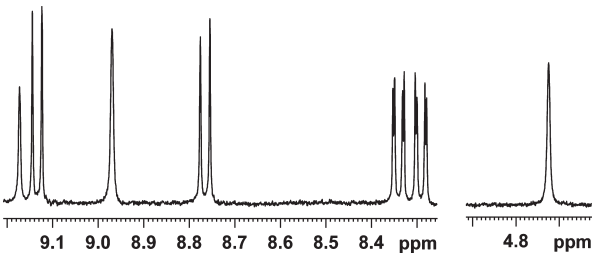

FIGURE 2. The 500 MHz proton NMR spectrum of porphodimethene analogue **20b** in CD_3CN.

peak near 500 nm. The proton and carbon-13 NMR data confirmed the identity of this system. In the proton NMR spectrum of **20**, the methylene bridge protons gave a 4H singlet at 4.72 ppm, while the conjugated methine bridges gave a 2H singlet at 9.17 ppm (Figure 2). The four azulene units are equivalent but asymmetrical and give rise to 5 resonances: a 4H singlet for the internal CHs at 8.96 ppm, two 4H doublets (J = 10.6 Hz) at 8.76 and 9.13 ppm, and two 4H doublets of doublets near 8.3 ppm. The conjugated tetraazulene was reasonably stable in solution, but addition of small amounts of calix[4]azulene **10b** gave rise to complex mixtures of products. Some reaction was noted immediately after the addition, but further changes were seen over a period of 1−2 h. These data indicate that intermolecular hydride abstraction is taking place to give mixtures including porphomethene analogue **19**. The conjugated system was also analyzed by electrospray ionization mass spectrometry. This gave a cluster of peaks near m/z 391 that corresponded to the expected doubly charged ion.

Following the completion of this study,[34] the synthesis of a *meso*-substituted tetraazulene tetracation related to structure **22** was reported. Didehydroporphyrins **9** have only been isolated as highly crowded nonplanar structures with 12 peripheral substituents,[20] and the tetraazulene tetracation is essentially an analogue of this highly distorted system. This interesting result further extends the structural diversity of azulene-containing macrocycles. However, unlike the diazuliporphyrin system **5**,[15] the tetraazulene tetracations lack any porphyrin-type aromatic characteristics.[34] The intermediary conjugated calixazulenes observed in our current studies indicate that valuable properties can be obtained at these oxidation levels as well, but further stabilization (e.g., by introducing *gem*-dialkyl groups at the *meso*-bridges) will be needed to allow these systems to achieve their full potential.

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Experimental Section

Porphodimethene Analogue 20b. Triphenylcarbenium hexafluorophosphate (49.5 mg) was added to a stirred suspension of calixazulene **10b** (20 mg, 0.025 mmol) in 10 mL of anhydrous acetonitrile, and the resulting solution was stirred for 30 min. The solution initially turned dark green and then quickly became dark blue. The volume of the solution was reduced to ca. 1 mL on a rotary evaporator, diluted with anhydrous ether, and placed in a freezer for 1 h. The dark precipitate was filtered and dried in vacuo to give the bis-hexafluorophosphate salt (14.3 mg, 0.13 mmol, 53%) as a dark solid, mp >300 °C; UV−vis (1% Et_3N−$CHCl_3$) λ_{max} (log ε) 616 (5.05), 701 nm (sh, 4.53); ^{1}H NMR (CD_3CN) δ 1.56 (36H, s), 4.72 (4H, s), 8.28 (4H, dd, J = 1.9, 10.6 Hz), 8.34 (4H, dd, J = 1.9, 10.5 Hz), 8.76 (4H, d, J = 10.6 Hz), 8.97 (4H, s), 9.13 (4H, d, J = 10.5 Hz), 9.17 (2H, s); ^{13}C NMR ($CDCl_3$) δ 25.3, 31.8, 70.6, 131.0, 135.0, 135.6, 137.6, 138.1, 138.5, 139.7, 141.6, 148.5, 150.2, 171.0. Anal. Calcd for $C_{60}H_{62}P_2F_{12}\cdot H_2O$: C, 66.05; H, 5.91. Found: C, 65.82; H, 6.00.

Acknowledgment. This material is based upon work supported by the National Science Foundation under Grant No. CHE-0616555 and the Petroleum Research Fund, administered by the American Chemical Society. Funding for a 500 MHz NMR spectrometer was also provided by the National Science Foundation under grant no. CHE-0722385.

Supporting Information Available: Synthetic procedures for **10b**, **10c**, and **18**, selected proton and carbon-13 NMR spectra, and MS data. This material is available free of charge via the Internet at http://pubs.acs.org.