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Review

Reaction mechanisms relevant to the formation of iron and ruthenium nitric oxide complexes

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Submitted in honor of Professor Henry Taube, mentor and friend

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Abstract

Presented here is a review of recent mechanistic work related to the formation of iron and ruthenium nitrosyl complexes. Given the importance of NO as a biological molecule and that the targets for NO in vivo are metal centers, knowledge of the mechanisms by which metal nitrosyls are formed is fundamental for understanding the diverse roles that NO plays in biology. The kinetics of metal nitrosyl formation from the reactions of free NO with metal complex precursors are dominated by the lability of the complexes. The free radical character of NO however, asserts itself especially if the precursors are relatively substitution inert or are coordinatively unsaturated.

Keywords: Nitric oxide; Reaction mechanisms; Ruthenium; Iron; Kinetics

Abbreviations: Cat, catalase; CytII, ferro-cytochrome *c*; CytIII, ferri-cytochrome *c*; edta, ethylenediaminetetraacetic acid; Hb, hemoglobin; MCPH, protohemin 3-(1-imadazoyl) propylamide stearyl ester; metMb, metmyoglobin; NOS, nitric oxide synthase; NP, nitroprusside; NPn, nitrophorin; nta, nitriloacetic acid; OEP, octaethylporphyrin; Por, porphyrin; PPIX, protoporphyrin IX; pz, pyrazine; RBS, Roussin's black salt; salen, *N*,*N*′-bis(salicylidene)ethylenediamine dianion; SCE, standard calomel electrode; sGC, soluble guanylyl cyclase; Sol, solvent; tBu_4salen, *N*,*N*′-ethylenebis(3,5-di-*t*-butlysalicylideneiminato) dianion; tBu_4salophen, *N*,*N*′-1,2-phenylenediamine-bis(3-*t*-butlysalicylideneiminato) dianion; TMPS, tetramesitylporphinato; TmTP, tetra(*meta*-tolyl)porphyrin; TPP, tetraphenylporphyrin; TPPS, tetra(4-sulfonato-phenyl)porphinato

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1. Introduction

Nitric oxide (nitrogen monoxide) is important to a wide variety of mammalian physiological processes [1,2], including blood pressure control, neurotransmission and immune response. Numerous disease states involving NO imbalances have been reported, although it is not always evident whether such imbalances are causal or symptomatic [2,3]. In this context, the reactions of NO with metal complexes are of particular interest since metal centers such as hemes are well established as targets for NO reactions in mammalian biology. Here, we present an overview of more recent developments involving the reactions leading to the formation of selected metal nitrosyl complexes.

NO is a stable free radical, and this feature is understandably a dominant theme in its chemistry and biochemistry. It reacts rapidly with other free radicals and with substitution labile, redox active metals, but it is not a strong one-electron oxidant or reductant. Its solubility and transport properties are similar to those of dioxygen [4,5]. Notably, its solubility in aqueous solution (1.9 mM atm^{-1} at 298 K and 1.4 mM atm^{-1} at 310 K [4]) is considerably less than in organic solvents (for example, 15.0 mM atm^{-1} in cyclohexane at 298 K). Thus in a heterogeneous environment such as a cell, NO would be expected to partition preferentially into hydrophobic regions.

The focus of this article will be the formation of metal nitrosyl complexes by the direct reaction of metal complexes with NO itself (Eq. (1)). However, it should be noted that metal nitrosyl bonds can also form by reaction with a nitric oxide precursor such as nitrite ion, alkyl nitrites or *S*-nitrosothiols [6] with a species such as HNO [7].

$$ML_nX + NO \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} ML_n(NO) + X \quad (1)$$

Coordinated NO can range in character (formally) from a nitrosyl cation (NO^+) to a nitroxyl anion (NO^-). The former is isoelectronic to CO with nearly linear M–N–O bonds and involves considerable charge transfer to the metal center. With the latter, charge transfer is in the opposite direction and a bond angle approaching 120° would be predicted. Between these two extremes would be the situation where NO binds to a 16 electron complex such as $Ru(H)(Cl)(CO)(NO)(PR_3)_2$. In this case it was concluded that NO is acting as a $2e^-$ donor with the unpaired e^- localized on the nitrosyl nitrogen [8]. The bonding of NO to metals was the subject of a generalized description by Feltham and Enemark [9]. These researchers proposed the $\{MNO\}^n$ formulation (where *n* is the sum of metal d-electrons and nitrosyl π* electrons) and used Walsh-type diagrams to predict M–N–O bond angles of ground state complexes. It should be noted that metastable complexes generated photochemically in low temperature solids display oxygen coordinated η^1-NO and η^2-NO structures [10,11]. Certain polynuclear complexes display bridging nitrosyls [12].

A key question to be asked when exploring formation of metal nitrosyl complexes is whether the free radical nature of NO leads to different substitution mechanisms than for other small diatomic ligands such as CO. Should the reactivity pattern be different from other small Lewis bases, given that the odd electron of NO resides in the π* orbital and may not be strongly involved until the M–NO bond is largely formed? As we will discuss in subsequent sections, there are examples where the kinetics of the bimolecular substitution (Eq. (1)) are dominated by the lability of ML_nX thus the nature of the incoming ligand is largely irrelevant. However, when considering the rates of metal–ligand bond formation from geminate pairs $\{ML_n,AB\}$, the situation is different. When such a species is formed, for example, by flash photolysis of a L_nM–AB complex, there are often significant reactivity differences between NO and CO. Furthermore, as described immediately below, kinetics data suggest that the radical nature of NO leads to associative substitution with the $4d^5$ ruthenium(III) ammine complex $Ru(NH_3)_6^{3+}$. Thus, there is a range of answers to the question posed above.

Nitric oxide is active as a diffusible signaling agent in blood pressure regulation and in nervous tissue. The concentrations present in the endothelial cells have been reported to be as high as 400 nM [13]; however, recent studies suggest that values as much as two orders of magnitude lower (4 nM) may represent true physiological conditions in tissue [13b]. In contrast, NO concentrations are much higher during episodes of immune response to pathogen invasions. Under these conditions other reactive nitrogen species such as peroxynitrite ($OONO^-$) and N_2O_3 may play important roles. The primary targets for NO in bioregulatory functions are metal centers, chiefly iron heme proteins [14]. The biological relevance of the "on" reaction in Eq. (1) is highlighted by noting that the activation of the ferro-heme enzyme soluble guanylyl cyclase (sGC), involves the formation of a nitrosyl complex where ML_nX is a Fe^{II}(PPIX) moiety (PPIX: protoporphyrin IX) [15]. Additional reports describe NO as an inhibitor for other metalloenzmes such as cytochrome P450 [16], cytochrome oxidase [17], catalase [18] and nitrile hydratase [19]. NO has also been shown to be a substrate for several peroxidase enzymes [20] and is responsible for the vasodilator properties of nitrophorins, which are salivary ferri-heme proteins found in certain blood sucking insects [21].

Fast reaction with its biological targets would be necessary for NO to serve as an effective regulatory agent at the sub-micromolar concentrations found in vivo. This is indeed the case for the reaction of NO with sGC for which $k_{on} = 1.4 \times 10^8\ M^{-1}\ s^{-1}$ (277 K) was measured [22]. Developing insight into the mechanisms of NO substitution reactions is key to understanding the diverse chemical biology of this seemingly simple molecule. For example, the low reactivity of ferro- and ferri-cytochrome *c* (Cyt^{II}, Cyt^{III}) toward NO can be attributed to occupation of the heme axial coordination sites by protein bound ligands [23]. As will be discussed below, NO requires a vacant or labile coordination

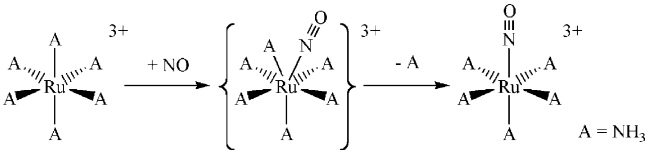
site for fast reaction with iron heme proteins and iron porphyrin model systems. Thus, unlike certain heme proteins where one axial site is unoccupied, reaction with Cyt^{II} and Cyt^{III} involves ligand displacement and a significant protein conformational change as well.

Knowledge of the "off" reactions is also important given that deactivation of sGC(NO) and the vasodilatory effects of nitrophorins must involve this step. NO release is also important during the biosynthesis of NO from the various forms of nitric oxide synthase (NOS) yet NO reacts rapidly with the heme centers in NOS ($k_{on} > 10^6\,M^{-1}\,s^{-1}$ [24]) and inhibits the enzyme [25]. Thus, the interplay between NO production and inhibition by forming nitrosyl species may be a self regulating mechanism of the enzyme.

2. Ruthenium(III) complexes

2.1. Ru(III) ammines

Until the discovery that NO is a mammalian bioregulatory agent, the only systematic mechanistic study of metal–NO bond formation involved the nitrosylation of the Ru(III) complex $Ru(NH_3)_6^{3+}$ to give $Ru(NH_3)_5NO^{3+}$ [26]. In 1969, Taube and co-workers [26a] reported the reaction to be second order (rate $= k_{NO}[Ru(NH_3)_6^{3+}][NO]$) with a rate constant $k_{NO} = 0.2\,M^{-1}\,s^{-1}$ (298 K) in acidic aqueous solution. Thus, NO displaced NH_3 at a rate greatly exceeding rates of substitution by ligands such as Cl^- or H_2O. In this context an associative mechanism was proposed, whereby the paramagnetic $4d^5$ Ru(III) center interacts with NO to give a seven coordinate intermediate $\{Ru(NH_3)_6(NO)^{3+}\}$ followed by loss of NH_3 to give the diamagnetic product $Ru(NH_3)_5(NO)^{3+}$ (Eq. (2)). Subsequently, Pell and Armor examined the temperature dependence and determined the activation enthalpy to be $36\,kJ\,mol^{-1}$ and the activation entropy to be $-138\,J\,K^{-1}\,mol^{-1}$ in acidic solution [26b]. The small $\Delta H^{\ddagger}$ and the large and negative $\Delta S^{\ddagger}$ are both consistent with the proposed associative mechanism.



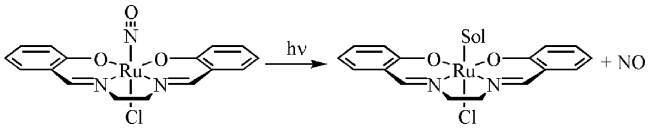
(2)

The kinetic behavior of this system was recently reexamined by Czap and van Eldik [27], who confirmed the general features of the earlier results ($k_{NO} = 0.30 \pm 0.01\,M^{-1}\,s^{-1}$ (299 K), $\Delta H^{\ddagger} = 41 \pm 2\,kJ\,mol^{-1}$ and $\Delta S^{\ddagger} = -114 \pm 7\,J\,mol^{-1}\,K^{-1}$). Furthermore, these researchers used hydrostatic pressure effects to determine a negative activation volume $\Delta V^{\ddagger} = -13.6 \pm 0.3\,cm^3\,mol^{-1}$, consistent with an associative mechanism. Similar activation parameters were determined for the reaction of NO with two other Ru(III) complexes $Ru(NH_3)_5(H_2O)^{3+}$ and $Ru(NH_3)_5Cl^{2+}$, the more labile H_2O and Cl^- being the ligands principally displaced [27]. It should be noted that in the Ru–NO product there has been considerable charge transfer from NO to Ru, so that the final product might be envisioned (formally) as having $Ru^{II}(NO^+)$ character [28]. This charge transfer has been proposed as a rationale for the ready loss of NH_3 from the intermediate in Eq. (2) [27]. Interestingly, a somewhat analogous seven-coordinate intermediate $[HRu(NH_3)_6^{3+}]$ was proposed by Taube and co-workers [29] as responsible for the acid catalyzed labilization of NH_3 from hexaammineruthenium(II) $Ru(NH_3)_6^{2+}$.

Entirely different products have been seen for the reaction of $Ru(NH_3)_6^{3+}$ with NO in alkaline solution [26b]. The sole ruthenium product was the dinitrogen complex $Ru(NH_3)_5(N_2)^{2+}$ and the rate law proved to be first order in $[Ru(NH_3)_6^{3+}]$, [NO] and $[OH^-]$. A likely mechanism is the reversible deprotonation of $Ru(NH_3)_6^{3+}$ to give $Ru(NH_3)_5(NH_2)^{2+}$, followed by electrophilic NO attack at the amido ligand to give the nitroso amine intermediate $Ru(NH_3)_5(NH_2NO)^{2+}$, which undergoes dehydration to the dinitrogen complex $Ru(NH_3)_5(N_2)^{2+}$. However, the kinetics evidence did not exclude other possible sequences.

2.2. Ruthenium(III) salen complexes

Several Ru(III) salen complexes of the type Ru^{III}(salen)(X)(NO) (X = Cl^-, ONO^-, H_2O; salen = *N*,*N*′-bis(salicylidene)ethylenediamine dianion) were prepared in this laboratory as possible precursors for NO delivery to biological targets [30]. Photoexcitation leads to NO labilization and the respective solvento species Ru^{III}(salen)(X)(Sol) (Eq. (3)). The kinetics of the reverse process, i.e. the reaction of NO with Ru^{III}(salen)(X)(Sol) to reform the nitrosyl complexes were studied as a function of the solvent (Sol) and of the reaction conditions. The reaction rates proved to be second order (first order in [NO]) and were dramatically dependent on the identity of the solvent. For Ru^{III}(salen)(Cl)(Sol) the rate constant k_{on} varied from $5 \times 10^{-4}\,M^{-1}\,s^{-1}$ in acetonitrile to $4 \times 10^{7}\,M^{-1}\,s^{-1}$ in toluene (298 K, X = Cl^-). The much slower rate in the more strongly donating solvent indicates that Ru^{III}–Sol bond breaking plays a rate-limiting role.



(3)

$$Ru(salen)(Cl)(Sol) + NO \xrightarrow{k_{on}} Ru(salen)(Cl)(NO) + Sol \quad (4)$$

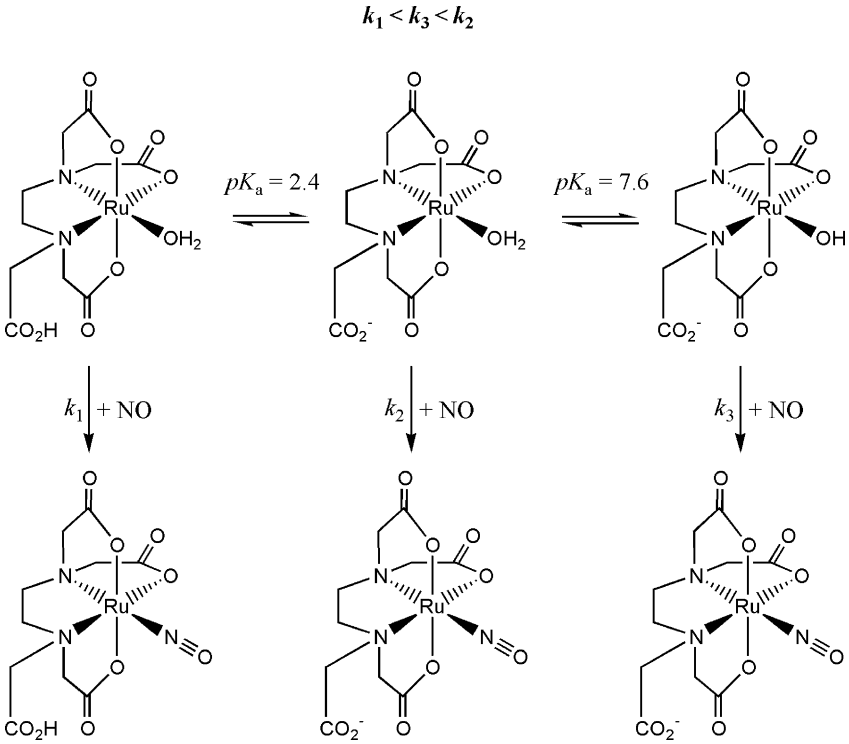
Activation parameters were measured for several reactions in toluene analogous to Eq. (4). Temperature dependence studies gave $\Delta H_{on}^{\ddagger}$ values of 34±2 and 20±1 kJ mol^{-1} and $\Delta S_{on}^{\ddagger}$ values of $+10 \pm 6$ and $-46 \pm 2\,J\,mol^{-1}\,K^{-1}$ for

Ru^{III}(tBu$_4$salen)(Cl)(Sol) and Ru^{III}(tBu$_4$salophen)(Cl)(Sol), respectively (tBu$_4$salen: *N*,*N*′-ethylenebis(3,5-di-*t*-butlysalicylideneiminato) dianion, tBu$_4$salophen: *N*,*N*′-1,2-phenylenediamine-bis(3-*t*-butlysalicylideneiminato) dianion) [30b]. Rates for the "on" reaction were determined as a function of hydrostatic pressure and $\Delta V_{on}^{\ddagger}$ values of $+22 \pm 2$ and $+16 \pm 2\,cm^3\,mol^{-1}$, respectively, were determined. These are quite different from the $\Delta V_{on}^{\ddagger}$ values recorded for the Ru(III) ammine complexes. Thus, rather than an associative mechanism, the kinetics of Eq. (4) would appear to be dominated by the lability of Sol. Not only does k_{on} vary by nearly 11 orders of magnitude depending upon the nature of Sol, but the large and positive values for $\Delta V_{on}^{\ddagger}$ in toluene indicate a ligand exchange mechanism dominated by dissociation of the Ru(III)–Sol bond prior to reaction with NO.

As a caveat it should be noted that $\Delta V_{on}^{\ddagger}$ values were not determined for the slow NO reactions of Ru(tBu$_4$salen)(Cl)(Sol) and Ru(tBu$_4$salophen)(Cl)(Sol) in acetonitrile [30]. Thus, it is possible that a change in mechanism accompanies the move from the weakly coordinating toluene to the stronger donor acetonitrile. However, the much larger $\Delta H_{on}^{\ddagger}$ values (87 ± 8 and $82 \pm 4\,kJ\,mol^{-1}$, respectively) and only modestly more negative $\Delta S_{on}^{\ddagger}$ values (-12 ± 24 and $-17 \pm 12\,J\,mol^{-1}\,K^{-1}$, respectively) continue to be consistent with a mechanism where bond breaking dominates. Nonetheless, it would be valuable to determine the activation volumes in donor solvents to evaluate whether bond formation between Ru(III) and NO plays a larger role when the leaving group is less labile.

2.3. Ru(EDTA) complexes

Ruthenium(III) polyaminocarboxylate complexes have been examined as possible therapeutic NO scavenging agents to treat septic shock [31]. Rate constants were determined for the NO reaction with $[Ru^{III}(Hedta)Cl]^-$ and $Ru^{III}(Hedta)(H_2O)$ (Hedta: ethylenediaminetetraacetic acid) and found to be 2.24×10^7 and $1.95 \times 10^7\,M^{-1}\,s^{-1}$ (pH 7.4, 280 K) forming $Ru^{III}(Hedta)(NO)$ in each case. In this study Davies et al. estimated the equilibrium constant to be $>10^8\,M^{-1}$ [31]. The equilibrium constant K_{NO} for formation of $Ru^{III}(Hedta)(NO)$ from $Ru^{III}(Hedta)(H_2O)$ was estimated by Wanat et al. to be $9 \times 10^7\,M^{-1}$ (pH 5.0, 298 K) using electrochemical and spectroscopic methods [32] to confirm the previous estimate. In aqueous solution, $Ru^{III}(Hedta)(H_2O)$ undergoes deprotonation of the pendant acidic group and of the coordinated water. Thus, the specific form of Ru^{III}(edta) is pH dependent (Scheme 1). Reactions of NO with $Ru^{III}(Hedta)(H_2O)$ under acidic (pH 1.0) and basic (pH 9.1) conditions gave k_{on} values of 3.8×10^4 and 1.2×10^5, respectively (298 K) [32]. These rate constants are significantly smaller than those measured at pH 7.4 [31a]. Thus one may conclude that the rate constants determined in neutral solution involve the reaction of $[Ru^{III}(edta)(H_2O)]^-$ with NO and that k_2 is much greater than k_1 or k_3. This is serendipitous since it makes



Scheme 1. Reactions of NO with $Ru^{III}(edta)(H_2O)^-$ in aqueous solution is pH dependent.

Ru^{III}(edta) an effective NO scavenger at physiological pH. These results are in agreement with the previous report that $[Ru^{III}(edta)(H_2O)]^-$ in aqueous solution is extremely labile and that ligand substitutions reactions occurred through an associative mechanism [33].

The differences in reactivity of the various forms of Ru^{III}(edta) are striking especially when one considers that k_2 is nearly three orders of magnitude faster than k_1 and involves changes in protonation of a pendant carboxylate. It has been speculated that hydrogen bonding to the coordinated water may distort the Ru–edta bonds to create a more accessible site for an entering ligand [33b]. This would be consistent with the proposal that ligand substitution reactions with $[Ru^{III}(edta)(H_2O)]^-$ occur through an associative mechanism [33].

2.4. Ru(Por)(NO)(X) complexes

Ruthenium porphyrin nitrosyl nitrito complexes of the form Ru^{II}(Por)(NO)(ONO) (Por: TPP, OEP and related porphyrins) are formed from NO reactions with Ru^{II}(Por)CO [34,35] according to Eq. (5) [34].

$$Ru^{II}(Por)CO + 4NO \rightarrow Ru^{II}(Por)(NO)(QNO) + N_2O + CO \quad (5)$$

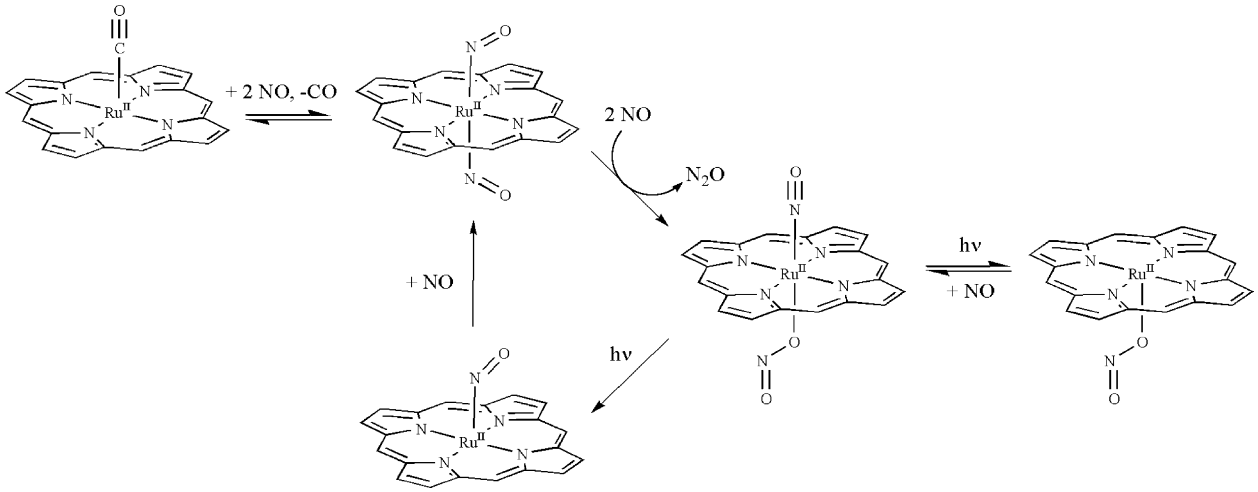
Stopped-flow kinetics studies showed that the reaction occurs in two steps [36]. The rapid first reaction was suppressed by excess CO or other coordinating ligands, while the second step was found to be second order in [NO] (Scheme 2). The intermediate formed after the first step was proposed to be a centro-symmetric *trans*-dinitrosyl complex Ru(Por)$(NO)_2$ based on the single ν_{NO} band at 1642 cm^{-1} (for Por: TmTP in cyclohexane solution) observed via time resolved infrared techniques [37]. Subsequent theoretical calculations have argued that the dinitrosyl complex has a *trans-syn*-Ru(Por)$(NO)_2$ geometry [38]. The observation of a single ν_{NO} band was explained by DFT calculations [38b]. While two ν_{NO} bands are predicted for *trans-syn*-Ru(Por)$(NO)_2$, the asymmetric stretch was predicted to have an intensity over 40-fold lower than the symmetric mode.

Laser flash photolysis of the Ru^{II}(Por)(NO)(ONO) product with 355 nm light resulted in the photodissociation of NO or NO_2. The back reaction of NO with Ru(Por)(ONO) is rapid with second order rate constants of 2.4–5.5 × 10^8 M^{-1} s^{-1} [39]. Trapping of Ru^{II}(Por)(NO) with NO was an order of magnitude slower ($k = 2.4 \times 10^7$ M^{-1} s^{-1}) and gave the analogous dinitrosyl according to step scan FTIR detection [39]. As in the stopped-flow experiments discussed above, the dinitrosyl species reacts with additional NO to reform Ru^{II}(Por)(NO)(ONO).

3. Ferric and ferrous complexes

3.1. Fe(III) and Fe(II) porphyrin complexes

Although rates of NO reactions with various iron porphyrins and heme proteins were first studied several decades ago [40], systematic mechanistic studies have been more recent. These were investigated by carrying out the flash photolysis of aqueous Fe(Por)(NO) and Fe(Por)(L)(NO) (Por: TPPS (tetra(4-sulfonato-phenyl)porphinato) and TMPS (tetramesitylporphinato)) solutions in the presence of excess NO. Excitation generally results in NO labilization from Fe(Por)(L)(NO) followed by relaxation of the system to equilibrium (Eq. (6)). Under such conditions, the transient spectra decayed exponentially, and the observed rate constant k_{obs} could be extracted for different [NO] and other variables. According to this model, $k_{obs} = k_{on}[NO] + k_{off}$, and a plot of k_{obs} versus [NO] should be linear with slope equal to k_{on} and intercept equal to k_{off} [23,41,42]. For such plots, slopes are inherently more accurate than intercepts, so k_{off} values so determined will have a high relative uncertainty, unless they are large. For systems where



Scheme 2. Reaction of NO with Ru^{II}(Por)CO. Porphyrin ligand substituents have been omitted for clarity.

Table 1
Kinetic data for NO "on" and "off" reactions for ruthenium and iron metal centers

"On" reactions[a]	k_{on} ($M^{-1}\,s^{-1}$)	$\Delta H^{\ddagger}_{on}$ (kJ mol^{-1})	$\Delta S^{\ddagger}_{on}$ (J mol^{-1} K^{-1})	$\Delta V^{\ddagger}_{on}$ (cm^3 mol^{-1})	Ref.
$Ru^{III}(NH_3)_6^{3+}$ + NO	0.3	41 ± 2	−114 ± 7	−13.6 ± 0.3	[26b,27]
$Ru^{III}(NH_3)_5Cl^{2+}$ + NO	0.75	34 ± 1	−132 ± 3	−18 ± 0.5	[27]
$Ru^{III}(NH_3)_5(H_2O)^{3+}$ + NO	55.6	31 ± 1	−108 ± 2	[b]	[27]
Ru^{III}(Tbu$_4$salen)(Cl)(Sol) + NO[c]	2.5 × 10^7	34 ± 2	10 ± 6	22 ± 2	[30b]
Ru^{III}(tBu$_4$salophen)(Cl)(Sol) + NO[c]	9.2 × 10^6	20 ± 1	−46 ± 2	16 ± 2	[30b]
Fe^{III}(TPPS) + NO	4.5 × 10^5	69 ± 3	95 ± 10	9 ± 1	[41c]
Fe^{III}(TMPS) + NO	2.8 × 10^6	57 ± 3	69 ± 11	13 ± 1	[41c]
metMb + NO	4.8 × 10^4	63 ± 2	55 ± 8	20 ± 6	[42]
$Fe^{II}(H_2O)_6$ + NO	1.4 × 10^6	37 ± 0.5	−3 ± 2	6.1 ± 0.4	[53]
Fe^{II}(Hedtra) + NO	6.1 × 10^7	26 ± 1	−12 ± 3	2.8 ± 0.1	[70]
Fe^{II}(edta) + NO	2.4 × 10^8	24 ± 1	−4 ± 3	4.1 ± 0.2	[70]
Fe^{II}(nta) + NO	2.1 × 10^7	24 ± 1	−22 ± 3	−1.5 ± 0.1	[70]
Fe^{II}(TPPS) + NO	1.5 × 10^9	24 ± 3	12 ± 10	5 ± 1	[41c]
Fe^{II}(TMPS) + NO	1.0 × 10^9	26 ± 6	16 ± 21	2 ± 2	[41c]
"Off" reactions	k_{off} (s^{-1})	$\Delta H^{\ddagger}_{off}$ (kJ mol^{-1})	$\Delta S^{\ddagger}_{off}$ (J mol^{-1} K^{-1})	$\Delta V^{\ddagger}_{off}$ (cm^3 mol^{-1})	
Fe^{III}(TPPS)(NO)	0.5 × 10^3	76 ± 6	60 ± 11	18 ± 2	[41c]
Fe^{III}(TMPS)(NO)	0.9 × 10^3	84 ± 3	94 ± 10	17 ± 3	[41c]
metMb(NO)	42	68 ± 4	14 ± 13	18 ± 3	[42]
$Fe^{III}(H_2O)_5(NO^-)$	3.2 × 10^3	48 ± 1	−15 ± 5	1.3 ± 0.2	[53]
Fe^{II}(Hedtra)(NO)	4.2	73 ± 1	11 ± 4	4.4 ± 0.8	[70]
Fe^{II}(edta)(NO)	91	61 ± 2	−5 ± 7	7.6 ± 0.6[b]	[70]
Fe^{II}(nta)(NO)	9.3	66 ± 1	−5 ± 4	−3.5 ± 0.7	[70]
Fe^{II}(TPPS)(NO)	6.4 × 10^{-4}	[b]	[b]	[b]	[41c]

[a] Abbreviations given in abbreviation list.
[b] Not determined.
[c] Sol: toluene.

the "off" reaction is too slow to give acceptably accurate intercepts, an alternative approach may be to measure NO labilization rates by following directly the disappearance of the Fe(Por)(L)(NO) complex after adding an efficient NO trapping agent.

$$\mathrm{Fe(Por)(L)} + \mathrm{NO} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \mathrm{Fe(Por)(L)(NO)} \qquad \mathrm{Fe(Por)(L)(NO)} \xrightarrow{h\nu} \mathrm{Fe(Por)(L)} + \mathrm{NO} \tag{6}$$

Laverman and co-workers carried out such studies with the iron(II) and iron(III) complexes of the water soluble porphyrin TPPS [41,42]. These studies involved systematic measurements of k_{on} and k_{off} as functions of 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 Fe^{III}(TPPS) and for the "on" reactions of Fe^{II}(TPPS) and related species (Table 1).

For the ferriheme model, which is present as the diaquo complex $Fe^{III}(TPPS)(H_2O)_2$, the large and positive $\Delta S^{\ddagger}_{on}$ and the large and positive $\Delta V^{\ddagger}_{on}$ (Table 1) indicate a substitution mechanism dominated by ligand dissociation as illustrated in Scheme 3. A key prediction of this mechanism is that H_2O exchange with the solvent should be much faster that the rate of nitrosyl formation since [NO] is much smaller than [H_2O] in aqueous solution. This prediction is consistent with earlier studies by Hunt et al. [43], who reported that H_2O exchange between solvent and $Fe^{III}(TPPS)(H_2O)_2$ is indeed quite rapid ($k_{ex} = 1.4 \times 10^7\ s^{-1}$ in 298 K).

If we assume that the NO substitution onto Fe^{III}(Por)$(H_2O)_2$ occurs via the dissociative mechanism depicted in Scheme 3 and the steady state approximation is taken with regard to the intermediate Fe^{III}(Por)(H_2O), the k_{obs} determined by the flash photolysis of $Fe^{III}(TPPS)(H_2O)_2$ would be

$$k_{obs} = \frac{k_1k_2[\mathrm{NO}] + k_{-1}k_{-2}[\mathrm{H_2O}]}{k_{-1}[\mathrm{H_2O}] + k_2[\mathrm{NO}]} \tag{7}$$

The rapid solvent exchange process indicates that $k_{-1}[H_2O] \gg k_2[NO]$; therefore, $k_{off} = k_{-2}$ and $k_{on} = k_1k_2/k_{-1}[H_2O]$. Thus, the apparent activation parameters for k_{on} would be $\Delta Y^{\ddagger}_{on} = \Delta Y^{\ddagger}_1 + \Delta Y^{\ddagger}_2 - \Delta Y^{\ddagger}_{-1}$, where $\Delta Y^{\ddagger}_1$ is $\Delta H^{\ddagger}_{on}$, $\Delta S^{\ddagger}_{on}$ or $\Delta V^{\ddagger}_{on}$. However, k_2 and the k_{-1} are the rate constants for similar (very fast) reactions of the unsaturated intermediate Fe^{III}(Por)(H_2O) with an uncharged ligand (NO and H_2O, respectively). Thus the differences in their activation

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

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

Scheme 3. A limiting dissociative mechanism for NO substitution onto $Fe^{III}(Por)(H_2O)_2$.

parameters (e.g. $\Delta V_2^{\ddagger} - \Delta V_{-1}^{\ddagger}$) should be small. Accordingly, the principal contributor to each $\Delta Y_{on}^{\ddagger}$ term would be $\Delta Y_1^{\ddagger}$, the activation parameter for the H_2O dissociation. The k_1 step should thus display a $\Delta H_1^{\ddagger}$ consistent with the energy necessary to break a Fe^{III}–OH_2 bond, a large, positive $\Delta S_1^{\ddagger}$ owing to formation of two species from one, and a substantially positive $\Delta V_1^{\ddagger}$ for the same reason. These conditions are met for k_{on} (Table 1). Furthermore, a recent reexamination of the exchange kinetics [44] using variable temperature/pressure NMR gave $\Delta H_{ex}^{\ddagger} = 67\,kJ\,mol^{-1}$, $\Delta S_{ex}^{\ddagger} = 99\,J\,mol^{-1}\,K^{-1}$ and $\Delta V_{ex}^{\ddagger} = 7.9\,cm^3\,mol^{-1}$ in excellent agreement with the activation parameters measured by flash photolysis for the k_{on} pathway with NO [41b,c]. Thus, it is clear that the factors determining the exchange between $Fe^{III}(TPPS)(H_2O)_2$ and solvent H_2O dominate the NO reaction with the same species. Both processes appear to be largely defined by a dissociative mechanism as illustrated by Scheme 3.

Based on the principle of microscopic reversibility, one may conclude that the intermediate(s) in the "off" step will be the same as those generated during the k_{on} pathway, thus Fe–NO bond breakage (k_{-2}) would be the energetically dominant step. Coordination of NO to Fe^{III}(Por) is accompanied by considerable charge transfer to give a linearly bonded, diamagnetic complex that can be formally represented as $Fe^{II}(Por)(NO^+)$. Thus, the "off" reaction must reflect intrinsic entropy and volume changes associated with the spin change and solvent reorganization as the charge localizes on the metal (Fig. 1).

The water-soluble ferrous complex Fe^{II}(TPPS) reacts with NO about 10^3 times faster than does the ferric analog [41a]. The small values of the activation parameters (Table 1) are consistent with rates largely defined by diffusional factors, although the k_{on} values reported are about an order of magnitude less than diffusion limits in water. High spin ferroheme proteins complexes tend to be considerably more reactive towards ligands than are the ferriheme analogs and a likely explanation would be that the former are often five-coordinate. Since such systems do not require displacement of a ligand prior to metal–NO bond formation, the rates are not limited by the lability of the metal center.

Flash photolysis proved to be unsuited for measuring the slow "off" reactions for the iron(II) model complex Fe^{II}(TPPS)(NO). The experimental uncertainties in the intercepts obtained by extrapolating k_{obs} versus [NO] plots to [NO] = 0 were larger than the values of the intercepts themselves. More reliable estimates for the "off" reaction were obtained by using $Ru(edta)^-$ as an NO scavenger. Addition of excess $Ru(edta)^-$ to an aqueous solution of Fe^{II}(TPPS)NO allowed measurements of the k_{off} value ($6.3 \times 10^{-4}\,s^{-1}$, 298 K) (Table 1) [41c].

The k_{off} can also be estimated using a Born-Haber type cycle to calculate an equilibrium constant K_{NO}^{II} for Fe^{II}(TPPS)(NO) formation ($K_{NO}^{II} = 7.5 \times 10^{12}\,M^{-1}$) from the experimental values for the ferric analog K_{NO}^{III} ($1.1 \times 10^3\,M^{-1}$) [23] and the reduction potentials for Fe^{III}(TPPS)(NO) (+0.35 V versus SCE) and Fe^{III}(TPPS) (−0.23 V versus SCE) in aqueous solution [45]. From the relationship $K_{NO}^{II} = k_{on}^{II}/k_{off}^{II}$ and the measured value

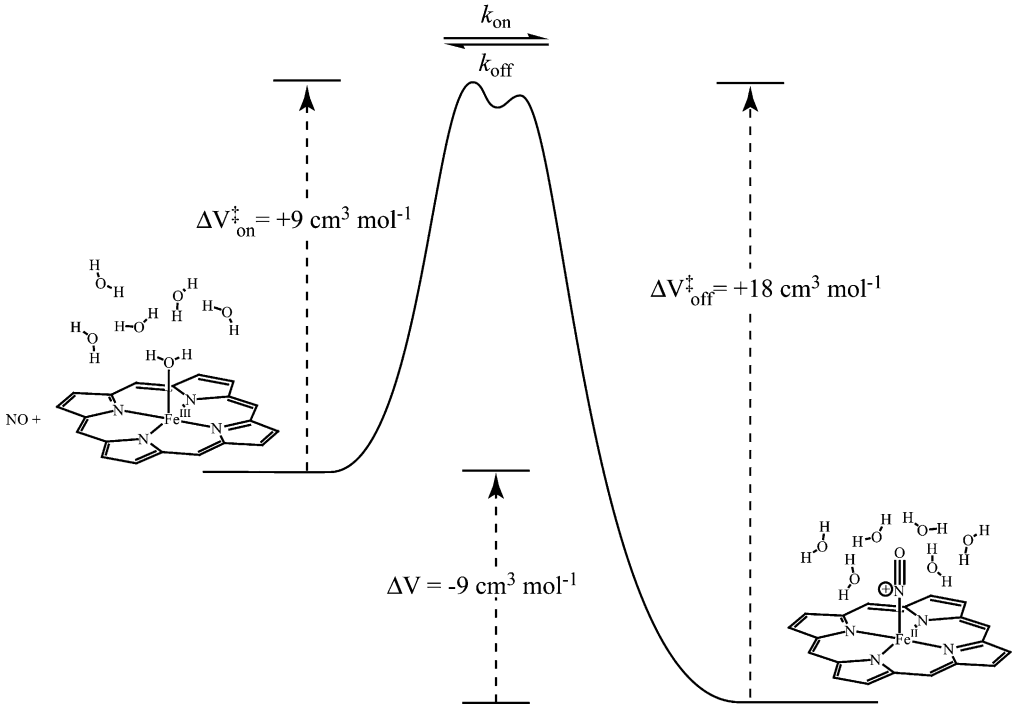


Fig. 1. Illustration of the effects of charge transfer in the reaction Fe^{III}(TPPS) with NO on solvent reorganization.

$k_{on}^{II} = 1.5 \times 10^9\,M^{-1}\,s^{-1}$, the value of k_{off}^{II} was estimated as $\sim 2 \times 10^{-4}\,s^{-1}$. This is about three-fold smaller than that measured by NO scavenging, but given the uncertainties the electrochemical potentials used to make this estimate, the agreement is quite reasonable.

Kinetics studies [29c,46] 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

$$Fe^{II}(Por) + L \underset{k_{-D}}{\overset{k_D}{\rightleftharpoons}} \{Fe^{II}(Por)||L\} \overset{k_a}{\rightarrow} Fe^{II}(Por)L \qquad (8)$$

In this model k_D is the rate constant for the diffusion of the $Fe^{II}(Por)$ and L together, k_{-D} is that for diffusion apart, and k_a is that for the "activation" step, where M–L bond formation is effected. Applying the steady state approximation gives $k_{on} = k_D k_a/(k_{-D} + k_a)$. There are two limiting cases in this model, one in which the reaction is diffusion limited ($k_a \gg k_{-D}$) so that $k_{on} = k_D$, the other in which the reaction is activation limited ($k_{-D} \gg k_a$) so $k_{on} = k_D k_a/k_{-D}$.

In the activation limited process, $\Delta V_{on}^{\ddagger} = \Delta V_a^{\ddagger} + \Delta V_D^{\ddagger} - \Delta V_{-D}^{\ddagger}$, where $\Delta V_D^{\ddagger} - \Delta V_{-D}^{\ddagger}$ is the volume difference between the encounter complex and the solvent separated species. Although unknown, this is likely to be small for a neutral ligand such as NO. The encounter complex does not involve formation or breaking of bonds and should have only modest impact on solvation. The dominant term for the activation limited case would be $\Delta V_a^{\ddagger}$, which should be negative owing to the formation of a Fe^{II}–L bond and the concomitant spin state change from high spin quintet $Fe^{II}(Por)\|$doublet NO encounter complex to the doublet product $Fe^{II}(Por)(NO)$.

For the diffusion limited case $\Delta V_{on}^{\ddagger} = \Delta V_D^{\ddagger}$. This would be positive owing to solvent viscosity increases at higher pressure [47]. The positive $\Delta V_{on}^{\ddagger}$ values observed for Fe^{II}(TPPS) (Table 1) are somewhat larger than expected for a diffusion limited process in aqueous solution. But they are significantly smaller than are the analogous parameters for the iron(III) analogs. Thus it was argued that since k_{on} is approaching the diffusion limit in water ($k_D \sim 10^{10}\,M^{-1}\,s^{-1}$ at 298 K) $\Delta V_{on}^{\ddagger}$ in this case would be small and positive [48]. Similarly, the activation entropy for diffusion in aqueous solution can be estimated as $\sim 34\,J\,mol^{-1}\,K^{-1}$ [49]; thus the measured $\Delta S_{on}^{\ddagger}$ for Fe^{II}(TPPS) ($12 \pm 10\,J\,mol^{-1}\,K^{-1}$) is reasonably consistent with a process limited by diffusion.

The model described by Eq. (8) applies to the analogous reactions with CO. The second order rate constant ($k_{CO} = 3.6 \times 10^7\,M^{-1}\,s^{-1}$) for the reaction of Fe^{II}(TPPS) with CO is several orders of magnitude below the diffusion limit [41c]. Since the rate is nearly three orders of magnitude smaller than k_D, the reaction must be activation limited. Furthermore, in contrast to the reaction with NO, the $\Delta V_{on}^{\ddagger}$ values for CO are negative ($-6\,cm^3\,mol^{-1}$). These results parallel other studies of ferro-heme complexes which found that reaction with NO is diffusion limited while reaction with CO is activation limited. This model was confirmed by a study of the CO reaction with Fe^{II}(MCPH) (MCPH: monochelated protoheme, or protohemin 3-(1-imadazoyl) propylamide stearyl ester) in toluene/mineral oil solutions. Pressure effects on the solvent viscosity were used to tune the reaction mechanism from an activation limited process at low hydrostatic pressure (large negative $\Delta V_{on}^{\ddagger}$) to a diffusion limited process at higher pressures (large positive $\Delta V_{on}^{\ddagger}$) where the solvent viscosity increased dramatically [46].

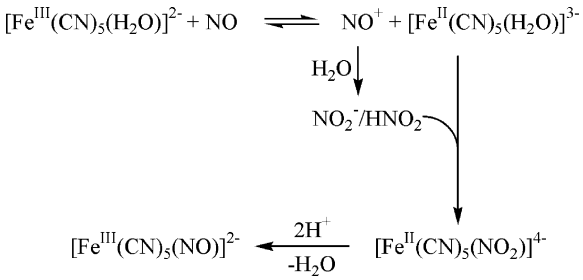
3.2. Hexaaquoiron(II)

The classic qualitative test for ferrous ion in acidic aqueous solution involves the reaction of NO with $[Fe(H_2O)_6]^{2+}$ to form the "brown ring complex" $[Fe(H_2O)_5(NO)]^{2+}$ (Eq. (9)). The mechanism by which this reaction occurs has recently been revisited by Wanat et al. [50]. Temperature and pressure dependent kinetics studies using laser flash photolysis and stopped flow techniques were used to determine the activation parameters for the "on" and "off" reactions (Table 1). These activation parameters, the small and positive volumes of activation in particular ($\Delta V_{on}^{\ddagger} = +6.1\,cm^3\,mol^{-1}$ and $\Delta V_{off}^{\ddagger} = +1.3\,cm^3\,mol^{-1}$), were deemed consistent with a dissociative interchange, I_d, mechanism. The exchange of H_2O between bulk solvent and the coordination sphere of $[Fe(H_2O)_6]^{2+}$ gave similar activation parameters, $\Delta H_{ex}^{\ddagger} = 41.4\,kJ\,mol^{-1}$, $\Delta S_{ex}^{\ddagger} = +21.2\,J\,mol^{-1}\,K^{-1}$ and $\Delta V_{ex}^{\ddagger} = +3.8\,cm^3\,mol^{-1}$. Thus it can be argued that the NO binding rates are largely dependent on the lability of the leaving group (H_2O) in Eq. (9) [51]. One might contend that the mechanism (and rates) for NO substitution into the iron centers is more defined by the coordination number (6 in this case) than the oxidation state.

$$[Fe(H_2O)_6]^{2+} + NO \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [Fe(H_2O)_5(NO)]^{2+} + H_2O \qquad (9)$$

3.3. Pentacyanoiron(II) and iron(III)

Olabe, van Eldik and co-workers have also studied the temperature and pressure dependent kinetics of the NO reactions with the pentacyano iron(III) and iron(II) complexes $[Fe^{III}(CN)_5(H_2O)]^{2-}$ and $[Fe^{II}(CN)_5(H_2O)]^{3-}$ in acidic aqueous solution [52,53]. The former reaction, which gives the nitroprusside anion (NP: $[Fe^{III}(CN)_5(NO)]^{2-}$) as the product, occurs at a second order rate ($k_{on} = 0.25\,M^{-1}\,s^{-1}$ at 298.5 K) many orders of magnitude faster than the analogous reactions of NCS^- and N_3^- with $[Fe^{III}(CN)_5(H_2O)]^{2-}$. The activation parameters: $\Delta H_{on}^{\ddagger} = 52\,kJ\,mol^{-1}$, $\Delta S_{on}^{\ddagger} = -82\,J\,mol^{-1}\,K^{-1}$ and $\Delta V_{on}^{\ddagger} = -13.9\,cm^3\,mol^{-1}$ are qualitatively similar to those reported above for the reactions of NO with $Ru(NH_3)_6^{3+}$. As noted above, an associative



Scheme 4. Mechanism proposed for nitroprusside formation from $Fe^{III}(CN)_5(H_2O)^{2-}$.

substitution mechanism was proposed for the latter reaction based largely on these activation parameter values.

However, the kinetics of the reaction of $[Fe^{III}(CN)_5(H_2O)]^{2-}$ with NO in the presence of other ligands suggested that simple associative displacement of the H_2O by NO may not be the sole pathway. For example, in the presence of excess SCN^-, NO catalyzes the substitution of this ion into the Fe^{III} coordination sphere. On this basis, the authors suggested a rate determining outer sphere electron transfer in which NO reduces the Fe(III) center giving rise to a much more labile ferrous intermediate, $[Fe^{II}(CN)_5(H_2O)]^{3-}$ plus NO^+. When other ligands are not present, the latter would be trapped by subsequent reactions with NO_2^- or HNO_2 ($k_{HNO_2} = 400\,M^{-1}\,s^{-1}$, $k_{NO_2^-} = 30\,M^{-1}\,s^{-1}$ [52]), formed by hydrolysis of the NO^+. The resulting $[Fe^{II}(CN)_5(NO_2)]^{4-}$ would undergo redox coupled dehydration in acidic solution to give NP (Scheme 4). When SCN^- is present, the $[Fe(CN)_5(H_2O)]^{3-}$ undergoes ligand substitution to form $[Fe(CN)_5(SCN)]^{4-}$ which reduces the $[Fe(CN)_5(H_2O)]^{2-}$ starting material to give $[Fe(CN)_5(SCN)]^{3-}$as a product and regenerates $[Fe(CN)_5(H_2O)]^{3-}$ as a catalytic intermediate.

An obvious concern about this mechanism is that NO reduction of $[Fe(CN)_5(H_2O)]^{3-}$ is very unfavorable ($\Delta E = -0.83$ V), although subsequent steps make the overall chemical transformation favorable. Direct spectroscopic evidence for the iron(II) intermediate was not obtained, however trapping experiments in the presence of pyrazine (pz) resulted in the formation of both $[Fe^{III}(CN)_5(pz)]^{2-}$ and $[Fe^{II}(CN)_5(pz)]^{3-}$. The rate constant for pz reacting with $[Fe^{II}(CN)_5H_2O]^{3-}$ had previously been reported to be $380\,M^{-1}\,s^{-1}$ at 298 K [54]. Electron transfer induced charge separation such as indicated in the first step would also be consistent with the observed negative $\Delta V_{on}^{\ddagger}$ owing to the increased solvation in the transition state [55].

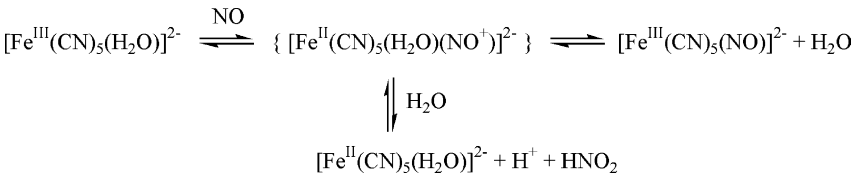
The high barrier to the electron transfer initiating the sequence of events in Scheme 4, might be lowered by a pathway whereby the first step involves formation of a seven coordinate inner sphere complex such as suggested above for the Ru(III) hexaammine ion (Scheme 5). If this can partition between H_2O dissociation and reaction of the coordinated NO^+ to form nitrite that is released, the barrier for Fe(III) reduction would be lowered and sufficient $Fe^{II}(CN)_5(H_2O)^{3-}$ would be formed to provide a catalytic pathway for ligand substitutions. Such reductive nitrosylations are common for ferriheme models and proteins [56].

In a subsequent study, Roncaroli et al. examined the pressure and temperature effects on the NO substitution reaction with the Fe(II) analog $[Fe^{II}(CN)_5H_2O]^{3-}$ to give $[Fe^{II}(CN)_5NO]^{3-}$ [52]. They determined the k_{on} to be $250\,M^{-1}\,s^{-1}$ (298.4 K) with activation parameters ($\Delta H_{on}^{\ddagger} = 70\,kJ\,mol^{-1}$, $\Delta S_{on}^{\ddagger} = +34\,J\,mol^{-1}\,K^{-1}$ and $\Delta V_{on}^{\ddagger} = +17.4\,cm^3\,mol^{-1}$), very similar to those for reaction of this complex with neutral ligands such as histidine or CO (Eq. (10)). It was thus concluded that NO is acting as a normal Lewis base and that ligand substitution rates are controlled by the Fe^{III}–OH_2 bond lability. The large and positive $\Delta V_{on}^{\ddagger}$ values point to a dissociative mechanism, where H_2O release from the Fe(II) coordination sphere would be rate limiting.

$$[Fe^{II}(CN_5)(H_2O)]^{2-} + L \underset{k_{-L}}{\overset{k_L}{\rightleftharpoons}} [Fe^{II}(CN_5)(L)]^{3-} + H_2O \quad (10)$$

These newer data offer an interesting twist to the mechanism proposed in Scheme 4. Since the NO concentration is considerably higher than that of the nitrite formed by the electron transfer mechanism, NO could easily compete for the Fe(II) intermediate in the absence of added trapping agents. This would give $[Fe^{II}(CN)_5(NO)]^{3-}$ that would be oxidized by the $[Fe^{III}(CN)_5(H_2O)]^{2-}$ to give NP plus $[Fe^{II}(CN)_5(H_2O)]^{3-}$. Thus the formation of NP from NO and $[Fe^{III}(CN)_5(H_2O)]^{2-}$ should be autocatalytic.

Notably, $[Fe^{II}(CN)_5(NO)]^{3-}$ was found to be not very labile to NO dissociation ($k_{off} = 1.6 \times 10^{-5}\,s^{-1}$, 298 K) [57], an observation that has possible relevance to the mechanism by which sodium NP functions as a vasodilator [58]. Since neither NP nor $[Fe^{II}(CN)_5(NO)]^{3-}$ are sufficiently labile to release NO on a time scale to explain this activity, another pathway for NO release or perhaps another mechanism for NP induced vasodilation would appear to be in order. On the other hand, $[Fe^{II}(CN)_5(NO)]^{3-}$ does readily dissociate a



Scheme 5. An alternative scheme for generation of Fe(II) intermediates during NP formation.

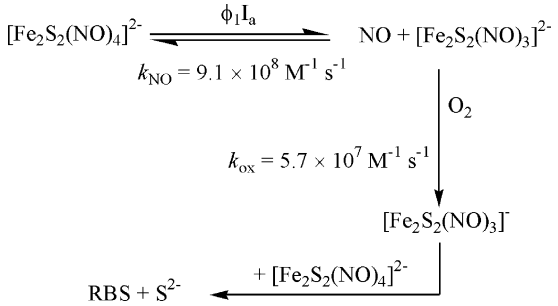
cyanide [57], presumably the *trans* CN^-. This follows earlier observations of the weakened bonding of ligands *trans* to NO in a tetragonal $\{MNO\}^7$ complex [9,28,59]. Such *trans*-labilization of a nitrosyl ferroheme center has been demonstrated to be a key feature of NO activation of sGC [60]. However, it is unclear whether the CN-labilization from reduced nitroprusside plays any role in the vasodilation properties of NP.

3.4. Iron(II) aminocarboxylato complexes

van Eldik and co-workers have also determined the rates and activation parameters for NO reactions with different iron aminocarboxylato complexes in aqueous solution [61]. The second order k_{on} values for these reactions ranged from 10^5 to $10^8\,M^{-1}\,s^{-1}$ for a series of Fe(II) complexes (Table 1). The reaction of NO with Fe^{II}(edta) gave a $\Delta V_{on}^{\ddagger}$ of $+4.1\,cm^3\,mol^{-1}$, and a dissociative interchange (I_d) mechanism was proposed. Other iron(II) aminocarboxylato complexes gave small positive activation volumes with the exception of the Fe^{II}(nta) (nta: nitriloacetic acid) complex for which $\Delta V_{on}^{\ddagger} = -1.5\,cm^3\,mol^{-1}$.

3.5. Iron sulfur nitrosyl clusters

The Roussin's red and black salt anions ($[Fe_2S_2(NO)_4]^{2-}$ and $[Fe_4S_3(NO)_7]^-$, respectively) and the red salt esters $Fe_2(SR)_2(NO)_4$ have been studied as possible thermal and photo-initiated precursors for nitric oxide delivery to biological targets [62]. Photolysis leads to NO dissociation and gives species that are readily regenerated by the back reaction with NO or are irreversibly trapped by O_2 to give other species [63]. Although not fully characterized, the intermediates generated in this way react extremely rapidly with NO, with rate constants approaching diffusion limits, even in a coordinating solvent such as water, alcohol or acetonitrile. For example, flash photolysis of the red salt anion labilizes NO with a quantum yield of ~0.5. The iron containing transient also generated, presumably $[Fe_2S_2(NO)_3]^{2-}$, reforms $[Fe_2S_2(NO)_4]^{2-}$ upon second order reaction with NO with a rate constant of $9 \times 10^8\,M^{-1}\,s^{-1}$ in ambient temperature aqueous solution (Scheme 6) [63b]. This back reaction is so fast that under continuous photolysis, there is very little net photoreaction unless dioxygen is present to trap $[Fe_2S_2(NO)_3]^{2-}$ to give eventual photochemical generation of the black salt anion $[Fe_4S_3(NO)_7]^-$. The intermediates generated by the flash photolysis of several red salt esters $Fe_2(SR)_2(NO)_4$ behave similarly [63c]. In this context, it seems unlikely that the back reactions of the unsaturated clusters $[Fe_2S_2(NO)_3]^{2-}$ or $Fe_2(SR)_2(NO)_3$ involve the displacement of a coordinated solvento ligand.



Scheme 6. Reactions of intermediates generated in the flash photolysis of Roussin's red salt (aq. solution, 295 K) [63b].

4. Examples from metalloprotein chemistry

The kinetics of the reactions of NO with various of ferri- and ferro-heme proteins under ambient conditions have been studied by time resolved spectroscopic techniques over the past 20 years [21,23,64–67]. Representative rate constants are summarized in Table 2 and demonstrate the sizable range of k_{on} and k_{off} values obtained for ferri-

Table 2
The rate constants (298 K) for the "on" and "off" reactions of NO with ferri- and ferro-heme proteins

	k_{on} ($M^{-1}\,s^{-1}$)	k_{off} (s^{-1})	Ref.
Ferric proteins[a]			
metMb[b]	1.9×10^5	13.6	[23]
metMb[c]	4.8×10^4	43	[42]
Cyt^{III}[d]	7.2×10^2	4.4×10^{-2}	[23]
Cat[e]	3.0×10^7	1.7×10^2	[23]
eNOS[f]	8.2×10^5	70	[64]
nNOS[g]	2.1×10^7	40	[64]
NPn[h]	$1.5–5.5 \times 10^6$	0.006–12.7	[21]
MPO[i]	1.07×10^6	10.8	[71]
Ferrous proteins			
Hb_4^T[j]	2.6×10^7	3.0×10^{-3}	[65]
Hb_4^R[j]	2.6×10^7	1.5×10^{-4}	[65]
Sgc[k]	1.4×10^8	$6–8 \times 10^{-4}$	[66]
sGC[l]	–	5.0×10^{-2}	[66]
Mb[m]	1.7×10^7	1.2×10^{-4}	[65]
Cyt^{II}[n]	8.3	2.9×10^{-5}	[23]
eNOS[o]	1.1×10^6	70	[64]
nNOS[p]	1.1×10^7	~0	[64]
MPO[q]	1.0×10^5	4.6	[71]

[a] Abbreviations given in abbreviation list.
[b] Sperm whale skeletal metMb H_2O, pH 6.5.
[c] Horse heart metMb, 50 mM phosphate, pH 7.0, 298 K.
[d] H_2O, pH 6.5, 293 K.
[e] H_2O, pH 6.5, 293 K.
[f] 283 K, 1 mM arginine.
[g] pH 7.8, 293 K, heme domain.
[h] 298 K rate constants are the range for NPn1, NPn2, NPn3 and NPn4, pH 5.0 and pH 8.0, the k_{off} displays two phases.
[i] pH 7.0, 283 K.
[j] pH 7.0, 293 K, two phases are observed for NO binding.
[k] pH 7.4, 293 K.
[l] pH 7.4, 293 K, 3 mM Mg^{2+}, 0.5 mM GTP.
[m] Phosphate buffer pH 7.0, 293 K.
[n] H_2O, pH 6.5.
[o] 283 K, 1 mM arginine.
[p] pH 7.8, 293 K, heme domain.
[q] pH 7.0, 283 K.

and ferro-heme proteins. Equilibrium constants measured for the formation of nitrosyl complexes of met-myoglobin (metMb), ferri-cytochrome *c* (Cyt^{III}) and catalase (Cat) are all in reasonable agreement when measured both by flash photolysis techniques ($K_{NO} = k_{on}/k_{off}$) and by spectroscopic titration in aqueous media (23). In several cases k_{off} values were too small to be determined accurately by flash photolysis methods and were measured by other means such as NO trapping with scavengers. The small values of k_{off} result in very large equilibrium constants for ferrous-hemes with the exception of ferro-cytochrome *c*, Cyt^{II}, which also displays a very small k_{on} value.

Temperature and pressure dependent kinetics were measured for the reaction of NO with metMb in aqueous solution (Table 1) [42]. The activation parameters were found to be $\Delta H^{\ddagger}_{on} = 63\,kJ\,mol^{-1}$, $\Delta S^{\ddagger}_{on} = +55\,J\,mol^{-1}\,K^{-1}$, $\Delta V^{\ddagger}_{on} = +20\,cm^3\,mol^{-1}$ and $\Delta H^{\ddagger}_{off} = 68\,kJ\,mol^{-1}$, $\Delta S^{\ddagger}_{off} = +14\,J\,mol^{-1}\,K^{-1}$, $\Delta V^{\ddagger}_{off} = +18\,cm^3\,mol^{-1}$ for the "on" and "off" reactions, respectively. These activation parameters are similar to those determined for reactions of NO with the water soluble ferri-heme complexes $Fe^{III}(TPPS)(H_2O)_2$ and $Fe^{III}(TMPS)(H_2O)_2$ (Table 1) and demonstrate that the latter compounds are reasonable models for the kinetics for the analogous reaction with metMb. As with the model complexes the k_{on} step would appear to be defined largely by the H_2O lability of metMb(H_2O) as shown in Scheme 3.

Nonetheless 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 [42,64]. These issues may be the cause of the lower $\Delta S^{\ddagger}$ values for both the "on" and "off" reactions on metMb. For example, Cao et al. carried out flash photolysis of the wild type horse heart metMb(NO) and a metMb mutant H64G in which a glycine is substituted for the distal histidine [68b]. It was observed that the k_{on} step is several orders of magnitude faster for the metMb mutant H64G than for wild type metMb and the greater reactivity of the mutant was interpreted in terms of hydrogen bonding from His-64 stabilizing the coordinated H_2O of the wild type protein. One might expect such stabilization to be reflected by a higher $\Delta H^{\ddagger}_{on}$ value for the wild type protein, but activation parameters were not reported for the mutant protein.

Dissociation of NO from ferri-heme systems in aqueous solution, formally Fe^{II}–(NO^+), leads to significant solvent reorganization and correspondingly large positive $\Delta S^{\ddagger}_{off}$ and $\Delta V^{\ddagger}_{off}$ as discussed above for model hemes in aqueous solution [41]. The solvation of NO coordinated to iron(III) and the resulting solvent reorganization upon NO dissociation finds some analogy with the nitrophorins. The crystal structure of one nitrophorin, NPn4, 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 NPn4 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 [21].

In general, iron heme proteins react rapidly with NO to form the corresponding nitrosyl complexes, $k_{on} = 10^4$–$10^8\,M^{-1}\,s^{-1}$ (Table 2). However, both Cyt^{III} and Cyt^{II} react with NO several orders of magnitude slower than other heme systems. This low reactivity can be attributed to occupation of both heme iron axial coordination sites by protein bound ligands, an imidazole nitrogen and a methionine sulfur [67]. In this case formation of the nitrosyl complex must also involve significant protein conformational changes. The protein structure does not always inhibit reactivity as shown by the greater reactivities of Cat and nNOS toward NO compared to the model complex $Fe^{III}(TPPS)(H_2O)_2$.

5. Summary

There have been other studies involving the reactions of metal centers with NO, so the present review has attempted to be representative, not comprehensive, of the more recent work in this area. In general, two themes emerge when one considers the mechanisms for the formation of metal nitrosyl complexes via the direct NO reaction with coordination compound in solution as illustrated in Eq. (1). The first qualitative, and perhaps obvious, conclusion is that the gross reactivities of these systems are largely defined by the labilities of the metal complex precursors. The rates tend to be very fast when the NO is entering a previously unoccupied coordination site or is replacing a very labile leaving group like the H_2O in $Fe^{III}(TPPS)(H_2O)_2$ (high spin d^5). But this is much slower in cases such as $Ru^{III}(NH_3)_6^{3+}$ or $Fe^{II}(CN)_5(H_2O)^{3-}$ (low spin d^5 and d^6, respectively) where the ligands are much less labile. For complexes such as $Fe^{III}(TPPS)(H_2O)_2$, metMb and Ru^{III}(salen)X(toluene), dissociative mechanisms prevail, and the reactivity appears to be defined almost entirely by this step. In contrast the slow reaction of NO with $Ru^{III}(NH_3)_6^{3+}$ appears to circumvent the low lability of the Ru^{III}–NH_3 bond by engaging an associative pathway which appears to be unique to NO.

This uniqueness apparently draws from the second general theme, namely the free radical character of nitric oxide. Clearly, this is reflected in the nearly diffusion limited reaction rates with other free radicals, such as with superoxide to form peroxynitrite $ONOO^-$ (several values have been reported all close to $10^{10}\,M^{-1}\,s^{-1}$ [69]). Furthermore, once metal complex lability is taken into account, NO's radical character and ability to undergo electron transfer reactions offer substitution pathways less readily available to other Lewis bases. For example, it is not NO's character as a nucleophile that facilitates the reaction with $Ru^{III}(NH_3)_6^{3+}$ Since the Ru(II) analog is also unreactive toward ammine replacement, the reaction with $Ru^{III}(NH_3)_6^{3+}$ cannot be attributed to an outer sphere electron transfer followed by reactions of a more labile reduced species as was suggested for $Fe^{III}(CN)_5(H_2O)^{2-}$ [52]. Instead it must be the result

of an inner sphere (i.e. associative) mechanism as originally proposed by Taube and co-workers 35 years ago [26]. Even when the coordination site is unoccupied, the electronic character on NO has a considerable impact on the rate of metal–ligand bond formation as reflected in its much greater reactivity with high spin ferrous porphyrins than CO.

From a physiological perspective, the principal (known) targets of NO in its roles in blood pressure control and neurological function are heme proteins, the best characterized example being the activation of sGC. Given the low NO concentrations generated for such purpose in the cardiovascular system, the "on" reactions must be very fast in order to provide prompt biological response. Clearly, defining the mechanisms of these reactions as functions of the media, conditions and the ligand field is crucial to interpreting NO's role in activation and inhibition of metalloproteins.

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References

[1] (a) S. Moncada, R.M.J. Palmer, E.A. Higgs, Pharmacol. Rev. 43 (1991) 109;
(b) M. Feelisch, J.S. Stamler (Eds.), Methods in Nitric Oxide Research, Wiley, Chichester, 1996, and references therein;
(c) D.A. Wink, I. Hanbauer, M.B. Grisham, F. F Laval, R.W. Nims, J. Laval, J. Cook, R. Pacelli, J. Liebmann, M. Krishna, P.C. Ford, J.B. Mitchell, Curr. Topics Cell. Regulat. 34 (1996) 159.

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

[3] F.C. Fang (Ed.), Nitric Oxide and Infection, Kluwer Academic Publishers, New York, 1999.

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

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

[6] (a) M.P. Doyle, D.M. LePoire, R.A. Pickering, J. Biol. Chem. 256 (1981) 12399;
(b) L.V. Andreasen, I.M. Lorkovic, G.B. Richter-Addo, P.C. Ford, Nitric Oxide: Chem. Biol. 6 (2002) 228.

[7] S.E. Bari, M.A. Martí, V.T. Amorebieta, D.A. Estrin, F. Doctorovich, J. Am. Chem. Soc. 125 (2003) 15272.

[8] A.V. Marchenko, A.N. Vedernikov, D.F. Dye, M. Pink, J.M. Zaleski, K.G. Caulton, Inorg. Chem. 43 (2004) 351.

[9] (a) J.H. Enemark, R.D. Feltham, J. Am. Chem. Soc. 96 (1974) 5002;
(b) R.D. Feltham, J.H. Enemark, Topics Stereochem. 12 (1981) 155.

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

[11] (a) M.D. Carducci, M.R. Pressprich, P. Coppens, J. Am. Chem. Soc. 119 (1997) 2669;
(b) C. Kim, I. Novozhilova, M.S. Goodman, K.A. Bagley, P. Coppens, Inorg. Chem. 39 (2000) 5791;
(c) P. Coppens, I. Novozhilova, A. Kavalevky, Chem. Rev. 102 (2002) 861.

[12] J.R. Norton, J.P. Collman, G. Dolcetti, W.T. Robinson, Inorg. Chem. 11 (1972) 382.

[13] T. Malinski, Z. Taha, Nature 358 (1992) 676.

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

[15] (a) S. Kim, G. Deinum, M.T. Gardner, M.A. Marletta, G.T. Babcock, J. Am. Chem. Soc. 118 (1996) 8769, and reference therein;
(b) A.E. Yu, S. Hu, T.G. Spiro, J.N. Burstyn, J. Am. Chem. Soc. 116 (1994) 4117;
(c) J.N. Burstyn, A.E. Yu, A.E. Dierks, B.K. Hawkins, J.H. Dawson, Biochemistry 34 (1995) 5896;
(d) G. Deinum, J.R. Stone, G.T. Babcock, M.A. Marletta, Biochemistry 35 (1996) 1540;
(e) T. Tomita, T. Ogura, S. Tsuyama, Y. Imai, T. Kitagawa, Biochemistry 36 (1997) 10155.

[16] Y. Minamiyama, S. Takemura, S. Imaoka, Y. Funae, Y. Tanimoto, M.J. Inoue, Pharmacol. Exp. Ther. 283 (1997) 1479.

[17] M.W.J. Cleeter, J.M. Cooper, V.M. Darley-Usmar, S. Moncada, A.H.V. Scapira, FEBS Lett. 345 (1994) 50.

[18] G.C. Brown, Eur. J. Biochem. 232 (1995) 188.

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

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

[21] (a) J.F. Andersen, X.D. Ding, C. Balfour, T.K. Shokhireva, D.E. Champagne, F.A. Walker, W.R. Montfort, Biochemistry 39 (2000) 10118;
(b) Y. Kaneko, Y. Masao, T. Iio, T. Murase, Y. Chinzei, Biochim. Biophys. Acta 1431 (1999) 492.

[22] Y. Zhao, P.E. Brandish, D.P. Ballou, M.A. Marletta, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 14753.

[23] M. Hoshino, K. Ozawa, H. Seki, P.C. Ford, J. Am. Chem. Soc. 115 (1993) 9568.

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

[25] J.M. Giscavage, J.M. Fukuto, Y. Komori, L.J. Ignarro, J. Biol. Chem. 269 (1994) 21644.

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

[27] A. Czap, R. van Eldik, Dalton Trans. (2003) 665.

[28] (a) J.C. Patterson, I.M. Lorkovic', P.C. Ford, Inorg. Chem. 42 (2003) 4902;

(b) S.I. Gorelski, S.C. da Silva, A.B.P. Lever, D.W. Franco, Inorg. Chim. Acta 300–302 (2000) 698.
[29] P.C. Ford, J.R. Kuempel, H. Taube, Inorg. Chem. 7 (1968) 1967.
[30] (a) C.F. Works, P.C. Ford, J. Am. Chem. Soc. 122 (2000) 7592;
(b) C.F. Works, C.J. Jocher, G.D. Bart, X. Bu, P.C. Ford, Inorg. Chem. 41 (2002) 3728.
[31] (a) N.A. Davies, M.T. Wilson, E. Slade, S.P. Fricker, B.A. Murrer, N.A. Powell, G.R. Henderson, Chem. Commun. (1997) 47;
(b) B.R. Cameron, M.C. Darkes, H. Yee, M. Olsen, S.P. Fricker, R.T. Skerlj, G.J. Bridger, N.A. Davies, M.T. Wilson, D.J. Rose, J. Zubieta, Inorg. Chem. 42 (2003) 1868.
[32] A. Wanat, T. Schneppensieper, A. Karocki, G. Stochel, R. van Eldik, J. Chem. Soc., Dalton Trans. (2002) 941.
[33] (a) T. Matsubara, C. Creutz, J. Am. Chem. Soc. 100 (1978) 6255;
(b) T. Matsubara, C. Creutz, Inorg. Chem. 18 (1979) 1956.
[34] K.M. Miranda, X. Bu, I.M. Lorkovic, P.C. Ford, Inorg. Chem. 36 (1997) 4838.
[35] (a) K.M. Kadish, V.A. Adamian, E.V. Caemelbecke, Z. Tan, P. Tagliatesta, P. Bianco, T. Boschi, G.-B. Yi, M.A. Khan, G.B. Richter-Addo, Inorg. Chem. 35 (1996) 1343;
(b) D.S. Bohle, P.A. Goodson, B.D. Smith, Polyhedron 15 (1996) 3147;
(c) G.-.B. Yi, M.A. Khan, G.B. Richter-Addo, J. Chem. Soc. Chem. Commun. (1996) 2045;
(d) G.-B. Yi, M.A. Khan, G.B. Richter-Addo, Inorg. Chem. 35 (1996) 3453;
(e) S.J. Hodge, L.-.S. Wang, M.A. Khan, V.G. Young, G.B. Richter-Addo, J. Chem. Soc. Chem. Commun. (1996) 2283;
(f) D.S. Bohle, C.-H. Hung, B.D. Smith, Inorg. Chem. 37 (1998) 5798.
[36] I.M. Lorkovic, P.C. Ford, Inorg. Chem. 38 (1999) 1467.
[37] I.M. Lorkovic, P.C. Ford, J. Chem. Soc. Chem. Commun. (1998) 1225.
[38] (a) J. Conradie, T. Wondimagegn, A. Ghosh, J. Am. Chem. Soc. 125 (2003) 4968;
(b) J.C. Patterson, I.M. Lorkovic, P.C. Ford, Inorg. Chem. 42 (2003) 4902.
[39] I.M. Lorkovic, K.M. Miranda, B. Lee, S. Bernhard, J.R. Schoonover, P.C. Ford, J. Am. Chem. Soc. 120 (1998) 11674.
[40] (a) E.G. Moore, Q.H. Gibson, J. Biol. Chem. 251 (1976) 2788;
(b) E.J. Rose, B.M. Hoffman, J. Am. Chem. Soc. 105 (1983) 2866;
(c) M. Hoshino, L. Laverman, P.C. Ford, Coord. Chem. Rev. 187 (1999) 75, and references therein.
[41] (a) L.E. Laverman, P.C. Ford, Chem. Commun. (1999) 1843;
(b) L.E. Laverman, M. Hoshino, P.C. Ford, J. Am. Chem. Soc. 119 (1997) 12663;
(c) L.E. Laverman, P.C. Ford, J. Am. Chem. Soc. 123 (2001) 11614.
[42] L.E. Laverman, A. Wanat, J. Oszajca, G. Stochel, P.C. Ford, R. van Eldik, J. Am. Chem. Soc. 123 (2001) 285.
[43] I.J. Ostrich, L. Gordon, H.W. Dodgen, J.P. Hunt, Inorg. Chem. 19 (1980) 619.
[44] T. Schneppensieper, A. Zahl, R. van Eldik, Angew. Chem. Int. Ed. Engl. 40 (2001) 1678.
[45] M.H. Barley, T.J. Meyer, J. Am. Chem. Soc. 108 (1986) 5876.
[46] T.G. Traylor, J. Luo, J.A. Simon, P.C. Ford, J. Am. Chem. Soc. 114 (1992) 4340.
[47] W.D. Turley, H.W. Offen, J. Phys. Chem. 88 (1984) 3605.
[48] E. Caldin, Fast Reactions in Solution, Wiley, New York, 1964.
[49] S. Glasstone, K.J. Laidler, H. Eyring, The Theory of Rate Processes, McGraw-Hill, New York, 1941.
[50] A. Wanat, T. Schneppensieper, G. Stochel, R. van Eldik, E. Bill, K. Wieghardt, Inorg. Chem. 41 (2002) 4.
[51] (a) T.J. Swift, R.E. Connick, J. Chem. Phys. 37 (1962) 307;
(b) Y. Ducommun, K.E. Newman, A.E. Merbach, Inorg. Chem. 19 (1980) 3639.
[52] F. Roncaroli, J.A. Olabe, R. van Eldik, Inorg. Chem. 41 (2002) 5417.
[53] F. Roncaroli, J.A. Olabe, R. van Eldik, Inorg. Chem. 42 (2003) 4179.
[54] H.E. Toma, J.M. Malin, Inorg. Chem. 12 (1973) 2080.
[55] D.R. Crane, P.C. Ford, J. Am. Chem. Soc. 113 (1991) 8510.
[56] M. Hoshino, M. Maeda, R. Konishi, H. Seki, P.C. Ford, J. Am. Chem. Soc. 118 (1996) 5702.
[57] R.P. Cheney, M.G. Simic, M.Z. Hoffman, I.A. Taub, K. Asmus, Inorg. Chem. 16 (1977) 2187.
[58] M. Feelisch, J.S. Stamler (Eds.), Methods in Nitric Oxide Research, Wiley, Chichester, 1996 (Chapter 7).
[59] G.R.A. Wyllie, W.R. Scheidt, Chem. Rev. 102 (2002) 1067.
[60] (a) E.A. Dierks, S. Hu, K.M. Vogel, A.E. Yu, T.G. Sprio, J.N. Burstyn, J. Am. Chem. Soc. 119 (1997) 7316;
(b) M.F. Reynolds, J.N. Burstyn, Pharmacol. Rev. 43 (1991) 109 (Chapter 25).
[61] T. Schneppensieper, A. Wanat, G. Stochel, S. Goldstein, D. Meyerstein, R. van Eldik, Eur. J. Inorg. Chem. (2001) 2317.
[62] (a) J. Bourassa, W. DeGraff, S. Kudo, D.A. Wink, J.B. Mitchell, P.C. Ford, J. Am. Chem. Soc. 119 (1997) 2853;
(b) A.R. Butler, I.L. Megson, Chem. Rev. 102 (2002) 1155.
[63] (a) J. Bourassa, B. Lee, S. Bernhard, J. Schoonover, P.C. Ford, Inorg. Chem. 38 (1999) 2947;
(b) J. Bourassa, P.C. Ford, Coord. Chem. Rev. 200–202 (2000) 887;
(c) C.L. Conrado, J.L. Bourassa, C. Egler, S. Wecksler, P.C. Ford, Inorg. Chem. 42 (2003) 2288.
[64] (a) H.M. Abu-Soud, K. Ichimori, A. Presta, D.J. Stuehr, J. Biol. Chem. 275 (2000) 17349;
(b) J.S. Scheele, E. Bruner, V.G. Kharitonov, P. Martásek, L.J. Roman, B.S. Masters, V.S. Sharma, D.J. Magde, Biol. Chem. 274 (1999) 13105.
[65] (a) J.S. Olson, G.N. Phillips, J. Biol. Chem. 271 (1996) 17593;
(b) M. Ikeda-Saito, Y. Dou, T. Yonetani, J.S. Olson, T. Li, R. Regan, Q.H. Gibson, J. Biol. Chem. 268 (1993) 6855.
[66] (a) V.S. Sharma, D. Magde, Methods Comp. Methods Enzym. 19 (1999) 494;
(b) V.G. Kharitonov, M. Russwurm, D. Madge, V.S. Sharma, D. Koesling, Biochem. Biophys. Res. Commun. 239 (1997) 284.
[67] T. Takano, O.B. Kallai, R. Swanson, R.E. Dickerson, J. Biol. Chem. 248 (1973) 5244.
[68] (a) H. Frauenfelder, B.H. McMahon, R.H. Austin, K. Chu, J.T. Groves, Proc. Natl. Acad. Sci. U.S.A. 98 (2001) 2370;
(b) W. Cao, J.F. Christian, P.M. Champion, F. Rosca, J.T. Sage, Biochemistry 40 (2001) 5728.
[69] (a) R.E. Huie, S. Padmaja, Free Radic. Res. Commun. 18 (1993) 195;
(b) S. Goldstein, G. Czapski, Free Radicals Biol. Med. 34 (1995) 4041;
(c) R. Kissner, T. Nauser, P. Bougnon, P.G. Lye, W.H. Koppenol, Chem. Res. Toxicol. 10 (1997) 1285.
[70] T. Schneppensieper, A. Wanat, G. Stochel, R. van Eldik, Inorg. Chem. 41 (2002) 2565.
[71] H.M. Abu-Soud, S.L. Hazen, J. Biol. Chem. 275 (2000) 37524.