Activation of Nitrite Ion by Iron(III) Porphyrins. Stoichiometric Oxygen Transfer to Carbon, Nitrogen, Phosphorus, and Sulfur

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Nitrite ion is well known to oxidize oxyhemoglobin in vivo.[1] Fetal hemoglobin is particularly susceptible to this reaction.[2] The ion is generated in the environment by the hydrolysis[3] of NO_x air pollutants and by the reduction of nitrate fertilizers in soil by bacteria.[4] Moreover, the biomessenger molecule NO[5] is oxidized in aerobic aqueous solutions to nitrite ion.[6] Acidic solutions of the ion (nitrous acid) are well known to diazotize and cross link DNA[7] and can generate carcinogenic nitrosamines in vivo.[8]

We report herein that nitrite ion can be activated by iron(III) porphyrins to a species capable of oxygen transfer to a range of substrates at room temperature under argon. The general stoichiometry of the process is given in eq 1, (P = porphyrin, S = substrate).

$$PFe^{III} + NO_2^- \overset{K}{\rightleftharpoons} (PFeNO_2) \xrightarrow[k_{rate}]{S} PFe^{II}(NO) + SO \quad (1)$$

The iron(II) nitrosyl adduct is produced quantitatively in all cases (visible spectra). Illustrative examples with chloroiron(III) octaethylporphyrin ($PFe^{III}Cl$) and potassium (crown ether) nitrite are given in Table 1. The reactions feature oxygen insertion into C–H bonds (cyclohexene, cyclohexenol, propionaldehyde), olefin epoxidation (styrene), and oxygen atom transfers to phosphorus (triphenylphosphine), carbon (carbon monoxide), sulfur (dimethyl sulfide), and nitrogen (nitric oxide). The phenylacetaldehyde characterized from reaction with styrene is the result of rearrangement of styrene oxide, both upon gas chromatography and upon standing in the reaction mixture. Cyclohexenol (not shown separately in Table 1) reacts more rapidly than cyclohexene to yield cyclohexenone. The ketone is produced by the sequence cyclohexene → cyclohexenol → cyclohexenone. Products were quantitated by GC or NMR analyses ($H^{13}CO_3^-$ $Ph_3{}^{31}PO$) using authentic standards. All reactions were conducted at least three and usually five times.

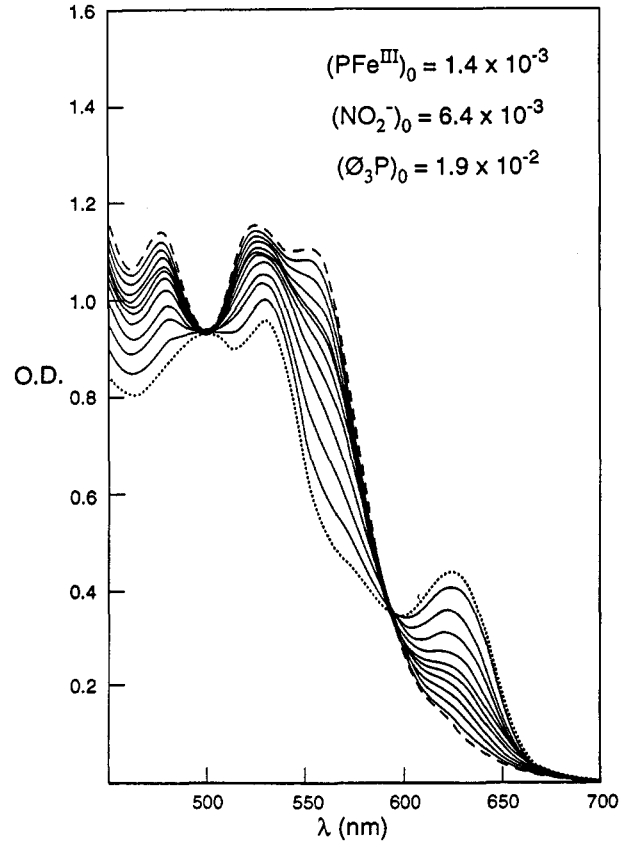

Figure 1. Visible spectra of the reaction of triphenylphosphine with $ClFe^{III}OEP$ and K (crown ether) NO_2 in NMP–1% HOAc at 22 °C. First scan within 1 min of mixing, (•••). The next seven scans were at 15 min intervals and the remaining at 30 min intervals. The final spectrum (– –) was taken at 3 h and 16 min after mixing.

The substrates are listed in an approximate order of decreasing reactivity. The NO–NO_2 conversion is complete in less than 5 min under these conditions, whereas the cyclohexene reaction requires 1.5 days.[9] No reaction occurs in the absence of either iron(III) porphyrin, nitrite ion, or substrate. The reactions are stoichiometric according to eq 1. They are not catalytic under these conditions.

A time course for the conversion of PFe^{III} to PFe^{II} NO by triphenylphoshine and nitrite ion is shown in Figure 1. The final spectrum matches exactly that of $PFe^{II}NO$ in this solvent. The latter was obtained by gassing the iron(II) porphyrin with nitric oxide.

The overall rate process is third order:

$$\frac{d(PFe^{II}NO))}{dt} = -\frac{d(PFe^{III})}{dt} = k'(PFe^{III})(NO_2^-)(Ph_3P)$$

This is in accord with the simple formulation given in eq 1 wherein $k' = Kk_{rate}$. The k' for triphenylphosphine calculated from linear pseudo-second-order plots of the data at 627 nm (disappearance of PFe^{III}) is 1.3 $L^2/mol^2/s$. Upon completion, a small portion of the entire reaction

(1) Doyle, M. P.; Herman, J. G.; Dykstra, R. L. J. *Free Radicals Biol. Med.* **1988**, *1*, 145.
(2) Martin, H.; Huisman, T. H. J. *Nature* **1963**, *200*, 898.
(3) Schwartz, E.; White, W. H. *Trace Atmospheric Constituents, Properties, Transformation and Fates*; John Wiley and Sons: New York, 1983; pp 1–117.
(4) (a) Zumft, W. G. *Arch. Microbiol.* **1993**, *160*, 253. (b) Steward, V. *Microbiol Rev.* **1988**, *52*, 190. (c) Elmewrich, C.; Zimmer, W.; Vielle, C. *Biological Nitrogen Fixation;* Chapman and Hall: New York, 1992; Chapter 6, p 212.
(5) (a) Clarke, M. J.; Gaul, J. *Structure and Bonding*; Springer-Verlag: Berlin, 1993; pp 147–181. (b) Moncada, S. R. M.; Palmer, J.; Higgs, A. E. *Biochem. Pharmacol.* **1989**, *38*, 1709.
(6) Wink, D. A.; Darbyshire, J. F.; Nims, R W.; Saavedva, J. E.; Ford, P. C. *Chem. Res. Toxicol.* **1993**, *6*, 23.
(7) Kirchner, J.; Sigurdsson, S. Th.; Hopkins, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 4021.
(8) Marletta, M. A. *Frontiers in Molecular Toxicology*; Marnett, L. J., Ed.; ACS: Washington, D.C., 1992; p 46.
(9) These reactions can be hastened by warming. For example, at room temperature the oxidation of propionaldehyde requires 1.5 days. At 70 °C, the reaction is complete in 3 h.
(10) It should be noted that ligand exchange with PFe^{III} Cl in NMP is fast, cf. Castro, C. E.; Jamin, M.; Yokoyama, W.; Wade, R. *J. Am. Chem. Soc.* **1986**, *108*, 4179. The initial spectrum is unchanged by the nitrite salt.

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Table 1. Oxidations with Chloroiron(III) Octaethylporphyrin and Potassium (18-Crown-6) Nitrite[a] in NMP–1% HOAC at 22 °C under Argon

substrate[b]	product	yield[c] (%)	characterization[d]
nitric oxide	nitrogen dioxide	100	GC and NO_3^- from product gases
triphenylphosphine	triphenylphosphineoxide	100	^{31}P-NMR
dimethyl sulfide	dimethyl sulfoxide[e]	90	GC, GC–MS
carbon monoxide-^{13}C	carbon dioxide-^{13}C	100	^{13}C-NMR of HCO_3^- from product gas
propionaldehyde	propionic acid	95	GC, GC–MS[f]
styrene	styrene oxide[g]	35	GC, GC–FT–IR–MS
	phenylacetaldehyde	65	GC, GC–FT–IR–MS
cyclohexene	cyclohexenone	90[c]	GC, GC-MS
	cyclohexenol	10	GC

[a] $(PFe^{III}Cl)_0 = (1-1.6) \times 10^{-3}$ M, $(K(\text{crown ether})NO_2^-)_0 = (2-6.4) \times 10^{-3}$ M, NMP = *N*-methylpyrrolidone. [b] (Substrate) = 2×10^{-3}, 2 M. [c] (Moles product/2 mol PFe)100. [d] GC = gas chromatography and analysis by comparison with authentic standards, GC–MS = gas chromatography and inline mass spectroscopy, GC–FT–IR–MS = inline GC followed by infrared and mass spectroscopy of emerging peaks. [e] The sulfoxide is not a substrate and it is the only product detected. [f] GC–MS of TMS ester. [g] Upon gas chromatography and standing in reaction mixtures, styrene oxide rearranges to phenylacetaldehyde.

mixture (0.3 mL) was transferred under argon to an NMR tube for ^{31}P analysis. Only two resonances corresponding to Ph_3P (8.0 ppm) and Ph_3PO (38.6 ppm) were visible. The yield was quantitated by comparison with the spectra of authentic solutions of phosphine and phosphine oxide acquired in the same manner.

Scheidt and colleagues[11a] have described the instability of tetraphenylporphine(TPP)iron(III) NO_2^- adducts and the generation of TPPFe(NO) upon treatment of TPP-iron(III) chloride with $AgNO_2$. This observation was attributed to an oxygen transfer to nitrite to yield nitrate ion. However, a bis nitrite adduct was obtained[11b] when potassium crown ether nitrite was employed as the nitrite source. This adduct is apparently stabilized by the K (crown ether) cation. In agreement with this observation, we find argon-purged solutions of PFe^{III} and NO_2^- are stable for weeks and show the initial spectrum in Figure 1.[11c] On the basis of the X-ray structures of sterically encumbered porphyrin Fe–NO_2 adducts by Scheidt and colleagues[11b,12] and the present results, we believe the reactions do represent an O atom transfer from PFe–NO_2 and that the original $TPPFe^{III}$ to TPPFe(NO) conversion[11a] reflected the oxidation of some other substance in the reaction mixture. Under more acidic conditions, in partially aqueous milieu, Bonnet has reported[11d] the reaction of nitrous acid with iron(III) octaethylporphyrin in air yields a meso nitro compound, as well as iron(II) NO adducts. It is presumed a meso nitroso compound was air oxidized to the nitro derivative.

Although the reactions described herein may be taken as biomimetic oxidations, similar in some way to those catalyzed by P-450 model systems,[13] we believe the driving force resides in the enormous stability of the heme-NO adduct.[14] Iron(IV) or iron–oxo cation radicals are not intermediates. These results with iron porphyrins also differ in character from those reported for oxidations by other transition metal–NO_2 species.[15] In general, the latter systems require either a ligand or metal "activator" ($BF_3{\cdot}Et_2O$ or Pd^{II}) for reaction to occur.

The present results hold promise for the development of mild selective oxidation reagents with iron porphyrins, certain heme proteins, and other iron(III) NO_2^- complexes. Reactions with heme proteins could be of consequence to processes in vivo that involve NO_2^- or NO in aerobic solution. For example, both NO synthase[16] and the NO receptor protein, guanylate cyclase,[17] are heme proteins. Moreover, the nitrite-promoted NO–NO_2 conversion could, in part, explain the $NO_2^-/H_2{}^{18}O$ exchange observed with whole cells containing cytochrome Cd1 nitrite reductase.[18,19]

Supplementary Material Available: Experimental procedures and characterization data (4 pages).

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(11) (a) Finnegan, M. G.; Lappin, A. G.; Scheidt, W. R. *Inorg. Chem.* **1990**, *29*, 181. (b) Nasri, H.; Goodwin, J. A.; Scheidt, W. R. *Inorg. Chem.* **1990**, *29*, 185. (c) Nitrite ion is recovered quantitatively, and nitrate is not detected: Chow, T. J.; Johnstone, M. S. *Anal. Chim. Acta* **1962**, *27*, 441. (d) Bonnet, R.; Charalambides, A.; Martin, R. A. *J. Chem. Soc., Perkin Trans. 1* **1978**, *1*, 974.

(12) Naasri, H.; Haller, K. J.; Wang, Y.; Huynh, B. H.; Scheidt, W. R. *Inorg. Chem.* **1992**, *31*, 3459.

(13) (a) McMurry, T. J.; Groves, J. T. *Cytochrome P-450 Structure, Mechanism and Biochemistry*; Plenum Press: New York, 1986; Chapter 1, pp 1–28. (b) Higuchi, T.; Shimada, K.; Maruyama, N.; Hirobe, M. *J. Am. Chem. Soc.* **1993**, *115*, 7551 and references therein.

(14) (a) Sharma, V. S.; Traylor, T.; Gardiner, G. R.; Mizuka, H. *Biochemistry* **1987**, *26*, 3837. (b) Gibson, Q. H. et al. *J. Biol. Chem.* **1991**, 226, 13097. (c) Petrich, J. W. et al. *Biochemistry*. **1991**, *30*, 2975.

(15) (a) Solar, J. P.; Mares, F; Diamond, S. E. *Catal. Rev.* **1985**, *27*, 1. (b) Andrews, M. A.; Chang, T. C.-T.; Cheng, C. W.-F. *Organometallics* **1985**, *4*, 268. (c) Leising, R. A.; Takeuchi K. *J. Am. Chem. Soc.* **1988**, *110*, 4079. (d) Ercolani, C.; Pavletti, A. M.; Pennesi, G.; Rossi, G. *J. Chem. Soc., Dalton Trans.* **1991**, 1317.

(16) White, K. A.; Marletta, M. A. *Biochemistry* **1992**, *31*, 6627.

(17) Ignarro, L. J. *Biochem. Soc. Trans.* **1992**, *20*, 465.

(18) Ye, R. W.; Toro-Suarez, I.; Tiedje, J. M.; Averill, B. A. *J. Biol. Chem.* **1991**, *266*, 12848.

(19) Conversion of intermediate NO to NO_2 and further reaction to form N_2O_3 followed by hydrolysis ($H_2{}^{18}O$) could result in $N^{18}O_2^-$.