Mechanistic Aspects of the Reactions of Nitric Oxide with Transition-Metal Complexes

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Contents

I. Introduction

It is now well established that nitric oxide (aka nitrogen monoxide) plays fundamental roles in biochemical processes.[1,2] Early concerns with the biology of NO were largely focused on the known toxicities of NO and other reactive nitrogen oxide species as constituents of air pollution including cigarette smoke.[3] However, natural physiological activities are now known to include roles in blood pressure control, neurotransmission, and immune response. Subsequent reports have identified a number of disease states involving NO imbalances,[2,4] and such observations have stimulated extensive research activity into the chemistry, biology, and pharmacology of NO. This has led to renewed interest in the solution-phase reactions of NO, since understanding the fundamental chemistry may provide new insights regarding the physiological roles of this "simple" molecule. This article summarizes some mechanism studies of solution-phase reactions of NO and other reactive nitrogen oxide species as well as certain biological implications.

The principal targets for NO under bioregulatory conditions are metal centers, primarily iron proteins.[5] The best characterized example is the ferro-heme enzyme soluble guanylyl cyclase (sGC).[6] Formation of a nitrosyl complex with Fe(II) leads to labilization of a trans axial (proximal) histidine ligand in the protein backbone, and the resulting change in the protein conformation is believed to activate the enzyme for catalytic formation of the secondary messenger cyclic-guanylyl monophosphate (cGMP) from guanylyl triphosphate (GTP). The enzymatic formation of cGMP leads to relaxation of smooth muscle tissue of blood vessels, hence lowering blood pressure. Other reports describe roles of NO as an inhibitor for metalloenzymes such as cytochrome P450,[7a] cytochrome oxidase,[7b] nitrile hydratase,[8] and catalase,[9] as a substrate for mammalian peroxidases,[10] and as a contributor to the vasodilator properties of a salivary ferri-heme protein of blood sucking insects.[11] Heme centers are also involved in the in vivo generation of NO by oxidation of arginine catalyzed by nitric oxide synthase (NOS) enzymes.[12]

For bioregulatory purposes, NO concentrations generated are low, and [NO] values less than 1 μM have been reported to be generated in endothelium cells for blood pressure control.[13] Thus, reactions with targets such as sGC must be very fast to compete effectively with other physical and chemical processes that deplete free NO. However, the NO concentrations produced during immune response to pathogen invasion are much higher, and under these conditions, reactive nitrogen species such as peroxynitrite anion ($OONO^-$) and N_2O_3 may have physiological importance.

These biomedical roles place a high premium on understanding the fundamental chemistry of NO under conditions relevant to its biological formation and decay. Of special interest are the reactions and

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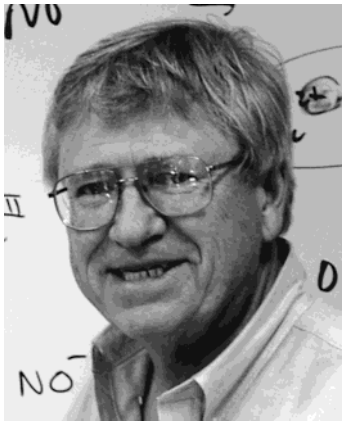
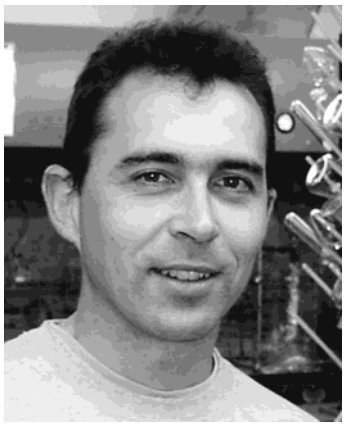


Peter C. Ford was born in California in 1941. His undergraduate work at Caltech was followed by graduate study at Yale (Ph.D. 1966) and a year as a NSF Postdoctoral Fellow at Stanford. In 1967 he joined the faculty of the University of California, Santa Barbara, where he has held the rank of Professor since1977 and has served as Department Chair (1994–1996). He has supervised the research of 44 students who completed their Ph.D. theses and numerous B.S., M.S., and postdoctoral students. He has been honored as a Dreyfus Foundation-Teacher Scholar, as a Senior Fulbright Fellow, with a Alexander von Humboldt-Stiftung US Senior Scientist Research Prize, with the 1992 Richard C. Tolman Medal of the American Chemical Society, and with election as a Fellow of the AAAS. His current research interests include the catalytic activation of CO and other small molecules, the photochemistry of coordination and organometallic compounds, and the bioinorganic chemistry of the nitrogen oxides.



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interactions with metal ion centers. In this context, presented here is an overview of selected developments in mechanistic chemistry involving the formation and reactions of transition-metal nitrosyl complexes. Such studies provide a quantitative understanding of pathways in which NO may participate and allow one to evaluate those which may be the most significant among the multitude of chemical trajectories that must be considered in interpreting biological systems. Given the high potential for artifacts resulting from the use of NO containing the highly reactive impurities NO_2 and N_2O_3, methods for purifying NO in the laboratory are also addressed.

It should be noted that the chemistry of nitric oxide complexes has long been of interest to transition-metal chemists and that a number of reviews and chapters have appeared over the past several decades.[14] The present article will not duplicate these previous efforts but will focus on mechanistic investigations of metal nitrosyl complexes, especially in the context of possible biomedical roles.

II. General Properties of Nitric Oxide and Metal Nitrosyl Complexes

A. Physical and Chemical Properties of NO

NO is a diatomic, stable free radical with an N−O bond length of 1.154 Å and a $^2\Pi$ ground state.[14h] Simple molecular orbital theory predicts a bond order of 2.5, consistent with its bond length between those of N_2 (1.06 Å) and O_2 (1.18 Å). The singly occupied MO is a π^* orbital, but polarized toward nitrogen in a manner opposing the polarization of the lower energy π^b orbitals. The result is a relatively nonpolar diatomic molecule; consequently, the NO stretch ν_{NO}, at 1875 cm^{-1} (15.9 mdynes/cm), has a very low intensity in the infrared absorption spectrum. Because of spin−orbit coupling of the unpaired electron with its π-orbital ($\sim$121 cm^{-1}), NO exhibits P, Q, and R rotational branches in its gas-phase vibrational spectrum.[15] A broadened, rotationally collapsed 'librational' version of this fine structure is visible in organic solvents (e.g., $CHCl_3$), giving a weak peak (ϵ $\sim$20 M^{-1} cm^{-1}) with a characteristic 'head and shoulders' shape.[16]

Nitric oxide is a colorless gas at STP with a boiling point (1 atm) at 121 K and a melting point at 110 K.[17] Dimerization of NO is significant at low temperature (D_0 = 2.14 kcal mol^{-1})[18] or high pressure.[19] Accordingly, the critical point of NO is 40 °C higher and the critical volume 30% lower than the averages for O_2 and N_2.[20] The gas-phase geometry of the N_2O_2 dimer is cisoid and nearly planar, with O=N−N bond angles of 97°.[21] Strong IR bands of N_2O_2 are observed at 1860 (symmetric NO stretch) and 1788 cm^{-1} (antisymmetric NO stretch).[22] NO absorbs significantly in the deep UV with sharp bands at 224, 213, and 203 nm, while the dimer shows a broad absorption centered at $\sim$205 nm.[23]

The solubility and transport of NO are similar to those of dioxygen.[24,25] The aqueous solution solubility of NO is 1.9 mM atm^{-1} at 298 K and 1.4 mM atm^{-1} at 310 K.[24] In organic solvents, the solubility is higher ranging from $\sim$3 mM atm^{-1} in DMSO to 15.0 mM atm^{-1} in cyclohexane at 298 K. NO is readily diffusible and has been reported to have a diffusion constant of 3300 $\mu m^2 s^{-1}$ under physiological conditions[25b] and to diffuse at a rate of 50 μ s^{-1} in biological systems.[25a] (However, see the treatment of diffusion in cellular and vascular systems by Lancaster[25b]).

The aqueous redox chemistry of NO is highly pH dependent, as both nitrite reduction (2 H^+/e^-) and NO reduction to HNO (1 H^+/e^-) are proton-coupled reductions (eqs 1−3). Hence, nitrous acid is relatively oxidizing under acidic conditions (eq 1), but near physiological conditions (pH 7.0), the reduction po-

tential of nitrite to NO drops to 0.37 V (vs NHE). At high pH, NO is relatively reducing (eq 2). The nitrosonium ion NO^+, which is isoelectronic to CO, is highly oxidizing; the reduction potential to NO has been measured in nonaqueous media (1.62 V in CH_3CN, 1.82 V in CH_2Cl_2 (vs NHE)) and estimated for water (eq 3).[26,27]

$$HNO_2 + H^+ + e^- \rightarrow NO + H_2O \qquad E° = 1.00 \text{ V (vs NHE)} \quad (1)$$

$$NO_2^- + H_2O + e^- \rightarrow NO + 2OH^- \qquad E° = -0.46 \text{ V (vs NHE)} \quad (2)$$

$$NO^+ + e^- \rightarrow NO \quad E° = \sim 1.2 \text{ V (vs NHE)} \quad (3)$$

The NO^+ cation is readily hydrolyzed to nitrite and is a potent nitrosating agent;[27] thus, it must be short-lived in biological media. However, many chemical species can act as NO^+ donors in reactions leading to the nitrosation of various substrates. For example, the reactions of certain metal nitrosyl complexes with nucleophiles such as RSH can lead to the transfer of NO^+ as illustrated in eq 4. Such reactions will be discussed in greater detail below.

$$RSH + L_xM{-}NO^+ \rightarrow RSNO + L_xM + H^+ \quad (4)$$

NO can also be reduced to the nitroxyl anion (NO^-) (eq 5). NO^- is isoelectronic to O_2 and like dioxygen the ground state is a triplet.[26] There is increasing interest in possible biological roles of the nitroxyl anion in both singlet and triplet forms as well as of the conjugate acid HNO.[28] Although the standard reduction potential for eq 5 has been estimated at −0.33 V vs NHE,[26] more recent studies have concluded that the data used in that estimate was incomplete and that the reduction of NO is even less favorable. New estimates for the $E_{1/2}$ of eq 5 fall in the range from −0.5 to −0.8 V.[28j]

$$NO + e^- \rightarrow {}^3NO^- \quad (5)$$

B. Techniques and Pitfalls in Working with NO

NO is generally produced by reduction of nitrite salts, followed by further purification. The main impurities present in commercial sources of NO are NO_2, N_2O, and N_2. At 78 K, solid NO (as crystalline N_2O_2) exerts a vapor pressure of ∼100 mTorr, so N_2 may be removed from solid NO by evacuation. Removal of NO_2 and associated species can be effected by passage of the NO stream through high surface area KOH.[29] NO_2 and N_2O can also be removed by low-temperature vacuum-line techniques. For example, pure NO can be transferred by distilling from the impure mixture at <100 K from a simple cold trap to a colder trap.[30] Alternatively, the less volatile impurities are removed by an absorptive material like silica gel chromatographically or by repeated distillation of NO from silica containing traps at less than 200 K.[23,31] Rigorously clean NO can be obtained by such vacuum-line techniques using glass and stainless steel tubing and connections with minimal exposure to septa, etc. Such septa should be deaerated (by storage under an inert atmosphere or under vacuum) prior to use.

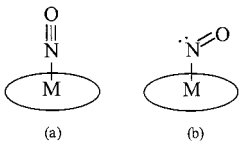


Figure 1. Illustration of limiting cases of NO binding to a metalloporphyrin center as (a) the nitrosyl cation (NO^+) with a M−N−O bond angle of ∼180° or (b) the nitroxyl anion (NO^-) with a M−N−O bond angle of ∼120°.

Because the facile reaction of O_2 with NO gives NO_2, N_2O_3, and N_2O_4 in aprotic media and NO_2^- in water, a major challenge of working with solutions of NO is maintenance of purity levels throughout the experiment. Higher oxides of nitrogen are not only more reactive toward many transition metals than is NO (vide infra), they are also much more soluble in organic solvents than NO[32] and form nitrous and nitric acids in aqueous solutions. Minute NO_x impurities concentrate in the solution phase, so when NO solutions are prepared by equilibration with gaseous NO, the impact of even trace impurities in the gas stream is magnified. Maximizing reagent concentrations and minimizing headspace help to alleviate effects due to NO_x impurities. Such impurities are undoubtedly responsible for some reactivity properties that have been attributed to NO itself.

Alternative sources for generating NO in solution are diazeniumdiolate salts such as $Na[Et_2N(O)NO]$, the synthesis and use of which have been pioneered by Keefer and co-workers.[33] A wide variety of these derivatives have been prepared from dialkylamines and NO. There is considerable pharmacological interest in the applications of these compounds (also called "NONOates") as controlled NO sources.[34] The rate of NO release depends on the nature of the alkyl functionalities as well as the solution conditions, so it is possible to use these to generate NO in known, low, steady-state concentrations.[33]

C. Structures and Spectra of Metal Nitrosyls

A dominant theme when considering the chemistry of NO is that it is a stable free radical with an electronic structure analogous to the dioxygen cation O_2^+. NO reacts rapidly with other free radicals and with substitution labile redox active metals, but it is not a strong one-electron oxidant or a strong one-electron reductant. In a complex with a metal center, the character of the NO ligand can range from that of a nitrosyl cation (NO^+), which binds to the metal with a M−NO angle of ∼180°, to that of a nitroxyl anion (NO^-), for which a bond angle of ∼120° might be anticipated (Figure 1). In the former case, considerable charge transfer to the metal has occurred, while in the latter, charge transfer is in the opposite direction. A generalized description of the metal−NO interaction was offered some years ago by Feltham and Enemark,[35] who proposed the $\{MNO\}^n$ formulation, where n is the sum of the metal d-electrons and the nitrosyl π^* electrons. Walsh-type diagrams were

Table 1. Fe−NO Bond Distances and Fe−N−O Angles of Nitrosyl Iron Porphyrins Determined by X-ray Crystallography[a]

complex	Fe−NO, Å	Fe−N−O angle (°)	ν_{NO} (cm^{-1})	ref
Fe^{II}(OEP)(NO)	1.726	143.6	1666	40b
Fe^{II}(TPP)(NO)	1.717	149.2	1670	41a
Fe^{II}(TPP)(NO)(4MePip)	1.740	143.7	1653	41b
$Fe^{II}(T_{piv}PP)(NO)$	1.716	143	1665	42
$[Fe^{II}(T_{piv}PP)(ONO)(NO)]^-$	1.802	138.3	1616	44b
Hb(NO)	1.74	145		43
$Fe^{II}(TPP)(NO_2)(NO)$	1.743	142.1	1625	44a
$[Fe^{III}(TPP)(H_2O)(NO)]^+$	1.652	174	1848	40a
$[Fe^{III}(OEP)(NO)]^+$	1.644	176.9	1862	40a

[a] Abbreviations are listed in section VII.

used to predict the bond angles of this unit. When the other ligands on the metal include a strong C_{4v} perturbation, as is the case with metalloporphyrins, the M−N−O angle is predicted to be linear for $n \leq 6$ but bent for $n > 6$. Notably, there are several reported examples of metastable complexes generated photochemically in low-temperature solids which have and η^1-NO coordinated at the oxygen and others with an η^2-NO coordinated with the NO bond perpendicular to the metal ligand axis.[36,37] In some polynuclear complexes, NO has been noted to bridge two metal ions via the nitrogen.[31b]

Numerous metal centers react with NO to give adducts. The ability to form a stable NO complex and the structure of that species depend strongly on the oxidation state of the metal center, although assigning oxidation state to the resulting M−NO species is subject to considerable ambiguity. In this context, one might compare the structures of NO adducts to the tetraphenylporphyrin complexes Mn^{II}(TPP), Fe^{II}(TPP), and Co^{II}(TPP), which display the respective M−N−O bond angles of 176.2°, 142.1°, and 128.5°.[38−40] The first is consistent with the nitrosyl cation formulation $Mn^{II}(TPP)(NO^+)$, the latter with that of the nitroxyl complex $Co^{III}(TPP)(NO^-)$, while the adduct with Fe^{II}(TPP) is intermediate in character. Recent structural studies show that tilting of the $Fe-N_{nitrosyl}$ bond a few degrees from perpendicular to the porphyrin plane is also common for ferrous heme nitrosyls.[40b] The metal−N_{NO} bond lengths follow the order $\{Mn^{II}-NO\}^6$ (1.644 Å) < $\{Fe^{II}-NO\}^7$ (1.717 Å) < $\{Co^{II}-NO\}^8$ (1.833 Å), indicative of decreasing π-bonding over this sequence. Notably, simple oxidation of Fe^{II}(TPP)(NO) gives the $\{FeNO\}^6$ system, which is predicted and found to be linear.

Table 1 summarizes structural data for NO adducts of some Fe(II) and Fe(III) porphyrin complexes that have received attention as models of natural heme proteins.[41−44] In these cases, the IR spectra reflect the nature of the binding between NO and the central metal. Higher NO stretching frequencies are seen for the linear complexes such as Fe(TPP)(Cl)(NO). For example, oxidation of Fe(TPP)(NO) to $Fe(TPP)(NO)^+$ in CH_2Cl_2 solution shifts ν_{NO} from 1678 to 1848 cm^{-1}.

However, $\{FeNO\}^6$ complexes are not always linear as shown in a recent study by Richter-Addo, Scheidt et al.,[45] who reported single-crystal X-ray structure observations for the six-coordinate trans σ-bonded aryl complexes Fe(OEP)(p-C_6H_4F)(NO) and Ru(OEP)(p-C_6H_4F)(NO). These revealed unprecedented bending and tilting of the MNO group. In Fe(OEP)(p-C_6H_4F)(NO), the Fe−N−O angle is 157.4(2)° and the nitrosyl N atom is tilted off the normal to the heme plane by 9.2°. In Ru(OEP)(p-C_6H_4F)(NO), the Ru−N−O angle is 154.9(3)° and the tilt is 10.8°. These structural features are apparently imposed by the strongly σ-donating aryl ligand trans to the nitrosyl given that the ν_{NO} frequencies for the solids were significantly reduced (1791 cm^{-1} for the Fe complex and 1773 cm^{-1} for the Ru complex) compared to other $\{MNO\}^6$ counterparts.

Even within a series of linear nitrosyls, the formal redox state of NO, as indicated by values of ν_{NO}, may vary.[46] This was illustrated by Manoharan and Gray with a series of metal pentacyanonitrosyl complexes $M(CN)_5(NO)^{n-}$ (M = Fe, Mn, Cr, V; n = 2, 3, 3, 3, respectively).[46b] For $Fe(CN)_5(NO)^{2-}$, the bonding picture is best described as $Fe^{II}-N\equiv O^+$ (ν_{NO} = 1925 cm^{-1}). The apparent bond order is M−N=O for M = Mn(III) or Cr(III) and is further shifted to M=N−O for V(III) (ν_{NO} = 1530 cm^{-1}) as one moves to the left on the periodic table.

There are other structural features introduced by the Walsh-type diagrams for the $\{MNO\}^n$ model described by Enemark and Feltham.[35,47] For a six-coordinate complex, not only does this model predict that going from n = 6 to n = 7 to n = 8 leads to increasing bending of the M−N−O angle, it also predicts the weakening of the metal−ligand bond trans to the nitrosyl. This is demonstrated by the structural studies of the porphyrin complex M(TPP)(L)(NO) (L = 4-methylpiperidine).[40c] For M = Mn^{II} (n = 6), not only is the Mn−NO angle nearly linear (176°), but the Mn−N_{pip} bond length is relatively short (2.20 Å). For M = Fe^{II} (n = 7), the Fe−NO angle is bent to 142° and the bond to the methylpiperidine nitrogen is considerably weakened (Fe−N_{pip} = 2.46 Å). For M = Co^{II} (n = 8), the Co−NO angle is even sharper (128°) and a stable complex with methylpiperidine could not be isolated.

It was on the basis of this trans labilizing effect for the n = 7 case that Traylor and Sharma[5a] proposed the mechanism of sGC activation by NO coordination at the Fe^{II}(PPIX) ("hemin") site of that enzyme. A fascinating test of this was offered by Burstyn and co-workers, who investigated the activity of non-native sGC prepared by substituting Mn^{II}(PPIX) and Co^{II}(PPIX) for the hemin of the native enzyme.[48] Addition of NO failed to activate the sGC(Mn) above basal activity, presumably because the proximal histidine was not labilized. In con-

trast, NO activation of sGC(Co) gave even greater activity than that reconstituted with hemin, consistent of the trans effect on the metal center lability having a major role in the NO activation of sGC.

One feature of terminally bound transition-metal nitrosyls that has received limited attention[48,49] is the invariance of the IR intensity per nitrosyl ligand (measured as the product of the extinction coefficient times the full width at half-maximum) over a wide range of redox states. In our experience, terminal metal nitrosyl complexes containing a single NO exhibit comparable IR intensity for ν_{NO} (within ~15%), while newly characterized centrosymmetric *trans*-dinitrosyls exhibit twice the intensity of the mononitrosyls.[16] If this behavior proves general, it could prove useful when following reactions of metal nitrosyls in solution and aid in transient product distribution analysis.

ESR spectra provide insight into the electronic structure of paramagnetic nitrosylmetalloporphyrins. For example, the manganese(III) complex Mn(TPP)(CN) ($S = 2$) reacts with NO to give Mn(TPP)(CN)(NO), for which the ESR spectrum indicates an $S = 1/2$ spin state.[50] Similarly, the NO adduct of Cr^{II}(TPP) ($S = 2$) exhibits an ESR spectrum consistent with an $S = 1/2$ spin state, while reaction of NO with Mn^{II}(TPP) ($S = 5/2$) gives an adduct with $S = 0$.[51,52] Thus, NO coordination usually gives strong field, low-spin complexes with such metal centers. However, one-electron reduction of Mn^{II}(TPP)(NO) (by γ-radiolysis in 2-methyltetrahydrofuran solution) gives $[Mn^{II}(TPP)(NO)]^-$, which exhibits the ESR spectrum of an $S = 3/2$ state at 77 K.[53] The ESR spectra of nitrosyl Fe(II) porphyrins clearly show super hyperfine splitting due to the nitrogen atom of the axial NO, indicating that the unpaired electron density is concentrated at the d_{z^2} orbital of the central iron atom.[54−59] The spectra display three unique *g* values consistent with the nonaxial symmetry and the bent form of the Fe−N═O moiety, in accordance with the X-ray structure (Table 1). For nitrosyl adducts of ferro-heme proteins having a histidine residue in the axial site, ESR spectra display the N hyperfine splitting of both NO and the imidazole moiety of histidine.[57]

^{15}N NMR and Mössbauer (for Fe complexes) spectroscopy have also been used to characterize the electronic structure of metal nitrosyls, and these techniques have been reviewed elsewhere.[14] The electronic absorption spectra of the extensively studied nitrosylmetalloporphyrins are dominated by the $\pi-\pi^*$ ligand bands which constitute the spectra of other metalloporphyrins as well as the free base ligand. These are but modestly perturbed by NO coordination. The spectra and a recent density functional theory treatment of the electronic structure of a series of *trans*-$Ru(NH_3)_4(L)(NO)^{n+}$ complexes (L = NH_3, H_2O, pyrazine, and pyridine ($n = 3$) and Cl^- and OH^- ($n = 2$)) have been reported.[60] For these complexes, the lowest energy absorptions are relatively weak bands assigned as $d_\pi(Ru) \rightarrow \pi^*(NO)$ transitions.[60a] These compounds are of interest as possible thermal or photochemical agents for NO delivery to biological targets.[60d]

III. Formation and Reactions of Coordinated Nitrosyls

A. Substitution Reactions Involving NO

In considering the formation of a metal nitrosyl complex (e.g., eq 6), one might pose a simple question: Does the free radical nature of NO lead to different mechanisms for ligand substitution reactions than those seen for other small ligands such as CO? As will be seen below, the answer is ambiguous. In many cases, the reactivity pattern for NO appears similar to that seen for other small Lewis bases. This might be rationalized on the basis that since the odd electron of NO resides in the π^* orbital, it does not become involved until the metal ligand bond is largely formed. However, back reactions of geminate pairs $\{L_nM, AB\}$ formed by flash photolysis of a L_nM-AB complex (or M−AB formation from an analogous encounter pair formed by the diffusion of L_nM and AB together) show significant reactivity differences between NO and CO. Furthermore, in the example described immediately below, kinetics data suggest that the radical nature of NO leads to an associative substitution pathway with a paramagnetic metal ion.

$$ML_nX + NO \rightleftharpoons ML_n(NO) + X \qquad (6)$$

1. Ruthenium(III) Ammine Complexes

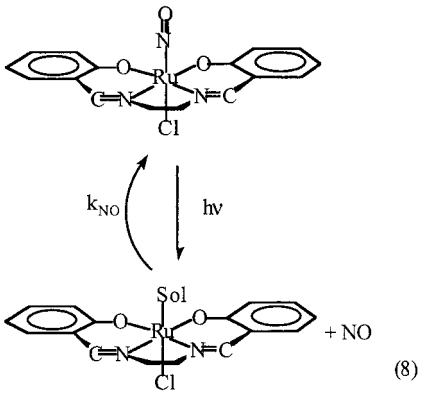
There are few systematic studies of the reaction mechanism(s) of metal−NO bond formation. Early studies by Armor and Taube[61] examined the kinetics of the nitrosylation of the ruthenium(III) complex $Ru(NH_3)_6^{3+}$ in aqueous solution (eq 7). Armor, Scheidegger, and Taube[61a] found the rate for this reaction ($k_{NO} = 0.2$ at 298 K) to be much faster than the replacement of NH_3 by other ligands. They concluded that the reaction very likely proceeds by an associative mechanism, where the unpaired electron of the d^5 Ru(III) center engages the odd electron of the NO to give a seven-coordinate intermediate $Ru(NH_3)_6(NO)^{3+}$. The associative mechanism gained further strong support from subsequent activation parameter studies by Pell and Armor,[61b] who found a small $\Delta H^‡$ (36 kJ mol^{-1}) but a large and negative $\Delta S^‡$ (−138 J K^{-1} mol^{-1}) for the reaction described by eq 7 in acidic solution.

$$Ru(NH_3)_6^{3+} + NO + H^+ \rightarrow Ru(NH_3)_5(NO)^{3+} + NH_4^+ \qquad (7)$$

Interestingly, Pell and Armor[61b] found entirely different products in alkaline solution. Above pH 8.3, the sole ruthenium product of the reaction of $Ru(NH_3)_6^{3+}$ with NO was the dinitrogen complex $Ru(NH_3)_5(N_2)^{2+}$. Under these conditions the rate law proved to be first order in $[Ru(NH_3)_6^{3+}]$, [NO], and $[OH^-]$. A likely mechanism is the equilibrium of $Ru(NH_3)_6^{3+}$ with OH^- to give the intermediate $Ru(NH_3)_5(NH_2)^{2+}$, followed by NO attack at the amide ligand. However, the kinetics evidence did not exclude other sequences.

2. Ruthenium(III) Salen Complexes

The photochemistry of several Ru(III) salen complexes of the type Ru(salen)(X)(NO) (X = Cl^-, ONO^-, H_2O; salen = N, *N′*-bis(salicylidene)ethylenediamine dianion) have been examined as possible photochemical NO precursors.[62] Photoexcitation leads to NO labilization to form the respective solvento species Ru(salen)(X)(Sol), and the kinetics of the subsequent back reactions to reform the nitrosyl complexes (e.g., eq 8) were studied as a function of the nature of the solvent (Sol) and the reaction conditions. The rates are dramatically dependent on the identity of Sol with values of the second-order rate constant k_{NO} (298 K, X = Cl^-) varying from 5×10^{-4} M^{-1} s^{-1} in acetonitrile to 4×10^{7} M^{-1} s^{-1} in the much weaker donor solvent toluene. In this case, Ru−Sol bond breaking clearly plays an important role in the rate-limiting step for NO substitution of Sol.



(8)

Sol = solvent

3. Metalloporphyrins

The kinetics of ligand substitution reactions leading to metal−nitrosyl bond formation were first studied for metalloporphyrins some time ago,[63] and this topic has been the subject of a recent review.[63d] However, even for metalloporphyrins, systematic mechanistic studies have been limited. The biological relevance of the "on" and "off" reactions (eq 9) is emphasized by noting that activation of soluble guanylyl cyclase involves such an "on" reaction where the acceptor site of sGC is an Fe^{II}(PPIX) moiety.[6] Other nitric oxide roles such as inhibition of cytochrome oxidase or catalase also apparently involve coordination at a heme iron, so delineation of the dynamics and mechanisms of the "on" reaction is essential to understanding the biochemistry of NO. Other biological processes such as sGC deactivation must involve labilization of M−NO bonds, so the "off" reaction mechanism is equally important.

$$\mathrm{M(Por)} + \mathrm{NO} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \mathrm{M(Por)(NO)} \qquad (9)$$

NO photodissociation from nitrosylmetalloporphyrins is commonly reversible, so pulsed laser techniques are well suited for investigating the kinetics of the nitrosylation reaction. In such studies, flash photolysis is used to labilize NO from the M(Por)(NO) precursor, and subsequent relaxation of the non-steady-state system back to equilibrium (eq 9) is monitored spectroscopically. Under excess NO, the transient spectra would decay exponentially to give the rate constant k_{obs}, and the following relationship should hold true.

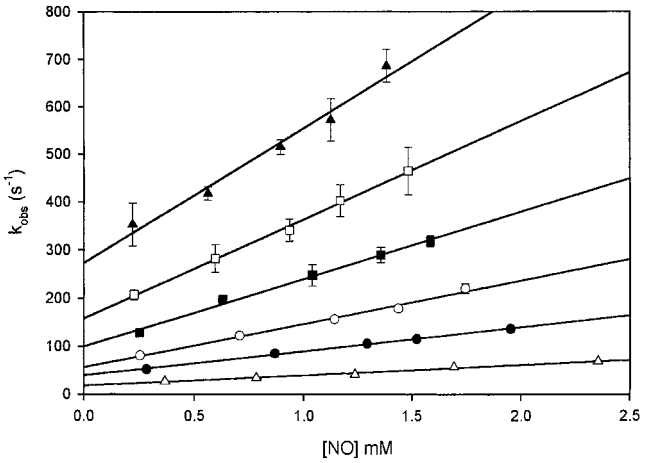


Figure 2. Plot of k_{obs} vs [NO] for the reaction of metMb with NO as measured by laser flash photolysis at different temperatures in pH 7.0 phosphate buffer solution (50 mM): 15 °C (△), 25 °C (●), 30 °C (○), 35 °C (■), 40 °C (□), and 45 °C (▲). (Reprinted with permission from ref 64c. Copyright 2001 American Chemical Society.)

$$k_{obs} = k_{on}[\mathrm{NO}] + k_{off} \qquad (10)$$

Accordingly, a plot of k_{obs} vs [NO] would be linear with a slope k_{on} and an intercept k_{off} as illustrated in Figure 2 for the postphotolabilization relaxation kinetics of the ferri-heme protein met-myoglobin (metMb) under excess NO.[64−66] In this case, spontaneous ligand dissociation (k_{off}) is sufficiently fast to determine an accurate value of the intercept; thus, the slope/intercept ratio (k_{on}/k_{off}) gives a reasonable value for the equilibrium constant (K) of nitrosyl complex formation. However, for many systems, especially those of ferro-heme complexes or proteins, the "off" reaction is too slow to give acceptably accurate intercepts, and it is difficult to determine either k_{off} or K from these plots. In certain cases, rates of NO loss have been determined following the thermal disappearance of the nitrosyl complex in the presence of an efficient trapping agent for the labilized NO, an example being the Ru(III) complex $Ru(EDTA)^-$.[66]

4. Kinetics of NO Reactions with Several Heme Proteins

Such time-resolved spectroscopic techniques have been used to investigate the kinetics of numerous nitrosylmetalloproteins and models under ambient conditions. Examples of these results are summarized in Table 2.[65−71] For example, equilibrium constants have been determined[65] for the formation of nitrosyl complexes of met-myoglobin (metMb), ferri-cytochrome-*c* (Cyt^{III}), and catalase (Cat) both by the kinetic flash photolysis technique ($K = k_{on}/k_{off}$) and by spectroscopic titration in aqueous media and are in reasonable agreement (Table 2). Table 2 summarizes the dramatic range of k_{on} and k_{off} values obtained for several ferri-heme and ferro-hemes

Table 2. Rate Constants k_{on} and k_{off} for Nitrosylations of Representative Ferro- and Ferri-Heme Proteins

	conditions[a]	k_{on} M^{-1} s^{-1}	k_{off} s^{-1}	ref
	Ferric proteins[a]			
metMb[b]	H_2O, pH 6.5	1.9×10^5	13.6	65
metMb[c]	50 mM phosphate, pH 7.0, 298 K	4.8×10^4	43	66
Cyt^{III}	H_2O, pH 6.5, 293 K	7.2×10^2	4.4×10^{-2}	65
Cat	H_2O, pH 6.5, 293 K	3.0×10^7	1.7×10^2	65
eNOS	283 K, 1 mM arginine	8.2×10^5	70	67
nNOS	pH 7.8, 293 K, heme domain	2.1×10^7	40	67
NP[b]	298 K	$1.5-2.2 \times 10^6$	0.006−2.2	68
	Ferrous proteins[a]			
Hb_4^T [d]	pH 7.0, 293 K	2.6×10^7	3.0×10^{-3}	69
Hb_4^R [e]	pH 7.0, 293 K	2.6×10^7	1.5×10^{-4}	69
sGC	pH 7.4, 293 K	1.4×10^8	$6-8 \times 10^{-4}$	70
sGC	pH 7.4, 293 K, 3 mM Mg^{2+}, 0.5 mM GTP	−	5.0×10^{-2}	70
Mb	phosphate buffer pH 7.0, 293 K	1.7×10^7	1.2×10^{-4}	69
Cyt^{II}	H_2O, pH 6.5	8.3	2.9×10^{-5}	65
eNOS	283 K, 1 mM arginine	1.1×10^6	70	67
nNOS	pH 7.8, 293 K, heme domain	1.1×10^7	∼0	67

[a] Abbreviations listed in section VII. [b] Sperm whale skeletal metMb. [c] Horse heart metMb. [d] Rate constants are the range for NP1, NP2, NP3, and NP4, pH 5.0 and pH 8.0; the k_{off} displays two phases. [e] Two phases are observed for NO binding.

proteins. For the latter, k_{off} values were too small to determine by the flash photolysis method and were measured by other means. The small values of k_{off} lead to very large association constants K for the ferrous species with the exception of Cyt^{II}, which also displays a very small k_{on} value. For example, NO binds deoxyhemoglobin with an equilibrium constant 3 orders of magnitude larger than that for CO.

The low reactivity of both Cyt^{III} and Cyt^{II} toward NO can be attributed to the occupation of the axial sites on the ferric ion center by an imidazole nitrogen and a methionine sulfur of the protein.[71] Thus, formation of the nitrosyl complex not only involves ligand displacement but also protein conformational changes. Catalase and nNOS are more reactive than the model complex $Fe^{III}(TPPS)(H_2O)_2$ (Table 3), indicating that the protein accelerates the nitrosyl formation. Conversely, the k_{off} values for metMb, Cyt^{III}, and Cat are all smaller than that for Fe^{III}-(TPPS), suggesting retardation of NO dissociation by these proteins.

The small k_{off} values for the ferro-heme proteins is of biological interest with regard to the question of how an enzyme such as soluble guanylyl cyclase, once activated by forming an NO complex, undergoes deactivation. Kharitonov et al.[70b] used stopped-flow kinetics techniques to determine the first-order loss of NO from sGC−NO and measured a rate constant of $\sim 7 \times 10^{-4}$ s^{-1} in 293 K, pH 7.4 buffered solution. This rate is comparable to those for various ferro-heme proteins listed in Table 2 but is much slower than needed for reversible deactivation of the enzyme. In the presence of excess substrate guanylyl triphosphate (GTP, 5 mM) and the Mg^{2+} cofactor (3 mM), the rate was about 70-fold faster ($k_{off} \sim 5 \times 10^{-2}$ s^{-1} at 293 K), but the rate acceleration with GTP alone was only ∼10-fold. A recent in vivo study[72] suggests that the actual rate of sGC deactivation is several orders of magnitude higher (3.7 s^{-1} at 310 K). Such differences illustrate potential complexities in comparing in vitro kinetics of purified proteins to analogous reactions in vivo.

Bohle and co-workers[73] demonstrated that varying the electronic and stereochemical properties of porphyrin substituents can strongly influence the rates of NO labilization (eq 11). For example, the displacement of NO from Fe(TPP)(NO) by pyridine is many orders of magnitude slower than that from Fe-(OBTPP)(NO) (OBTPP = octabromotetraphenylporphyrin). The kinetics of the latter reaction showed saturation behavior in [L], and the mechanism was suggested to involve reversible formation of Fe-(OBTPP)(L)(NO) followed by NO dissociation. The key point is that changes in porphyrin properties can lead to enhanced reactivity toward NO loss.

$$Fe(Por)(NO) + 2L \rightleftharpoons Fe(Por)L_2 + NO \quad (11)$$

5. Mechanism Studies with Ferric Porphyrin Models

Laverman and co-workers reported activation parameters for the aqueous solution reactions of NO with the iron(II) and iron(III) complexes of the water-soluble porphyrins TPPS and TMPS:[64] This involved systematic measurements of k_{on} and k_{off} as functions of the temperature (298−318 K) and hydrostatic pressure (0.1−250 MPa) to determine values of $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta V^{\ddagger}$ for the "on" and "off" reactions of the ferri-heme models and for the "on" reactions of the ferro-heme model (Table 3). Figure 3 illustrates hydrostatic pressure effects on k_{on} and k_{off} for Fe^{III}-(TPPS).

For the ferri-heme complexes, the large and positive $\Delta S^{\ddagger}$ and, more emphatically, the large and positive $\Delta V^{\ddagger}$ values for k_{on} and k_{off} represent signatures for a substitution mechanism dominated by ligand dissociation, i.e.

$$Fe^{III}(Por)(H_2O)_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Fe^{III}(Por)(H_2O) + H_2O \quad (12)$$

$$Fe^{III}(Por)(H_2O) + NO \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Fe^{III}(Por)(H_2O)NO \quad (13)$$

Consistent with this mechanism is the report by Hunt et al.[74] that H_2O exchange between solvent and $Fe^{III}(TPPS)(H_2O)_2$ occurs at a first-order rate ($k_{exchange} = 1.4 \times 10^7$ s^{-1} in 298 K water) far exceeding the k_{obs} values determined at any [NO]. If the steady-

Table 3. Rate Constants (298 K) for the "On" and "Off" Reactions of NO and CO with Certain Water-Soluble Ferri- and Ferro-Heme Complexes in Aqueous Solution[64c]

"on" reactions[a]	k_{on} M^{-1} s^{-1}	$\Delta H^{\ddagger}$ kJ mol^{-1}	$\Delta S^{\ddagger}$ J mol^{-1} K^{-1}	$\Delta V^{\ddagger}$ cm^3 mol^{-1}
Fe^{III}(TPPS) + NO	4.5×10^5	69 ± 3	95 ± 10	9 ± 1
Fe^{III}(TMPS) + NO	2.8×10^6	57 ± 3	69 ± 11	13 ± 1
Fe^{II}(TPPS) + NO	1.5×10^9	24 ± 3	12 ± 10	5 ± 1
Fe^{II}(TMPS) + NO	1.0×10^9	26 ± 6	16 ± 21	2 ± 2
Fe^{II}(TPPS) + CO	3.6×10^7	11 ± 6	−64 ± 2	−6.6 ± 0.6
Fe^{II}(TMPS) + CO	6.0×10^7	31 ± 4	6 ± 13	−4.0 ±0.7
Co^{II}(TPPS) + NO	1.9×10^9	28 ± 2	26 ± 7	*b*
"off" reactions[a]	**k_{off} s^{-1}**	**$\Delta H^{\ddagger}$ kJ mol^{-1}**	**$\Delta S^{\ddagger}$ J mol^{-1} K^{-1}**	**$\Delta V^{\ddagger}$ cm^3 mol^{-1}**
Fe^{III}(TPPS)(NO)	0.5×10^3	76 ± 6	60 ± 11	18 ± 2
Fe^{III}(TMPS)(NO)	0.9×10^3	84 ± 3	94 ± 10	17 ± 3
Fe^{II}(TPPS)(NO)	6.4×10^{-4}			
Co^{II}(TPPS)(NO)	1.5×10^{-4}			

[a] Abbreviations given in section VII. [b] Not determined.

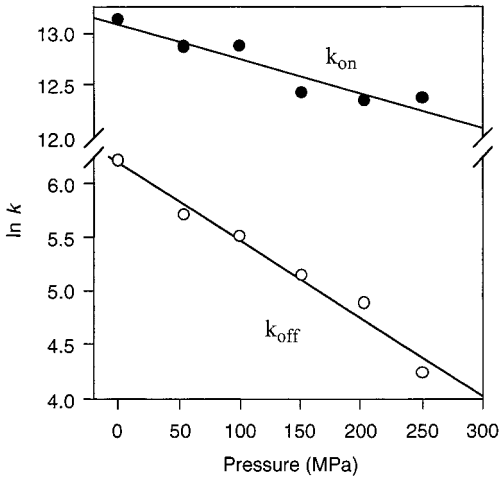


Figure 3. Plots of ln(k_{on}) (●) and ln(k_{off}) (○) vs hydrostatic pressure to determine activation volume values $\Delta V_{on}^{\ddagger}$ and $\Delta V_{off}^{\ddagger}$ for the reaction of NO with Fe^{III}(TPPS) in aqueous solution at 298 K. (Reprinted with permission from ref 64c. Copyright 2001 American Chemical Society.)

state approximation were taken with regard to intermediate Fe^{III}(Por)(H_2O), the k_{obs} for the exponential relaxation of the nonequilibrium mixture generated by the flash photolysis experiment would be

$$k_{obs} = \frac{k_1 k_2[NO] + k_{-1}k_{-2}[H_2O]}{k_{-1}[H_2O] + k_2[NO]} \qquad (14)$$

One may conclude that $k_{-1}[H_2O] \gg k_2[NO]$ since both steps involve trapping of an unsaturated metal center and $[H_2O] \gg [NO]$. Accordingly, $k_{on} = k_1k_2/k_{-1}[H_2O]$ and $k_{off} = k_{-2}$. In this context, the apparent activation parameters for k_{on} would be

$$\Delta S^{\ddagger}_{on} = \Delta S^{\ddagger}_1 + \Delta S^{\ddagger}_2 - \Delta S^{\ddagger}_{-1} \text{ and}$$
$$\Delta V^{\ddagger}_{on} = \Delta V^{\ddagger}_1 + \Delta V^{\ddagger}_2 - \Delta V^{\ddagger}_{-1} \qquad (15)$$

Since the k_2 and the k_{-1} steps represent similar (very fast) reactions of the unsaturated intermediate Fe^{III}(Por)(H_2O) with an incoming ligand (NO and H_2O, respectively), the differences in their activation parameters (e.g., $\Delta S^{\ddagger}_2 - \Delta S^{\ddagger}_{-1}$ and $\Delta V^{\ddagger}_2 - \Delta V^{\ddagger}_{-1}$) should be small. In such a case the dominant contributor to $\Delta S^{\ddagger}_{on}$ would be $\Delta S^{\ddagger}_1$, the activation entropy for the H_2O dissociative step. The k_1 step should thus display a positive $\Delta H_1^{\ddagger}$ consistent with the energy necessary to break the $Fe^{III}-OH_2$ bond, a large, positive $\Delta S_1^{\ddagger}$ owing to formation of two species, and a substantially positive $\Delta V_1^{\ddagger}$ for the same reason. These conditions are met for the k_{on} activation parameters for both complexes (Table 4). Furthermore, the values measured by Hunt et al. for $\Delta H^{\ddagger}_{ex}$ (57 kJ mol^{-1}) and $\Delta S^{\ddagger}_{ex}$ (+84 J K^{-1} mol^{-1}) for the H_2O exchange[74] on Fe^{III}(TPPS)(H_2O)$_2$ are very similar to the respective k_{on} activation parameters. A recent study by van Eldik et al.[75] using variable-temperature/pressure NMR techniques reported $\Delta H^{\ddagger}_{ex} = 67$ kJ mol^{-1}, $\Delta S^{\ddagger}_{ex} = 99$ J mol^{-1} K^{-1}, and $\Delta V^{\ddagger}_{ex} = 7.9$ cm^3 mol^{-1} for Fe^{III}(TPPS)(H_2O)$_2$. These values are in even better agreement with those for the k_{on} pathway with NO. Thus, the factors that determine the solvent-exchange kinetics for Fe^{III}(TPPS)(H_2O)$_2$ with solvent H_2O dominate the NO reaction with the same species, i.e., the k_{on} activation parameters are largely defined by a dissociative mechanism, the limiting step being eq 12.

Microscopic reversibility argues that the intermediate(s) in the "off" step will be the same as those generated during the k_{on} pathway with breaking the iron−nitrosyl bond (k_2) being the energetically dominant step. Coordination of NO to Fe^{III}(Por) is accompanied by considerable charge transfer to give linearly bonded diamagnetic {FeNO}^{6} complex that can be formally represented as Fe^{II}(Por)−(NO^+). Thus, the activation parameters of the "off" reaction reflect the intrinsic entropy and volume changes associated with the spin change and solvent reorganization as the charge localizes on the metal. The large positive $\Delta V^{\ddagger}_{ex}$ values for Fe^{III}(TPPS)(H_2O)(NO) are consistent with the limiting dissociative mechanism as outlined in eqs 12 and 13. The specific solvation of the NO coordinated to Fe(III) and the resulting solvent reorganization upon NO dissociation (Figure 4) has some analogy in the NO carrying nitrophorins. The crystal structure of one nitrophorin, NP4, shows that binding of NO to the Fe(III) center leads to a collapse of the protein around the coordinated NO. The distal heme-binding pocket in nitrophorin NP4 is quite open to solvent in the absence of NO. It was postulated that collapse of the protein around the heme nitrosyl led to increased retention of bound NO at low pH.[68]

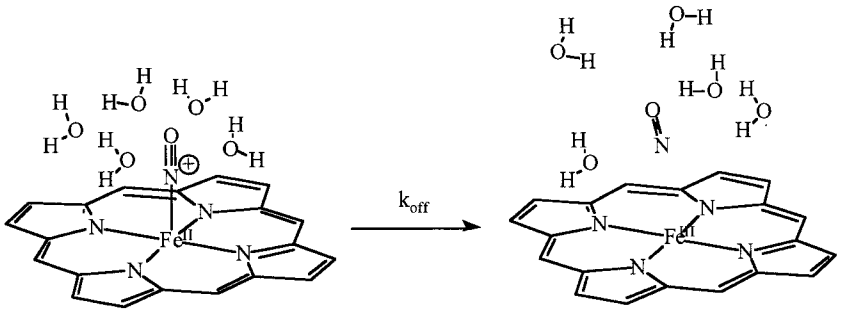


Figure 4. Schematic representation of the solvent reorganization that may occur upon the dissociation of nitric oxide from Fe^{III}(Por) in aqueous solution.

Table 4. Rate Constants (300 K) and Activation Parameters for Reactions of M(P) (P = TPP or OEP) with NO in Toluene Solution Determined from Second-Order Relaxation of Flash Photolysis Transients[a]

	Fe^{II}(TPP)	Co^{II}(TPP)	Mn^{II}(TPP)	Co^{II}(OEP)	Mn^{II}(OEP)
k_{on} (M^{-1} s^{-1})	5.2×10^9	2.5×10^9	$3.3 \times 10^{7\,a}$	2.3×10^9	3.0×10^7
$\Delta H^{\ddagger}$(kJ/mol)	2.6	1.2	9.3	3.4	5.9
$\Delta S^{\ddagger}$(J/mol K)	−51	−61	−72	−55	−82

[a] Reprinted with permission from ref 77. Copyright 1989 American Chemical Society. [b] A value of k_{on} (5×10^8 $M^{-1}s^{-1}$) was recently measured for Mn^{II}(TPP) using competitive trapping to intercept a Mn^{II}(TPP) intermediate generated by photoreduction of Mn(TPP)ONO in toluene (ref 78). The origins of this difference remain to be resolved.

Studies in this laboratory in collaboration with van Eldik and Stochel determined activation parameters for the reaction of NO with metMb according to eq 16.[66] Values for $\Delta H^{\ddagger}_{on} = 63 \pm 2$ kJ mol^{-1}, $\Delta S^{\ddagger}_{on} = 55 \pm 8$ J mol^{-1} K^{-1}, and $\Delta V^{\ddagger}_{on} = 20 \pm 6$ cm^3 mol^{-1} as well as $\Delta H^{\ddagger}_{off} = 68 \pm 4$ kJ mol^{-1}, $\Delta S^{\ddagger}_{off} = 14 \pm 13$ J mol^{-1} K^{-1}, and $\Delta V^{\ddagger}_{off} = 18 \pm 3$ cm^3 mol^{-1} were determined, respectively. Comparison of these activation parameters with those determined for reactions of NO with the water soluble ferri-heme complexes $Fe^{III}(TPPS)(H_2O)_2$ and $Fe^{III}(TMPS)(H_2O)_2$ demonstrate that these compounds are reasonable models for the kinetics for the analogous reaction with metMb. For example, the k_{on} step would appear to be defined largely by the lability of metMb(H_2O), although it is clear that the diffusion through protein channels, the distal residues, and the proximal histidine binding to the Fe(III) center must all influence the NO binding kinetics.[66,76] These issues may indeed be reflected in the lower $\Delta S^{\ddagger}$ values for both the "on" and "off" reactions on metMb. In a related study, Cao et al. recently reported observing the five-coordinate intermediate generated by flash photolysis of metMb(NO) and trapping of that species by H_2O.[76b] They further showed that the k_{on} step is several orders of magnitude faster for the metMb mutant H64G than for native horse heart metMb. In H64G glycine is substituted for the distal histidine, and this result was interpreted in terms of His-64 hydrogen bonding stabilizing the coordinated H_2O in the native protein. One might expect such stabilization to be reflected in a higher $\Delta H^{\ddagger}_{on}$ value for the native protein, but activation parameters were not reported for the mutant protein.

Other ferri-heme proteins for which k_{on} and k_{off} values have been reported include two forms of nitric oxide synthase eNOS and nNOS as well as several forms of nitrophorin (Table 2).

$$\text{metMb}(H_2O) + NO \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \text{metMb}(NO) + H_2O \quad (16)$$

6. Reactions of Fe(II) Porphyrin Complexes

High-spin Fe^{II}(Por) complexes are considerably more labile than the Fe^{III}(Por) analogues not only for the model compounds but also for the heme proteins (Table 2). Since the ferro-heme center may be five-coordinate in such cases, formation of a metal−NO bond does not require initial displacement of another ligand; thus, it is not limited by the rate of ligand labilization. Hoshino et al.[77] reported rates for the nitrosylation of model compounds M(Por) (M = Fe(II), Co(II), and Mn(II), Por = TPP or OEP) in toluene solutions by flash photolysis of M(Por)(NO) in the absence of excess NO. The bimolecular rate constants k_{on} were directly obtained from the decay analysis of the transient at various temperatures to give $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Table 4).[77,78] The general pattern seen was that all the rates are fast, the activation enthalpies are small, and activation entropies are negative. This pattern would be consistent with bimolecular NO trapping of a M(Por) species that is at most weakly coordinated by the toluene solvent. The trapping rates follow the order Mn^{II}(Por) > Fe^{II}(Por) > Co^{II}(Por), and it was noted that since nitrosylation changes the spin state ($S = \Sigma m_s$ from 5/2, 2, and 1/2, respectively, to 0, 1/2, and 0), the slower rates were observed for those complexes showing the largest reorganization of spin multiplicity.

For the water-soluble ferrous complexes Fe^{II}(TPPS) and Fe^{II}(TMPS), the NO "on" rates are about 3 orders of magnitude larger than for the iron(III) analogues (Table 3). Correspondingly, the activation parameters demonstrate much lower values of $\Delta H^{\ddagger}_{on}$ and $\Delta S^{\ddagger}_{on}$. The magnitude of the latter is consistent with rates largely defined by diffusional factors, although the k_{on} values reported are nearly an order of magnitude less than diffusion limits in water.

Previous kinetics studies[63c,79] of ferro-heme proteins and model compounds have led to a suggested mechanism in which an encounter complex, {Fe^{II}(Por)||L},

is formed prior to ligand bond formation according to eq 17.

$$Fe^{II}(Por) + L \underset{k_{-D}}{\overset{k_D}{\rightleftharpoons}} \{Fe^{II}(Por)||L\} \xrightarrow{k_a} Fe^{II}(Por)L \quad (17)$$

In this equation, k_D is the rate constant for the diffusion-limited formation of the encounter complex, k_{-D} is the rate constant for diffusion apart, and k_a is that for the "activation" step, M−L bond formation. On the basis of the steady-state approximation for the encounter complex, the apparent rate constant for the "on" reaction is $k_{on} = k_D k_a/(k_{-D} + k_a)$ and the activation volume is defined as

$$\Delta V^{\ddagger}_{on} = V^{\ddagger}_{D} + V^{\ddagger}_{a} - RT\left(\frac{d \ln(k_a + k_{-D})}{dP}\right) \quad (18)$$

This scheme has two limiting cases, one in which the reaction is diffusion limited ($k_a \gg k_{-D}$) and the other in which the reaction is activation limited ($k_{-D} \gg k_a$). In the activation-limited process, eq 18, simplifies to

$$\Delta V^{\ddagger}_{on} = \Delta V^{\ddagger}_{D} + \Delta V^{\ddagger}_{a} - \Delta V^{\ddagger}_{-D} \quad (19)$$

where $\Delta V^{\ddagger}_{D} - \Delta V^{\ddagger}_{-D}$ is the volume difference between the encounter complex and the solvent-separated species. Although unknown, this is likely to be small for a small neutral ligand such as NO, since the encounter complex does not involve the formation or breaking of bonds and should have only modest impact on solvation. The dominant term would be $\Delta V^{\ddagger}_{a}$, which should give negative contributions owing to Fe^{II}−L bond formation and the concomitant change of the spin state from high- (quintet Fe^{II}(Por) plus doublet NO) to low-spin (doublet Fe^{II}(Por)(NO)).

If $k_a \gg k_{-D}$, the reaction would be diffusion-limited and eq 18 reduces to $\Delta V^{\ddagger}_{on} = \Delta V^{\ddagger}_{D}$. Activation volumes for diffusion in various solvents are positive owing to viscosity increases with increased pressure (+7.5, +9.5, and +0.8 cm^3 mol^{-1} in CH_3CN, EtOH, and H_2O, respectively).[82] For $Fe^{II}(TPPS)(H_2O)_2$ and $Fe^{II}(TMPS)(H_2O)_2$, the positive $\Delta V^{\ddagger}_{on}$ values are somewhat larger than would be expected for a diffusion-limited process in aqueous solution but are significantly smaller than those measured for the iron(III) analogues. Therefore, the pressure data are consistent with a process having a k_{on} value within an order of magnitude of the diffusion limit in water ($k_D \sim 10^{10}$ M^{-1} s^{-1} at 298 K).[80] If a similar analysis was made with respect to $\Delta S^{\ddagger}_{on}$, then $\Delta S^{\ddagger}_{on} = \Delta S^{\ddagger}_{D}$ in the diffusion-limited case. The activation entropy for diffusion in aqueous solution can be calculated as ~34 J mol^{-1} K^{-1}.[81] The measured $\Delta S^{\ddagger}_{on}$ values for $Fe^{II}(TPPS)(H_2O)_2$ and $Fe^{II}(TMPS)(H_2O)_2$ (12 ± 10 and 16 ± 21 J mol^{-1} K^{-1}, respectively) are consistent with a process limited by diffusion. Similar arguments can be made for the aqueous solution reaction of NO with $Co^{II}(TPPS)$.[64]

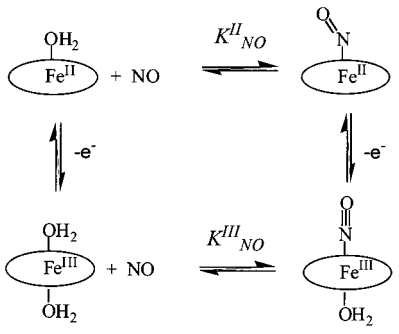
In order for NO to act as an intracellular signaling agent at submicromolar concentrations, it must be generated near the target and the reactions with ferro-hemes must be very fast to compete with other chemical and physiological processes leading to NO depletion. The above study is consistent with the intuitive notion that the fast reactions of ferro-heme proteins with NO are due to a vacant or exceedingly labile coordination site.

The model proposed in eq 17 and subsequent analysis for the reaction of NO with Fe^{II}(Por) applies to the analogous reactions with CO. The second-order rate constants for the reaction of $Fe^{II}(TPPS)(H_2O)_2$ with CO is several orders of magnitude below the diffusion limit, and as a consequence, this must be activation limited. In contrast to the reaction with NO, the $\Delta V^{\ddagger}_{on}$ values for CO are negative. These results parallel other studies of ferro-heme complexes that found reaction with NO to be diffusion limited while reaction with CO is activation limited. This model was confirmed by a study of the reaction of CO with Fe^{II}(MCPH) (MCPH = monochelated protoheme or protohemin 3-(1-imadazoyl) propylamide stearyl ester) in toluene/mineral oil solutions. By exploiting pressure effects it was possible to tune the reaction mechanism from an activation-limited process to a diffusion-limited process.[79] Hydrostatic pressure increases led to greater solvent viscosity, hence slower limiting diffusion rates, i.e., smaller values of k_D and k_{-D}.

The "off" reactions for the iron(II) model complexes such as $Fe^{II}(TPPS)(NO)$ were too slow to measure by the flash photolysis technique, since the experimental uncertainties in the extrapolated intercepts of k_{obs} vs [NO] plots were larger than the values of the intercepts themselves. When trapping methods were used in an attempt to evaluate loss of NO from $Fe^{II}(TPPS)(NO)$, k_{off} values were found to be quite small but were sensitive to the nature of the trapping agents used, since Lewis bases that could coordinate the metal center appeared to accelerate NO loss. More reliable estimates for the uncatalyzed "off" reaction were obtained by using $Ru(EDTA)^-$ as a NO scavenger, and the k_{off} values listed in Table 2 were obtained in this manner.[64c] The small k_{off} values found for the Fe(II) models are consistent with the behavior seen for the ferro-heme proteins discussed above.

Another method for estimating k_{off} is shown in Scheme 1. This involves using a Born−Haber-type cycle to calculate the equilibrium constant K^{II}_{NO} for formation of $Fe^{II}(TPPS)(NO)$ from the determined

Scheme 1



$$k^{II}_{off} = k^{II}_{on}(K^{III}_{NO}\, e^{nF\Delta E/RT})^{-1}$$

Table 5. Selected Reactions of Metal Nitrosyls with Nucleophiles

nucleophile	substrate	product	ref
OH^-	$Ru(hedta)(NO)^{3-}$	$Ru(hedta)(NO_2)^+$	84a,c
ROH, OR^-	$IrCl_3(PPh_3)_2(NO)^+$	$IrCl_3(PPh_3)_2(N(O)OR)$	84b
RSH, SR^-	$Fe(CN)_5(NO)^{2-}$	$Fe(CN)_5(OH_2)^{3-}$ + RSSR + NO	87
S_2^-	$Fe(CN)_5(NO)^{2-}$	$[Fe(CN)_5N(O)S]_2^{6-}$	86
NH_3	$Fe(CN)_5(NO)^{2-}$	$Fe(CN)_5(OH_2)^{3-} + N_2$	84c
RNH_2	$Fe(CN)(NO)^{2-}$	$Fe(CN)_5(H_2O)^{3-} + N_2$ + ROH	90
N_2H_4	$Fe(CN)(NO)^{2-}$	$Fe(CN)_5(H_2O)^{3-} + N_2O + NH_3 + H^+$	92
N_3^-	$[Ru(Cl)(das)_2NO]^{2-}$	$Ru(Cl)(das)_2N_3 + N_2 + N_2O$	84d

equilibrium constant K^{III}_{NO} for formation of the iron(III) analogue $Fe^{III}(TPPS)(NO)$ ($4.9 \pm 0.1 \times 10^3\ M^{-1}$)[64] and the measured reduction potentials for Fe^{III}(TPPS)(NO) (+0.35 V vs SCE) and Fe^{III}(TPPS) (−0.23 V vs SCE) in aqueous solution.[82] From the relationship $k^{II}_{off} = k^{II}_{on}/K^{II}$, the value $k^{II}_{off} = 2 \times 10^{-5}\ s^{-1}$ was estimated. This is about 3-fold smaller than the value measured by NO scavenging, but given the uncertainties in the electrochemical values used in the estimate, the agreement is quite reasonable.[64c]

B. Reactions of Coordinated NO

The versatility of nitric oxide as a ligand is illustrated in Figure 1, where the linear and bent coordination modes of metal−NO bonding are displayed. Linear coordination is often viewed in terms of charge transfer to the metal giving formally the nitrosyl (NO^+) ligand, which would be isoelectronic to carbon monoxide. Such charge transfer from the π^*_{NO} orbital to the metal is qualitatively consistent with the relatively high ν_{NO} stretching frequencies (~1,800−1,950 cm^{-1}) usually observed for these species and reflects the triple-bond character of the N−O bond. The bent MNO coordination implies less electronic charge transfer from NO to M, and consequently the ν_{NO} values are lower. Indeed, as the angle approaches 120°, the polarity of the charge transfer is reversed and the ligand is formally a nitroxyl anion (NO^-). In this context one can easily speculate that a NO coordinated linearly to a cationic metal center may be susceptible to nucleophilic attack, while the bent nitroxyl complexes would be more inclined to react with electrophiles such as H^+. This qualitative picture has indeed been realized for each limiting case. Such reactivity patterns of coordinated NO have been reviewed by McCleverty (1977)[14b] and Bottomley (1989),[14d] so the present article will largely focus on more recent examples.

1. Nucleophilic Reactions with the Coordinated Nitrosyls

This behavior is illustrated by the long known reversible reaction of hydroxide with the nitrosyl ligand of the nitroprusside ion (NP) (eq 20). The rate

$$Fe(CN)_5(NO)^{2-} + 2OH^- \rightarrow Fe(CN)_5(NO_2)^{4-} + H_2O \quad (20)$$

of this reaction is first order in $[OH^-]$ and in $[Fe(CN)_5(NO)^{2-}]$,[83] so the likely reactive intermediate is the adduct $Fe(CN)_5(N(O)OH)^{3-}$. The reaction is reversed in strongly acidic solution. Similar reactions are seen with the ruthenium and osmium analogues[83c,d] as well with numerous other simple coordination compounds of NO (Table 5).[84]

Olabe and co-workers[83c,d] systematically studied the mechanism of reaction 20 and the analogous transformations of $Ru(CN)_5(NO)^{2-}$ and $Os(CN)_5(NO)^{2-}$. The equilibrium constant K is quite dependent on the nature of the metal center with values of 1.5×10^5, 4.4×10^6, and 42 M^{-2} for the Fe^{II}, Ru^{II}, and Os^{II} species, respectively. The much lower K for the osmium complex correlates qualitatively with a relatively low ν_{NO} value for this species (1897 cm^{-1}), and Olabe points out that the correlation of K with the value of ν_{NO} holds well within a series of complexes containing the same metal center (e.g., Ru^{II}). The rationale for this correlation is that the ν_{NO} value reflects the triple-bond character of the coordinated NO, the higher frequencies being seen with the more electron-accepting metal centers. A similar correlation has been described for activation of coordinated CO by nucleophiles.[85]

The rate laws for the ruthenium and osmium analogues of eq 20 are also first order in $[OH^-]$, and the k_{OH} (298 K) values follow a pattern similar to that for the equilibrium constants with k_{OH}(Ru) being comparable to k_{OH}(Fe) (0.95 vs 0.55 $M^{-1}\ s^{-1}$, respectively) while k_{OH}(Os) is much smaller ($1.4 \times 10^{-4}\ M^{-1}\ s^{-1}$).[83d] The difference lies largely in the activation enthalpies; $\Delta H^‡$ is 23 kJ mol^{-1} smaller for the Ru complex than for the Os complex.

There have been numerous studies regarding reactions of various nucleophiles with nitroprusside. Reaction of HS^- with NP leads initially to a species interpreted to be the strongly colored thiol analogue of the nitro product, namely, $Fe(CN)_5(N(O)S)^{4-}$; however, this is not stable and undergoes oligimerization, possibly via the formation of bridging disulfide bonds.[86] The reaction of $Os(CN)_5(NO)^{2-}$ with SH^- leads to the loss of the NO^+ and formation of $Os(CN)_5(H_2O)^{3-}$, which can be trapped by the addition of pyrazine.[83d] Notably, the reactions of the $M(CN)_5(NO)^{2-}$ ions with the SH^- ion are much faster than the analogous reactions with OH^-; the rate constants k_{SH}(M) are several orders of magnitude larger than the k_{OH}(M) values for the same complexes.[83d]

The reactions of NP with mercaptans (RSH) and mercaptides (RS^-) appear to form metal nitrosothiolato intermediates with deep red or purple colors.[87] These intermediates are unstable and decay via formation of disulfides and reduced nitroprusside, which subsequently decomposes by both cyanide and NO loss. A similar processes may be responsible for the biological activity of sodium nitroprusside, which is used as an intravenously administered vasodilator

drug.[88] The reactivity of thiols with metal nitrosyls continues to be a fertile field for discovery, particularly in the context of the high concentration of reduced sulfur species in vivo.

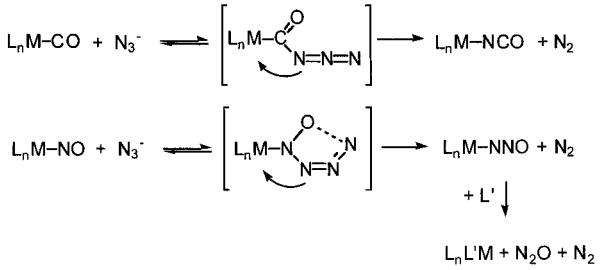
In pH 10.5 solutions with relatively high ammonia concentrations, NH_3 reacts with nitroprusside to give $Fe(CN)_5(H_2O)^{3-}$ plus N_2. This reaction is effectively the comproportionation of NH_3 and NO^+ to N_2.[89] Likewise, primary amines RNH_2 are diazotized by aqueous NP to give the alcohols plus N_2, with the maximum rate occurring about pH 10.5.[90] The rates of these reactions are first order in [NP] and [RNH_2] and increase with the basicity of the amines. The protonated amines are not reactive. At higher pH, nitroprusside reacts with OH to give $Fe(CN)_5(NO_2)^{4-}$.

The reaction of NP with hydrazine leads to formation of NH_3 and nitrous oxide (eq 21) with the rate law $-d[NP]/dt = k[NP][NH_2NH_2]$.[91] The hydrazinium ion $N_2H_5^+$ was inactive, so the rate dropped to near 0 at pH 6 in accord with the pK_a of this species.

$$Fe(CN)_5(NO)^{2-} + NH_2NH_2 \rightarrow Fe(CN)_5(H_2O)^{3-} + NH_3 + N_2O + H^+ \quad (21)$$

Reaction of metal nitrosyls with azide ion proceeds with formation of N_2 and N_2O.[92] This can be viewed as the result of a nitrene transfer reaction in analogy with the Curtius rearrangement[93] and its organometallic counterpart discovered by Hieber (Scheme 2).[94]

Scheme 2



Other recent studies of the reactions of metal nitrosyls $L_xM(NO)$ with various nucleophiles (Nuc) are summarized in Table 5.[84] In general, the pattern indicated by the studies described above are repeated. Simple adduct formation occurs when the coordinated nitrosyls are sufficiently electrophilic and the nucleophiles sufficiently basic. The first species formed is likely the N-coordinated nucleophile nitrosyl adduct $L_xM(N(O)Nuc)$. Subsequent reactions are dependent on the substitution lability of these species as well as the redox stability of the complex and of the ligand. For example, the substituted aniline Ar–NH_2 (Ar = *p*-$CH_3OC_6H_4$–) reacts with the ruthenium nitrosyl complex $Ru(bpy)_2Cl(NO)^{2+}$ (bpy = 2,2′-bipyridine) to give a complex of the diazo ligand, namely, $Ru(bpy)_2Cl(NNAr)^{2r}$.[95] Reaction of this amine with the ^{15}N-labeled nitrosyl complex $Ru(bpy)_2Cl(^{15}NO)^{2+}$ gave the ^{15}N-coordinated product $Ru(bpy)_2Cl(^{15}NNAr)^{2+}$, demonstrating that the reaction occurs within the metal complex coordination sphere. Furthermore, in nonprotic solvents, nucleophile–nitrosyl adducts were isolated.

2. Reductive Nitrosylation Reactions

Facile nucleophilic attack at a coordinated nitrosyl has also been invoked as a mechanism for the redox reactions involving NO. During 'reductive nitrosylation' NO serves as a one-electron reductant of a transition-metal center while being oxidized to nitrite or another N(III) species. Ferric porphyrins and other redox-active metal centers have long been known to undergo reductive nitrosylation in the presence of excess NO.[96–98] For example, the iron(III) porphyrin complex, $Fe^{III}TPP(Cl)$, reacts with NO in toluene containing a small amount of methanol to give Fe^{II}-TPP(NO), consistent with the reductive nitrosylation scheme shown in eqs 22–24.[96,97c] In the same context, when an aqueous ferri-hemoglobin, metHb, is exposed to NO, the product is the ferro-hemoglobin NO adduct, Hb(NO).[98]

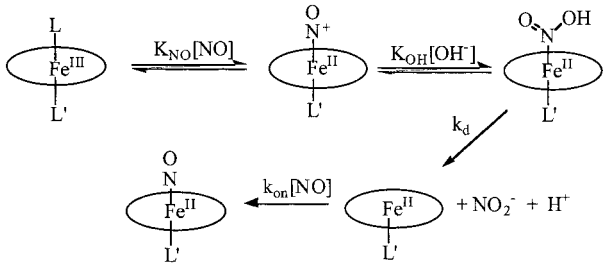
$$Fe^{III}(TPP)Cl + NO \rightleftarrows Fe^{III}(TPP)(Cl)(NO) \quad (22)$$

$$Fe^{III}(TPP)(Cl)(NO) + CH_3OH \rightarrow Fe^{II}(TPP) + CH_3ONO + HCl \quad (23)$$

$$Fe^{II}(TPP)\ NO \rightarrow Fe^{II}(TPP)(NO) \quad (24)$$

To gain better mechanistic insight into the reductive nitrosylation of ferri-heme proteins, kinetics studies were carried out on aqueous solutions of Cyt^{III}, metMb, and metHb at various pH.[99] For example, Cyt^{III} undergoes reduction by NO to Cyt^{II} in aqueous solutions at pH values >6.5. A hypothetical reaction mechanism is shown in Scheme 3.

Scheme 3[a]



[a] Porphyrin ligands are represented as the equatorial circles.

The rate law predicted by this scheme is presented in eq 25.[99]

$$\frac{d[Fe^{II}]}{dt} = k_d \times \frac{K_{NO}[NO]}{1 + K_{NO}[NO]} \times \frac{K_{OH}[OH^-]}{1 + K_{OH}[OH]} \times [Fe^{III}(Por)] \quad (25)$$

Since the reaction of NO with Cyt^{II} to form Cyt^{II}-(NO) is very slow (see section III.A), the formation of Cyt^{II} could be observed directly. The observed rates are functions of [NO] and [OH^-] as predicted by eq 25, namely, $k_{obs} = k_{OH} \times K_{NO}[NO][OH^-]/(1 + K_{NO}[NO])$ at low pH (where $k_{OH} = k_d \times K_{OH}$) and $k_{obs} = k_{OH}[OH^-]$ at high [NO]. Figure 5 illustrates the response of k_{obs} to [OH^-] for the NO reduction of Cyt^{III}, namely, a simple first-order dependence on [OH^-] at constant [NO]. No evidence for the N-bound nitrous acid complex $Fe^{II}(N(O)OH)$ was found for the

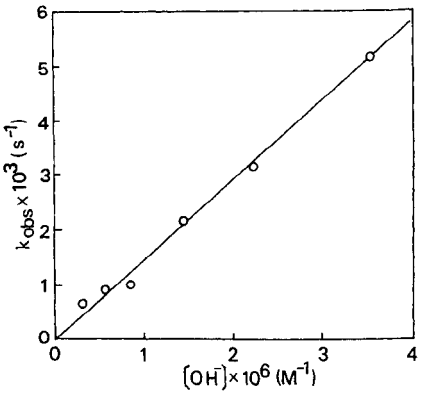


Figure 5. Rate constants for the formation of Cyt^{II} from Cyt^{III} in 298 K aqueous solution under a constant pressure of NO (100 Torr) as a function of [OH^-]. (Reprinted with permission from ref 99. Copyright 1996 American Chemical Society.)

Table 6. Reductive Nitrosylation of Ferrihemoproteins. Values of Constants Determined[a]

	Cyt^{III}	metMb	metHb[a]
K_1	1.4×10^4	$(1.3-0.62) \times 10^3$ [b]	$1.3 \times 10^4\ M^{-1}$
k_{OH}	1.5×10^3	3.2×10^2	$3.2 \times 10^3\ M^{-1}\ s^{-1}$
k_{NO}	8.3	1.7×10^7	$2.5 \times 10^7\ M^{-1}\ s^{-1}$
pH	6.1−8.45	6.0−7.2	5.6−7.4

[a] Reprinted with permission from ref 99. Copyright 1996 American Chemical Society. [b] MetHb(NO) reacts with H_2O in pH 6 water with a rate constant $k_{H_2O} = 1.1 \times 10^{-3}\ s^{-1}$. [c] K_1 for metMb is pH dependent dropping to half at higher pH.

three ferri-heme proteins studied. Thus, either the formation of this intermediate is rate limiting or K_{OH} is very small in each case. Values of K_{NO} were determined from the spectroscopic titration of the respective ferri-heme protein by NO, and kinetics studies gave the values for k_{OH} listed in Table 6.

The mechanisms for reductive nitrosylation of metMb and metHb are regarded to be similar to that for Cyt^{III}; however, since both Mb and Hb readily react with NO, the only observable products were Mb(NO) and Hb(NO). For metMb, K_{NO} values decreased at the higher pH's, suggesting that pH change may bring forth protein conformation changes. Reductive nitrosylation of metHb also occurs at lower pH values (<6), implying that metHb(NO) reacts with not only OH^- but also with H_2O (eq 26).[99] The pseudo-first-order rate constant, k_{H2O}, was determined to be $1.1 \times 10^{-3}\ s^{-1}$ in 298 K aqueous solution. Reductive nitrosylations of metMb and Cyt^{III} were not observed at low pH; therefore, direct reactions of metMb(NO) and $Cyt^{III}(NO)$ with H_2O appear to be much slower than for metHb.[99]

$$Hb^{III}(NO) + H_2O \xrightarrow{k_{H_2O}} Hb^{II} + ONO^- + 2H^+ \quad (26)$$

A recent investigation[100] demonstrated the NO reduction of metMb in pH 7.4 phosphate buffer solution in the presence of the biological antioxidant glutathione GSH. Spectral changes in the porphyrin Q-band region indicated the formation Mb(NO) as one product, while amperometric sensor experiments were interpreted in terms of the nitrosoglutathione (GSNO) being the other product. The second-order rate constant for reaction of GSH with metMb(NO) was determined to be 47 $M^{-1}\ s^{-1}$. This is a somewhat surprising result given that k_{OH} for the smaller and more basic hydroxide ion[99] is only an order of magnitude higher (Table 6).

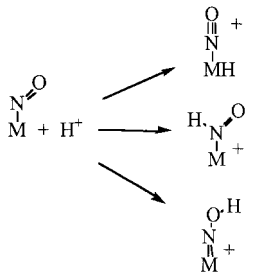
Ongoing studies[101] of the water-soluble ferri-heme model Fe^{III}(TPPS) in aqueous solution have shown that this species is also subject to reductive nitrosylation in solutions that are moderately acidic (pH 4−6) (eq 27). However, while the kinetics of eq 27 demonstrate a pH-independent component, this term includes a buffer dependence and indicates that the reaction of the Fe^{III}(TPPS)(NO) complex with H_2O is subject to general base catalysis. Another feature of the reaction depicted in eq 27 is that it is not observable at pH values <3. The reason for this is straightforward; the half-cell reduction potential for the nitrite anion ($NO_2^- + e^- + 2H^+ \rightarrow NO + H_2O$) is quite pH dependent, and eq 27 is no longer thermodynamically favorable at lower pH.

$$Fe^{III}(TPPS)(NO) + H_2O + NO \xrightarrow{k_{H_2O}} Fe^{II}(TPPS)(NO) + ONO^- + 2H^+ \quad (27)$$

2. Reactions of Metal Nitrosyls with Electrophiles

In general, nucleophilic attack at coordinated nitrosyl occurs at the nitrogen atom bound to the metal. Electrophilic attack at coordinated nitrosyl is not as selective. For example, protonation may occur at the metal center, at the nitrosyl nitrogen, or at the nitrosyl oxygen (Scheme 4). An early example of

Scheme 4



nitrosyl protonation was reported by Reed and Roper.[102] Addition of HCl to the osmium complex $Os(PPh_3)_2Cl(NO)$ gave the first characterized example of an N-coordinated HNO complex $OsCl_2(PPh_3)_2$(HNO) via reversible protonation of a coordinated NO (eq 28). This structure has been confirmed by X-ray crystallography.[103] Notably, the metal was not protonated, although the HOMO must have a fair degree of metal character. Isolation of bound HNO is significant in light of the instability of HNO toward dimerization and ultimately to N_2O and H_2O. The same workers also demonstrated that the HCl reaction of the iridium complex $Ir(PPh_3)_3(NO)$ gave the hydroxylamine complex $IrCl_3(PPh_3)_2(NH_2OH)$ with the HNO complex $IrCl(PPh_3)_3$(HNO) invoked as a possible intermediate.[103]

$$Os(PPh_3)_2Cl(NO) + HCl \rightarrow OsCl_2(PPh_3)_2(HNO) \quad (28)$$

One important facet of protonating a coordinated nitrosyl is choice of the conjugate base counterion. If

anion coordination occurs at the metal, this promotes electron release to the nitrosyl making the latter more basic. Hence, a strong acid with a noncoordinating counterion might not protonate a coordinated nitrosyl, while a weaker acid with a more strongly binding counterion would give a HNO complex (e.g., eq 28). This would be, effectively, the result of HX oxidative addition across M−NO.[104] Similarly, protonation at the nitrosyl oxygen or the metal center is more likely when a strong acid with a noncoordinating counterion is employed.

An alternative path to protonation of coordinated NO is to reduce the M−NO unit electrochemically.[105] Such coupled reduction/protonation schemes have been argued to have relevance to enzymatic nitrogen oxide reductases.[82] Farmer and co-workers[106] have done this using graphite electrodes modified by depositing surfactant films of Mb(NO) on the surface. Electrochemical reduction of $Mb(NO)_{surface}$ ($E_{1/2}$ = −0.63 V vs NHE) to $Mb(NO^-)_{surface}$ was accompanied by protonation to provide a $Mb(HNO)_{surface}$ complex. The $Mb(NO^-)_{surface}$ was found to undergo catalytic reaction with excess NO in solution at more negative potentials to give N_2O, suggesting that a N−N coupling reaction occurs between the bound nitroxyl ion and free NO. A surprisingly stable solution-phase version of Mb(HNO) was prepared independently in aqueous solution by reacting Mb(NO) with Cr^{2+} (eq 29) and was isolated by size exclusion chromatography.[106b] The ^1H NMR displayed a singlet at 14.8 ppm. The pK_a of the coordinated HNO was not reported.

$$Mb(NO) + Cr^{2+} + H^+ \rightarrow Mb(HNO) + Cr^{3+} \quad (29)$$

Other electrophiles, such as Li^+ and BF_3 have been shown to bind weakly to Co(salophen)(NO) complexes (salophen = *N*,*N*′-1,2-phenylendiamine-bis(salicylideniamato)), presumably at the oxygen, causing ν_{NO} to shift ∼20 cm^{-1} to higher frequency.[107] This also serves to labilize the nitrosyl. Dioxygen and other oxidants may also be electrophiles in reactions with coordinated NO. However, since these reactions are generally accompanied by subsequent processes leading to nitro or nitrito ligands or to dissociated NO_x products as well as other transformations of the metal complex, these reactions will be discussed in a following section on atom transfer reactions.

IV. Redox Reactions of NO Involving Transition Metals

Whenever a ligand binds to a metal center there is electronic redistribution owing to the balance between ligand-to-metal σ- and π-donation and metal-to-ligand π-back-bonding. As discussed above, NO is especially versatile in this regard. Therefore, simple substitution of a ligand by NO may involve considerable net charge reorganization at the metal center. For example, NO substitution of one water of Fe^{III}-(TPPS)$(H_2O)_2$ gives a $\{FeNO\}^6$ species with a linear Fe−NO bond. As mentioned in an earlier section, this can be considered (formally) to be an $Fe^{II}(NO^+)$ complex, consistent with the reactivity pattern toward nucleophiles. However, the reverse dissociation of neutral NO is facile (see above), so one tends not to view this as a redox reaction. In this section we address redox reactions involving NO where there are more definitive changes in the oxidation state of the metal complex partner and of the nitrogen products.

That redox reactions involving nitric oxide have important implications beyond their fundamental chemistry is easily seen given the debate in the biomedical literature regarding whether the generation of NO leads to the amelioration or the exacerbation of oxidative stress in mammalian systems.[108] "Oxidative stress" is defined as a disturbance in the balance between production of reactive oxygen species (pro-oxidants) and antioxidant defenses.[109] Reactive oxygen species include free radicals and peroxides as well as other reactants such as oxidative enzymes with metal-ion sites in high oxidation states. The physiological damage done to the organism by high oxidative stress during, for example, cardiovascular events or by lower level problems such as chronic autoimmune disease or infection is an important issue in many disease states.

The role of NO in biology is ultimately defined by its activity at the molecular level. For example, as a free radical NO readily reacts with other free radicals such as the hydroxyl radical to give nitrite or with superoxide to give peroxynitrite (eq 30) at near diffusion-limited second-order rates (e.g., $k_2 \sim 10^{10}$ M^{-1} s^{-1} for O_2^-).[110]

$$NO + O_2^- \rightarrow ONOO^- \quad (30)$$

In contrast, processes requiring multiple electron changes, such as the reaction of NO with O_2 in aqueous media to give nitrite (eq 31)[111]

$$4NO + O_2 + 2H_2O \rightarrow 4H^+ + 4NO_2^- \quad (31)$$

generally are much slower under physiological conditions. The reason is straightforward; the autoxidation of NO in aqueous solution follows a third-order kinetics rate law (eq 32).[111,112]

$$-\frac{d[NO_2^-]}{dt} = 4k_{aq}[NO]^2[O_2] \quad \text{where } k_{aq} = 9 \times 10^6\ M^{-2}\ s^{-1} \quad (32)$$

Thus, at the low [NO] relevant to bioregulatory processes such as blood pressure regulation and neurotransmission, autoxidation is slow relative to other depletion pathways and lifetimes are sufficient to allow for fast reactions with ferro-heme proteins such as guanylyl cyclase which are in close proximity.[112] In contrast, when much higher NO levels are produced, e.g., by stimulated macrophages under immune response, autoxidation is faster and has greater biological significance. The autoxidation intermediates, most prominently a species with the stoichiometry N_2O_3, are responsible for oxidative and nitrosative reactions that contribute to cytotoxic and mutagenic activities under these conditions.[113,114]

Thus, the third-order kinetics behavior for NO autoxidation in aqueous media reveals how this reactive molecule can play important bioregulatory roles in oxygenated media yet participate in cytotoxic

action when generated at higher concentration. An alternative species, peroxynitrite (formed from NO plus O_2^-, eq 30), has received considerable attention as a possible toxic/mutagenic agent formed during immune response.[115] The role of peroxynitrite in this regard is a matter of continuing debate given that another school of thought argues that $ONOO^-$ is less damaging than superoxide, so reaction of the latter with NO is actually a cytoprotective mechanism.[113a]

Autoxidation of NO in aprotic solvents also follows a third-order rate law but differs from the reaction in aqueous solution given that the product under these conditions is nitrogen dioxide. NO_2 is much more reactive especially toward nitration of various substrates than nitrite ion, which is the autoxidation product in aqueous solution.[113,116] From a biological perspective, aprotic autoxidation may have relevance owing to the higher solubility of both NO and O_2 in hydrophobic media. As a consequence of reactant partitioning between cellular hydrophobic and hydrophilic regions and the third-order nature of this reaction, a disproportionately large fraction of autoxidation may occur in hydrophobic regions to give nitrogen dioxide as the key intermediate under these conditions.[117]

The reactivity of NO with O_2 is dramatically affected by coordination of one or the other ligand to a metal center. For example, the second-order reactions of NO with oxyhemoglobin $Hb(O_2)$ and oxymyoglobin (e.g., eq 33) are quite fast, and the nitrogen product is nitrate rather than nitrite.[118] Superficially, the reaction of O_2 with nitrosyl myoglobin Mb(NO) appears similar (eq 34) but is much slower and follows a different rate law.[119] Possible mechanisms will be discussed.

$$NO + Mb(O_2) \rightarrow metMb + NO_3^- \quad (33)$$

$$O_2 + Mb(NO) \rightarrow metMb + NO_3^- \quad (34)$$

The subsequent discussion has been divided into sections on electron transfer and atom transfer mechanisms, but as will be seen, this categorization is somewhat arbitrary and ambiguous.

A. Electron Transfer Reactions

Although iron is the most important metal target for nitric oxide in mammalian biology, other metal centers might also react with NO. For example, both cobalt (in the form of cobalamin, Cbl)[120,121] and copper (in the form of different types of copper proteins)[122] have been identified as potential NO targets. In addition, a substantial fraction of the bacterial nitrite reductases (which catalyze reduction of NO_2^- to NO) are copper enzymes.[123] In this context, the interactions of NO with such metal centers remains a rich area for further investigation.

With regard to cobalamin, several studies have claimed that the Co(III) complex aquacobalamin (Vitamin B_{12a}) reacts with NO to form a stable complex and have attributed biological roles to this reaction.[120] These proposals contradicted an earlier conclusion by Williams and co-workers[124] that B_{12a} is unreactive with nitric oxide. However, van Eldik and co-workers[121a] recently attributed the reported reactivity of NO with B_{12a} to the presence of the common aqueous solution impurity NO_2^- formed as the result of NO disproportionation to N_2O_3 in high-pressure NO tanks or by oxidation with traces of O_2. These workers demonstrated[121c] that NO reacts rapidly with the reduced (Co(II)) form of B_{12r} to give a $B_{12r}(NO)$ complex with a second-order rate constant k_{on} of $7.4 \times 10^8\ M^{-1}\ s^{-1}$ at pH 7.4 (298 K). The water-soluble cobalt(II) porphyrin complex Co^{II}(TPPS) has been shown to react with NO to give the nitrosyl adduct with comparable rates (Table 3).[64]

Reduction of the Cu(II) complex $Cu(dmp)_2(H_2O)^{2+}$ (dmp = 2,9-dimethyl-1,10-phenanthroline) by NO (eq 35) was studied in aqueous solution and various mixed solvents.[125] The reduction potential for $Cu(dmp)_2(H_2O)^{2+}$ (0.58 V vs NHE in water)[126] is substantially more positive than most other cupric complexes owing to steric repulsion between the 2,9-methyl substituents favoring the tetrahedral coordination of Cu(I) over the tetragonal pyramidal structure of Cu(II). The less distorted bis(1,10-phenanthroline) analogue $Cu(phen)_2(H_2O)^{2+}$ is a weaker oxidant (0.18 V).[126] In methanol, the product of the $Cu(dmp)_2(H_2O)^{2+}$ oxidation of NO is CH_3ONO; in water, it is NO_2^-. The reaction did not occur in CH_2Cl_2 unless methanol was added.

$$Cu(dmp)_2(H_2O)^{2+} + NO + ROH \rightarrow Cu(dmp)_2^{+} + RONO + H^+ + H_2O \quad (35)$$

The kinetics of this reaction were followed by tracking the formation of $Cu(dmp)_2^+$ at 455 nm, the λ_{max} of the metal to ligand charge transfer (MLCT) absorption band. At a fixed pH, the kinetics in aqueous solution followed the rate law.

$$\frac{d[Cu(dmp)_2^+]}{dt} = k_{NO}[NO][Cu(dmp)_2^{2+}] \quad (36)$$

Addition of $NaNO_2$ (5×10^{-5} M) had no effect on the reaction profile with NO present, and no reaction was observed (on the time scale of the stopped flow experiment) when NO was absent. However, at higher concentrations, anions, including the conjugate bases of various buffers (B^-), slowed the reaction. This was attributed to the competition between water and these anions for the labile fifth coordination site of $Cu(dmp)_2(H_2O)^{2+}$.

Two mechanisms come to mind. The first would be simple outer-sphere electron transfer followed by hydrolysis of NO^+ (eqs 37 and 38)

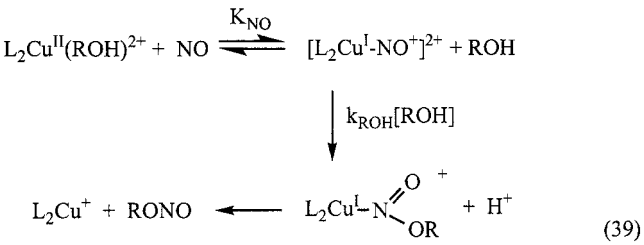
$$Cu(dmp)_2^{2+} + NO \underset{k_{-os}}{\overset{k_{os}}{\rightleftharpoons}} Cu(dmp)_2^{+} + NO^+ \quad (37)$$

$$NO^+ + H_2O \xrightarrow{k_{hyd}} H^+ + HNO_2 \quad (38)$$

The outer-sphere kinetics give two limiting cases, both first order in [NO]. One would involve a reversible equilibrium (eq 37) followed by rate-limiting hydrolysis of the nitrosonium ion, and the second-order rate constant would be $k_{NO} = K_{os}k_{hyd}$ where $K_{os} = k_{os}/k_{-os}$. At the other extreme k_{os} would be rate limiting ($k_{NO} = k_{os}$) and electron transfer is effectively

irreversible owing to rapid hydrolysis of NO^+. The latter would appear more likely given the expectation that k_{hyd} is quite large.[127] For both cases, the reaction rate would be expected to be slower when an anion is coordinated to the Cu(II) instead of H_2O owing to the (likely) lower reduction potential of a $Cu(dmp)_2(B)^+$ species. For either limit, k_{os} is the maximum rate constant by which NO reduction of Cu(II) would occur, and a value for this can be estimated from the Marcus cross relation,[128] i.e., $k_{os} \sim (k_{11}k_{ex}K_{os})^{1/2}$, where k_{11} is the $Cu(dmp)_2^{2+}/Cu(dmp)_2^+$ self-exchange rate constant and k_{ex} is the self-exchange rate constant for NO^+/NO. This treatment gave $\sim 3 \times 10^{-3}$ M^{-1} s^{-1} as an estimate for k_{os}, a value 5 orders of magnitude smaller than the value of k_{NO} measured for eq 36 at lower pHs. On this basis, the outer-sphere reaction mechanism was concluded to be unlikely.

Alternatively, the kinetics for NO reduction of aqueous $Cu(dmp)_2(H_2O)^{2+}$ can be rationalized in terms of an inner-sphere mechanism.



(39)

The three steps would be (i) the reversible equilibrium displacement of solvent (H_2O or ROH) by NO to form an inner-sphere Cu(II)−nitric oxide complex, which is activated toward nucleophilic attack by ROH (ii) owing to charge transfer from NO to the metal ($Cu^{II}-NO \leftrightarrow Cu^{I}-NO^+$). Dissociation of the RONO complex (iii) would be rapid owing to the preference of the cuprous complexes for tetrahedral coordination. This inner-sphere pathway obviously parallels the reductive nitrosylation mechanisms discussed above with the exception that the $Cu^{II}-NO$ complex is formed with a very low K_{NO}. (Attempts to observe formation of the putative inner-sphere complex $Cu(dmp)_2(NO)^{2+}$ gave no spectral evidence for a new species). In this context, the rate law predicted for eq 39 would also be second order ($k_{NO} = K_{NO}k_{ROH}$) if ROH is the solvent. While [ROH] is not a variable in aqueous or methanolic solution, kinetics dependence on [MeOH] in methanolic dichloromethane agreed with this model.

Even though the rate law for eq 35 might suggest a simple outer-sphere electron-transfer mechanism from NO, the evidence in this case points to an inner-sphere pathway involving NO coordination *followed* by the reaction with a solution nucleophile. Perhaps this is not surprising given the relatively high potential required for the simple one-electron *oxidation* of NO (eq 3).

B. Atom Transfer Reactions of NO Complexes

At room temperature, NO is thermodynamically unstable although unreactive toward disproportionation to N_2O and NO_2 or to N_2 plus NO_2 (eqs 40 and 41). Oxygen transfer from NO to CO to give CO_2 plus N_2O or N_2 is even more exergonic at room temperature but also very slow. Catalytic converters in automobiles and power plants are designed to take reaction 42 and reaction 43 as far to completion as possible. There is a sizable body of literature in the heterogeneous catalysis field devoted to this topic.[129]

$$3NO \rightharpoonup N_2O + NO_2 \quad \Delta G° = -104.2 \text{ kJ/mol} \quad (40)$$

$$4NO \rightarrow N_2 + 2NO_2 \quad \Delta G° = -121.8 \text{ kJ/mol} \quad (41)$$

$$2NO + CO \rightharpoonup N_2O + CO_2 \quad \Delta G° = -326.3 \text{ kJ/mol} \quad (42)$$

$$2NO + 2CO \rightarrow N_2 + 2CO_2 \quad \Delta G° = -343.9 \text{ kJ/mol} \quad (43)$$

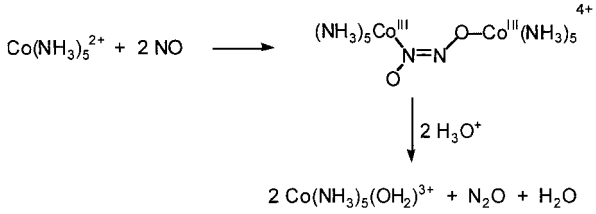
1. NO Disproportionation

In homogeneous solutions NO disproportionation may be promoted by transition-metal complexes, and a variety of mechanisms seem to be available owing to the many possible modes of coordination. One example is the reaction of NO with nickel carbonyl shown in eq 44,[130] where the nitrogen-containing products are N_2O (oxidation state formally N(I)) and coordinated NO^+ and ONO^- (both N(III)). A number of other metal complexes have been shown to promote similar transformations.[131] Wilkinson et al.[132] used a similar reaction to prepare Ru(salen)(NO)(ONO) from $Ru^{II}(salen)(PPh_3)_2$ and NO but did not report evolution of N_2O.

$$Ni(CO)_4 + 4NO \rightarrow [Ni(NO)(NO_2)]_n + 4CO + N_2O \quad (44)$$

Pentaamminecobalt(II) reacts with NO to give a μ-hyponitrito dimer, dubbed the "red isomer" of nitrosylpentamminecobalt by Werner, characterized by Feltham conductometrically as a tetracationic dimer and crystallographically by Hoskins[133] as having Co−N(O)=N−O−Co bridging linkage (Scheme 5).

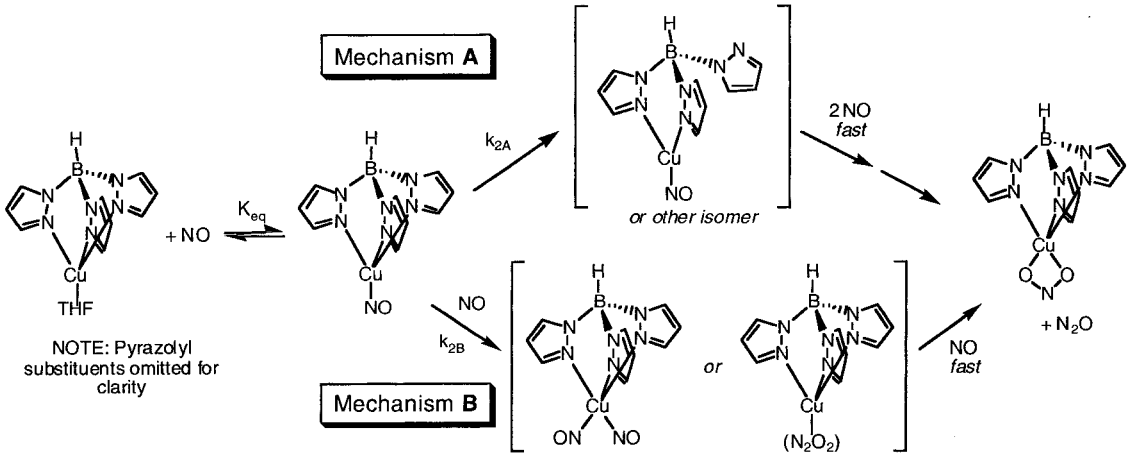
Scheme 5



This dimer further reacts with NO to give N_2O and NO_2^-.[134] On the other hand, $Co^{II}(en)_2Cl$, follows a mononuclear pathway and a head-to-tail N_2O_2 ligand was proposed as a key intermediate prior to reaction with a third NO to give disproportionation products.[135] A different reaction was described by Miki et al.[136] for the reaction of Co^{II}(quinolinolate) complexes, which catalyzed the slow disproportionation of NO to N_2O and nitrate.

More recently, Tolman and co-workers[137] found that the copper(I) complex $Cu^{I}Tp^{R2}$ (Tp^{R2} = tris(3-(R^2)-5-methylpyrazol-1-yl)hydroborate) promotes NO disproportionation via a weakly bound $Cu^{I}Tp^{R2}(NO)$

Scheme 6. Possible Mechanisms for Disproportionation of NO Mediated by $Tp^{R2}Cu^{I}$ Complexes[a]



[a] Reprinted with permission from ref 137b. Copyright 1998 American Chemical Society.

intermediate (formally a $\{MNO\}^{11}$ species). The products are N_2O and a copper(II) nitrito complex (eq 45). The rate law for this reaction proved to be first order in copper and second order in [NO]. This was interpreted in terms of preequilibrium of NO and the Cu(I) precursor to give the $Cu^{I}(NO)$ adduct followed by rate-limiting electrophilic attack of a second NO molecule (mechanism B of Scheme 6).[137b]

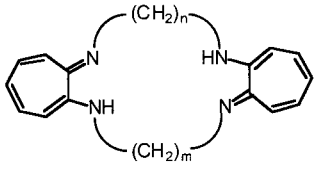
$$Cu^{I}Tp^{R2} + 3NO \rightarrow Cu^{II}Tp^{R2}(NO_2) + N_2O \quad (45)$$

Complexes of the N−N-bonded dinitrogen dioxide such as depicted in pathway B of Scheme 6 would appear to be necessary in order to effect the formation of the N−N bond. This has been treated theoretically as a metal-promoted reductive coupling of 2NO to form a hyponitrite complex.[181] Despite the latter's general instability in protic solvents toward decomposition to N_2O and water, hyponitrite complexes have been isolated, e.g., $L_2Pt^{II}(ONNO)$, ($L = PPh_3$) formed by reaction of $Pt^{0}L_4$ with NO and featuring a bidentate bis-oxygen-bound hyponitrite ligand.[182]

The $Cu^{I}(Tp^{R2})$ system was also shown to catalyze NO oxidations of benzyl and isopropyl alcohol to benzaldehyde and acetone (eq 46). Electrospray mass spectrometry indicated higher oligomers of copper to be involved in the transfer of oxidizing equivalents to substrate.[138]

$$2NO + R_2CHOH \xrightarrow{Cu^{I}(Tp^{R2})} N_2O + H_2O + R_2C{=}O \quad (46)$$

A related observation is the report by Tanaka et al.[139] that the copper(II) complexes $Cu(tpa)^{2+}$ (tpa = tris[(2-pyridyl)methyl]amine) can serve as a catalyst for the electrochemical reduction of nitrite to N_2O and traces of NO in aqueous solution. NO and/or a copper nitrosyl complex would appear to be the likely intermediates in this process.[139a]



$H_2TC\text{-}5,5$, m = n = 5

Franz and Lippard reported NO disproportionation promoted by the Fe(II) and Mn(II) tropocoronand complexes Fe(TC-5,5) and Mn(TC-5,5).[140] Reaction with Mn(TC-5,5) (eq 47) proved to be stoichiometric with 3 equiv of NO leading to formation of N_2O and O-coordinated nitrito ligand with the electron balance being provided by oxidation of Mn(II) to Mn(III). The mononitrosyl complex Mn(TC-5,5)(NO) was characterized crystallographically as having a linear nitrosyl. This was proposed to react with NO to form first an unstable *cis*-dinitrosyl $Mn(TC\text{-}5,5)(NO)_2$, which is then poised to form an N-coordinated hyponitrito (O=N−N=O) ligand from which oxygen transfer occurs to another NO.[140a] This pathway, in particular the intermediacy of a hyponitrito ligand, parallels other proposed mechanisms for metal complex promoted NO disproportionation.[14a−d,182]

$$Mn(TC{-}5,5) + 3NO \rightarrow Mn(TC{-}5,5)(ONO) + N_2O \quad (47)$$

For the Fe(II) system the mononitrosyl complex Fe(TC-5,5)(NO) was also characterized and suggested to be a logical intermediate in the disproportionation mechanism.[140b] An interesting feature of the NO reaction with Fe(TC-5,5) is that NO_2 was released from the iron (eqs 48 and 49). However, the NO_2 nitrates the aromatic rings of the tropocoronand ligand and renders the resulting complex inactive as a disproportionation catalyst.

$$Fe(TC\text{-}5,5) + 4NO \rightarrow Fe(TC\text{-}5,5)(NO) + NO_2 + N_2O \quad (48)$$

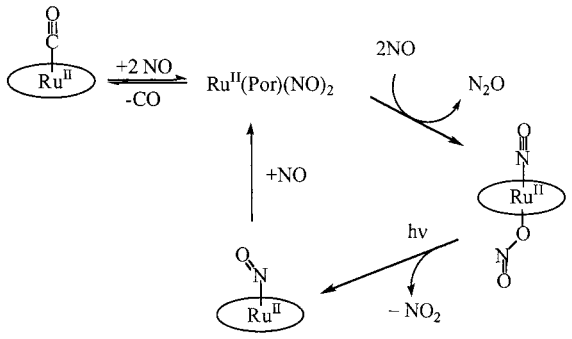
$$Fe(TC\text{-}5,5)(NO) + NO_2 \rightarrow Fe(TC\text{-}5,5\text{-}NO_2)(NO) \quad (49)$$

Several groups have demonstrated that the ruthenium(II) complexes $Ru^{II}(Por)CO$ react with NO to give the nitrosyl nitrito complex Ru(Por)(NO)(ONO) (Por = TPP, OEP, and related porphyrins).[141,142] Stoichiometric quantities of N_2O and free CO were formed according to eq 50.[141] Reaction of the osmium(II) complex $Os^{II}(OEP)(CO)$ with NO gives analogous products.[143]

$$Ru^{II}(Por)CO + 4NO \rightarrow Ru(Por)(NO)(ONO) + N_2O + CO \quad (50)$$

A detailed stopped-flow kinetics investigation[144] of eq 50 (Por = TmTP and OEP) showed the mechanism to proceed in two distinct stages. The first stage was quite fast but was suppressed by the presence of excess CO and other coordinating ligands. Time-resolved infrared spectral studies indicate that this intermediate is the dinitrosyl complex $Ru(Por)(NO)_2$ characterized by a strong, single ν_{NO} band at 1642 cm^{-1} (for Por = TmTP in cyclohexane solution).[145] The rate of the second stage leading to formation of Ru(Por)(NO)(*O*NO) proved to be second order in [NO] (Scheme 7).

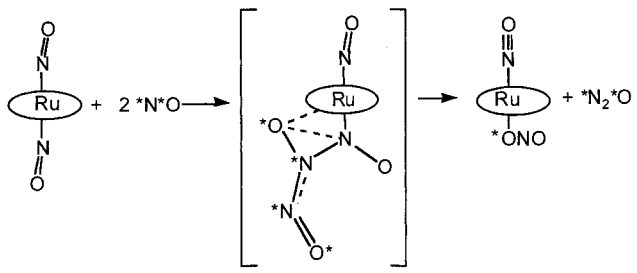
Scheme 7[a]



[a] Circle is porphyrin ligand.

The analogous dinitrosyl intermediate was also seen in time-resolved optical and IR studies of the species generated via the 355 nm flash photolysis of Ru(Por)(NO)(ONO) under excess NO.[146] Photoinduced dissociation of NO_2 from Ru(Por)(NO)(ONO) followed by trapping with NO gave $Ru(Por)(NO)_2$ as observed by flash photolysis experiments with stepped scan FTIR detection.[146] The dinitrosyl continued to react with additional NO to regenerate Ru(Por)(NO)(ONO) via the disproportionation shown above. When the flash photolysis was carried out with unlabeled Ru(P)(NO)(ONO) and doubly labeled $^{15}N^{18}O$ in solution, only singly and triply labeled nitrite ligand and fully labeled $^{15}N_2{}^{18}O$ were formed. This indicates that the nitrito ligand is formed by an oxygen transfer from two $^{15}N^{18}O$ to one of the two coordinated NO's of the dinitrosyl, one of which must be an unlabeled NO from the original substrate. Scheme 8 offers a hypothetical pathway for these steps.

Scheme 8



The literature regarding the reaction of the Fe(II) porphyrins with NO appears fraught with inconsistent observations. Despite the facile NO disproportionation promoted by Ru(II) and Os(II) porphyrins to give N_2O and the respective M(Por)(NO)(ONO) complexes, the reactivity appears to be different with analogous Fe(II) complexes. For example, ferrous porphyrins such as Fe^{II}(TPP) undergo NO addition in ambient-temperature solution to give the relatively stable paramagnetic mononitrosyls, e.g., Fe(TPP)(NO). There are significant ambiguities regarding the subsequent reaction with excess NO. Fe(TPP)(NO) was reported to promote NO disproportionation in a manner similar to Ru(II) porphyrins to give the N-bonded nitro species $Fe(TPP)(NO)(NO_2)$ rather than the linkage isomer O-coordinated nitrito complex seen for the heavier metals.[147] However, recent studies[148] demonstrated that ambient-temperature solutions of Fe(TPP)(NO) display no changes in IR or optical spectra *when treated with NO carefully cleaned of higher NO_x impurities.* This is consistent with an early report by Wayland and Olson.[149] Hence, it appears that the nitro complexes are formed when NO_2 impurities are present in the NO source, i.e.

$$Fe(TPP)(NO) + NO_2 \rightarrow Fe(TPP)(NO)(NO_2) \quad (51)$$

Wayland and Olson[149] also described low-temperature properties of the Fe(TPP)(NO)/NO system, namely, the reversible disappearance of the ESR signal for Fe(TPP)(NO) under excess NO (400 Torr), and proposed the formation of the dinitrosyl $Fe(TPP)(NO)_2$. Another early report[150] suggested the dinitrosyl to be stable in room-temperature toluene, but the optical spectrum reported appears to be more consistent with that of $Fe(TPP)(NO)(NO_2)$. This system has been reexamined using optical, IR, and NMR spectral techniques to probe NO reactions with Fe(TPP)(NO) and the more soluble Fe(TmTP)(NO).[151] These studies confirmed the formation of $Fe(Por)(NO)_2$ in low-temperature toluene-d_8 (eq 52). NMR line shape analysis was used to calculate $K_{52} = 23$ M^{-1} at 253 K (3100 M^{-1} at 179 K, $\Delta H° = -28$ kJ mol^{-1}).[151] The failure of the Fe^{II}(Por) complexes to promote NO disproportionation, in contrast to the behavior of the respective Ru(II) and Os(II) analogues, must find its origin in the relatively low stability of the di(nitrosyl) intermediate (K_{52}(est) = 2.8 M^{-1} at 298 K) and unfavorable kinetics of subsequent reaction of this species with NO.

$$Fe^{II}(TmTP)(NO) + NO \overset{K_{52}}{\rightleftharpoons} Fe^{II}(TmTP)(NO)_2 \quad (52)$$

It might be noted that Kadish et al.[152] reported UV−Vis and EPR spectra of the 19-electron complex $Fe(P)(NO)_2^+$, at room temperature. Recently the 20-electron species $M(Pc)(NO)_2^-$ (M = Re, Mn, Pc = phthalocyaninato), electronically analogous to $Fe(P)(NO)_2$, have also been described.[153]

2. Oxidation of Carbon Monoxide

There has been considerable interest in the catalytic reactions of NO with CO because these gases represent undesirable postcombustion components, NO from oxidation of N_2 and CO from underoxidation of hydrocarbons and coal.

$$2NO + CO \rightarrow N_2O + CO_2 \quad (53)$$

$$2NO + 2CO \rightarrow N_2 + 2CO_2 \quad (54)$$

Metal-catalyzed NO oxidations of CO are more likely to be catalytic than NO disproportionations, since the products N_2, N_2O, and CO_2 are rather poor ligands. Most studies in this field have been concerned with heterogeneous catalysts owing to possible applications in cleaning automobile and other combustion source exhausts and are outside the purview of this article. Several homogeneous reaction studies are discussed, but much of this work was described in earlier reviews.[14]

In the early 1970s Johnson and Bhaduri[154] demonstrated that $IrL_2(NO)_2^+$ (L = PPh_3) reacted with CO to give CO_2, N_2O, and $IrL_2(CO)_3^+$ (eq 55). The iridium(I) product was converted back to $IrL_2(NO)_2^+$ upon reaction with NO with the formation of additional CO_2 and N_2O, thereby closing the cycle. The process was shown to be catalytic by Haymore and Ibers,[155] who proposed a dinitrogen dioxide complex $[IrL_n(CO)(N_2O_2)]^+$ as the reactive O-atom transfer intermediate. This was further supported by labeling studies on an analogous Rh system.[156]

$$Ir(PPh_3)_2(NO)_2^+ + 4CO \rightharpoonup Ir(PPh_3)_2(CO)_3^+ + CO_2 + N_2O \quad (55)$$

Eisenberg and co-workers[157] demonstrated a complete catalytic cycle for reaction 53 using ethanolic $RhCl_3$ and concluded that reduction to Rh(I) carbonyl chlorides such as $Rh(CO)_2Cl_2^-$ was a prerequisite for the onset of catalysis under a NO/CO atmosphere. Water is also a requirement for catalytic activity, so CO oxidation likely results from a water−gas shift type reaction, providing the equivalents necessary to reduce two coordinated nitrosyls to N_2O.

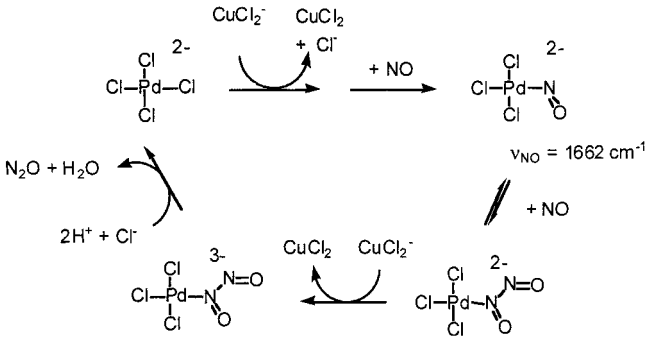
Mechanistic studies have been reported for catalysts of the NO/CO reaction based on Rh,[158] Ni,[159] and Pd[160] complexes. Although the palladium system is highly reactive, Pd metal rapidly plated out under catalytic conditions. Kubota et al. found that addition of $CuCl_2$ to the reaction mixture inhibited the plating reaction and maintained the catalytic activity.[160] Use of copper salts to prevent noble-metal plating has been applied to a $PtCl_4^{2-}$ system by Cheng et al.,[161] who also used olefins as substrates in place of CO, giving ketones and N_2O.

Kinetics studies by Trogler et al.[162] of the Pd/Cu-catalyzed NO reduction by CuCl determined that the rate-limiting step in this aqueous system is CuCl reduction of the dinitrogen dioxide $PdCl_3(N_2O_2)^{2-}$ complex (formed reversibly by attack of NO on $PdCl_3(NO)^{2-}$) to give N_2O, water, and $PdCl_4^-$. The latter subsequently binds to NO to complete the cycle (Scheme 9).

3. Reactions with Dioxygen

The possible use of metal nitrosyls to activate the 4-electron oxidant O_2 has long been of interest.[163−172] For example, Clarkson and Basolo[163] reported in 1973 a systematic study of dioxygen reactions with various Co(II) Schiff base nitrosyl complexes such as Co(salen)(NO). These reactions proceeded in the presence of coordinating bases such as pyridine to give cobalt nitro complexes (e.g., eq 56). Base coordination would increase electron density at the nitrosyl and make it more susceptible toward reaction with an electrophile such as O_2. This would give an N-coordinated peroxynitrite species such as Co(salen)(py)($N(O)O_2$) that can transfer an oxygen atom to a second equivalent of Co(salen)(py)(NO) (pathway a in Scheme 10). Goodwin and co-workers[171] recently proposed a catalytic cycle for alkene oxidations via O-atom transfer from an analogous peroxynitrite intermediate formed from Co(TPP)(NO) and O_2.

Scheme 9

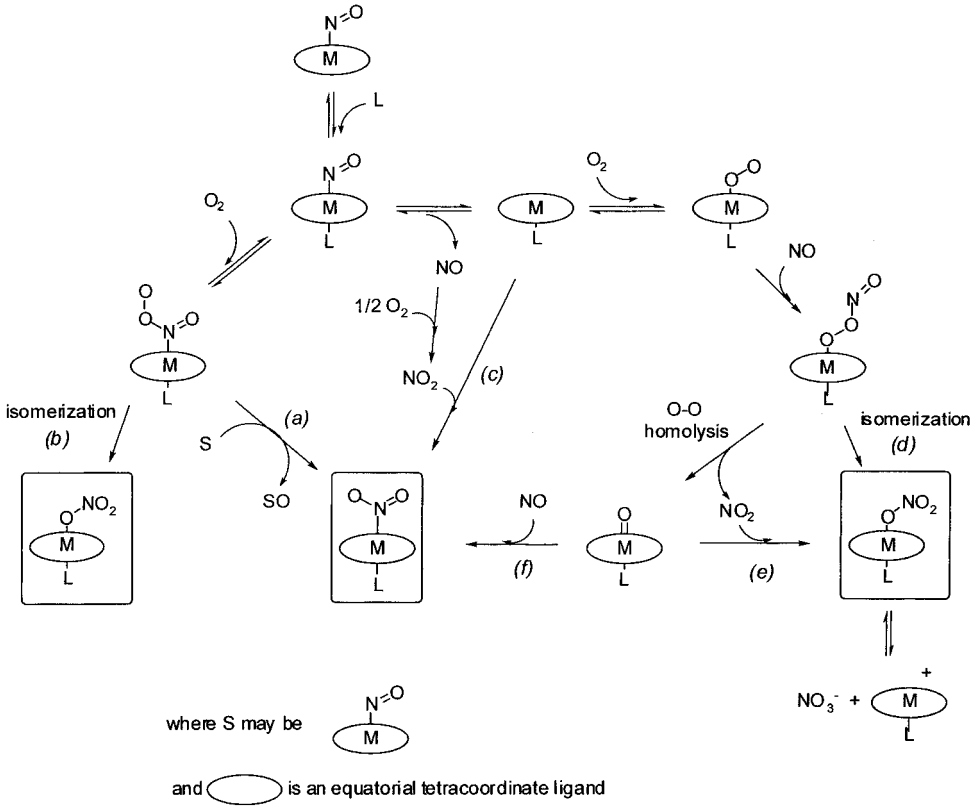


$$2Co(salen)(NO) + 2py + O_2 \rightarrow 2Co(salen)(py)(NO_2) \quad (56)$$

Marzilli and Trogler[164] similarly demonstrated that $Co(dmg)_2(NO)$ (dmg = dimethylglyoximato) reacts with organic bases and O_2 to give a mixture of $Co(dmg)_2(ONO_2)$ and $Co(dmg)_2(NO_2)$. The latter product presumably would be formed by a mechanism similar to that for the salen analogues, while unimolecular isomerization of the N-coordinated peroxynitrite ligand (pathway b in Scheme 10) would account for the appearance of the nitrato complex. The latter pathway appears to be only followed in reactions of O_2 with the coordinated nitrosyl of $Ir(PPh_3)_2(CO)(Cl)(X)(NO)$ (L = PPh_3; X = I, Br, Cl, NCS^-, NCO^-, N_3^-). In 1975 Kubota and Phillips[165] reported that the nitrate complexes $Ir(PPh_3)_2(CO)(Cl)(X)(NO_3)$ were formed quantitatively and interpreted these results in terms of the formation of a nitrogen-coordinated peroxynitrite complex as an intermediate followed by intramolecular isomerization to the O-bound nitrato product at a rate faster than bimolecular reaction with a second iridium nitrosyl substrate. Notably, for cases where reaction of O_2 with metal nitrosyl gives both nitro (bimolecular pathway) and nitrato (unimolecular rearrangement) products, the partitioning between these paths should be concentration dependent.[173]

Conceivably, autoxidation of a metal nitrosyl complex might involve NO dissociation followed by uncatalyzed reaction of the free NO with O_2 to give NO_2 and rebinding to the metal center to give a nitro or nitrito complex (pathway c in Scheme 10). However, since the NO autoxidation rate is second order in [NO] in aqueous or aprotic media,[112a] accumulation of sufficient free NO to make such a sequence viable seems unlikely.

Scheme 10



Alternatively, NO dissociation followed by reaction of the denitrosylated metal center with O_2 would give a metal superoxide species[174] of the type L_nM-OO known to react rapidly with free NO[118,175,176] to form an O-bound peroxynitrite complex $L_nM-OONO$ (e.g., eq 33). The latter species may undergo unimolecular isomerization to the nitrato complex (pathway d in Scheme 10) or O−O bond fragmentation to $L_nM{=}O + NO_2$ followed by recombination to give a nitrato complex (pathway e) or reaction of the putative oxo complex $L_nM{=}O$ with NO to give the nitrito analogue (pathway f). The latter reaction has precedence for being quite rapid. A second-order rate constant of 3.1×10^6 M^{-1} s^{-1} has been measured for reaction of a $Cr^{IV}{=}O$ species to give a Cr(III) nitrito complex,[177] while a value of 1.8×10^7 M^{-1} s^{-1} was measured for the reaction of NO with $MbFe^{IV}{=}O$, the "ferryl" form of myoglobin generated by H_2O_2 oxidation of myoglobin.[178] It might also be noted that the reaction of NO with oxo complexes such as $Cr^{IV}{=}O$ to give nitrite ligand finds analogy in a recent report by Mayer et al.[179] that NO reacts with metal nitride L_nMN complexes to give the respective NNO complexes that are relatively labile. For example, osmium(VI) complex $TpOs(N)Cl_2$ (Tp = hydrotris(pyrazolyl)borate) reacts slowly with excess NO in benzene ($k_2 = 3 \times 10^{-4}$ M^{-1} s^{-1} at 294 K) to give stoichiometric conversion to N_2O and $TpOs(NO)Cl_2$.[179]

Among the important sinks for endogenously generated NO are the very fast reactions with oxyhemoglobin to form nitrate plus methemoglobin with a second-order rate constant of 8.9×10^7 M^{-1} s^{-1} (eq 57, pH 7.0).[176b] The analogous reaction of NO with oxymyoglobin (eq 34) is also quite fast with a second-order rate constant 4×10^7 M^{-1} s^{-1} (pH 7.0),[118a,176b] and this reaction has been used as a colorimetric test for NO.[118b] Herold and co-workers[118] examined the time-resolved spectroscopy of reactions 33 and 57 and concluded that NO reacts with the $Fe^{II}(O_2)$ species to give the peroxynitrito intermediates $Fe^{III}(OONO)$. Under neutral or acidic conditions, the latter rapidly decays to the "met", i.e., Fe^{III}, forms of the proteins with the quantitative formation of nitrate. Thus, the metal mediates the isomerization of peroxynitrite to nitrate.[118]

$$Hb(O_2) + NO \rightarrow NO_3^- + metHb \qquad (57)$$

As noted in a section above, reaction of the analogous nitrosyl myoglobin complex with dioxygen, a reaction of very great importance regarding the stability of cured meats, is much slower. The kinetics of eq 34 were studied by Skibsted et al.,[119] who reported that, even at low dioxygen concentrations, the rate displayed limiting first-order behavior with a k_{obs} of 2.3×10^{-4} s^{-1} in 298 K aqueous solution with $\Delta H^{\ddagger} = 110$ kJ mol^{-1} and $\Delta V^{\ddagger} = +8$ cm^3 mol^{-1}. These authors proposed that the reaction proceeded via prior formation of an O_2 complex with the nitrosyl myoglobin, for example, an N-bonded peroxynitrite (the analogue of pathway a in Scheme 10). However, the similarity of the limiting rate constant to the rate of NO dissociation (2×10^{-4} s^{-1}) from Mb(NO)[180] tempts one to think in terms of a mechanism such as pathway c. Regardless, formation of NO_3^- as the nitrogen product indicates that the metal must be involved in the eventual oxidation step, since uncatalyzed NO autoxidation in aqueous media gives nitrite products as seen in eq 34.

V. Overview and Summary

This article has reviewed mechanistic studies of the reactions of NO with transition-metal complexes in the context of the numerous roles such chemistry may play in the biological functions of NO.[1,2] There have been several earlier comprehensive reviews of the reactions and properties of metal nitrosyls.[14] The volume of relatively recent information regarding the chemistry, biochemistry, and pathobiology of NO is huge, but certain patterns dominate. The most obvious is that NO as a stable free radical participates very readily in one-electron events such as coupling to other free radicals. For example, the NO reaction with O_2^- to form $OONO^-$ proceeds via kinetics first order in [NO] at near diffusion limits.[110] However, whether this reaction is a particularly dangerous contributor to oxidative and nitrosative stress owing to formation of the peroxynitrite ion[115] or is protective to the organism owing to removal of the even more deleterious superoxide[183] ion remains hotly debated. Free radical trapping is also the role of NO in its actions as a sensitizer of radiation damage to cells, and this reaction may offer therapeutic potential for NO donors in radiation treatment of tumors.[184]

NO is also very reactive with redox-active metal centers, especially if these are ligand substitution labile. Reactions with such species generally display kinetic rate laws first order in [NO]. In contrast, reactions leading to overall two-electron changes, for example, oxidation of a substrate such as Ph_3P, generally will require two or more equivalents of NO in a third-order process unless promoted or catalyzed by another reagent such as a transition-metal complex. Even (perhaps especially) autoxidation is a third-order kinetic process, second order in [NO], unless catalyzed. Thus, NO autoxidation and related third-order processes are relatively slow under the conditions of bioregulation by this species. The same might not be the case in the locale of immune response to pathogen infection were higher [NO] the norm.[112]

With respect to bioregulatory roles in blood pressure control and neurological function, the principal action of NO centers on formation of a metal nitrosyl complex, namely, the activation of sGC by reaction with the iron(II) site of that ferroheme enzyme.[5,48] Given the low NO concentrations generated for such functions, the "on" reaction must be very fast in order to provide the appropriate response to stimuli. Formation of nitrosyl complexes is generally facile when the metal center has a vacant coordination site or is very labile but tends to be quite slow for nonlabile coordinatively saturated metals even when the net reaction is very favorable. Accelerating ligand lability by an associative mechanism is certainly possible in such systems, but the only convincing example of this mechanism involving NO is the displacement of NH_3 on the Ru(III) complex $Ru(NH_3)_6^{3+}$ (eq 7).[61] The "off" reaction of metal nitrosyls may be equally important given, for example, that this is a likely mechanism for deactivation of sGC. There is a need for more systematic investigations of such metal nitrosyl reactions as functions of the media, conditions, and the ligand field.

There is also considerable biological interest in NO reactions with ligands coordinated to a redox-active metal. For example, the facile second-order trapping of NO by $Mb(O_2)$ or $Hb(O_2)$ is very fast and is mechanistically very distinct[118,175,176] from the third-order autoxidation of NO.[112a] The result is oxidation of Fe(II) to Fe(III) concomitant with NO oxidation to NO_3^-. In contrast, the facile reaction of $M^{IV}{=}O$ species (M = Fe or Cr) with NO to give M^{III}-(ONO)[177,178] leads to reduction of the metal along with oxidation of NO. The reaction with $Hb(O_2)$ is an important sink for NO in the cardiovascular system, while trapping of ferryl intermediates (or other strong oxidants) by NO may play a role in reducing oxidative stress. Oxidative stress may also be reduced by NO coordination with metal centers catalytic for Fenton chemistry (the generation of strongly oxidizing intermediates from H_2O_2).[183] Along these lines, it is noted that the oxidative degradation of meats is inhibited by curing with nitrite, and stable nitrosyls are formed.[186] On the other hand, the ambiguous nature of possible NO function in oxidative stress is illustrated by its inhibition of catalase;[9] therefore, the protective function of this enzyme in removing endogenous H_2O_2.

Once formed, the nitrosyl complex can serve to activate the coordinated NO toward either nucleophilic or electrophilic attack depending on the nature of the metal and its oxidation state and the ligand field. Of particular interest biologically is the reaction with nucleophiles since this may well be a mechanism for thionitrosyl formation (e.g., eq 58)

$$L_nM^{III}(NO) + RSH \rightarrow RSNO + L_nM^{II} + H^+ \quad (58)$$

as well as for reductively labilizing metals in insoluble matrixes such as ferritin. The metal center may also promote NO reactivity toward disproportionation or substrate oxidation ($2NO + S \rightarrow SO + N_2O$) by serving as a template where multiple NOs are gathered in association with a substrate molecule. These reactions are less likely to be important biologically given the relatively low [NO] generated with the possible exceptions of localized higher concentrations generated during immune response. On the other hand, such concentrations are certainly generated in the laboratory or in possible applications of nitrosyls in oxidation catalysis.

VI. Abbreviations

1-MeIm	1-methyl imidazole
bpy	2,2′-bipyridine
Cbl	cobalamin
Cat	catalase
cGMP	cyclic guanylyl monophosphate
Cyt	cytochrome *c*
dmg	dimethylglyoximato
dmp	2,9-dimethyl-1,10-phenanthroline
DMSO	dimethyl sulfoxide
EDRF	endothelium-derived relaxation factor
ESR	electron spin resonance
FTIR	Fourier transform infrared
GTP	guanylyl triphosphate
Hb	ferro-hemoglobin
HOMO	highest occupied molecular orbital

IR	infrared
LUMO	lowest unoccupied molecular orbital
Mb	ferro-myoglobin
MCPH	monochelated protoheme
metHb	ferri-hemoglobin or met-hemoglobin
MLCT	metal to ligand charge transfer
metMb	ferri-myoglobin or metmyoglobin
NHE	normal hydrogen electrode
NOS	nitric oxide synthase
NP	nitroprusside ion
OBTPP	octabromotetraphenylporphine
OEP	octaethylporphine
Pc	phthalocyaninato
phen	1,10-phenanthroline
Por	"generic" porphyrinato ligand
PPIX	protoporphyrin IX
RSNO	generic thionitrosyl
salen	*N*,*N*′-bis(salicylidenato)ethylenediamine
salophen	*N*,*N*′-1,2-phenylendiamine-bis(salicylidenimato)
SCE	standard calomel electrode
sGC	soluble guanylyl cyclase
STP	standard temperature and pressure
TMPS	tetra(sulfonatomesityl)porphyrin
TmTP	tetra-*m*-tolylporphyrin
Tp^{R2}	tris(3-(R^2)-5-methylpyrazol-1-yl)hydroborate
tpa	tris[(2-pyridyl)methyl]amine
TpivPP	picket fence porphyrin (α,α,α,α-tetrakis(*o*-pivalanidophenyl)porphinato)
TPP	meso-tetraphenylporphyrin
TPPS	tetra(4-sulfonatophenyl)porphine
UV−Vis	ultraviolet−visible

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VIII. References

(1) (a) Moncada, S.; Palmer, R. M. J.; Higgs, E. A. *Pharmacol. Rev.* **1991**, *43*, 109. (b) Feldman, P. L.; Griffith, O. W.; Stuehr, D. J. *Chem. Eng. News* **1993**, *71* (10), 26. (c) Butler, A. R.; Williams, D. L. *Chem. Soc. Rev.* **1993**, 233. (d) *Methods in Nitric Oxide Research*; Feelisch M., Stamler, J. S., Eds.; John Wiley and Sons: Chichester, England, 1996 and references therein. (e) Wink, D. A.; Hanbauer, I.; Grisham, M. B.; Laval, F.; Nims, R. W.; Laval, J.; Cook, J.; Pacelli, R.; Liebmann, J.; Krishna, M.; Ford, P. C.; Mitchell, J. B. *Curr. Top. Cell. Regul.* **1996**, *34*, 159.

(2) *Nitric Oxide: Biology and Pathobiology*; Ignarro, L. J., Ed.; Academic Press: San Diego, 2000.

(3) Schwartz, S. E.; White, W. H. *Trace Atmospheric Constitutents. Properties, Transformation and Fates*; J. Wiley & Sons: New York, 1983.

(4) *Nitric Oxide and Infection*; Fang, F. C., Ed.; Kluwer Academic/Plenum Publishers: New York, 1999.

(5) (a) Traylor, T. G.; Sharma, V. S. *Biochemistry* **1992**, *31*, 2847. (b) Radi, R. *Chem. Res. Toxicol.* **1996**, *9*, 828.

(6) (a) Kim, S.; Deinum, G.; Gardner, M. T.; Marletta, M. A.; Babcock, G. T. *J. Am. Chem. Soc.* **1996**, *118*, 8769 and references therein. (b) Burstyn, J. N.; Yu, A. E.; Dierks, E. A.; Hawkins, B. K.; Dawson, J. H. *Biochemistry* **1995**, *34*, 5896.

(7) (a) Minamiyama, Y.; Takemura, S.; Imaoka, S.; Funae, Y.; Tanimoto, Y.; Inoue, M. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 1479. (b) Cleeter, M. W. J.; Cooper, J. M.; Darley-Usmar, V. M.; Moncada, S.; Scapira, A. H. V. *FEBS Lett.* **1994**, *345*, 50.

(8) (a) Noguchi, T.; Hoshino, M.; Tsujimura, M.; Odaka, M.; Inoue, Y.; Endo, I. *Biochemistry* **1996**, *35*, 16777. (b) Odaka, M.; Fujii, K.; Hoshino, M.; Noguchi, T.; Tsujimura, M.; Nagashima, S.; Yohda, M.; Nagamune, T.; Inoue, Y.; Endo, I. *J. Am. Chem. Soc.* **1997**, *119*, 3785. (c) Tsujimura, M.; Dohmae, N.; Odaka, M.; Chijimatsu, M.; Takio, K.; Yohda, M.; Hoshino, M.; Nagashima, S.; Endo, I. *J. Biol. Chem.* **1997**, *272*, 29454.

(9) Brown, G. C. *Eur. J. Biochem.* **1995**, *232*, 188.

(10) Abu-Soud, H. M.; Khassawneh, M. Y.; Sohn, J.-T.; Murray, P.; Haxhiu, M. A.; Hazen, S. L. *Biochemistry* **2001**, *40*, 11866.

(11) (a) Ribiero, J. M. C.; Hazzard, J. M. H.; Nussenzveig, R. H.; Champagne, D. E.; Walker, F. A. *Science* **1993**, *260*, 539. (b) Walker, F. A.; Ribiero, J. M. C.; Monfort, W. R. *Metal Ions in the Biological System*; Sigel, H., Sigel, A., Eds.; M. Dekker: New York, 1998; Vol. 36, p 621.

(12) (a) Tayeh, M. A.; Marletta, M. A. *J. Biol. Chem.* **1989**, *264*, 19654. (b) Abu-Soud, H. M.; Ichimori, K.; Nakazawa, H.; Stuehr, D. J. *Biochemistry* **2001**, *40*, 6876. (c) Stuehr, D.; Pou, S.; Rosen, G. M. *J. Biol. Chem.* **2001**, *276*, 14533 and references therein.

(13) Malinski, T.; Czuchajowski, C. *Methods in Nitric Oxide Research*; Feelisch M., Stamler, J. S., Eds.; John Wiley and Sons: Chichester, England, 1996; Chapter 22.

(14) (a) Eisenberg, R.; Meyer, C. D. *Acc. Chem. Res.* **1975**, *8*, 26. (b) McCleverty, J. A. *Chem. Rev.* **1979**, *79*, 53. (c) Bottomley, F. *React. Coord. Ligands* **1989**, *2*, 115. (d) Fanning, J. C. *Coord. Chem. Rev.* **1991**, *110*, 235. (e) Richter-Addo, G. B.; Legzdins, P. *Metal Nitrosyls*; Oxford University Press: New York, 1992. (f) Westcott, B. L.; Enemark, J. H. In *Inorganic Electronic Structure and Spectroscopy*; Solomon, E. I., Lever, A. B. P., Eds.; John Wiley & Sons: New York, 1999; Vol. 2, p 403. (g) Cheng, L.; Richter-Addo, G. B. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2000; Vol. 4, Chapter 33. (h) Greenwood, N. N. Earnshaw *Chemistry of the Elements*; Pergamon Press: Oxford, 1993; p 508. (i) Mingos, D. M. P.; Sherman, D. J. *Adv. Inorg. Chem.* **1989**, *34*, 293. (j) Bonner, F. T.; Stedman, G. *Methods in Nitric Oxide Research*; Feelisch M., Stamler, J. S., Eds.; John Wiley and Sons: Chichester, England, 1996; Chapter 1.

(15) Laane, J.; Ohlsen, J. R. *Prog. Inorg. Chem.* **1980**, *27*, 465.

(16) Lorkovic, I. Unpublished observations.

(17) *CRC Handbook of Chemistry and Physics*, 73rd ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, 1993.

(18) Dkhissi, A.; Soulard, P.; Perrin, A.; Lacome, N. *J. Mol. Spectrosc.* **1997**, *183*, 12.

(19) Forte, E.; Van Den Bergh, H. *Chem. Phys.* **1978**, *30*, 325.

(20) Scott, R. L. *Mol. Phys.* **1966**, *11*, 399.

(21) (a) McKellar, A. R. W.; Watson, J. K. G.; Howard, B. J. *Mol. Phys.* **1995**, *86*, 273. (b) Kukolich, S. G. *J. Am. Chem. Soc.* **1982**, *104*, 4715.

(22) Dinerman, C. E.; Ewing, G. E. *J. Chem. Phys.* **1970**, *53*, 626.

(23) Billingsley, J.; Callear, A. B. *Trans. Faraday Soc.* **1970**, *67*, 589.

(24) (a) Dean, J. A. *Lange's Handbook of Chemistry*, 13th ed.; McGraw-Hill Book Company: New York, 1985. (b) Armor, J. N. *J. Chem. Eng. Data* **1974**, *19*, 84. (c) *IUPAC Solubility Series: Oxides of Nitrogen*; Young, C. L., Ed.; Pergamon Press: Oxford, U.K., 1983.

(25) (a) Gally, J. A.; Montague, P. R.; Reeke, G. N.; Edelman, G. M. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 3547. (b) Lancaster, J. R., Jr. *Nitric Oxide, Biol. Chem.* **1997**, *1*, 18.

(26) Stanbury, D. M. *Adv. Inorg. Chem.* **1989**, *33*, 69.

(27) Lee, K. Y.; Kuchynka, D. J.; Kochi, J. K. *Inorg. Chem.* **1990**, *29*, 4196.

(28) examples are (a) Fukuto, J. M.; Hobbs, A. J.; Ignarro, L. J. *Biochem. Biophys. Res. Commun.* **1993**, *196*, 707. (b) Schmidt, H. H. H. W.; Hofmann, H.; Schindler, U.; Shutenko, Z. S.; Cunningham, D. D.; Feelisch, M. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14492. (c). DeMastter, E. G.; Redfern, B.; Nagasawa, H. T. *Biochem. Pharmacol.* **1998**, *55*, 20007. (d) Hughes, M. N. *Biochim. Biophys. Acta-Bioenergetics* **1999**, *1411*, 263. (e) Chazotte-Aubert, L.; Oikawa, S.; Gilibert, I.; Bianchini, F.; Kawanishi, S.; Ohshima, H. *J. Biol. Chem.* **1999**, *274*, 20909. (f) Ellis, A.; Li, C.; Rand, M. J. *Br. J. Pharm* **2000**, *129*, 315. (g) Xu, Y. P.; Alavanja, M. M.; Johnson, V. L.; Yasaki, G.; King, S. B. *Tetrahedron Lett.* **2000**, *41*, 4265. (h) Miranda, K. M.; Espey, M. G.; Yamada, K.; Krishna, M.; Ludwick, N.; Kim, S.; Jourd'heuil, D.; Grisham, M. B.; Feelisch, M.; Fukuto, J. M.; Wink, D. A. *J. Biol. Chem.* **2001**, *276*, 1720. (i) Bartberger, M. D.; Fukuto, J. M.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 2194. (j) Fukuto, J. M. Private communication.

(29) Wayland, B. B.; Olson, L. W *J. Am. Chem. Soc.* **1974**, *96*, 6037.

(30) Ohlsen, J. R.; Laane, J. *J. Am. Chem. Soc.* **1978**, *100*, 6948.

(31) (a) Hughes, E. E. J. *Chem. Phys.* **1961**, *35*, 1531. (b) Norton, J. R.; Collman, J. P.; Dolcetti, G.; Robinson, W. T. *Inorg. Chem.* **1972**, *11*, 382. (c) Bonner, F. T.; Pearsall, K. A. *Inorg. Chem.* **1982**, *21*, 1973. (d) Ellison, M. K.; Schulz, C. E.; Scheidt, W. R. *Inorg. Chem.* **1999**, *38*, 100. (e) Lorkovic, I.; Ford, P. C. *Inorg. Chem.* **2000**, *39*, 632.

(32) Shaw, A. W.; Vosper, A. J. *J. Chem. Soc. A* **1971**, 1592.

(33) Davis, K. M.; Wink, D. A.; Saavedra, J. E.; Keefer, L. K. *J. Am. Chem. Soc.* **2001**, *123*, 5473 and references therein.

(34) (a) Fitzhugh, A. L.; Keefer, L. K. *Free Radical Biol. Med.* **2000**, *28*, 1463−1469. (b) Keefer, L. K. *Pharm. News* **2000**, *7*, 27.

(35) (a) Enemark, J. H.; Feltham, R. D. *J. Am. Chem. Soc.* **1974**, *96*, 5002. (b) Feltham, R. D.; Enemark, J. H. *Top. Stereochem.* **1981**, *12*, 155.

(36) (a) Fomitchev, D. V.; Furlani, T. R.; Coppens, P. *Inorg. Chem.* **1998**, *37* 1519. (b) Fomitchev, D. V.; Novozhilova, I.; Coppens, P. *Tetrahedron* **2000**, *56*, 6813. (c) Cheng, L.; Novozhilova, I.; Kim, C.; Kovalevsky, A.; Bagley, K. A.; Coppens, P.; Richter-Addo, G. B. *J. Am. Chem. Soc.* **2000**, *122*, 7142. (d) Fomitchev, D. V.; Coppens, P.; Li, T. S.; Bagley, K. A.; Chen, L.; Richter-Addo, G. *Chem. Commun.* **1999**, 2013.

(37) (a) Carducci, M. D.; Pressprich, M. R.; Coppens, P. *J. Am. Chem. Soc.* **1997**, *119*, 2669. (b) Kim, C.; Novozhilova, I.; Goodman, M. S.; Bagley, K. A.; Coppens, P. *Inorg. Chem.* **2000**, *39*, 5791.

(38) Scheidt, W. R.; Hoard, J. L. *J. Am. Chem. Soc.* **1973**, *95*, 8281.

(39) Piciulo, P. L.; Rupprecht, G.; Scheidt, W. R. *J. Am. Chem. Soc.* **1974**, *96*, 5293.

(40) (a) Scheidt, W. R.; Lee, Y. J.; Hatano, K. *J. Am. Chem. Soc.* **1984**, *106*, 3191. (b) Scheidt, W. R.; Duval, H. F.; Neal, T.; Ellison, M. K. *J. Am. Chem. Soc.* **2000**, *122*, 4651. (c) Scheidt, W. R.; Hatano, K.; Rupprecht, G. A.; Piciulo, P. L. *Inorg. Chem.* **1979**, *18*, 292.

(41) (a) Scheidt, W. R.; Frisse, M. E. *J. Am. Chem. Soc.* **1975**, *97*, 17. (b) Scheidt, W. R.; Brinegar, A. C.; Ferro, E. B.; Kerner, J. F. *J. Am. Chem. Soc.* **1977**, *99*, 7315.

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

(43) Deatherage, J. F.; Moffat, K. *J. Mol. Biol.* **1979**, *134*, 401.

(44) (a) Scheidt, W. R.; Piciulo, L. *J. Am. Chem. Soc.* **1976**, *98*, 1913. (b) Nasri, H.; Ellison, M. K.; Chen, S.; Huynh, B. H.; Scheidt, W. R. *J. Am. Chem. Soc.* **1997**, *119*, 6274. (c) Scheidt, W. R.; Ellison, M. K. *Acc. Chem. Res.* **1999**, *32*, 350.

(45) Richter-Addo, G. B.; Wheeler, R. A.; Hixson, C. A.; Chen, L.; Khan, M. A.; Ellison, M. K.; Schulz, C. E.; Scheidt, W. R. *J. Am. Chem. Soc.* **2001**, *123*, 6314.

(46) (a) Mingos, D. M. P.; Sherman, D. J. *Adv. Inorg. Chem.* **1989**, *34*, 293. (b) Manoharan, P. T.; Gray, H. B. *Inorg. Chem.* **1966**, *5*, 823. (c) Collman, J. P.; Farnham, P.; Dolcetti, G. *J. Am. Chem. Soc.* **1971**, *93*, 1788.

(47) Hoffmann, R.; Chen, M. M. L.; Elian, M.; Rossi, A. R.; Mingos, D. M. P. *Inorg. Chem.* **1974**, *13*, 2666.

(48) (a) Dierks, E. A.; Hu, S.; Vogel, K. M.; Yu, A. E.; Sprio, T. G.; Burstyn, J. N. *J. Am. Chem. Soc.* **1997**, *119*, 7316. (b) Reynolds, M. F.; Burstyn, J. N. *Nitric Oxide: Biology and Pathobiology*; Ignarro, L. J., Ed.; Academic Press: San Diego, 2000; Chapter 25.

(49) (a) Kini, A. D.; Washington, J.; Kubiak, C. P.; Morimoto, B. H. *Inorg. Chem.* **1996**, *35*, 6904. (b) Richter-Addo, G. B.; Hodge, S. J.; Yi, G.-B.; Khan, M. A.; Ma, T.; Van Caemelbecke, E.; Guo, N.; Kadish, K. M. *Inorg. Chem.* **1996**, *35*, 6530. (c) Kadish, K. M.; Mu, X. H.; Lin, X. Q. *Inorg. Chem.* **1988**, *27*, 1489. (d) Citra, A.; Andrews, L. *J. Phys. Chem. A* **2000**, *104*, 11897. (e) Wang, X.; Zhou, M.; Andrews, L. *J. Phys. Chem. A* **2000**, *104*, 10104. (f) Mu, X. H.; Kadish, K. M. *Inorg. Chem.* **1988**, *27*, 4720−4725. Mu, X. H.; Kadish, K. M. *Inorg. Chem.* **1990**, *29*, 1031.

(50) Wayland, B. B.; Olson, L. W.; Siddiqui, Z. U. *J. Am. Chem. Soc.* **1976**, *98*, 94.

(51) Hoffman, B. M.; Weschler, C. J.; Basolo, F. *J. Am. Chem. Soc.* **1976**, *98*, 5473.

(52) Konishi, S.; Hoshino, M.; Imamura, M. *J. Phys. Chem.* **1982**, *86*, 1412.

(53) Hoshino, M.; Konishi, S. *Chem. Phys. Lett.* **1982**, *86*, 228.

(54) Wayland, B. B.; Olson, L. W. *J. Am. Chem. Soc.* **1974**, *95*, 6037.

(55) Kon, H. *Biochim. Biophys. Acta* **1975**, *379*, 103.

(56) Yoshimura, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2819.

(57) Palmer, G. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1979; Vol. IV, Chapter 6.

(58) Kon, H.; Kataoka, N. *Biochemistry* **1969**, *8*, 4757.

(59) Gouterman, M. *J. Mol. Spectrosc.* **1961**, *6*, 138. Also in *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. III, Chapter 1.

(60) (a) Gorelski, S. I.; da Silva, S. C.; Lever, A. B. P.; Franco, D. W. *Inorg. Chim. Acta* **2000**, *300*−*302*, 698. (b) Gomes, C. U.; Davanzo, C. U.; da Silva, S. C.; Franco, D. W. *J. Chem. Soc., Dalton Trans.* **1998**, 601. (c) McGarvey, B. R.; Ferro, A. A.; Tfouni, E.; Bezerra, C. W.; Bagatin, I.; Franco, D. W. *Inorg. Chem.* **2000**, *39*, 3577. (d) Tfouni, E.; Krieger, M.; McGarvey, B. R.; Franco, D. W. submitted, Private communication from E. Tfouni.

(61) (a) Armor, J. N.; Scheidegger, H. A.; Taube, H. *J. Am. Chem. Soc.* **1968**, *90*, 5928. (b) Armor, J. N.; Pell, S. D. *J. Am. Chem. Soc.* **1973**, *95*, 7625.

(62) (a) Works, C. F.; Ford, P. C. *J. Am. Chem. Soc.* **2000**, *122*, 7592. (b) Works, C. F. Ph.D. Dissertation, University of California at Santa Barbara 2001.

(63) e.g., (a) Moore, E. G.; Gibson, Q. H. *J. Biol. Chem.* **1976**, *251*, 2788. (b) Tamura, M.; Kobayashi, K.; Hayashi, K. *FEBS Lett.* **1978**, *88*, 124. (c) Rose, E. J.; Hoffman, B. M. *J. Am. Chem. Soc.* **1983**, *105*, 2866. (d) Hoshino, M.; Laverman, L.; Ford, P. C. *Coord. Chem. Rev.* **1999**, *187*, 75 and references therein.

(64) (a) Laverman, L. E.; Ford, P. C. *Chem. Commun.* **1999**, 1843. (b) Laverman, L. E.; Hoshino, M.; Ford, P. C. *J. Am. Chem. Soc.* **1997**, *119*, 12663. (c) Laverman, L. E.; Ford, P. C. *J. Am. Chem. Soc.* **2001**, *123*, 11614.

(65) Hoshino, M.; Ozawa, K.; Seki, H.; Ford, P. C. *J. Am. Chem. Soc.* **1993**, *115*, 9568.

(66) Laverman, L. E.; Wanat, A.; Oszajca, J.; Stochel, G.; Ford, P. C.; van Eldik, R. *J. Am. Chem. Soc.* **2001**, *123*, 285.

(67) (a) Abu-Soud, H. M.; Ichimori, K.; Presta, A.; Stuehr, D. J. *J. Biol. Chem.* **2000**, *275*, 17349. (b) Scheele, J. S.; Bruner, E.; Kharitonov, V. G.; Martásek, P.; Roman, L. J.; Masters, B. S.; Sharma, V. S.; Magde, D. *J. Biol. Chem.* **1999**, *274*, 13105.

(68) Andersen, J. F.; Ding, X. D.; Balfour, C.; Shokhireva, T. K.; Champagne, D. E.; Walker, F. A.; Montfort, W. R. *Biochemistry* **2000**, *39*, 10118.

(69) (a) Olson, J. S.; Phillips, G. N. *J. Biol. Chem.* **1996**, *271*, 17593. (b) Ikeda-Saito, M.; Dou, Y.; Yonetani, T.; Olson, J. S.; Li, T.; Regan, R.; Gibson, Q. H. *J. Biol. Chem.* **1993**, *268*, 6855.

(70) (a) Sharma, V. S.; Magde, D. *Methods−Comput. Methods Enzymol.* **1999**, *19*, 494. (b) Kharitonov, V. G.; Russwurm, M.; Madge, D.; Sharma, V. S.; Koesling, D. *Biochem. Biophys. Res. Commun.* **1997**, *239*, 284.

(71) Takano, T.; Kallai, O. B.; Swanson, R.; Dickerson, R. E. *J. Biol. Chem.* **1973**, *248*, 5244

(72) Bellamy, T. C.; Garthwaite, J. *J. Biol. Chem.* **2001**, *276*, 4287.

(73) (a) Bohle, D. S.; Hung, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 9584. (b) Bohle, D. S.; Debrunner, P.; Fitzgerald, J. P.; Hansert, B.; Hung, C.-H.; Thomson, A. J. *Chem. Commun.* **1997**, 91.

(74) Ostrich, I. J.; Gordon, L.; Dodgen, H. W.; Hunt, J. P. *Inorg. Chem.* **1980**, *19*, 619.

(75) Schneppensieper, T.; Zahl, A.; van Eldik, R. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1678.

(76) (a) Frauenfelder, H.; McMahon, B. H.; Austin, R. H.; Chu, K.; Groves, J. T. *Proc. Natl. Acad. Sci., U.S.A.* **2001**, *98*, 2370. (b) Cao, W.; Christian, J. F.; Champion, P. M.; Rosca, F.; Sage, J. T. *Biochemistry* **2001**, *40*, 5728.

(77) Hoshino, M.; Kogure, M. *J. Phys. Chem.* **1989**, *93*, 5478.

(78) Hoshino, M.; Nagashima, Y.; Seki, H.; De Leo, M.; Ford, P. C. *Inorg. Chem.* **1998**, *37*, 2464.

(79) Traylor, T. G.; Luo, J.; Simon, J. A.; Ford, P. C. *J. Am. Chem. Soc.* **1992**, *114*, 4340.

(80) Caldin, E. *Fast Reactions in Solution*; J. Wiley and Sons: New York, 1964.

(81) Glasstone, S.; Laidler, K. J.; Eyring, H. *The Theory of Rate Processes*; McGraw-Hill: New York, 1941.

(82) Barley, M. H.; Takeuchi, K. J.; Meyer, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 5876.

(83) (a) Swinehart, J. H. *Coord. Chem. Rev.* **1967**, *2*, 385. (b) Swinehart, J. H.; Rock, P. A. *Inorg. Chem.* **1966**, *5*, 573. (c) Olabe, J. A.; Gentil, L. A.; Rigotti, G.; Navaza, A. *Inorg. Chem.* **1984**, *23*, 4297. (d) Baraldo, L. M.; Bessega, M. A.; Rigotti, G. E.; Olabe, J. A. *Inorg. Chem.* **1994**, *33*, 5890.

(84) (a) Chen, Y.; Lin, F.-T.; Shepherd, R. E. *Inorg. Chem.* **1999**, *38*, 973, and references therein. (b) Reed, C. A.; Roper, W. R. *J. Chem. Soc., Dalton Trans.* **1972**, 1243. (c) Maciejowska, I.; Stasicka, Z.; Stochel, Z.; van Eldik, R. *J. Chem. Soc., Dalton Trans.* **1999**, 3643. (d) Douglas, P. G.; Feltham, R. D. *J. Am. Chem. Soc.* **1972**, *94*, 5254. (e) Toma, H. E.; Silva, D. de O.; Saika, J. J. *J. Chem. Res.* **1996**, 456.

(85) (a) Ford, P. C.; Rokicki, A. *Adv. Organomet. Chem.* **1988**, *28*, 139. (b) Angelici, R. J. *Acc. Chem. Res.* **1972**, *5*, 335.

(86) Baran, E. J.; Muller, A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 890.

(87) (a) Butler, A. R.; Calsy-Harrison, A. M.; Glidewell, C.; Sorensen, P. E. *Polyhedron* **1988**, *7*, 1197. (b) Szacilowski, K.; Stochel, G.; Stasicka, Z.; Kisch, H. *New J. Chem.* **1997**, *21*, 893.

(88) Kruszyna, H.; Kruszyna, R.; Rochelle, L. G.; Smith, R. P.; Wilcox, D. E. *Biochem. Pharmacol.* **1993**, *46*, 95.

(89) (a) Maciejowska, I.; Stasicka, Z.; Stochel, G.; van Eldik, R. *J. Chem. Soc., Dalton Trans.* **1999**, 3643. (b) Katz, N. E.; Blesa, M. A.; Olabe, J. A.; Aymonino, P. J. *J. Inorg. Nucl. Chem.* **1980**, *42*, 581.

(90) (a) Kathò, Á.; Bodi, Z.; Dozsa, L.; Beck, M. T. *Inorg. Chim. Acta* **1984**, *83*, 145. (b) Dozsa, L.; Kormos, V.; Beck, M. T. *Inorg. Chim. Acta* **1984**, *82* (1), 69.

(91) Kathò, Á.; Beck, M. T. *Inorg. Chim. Acta* **1988**, *154*, 99.

(92) Chevalier, A. A.; Gentil, L. A.; Amorebieta, V. T.; Gutiérrez, M. M.; Olabe, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 11238.

(93) March, J. *Advanced Organic Chemistry*; John Wiley and Sons: New York, 1992.
(94) Beck, W.; Smedal, H. S. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 253.
(95) Bowden, W. L.; Little, William F.; Meyer, T. J. *J. Am. Chem. Soc.* **1977**, *99*, 4340.
(96) Mu, X. H.; Kadish, K. M. *Inorg. Chem.* **1988**, *27*, 4720.
(97) (a) Keilin, D.; Hartree, E. F. *Nature* **1937**, *139*, 548. (b) Ehrenberg, A.; Szczepkowski, T. W. *Acta Chem. Scand.* **1960**, *14*, 1684. (c) Gwost, D.; Caulton, K. G. *J. Chem. Soc., Chem. Commun.* **1973**, 64. Gwost, D.; Caulton, K. G. *Inorg. Chem.* **1973**, *12*, 2095. (d) Yoshimura, T.; Suzuki, S.; Nakahara, A.; Iwasaki, H.; Masuko, M.; Matsubara, T. *Biochemistry* **1986**, *25*, 2436.
(98) (a) Chien, J. C. W. *J. Am. Chem. Soc.* **1969**, *91*, 2166. (b) Addison, A. W.; Stephanos, J. J. *Biochemistry* **1986**, *25*, 4104. (c) Rogers, K. R.; Lukat-Rogers, G. S. *J. Biol. Inorg. Chem.* **2000**, *5*, 642.
(99) Hoshino, M.; Maeda, M.; Konishi, R.; Seki, H.; Ford, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 5702.
(100) Reichenbach, G.; Sabatini, S.; Palombari, R.; Palmerini, C. A. *Nitric Oxide* **2001**, *5*, 395.
(101) Fernandez, B.; Ford, P. C. Studies in progress.
(102) Grundy, K. R.; Reed, C. A.; Roper, W. R. *Chem. Commun.* **1971**, 1501.
(103) Wilson, R. B.; Ibers, J. A. *Inorg. Chem.* **1979**, *18*, 336.
(104) (a) Enemark, J. H.; Feltham, R. D.; Rikker-Nappier, J.; Bizot, K. F. *Inorg. Chem.* **1975**. *14*, 624. (b) Stevens, R. E.; Guettler, R. D.; Gladfelter, W. L. *Inorg. Chem.* **1990**, *29*, 451. (c) Legzdins, P.; Nurse, C. R.; Rettig, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 3727. Sharp, W. B.; Legzdins, P.; Patric, B. O. *J. Am. Chem. Soc.* **2001**, *123*, 8144.
(105) (a) Lançon, D.; Kadish, K. M. *J. Am. Chem. Soc.* **1982**, *104*, 2042. (b) Liu, Y. M.; Desilva, C.; Ryan, M. D. *Inorg. Chim. Acta* **1997**, *258*, 247. (c) Liu, Y.; Ryan, M. D. *J. Electroanal. Chem.* **1994**, *368*, 201.
(106) (a) Bayachou, M.; Lin, R.; Cho, W.; Farmer, P. J. *J. Am. Chem. Soc.* **1998**, *102*, 9888. (b) Lin, R.; Farmer, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 2393.
(107) Tovrog, B. S.; Diamond, S. E.; Mares, F.; Szalkiewicz, A. *J. Am. Chem. Soc.* **1981**, *103*, 3522.
(108) (a) Wink, D. A.; Mitchell, J. B. *Free Radical Biol. Med.* **1998**, *25*, 434. (b) Wink, D. A.; Hanbauer, I.; Krishna, M. C.; DeGraff, W.; Gamson, J.; Mitchell, J. B. *Proc. Natl. Acad. Sci., U.S.A.* **1993**, *90*, 9813. (c) Kagan, V. E.; Kozlov, A. V.; Tyurina, Y. Y.; Shvedova, A. A.; Yalowich, J. C. *Antioxid. Redox Signaling* **2001**, *3*, 189.
(109) (a) Betteridge D. *J. Metab.: Clin. Exp.* **2000**, *49*, 3. (b) Sies, H. *Dev. Cardiovasc. Med.* **2000**, *224*, 1. *Peroxidases in Chemistry and Biology*; Everse, J., Everse, K. E., Grisham, M. B., Eds.; CRC Press: Boston, 1991.
(110) Several values have been reported all close to 10^{10} M^{-1} s^{-1}. (a) Huie, R. E.; Padmaja, S. *Free Radical Res. Commun.* **1993**, *18*, 195. (b) Goldstein, S.; Czapski, G. *Free Radical Biol. Med.* **1995**, *34*, 4041. (c) Kissner, R.; Nauser, T.; Bougnon, P.; Lye, P. G.; Koppenol, W. H. *Chem. Res. Toxicol.* **1997**, *10*, 1285.
(111) (a) Wink, D. A.; Darbyshire, J. F.; Nims, R. W.; Saveedra, J. E.; Ford, P. C. *Chem. Res. Toxicol.* **1993**, *6*, 23. (b) Awad, H. H.; Stanbury, D. M. *Int. J. Chem. Kinet.* **1993**, *25*, 375.
(112) (a) Ford, P. C.; Wink, D. A.; Stanbury, D. M. *FEBS Lett.* **1993**, *326* 1. (b) Thomas, D. D.; Liu, X.; Kantrow, S. P.; Lancaster, J. R., Jr. *Proc. Natl. Acad. Sci., U.S.A.* **2001**, *98*, 355.
(113) (a) Miranda, K. M.; Espey, M. G.; Jourd'heuil, D.; Grisham, M. B.; Fukuto, J. M.; Feelisch, M.; Wink, D. A. *Nitric Oxide: Biology and Pathobiology*; Ignarro, L. J., Ed.; Academic Press: San Diego, 2000; Chapter 3 and references therein. (b) Wink, D. A.; Kasprzak, K. S.; Maragos, C. M.; Elsepuru, R. K.; Misra, M.; Dunams, T. M.; Cebula, T. A.; Koch, W. H.; Andrews, A. W.; Allen, J. S.; Keefer, L. K. *Science* **1991**, *254*, 1001. (c) Nguyen, T.; Brunson, D.; Crespi, C. L.; Penman, B. W.; Wishnok, J. S.; Tannenbaum, S. R. *Proc. Natl. Acad. Sci., U.S.A.* **1992**, *89*, 3030. (d) deRojas-Walker, T.; Tamir, S.; Ji, H.; Wishnok J. S.; Tannenbaum, S. R. *Chem. Res. Toxicol.* **1995**, *8*, 473.
(114) (a) Lewis, R. S.; Deen, W. M. *Chem. Res. Toxicol.* **1994**, *7*, 568. (b) Pires, M.; Ross, D. S.; Rossi, M. J. *Int. J. Chem. Kinet.* **1994**, *26*, 1207. (c) Kharitonov, V. G.; Sundquist, A. R.; Sharma, V. S. *J. Biol. Chem.* **1994**, *269*, 5881. (d) Goldstein, S.; Czapski, G. *J. Am. Chem. Soc.* **1995**, *117*, 12078.
(115) (a) Radi, R.; Denicola, A.; Ferrer-Sueta, G.; Rubbo, H. *Nitric Oxide: Biology and Pathobiology*; Ignarro, L. J., Ed.; Academic Press: San Diego, 2000; Chapter 4 and references therein. (b) Beckman, J. S.; Beckman, T. W.; Chen, J.; Marshall, P. A.; Freeman, B. A. *Proc. Natl. Acad. Sci., U.S.A.* **1990**, *87*, 1620.
(116) Nottingham, W. C.; Sutter, J. R. *Int. J. Chem. Kinet.* **1989**, *18*, 1289.
(117) Liu, X.; Miller, Mark J. S.; Joshi, M. S.; Thomas, D. D.; Lancaster, J. R., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 2175.
(118) (a) Doyle, M. P.; Hoekstra, J. W. *J. Inorg. Biochem.* **1981**, *14*, 351. (b) Feelisch, M. *Cardiovas. Pharmacol.* **1991**, *17*, S25.
(119) (a) Andersen, H. J.; Skibsted, L. H. *J. Agric. Food Chem.* **1992**, *40*, 1741. (b) Bruun-Jensen, L.; Skibsted, L. H. *Meat Sci.* **1996**, *44*, 145.
(120) (a) Greenberg, S. S.; Xie, J.; Zatariarn, J. M.; Kapusta, D. R.; Miller, M. J. S. *J. Pharmacol. Exp. Ther.* **1995**, *273*, 257. (b) Brouwer, M.; Chamulitrat, W.; Ferruzzi, G.; Sauls, D. L.; Weinberg, J. B. *Blood* **1996**, *88*, 1857. (c) Kruszyna, H.; Magyar, J. S.; Rochelle, L. G.; Russell, M. A.; Smith, R. P.; Wilcox, D. E. *J. Pharmacol. Exp. Ther.* **1998**, *285*, 665.
(121) (a) Wolak, M.; Stochel, G.; Hamza, M.; van Eldik, R. *Inorg. Chem.* **2000**, *39*, 2018. (b) Zheng, D.; Birke, R. L. *J. Am. Chem. Soc.* **2001**, *123*, 4637. (c) Wolak, M.; Zahl, A.; Schneppensieper, T.; Stochel, G.; van Eldik, R. *J. Am. Chem. Soc.* **2001**, *123*, 9780.
(122) (a) Gorren, A. C. F.; de Boer, E.; Wever, R. *Biochim. Biophys. Acta* **1987**, *916*, 38. (b) Torres, J.; Wilson, M. T. *Biochim. Biophys. Acta* **1999**, *1411*, 310.
(123) (a) *Bioinorganic Chemistry of Copper*; Karlin, K. D., Tyeklár, Z., Eds.; Chapman & Hall, Inc.: New York, 1993. (b) Averill, B. A. *Chem. Rev.* **1996**, *96*, 2951. (c) Halfen, J. A.; Mahapatra, S.; Wilkinson, E. C.; Gengenbach, A. J.; Young, V. G., Jr.; Que, L., Jr.; Tolman, W. B. *J. Am. Chem. Soc.* **1996**, *118*, 763.
(124) Firth, R. A.; Hill, H. A. O.; Pratt, J. M.; Williams, R. J. P. *J. Chem. Soc. A* **1969**, 381.
(125) Tran, D.; Shelton, B. W.; White, Al. H.; Laverman, L. E.; Ford, P. C. *Inorg. Chem.* **1998** *37*, 2505.
(126) Lei, Y.; Anson, F. C. *Inorg. Chem.* **1994**, *33*, 5003.
(127) Wolfe, S. K.; Swinehart, J. H. *Inorg. Chem.* **1994**, *33*, 5003.
(128) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891.
(129) See for example, *Environmental Catalysis*; Armor, J. M., Ed.; American Chemical Society: Washington, D.C., 1994; Vol. 552.
(130) (a) Berthelot, M. *Compt. Rend.* **1891**, *112*, 1243 (as cited in ref 130b). (b) Griffith, W. P.; Lewis, J.; Wilkinson, G. *J. Chem. Soc.* **1959**, 1775. (c) Booth, G.; Chatt, J. *J. Chem. Soc.* **1962**, 2099. (d) Feltham, R. D.; Carriel, J. T. *Inorg. Chem.* **1964**, *3*, 121.
(131) (a) Hughes, W. B. *J. Chem. Soc., Chem. Commun.* **1969**, 1126. (b) Gans, P. *J. Chem. Soc. A* **1967**, 943. (c) Rossi, M.; Sacco, A. *J. Chem. Soc., Chem. Commun.* **1971**, 694. (d) Gargano, M.; Giannoccaro, P.; Rossi, M.; Sacco, A.; Vasapollo, G. *Gazz. Chim. Ital.* **1975**, *105*, 1279. (e) Gwost, D.; Caulton, K. G. *Inorg. Chem.* **1974**, *13*, 414.
(132) Carrondo, M. A. A. F. de C. T.; Rudolf, P. R.; Skapski, A. C.; Thornback, J. R.; Wilkinson, G. *Inorg. Chim. Acta* **1977**, *24*, L95.
(133) (a) Werner, A.; Karrer, P. *Helv. Chim. Acta* **1918**, *1*, 54. (b) Feltham, R. D. *Inorg. Chem.* **1964**, *3*, 1038. (c) Hoskins, B. F.; Whillans, F. D.; Dale, D. H.; Hodgkin, D. C. *J. Chem. Soc., Chem. Commun.* **1969**, 69.
(134) Gans, P. *J. Chem. Soc. A* **1967**, 943.
(135) Gwost, D.; Caulton, K. G. *Inorg. Chem.* **1974**, *13*, 414.
(136) Miki, E. *Chem. Lett.* **1980**, 835. (b) Miki, E.; Ishimaru, K.; Mizumachi, K.; Ishimori, T.; Tanaka, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 962.
(137) (a) Ruggiero, C. E.; Carrier, S. M.; Tolman, W. B. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 895. (b) Schneider, J. L.; Carrier, S. M.; Ruggiero, C. E.; Young, V. G., Jr.; Tolman, W. B. *J. Am. Chem. Soc.* **1998**, *120*, 11408.
(138) Mahapatra, S. M.; Halfen, J. A.; Tolman, W. B. *J. Chem. Soc., Chem Commun.* **1994**, 1625.
(139) (a) Komeda, N.; Nagao, H.; Kushi, Y.; Adachi, G.; Suzuki, M.; Uehara, A.; Tanaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 581. (b) Tanaka, K.; Komeda, N.; Matsui, T. *Inorg. Chem.* **1991**, *30*, 3282.
(140) (a) Franz, K. J.; Lippard, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 9034. (b) Franz, K. J.; Lippard, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 10504.
(141) Miranda, K. M.; Bu, X.; Lorkovic, I. M.; Ford, P. C. *Inorg. Chem.* **1997**, *36*, 4838.
(142) (a) Kadish, K. M.; Adamian, V. A.; Caemelbecke, E. V.; Tan, Z.; Tagliatesta, P.; Bianco, P.; Boschi, T.; Yi, G.-B.; Khan, M. A.; Richter-Addo, G. B. *Inorg. Chem.* **1996**, *35*, 1343. (b) Bohle, D. S.; Goodson, P. A.; Smith, B. D. *Polyhedron* **1996**, *15*, 3147. (c) Yi, G.-B.; Khan, M. A.; Richter-Addo, G. B. *J. Chem. Soc., Chem. Commun.* **1996**, 2045. (d) Yi, G.-B.; Khan, M. A.; Richter-Addo, G. B. *Inorg. Chem.* **1996**, *35*, 3453. (f) Hodge, S. J.; Wang, L.-S.; Khan, M. A.; Young, V. G.; Richter-Addo, G. B. *J. Chem. Soc., Chem. Commun.* **1996**, 2283. (g) Bohle, D. S.; Hung, C.-H.; Smith, B. D. *Inorg. Chem.* **1998**, *37*, 5798.
(143) Leal, F.; Lorkovic, I.; Ford, P. C. Unpublished observations. Presented at the National Meeting of the American Chemical Society, San Diego, April 2001.
(144) Lorkovic, I. M.; Ford, P. C. *Inorg. Chem.* **1999**, *38*, 1467.
(145) Lorkovic, I. M.; Ford, P. C. *J. Chem. Soc., Chem. Commun.* **1998**, 1225.
(146) Lorkovic, I. M.; Miranda, K. M.; Lee, B.; Bernhard, S.; Schoonover, J. R.; Ford, P. C. *J. Am. Chem. Soc.* **1998**, *120*, 11674.
(147) (a) Yoshimura, T. *Inorg. Chem. Acta* **1984**, *83*, 17. (b) Settin, M. F.; Fanning, J. C. *Inorg. Chem.* **1988**, *27*, 1431. (c) Ellison, M.; Schulz, C. E.; Scheidt, W. R. *Inorg. Chem.* **1999**, *38*, 100. (d) Lin, R.; Farmer, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 1143.
(148) Lorkovic, I. M.; Ford, P. C. *Inorg. Chem.* **2000**, *39*, 632.
(149) Wayland, B. B.; Olson, L. W. *J. Am. Chem. Soc.* **1974**, *96*, 6037.

(150) Lançon, D.; Kadish, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 5610.
(151) Lorkovic, I. M.; Ford, P. C. *J. Am. Chem. Soc.* **2000**, *122*, 6516.
(152) Olson, L. W.; Schaeper, D.; Lançon, D.; Kadish, K. M. *J. Am. Chem. Soc.* **1982**, *104*, 2042.
(153) Göldner, M.; Geniffke, B.; Franken, A.; Murray, K. S.; Homborg, H. *Z. Anorg. Allg. Chem.* **2001**, *627*, 935.
(154) Johnson, B. F. G.; Bhaduri, S. *J. Chem. Soc., Chem. Commun.* **1973**, 650.
(155) Haymore, B. L.; Ibers, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 3325.
(156) Bhaduri, S.; Johnson, B. F. G.; Savory, C. J.; Segal, J. A.; Walter, R. H. *J. Chem. Soc., Chem. Commun.* **1974**, 809.
(157) (a) Reed, J.; Eisenberg, R. *Science* **1974**, *184*, 568. (b) Meyer, C. D.; Eisenberg, R. *J. Am. Chem. Soc.* **1976**, *98*, 1364.
(158) (a) Kaduk, J. A.; Tulip, T. H.; Budge, J. R.; Ibers, J. A. *J. Mol. Catal.* **1981**, *12*, 239. (b) Naito, S.; Tamaru, K. *Chem. Lett.* **1982**, 1833. (c) Fang, W. P.; Cheng, C. H. *J. Chem. Soc., Chem. Commun.* **1986** 503. (d) Lee, J. D.; Fang, W. P.; Li, C. S.; Chen, C. H. *J. Chem. Soc., Dalton Trans.* **1991**, 1923.
(159) Bhaduri, S. A.; Johnson, B. F. G. *J. Chem. Soc., Dalton Trans.* **1981**, 234.
(160) Kubota, M.; Evans, K. J.; Koerntgen, C. A.; Marsters, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 342.
(161) (a) Sun, K. S.; Cheng, C. H. *J. Chem. Soc., Chem. Commun.* **1988**, 209. (b) Cheng, C. H.; Sun, K. S. *Inorg. Chem.* **1990**, *29*, 2547. (c) Sun, K. S.; Kong, K. C.; Cheng, C. H. *Inorg. Chem.* **1991**, *30*, 1998.
(162) MacNeil, J. H.; Berseth, P. A.; Bruner, E. L.; Perkins, T. L.; Wadia, Y.; Westwood, G.; Trogler, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 1668.
(163) Clarkson, S. G.; Basolo, F. *Inorg. Chem.* **1973**, *12*, 1528.
(164) Trogler, W. C.; Marzilli, L. G. *Inorg. Chem.* **1974**, *13*, 1008.
(165) Kubota, M.; Phillips, D. A. *J. Am. Chem. Soc.* **1975**, *97*, 5637.
(166) See, e.g., Tovrog, B. S.; Diamond, S. E.; Mares, F. *J. Am. Chem. Soc.* **1979**, *101*, 270.
(167) Ugo, R.; Bhaduri, S.; Johnson, B. F. G.; Khair, A.; Pickard, A.; Benn-Taarit, Y. *J. Chem. Soc., Chem. Commun.* **1976**, 694.
(168) Chen, L.; Powell, D. R.; Khan, M. A.; Richter-Addo, G. B. *J. Chem. Soc., Chem. Commun.* **2000**, 2301.
(169) Ercolani, C.; Paoletti, A. M.; Pennisi, G.; Rossi, G. *J. Chem. Soc., Dalton Trans.* **1991**, 1317.
(170) (a) Andrews, M. A.; Chang, T. C.-T.; Cheng, C.-W.; Kelly, K. P. *Organometallics* **1984**, *3*, 1777. (b) Andrews, M. A.; Chang, T. C.-T.; Cheng, C.-W. *Organometallics* **1985**, *4*, 268. (c) Mares, F.; Diamond, S. E.; Regina, F. J.; Solar, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3545. (d) Muccigrosso, D. A.; Mares, F.; Diamond, S. E.; Solar, J. P. *Inorg. Chem.* **1983**, *22*, 960.
(171) Goodwin, J.; Bailey, R.; Pennington, W.; Rasberry, R.; Green, T.; Shasho, S.; Yongsavanh, M.; Echevarria, V.; Tiedeken, J.; Brown, C.; Fromm, G.; Lyerly, S.; Watson, N.; Long, A.; De Nitto, N. *Inorg. Chem.* **2001**, *40*, 4217.
(172) Taqui Khan, M. M.; Chatterjee, D.; Shirin, Z.; Bajaj, H. C.; Siddiqui, M. R. H.; Venkatasubramanian, K.; Bhadbhade, M. M. *J. Mol. Catal.* **1992**, *72*, 271.
(173) Bohle, D. S.; Hung, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 9584.
(174) See, for example, Carter, M. J.; Rillema, D. P.; Basolo, F. *J. Am. Chem. Soc.* **1974**, *96*, 392.
(175) Doyle, M. P.; Pickering, R. A.; Dykstra, R. L.; Cook, B. R. *J. Am. Chem. Soc.* **1982**, *104*, 3392.
(176) (a) Herold, S.; Matsui, T.; Watanabe, Y. *J. Am. Chem. Soc.* **2001** *123*, 4085. (b) Herold, S.; Exner, M.; Nauser, T. *Biochem*istry **2001**, *40*, 3385.
(177) DeLeo, M. A.; Ford, P. C. *J. Am. Chem. Soc.* **1999**, *121*, 1980.
(178) (a) Herold, S. *FEBS Lett.* **1998**, *439*, 85. (b) Herold, S.; Rehmann, F.-J. K. *J. Biol. Inorg. Chem.* **2001**, *6*, 543−555. Private communication from S. Herold.
(179) McCarthy, M. R.; Crevier, T. J.; Bennett, B.; Dehestani, A.; Mayer, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 12391.
(180) Moore, E. G.; Gibson, Q. H. *J. Biol. Chem.* **1976**, *251*, 2788.
(181) Casewit, C. J.; Rappe, A. K. *J. Catal.* **1984**, *89*, 250.
(182) Bhaduri, S.; Johnson, B. F. G.; Pickard, A.; Raithby, P. R.; Sheldrick, G. M.; Zuccaro, C. I. *J. Chem. Soc., Chem. Commun.* **1977**, 354.
(183) Wink, D. A.; Vodovotz, Y.; DeGraff, W., Cook, J. A.; Pacelli, R.; Krishna, M.; Mitchell, J. B. *Trace Atmospheric Constitutents. Properties, Transformation and Fates*; J. Wiley & Sons: New York, 1983; Chapter 9.
(184) (a) Howard-Flanders, P. *Nature (London)* **1957**, *180*, 1191−1192. (b) Mitchell, J. B.; Wink, D. A.; DeGraff, W.; Gamson, J. *Cancer Res.* **1993**, *53*, 5845. (c) Bourassa, J.; DeGraff, W.; Kudo, S.; Wink, D. A.; Mitchell, J. B.; Ford, P. C. *J. Am. Chem. Soc.* **1997**, *119*, 2853.
(185) Lim, M.; Lorkovic, I.; Ford, P. C. *Inorg. Chem.* **2002**, in press.
(186) Kroger-Ohlsen, M. V.; Skibsted, L. H. *Food Chem.* **2000**, *70*. 209.

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