Binding of Organic Nitroso Compounds to Metalloporphyrins

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Introduction

In 1992, nitric oxide (NO) was selected by *Science* magazine as the "Molecule of the Year".[1] This was due largely to the discovery of a host of biological functions that NO participates in.[2,3] That same year, a book dealing exclusively with metal nitrosyls (metal−NO compounds) was published.[4] NO binds to the metal centers of heme-containing biomolecules such as the enzyme guanylyl cyclase (forming Fe−NO bonds).[5−7] These observations have helped make the study of metal−NO compounds interdisciplinary in nature, bridging traditional inorganic chemistry with biochemistry and pharmacology.

NO and related N_xO_y compounds effect nitrosation of organic substrates,[8] and the resulting X−N═O products (X = N, C, S, O donors) themselves exhibit diverse chemical and biological reactivity. Although a significant body of knowledge has been accumulated over the last 30 years or so on the interaction of NO with the metal centers in heme-containing biomolecules and heme models, the complementary structural studies and reaction chemistry of X−N═O compounds with heme and heme models were relatively unexplored at the time we initiated our studies in 1993. We were particularly interested in determining the modes of primary interactions of such X−N═O compounds (Figure 1) with metalloporphyrins (M = transition metal) as heme models, since the binding modes should play significant roles in the subsequent chemical reactivity of such groups. In this Account, our studies of the X−N═O interactions with synthetic metalloporphyrins as heme models are summarized and discussed. The X−N═O compounds investigated include *N*-nitroso, *C*-nitroso, *S*-nitroso, and *O*-nitroso functionalities (Figure 2). Each of these will be described in turn.

Nitrosamines (*N*-Nitroso)

Nitrosamines are carcinogenic and are known to interact with heme-containing biomolecules, resulting in activation and/or denitrosation of the nitrosamines.[9,10] Prior to 1995, no isolable metalloporphyrin complexes of nitrosamines had been reported, despite the observation that certain nitrosamines were proposed (by absorption and EPR spectroscopy) to bind directly to the ferric heme site of cytochrome P450.[11,12] We were able to prepare and isolate a ferric bis-nitrosamine complex by solvent displacement from a cationic ferric tetraphenylporphyrinato (TPP) complex (eq 1).[13,14] The resulting complex was

$$[(TPP)Fe(THF)_2]^+ + \text{excess } Et_2NNO \rightarrow [(TPP)Fe(ONNEt_2)_2]^+ + 2THF \quad (1)$$

crystallized as the perchlorate salt, and its solid-state structure was determined by single-crystal X-ray crystallography. The molecular structure (Figure 3) revealed a distinct η^1-O binding of the nitrosamine to the formally

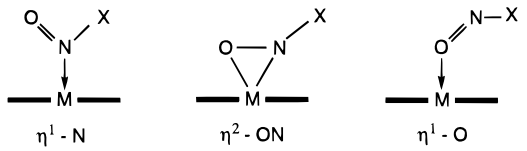

FIGURE 1. Binding modes of organic nitroso compounds to monometallic metal centers.

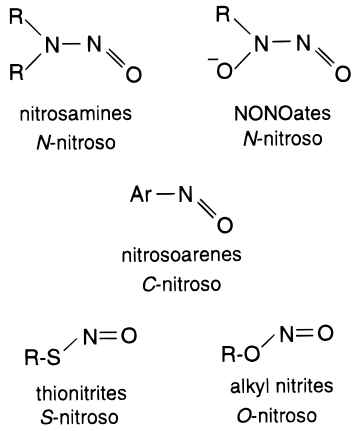

FIGURE 2. Representative organic nitroso compounds.

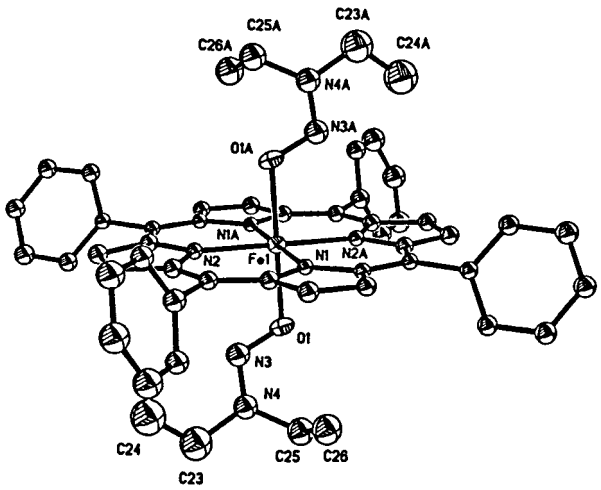

FIGURE 3. Molecular structure of $[(TPP)Fe(ONNEt_2)_2]^+$.

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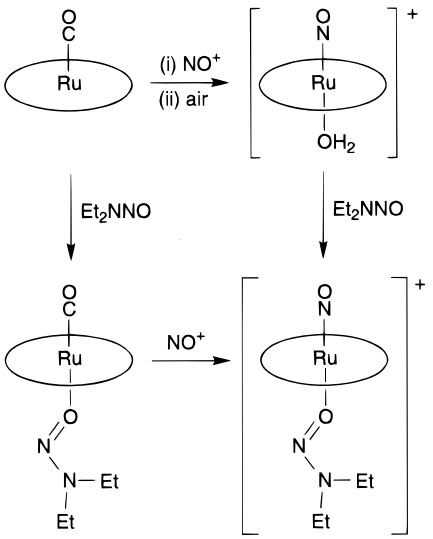
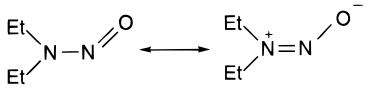


FIGURE 4. Nitrosamine complexes of ruthenium carbonyl and nitrosyl porphyrins.

high-spin Fe^{III} d^5 center. Importantly, the average N−O and N−N distances of the Et_2NNO ligands (1.273 and 1.282 Å, respectively) were suggestive of a contribution of the dipolar resonance structure (**B**) similar to that seen in the low-temperature solid-state structure of Me_2NNO.[15]



A **B**

Our attempts to prepare the analogous ferrous derivatives were not successful. However, the reaction of the ferric $[(TPP)Fe(ONNEt_2)_2]^+$ complex with NO gas resulted in the formation of a complex tentatively assigned as $[(TPP)Fe(ONNEt_2)(NO)]^+$, which should yield an Fe^{II} center if the nitrosyl ligand is formally assigned as NO^+. However, this nitrosyl nitrosamine complex is thermally unstable and readily loses the NO ligand. We then approached the stability problem by attempting to prepare the analogous Ru^{II} derivative, since Ru forms strong bonds to NO. The reactions involving the (OEP)Ru derivatives (OEP = octaethylporphyrinato dianion) are displayed in Figure 4.[14,16]

We succeeded in preparing diamagnetic Ru^{II}−carbonyl and −nitrosyl nitrosamine derivatives, with a successful X-ray crystallographic determination of the η^1-O binding mode of the nitrosamine in $(OEP)Ru(CO)(ONNEt_2)$. We were also able to prepare the related diamagnetic Os−carbonyl and −nitrosyl nitrosamine analogues of Figure 4 and determined that the nitrosamine ligand in (TTP)-$Os(CO)(ONNEt_2)$ (TTP = tetratolylporphyrinato dianion) was also η^1-O bound to the metal center.[14] The assignments of the vibrational frequencies for the bound nitrosamine ligands were aided by appropriate ^{15}N,^{18}O-isotopic substitutions. The isolation and full characterization of these complexes are of fundamental importance due to the biological significance of heme−nitrosamine interactions.

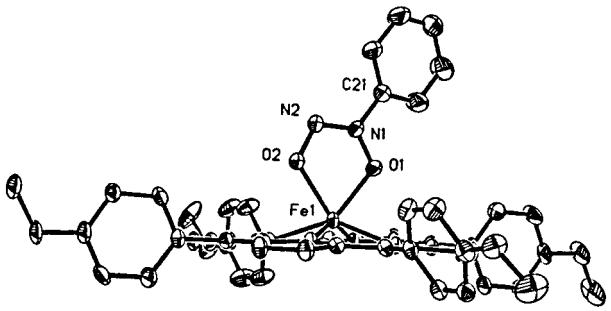


FIGURE 5. Molecular structure of $(T(p\text{-}OCH_3)PP)Fe(\eta^2\text{-}ON(Ph)NO)$.

NONOates/Cupferron (*N*-Nitroso)

Anionic compounds of the form $X[N_2O_2]^-$ are generally referred to as NONOates, due to the fact that they contain two NO groups ("NONO−") and are anionic ("-ate"). They are frequently employed as physiological NO-delivery agents.[17] We are interested in the possibility that heme groups are involved in the binding and activation of biologically important $X[N_2O_2]^-$ groups (X = R_2N, Ph; R = alkyl). Prior to our work, there were no definitive reports that illustrated how such groups could bind to the iron centers in heme models. We reported the first such metalloporphyrin−$(X[N_2O_2])$ complexes, and these were obtained from the metathesis reaction of the five-coordinate $(T(p\text{-}Y)PP)FeCl$ (Y = H, OCH_3) with AgON(Ph)-NO.[18] The X-ray structure of $(T(p\text{-}OCH_3)PP)Fe(\eta^2\text{-}ON(Ph)$-NO) is shown in Figure 5, and it revealed an η^2-O,O chelating mode of the axial ligand with an O−Fe−O bite angle of 71.52(9)°. The high-spin Fe^{III} d^5 atom is apically displaced by 0.69 Å out of the plane of the 24-atom porphyrin ring. To the best of our knowledge, this is the largest mean displacement of an Fe atom from a porphyrin ring. The origin and significance of this unusual structural feature is still under investigation.

Interestingly, protonation of $(TPP)Fe(\eta^2\text{-}ON(Ph)NO)$ with triflic acid generated the known (TPP)Fe(NO) compound, and nitrosobenzene was detected by IR and GC as the major organic byproduct in this reaction. Previously proposed mechanisms of physiological nitrosyl heme formation from NONOates excluded the possibility of a competing direct interaction between the NONOate and the heme center prior to nitrosyl heme formation. Our results demonstrated, for the first time, that the possibility exists for a direct interaction between metalloporphyrins and biologically active $X[N_2O_2]^-$ groups.

Nitrosoarenes (*C*-Nitroso)

Nitrosobenzene and its substituted analogues (ArNO; Ar = aryl) are known to bind to hemoglobin (Hb)[19] and cytochrome P450.[20] The related nitroso*alkanes* (RNO; R = alkyl) are also known to bind to Hb,[19,21] myoglobin (Mb),[21] guanylyl cyclase,[22] and NO synthase.[23] Mansuy prepared and structurally characterized the (TPP)Fe(*i*-PrNO)(*i*-$PrNH_2$) complex from the reaction of (TPP)FeCl with *i*-PrNHOH and *i*-$PrNH_2$.[24] The molecular structure of this complex revealed an η^1-N binding mode of the *i*-PrNO ligand. We were thus interested in the structural

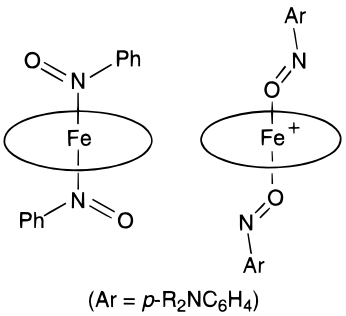


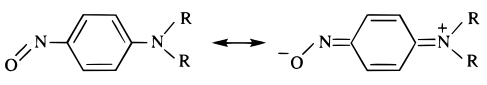
FIGURE 6. Nitrosoarene η^1-N binding to ferrous (left) and η^1-O binding to ferric (right) porphyrins.

aspects of ArNO binding to Fe and other group 8 metalloporphyrins in order to unambiguously establish the mode(s) of binding (Figure 1). To this end, we prepared and isolated representative nitrosoarene complexes of metalloporphyrins of Fe, Mn, and Os.

Iron and Manganese. Reaction of (TPP)Fe or (TPP)Fe(SR) with excess PhNO gives (TPP)Fe(PhNO)$_2$.[25] Interestingly, the reaction with (TPP)Fe(SR) involves a formal reduction of Fe^{III} to Fe^{II} during complex formation. The X-ray crystal structure of (TPP)Fe(PhNO)$_2$ reveals η^1-N binding of the PhNO ligands to the Fe^{II} center (Figure 6 (left)). The two PhNO ligands are oriented perpendicular to each other, and their C−NO groups bisect the porphyrin nitrogens. This is consistent with the view that the π-acid character of PhNO enables it to overlap favorably with the filled HOMO's of the low-spin d^6 Fe^{II} center, namely the $(d_{xz})^2(d_{yz})^2$ orbitals.

Attempts to obtain the analogous *ferric* [(TPP)Fe(PhNO)$_2$]$^+$ proved futile. For example, attempted oxidation of (TPP)Fe(PhNO)$_2$ resulted in loss of the axial PhNO ligands. Interestingly, similar losses of RNO/ArNO ligands from biologically relevant ferrous hemes have been observed upon oxidation of a nitrosomethane complex of guanylyl cyclase,[22] a nitrosobenzene complex of cytochrome P450,[20] and nitrosoalkane complexes of NO synthase.[23]

We previously suggested that the η^1-O binding of the nitrosamine ligands in [(TPP)Fe^{III}(ONNEt$_2$)$_2$]$^+$ (Figure 3) was stabilized by a contribution from a dipolar structure that places a substantial negative charge on the nitroso oxygen. We then attempted the use of diakylamino-substituted nitrosoarenes, since a related dipolar contribution (**D**) might play a role in stabilizing nitroso η^1-O



binding to the cationic ferric center in [(TPP)Fe(ONC$_6$H$_4$NR$_2$)$_2$]$^+$ (R = Me, Et). Indeed, the use of the dialkylamino-substituted nitrosoarenes provided a convenient basis for synthesizing the ferric compounds [(TPP)Fe(ONC$_6$H$_4$NR$_2$)$_2$]$^+$, and the crystal structure of the diethylamino analogue revealed a distinct η^1-O binding to Fe^{III} as drawn in Figure 6 (right).

These structural features (i.e., η^1-N binding to the "softer" Fe^{II} and η^1-O binding to the "harder" Fe^{III}) were

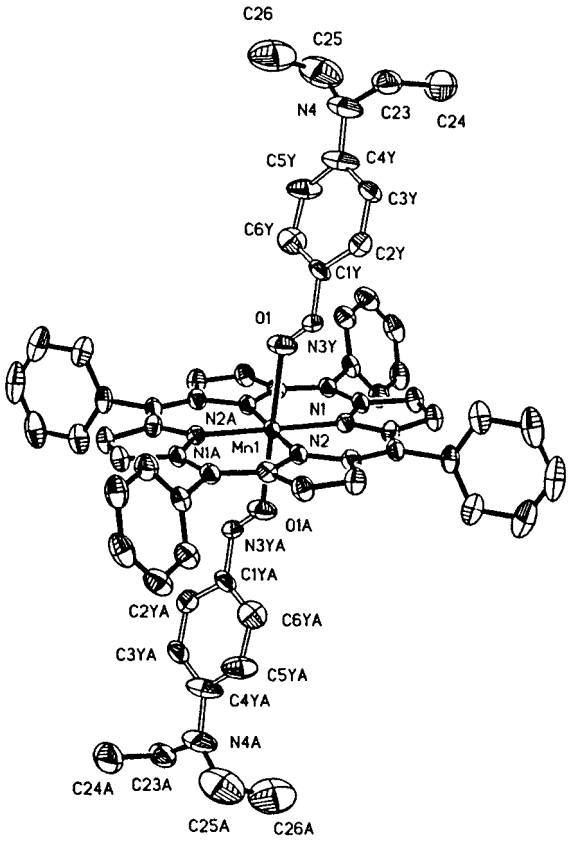


FIGURE 7. Molecular structure of [(TPP)Mn(ONC$_6$H$_4$NEt$_2$)$_2$]$^+$.

not entirely unexpected; however, it was the first time that this difference in nitroso binding to metalloporphyrins was demonstrated. The related Mn^{III} d^4 analogue, [(TPP)Mn(ONC$_6$H$_4$NEt$_2$)$_2$]$^+$, also exhibited the unique η^1-O binding mode of the nitrosoarene (Figure 7).[26] Prior to our work in this area, it had been suggested (based on the structural data available at the time) that η^1-O binding of RNO ligands was probably limited only to main group and d^{10} metals.[27] Importantly, the Fe^{III} and Mn^{III} nitrosoarene porphyrin compounds represent the first distinct η^1-O bound RNO complexes of non-d^{10} transition metals to be reported.

Osmium. We extended our studies on ArNO binding to include Os porphyrins (Figure 8), and we were able to isolate a series of Os^{II}−ArNO porphyrins that provided us with a better understanding of the π-acid nature of the ArNO ligands in their group 8 metalloporphyrin complexes.[28]

The reactions of the (por)Os(CO) precursors (por = TPP, TTP, OEP, TMP (tetramesitylporphyrinato dianion)) with PhNO in refluxing toluene generated the respective (por)Os(PhNO)$_2$ complexes. The ν_{NO}'s of the coordinated PhNO groups in the (por)Os(PhNO)$_2$ complexes occurred in the 1295−1276 cm^{-1} range and decreased only slightly in the order TPP (1295 cm^{-1}) > TTP (1291 cm^{-1}) > OEP (1286 cm^{-1}) > TMP (1276 cm^{-1}). Interestingly, we found that the reaction of (TTP)Os(CO) with 1 equiv of PhNO in CH_2Cl_2 at room temperature generated a 3:1 mixture of (TTP)Os(PhNO)$_2$ and (TTP)Os(CO)(PhNO). The ν_{CO} of the mono-nitrosobenzene (TTP)Os(CO)(PhNO) complex was

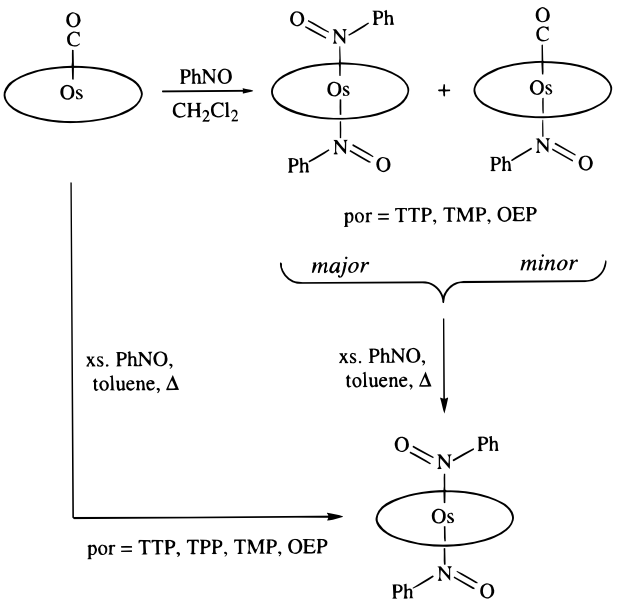


FIGURE 8. Nitrosobenzene complexes of osmium porphyrins.

observed at 1972 cm^{-1} (KBr), which is 56 cm^{-1} *higher* in energy than that of the precursor (TTP)Os(CO). IR monitoring of the reactions of the other (por)Os(CO) compounds with 1 equiv of PhNO in CH_2Cl_2 revealed similar formations of the respective (por)Os(CO)(PhNO) intermediates for the TTP ($\Delta\nu_{CO} = +74$ cm^{-1}), TMP ($\Delta\nu_{CO} = +63$ cm^{-1}), and OEP ($\Delta\nu_{CO} = +72$ cm^{-1}) analogues. These observations are consistent with the PhNO ligand acting as a π-acid ligand toward the (por)Os(CO) fragments, thus making *less* electron density available for Os^{II}−CO back-donation, thereby raising ν_{CO}. For comparison, the coordination of Lewis bases to (por)Os(CO) compounds generally results in a lowering of ν_{CO} in the (por)Os(CO)(L) derivatives (L = Lewis base).

Not surprisingly, quantitative conversion to the (TTP)Os$(PhNO)_2$ product occurred when the mixture of (TTP)Os$(PhNO)_2$ and (TTP)Os(CO)(PhNO) was dissolved in toluene and the solution was heated to reflux in the presence of excess PhNO. The PhNO ligands in these complexes are attached to the formally Os^{II} centers via an η^1-N binding mode, as determined by single-crystal X-ray crystallography for several of these complexes. The PhNO ligands in the (por)Os$(PhNO)_2$ complexes are also oriented perpendicular to each other and essentially bisect porphyrin nitrogens as shown in Figure 9 (similar orientations were observed for the (TPP)Fe$(PhNO)_2$ complex described earlier).

To determine if steric effects on the porphyrin macrocycle could alter axial PhNO ligand orientations, we employed the sterically demanding TMP macrocycle to determine if the sterically enhanced meso position of the TMP macrocycle would force the PhNO nitroso fragments to move away from the meso carbons so as to essentially eclipse the porphyrin nitrogens. As shown in Figure 9, the TMP macrocycle did not have any substantial effect on the orientations of the axial PhNO ligands in the (TMP)Os$(PhNO)_2$ complex, although the TMP macrocycle was found to be the most distorted from ideal planarity in this

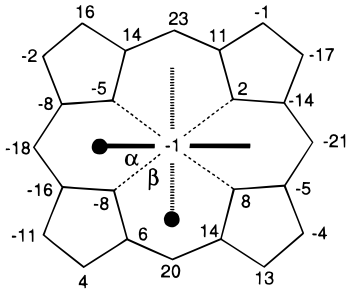


FIGURE 9. Nitrosobenzene orientations in (TMP)Os$(PhNO)_2$: α and β are torsion angles involving O−N−Os−N(por). The solid dot represents the nitroso oxygen atom, the solid line represents the O−N−C unit of the PhNO ligand situated above the plane, and the dashed line represents the equivalent group situated below the plane. Perpendicular atom displacements from the 24-atom porphyrin plane (in 0.01 Å units) are also shown.

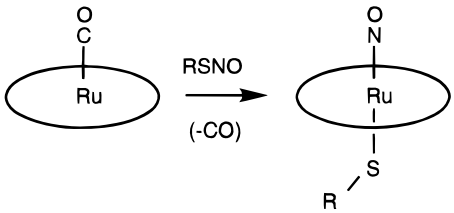


FIGURE 10. Formal trans addition of thionitrites (RSNO) to ruthenium carbonyl porphyrins.

series of bis-nitrosobenzene complexes. This observation implies that the PhNO binding orientations are largely determined by the electronic environment rather than steric effects in this series of complexes.

Thionitrites (*S*-Nitroso) and Alkyl Nitrites (*O*-Nitroso)

With structural information on the binding of *N*-nitroso and *C*-nitroso compounds to metalloporphyrins at hand, we turned our attention to the *S*-nitroso and *O*-nitroso compounds, since these latter nitroso compounds display vasodilator properties. We were especially interested in the interactions of these X−N═O derivatives with heme models, since these X−N═O compounds are frequently employed as vasodilator drugs. Indeed, the reported ability of RSNO to activate guanylyl cyclase (without *prior* NO release from simple decomposition of RSNO)[29−31] leads to the intriguing question of how RSNO might bind directly to the heme site of guanylyl cyclase. Hence, our initial goal was to prepare isolable adducts of RSNO and/or RONO compounds with group 8 metalloporphyrins.

Ruthenium and Osmium. We were intrigued to find that the reaction of (OEP)Ru(CO) with 1 equiv of *S*-nitroso-*N*-acetyl-L-cysteine methyl ester at room temperature was instantaneous and generated the nitrosyl thiolate (OEP)Ru(NO)(*S*-NACysMe) (*S*-NACysMe = *N*-acetyl-L-cysteinate methyl ester) as shown in a general form in Figure 10.[32,33] These additions occur for RSNO groups with primary carbons attached to sulfur (cysteine derivatives) as well as with tertiary carbons attached to sulfur (penicillamine

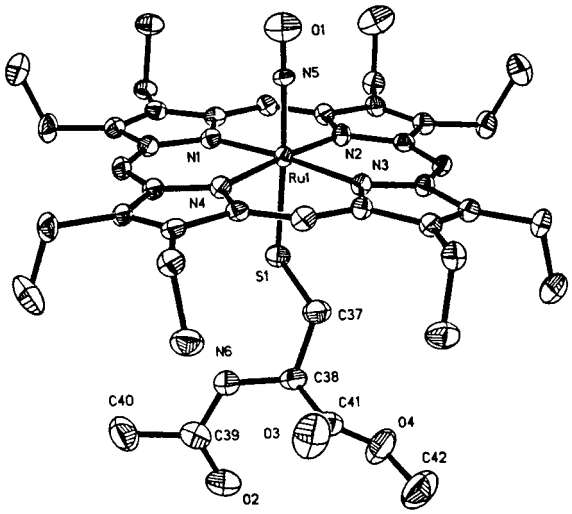


FIGURE 11. Molecular structure of (OEP)Ru(NO)(*S*-NACysMe).

derivatives). The molecular structure of the cysteinate (OEP)Ru(NO)(*S*-NACysMe) product, resulting from a formal trans addition of RSNO to the metal center, is shown in Figure 11. We have established similar reactivity of RSNO and RONO with Ru^{II} and Os^{II} porphyrins. We found that the RONO reactions and the Os reactions were slower and were more amenable to IR spectroscopic monitoring of ν_{CO} and ν_{NO}.

Our observation of the formal trans addition of RSNO and RONO to the metal site in metalloporphyrins is unprecedented in chemistry and biochemistry. Thus, although the reaction of (por)Ru(CO) with RSNO resulted in the generation of the nitrosyl thiolate (por)Ru(NO)(SR) in high yields, questions arose as to the plausible reaction pathway(s) for this formal trans addition. In general, two main paths were envisaged (Figure 12).

Initial *S*-binding of RSNO (top of Figure 12) could result in S−N bond cleavage to give the stable NO radical which could then react with the (por)M(CO)(SR) intermediate to generate the observed nitrosyl product. Another possibility is the direct attack of the generated NO radical on the precursor (por)M(CO). We favor the former possibility, since we[34] and others[35,36] have shown that reactions between (por)Ru(CO) (por = TPP, OEP) or $[(TTP)Ru]_2$ and NO gas lead to the formation of (por)Ru(NO)(ONO) complexes.

N-Binding of RSNO (bottom of Figure 12) would generate a Ru−NO bond, which is generally strong. The SR thus released could either form disulfide or react with the proposed (por)M(CO)(NO) to give the product. We do not favor this bottom pathway, since in our studies the formation of (por)M(CO)(NO) was not observed, nor did we detect any RSSR either in the bulk scale reaction or in the ^{1}H NMR tube reaction.

IR spectroscopic monitoring of the reaction of (OEP)Os(CO) with PhSNO revealed the formation of an intermediate complex (OEP)Os(CO)(SPh) with ν_{CO} 1957 cm^{-1} (top of Figure 13).[37] The higher ν_{CO} of this intermediate compared to the starting compound (OEP)Os(CO) is consistent with moving from the Os^{II} oxidation state in starting (OEP)Os(CO) to the Os^{III} state in the (OEP)Os(CO)(SPh) intermediate. In time, the nitrosyl thiolate product formed from the attack of NO on the carbonyl thiolate intermediate.

To further examine this PhSNO addition reaction, we employed the valence isoelectronic phenyl aryl azo sulfide (PhSN=NAr; Ar = *p*-$C_6H_4NO_2$) as shown at the bottom of

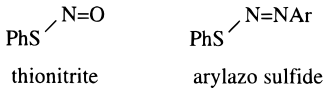


Figure 13.[37] In this particular reaction, the same (OEP)Os(CO)(SPh) intermediate formed (as judged by IR spectroscopy), but the azo radical that was produced did not survive the reaction conditions to give the aryldiazonium thiolate product. Reaction of the carbonyl thiolate intermediate with NO gave the expected (OEP)Os(NO)(SPh) product as well as some $(OEP)Os(NO)_2$. This latter dinitrosyl byproduct[38] results from the reaction of excess NO with the nitrosyl thiolate complex. Thus, we postulate that, indeed, the reaction proceeds via *sulfur* attack (and not nitrogen attack) at the osmium center in these complexes (top of Figure 12).

If sulfur attack was indeed the case, then the use of the non-carbonyl-containing $[(OEP)Os]_2$ dimer in the reaction with PhSN=NAr (Figure 14) would be predicted to generate the bis-thiolate species shown as the final product. We tested this hypothesis and found that the

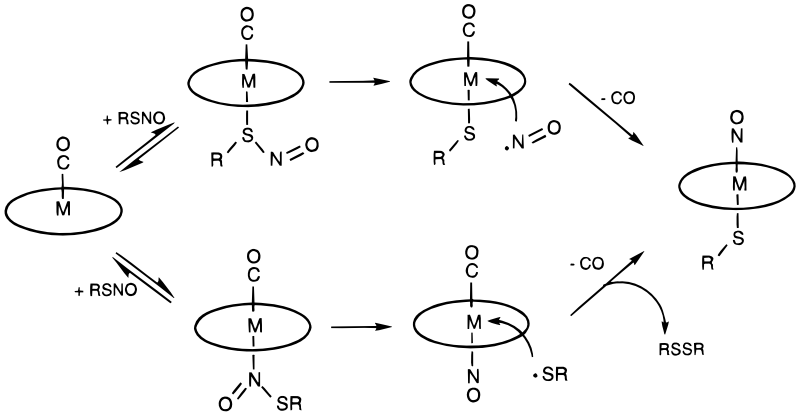


FIGURE 12. Two pathways for thionitrite addition to carbonyl metalloporphyrins (M = Ru, Os).

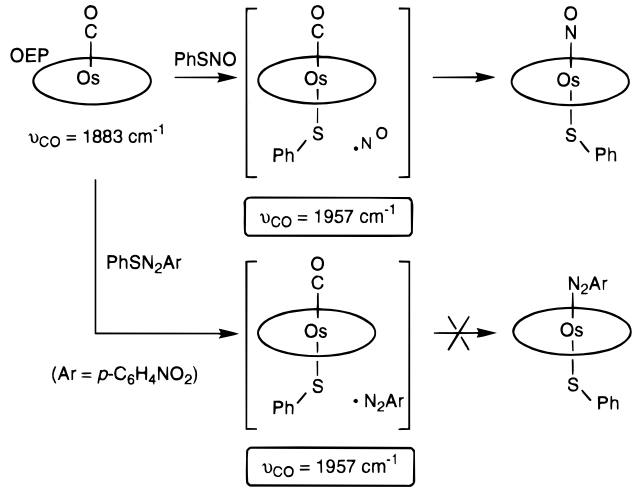


FIGURE 13. Comparative reactions of thionitrites and arylazo sulfides with (OEP)Os(CO).

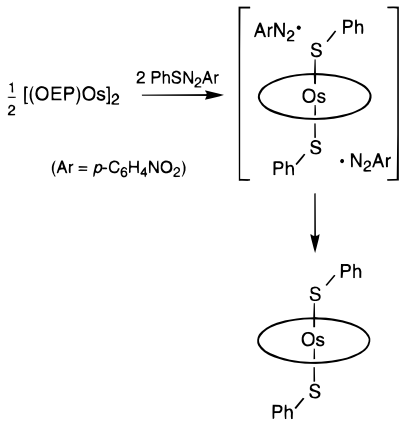


FIGURE 14. Reaction of arylazo sulfides with the non-carbonyl-containing [(OEP)Os]$_2$.

reaction proceeded as predicted, with the final (and previously reported)[39] product being characterized by conventional spectroscopic techniques and by single-crystal X-ray crystallography.

We then turned our attention to the reaction of RSNO with Os^{III} porphyrins. These reactions were not as straightforward, and an example is shown in eq 2. In this

$$[(OEP)Os]_2(PF_6)_2 + i\text{-}C_5H_{11}SNO \rightarrow 2[(OEP)Os(NO)]PF_6 \rightarrow 2(OEP)Os(NO)(O_2PF_2) \quad (2)$$

particular reaction, the RSNO group transfers the NO moiety to the Os porphyrin to form the cationic [(OEP)-Os(NO)]PF_6 intermediate, which undergoes anion hydrolysis to generate the difluorophosphate nitrosyl complex shown in Figure 15.

Iron. These RSNO and RONO addition reactions for Ru and Os were extended to Fe porphyrins as well.[32] The reaction of *S*-nitroso-*N*-acetyl-L-cysteine methyl ester (RSNO) with ferrous (TPP)Fe(THF)$_2$ only led to the generation of the known five-coordinate (TPP)Fe(NO) product in almost quantitative yield (top of Figure 16).

On the other hand, the reaction of ferric [(TPP)Fe-(THF)$_2$]$^+$ with isoamyl nitrite (RONO) resulted in the

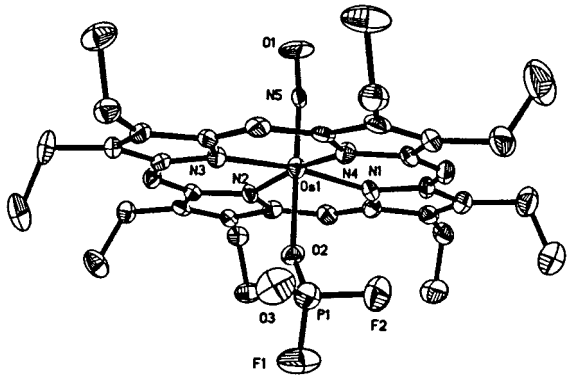


FIGURE 15. Molecular structure of (OEP)Os(NO)(O_2PF_2).

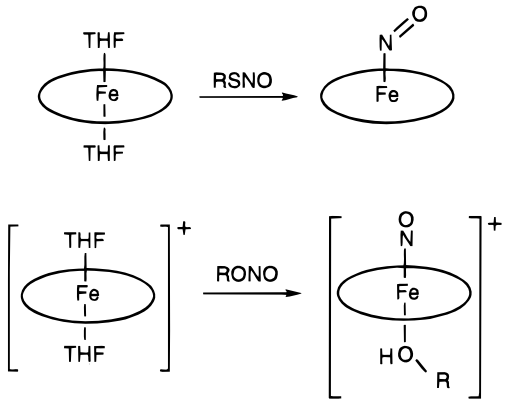


FIGURE 16. Reactions of thionitrites (RSNO) and alkyl nitrites (RONO) with iron porphyrins.

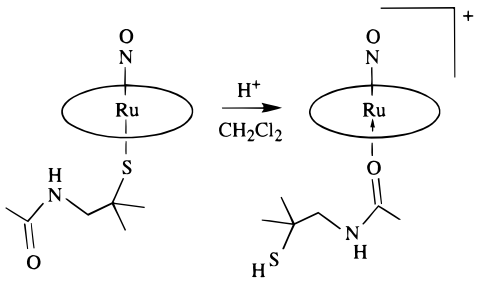


FIGURE 17. Protonation of a ruthenium nitrosyl thiolate.

formation of the cationic nitrosyl alcohol complex [(TPP)-Fe(NO)(HO-i-C_5H_{11})]$^+$ (bottom of Figure 16), whose X-ray crystal structure has been determined.

Protonation Reactions. We are currently exploring the characteristic reaction chemistry of the resulting six-coordinate (por)M(NO)(SR) compounds. Protonation of (OEP)Ru(NO)(SCH_2CF_3) with triflic acid gives (OEP)Ru-(NO)(OTf) and the free thiol. This low affinity of thiols for the cationic Ru−NO center is best exemplified by a related reaction involving heteroatom-containing thiolate ligands. Protonation of one such complex (containing an amide-thiol ligand) resulted in a remarkable ligand rearrangement process (Figure 17).[40] The molecular structures of both Ru compounds in Figure 17 were determined by X-ray crystallography. Extensions of the type of chemistry described in this section to biologically important RSNO and RONO ligands are in progress.

Concluding Remarks

During the last four years, we have investigated the fundamental bio-coordination chemistry of biologically important X−N═O groups, and we have established the nature of the interactions of *N*-nitroso groups (in nitrosamines and NONOates), *C*-nitroso groups (in nitrosoarenes), *S*-nitroso groups (in thionitrites), and *O*-nitroso groups (in alkyl nitrites) with the metal centers in metalloporphyrins. In summary, we have succeeded in isolating and characterizing discrete adducts of *N*-nitroso (nitrosamines, NONOates) and *C*-nitroso (nitrosoarenes) compounds with metalloporphyrins and have shown that the nitroso groups interact with the metal centers via either the N or O atoms.

We have so far not been successful in isolating discrete complexes of *S*-nitroso or *O*-nitroso compounds with metalloporphyrins. Interestingly, these latter nitroso compounds are those that interact with the metal centers via the non-nitrosyl heteroatoms (releasing NO). This dichotomy of the *N*- and *C*-nitroso compounds versus the *S*- and *O*-nitroso compounds provides grounds for further study of their diverse reaction chemistry. Information gained by further examination of metal−nitroso interactions should be relevant to diverse chemical and physiological processes involving nitroso ligands in particular and to nitrosyl chemistry in general.

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