Facile Nitrite Reduction and Conversion Cycle of {Fe(NO)}$^{6/7}$ Species: Chemistry of Iron N-Confused Porphyrin Complexes via Protonation/Deprotonation

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Nitrite anion (NO_2^-) is considered as a major intravascular nitric oxide (NO) storage pool.[1] Recently, in a mammalian system, Gladwin et al. demonstrated that infusion of nitrite into an artery can induce vasodilation even when NO synthase is inhibited.[2] It is therefore conceivable that NO_2^- can be transformed into NO by deoxyhemoglobin (deoxyHb) under hypoxic conditions. In bacteria, NO_2^- is reduced to NO by heme-containing nitrite reductases (NiRs), e.g., cytochrome cd_1 NiR from *Paracoccus pantotrophus*,[3] cytochrome c NiR from *Wolinella succinogenes*,[4] and sulfite reductase from *E. coli*,[5] etc. Most recently, a literature report provided structural evidence of an O-bound nitrite on the heme center of human hemoglobin.[6] Meanwhile, mechanistic studies carried out by Estrin et al. indicate that protonation on N-bound NO_2^- facilitates the nitrite reduction to a labile Fe(III)−NO species and the release of a water molecule. Alternatively, O-bound NO_2^- generates a hydroxo-ferric porphyrin complex and molecular NO via protonation on the coordinating oxygen atom.[7] Evidently, in both N- and O-bound reaction mechanisms, deliverable proton(s) and oxidation of iron are essential characteristics in deciphering the mechanism of nitrite reduction.

Scheme 1[a]
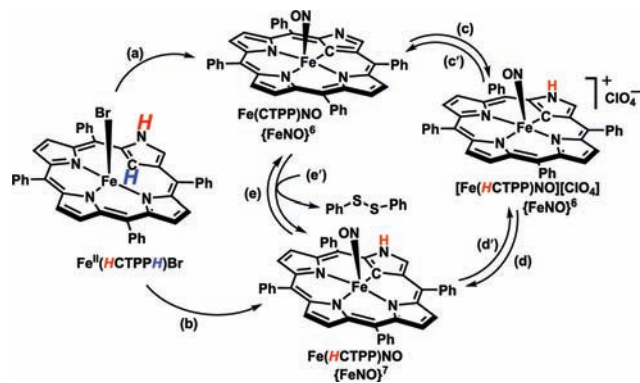
[a] (a) 1 equiv of NaNO₂; (b) 0.5 equiv of [PPN(NO₂)]; (c) HClO₄; (d) Co(Cp)₂; (e) air; (c′) NEt₃; (d′) AgClO₄; (e′) PhSH.

Despite the vast number of studies, thus far only the electrochemistry[8] and oxygen acceptor assisting nitrite reduction[9−11] have been documented. To the best of our knowledge, there is no report on a ferrous porphyrin complex that can biomimetically convert NO_2^- to form an {Fe(NO)}^{6} nitrosyl species. To model the reduction of nitrite anion, the unique properties of altering the

tautomer form of the porphyrin skeleton[12] and simultaneously serving as a one- or two-proton donor within [Fe(HCTPP*H*)Br][13] are utilized; herein we report a facile nitrite reduction by [Fe(HCTPP*H*)Br] without the presence of a reductant or an oxygen acceptor (Scheme 1). It is noteworthy that, by controlling the stoichiometry of nitrite, either [Fe(CTPP)NO] ({Fe(NO)}^{6}) or [Fe(HCTPP)NO] ({Fe(NO)}^{7}) can be obtained. Also, [Fe(HCTPP)NO][ClO₄] was isolated as an intermediate between the conversion process of [Fe(CTPP)NO] and [Fe(HCTPP)NO], demonstrating that protonation on the peripheral nitrogen of N-confused porphyrin can tune the electronic structure of the Fe−NO moiety.
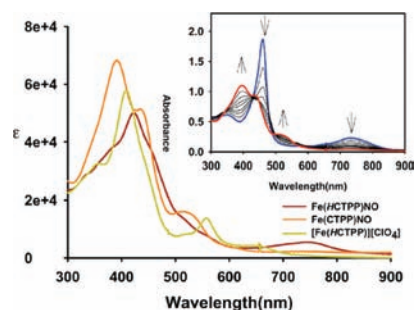
Figure 1. Absorption spectra of iron N-confused porphyrin nitrosyl complexes in CH_2Cl_2. The insert shows changes in the absorption spectrum over 90 min when 2.5 mL of [Fe(HCTPP*H*)Br] (2.05×10^{-5} M in CH_2Cl_2) was treated with 52 μL of NaNO₂ (9.97×10^{-3} M in MeOH).

In this study, we find that reaction of Fe^{II}(HCTPP*H*)Br with 1 equiv of NaNO₂ under an inert atmosphere at ambient temperature results in [Fe(CTPP)NO] (Scheme 1a). The UV−vis spectrum, shown in Figure 1, exhibits absorption maxima at 392, 435, and 515 nm for [Fe(CTPP)NO]. Notably, [Fe(CTPP)NO], which is isolated in 97% yield, is an air-stable compound and can be further purified by means of silica gel column chromatography in a room atmosphere. The FT-IR spectrum of this product gives a ν(NO) at 1771 cm^{-1}, and the crystallographic analysis (Figure 2) reveals an Fe−N−O angle of 180° and a N−O distance of 1.128(10) Å, which are consistent with the {Fe(NO)}^{6} electronic structure according to the Enemark−Feltham notation.[14] Furthermore, the EPR silent characteristic, the ^{1}H NMR spectrum with six sets of doublet resonances between 8.30 and 8.10 ppm for β-pyrrolic protons, and the singlet at 9.50 ppm for the proton alongside the outer nitrogen explicitly confirm the {Fe(NO)}^{6} electronic structure. Although further spectroscopic information is required, the observation of a resonance at −19.92 ppm (vs MeNO₂) for NO in the ^{15}N NMR spectrum using isotopically enriched [Fe(CTPP)(^{15}NO)] in CDCl₃

suggests that nitrosonium (NO^+) is the most likely electronic configuration present in this NO complex.[15]
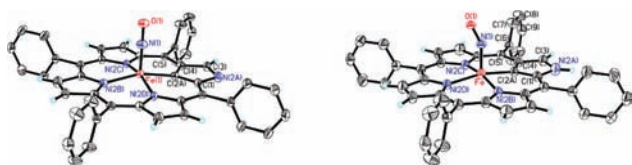
Figure 2. ORTEP representation of [Fe(CTPP)NO] (left) and [Fe(*H*CTPP)NO] (right) in 25% ellipsoids. Only one conformation of the disordered NCP ring and NO moiety are presented in each complex.

Distinctive differences in chemical reactivity and stability between regular and N-confused iron-nitrosyl porphyrin complexes were observed. First, regular iron(III)-nitrosyl porphyrin complexes have been reported to slowly release NO in the solid state and rapidly lose NO while in solution; however, [Fe(CTPP)NO] in solution is stable under atmospheric conditions. Second, instantaneous nitrite reduction was observed as long as NO_2^- salt was treated with the solution of [Fe(*H*CTPP*H*)Br] at ambient temperature. This is in striking contrast to the observation that nitrite can stably coordinate to the iron(II) center of a normal porphyrin complex without evidence of any further reaction.[16] This nitrite reduction carried out by [Fe(*H*CTPP*H*)Br] is, in addition, distinctively different from that induced by iron-corrole complexes, which reduce nitrite to NO from the Fe(IV) oxidation state at elevated temperature.[17] Importantly, for the formation of an iron-nitrosyl complex, nitrite transformation to NO by a disproportionation reaction is also a potential mechanism.[18] Nevertheless, the quantitative yield of [Fe(CTPP)NO] from nitrite reduction under nonacidic conditions suggests that the disproportionation reaction is improbable. The presence of inner C—H and peripheral N—H protons on [Fe(*H*CTPP*H*)Br], which can be readily transferred to a nitro group to release molecular water or hydroxide, on the other hand, appears to play an essential role in the facile nitrite reduction.

To better understand the electron/proton-transfer process during the nitrite reduction, stoichiometric control of [Fe^{II}(*H*CTPP*H*)Br] and nitrite salt was performed. Quantitative yields of {Fe(NO)}^{7} [Fe(*H*CTPP)NO] together with an equal equivalent of [Fe^{III}(*H*CTPP)Br] were isolated on treating [Fe^{II}(*H*CTPP*H*)Br] with 0.5 equiv of [PPN(NO$_2$)] (PPN: bis(triphenylphosphine)iminium) under an inert atmosphere (Scheme 1b). As expected, the {Fe(NO)}^{7} [Fe(*H*CTPP)NO] is extremely air-sensitive and will be rapidly oxidized to [Fe(CTPP)NO] when exposed to air. The crystallographic analysis of [Fe(*H*CTPP)NO] (Figure 2) reveals an angle of 151.8(6)° for Fe—N—O and a N—O bond distance of 1.171(13) Å; both are in the range for a {Fe(NO)}^{7} electronic structure. The UV–vis spectrum, shown in Figure 1, exhibits absorption maxima at 423 and 750 nm for [Fe(*H*CTPP)NO], which is distinctively different from that of {Fe(NO)}^{6} [Fe(CTPP)NO]. The ν(NO) of 1640 cm^{-1} for [Fe(*H*CTPP)NO] is in agreement with an {Fe(NO)}^{7} electronic structure. In addition, an isotropic EPR absorption envelope at 298 K ($g = 2.0289$ and $a_N = 16.309$ G) and broadened ^{1}H NMR resonances between 5.5 and 10.5 ppm for [Fe(*H*CTPP)NO] also imply a paramagnetic {Fe(NO)}^{7} compound.

By taking advantage of the dual tautomeric forms on the N-confused porphyrin ring, which alternate during the protonation/deprotonation process,[19] it is possible to study the interconversion between the {Fe(NO)}^{6} [Fe(CTPP)NO] and {Fe(NO)}^{7} [Fe(*H*CTPP)NO]. The protonation on [Fe(CTPP)NO] by HClO$_4$ resulted in the cationic complex [Fe(*H*CTPP)NO][ClO$_4$]. The same product

can be prepared by oxidation of [Fe(*H*CTPP)NO] with AgClO$_4$. As expected, in the presence of a base, [Fe(*H*CTPP)NO][ClO$_4$] is readily converted back to [Fe(CTPP)NO]. Moreover, cobaltocene, which is a potent reductant, can reduce [Fe(*H*CTPP)NO]$^+$ back to [Fe(*H*CTPP)NO]. The ν(NO) at 1796 cm^{-1} for [Fe(*H*CTPP)NO]-[ClO$_4$] is 25 cm^{-1} higher in energy than that in [Fe(CTPP)NO], but it is still in the range of a {Fe(NO)}^{6} electronic structure. Direct reduction of {Fe(NO)}^{6} [Fe(CTPP)NO] to {Fe(NO)}^{7} [Fe(*H*CTPP)NO] by PhSH along with its backward oxidation reaction by dioxygen completes a conversion cycle for these three iron-nitrosyl N-confused porphyrin complexes. The shift of ν(NO) toward higher energy and the increased bending angle of Fe—N—O from the crystal structure of [Fe(*H*CTPP)NO](ClO$_4$) (Figure S10) confirm that protonation is an effective route to alter the electronic structure of N-confused metalloporphyrin.

In summary, we have, without complicated synthetic procedures possibly involving additional substituents as proton donors, demonstrated that [Fe^{II}(*H*CTPP*H*)Br] can readily reduce nitrite by taking advantage of the acidic peripheral N—H proton and the inner C—H proton. [Fe^{II}(*H*CTPP*H*)Br] is the first model complex to successfully mimic the reactions in heme-assistant NiRs. Additionally, [Fe^{II}(*H*-CTPP*H*)Br] represents a new bioinorganic model compound to orchestrate proton delivery and small-molecule activation. Furthermore, protonation on the peripheral nitrogen of the N-confused porphyrin ring is an attractive and novel way to further tune the electronic structure of porphyrin complexes.

Supporting Information Available: Experimental Section, including detailed synthetic procedure, characterization data, and CIFs. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA901796J