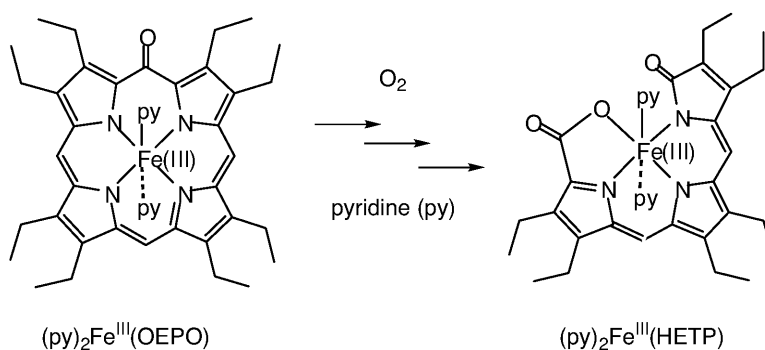Communication

Formation and Isolation of an Iron-Tripyrrole Complex from Heme Degradation

Sankar Prasad Rath, Marilyn M. Olmstead, Lechoslaw Latos-Grayski, and Alan L. Balch

(py)$_2$Fe^{III}(OEPO) → O$_2$, pyridine (py) → (py)$_2$Fe^{III}(HETP)

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Formation and Isolation of an Iron-Tripyrrole Complex from Heme Degradation

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The iron oxaphlorin complex, (py)$_2$Fe(OEPO) (**1**),[1–3] has been identified as an intermediate in the degradation of heme in pyridine by the coupled oxidation process.[4] The coupled oxidation process utilizes dioxygen and a reducing agent to convert heme into verdoheme and an iron biliverdin complex (py)$_2$Fe^{III}(OEB) (**2**).[5,6] Coupled oxidation can also be performed on heme proteins[7] and has been used as a model for degradation of heme catalyzed by heme oxygenase.[8] Although **1** is sufficiently stable to be isolated when handled under the strict exclusion of dioxygen,[9] it is known to be highly reactive toward further oxidation. Nevertheless, the reaction of **1** with dioxygen has only been examined in the presence of the sacrificial reducing agent that is a part of the coupled oxidation process.[4] Here, we report a study of the reaction of **1** with dioxygen in pyridine solution without additional reducing agents present.
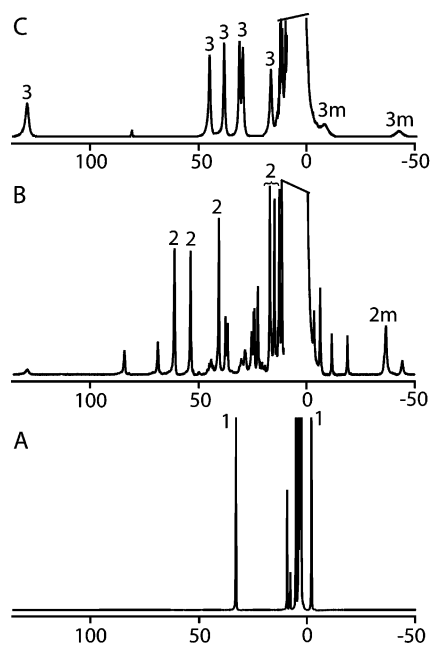

Figure 1. 500 MHz ^{1}H NMR spectra taken from a solution of (py)$_2$Fe-(OEPO) (**1**) at 23 °C in pyridine-d_5 (A) before addition of O$_2$, (B) 4 h after exposure to O$_2$, and (C) 1 day after exposure to O$_2$. Resonances labeled 1 are assigned to the methylene resonances of (py)$_2$Fe(OEPO) (**1**), those labeled 2 and 2m are assigned to the methylene and meso resonances of (py)$_2$Fe(OEB), and those labeled 3 and 3m are assigned to the methylene and meso resonances of (**3**).

Addition of dioxygen to a solution of (py)$_2$Fe(OEPO) (**1**) in pyridine-d_5 at 23 °C results a series of changes that have been followed by ^{1}H NMR spectroscopy as shown in Figure 1. The species identified in these processes are shown in Scheme 1. In

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Scheme 1
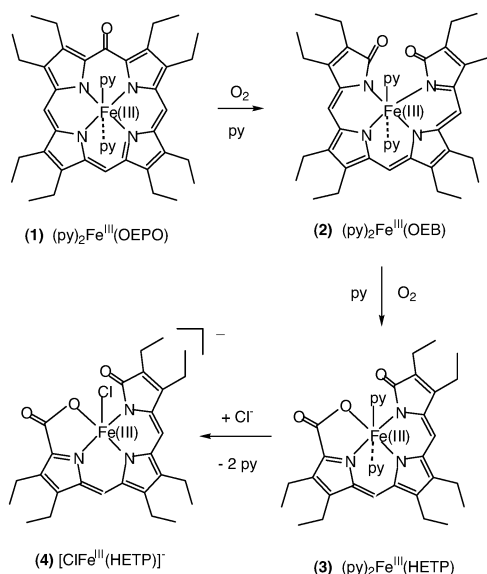
trace A, a portion of the paramagnetically shifted ^{1}H NMR spectrum of (py)$_2$Fe(OEPO) is shown. The two prominent resonances arise from two of the four chemically distinct methylene groups of **1**. The other methylene resonances occur in the crowded 0–10 ppm range, and the meso resonances occur far upfield as noted previously.[1–4] Upon addition of dry dioxygen and storage under 1 atm of dioxygen, a series of changes occur over a period of several hours.

The spectrum shown in trace B was taken after 4 h. At this point, the resonances of **1** have vanished, while several sets of new resonances have developed. The most intense of these are labeled 2 and are identified as belonging to (py)$_2$Fe^{III}(OEB) (**2**) by comparison with the previously obtained spectrum of this species.[6] Several other resonances are apparent in the spectrum, and at least two new species are present.

After the sample was left standing for 1 day, further changes occur which produce a sample with the spectrum shown in trace C of Figure 1. This sample is stable, because ^{1}H NMR spectroscopic examination reveals no changes on further exposure to dioxygen or air. At this stage, there is no evidence of the presence of either **1** or **2** in the sample, and several of the unidentified resonances in trace B have vanished as well. The resonances labeled 3 and 3m in trace C of Figure 1 are indicative of the formation of the product (py)$_2$Fe^{III}(HETP) (**3**) (HETP is the dianion of the hexaethyltripyrrole shown in Scheme 1). The pattern of resonances for **3** seen in trace C is consistent with the proposed structure, which has six chemically distinct methylene groups and two meso protons.

Attempts to crystallize **3** directly from the pyridine solution have not been fruitful. However, evaporation of the pyridine solution of
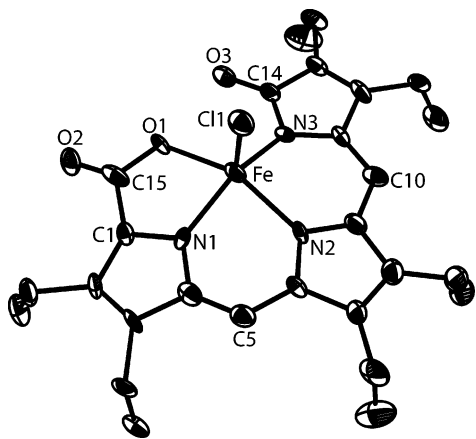
Figure 2. A perspective view of the anion in (*n*-Bu₄N)[ClFe^{III}(HETP)·
1.5cyclohexane·0.5water (**4**) showing 30% thermal contours for all non-
hydrogen atoms. Selected bond distances for molecules 1 and 2 (Å): Fe−
N1, 1.990(7), 2.049(8); Fe−N2, 2.077(8), 2.077(9); Fe−N3, 2.001(7),
2.001(6); Fe−O1, 2.008(11), 1.933(14); Fe−Cl, 2.251(3), 2.253(3). Selected
bond angles (deg): N1−Fe−N2, 85.3(3), 85.2(3); N2−Fe−N3, 86.7(3),
83.7(4); N1−Fe−N3, 143.6(3), 140.0(3); N1−Fe−O1, 75.1(3), 76.5(5);
N3−Fe−O1, 100.2(4), 102.4(4); N1−Fe−Cl1, 108.5(2), 111.0(3); N2−
Fe−Cl1, 101.1(2) 100.4(3); N3−Fe−Cl1, 107.9(2), 108.8(2); O1−Fe−Cl1,
99.3(3), 97.6(4).

3 to dryness, dissolution in chloroform, followed by the addition
of solid tetra(*n*-butyl)ammonium chloride to the sample, filtration,
and careful layering with *n*-hexane produces deep red crystals of
(*n*-Bu₄N)[ClFe^{III}(HETP)]·1.5cyclohexane·0.5water (**4**) in 45% yield.
A sample suitable for single-crystal X-ray diffraction allowed
identification of the anion, whose structure is shown in Figure 2.[10]
There are two independent anions in the asymmetric unit, but they
have similar structures. As the drawing shows, the porphyrin has
been converted into a tripyrrole. The iron ion is five-coordinate
and is bound by three nitrogen atoms, a carboxylate oxygen of the
tripyrrole ligand, and an apical chloride ligand. In the two
independent anions, the Fe−N distances, 1.990(7) (2.049(8));
2.077(8) (2.077(9)); 2.001(7) (2.001(6)) Å, and the Fe−Cl distances,
2.251(3) (2.253(3)) Å, are similar to those of five-coordinate
ClFe^{III}(OEP) with an Fe−N distance of 2.073(8) Å and an Fe−Cl
distance of 2.235(9) Å.[11] The structure of **4** shows disorder which
flips the orientation of both of the two anions (see Supporting
Information), and there is a high degree of thermal motion in some
of the *n*-Bu groups in the cations.

The ¹H NMR spectrum obtained from a chloroform-*d* solu-
tion of the crystal used for the X-ray structure determination is
shown in Figure 3. The spectrum shows significant hyperfine shifts
for the methylene protons which produce 10 resonances (two with
twice the intensity of the other eight) in the 70−20 ppm region
and two meso resonances. The methyl resonances are found in the
crowded region between 0 and 10 ppm. When a sample of **4** is
dissolved in pyridine-*d*₅, the ¹H NMR spectrum of the solution is
identical to that shown in trace C of Figure 1, which indicates that
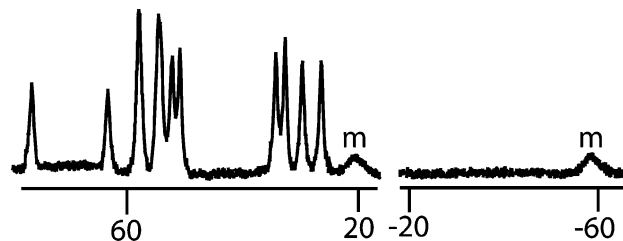**3** is reformed.

Figure 3. The 500 MHz ¹H NMR spectrum of a chloroform-*d* solution at
23 °C of the crystal of (*n*-Bu₄N)[ClFe^{III}(SETP)]·1.5cyclohexane·0.5water
(**4**) used for the X-ray study. The meso proton resonances are labeled m,
and the other resonances are assigned to the methylene protons.

The results presented here show that heme degradation can
proceed beyond the ring opening that produces **2** as well as
verdoheme. In independent experiments, we have shown that
pyridine solutions of octaethylverdoheme and of **2** are converted
into **3** by exposure to dioxygen. A recent study of the reaction of
(py)₂Fe(meso-NH₂OEP) with dioxygen has produced a meta-stable,
ring-opened tetrapyrrole that has been oxygenated at a second meso-
position and that serves as a model for the oxidative removal of
the terminal pyrrole group.[12]

Supporting Information Available: UV/vis spectra of **3** and **4** and
a picture of the crystallographic disorder in the anion in **4** (PDF). X-ray
crystallographic data for **4** in CIF format. This material is available
free of charge via the Internet at http://pubs.acs.org.

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(10) Crystal data for C₅₂H₈₇ClFeN₄O₃.₅: deep red block, 0.45 × 0.23 × 0.13
    mm, orthorhombic, space group *Pna*2₁, *a* = 33.341(6), *b* = 14.642(3), *c*
    = 21.305(4) Å, *V* = 10401(3) Å³, *Z* = 8, *λ* = 0.71073 Å, *D*_c = 1.168 Mg
    m⁻³; *μ* = 0.385 mm⁻¹; *ω* scans, 2*θ*_{max} = 50.50°; *T* = 90(2) K; 108 728
    refl. collected; 18 850 independent (*R*_{int} = 0.086) included in the
    refinement; min/max transmission = 0.846/0.952; Patterson and difference
    Fourier methods solution (SHELXS-97, Sheldrick, 1990); full-matrix least
    squares based on *F*² (SHELXL-97; Sheldrick, 1998); R1 = 0.16, wR2 =
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