The Synthetic and Structural Chemistry of Heme Derivatives with Nitric Oxide Ligands

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Introduction

We begin this Account with a brief historical note describing the origins of our work with metalloporphyrin nitric oxide (NO) complexes. In 1969, I (W.R.S.) suggested to my then postdoctoral mentor, the late Professor J. L. Hoard, that synthetic and structural studies on metalloporphyrin NO complexes would be a useful scientific study. I thought that investigations of this diatomic ligand with metalloporphyrins would be interesting in their own right and could also provide a better understanding of the geometric and electronic structure of the analogous and more biologically significant O_2 and CO metalloporphyrin complexes. NO was then known to bind strongly to heme in deoxyhemoglobin from the work of Roughton and Gibson.[1] NO was also known to be toxic but otherwise thought to be biologically unimportant. I am certain that neither Professor Hoard nor I then anticipated that NO would become *Science*'s "Molecule of the Year" in 1992.[2]

NO became *Science*'s molecule of the year because of its important role in mammalian physiology. Importantly, much of this biological significance relates to the interaction of NO with iron porphyrins. NO is synthesized in vivo by the heme protein nitric oxide synthase. NO acts as a physiological messenger by binding to the heme cofactor of soluble guanylate cyclase, forming an iron(II) nitrosyl compound.[3] This new complex leads to catalytic conversion of GTP to cGMP.[4] The production of cGMP regulates many biological functions including vasodilation, inhibition of platelet aggregation, cell adhesion, neurotransmission, and penile erection.[2,5] Another important role for hemes is the control of NO concentration in the blood by conversion to NO_3^-. In the global nitrogen cycle of N_2 fixation and denitrification, iron(II) and -(III) porphyrin complexes of NO and/or NO_2^- play important roles.[6] Iron-(III) heme proteins (nitrophorins) have been isolated from the salivary glands of two bloodsucking insects.[7,8] Nitrophorins reversibly bind NO without being reduced to the

iron(II) form. The pH-dependent NO binding affinity enables the insect to release NO in host tissues to induce local vasodilation and obtain a larger blood meal. Finally, nitric oxide is used as a probe molecule in the study of hemoproteins;[9,10] the EPR signal often provides direct evidence for the identity of the trans ligand in the protein.

In this Account we will summarize the structural, synthetic, and relevant biophysical features of the metalloporphyrin complexes formed by NO. These display predictably differing features that depend on the formal oxidation state of the metal and further ligation at the metal center. This Account particularly focuses on the nature of the various iron species.

M−N−O Geometry

Early descriptions of the electronic structure of nitric oxide as a ligand emphasized two distinct forms: NO^+ and NO^-. These were associated with two limiting geometries for M−N−O: linear and bent, respectively. In addition to the obvious difficulty of requiring knowledge of the structure to assign the oxidation states of the ligand and metal, the NO^+/NO^- formalism leads, on occasion, to unusual metal oxidation state assignments. In our opinion, this formalism has little or no heuristic value. Indeed for predicting geometry or properties, a preferable formalism for the metalloporphyrin nitrosyls is the electron counting formalism of Enemark and Feltham.[11] In this system the NO ligand is not the independent entity that defines the geometry of the complex, but rather the entire MNO group is the independent unit. Thus, the formal oxidation state of the metal ion is always that computed considering the NO ligand as a neutral species. The critical value defining the geometry is the number of metal d-electrons plus the electron in the π^* orbitals of NO. In the notation $\{MNO\}^n$ the number of electrons (n) defines the MNO geometry; this notation will be used throughout this Account.[12]

For nitrosylmetalloporphyrin complexes, which must have square-pyramidal and pseudooctahedral geometries for the five- and trans six-coordinate derivatives, respectively, the most important values of n are 6, 7, and 8. Structures for first-row metalloporphyrins show that for $n = 6$, MNO is linear, while for $n = 8$, MNO is strongly bent ($\angle MNO \approx 120°$). Complexes with the intermediate value of $n = 7$ have intermediate MNO angles. This behavior has been rationalized in a number of analyses that effectively follow the logic of Walsh rule correlations.[11,13,14] The most important metal bonding orbitals are the two d_π and the d_{z^2} orbitals; for $n \geq 7$ systems, one of the d_π orbitals must change its bonding character from π toward σ.

Five-Coordinate Nitrosyl Derivatives

The first nitrosyl porphyrin characterized was the $\{CoNO\}^8$ derivative, $[Co(TPP)(NO)]$,[15] followed by the $\{FeNO\}^7$ complex, $[Fe(TPP)(NO)]$.[16] An undergraduate, Mark Frisse, developed simple anaerobic techniques necessary for
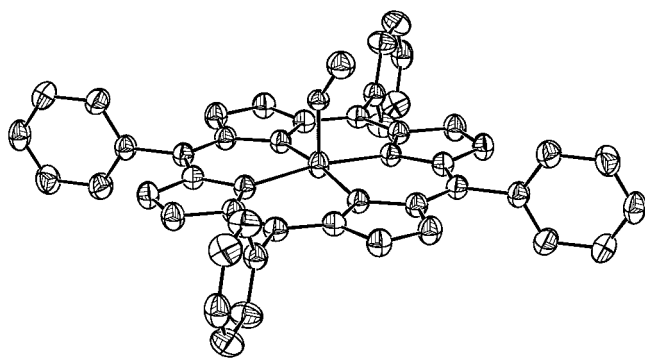
FIGURE 1. ORTEP diagram illustrating the structure of five-coordinate [Fe(TPP)(NO)]. Drawn from coordinates reported in ref 16.

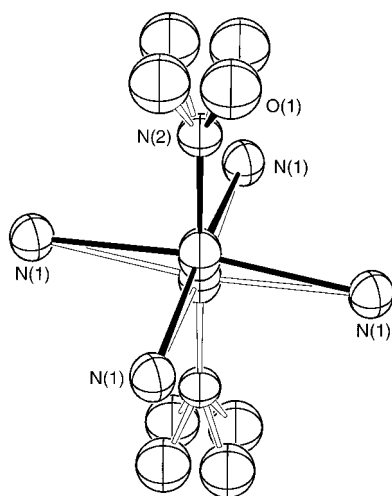**FIGURE 2.** Diagram illustrating the required crystallographic disorder in five-coordinate [Fe(TPP)(NO)]. The disorder often found in nitrosyl derivatives is similar but usually not quite as complex. (Drawn from ref 16.)

preparing crystals of [Fe(TPP)(NO)]; we still use his methods. The two molecules crystallize with the same solid-state molecular arrangement (Figure 1). Important differences in the two species are the M−N−O bond angle and the metal displacement out of the porphyrin plane. The 4/m crystallographically demanded symmetry (Figure 2) is much higher than either molecule can actually possess. The graphic hydra-like display of nitrosyl group disorder represents a serious difficulty for many other nitrosyl complexes: solid-state disorder limits the accuracy of M−N(NO) and N−O bond lengths and the M−N−O angle. Subsequent solid-state NMR studies by J. Mason showed,[17] for [Co(TPP)(NO)], that there is a dynamic 4-fold disorder of the nitrosyl group around the Co−N(NO) bond above 200 K; this likely pertains for [Fe-(TPP)(NO)] as well.

The frequent problems caused by disorder are not always recognized in the determination of precise MNO geometries. An examination of the N−O bond length is the first of two simple tests for structure quality. Any significant departure from that seen in NO (1.15 Å) suggests experimental difficulties; there is no credible evidence for significant variation in N−O length with metal−NO coordination modes. The second is the nature

of the ellipsoids in a thermal ellipsoid plot (ORTEP) diagram. The appearance of ellipsoids that either are too large or display apparent motion of the atoms that is kinematically unusual or impossible is a real warning sign. Ellipsoids elongated along the M−N bond vector almost always signal real errors in the position of the nitrogen atom. Careful consideration of the structural results is always appropriate since other difficulties, less obvious, may also exist. Despite the limitations of disorder in the two structures, they do show that the Co−N−O angle is clearly smaller than the Fe−N−O angle and that the axial M−N(NO) bonds differ by >0.1 Å (Co−N = 1.833 Å, Fe−N = 1.717(7) Å). Indeed, subsequent structure determinations[18] of cobalt nitrosyl porphyrins suggest that the true value of the Co−N−O angle is closer to 120° and the angle difference in {CoNO}^{8} vs {FeNO}^{7} is greater than 20°. The shorter Fe−N distance and larger angle suggest that there is stronger π bonding between the nitrosyl and the iron.

The synthesis of the iron and cobalt derivatives also demonstrates important chemical differences. The cobalt-(II) nitrosyl derivative is conveniently prepared by the reaction of NO with [Co(TPP)]:

$$[Co(TPP)] + NO \rightarrow [Co(TPP)(NO)]$$
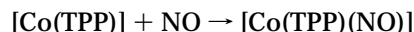
In the iron system a similar reaction can be used; however, an iron(III) compound can also be used as the starting reagent

$$[Fe(TPP)Cl] + 2NO + H-(acceptor) \rightarrow$$
$$[Fe(TPP)(NO)] + NO-(acceptor) + HCl$$
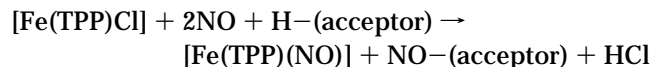
and is a more convenient process. The reaction product above is a (paramagnetic) {FeNO}^{7} species, and the reaction clearly must involve a redox process. Since NO is always a neutral ligand in the {MNO}^{n} formalism, iron is assigned as Fe(II) and the reaction is called reductive nitrosylation. Reductive nitrosylation requires the presence of an acceptor and can be avoided by careful choice of conditions; hence, (nitrosyl)iron(III) derivatives can also be prepared.

Different iron(III) hemoprotein derivatives display a wide range of stabilities toward reduction with NO. Early work[19] showed that the reaction of iron(III) hemoproteins with NO generally led to iron(II) derivatives by reductive nitrosylation. Reduction rates for hemoglobin and myoglobin derivatives show significant variation,[20] and recently, Ford et al.[21] have shown a pH dependency toward reductive nitrosylation. Nitrophorins from the kissing bug reversibly bind NO but remain in the iron(III) state under all conditions.[7]

The interesting structural difference observed between the {CoNO}^{8} and {FeNO}^{7} systems led us to characterize {MNO}^{6} systems. The initial five-coordinate {MnNO}^{6} targets proved difficult to synthesize because of their high affinity for a trans axial ligand. The structure of [Mn(TTP)-(NO)][22] resulted from crystals obtained under rigorously dry conditions; the complex has an effectively linear Mn−N−O group (177.8(3)°) and a quite short Mn−N(NO) bond length (1.641(2) Å). Subsequently, we prepared the iso-
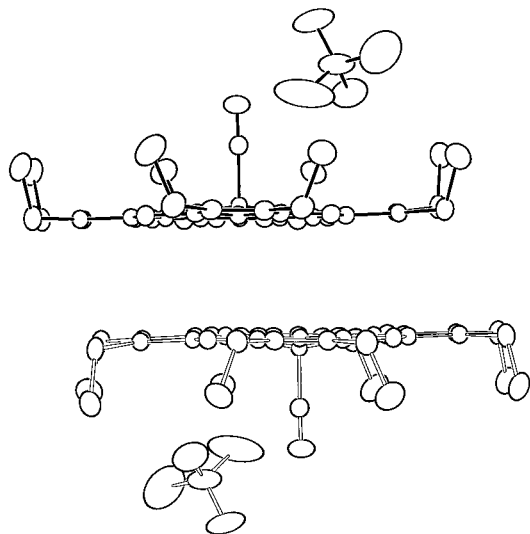
FIGURE 3. ORTEP diagram illustrating the structure and the $\pi-\pi$ interaction in five-coordinate [Fe(OEP)(NO)]ClO$_4$. Diagram drawn from coordinates reported in ref 23.

electronic cationic {FeNO}^{6} complex, [Fe(OEP)(NO)]$^+$, which can be synthesized by the simple reaction of NO with [Fe(OEP)(OClO$_3$)].[23] The linear Fe−N−O group (176.9-(3)°) and Fe−N(NO) bond length of 1.644(3) Å are almost identical to those of the manganese analogue. The synthesis of five-coordinate [Fe(Porph)(NO)]$^+$ species requires careful consideration of synthetic conditions. In addition to avoiding reductive nitrosylation, the required counteranion of the iron(III) starting complex must be very weakly binding. The reaction of [Fe(TPP)(Cl)] with NO, for example, yields the six-coordinate complex, [Fe(TPP)(Cl)-(NO)].[13] The synthesis of five-coordinate iron(III) species appears to be aided by the use of porphyrin ligands that can readily form $\pi-\pi$ dimers. Figure 3 shows the dimeric interaction found for the cationic {FeNO}^{6} complex, [Fe-(OEP)(NO)]$^+$.[23]

Thus, the {MNO}^{n} series shows systematic variation in the M−N−O angle, M−N(NO) bond length, and metal ion displacement (cf. Figure 4). The data entered for each of the three {MNO}^{n} systems is a "consensus" structure based on the structural data of Table 1. All compounds listed have a low-spin electronic ground state which is unusual for five-coordinate metalloporphyrin species. This

feature leads to the relatively small values of the metal atom displacement from the 24-atom porphyrin cores. The displacements are probably somewhat increased because of the steric interaction between the nitrosyl nitrogen atom and atoms of the core. The differences in the three groups reflect the changing M−N(NO) distance in the series; note that the Ct⋯N(NO) distance is essentially constant across the series.

During recent work investigating (nitrosyl)iron(III) complexes, we isolated superb crystals of (five-coordinate) [Fe(OEP)(NO)].[26] The overall quality of the resulting ordered structure was excellent with small standard uncertainties and very small differences between equivalent structural parameters in the porphyrin core. Thus, we were surprised to observe a relatively large spread in the Fe−N$_p$ distances. The axial Fe−N(NO) bond was also observed to be significantly tilted from the porphyrin plane normal. Careful consideration suggested that the Fe−N$_p$ bond distance pattern was related to the orientation of the bent and tilted {FeNO} group. The same pattern of bond distance differences and bond tilting were also seen in a second (triclinic) crystalline form that gave an even more superlative X-ray crystal structure. Figure 5 schematically shows the pattern of Fe−N$_p$ bond distance changes observed in the (nitrosyl)(porphinato)iron(II) derivatives. The two Fe−N$_p$ bonds along the Fe−N(NO) bond-tilt direction are shortened while the other two Fe−N$_p$ bonds away from the bond-tilt direction are lengthened. Although the distance changes are small ($\Delta \approx 0.025$ Å) and the tilt of the Fe−N vector off the heme normal is also small (tilts 6−8°), the high quality of the two structures leads to statistically significant differences. That the same pattern of tilt/asymmetry was seen in two derivatives suggests that this is an intrinsic feature of the {FeNO}^{7} porphyrin system. Moreover, Bohle et al.[27] had just reported the structure of five-coordinate [Fe(OETAP)-(NO)]; we noted the same tilt/asymmetry pattern was also present in that structure. We have looked further at whether this tilt/asymmetry is a general effect with the preparation and characterization of iron(II) nitrosyls for two additional porphyrin systems. These yield a total of four new, independent structures; all but one are well-ordered.[29] An oxochlorin derivative, [Fe(oxoOEC)(NO)],
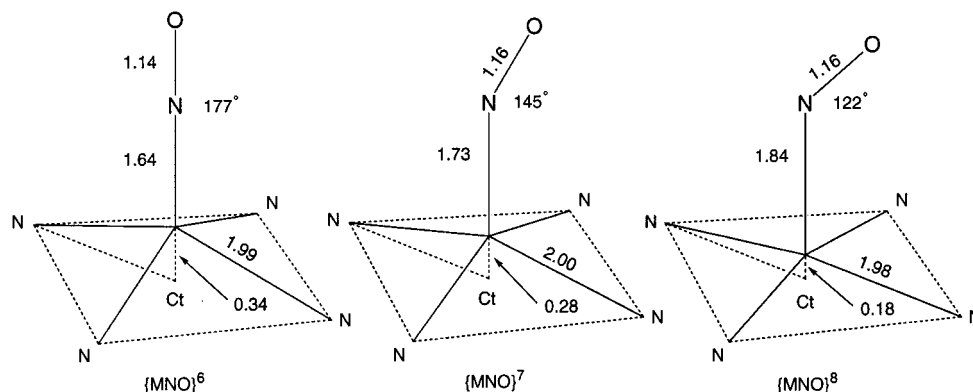

FIGURE 4. Formal diagrams of the "consensus" five-coordinate coordination groups in the (nitrosyl)metalloporphyrin series {MNO}^{n}, $n =$ 6, 7, 8.

Table 1. Summary of Coordination Group Geometry for Five-Coordinate Nitrosyl Metalloporphyrin Derivatives

| complex	$M-N_p{}^a$	$M-N_{NO}{}^a$	$\angle MNO{}^b$	$N-O{}^a$	$\Delta^{a,c}$	$\nu(NO)$	ref
		A. $\{MNO\}^8$ Derivatives					
[Co(TPP)(NO)]	1.978(4)	1.833(53)	~135	1.01(2)	0.09	1689^d	15
[Co(OEPBu$_2$)(NO)]	1.949(9)	1.842(5)	124.7(5)	1.177(7)^e	0.10	NA	18c
[Co(Tp-OCH$_3$PP)(NO)]	1.972(8)	1.855(6)	120.6(5)	1.159(8)	0.20	1696^d	18b
[Co(OEP)(NO)]	1.984(8)	1.8444(9)	122.70(8)	1.1642(13)	0.16	1677^f	18a
	$\{1.9915(30), 1.9774(1)\}^g$		2.2^h				
		B. $\{MNO\}^7$ Derivatives					
[Fe(TPP)(NO)]	2.001(3)	1.717(7)	149.2(6)	1.122(12)	0.21	1670^d	16
[Fe(TpivPP)(NO)]	1.981(26)	1.716(15)	143.8(17)	1.197(9)	0.27	1665^d	24
[Fe(OBTPP)(NO)]	1.986(23)	1.75(6)	146(2)	1.42(7)	NA^i	1685^d	25
[Fe(TDCPP)(NO)]	2.004	1.703(8)	138.8(9)	not reported	NA^i	1688^d	25
[Fe(OEP)(NO)]	2.004(15)	1.722(2)	144.4(2)	1.167(3)	0.29	1666^f	26
(monoclinic)	$\{2.016(1), 1.991(3)\}^g$		6.5^h				
[Fe(OEP)(NO)]	2.010(13)	1.7307(7)	142.74(8)	1.1677(11)	0.27	1673^f	26
(triclinic)	$\{2.020(4), 1.999(1)\}^g$		8.2^h				
[Fe(OETAP)(NO)]	1.931(9)	1.721(4)	143.7(4)	1.155(5)	0.31	1666^d	27
	$\{1.940(2), 1.924(2)\}^g$		7.6^h				
[Fe(TPPBr$_4$)(NO)]^j	2.006(35)	1.734(8)	147.9(8)	1.119(11)	0.37	1678^f	29
(complex 1)	$\{2.041(9), 2.031(8)\}^g$		5.6^h				
[Fe(TPPBr$_4$)(NO)]^j	1.996(24)	1.726(9)	146.9(9)	1.144(12)	0.32	1678^f	29
(complex 2)	$\{2.027(7), 2.004(7)\}^g$		7.1^h				
[Fe(TPPBr$_4$)(NO)]^k	1.951(35)	1.691(11)	145(1)	1.145(16)	0.29	1681^f	29
[Fe(oxoOEC)(NO)]	2.009(9)	1.7320(13)	143.11(15)	1.1696(19)	0.26	1690^f	29
			7.3^h				
		C. $\{MNO\}^6$ Derivatives					
[Mn(TTP)(NO)]	2.004(5)	1.641(2)	177.8(3)	1.160(3)	0.40	1735^d	22
[Fe(OEP)(NO)]$^+$	1.994(1)	1.644(3)	176.9(3)	1.112(4)	0.29	1862^d	23
[Fe(OECor)(NO)]	1.909(9)^l	1.631(3)	176.9(3)	1.171(4)		1758^m	28
[Fe(OECor)(NO)]$^+$	1.912(8)^l	1.655(10)	171.4(9)	1.115(12)		1809^m	28

^{a} Value in angstroms. ^{b} Value in degrees. ^{c} Displacement of the metal atom out of the 24-atom porphyrin plane. ^{d} KBr pellet. ^{e} Value after correction for thermal foreshortening. ^{f} Nujol mull. ^{g} Long and short equatorial distances related to off-axis tilt of NO; see the text. ^{h} Value of off-axis tilt (deg). ^{i} Obscured by required crystallographic disorder. ^{j} Saddled form with two independent molecules. ^{k} Ruffled form, disordered. ^{l} Short Fe−N distance because of 15-membered ring in OECor. ^{m} CsI pellet.
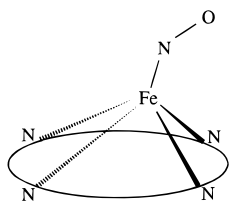
FIGURE 5. Formal diagram illustrating the tilt/asymmetry found in the ordered five-coordinate [Fe(Porph)(NO)] derivatives. All distortions have been exaggerated for clarity.

related to the d_1 heme of the cd_1 dissimilatory nitrite reductase, shows a similar tilt/asymmetry pattern. Iron-(II) nitrosyl derivatives with TPPBr$_4$ display two distinctly different saddled conformations in which the NO group tilts toward one of the trans brominated pyrroles.

The structures for all ordered five-coordinate iron(II) nitrosyls are strongly supportive of tilt/asymmetry as an intrinsic feature of the total bonding interactions in the complex. Qualitatively, the molecular orbital picture used to explain the M−N−O geometry for $\{MNO\}^n$ systems can also be used to rationalize the tilt/asymmetry. The critical bonding interactions that lead to bending of the $\{MNO\}^n$ group (taken here to be in the xz plane) for $n \geq 7$ are the interactions of the metal d_{z^2} and d_{xz} orbitals with NO. Hoffman et al.[14] rationalized the opposite tilting seen in some $\{MNO\}^8$ complexes by a sideways movement of the nitrosyl with respect to the normal in order to increase overlap of the $\pi^*{}_{NO}$ orbital with metal d_{z^2}. This is illustrated schematically in Figure 6 (top). An alternate way to achieve comparable overlap of these two orbitals is illustrated in
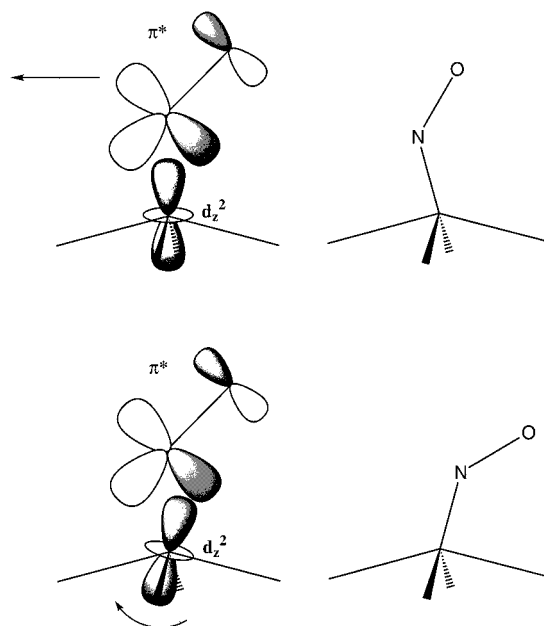
FIGURE 6. Diagram illustrating possible distortions leading to greater overlap of the half-occupied $\pi^*{}_{NO}$ orbital with the iron d_{z^2} orbital that leads to two different tilt directions.

Figure 6 (bottom). However, the rotation of the d_{z^2} orbital with respect to the heme normal must lead to tilting in the opposite sense *and* small differences in the σ interaction of the metal with the basal donor atoms. The basal σ interactions in the direction of the tilt will have a slightly stronger interaction than those in the direction opposite

**Table 2. Summary of Coordination Group Geometry for Six-Coordinate {MNO}[7] Metalloporphyrin Derivatives**

complex	M−N$_p$[a]	M−N$_{NO}$[a]	∠MNO[b]	M−L[a]	N−O[a]	Δ[a,c]	ν(NO)[d]	ref
[Fe(TPP)(NO)(1-MeIm)]	2.008(12)	1.743(4)	142.1(6)	2.180(4)	1.121(8)	0.07	1625	30, 31
[Fe(TPP)(NO)(4-MePip)](form 1)	2.004(9)	1.721(10)	138.5(11)	2.328(10)	1.141(13)	0.09	1640	32
[Fe(TPP)(NO)(4-MePip)](form 2)	1.998(10)	1.740(7)	143.7(6)	2.463(7)	1.112(9)	0.11	1653−1656	32
[Fe(TpivPP)(NO$_2$)(NO)]$^-$ (average of three values)	1.990(12)	1.802(34)	138.1(12)	2.075(5)	1.155(21)	0.09	1616,[e] 1668[f]	33
[Fe(TPP)(1-VinIm)$_2$]	2.001(2)			2.004(2)				34
[Fe(TPP)(1-BzlIm)$_2$]	1.993(9)			2.017(4)				34
[Fe(TPP)(1-MeIm)$_2$]	1.997(6)			2.014(2)				35
[Fe(TPP)(Pip)$_2$]	2.004(4)			2.127(3)				36

[a] Value in angstroms. [b] Value in degrees. [c] Displacement of the metal atom out of the 24-atom porphyrin plane. [d] KBr pellet. [e] ⊥ form. [f] ∥ form.

the tilt. It is yet to be determined whether this tilting leads to any particular reactivity, but tilting is consistent with the FeNO unit dominating the bonding in the complexes.

Six-Coordinate {FeNO}[7] Nitrosyl Derivatives

The five-coordinate square-pyramidal nitrosyl complexes are coordinatively unsaturated species that should readily add a sixth ligand:

$$[M(TPP)(NO)] + L \xrightleftharpoons{K_1} [M(TPP)(NO)(L)]$$
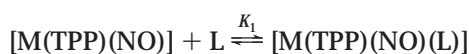
However, changes in the metal and/or the oxidation state lead to large differences in the value of K_1 and the stability of the nitrosyl. Thus, while the addition of a neutral nitrogen ligand L to [Fe(TPP)(NO)] can lead to the isolation of the six-coordinate complex [Fe(TPP)(NO)(L)], the value of K_1 is quite small. As a result, reactions with neutral donors lead to mixtures of the five- and six-coordinate nitrosyl complexes. Nonetheless, three crystal structures of six-coordinate derivatives have been carried out; the results of the analyses are given in Table 2. The Fe−N(NO) distance and the Fe−N−O angle do not change significantly upon coordination of a sixth ligand. This is a reflection of the dominant bonding interactions within the Fe−N−O group. Importantly, however, the structure determinations show that the bond trans to the nitrosyl ligand is unusually long, i.e., the NO ligand exerts a strong trans effect. The trans bond is 0.16−0.18 Å longer in the mixed nitrosyl imidazole system than in the analogous bisimidazole compounds given in Table 2. The long value and apparent weakness of the iron−imidazole bond led us to use piperidine as the sixth ligand. We expected that the relative elongation of the trans bond in the piperidine derivative would be even greater due to steric effects. What we did not expect was that two crystalline forms of the six-coordinate species [Fe(TPP)(NO)(4-MePip)] would have large differences in the Fe−N(4-MePip) bond length. The trans lengthening is 0.20−0.34 Å in the two piperidine systems and is consistent with an even weaker trans bond than in the imidazole derivative. The related ligand carbon monoxide (CO) does not lead to substantial lengthening of the trans bond,[37] showing the unique nature of the NO ligand.

The trans effect in six-coordinate {FeNO}[7] complexes results from the partial population of the d$_{z^2}$ orbital by the unpaired electron derived from the nitrosyl ligand. As shown by Kon[38] and later by Wayland,[39] the EPR spectrum

of six-coordinate derivatives with neutral nitrogen donors as the sixth ligand display hyperfine splittings from that nitrogen atom as well as splitting from the nitrogen atom of NO. This conclusively demonstrates that the unpaired electron is in an orbital with substantial d$_{z^2}$ character; this orbital combination must be antibonding with respect to binding the sixth ligand. In the {CoNO}[8] complex there are contributions by the unpaired electron of nitrosyl as well as the original d$_{z^2}$ unpaired electron from low-spin cobalt(II), making this orbital combination even more antibonding. It can thus be expected that the affinity of five-coordinate cobalt nitrosyls for a sixth ligand will be even less than that of the iron(II) species. Indeed, no six-coordinate cobalt nitrosyl species have been isolated.[40]

The nitrosyl trans effect in iron(II) porphyrinate derivatives has since been found to be physiologically significant. Bond breaking appears to be the process by which NO turns on the enzyme guanylate cyclase which in turn regulates many biological functions. NO as a signaling agent coordinates to the five-coordinate iron(II) heme; the consequent NO trans effect leads to the breaking of the trans iron−histidine bond. A proposed conformation change of the multiunit protein leads to activity.[3] The NO structural trans effect also leads to significant differences in the physical properties of nitrosylhemoglobin in the presence and absence of allosteric effectors. Investigation of the addition of inositol hexaphosphate to nitrosylhemoglobin by IR, RR, or EPR spectroscopy leads to the conclusion that some bond breakage occurred.[41,42]

We have also investigated iron species that contain nitrite ion as well as NO. The mixed (nitro)(nitrosyl)iron-(II) species was synthesized by reaction of NO with five-coordinate iron(II) nitrite:

$$[Fe(TpivPP)(NO_2)]^- + NO \rightleftharpoons [Fe(TpivPP)(NO_2)(NO)]^-$$
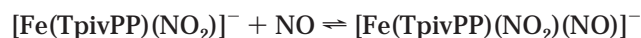
Although in solution there is clearly an equilibrium mixture of the two species and probably [Fe(TpivPP)(NO)] as well, the indicated crystalline six-coordinate product can be obtained.[33] In this complex as well as all other iron nitrite species we have characterized,[24,45] the nitrite ligand is N-bound. Our interest in this system was in investigating the bonding competition between the two strong π-acceptor ligands. We isolated two crystalline forms of the complex; the important difference in the two forms is the relative orientation of the axial ligand planes. In one form the Fe−N−O plane is nearly perpendicular to the
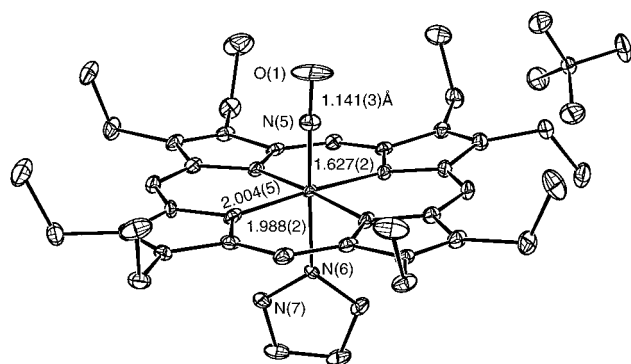
FIGURE 7. ORTEP diagram illustrating the structure of (nitrosyl)-(pyrazole)(octaethylporphinato)iron(III). Diagram drawn from coordinates reported in ref 48.

NO_2 plane, and in the other the two planes are nearly parallel. Electronic structure information for the two different species, seen principally in the Mössbauer spectra, shows that both act as π acceptors when the two planes are perpendicular and each axial ligand can interact with a distinct iron d_π orbital. However, when both axial ligands are in the same plane and are competing for the same π density, the nitrosyl ligand appears to dominate in the π bonding.[33]

Six-Coordinate {FeNO}[6] Nitrosyl Derivatives

The preparation of six-coordinate iron(III) nitrosyl derivatives follows the same reaction used for the iron(II) species with the five-coordinate iron(III) nitrosyl prepared in situ. Although K_1 for the binding of a neutral nitrogen donor is clearly larger, there are significant difficulties in the preparations. The affinity of NO for the iron(III) center is much lower than that in the iron(II) center. This requires that the synthesis and crystallization of six-coordinate derivatives be performed under an NO atmosphere which has the unfortunate side effect of facilitating reductive nitrosylation. The lowered NO affinity also means that NO can be displaced by neutral nitrogen donors to yield bis-ligated iron(III) derivatives. Avoidance of these undesirable reactions in the synthesis of six-coordinate iron(III) nitrosyls requires careful attention to details largely derived empirically.[47]

The sixth ligand in iron(III) nitrosyl derivatives has little effect on the FeNO geometry. Again this reflects the dominance of the Fe–N–O group. One possible difference

is that the Fe–N(NO) bond becomes slightly *shorter* on addition of the sixth ligand; it is clear that the bond does not lengthen. There are steric interactions between the nitrogen atom of the nitrosyl and atoms of the porphyrin core, and all six-coordinate species show modest, but real, distortions from core planarity that increase the distance between the nitrosyl nitrogen and the porphyrin core nitrogen atoms. The core of the (nitrosyl)(pyrazole) derivative (cf. Figure 7) has both a ruffling and a reverse doming which increases the N_{NO}···N_p separations.[47] Despite the nonbonded axial–core interactions, the iron atom is nearly centered in the porphyrin plane with very small iron displacements toward the NO ligand (Table 3). The displacements in the six-coordinate iron(II) derivatives (Table 2) are slightly larger than those for the iron-(III), surely reflecting the stronger interaction toward the sixth ligand in the iron(III) systems. Unlike the iron(II) case, there is no apparent trans effect exerted by the nitrosyl in the iron(III) cases. The Fe–N(imidazole) value quoted[49] in Table 3 is representative of the large number of values that have been determined.

The mixed nitrite/nitrosyl iron(III) equilibrium systems used to prepare [Fe(Porph)(NO$_2$)(NO)] are at least as complex as the [Fe(Porph)(NO$_2$)(NO)]$^-$ case described earlier. The mixed axial ligand species can be prepared by the reaction of a variety of starting iron species and nitric oxide. These include the reaction of [Fe(Porph)-(NO)],[48,50] [Fe(Porph)(NO$_2$)$_2$]$^-$,[48,51] or [Fe(Porph)]$_2$O[54] with NO. The use of picket fence porphyrin was necessary to obtain derivatives in which the axial ligands are ordered;[48] the Fe–N–O group is close to linear. The two axial ligands appear to be good π acceptors; both of the Fe–N distances are slightly longer than those found in related six-coordinate species, suggesting strong competition between the two ligands.

Spectroscopic Correlations. Electronic and Vibrational

Figure 8 illustrates representative electronic spectra for all important classes of nitrosyl derivatives. The spectra are for (synthetic) octaethylporphyrin derivatives, but should be quite representative of the spectra obtained with the naturally occurring protoporphyrin IX derivatives as well. Five-coordinate [Fe(OEP)(NO)]$^+$ is seen to have a very blue-shifted Soret band and a strong single feature

Table 3. Summary of Coordination Group Geometry for Six-Coordinate {MNO}[6] Metalloporphyrin Derivatives

complex	M–N$_p$[a]	M–N$_{NO}$[a]	∠MNO[b]	M–L[a]	N–O[a]	Δ[a,c]	ν(NO)	ref
[Mn(TPP)(NO)(4-MePip)]	2.027(3)	1.644(5)	176.2(5)	2.206(5)	1.176(7)	0.08	1740[d]	22
[Fe(TPP)(NO)(H$_2$O)]$^+$	1.999(6)	1.652(5)	174.4(10)	2.001(5)	1.150	NA[e]	1937[d]	23
[Fe(TPP)(NO)(HO-iC$_5$H$_{11}$)]$^+$	2.013(3)	1.776(5)	177.1(7)	2.063(3)	0.925(6)	0.05[f]	1935[d]	46
[Fe(OEP)(1-MeIm)(NO)]$^+$	2.003(5)	1.6465(17)	177.28(17)	1.9889(16)	1.135(2)	0.02	1921[g]	47
[Fe(OEP)(Iz)(NO)]$^+$	1.996(4)	1.632(3)	177.6(3)	2.010(3)	1.136(4)	0.04	1914[g]	47
{[Fe(OEP)(NO)]$_2$Prz}$^{2+}$	1.995(8)	1.632(3)	176.5(3)	2.039(2)	1.131(4)	0.06	1899[g]	47
[Fe(OEP)(Pz)(NO)]$^+$	2.004(5)	1.627(2)	176.9(3)	1.988(2)	1.141(3)	0.01	1894[g]	47
[Fe(TpivPP)(NO$_2$)(NO)]	1.996(4)	1.671(2)	169.3(2)	1.998(2)	1.144(3)	0.09	1893[g]	48
[Fe(TPP)(NO)(Cl)]							1880[g]	13
[Fe(TPP)(1-MeIm)$_2$]$^+$	1.982(11)			1.974(6)				49

[a] Value in angstroms. [b] Value in degrees. [c] Displacement of the metal atom out of the 24-atom porphyrin plane. [d] KBr pellet. [e] Obscured by required crystallographic disorder. [f] Displacement of the metal atom from the mean plane of the 4 nitrogen atoms. [g] Nujol mull.
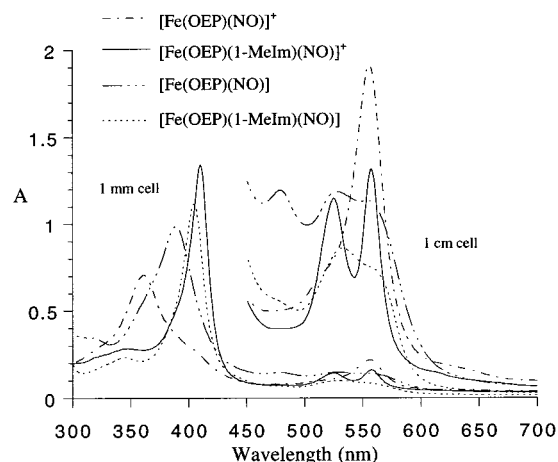
FIGURE 8. UV/vis spectra for the four classes of (nitrosyl)-(octaethylporphinato)iron derivatives in CH_2Cl_2.

Table 4. Mössbauer Parameters for Nitrosyl Complexes

	ΔE_q, mm/s	δ_{Fe}, mm/s	T, K	ref
{MNO}[7] Complexes				
[Fe(TPP)(NO)]	1.24	0.35	4.2	33
[Fe(OEP)NO]	1.26	0.35	100	27
[Fe(TpivPP)(NO$_2$)(NO)]$^-$ ($\perp$ form)	1.78	0.22	200	33
[Fe(TpivPP)(NO$_2$)(NO)]$^-$ ($\parallel$ form)	1.20	0.35	4.2	33
{MNO}[6] Complexes				
[Fe(OEP)NO]ClO$_4$	1.63	0.12	293	56
	1.64	0.20	4.2	56
[Fe(TPP)(NO$_2$)(NO)]	1.37	0.02	293	48
	1.36	0.13	4.2	48
	1.36	0.13	77	54
[Fe(Tp-OCH$_3$PP)(NO$_2$)(NO)]	1.43	0.04	293	48
[Fe(TpivPP)(NO$_2$)(NO)]	1.48	0.01	293	48
	1.43	0.09	4.2	48

in the visible region. The addition of a ligand gives a strongly red-shifted Soret and the quite characteristic, well-developed pair of bands in the visible region. The spectral differences between derivatives with a neutral or an anionic axial sixth ligand is minimal. The five-coordinate iron(II) species has a quite broad Soret and a characteristic 480 nm band in the visible region. Addition of the sixth ligand leads to a distinct sharpening of the Soret band and the disappearance of the 480 nm band. Thus, each major derivative group has a distinctive electronic spectrum.

The determination of the (porphinato)iron NO stretching frequency allows definitive assignments of the Fe–N–O geometry. Although there are well-known problems with the use of absolute nitrosyl stretching frequencies to assign MNO geometry,[55] the assignment of linear or bent nitrosyls in the (porphinato)iron case is clear-cut. The observed solid-state stretching frequencies have been tabulated in Tables 1–3. All iron(II) species (bent Fe–N–O groups) are seen to have ν(NO) below 1700 cm^{-1} while all iron(III) derivatives (linear Fe–N–O groups) are observed to have ν(NO) above 1800 cm^{-1}. Equally importantly, there is significant information about the (possible) sixth ligand in both oxidation states of iron. All derivatives, in either oxidation state or coordination number, display an extremely intense NO band. The effects of porphyrin variation are small, comparable to that of other environmental effects.

In the iron(II) derivatives, the five-coordinate species have (Table 1) nitrosyl stretching frequencies in the narrow range of 1690–1665 cm^{-1}. The stretching frequency shows some sensitivity to environmental effects. The coordination of a sixth ligand such as an imidazole leads to a decrease in the stretching frequency to 1625 cm^{-1}.[31] The decrease is readily understood in terms of increased iron donation into the π^*_{NO} orbital of NO and a modest weakening of the N–O bond as a result of the sixth ligand. The piperidine derivatives display intermediate NO stretching frequencies in apparent consonance with the longer trans bond distance.[32] Within the limited set of compounds available, the value of ν(NO) varies linearly

with the variation in trans bond length and presumed differences in σ donation by the nitrogen donor. Indeed, the NO vibrational spectra are an exquisitely sensitive reporter of structure change.[32] Five-coordinate iron(III) nitrosyls display ν(NO) in the region of 1860 cm^{-1} and, like the iron(II) species, show variation in response to solid-state environmental effects.[56] The observed frequencies of the six-coordinate species (Table 3) are all significantly higher than that of five-coordinate [Fe(OEP)(NO)]$^+$. Most of the six-coordinate neutral nitrogen donor derivatives show this NO band in a narrow range (1910–1920 cm^{-1}). The reduction of ν(NO) by about 15 cm^{-1} in a few derivatives appears to be an effect resulting from the interactions of NO ligand pairs in the solid state.[47] Derivatives with an oxygen donor as the sixth ligand are at still higher frequencies, while the coordination of anionic ligands leads to decreased values of ν(NO) that are still higher than those of the five-coordinate complex. This change in ν(NO) upon coordination of a sixth ligand is distinctly different from that seen for the iron(II) nitrosyls.

The electronic structures of the iron nitrosyl derivatives have been investigated to a limited extent by Mössbauer spectroscopy. The first measurement was for nitrosylhemoglobin,[57] where the distinction between iron(II) and iron(III) states were blurred. The relatively few data available for (nitrosyl)iron porphyrinates are given in Table 4. In both the iron(II) and -(III) systems, the isomer shift value is closer to that expected for a higher oxidation state, which we take to be indicative of strongly delocalized FeNO units. The spectra of the iron(II) species, [Fe(TPP)(NO)], and the parallel form of [Fe(TpivPP)(NO$_2$)(NO)]$^-$, have been obtained in an 8T applied field as well as in zero field. Detailed fits of the spectra have been reported;[33] the two species have strikingly similar, but not identical, spectra in applied magnetic field. Interestingly, the signs and magnitudes of hyperfine parameters of the two derivatives compare well with those observed for three different NO-bound iron(II) heme proteins,[58] each of which contains a very different heme. The strong similarity in the spectral fit parameters again suggests that the electronic structure of nitrosyl hemes is predominantly determined by the Fe–N–O moiety.

Summary

The currently available information on the synthesis and structures of the nitrosyl derivatives of iron(II) and iron-(III) porphyrinates has been summarized. All data obtained suggest that the FeNO unit should be regarded as the strongly delocalized entity that determines physical and structural properties. There are two limiting structures for the FeNO unit that depend on the oxidation state of iron. The assignment of the oxidation state of iron can be easily made and is preferable to an assignment of NO oxidation state that is likely to be arbitrary. All iron(III) derivatives have an essentially linear Fe–N–O group (170–180°) and a very short Fe–N(NO) bond distance of 1.63–1.65 Å. This geometry remains unchanged in the six-coordinate species. The iron(II) derivatives have a partly bent Fe–N–O group (angle 140–150°) and a short Fe–N(NO) bond distance of 1.72–1.74 Å. The bond trans to NO is very long in the six-coordinate iron(II) species; this trans effect is physiologically important. The iron(II) porphyrinate systems are unique; there are no isolated nitrosylporphyrin species equivalent to iron(II) based on another metal. Spectroscopic properties (vibrational and electronic) can be used to assign iron oxidation state and hence the FeNO geometry.

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imidazole; 1-BzlIm, 1-benzylimidazole; Pip, piperidine; Iz, indazole (benzopyrazole); Prz, pyrazine; Pz, pyrazole; Ct, center of the 24-atom porphyrin core; N_p, porphyrinato nitrogen.

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