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Synthesis of a Metal-Free Texaphyrin

Sharon Hannah,[†] Vincent M. Lynch,[†] Nikolay Gerasimchuk,[‡] Darren Magda,[‡] and Jonathan L. Sessler*,[†]

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, and Pharmacyclics, Inc., 995 E. Arques Avenue, Sunnyvale, California 94085

sessler@mail.utexas.edu

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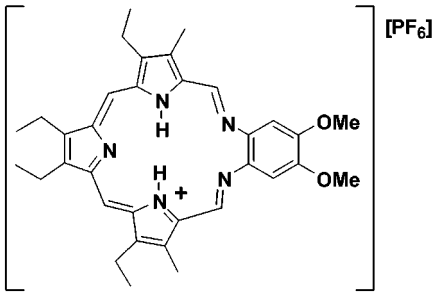
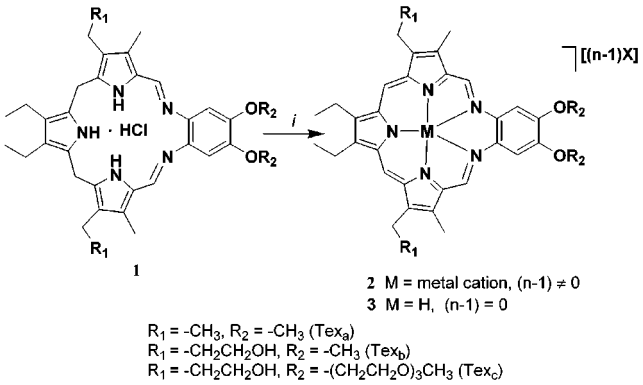
ABSTRACT



The synthesis of a metal-free form of texaphyrin, an aromatic porphyrin-like macrocycle, is described. Previously, texaphyrins could only be obtained reproducibly in the form of metal complexes. Using ferrocenium cation as the oxidizing agent and starting with a reduced porphyrinogen-like nonaromatic form of texaphyrin, we isolated, in good yield, the metal-free oxidized texaphyrin as its HPF_6 salt. This product was characterized by X-ray diffraction analysis, UV–vis spectroscopy, and cyclic voltammetry.

The synthesis of the first metal complex of texaphyrin, an aromatic Schiff base macrocycle comprised of a tripyrrolyldimethene unit joined to a phenylenediamine through two imine-type linkages, was reported in 1988.[1] This species, an aromatic cadmium(II) complex, was prepared via a simultaneous oxidation−metalation process, shown in Scheme 1, that involved treating a nonaromatic porphyrinogen-like precursor, **1**, so-called "sp^3-texaphyrin"[2] (named to reflect the hybridrization at the bridging carbon atoms) with a Cd(II) salt and air. Analysis of this first metallotexaphyrin, **2**, which showed that it contained a central core that is 20% larger than that of porphyrin, led to the conclusion that this "expanded porphyrin" should coordinate other large cations, including ones that do not fit within the confines of the porphyrin core. This prediction was subsequently realized with nearly the full series of lanthanide(III),[3] as well as Y(III) and In(III), texaphyrin complexes[4] now known. Two of these complexes, water-soluble gadolinium(III) and lutetium(III) texaphyrin (Gd(III)−Tex_c^{2+} and Lu(III)−Tex_c^{2+}, respec-

Scheme 1[a]



1

2 M = metal cation, (n-1) ≠ 0
3 M = H, (n-1) = 0

R_1 = -CH_3, R_2 = -CH_3 (Tex_a)
R_1 = -CH_2CH_2OH, R_2 = -CH_3 (Tex_b)
R_1 = -CH_2CH_2OH, R_2 = -$(CH_2CH_2O)_3CH_3$ (Tex_c)

[a] (i) Metal salt [$M^{n+}\cdot X_n$] (for **2**), base, and methanol. Reflux or stir open to air.

[†] University of Texas at Austin.
[‡] Pharmacyclics, Inc.

(1) Sessler, J. L.; Murai, T.; Lynch, V.; Cyr, M. *J. Am. Chem. Soc.* **1988**, *110*, 5586−5588.
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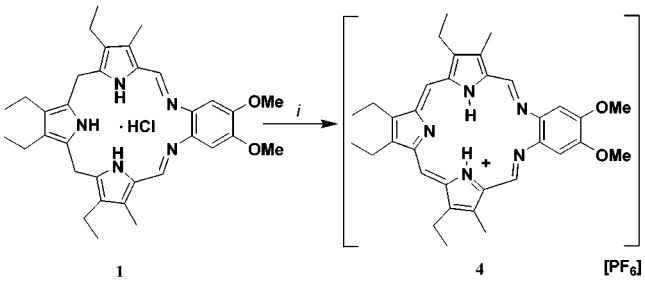
tively) are in late stage clinical trials as adjuvants for X-ray radiation and photodynamic therapies, respectively.[5] A Mn(II)−Tex_c^+ complex has also shown activity as a catalyst for the decomposition of peroxynitrite, a reactive nitrogen radical species implicated in several diseases and conditions.[6] Despite these advances, it has proved difficult to prepare the metal-free oxidized form of texaphyrin. In early work, we were able to isolate the free-base form, **3**, of an organic-soluble texaphyrin similar to Tex_a by heating a solution of sp^3-texaphyrin and *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine to reflux while open to air.[1,7] All efforts to reproduce and generalize this result, however, met with failure. As a result, the chemistry and characterization of metal-free texaphyrins have been limited. In this paper, we report an efficient synthesis of this long-sought species.

The classic approach to preparing metalated texaphyrins, and that used to prepare the lanthanide complexes now in clinical trials, relies on air or oxygen as the oxidant and is predicated on the concurrent oxidation and metalation of a reduced, sp^3-bridged precursor (e.g., **1**), as noted above. Recently, during studies directed toward the synthesis of transition metal texaphyrin complexes, it was found that metals of a sufficiently high reduction potential could act to oxidize the sp^3-texaphyrin in the absence of oxygen. For example, Mn(III) acetate hydrate (Mn(III) $E_{red} = 1.5$ V vs SHE[8]) was found to oxidize the reduced macrocycle to yield the aromatic, metalated texaphyrin complex, Mn(II)−Tex^+, even when the reaction was carried out under Ar.[6] While oxidations such as these that are effected using cations capable of being coordinated within the macrocycle lead inevitably to complex formation, the finding that an aromatic, metalated texaphyrin could be produced in the absence of air led us to take up the challenge of producing texaphyrin in its aromatic, metal-free form. Here, our thinking was that by choosing an oxidant that was unable to coordinate to the final product, we might be able to effect the direct conversion of **1** into **3**.

In accordance with this hypothesis, a wide range of oxidants were tested, including PtO_2, SeO_2, and PbO_2. Unfortunately, in no cases were isolable quantities of **3** obtained. Rather, depending on the choice of oxidant, either no reaction took place or decomposition was observed. In the case of 2,3-dichloro-5,6-dicyanoquinone (DDQ), the reduced macrocycle was successfully oxidized (as judged from UV−vis spectroscopy and mass spectrometry). Unfortunately, it was found that the aromatic macrocycle formed a complex with the reduced quinone, possibly through hydrogen-bonding interactions, leading to a fairly insoluble mixture of monomeric and polymeric products that could not be readily separated.

The above failures led us to consider the use of ferrocenium cation. This classic outer sphere oxidant has a high reduction potential, and its reduced form, ferrocene, was considered unlikely to interact with **3**. As illustrated in Scheme 2, success was encountered using this approach.

Scheme 2[a]



[a] (i) $[Cp_2Fe][PF_6]$, 2,6-lutidine, and CH_3CN.

Specifically, addition of 4 equiv of $[Cp_2Fe][PF_6]$ to an acetonitrile solution of the sp^3-Tex_a **1** under argon in the presence of 2,6-lutidine yielded the metal-free texaphyrin **3** in the form of its HPF_6 salt, **4**, isolated in up to 56% yield after purification (see Supporting Information).[9,10]

The metal-free texaphyrin salt, **4**, is fairly stable in the solid state, as well as in acetonitrile or benzonitrile solution. On the other hand, decomposition involving mainly reduction back to the sp^3 form was found to take place slowly in most other organic solvents and rapidly in the presence of alcohols and alkylamines.

Crystals suitable for single-crystal X-ray diffraction analysis were grown by slow diffusion of diethyl ether into an acetonitrile solution of **4**.[11] The resulting structure, displayed in Figure 1, revealed that the carbon atoms bridging the pyrroles were sp^2 hybridized and that the macrocycle was completely planar. These structural features, consistent with the proposed aromatic formulation, are analogous to what is seen in the various texaphyrin metal complexes, **2**,

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(9) 2,6-Lutidine is added in a 10 mol equiv excess to **1** to neutralize the HCl and the H^+ produced by oxidation of **1**. Since the acid-salt, **4**, is recovered from the reaction, presumably **3** is a stronger base than lutidine.

(10) Characterization data for **4**. UV−vis (CH_3CN) [λ_{max}, log ϵ]: 397 (4.73), 457 (4.72), 721 (4.52). ^{1}H NMR (CD_3CN): δ −5.66 (2H, s, NH), 1.57, 1.63 (6H, t, $-CH_2CH_3$), 3.01 (6H, s, CH_3−pyr), 3.69 (8H, m, $-CH_2$-CH_3), 4.36 (6H, s, $-OCH_3$), 8.19 (2H, s, H−aryl), 9.27 (2H, br s, *meso*-H), 10.52 (2H, s, imine). ^{1}H NMR (CD_2Cl_2): δ −3.15 (2H, s, NH), 1.82, 1.84 (6H, t, $-CH_2CH_3$), 3.53 (6H, s, CH_3−pyr), 3.87, 3.99 (8H, q, $-CH_2$-CH_3), 4.58 (6H, s, $-OCH_3$), 9.17 (2H, s, H−aryl), 10.04 (2H, s, *meso*-H), 11.93 (2H, s, imine). Anal. Calcd for $C_{34}H_{40}N_5O_2PF_6$: C, 58.68; H, 5.80; N, 10.07. Found: C, 58.53; H, 5.77; N, 10.27.

(11) Crystal data for **4**: $C_{34}H_{40}F_6N_5O_2P \cdot CH_3CN$, MW = 736.73, triclinic, *P*1, $a = 9.8492(1)$ Å, $b = 16.0918(2)$ Å, $c = 23.6877(3)$ Å, $\alpha = 89.730(1)°$, $\beta = 80.500(1)°$, $\gamma = 74.680(1)°$, $T = 153(2)$ K, $Z = 4$, $V = 3568.24(7)$ Å^3, 10 466 reflections with $I > 2\sigma$ used, $R = 0.0535$, and $R_w = 0.1101$.

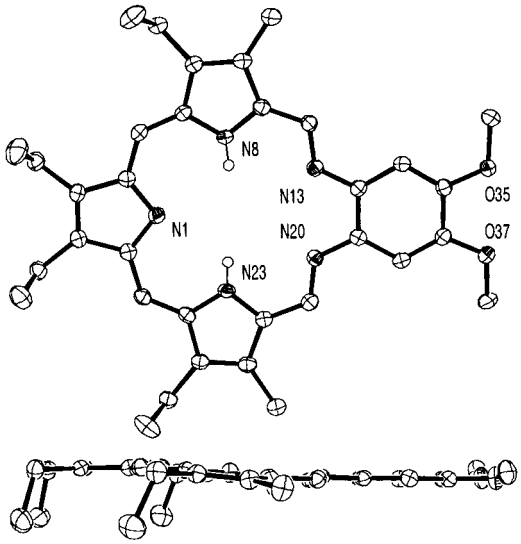

Figure 1. X-ray crystallographic structure of **4**, front and side views. All hydrogen atoms except for the pyrrolic protons have been removed for clarity. The [PF_6^-] counteranion is not shown.

characterized to date. After anisotropic refinement of all non-hydrogen atoms, the core hydrogen atoms were located and refined without constraint. They were found to be located on the outer two pyrroles in the solid state. The N−C bond lengths of the three pyrroles show no difference between those that are protonated and the one that is not. The macrocycle showed no interaction with the PF_6^- counteranion in the solid state. On the other hand, the texaphyrin rings themselves form infinite stacks within the crystal lattice.

A second product is also produced during the reaction leading to **4**. Isolated in roughly 20% yield by filtration of the concentrated crude reaction mixture prior to subjecting it to column chromatography,[12] this product was identified as being the bis-[HPF_6] salt **5**, as judged from elemental analysis.[13] While apparently as stable, or more so, than the mono-[HPF_6] salt in the solid state, this doubly protonated species proved to be only sparingly soluble in all common organic solvents. This has precluded further characterization of this species.

By washing an acetonitrile solution of **4** with 10% NaOH, we obtained the "free-base" form of Tex_a, **3**. This compound, now poorly soluble in acetonitrile, is soluble in chlorinated solvents and was analyzed by ^{1}H NMR and UV−vis spectroscopies.[14]

The spectroscopic data obtained for the monoprotonated and free-base forms of the metal-free texaphyrin provided further support for their proposed aromatic structures. For instance, the ^{1}H NMR spectrum of **4** recorded in CD_3CN at ambient temperature displayed a broad resonance for the meso-like protons at 9.27 ppm and a sharp singlet for the imine protons at 10.52 ppm. The pyrrolic protons within the core displayed a single peak at −5.66 ppm. Adding a drop of D_2O to the CD_3CN NMR sample of **4** and noting the disappearance of the resonance at −5.66 ppm as exchange occurred verified the assignment of this pyrrolic peak. A high-upfield shift for the pyrrolic protons is characteristic of aromatic protonated porphyrins[15] and expanded porphyrins, although this value is higher than most.[16] In fact, the change in chemical shift for the pyrrolic NH proton in **4**, relative to the reduced sp^3 form **1**, is more than 12 ppm,[2] a $\Delta\delta$ value that is greater than that seen upon the conversion of porphyrinogens to porphyrins.[17] This provides further support for the aromatic nature of **4**.

The positions of the ^{1}H NMR resonances of **4** were observed to shift with changes in solvent. For instance, in CD_2Cl_2, the meso-like protons and the imine protons, now both sharp singlets, are located at 10.04 and 11.93 ppm, respectively, and the pyrrolic protons were not observed at ambient temperature.

The fact that only a single peak is observed for the pyrrolic protons, with little broadening at room temperature, is consistent with the two protons either being localized on the two outer magnetically equivalent nitrogens, as seen in the solid state, or undergoing fast exchange among all three core nitrogens on the NMR time scale. On the basis of temperature-dependent ^{1}H NMR analyses, carried out in CD_2Cl_2 to allow the greatest range of study, we currently favor the latter possibility. For instance, while no NH peak was observed in the room-temperature spectrum of **4**, as the sample was cooled to 233 K, a slightly broad peak for the pyrrolic protons was observed at −3.15 ppm. At 198 K, the peak had broadened considerably and was shifted to −5.1 ppm. While such changes could be ascribed to enhanced intermolecular interactions (other peaks were found to be broadened, although to a considerably lesser extent), these are most easily interpreted in terms of a reduced rate of "pyridine-like" N: to pyrrole NH tautomeric exchange.

Unfortunately, for compound **3**, no clean signal ascribable to the pyrrolic N*H* proton was observed. Presumably, this reflects the same kind of fast tautomeric exchange inferred in compound **4**. On the other hand, clear and distinct meso- and imine proton signals were observed at 9.23 and 11.02 ppm, respectively, that are barely shifted compared to that seen for **4** in CD_2Cl_2.

The UV−vis spectra of **3**−**5**, reproduced in Figure 2, are dominated by the classic Soret- and Q-like bands in the ca.

(12) The relative yields of salts **4** and **5** depend on the reaction conditions used. For instance, carrying out the oxidation procedure at the same 4:1 oxidant-to-sp^3-texaphyrin stoichiometry but at a higher concentration was found to increase the yield of **5** at the account of **4**.

(13) Characterization data for **5**. UV−vis (CH_3CN) [λ_{max}, log ϵ]: 414 (4.56), 459 (4.80), 723 (4.31). Anal. Calcd for $C_{34}H_{41}N_5O_2F_{12}P_2$: C, 48.52; H, 4.91; N, 8.32. Found: C, 49.88; H, 4.95; N, 8.12.

(14) Characterization data for **3**. UV−vis (CH_3CN) [λ_{max}, log ϵ]: 403 (4.66), 457 (4.90), 719 (4.59). ^{1}H NMR ($CDCl_3$): δ 1.66, 1.63 (6H, t, $-CH_2CH_3$), 3.06 (6H, s, CH_3−pyr), 3.55 (8H, m, $-CH_2CH_3$), 4.42 (6H, s, $-OCH_3$), 8.67 (2H, s, H−aryl), 9.23 (2H, s, *meso*-H), 11.02 (2H, s, imine.)

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(16) Sessler, J. L.; Weghorn, S. J. *Expanded, Contracted, and Isomeric Porphyrins*; Elsevier: Oxford, 1997.

(17) For instance, oxidative conversion of octaethylporphyrinogen to the corresponding porphyrin, H_2OEP, leads to an upfield shift of 10.6 ppm for the N*H* protons; see: (a) Whitlock, H. W., Jr.; Buchanan, D. H. *Tetrahedron Lett.* **1969**, *42*, 3711−3714. (b) Scheer, H.; Katz, J. J. In *Porphyrins and Metalloporphyrins*; Smith, K., Ed.; Elsevier: Amsterdam, 1975; Chapter 10.

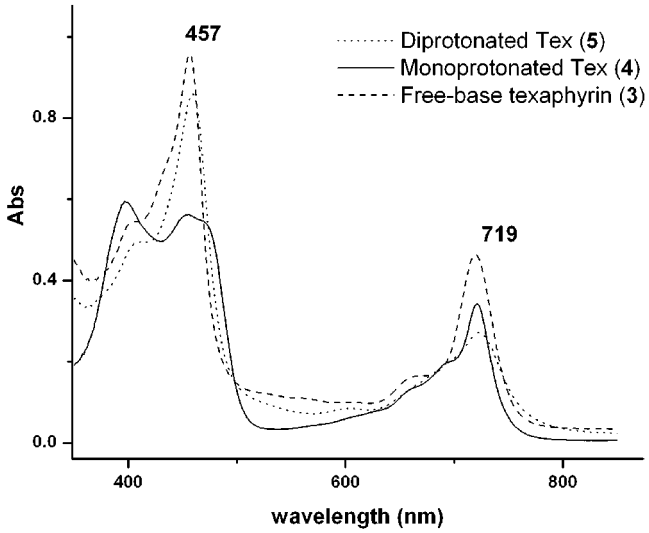

Figure 2. UV−vis spectra of 12−13 μM CH_3CN solutions of **3**−**5**. Peak positions noted are for the free-base species.

420−480 and 705−750 nm spectral regions, respectively, characteristic of metallotexaphyrins. This congruence underscores, as has long been assumed, that the basic spectral features of texaphyrins are ligand derived as opposed to metal derived. Nonetheless, within the confines of this conclusion, it is important to appreciate that the spectra of the metal-free texaphyrins reveal subtle features ascribable to the individual species in question. For instance, while the higher-energy Soret-like absorbances of both **3** and **5** display shapes analogous to those of most texaphyrin metal complexes, namely, a narrow band with a small shoulder, the main Soret-like band for **4**, appears to have "donated" half of its intensity into the shoulder band. As a consequence, the Soret band of **4** is broad and split. These differences are not as apparent in the Q-like region; here, all three protonated forms display an absorbance band around 723 nm that is close to the position observed for Mn(II)−Tex^+ and, as such, diagnostic of an extended π-framework.

One of the salient features of texaphyrins is their ease of reduction relative to porphyrins. For instance, the first ring-centered reduction wave for Gd(III)−Tex_c^{2+} appears at −263 mV vs Ag/AgCl in DMF[4] compared with −1.19 or −1.47 V for free-base octaethyl porphyrin or Zn(OEP), respectively, under similar conditions.[18] This ease of reduction has been implicated in the mechanism of texaphyrin action and thus provides an incentive to explore the electrochemical features of the metal-free form.[19] Cyclic voltammetric measurements carried out on acetonitrile solutions of **4**, with tetrabutylammonium perchlorate as the supporting electrolyte and Ag/AgCl as the reference electrode, revealed two quasi-reversible peaks representing ring reductions, the first at −87 mV and the second at −799 mV. These two reduction peaks, also observed for most metallotexaphyrins, can be compared in magnitude to those for Lu(III)−Tex_c^{2+} at −266 and −725 mV,[4] as well as the more negative reduction potential values of −470 and −956 mV found for Mn(II)−Tex_a^+,[20] both in DMF with an Ag/AgCl reference. On the basis of these comparisons, it is clear that it is much easier to reduce the monoprotonated, metal-free form of texaphyrin (**4**) than any of its metalated analogues. This greater susceptibility, which likely reflects the greater electron-withdrawing capacity of a single, tightly bound proton than that of a coordinated Lewis acidic metal center, could account for the ease with which **3**−**5** undergo re-reduction to the porphyrinogen-like species **1** upon exposure to base and common solvents. Consistent with this thinking is the finding that it is considerably easier to reduce the dicationic species, Lu(III)−Tex_c^{2+}, than its monocationic analogue, Mn(II)−Tex_a^+.

In conclusion, we have developed an efficient and straightforward method for producing the metal-free form of texaphyrin from its readily available, reduced, porphyrinogen-like sp^3 precursor. Current work is devoted to exploring the generality of this ferrocenium cation-based oxidation procedure in the context of expanded porphyrin chemistry and studying the extent to which the metal-free forms of texaphyrin may be used to produce novel metal complexes or known metallotexaphyrins more readily. We are also studying the protonated species **4** and **5** as possible anion-binding agents.

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Supporting Information Available: Synthetic experimental, electrochemical, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Unpublished results.