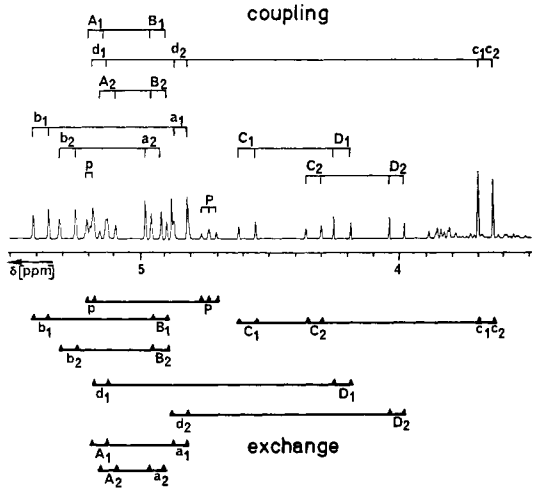

Figure 3. Coupling and exchange pattern in *cyclo*[L-Pro-NBGly$_2$] in $CDCl_3$ at 298 K. The spectrum is resolution enhanced. The signals of the boat conformations are indicted by capital letters, those of the crown in small letters.

mations can be extracted directly. It is obvious that the low-field proton of each AB system exchanges with the high-field proton of the corresponding AB system in the other conformation.

The combined analysis of both spectra yields the assignments shown in Figure 3.

The final question, which signal set belongs to which NBGly in the amino acid sequence, cannot be answered by our experiments because one does not know the population of the rapidly interconverting three boat conformations.[6,7]

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Registry No. *cyclo*[Pro-NBGly$_2$], 67152-52-7.

Isolation of an Iron–Nitrene Complex from the Dioxygen and Iron Porphyrin Dependent Oxidation of a Hydrazine

D. Mansuy,* P. Battioni, and J. P. Mahy

Laboratoire de Chimie de l'Ecole Normale Supérieure (associé au CNRS) 24 rue Lhomond, 75231 Paris Cedex 05, France

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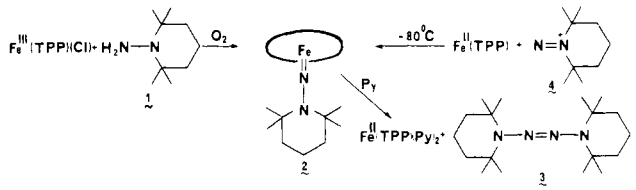
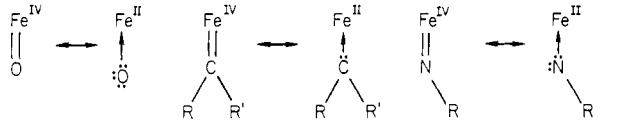
Oxo-iron porphyrin complexes have been proposed as intermediate active oxygen complexes in the hydroxylation of alkanes and other substrates by cytochromes-P-450.[1] Evidence has been provided for the formation of Fe^{IV}=O complexes upon decomposition of μ-peroxo-iron(III) porphyrin dimers in the presence of imidazoles,[2] and, of a π-cation porphyrin Fe^{IV}=O complex upon reaction of an iron(III) porphyrin with iodosoarenes.[3] Their carbon analogues, the more stable iron carbene complexes, have been prepared by reduction of polyhalogenated compounds by iron(II) porphyrins[4] and appear to be formed upon metabolic

Scheme I



reduction of polyhalogenated compounds[5] and metabolic oxidation of 1,3-benzodioxole derivatives by cytochromes P-450.[6] However,



there is so far no direct evidence for the formation of their nitrogen analogues, the nitrene- or imido-iron complexes, [Fe^{II}←NR] ↔ [Fe^{IV}=N-R],[7] although it has been proposed that the iron complexes formed during metabolic oxidation of 1,1-dialkylhydrazines by cytochrome P-450 could involve an iron–nitrene bond.[8]

The present communication reports the isolation and some properties of the first nitrene complex of a metalloporphyrin, which is formed by an O_2-dependent oxidation of 1-amino-2,2,6,6-tetramethylpiperidine, **1**, in the presence of an iron porphyrin.

Fe^{III}(TPP)Cl (*meso*-tetraphenylporphyrin = TPP), 10^{-2} M in aerobic CH_2Cl_2, reacts with the hydrazine **1**[9] (10^{-1} M) leading to the quantitative formation of the new complex **2**, which exhibits a characteristic visible spectrum at 437, 558, and 596 nm, within 10 min at 20 °C. As soon as complex **2** is completely formed, as shown by visible spectroscopy, dioxygen is removed from the solution by argon bubbling; the complex is then precipitated by CH_3OH addition and obtained as purple crystals (yield 90%). This complex is relatively stable toward O_2 since, being 10^{-2} M in aerated $CDCl_3$, it decomposes only slowly into the μ-oxo dimer [Fe^{III}(TPP)]$_2$O (5% after 1 h at 20 °C).

A comparison of the ^{1}H NMR spectra of complex **2** and of its analogue prepared from a tetrakis(pentadeuteriophenyl)porphyrin partially deuterated on the pyrrole rings[10] allows one to assign the different signals of this paramagnetic compound (Figure 1).

In addition to the porphyrin signals (δ 66.8 (8 H, pyrrole), 9.61, 8.81, 7.53 ((20 H, phenyl)), one observes three signals for the protons of an axial ligand: δ 23.5 (12 H, CH_3), 81.5 (4 H, CH_2) −15.63 (2 H, CH_2). These data are in agreement with a paramagnetic complex with an axial symmetry and containing an axial

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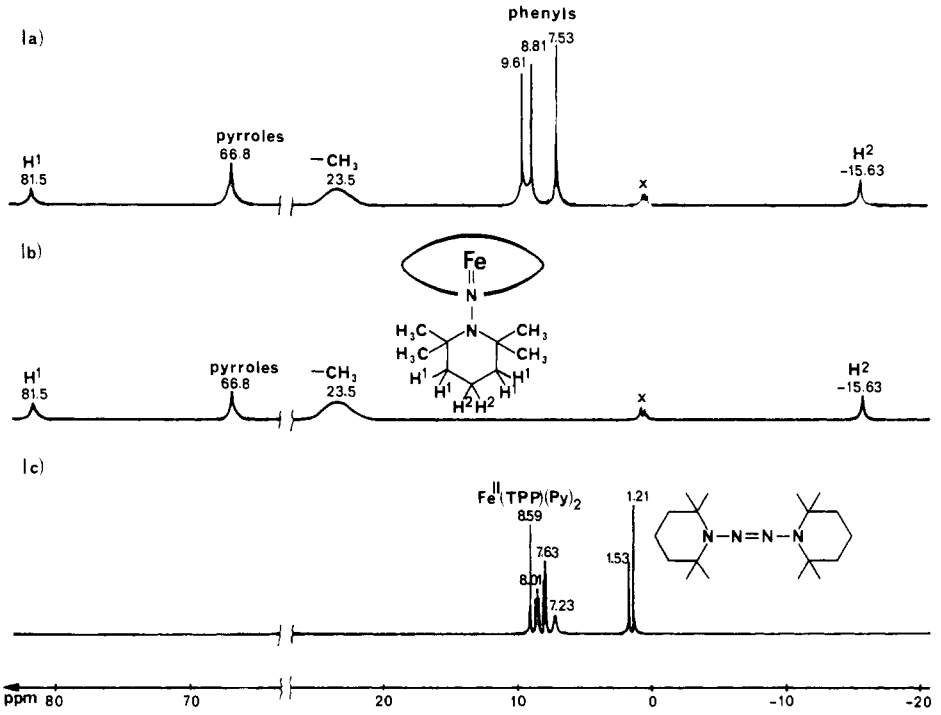

Figure 1. ^{1}H NMR characteristics of complex **2**; (a) ^{1}H NMR spectrum of complex **2** (10^{-2} M in anaerobic $CDCl_3$ at 34 °C, δ in ppm from $(CH_3)_4Si$, Cameca 250 MHz), X = impurities; (b) ^{1}H NMR spectrum of the analogue of complex **2** obtained from tetra(pentadeuteriophenyl)-d_5 porphyrin, $C_{44}H_3D_{25}N_4$, for the dianion,[10] exhibiting thus no signal for the phenyl rings and a reduced intensity for the signal of the pyrrole hydrogens (3/8); (c) ^{1}H NMR spectrum of complex **2** after addition of 100 μL pyridine-d_5. The signals at δ 8.59, 8.01, and 7.63 and those at δ 1.53 and 1.21 were also found respectively in the spectra of authentic samples of $Fe(TPP)(Py)_2$ and the tetrazene **3**,[9] recorded in identical conditions. The signal at δ 7.23 corresponds to nondeuterated pyridine present in pyridine-d_5.

ligand retaining at least the starting 2,2,6,6-tetramethylpiperidyl moiety. Accordingly, the addition of an excess of pyridine-d_5 to the $CDCl_3$ solution of complex **2**, in anaerobic conditions, leads to the immediate replacement of the axial ligand of complex **2** and appearance of the signals of $Fe^{II}(TPP)(pyridine)_2$ and of the tetrazene **3**[9] (Figure 1c) (Scheme I), with the molar ratio 2:1. This suggests that **2** could be the nitrene $Fe(TPP)(N{-}NC_9H_{18})$ complex (NC_9H_{18} = 2,2,6,6-tetramethylpiperidyl). This is further confirmed by the following: (i) its elemental analysis;[11] (ii) its IR spectrum (KBr), which exhibits an intense band at 1150 cm^{-1}, in a region where one should expect a band corresponding to a Fe=N(nitrene) stretching vibration (the metal–nitrene complexes described so far[13a,13b] give ν_{M-N} bands between 1100 and 1300 cm^{-1} [13c]), and a weaker band at 1520 cm^{-1}, which could correspond to a N–N stretching vibration[14] (these bands are absent in the IR spectra of different previously described Fe(TPP) complexes such as $Fe^{III}(TPP)(Cl)$ or $Fe^{II}(TPP)$ and of the hydrazine **1**); (iii) its very fast formation upon direct reaction of $Fe^{II}(TPP)$ with the nitrene **4**[15] at −80 °C in CH_2Cl_2 in the absence of dioxygen (Scheme I). It is noteworthy that nitrene **4**, which is stable at −80 °C, was reported to exhibit a ν_{N-N} band at 1595 cm^{-1};[14] its binding to $Fe^{II}(TPP)$ would thus lead to a 75-cm^{-1} shift of this band toward lower frequencies.

Compound **2** can be described either as a ($Fe^{II}{\leftarrow}N{-}NC_9H_{18}$) or as a ($Fe^{IV}{=}N{-}NC_9H_{18}$) complex. Its magnetic susceptibility measured by the Evans method[16] was found to be 5.0 ± 0.1 μ_B at 34 °C, indicating a S = 2 high-spin Fe^{II} or Fe^{IV} state. The high-spin Fe^{II} state would be in agreement with the lack of signals in the EPR spectrum of complex **2** even at 4 K and the chemical shifts of the porphyrin protons (Figure 1a),[17a] which are in the range of those described for high-spin Fe^{II} pentacoordinate complexes such as $Fe^{II}(TPP)$(2-methylimidazole).[17b,c,d]

Dioxygen seems to play a key role in the formation of complex **2** since, under conditions identical with those previously mentioned but in the absence of dioxygen, one did not observe its formation. Moreover, it is noteworthy that we were unable to prepare the equivalent of complex **2** from 1-aminopiperidine, the main product being in this case the hemochrome $Fe^{II}(TPP)(NH_2{-}NC_5H_{10})_2$.

Complex **2** is the first described mononuclear iron-nitrene complex,[18] since the only related complexes reported so far involve an imido ligand bridging at least two iron centers.[7,13] Neither of the two methods described for the preparation of complex **2**, the oxidation of an amino compound by dioxygen in the presence

(11) Performed on a sample recrystallized from CH_2Cl_2–CH_3OH and containing 0.2 mol of CH_2Cl_2 of crystallization (as shown by ^{1}H NMR). Anal. Calcd for $Fe(TPP)(N{-}NC_9H_{18})\cdot 0.2CH_2Cl_2$: C, 76.05; H, 5.68; N, 10.00; Cl, 1.60. Found: C, 75.94; H, 5.65; N, 10.05; Cl, 1.61. The presence of the intact Fe(TPP) moiety in complex **2** is further confirmed by its mass spectrum (70 eV, 220 °C), which exhibits a major peak at M^+ 668 (Fe(TPP)) but no molecular peak, because of fast decomposition of **2** as of Fe(TPP)-(RNO)[12] in these conditions.

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(14) By comparison ν_{NN} = 1595 cm^{-1} in the free nitrene $N{-}NC_9H_{18}$: Hinsberg, W. D.; Dervan, P. B. *J. Am. Chem. Soc.* **1978**, *100*, 1608–1610.

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(16) Evans, D. F. *J. Chem. Soc.* **1959**, 2003.

(17) (a) The temperature dependence of the porphyrin and ligand signals of **2** (between −74 and 34 °C) corresponds to a Curie law. Moreover, preliminary results from magnetic susceptibility measurements show that the magnetic moment of crystalline complex **2** (μ = 5.0 ± 0.1 μ_B), is constant between +34 and −200 °C. These results are indicative of an iron porphyrin complex in a well-defined paramagnetic noninteracting state (S = 2) and support the proposed monomeric structure. (b) Collman, J. P.; Reed, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 2048–2049. (c) Goff, H.; La Mar, G. N. *Ibid.* **1977**, *99*, 6599–6606. (d) Collman, J. P.; Brauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Bunnenberg, E.; Linder, R. E.; La Mar, G. N.; Del Gaudio, J.; Lang, G.; Spartalian, K. *Ibid.* **1980**, *102*, 4182–4192.

(18) It is noteworthy that hydrazido(2–) complexes of other transition metals are known; see ref 13 and the following: (a) Bishop, M. W.; Chatt, J.; Dilworth, J. R.; Hursthouse, M. B.; Motevalle, M. *J. Less. Common. Metals* **1977**, *54*, 487–493. (b) Chatt, J.; Diamantis, A. A.; Health, G. A.; Hooper, N. E.; Leigh, G. J. *J. Chem. Soc. Dalton Trans.* **1977**, 688–697.

of a transition-metal complex or the direct reaction of a transition-metal complex with a free nitrene, has been previously reported for the synthesis of a metal–nitrene complex. From the aforementioned results, showing that porphyrin iron–nitrene bonds do exist and are formed by an O_2 and iron porphyrin dependent oxidation of a 1,1-dialkylhydrazine, it seems likely that the cytochrome P-450 complexes formed by an O_2- and NADPH-dependent metabolic oxidation of 1,1-dialkylhydrazines also involve an iron-nitrene bond as proposed previously.[8]

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Registry No. 1, 6130-92-3; **2**, 82281-71-8; **3**, 42053-22-5; **4**, 66337-86-8; Fe^{III}(TPP)Cl, 16456-81-8; Fe^{II}(TPP), 16591-56-3; Fe^{II}(TPP)$(Py)_2$, 16999-25-0.

Short Synthesis of Parabactin

Raymond J. Bergeron* and Steven J. Kline

Department of Medicinal Chemistry
University of Florida, Gainesville, Florida 32610
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In 1975 Tait[1] isolated two rather unique siderophores from *Paracoccus denitrificans*: N^1,N^8-bis(2,3-dihydroxybenzoyl)-spermidine (II) and N^4-[*N*-(2-hydroxybenzoyl)-L-threonyl]-N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine (III), Figure 1a. He demonstrated the former catecholamide to be the biochemical precursor of the latter. Shortly after the isolation and identification of these iron-sequestering agents, Jacobs and Tait[2] were able to show the potential of these catecholamides as therapeutic devices for the treatment of various iron-overload syndromes, e.g., Cooley's anemia.[3,4] Compound II, a tetradentate ligand, removed iron from transferrin, one of the body's iron-binding proteins, substantially better than compound III, a potentially hexacoordinate ligand. Furthermore, both of these catecholamides were more effective at removing iron from this iron-shuttle protein than was desferrioximine, the clinical device currently used in chelation therapy. Unfortunately, because compounds II and III were only accessible in milligram quantities from bacteria, a complete biological evaluation was not possible. However, these findings did spark further interest in this new family of siderophores. Following Tait's discovery, Raymond synthesized a number of catecholamide siderophores and evaluated both the binding stoichiometries as well as the thermodynamics of iron binding.[5-9] However, neither II nor III was actually synthesized until recently.[10-13]

Initially, it seemed peculiar to us that nature should produce a structurally more complicated, less effective iron chelator (III) from a less complicated, more effective chelator (II). However, Neilands[10,11] rather cleverly demonstrated that this unsettling inefficiency could be easily explained by reconsidering Tait's original proof of structure for compound III. He demonstrated that the group fixed to the central nitrogen of the spermidine backbone was not an *N*-(2-hydroxybenzoyl)-L-threonyl moiety but rather a (2-hydroxyphenyl)-4-carboxyl-5-methyl-2-oxazoline

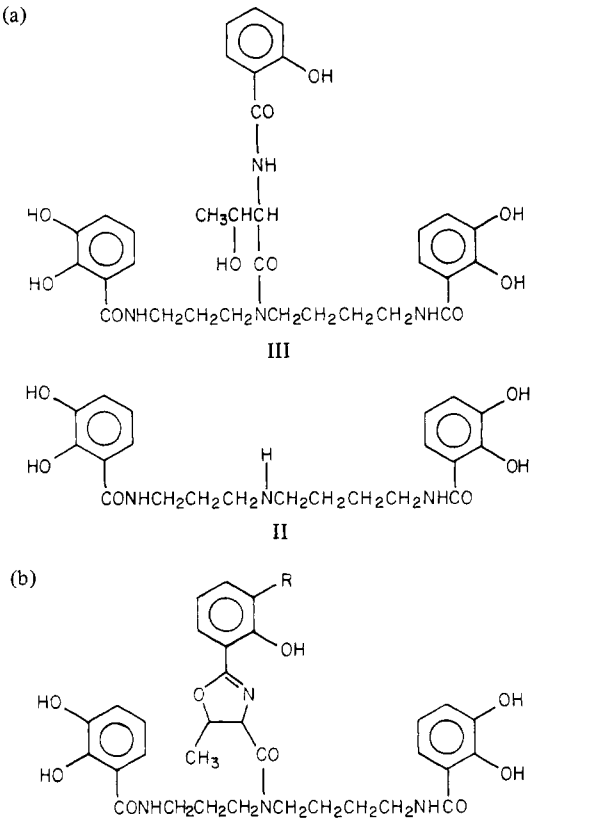

Figure 1. (a) Siderophores N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine (II) and N^4-[*N*-(2-hydroxybenzoyl)threonyl]-N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine (parabactin A) (III). (b) Parabactin (R = H); agrobactin (R = OH).

(Figure 1b) and that this oxazole ring was opened to the threonyl compound under the acidic conditions of Tait's isolation.[10] In the oxazoline or closed form, compound III represents a hexacoordinate Fe(III) ligand that, in fact, binds Fe(III) tighter than either compound II or the open form of compound III. These findings stimulated our interest in the total synthesis of compound III in its oxazoline form.

In earlier studies, we were able to develop several syntheses of compound II and several analogues, as well as of compound III analogues.[12-15] We have since shown these catecholamides to be potent iron chelators and effective at removing iron from iron-overloaded animals.[13,16] Now, we report on the first synthesis of the closed form of compound III, parabactin. This procedure allows for the generation of not only parabactin in high yield but also of the corresponding homo- and norspermidine homologues.

The synthesis begins with N^1,N^8-bis(2,3-dimethoxybenzoyl)-spermidine (**1**), a very versatile reagent for the generation of spermidine catecholamides.[15] This compound is coupled with *N*-carbobenzoxy-L-threonine via the *N*-hydroxysuccinimide ester. Compound **1** is reacted with *N*-carbobenzoxy-L-threonine and the condensing reagents dicyclohexylcarbodiimide and *N*-hydroxysuccinimide in the presence of triethylamine in tetrahydrofuran (0 °C) to produce the secondary N^4-acylated product, N^4-(*N*-carbobenzoxy-L-threonyl)-N^1,N^8-bis(2,3-dimethoxybenzoyl)-spermidine (**2**), in 90% crude yield. This threonyl amide was easily purified by silica gel chromatography eluting with 5% MeOH in EtOAc;[17] ^1H NMR (60 MHz in $CDCl_3$) δ 1.16 (3 H, CH_3), 1.58

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(16) To be submitted for publication.

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