Interactions of Organic Nitroso Compounds with Metals

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I. Introduction

The chemistry of organic nitroso compounds (X−N═O) is in many ways linked to the chemistry of nitric oxide (NO). In addition to reacting with metal compounds to form metal nitrosyl derivatives,[1] the "NO" group or its activated forms may react with some organic fragments to form X−N═O species. In this review, we will examine four main types of X−N═O compounds and their interactions with metal centers. The four main types of X−N═O compounds discussed in this review are illustrated in Figure 1, and they are the *C*-nitroso (nitrosoalkane, nitrosoarene), *N*-nitroso (nitrosamine), *O*-nitroso (alkyl nitrite), and *S*-nitroso (alkyl/aryl thionitrite; nitrosothiol) compounds. For each of these, we will briefly describe the syntheses and properties of the organic X−N═O compounds and then examine the published literature on their reactions with metal compounds. We will limit our coverage to the interactions that produce isolable or spectroscopically detectable metal−XNO derivatives.

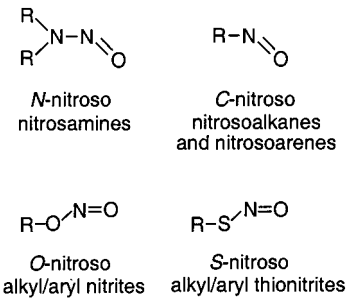

Figure 1. Classification of X−N═O compounds in this work.

II. C-Nitroso Compounds

A. Organic Compounds

1. Synthesis

A variety of methods have been used to prepare *C*-nitroso compounds, and comprehensive reviews up to 1979[2] and 1988[3] have been published. In general, *C*-nitrosation can be accomplished by the following processes.

(1) Oxidation of Amines and N-Substituted Hydroxylamines (e.g., by peroxy acids)

$$RNH_2 \rightarrow RNHOH \rightarrow RNO \qquad (1)$$

In some cases, the *N*-substituted hydroxylamine is obtained by reduction of the nitro RNO_2 compound.[2]

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Jonghyuk Lee was born in Seoul, Korea, in 1971. He served in the Army of the Republic of Korea from 1992 to 1994. He received his B.S. degree in Chemistry under the guidance of Professor Sang Woo Lee from Kwangwoon University in Korea in 1997. He joined the laboratory of George Richter-Addo at the University of Oklahoma in 1997. His research deals with the interactions of *C*-nitroso, *O*-nitroso, and *S*-nitroso compounds with synthetic heme models. He received the J. J. Zuckerman Award for Outstanding Research Achievement in Chemistry (OU) in 2001. He is currently writing his Ph.D. thesis.

Li Chen received her B.S. (1988) and M.S. (1991) degrees in Physical Chemistry from the University of Science and Technology of China in Hefei. She subsequently worked for SINOCHEM Lianyungang Imp/Exp Company in Lianyungang, China, from 1991 to 1994. She then pursued doctoral studies at the University of Oklahoma, where she performed research in bioinorganic chemistry under the direction of George Richter-Addo. She obtained her Ph.D. degree in 1998 and stayed on as a postdoctoral research associate until 2001. She currently works for the ExxonMobil Exploration Company located in Houston, TX.

Oxidation of the hydroxylamine then gives the desired nitroso product. Aromatic *C*-nitroso compounds have also been prepared by oxidation of hydroxylamines using ferric chloride,[4] pyridinium chlorochromate in THF,[5] or *tert*-butyl hypochlorite in diethyl ether or THF.[6]

(2) H-Replacement in C−H Bonds. Nitrous acid and other nitrosating agents can react with the C−H bonds adjacent to electron-withdrawing groups (eq 2; X = NO_2, CN, etc.) to result in *C*-nitrosation.

$$R_2C(H)X \rightarrow R_2C(NO)X \qquad (2)$$

Nitrosation of ketones has been achieved in this manner. These nitrosations frequently result in the production of oxime tautomers R′CH=NOH as the final products if the nitrosation occurs at a methylene or methyl group. Aromatic *C*-nitrosation has also been accomplished using nitrous acid, NO^+, or other nitrogen oxides (N_xO_y).[2,3,7]

Ann West is an Assistant Professor in the Department of Chemistry and Biochemistry at the University of Oklahoma. Her Ph.D. degree (1991) is in Genetics from Yale University, where she worked with Arthur Horwich on mitochondrial protein import. She received postdoctoral research training in protein biochemistry and X-ray crystallography with Ann Stock at the University of Medicine and Dentistry of New Jersey. During her postdoctoral training, she studied signal transduction proteins that control bacterial chemotaxis. Since joining the faculty at OU, research in her laboratory has focused on phosphorylation-regulated signal transduction proteins that control the ability of yeast cells to adapt to hyperosmotic stress. Her studies are aimed at biochemical and X-ray crystallographic characterization of signal transduction proteins and, in collaboration with George Richter-Addo's laboratory, heme-binding proteins.

George Richter-Addo was born in Glasgow, Scotland, to a Ghanaian father and German mother. He received his Honors B.S. and Dip.Ed. degrees (1982) from the University of Cape Coast in Ghana. He joined graduate school at the University of British Columbia in Canada in 1983 and performed research in organometallic nitrosyl chemistry under the direction of Peter Legzdins. He obtained his Ph.D. degree in 1988 and subsequently did postdoctoral work at the University of Alberta (with Allen Hunter), UBC (with Legzdins), and the University of Utah (with John Gladysz). He joined the faculty at the University of Oklahoma in 1993, where he is now a Professor in the Inorganic Division and a University of Oklahoma Presidential Professor. His research work lies at the interface of inorganic chemistry and biochemistry and deals with the interactions of NO and organic nitroso compounds with metalloporphyrins and heme. He completed a one-year sabbatical (2000) in the laboratory of Ann West, where they established a collaborative research program on heme-binding proteins.

Kochi and co-workers demonstrated the direct and selective nitrosation of arenes (polymethylbenzenes and anisoles) by the nitrosonium NO^+ cation in acetonitrile,[8] e.g.

$$C_6H_5OMe + NOBF_4 \rightarrow p\text{-}ONC_6H_4OMe + HBF_4 \qquad (3)$$

They also used femtosecond time-resolved laser spectroscopy to directly observe the Wheland intermediate (the σ-complex nitrosoarenium cation, $[Ar(H)NO]^+$) in the electrophilic aromatic substitution reaction.[9] Aromatic nitrosations using nitrosonium ethyl sulfate have been reported.[10] Alkyl nitrites may also react with substituted phenolate ions in aqueous solution to give the aromatic *C*-nitroso compounds as the final products.[11]

(3) Reaction of Organometallic Reagents with Nitrosating Agents. The coordinated R groups in a number of organometallic compounds can be nitrosated,[12] e.g.

$$\{CH_3(CH_2)_3C{\equiv}C\}_2Hg + 2\ ClNO \rightarrow 2\ CH_3(CH_2)_3C{\equiv}CNO \quad (4)$$

Similar reactions with Grignard and alkyllithium reagents have been reported.[2,3,12]

(4) Addition of Nitrosyl Halides or Other XNO Compounds Across the Double Bonds of Alkenes. An example of this type of reaction is shown in eq 5.

$$R_2C{=}CR_2 + ClNO \rightarrow R_2(Cl)C{-}C(NO)R_2 \quad (5)$$

(5) Nitrosation of Alkanes by ClNO. This reaction probably proceeds via initial photogeneration of $Cl^\bullet$ (and NO) which initiates production of $R^\bullet$ radicals that combine with NO to give RNO. Photolysis of the perfluoroalkyl iodides R_FI ($R_F = CF_3$, C_3F_7) similarly gives $R_F^\bullet$, which can combine with NO to give R_FNO.[13]

2. Spectroscopy and Structure

C-Nitroso compounds can exist either as monomers or dimers. The dimers are azodioxy compounds and can be either cis (*Z*-dimers) or trans (*E*-dimers) as illustrated in Figure 2.

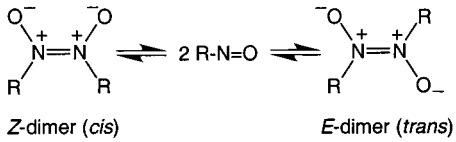


Figure 2. Dimerization of *C*-nitroso compounds.

In general, the dimers are colorless, but the monomers are blue (aliphatic) or green (aromatic) due to a weak $n \rightarrow \pi^*$ transition at 630−790 nm.[2] The characteristic absorption in the visible region giving monomeric *C*-nitroso compounds their blue color was first identified in perfluoroalkyl nitroso compounds R_FNO in the early 1950s by Banus (Mason).[13,14] The *trans*-dimers of aliphatic RNO compounds have a $\pi \rightarrow \pi^*$ transition at ~276−291 nm, and the absorption bands for the *cis*-dimers are at 265−271 nm.[2] Mason (Banus) suggested that in the perfluoroalkyl nitroso compounds R_FNO ($R_F = CF_3$, C_3F_7), the strongly electron-withdrawing R_F substituents on nitrogen effectively prevent the N→O electron density transfer required for the dimerization process.[13] Glaser and co-workers suggested that the electron density transfer to the most electronegative element is the driving force for dimer formation and that this density transfer is made possible by *N*-rehybridization.[15] Gowenlock, Orrell, and co-workers utilized activation free energies for nitroso group rotation (obtained from NMR spectroscopy, in combination with the nitroso $^{14,15}N$ and ^{17}O chemical shifts) as reliable indicators of self-dimerization of RNO compounds.[16] For example, they found that RNO compounds with NO rotational free energies >38 kJ mol^{-1} showed no tendency to dimerize. In contrast, those having NO rotational free energies <38 kJ mol^{-1} existed as dimers in the solid phase and as monomer−dimer mixtures in equilibrium in solution.[16] The NMR criteria are considered more reliable indicators than previously described IR criteria.[16b] The spectral properties of *C*-nitroso compounds depend on their structures either as monomers or *cis*- or *trans*-dimers. Hence, we will briefly examine the structures of *C*-nitroso compounds and then discuss their spectroscopic properties.

Single-crystal X-ray crystallographic data for *C*-nitroso compounds are listed in Tables 1−4. The data from microwave spectroscopy and electron diffraction for CH_3NO, CF_3NO, CH_3CH_2NO, and $CClF_2NO$ are included for comparison.

Table 1 lists the data for nitrosoalkanes (NO bonded through the N-atom to an sp^3 carbon atom). The *monomeric* aliphatic RNO compounds display N−O bond lengths in the 1.1−1.22 Å range and C−N−O angles in the broad 103−121° range. It has been suggested that a contribution of the ionic form $(CF_3)^-(NO)^+$ is responsible for the somewhat longer C−N and shorter (and stronger) N−O bonds in CF_3NO vs CH_3NO, although the differences are small.[17a,20a] This $X^-(NO)^+$ contribution is similar to that proposed by Ketelaar and Palmer for the nitrosyl halides.[17b] The *dimeric* compounds display N−N bond distances of 1.22−1.33 Å, which are significantly shorter than a formal N−N single bond distance of 1.42 Å,[95] and imply double-bond character to this unit. Consistent with this is the observation of distinct cis and trans isomers. Only one X-ray crystal structure of a nonconstrained *cis*-dimer of a nitrosoalkane has been determined, namely, that of *cis*-$(CH_3NO)_2$. In this compound, the N−N and N−O bond distances are both 1.31(2) Å.[19a] Several crystal structures of constrained *cis*-$(RNO)_2$ compounds containing a "cyclic" (R_2)-link have been determined.[30−32] In these latter compounds, the N−N and N−O bond lengths fall in the ranges of 1.29−1.32 and 1.25−1.27 Å, respectively. Importantly, the increased N−O bond lengths relative to those of monomeric RNO compounds are consistent with a contribution of the dipolar azodioxy structure. The crystal structures of the aliphatic *trans*-$(RNO)_2$ compounds show N−N and N−O bond distances of 1.22−1.33 and 1.25−1.30 Å, respectively.

Table 2 lists the crystal structure data for nitrosoarenes. The N−O bond lengths in the monomers generally fall in the 1.13−1.29 Å range, although a bond length of 1.34 Å has been reported for a disordered component of a nitrosoarene.[62] The related N−O bond lengths in the dimeric compounds fall in the rather narrow range of 1.25−1.28 Å, with the

Table 1. Structural Data for Nonaromatic *C*-Nitroso Monomers and Dimers

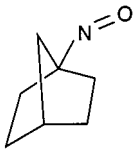
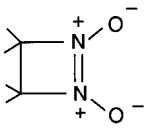
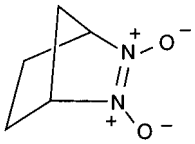
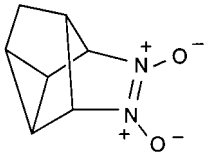
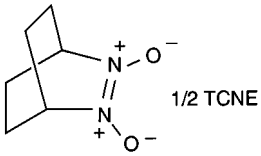
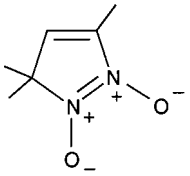
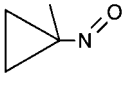
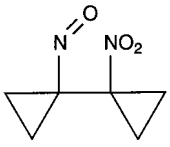
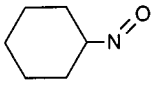
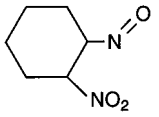
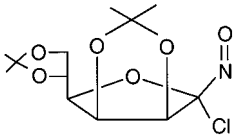
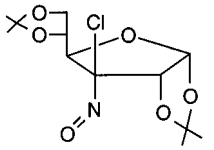
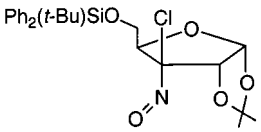
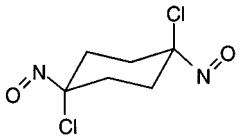
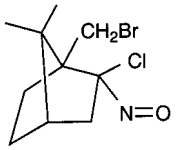
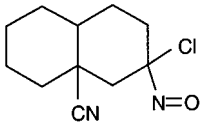
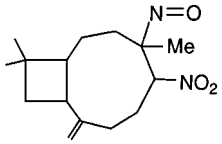
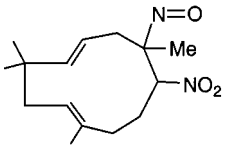
compound		N−N (Å)	C−N (Å)	N−O (Å)	C−N−O (°)	ref
CH_3NO[a]	monomer		1.480	1.211	113.2	18a
CH_3NO[a]	monomer		1.49(3)	1.22(3)	112.6(10)	18b
CH_3NO	*cis*-dimer	1.31(2)	1.47(3)	1.31(2)	120.0(15)	19a
CH_3NO	*trans*-dimer	1.22	1.57	1.25	125	19b
CF_3NO[b]	monomer		1.555(15)	1.171(8)	121.0(16)	20a
CF_3NO[b]	monomer		1.546(8)	1.197(5)	113.2(13)	20b
CF_3NO[a]	monomer		1.512(16)	1.198(4)	112.4(3)	20c
$CClF_2NO$[b]	monomer					
	syn form		1.567(5)	1.175(3)	110.8(12)	21
	gauche form		1.559(5)	1.179(3)	110.7(12)	21
CH_3CH_2NO[a]	monomer					
	syn form		1.490(9)	1.213(6)	113.7(3)	22
$O_2NCH_2CH_2NO$	*trans*-dimer	1.304(6)	1.470(4)	1.262(4)	121.38(30)	23
$O_2NCH_2CH(Ph)NO$	*trans*-dimer	1.301(4)	1.479(3)	1.269(3)	120.9(2)	24
Me_2CHCH_2NO	*trans*-dimer	1.27(2)	1.51(2)	1.30(2)	120.5	25
$ClMe_2CCH(Me)NO$	*trans*-dimer	1.315(4)	1.500(3)	1.270(3)	120.02(19)	13
t-BuNO	*trans*-dimer	1.309(2)	1.533(2)	1.265(2)	119.65(14)	26
O_2NCMe_2NO	*trans*-dimer	1.329(3)	1.506(2)	1.251(2)	121.2(1)	27
$(B_{10}C_{12}H_{31}O)CH_2NO$	*trans*-dimer	1.272(6)	1.485[c]	1.293(6)	121.1[c]	28
	*trans*-dimer	1.308(6)	1.483(5)	1.269(4)	120.7(3)	29
		1.292(10)	1.527(7)	1.250(6)	135.4(5)	30
		1.303(1)	1.496(2) 1.490(2)	1.256(1) 1.264(1)	128.0(1) 127.4(1)	30
		1.307(2)	1.486(2) 1.485(1)	1.259(1) 1.265(1)	128.0(1) 127.2(1)	30
		1.318[c]	1.484[c] 1.478[c]	1.267[c] 1.261[c]	124.2[c] 125.8[c]	31
		1.311(3)	1.490(3) 1.443(3)	1.265(2) 1.258(2)	126.6(2) 127.3(2)	32
cyclo-C_3H_5NO	*trans*-dimer	1.312(2)	1.454(3)	1.276(2)	120.75(13)	33a
cyclo-C_4F_7NO	monomer		1.521(15)	1.20[d]	111.9(22)	33b
	*trans*-dimer	1.321(2)	1.471(2)	1.272(2)	122.05(13)	33a
	monomer		1.573	1.246	106.8	33c
	*trans*-dimer	1.319(6)	1.488(6)	1.272(6)	121.4(4)	34

Table 1 (Continued)

compound		N−N (Å)	C−N (Å)	N−O (Å)	C−N−O (°)	ref
	*trans*-dimer	1.302(4)	1.487(2)	1.274(3)	121.4(2)	24
	monomer		1.530(6)	1.171(4)	113.2	35
	monomer		1.515(8)	1.153(8)	113.7(7)	36
	monomer		1.504(9)	1.178(7)	116.2(7)	36
	monomer		1.505(7)	1.139(5)	116.5(6)	37
	monomer		1.52 1.44[e]	1.16 1.21[e]	117 119[e]	38a
	monomer		1.542(10)	1.121(10) 0.978(20)[f]	118.4(3)	38b
	monomer		1.65(3)	1.10(2)	103(2)	39
	monomer form 1 form 2		 1.51[c] 1.53[c]	 1.13[c] 1.19[c]	 119.5[c] 114.4[c]	 40 41

[a] Determined by microwave spectroscopy. [b] Determined by electron diffraction. [c] Data obtained from the Cambridge Structural Database. [d] This value was constrained. [e] Data for second molecule. [f] Data for disordered (minor) component.

exception of a reported length of ~1.35 Å for the *trans*-dimer of *p*-bromonitrosobenzene.[43] Both monomeric and dimeric (trans) structures of *p*-iodonitrosobenzene are known; the N−O bond length in the dimer is ~0.07 Å longer than that in the monomer.[16b,37,44]

Ionic *C*-nitroso compounds that have been characterized by X-ray crystallography are listed in Table 3 and are compared with data from nitrosodicyanomethanide and related anions. Table 4 contains a listing of other *C*-nitroso compounds that have been characterized in the solid state by X-ray crystallography.

The data contained in Tables 1−4 show a somewhat wide variation in bond lengths and angles for the C−NO functional group that depends on the specific "R" group attached to the NO functionality and whether the NO group is engaged in intramolecular interactions with other atoms.

Infrared spectroscopy has been very useful in the characterization of *C*-nitroso compounds.[2,3,96] It is generally accepted that the NO stretching frequencies (υ_{NO}'s) of monomeric aliphatic RNO compounds are in the 1539−1621 cm^{-1} range. For example, the υ_{NO}'s of monomeric CH_3NO, CF_3NO, and nitrosocyclohexane are at 1564, 1595, and 1558 cm^{-1},

Table 2. Structural Data for Aromatic *C*-Nitroso Monomers and Dimers

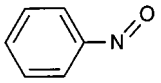
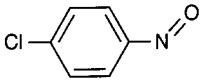
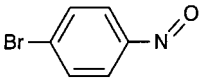
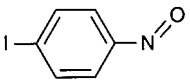
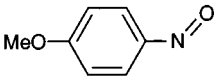
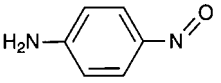
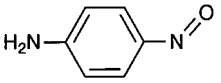
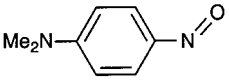
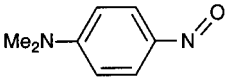
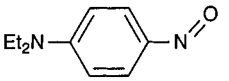
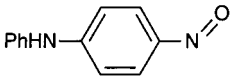
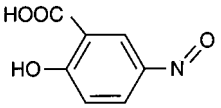
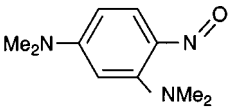
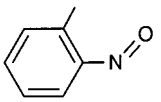
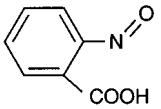
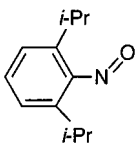
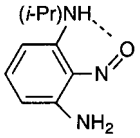
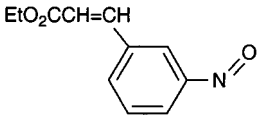
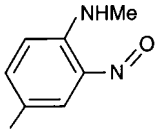
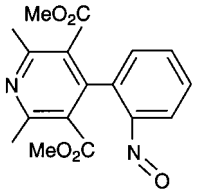
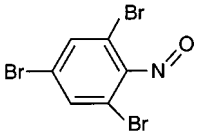
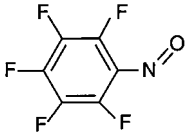
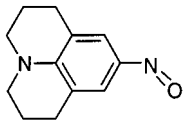
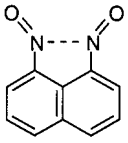
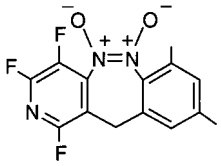
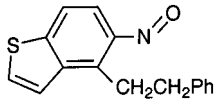
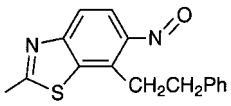
compound		N−N (Å)	C−N (Å)	N−O (Å)	C−N−O (°)	ref
	*cis*-dimer	1.321(5)	1.454(5) 1.463(5)	1.268(4) 1.261(4)	120.4(2) 120.8(3)	42
	*trans*-dimer	1.318(5)	1.453(4)	1.265(3)	119.7(2)	43a
	*trans*-dimer	∼1.31	1.40	∼1.35	∼120	43b
	*trans*-dimer monomer	1.316(7)	1.467(6) 1.43[a]	1.279(5) 1.21[a]	120.3(4) 113.2[a]	16b 37,44
	monomer		1.467(10)	1.228(8)	113.6(6)	45
 (*complexed with 18C6*)	monomer		1.460(7)	1.203(8)	108.0(5)	46
 (*complex with $^1/_2$DCH-6B*)	monomer		1.529(9)	1.178(8)	101(1)	46
	monomer[b]		1.390(11) [1.445(11)]	1.131(11) 1.212(11) [1.212(11) 1.292(11)]	126.2(10) 115.2(10) [116.4(10) 116.2(10)]	47
 (*complex with DPA*)	monomer		1.367(2)	1.243(3)	116.1(2)	48
	monomer[b]		1.438[c] 1.458[c]	1.253[c] 1.215[c]	110.9[c] 109.9[c]	49
	monomer		1.403(5)	1.256(5)	112.8(3)	50
	monomer		1.426(2)	1.234(2)	114.3(2)	51
	monomer		1.372(2)	1.276(2)	116.3(1)	52
	*cis*-dimer	*d*	*d*	*d*	*d*	53
	*trans*-dimer	1.308(3)	1.460(3)	1.267(3)	120.5(2)	42
	*trans*-dimer	1.323(2)	1.467(2)	1.267(2)	120.9(1)	54
	monomer		1.350(4) 1.352(4)	1.281(3) 1.285(3)	118.3(3) 118.2(3)	55

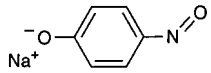
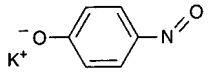
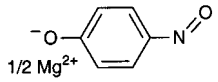
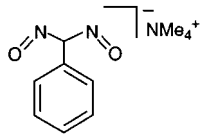
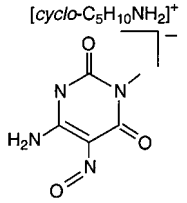
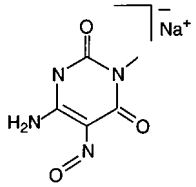
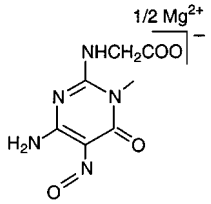
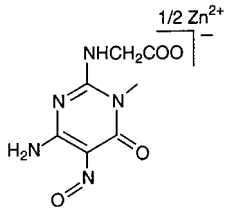
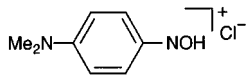
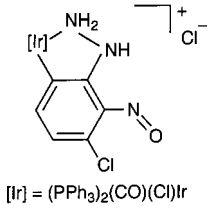
Table 2 (Continued)

compound		N−N (Å)	C−N (Å)	N−O (Å)	C−N−O (°)	ref
	monomer		1.451(4)	1.229(3)	113.5(3)	56
	monomer[b]		1.371(3) 1.354(3)	1.254(2) 1.254(2)	116.8(2) 116.8(2)	57
	monomer[b]		1.429(8) [1.418(7)]	1.16(3) 1.25(3) [1.221(5)]	115.5(12) [114.8(6)]	58
	*trans*-dimer	∼1.4				59
	*cis*-dimer	1.324(5)	1.439(6)	1.267(5)	120.6(4) 120.8(4)	60
	monomer		1.452(10)[e] 1.257(34)[f]	1.227(10)[e] 1.343(47)[f]	112.67(72)[e] 107.9(28)[f]	62
		1.376(8)	1.430(8) 1.439(8)	1.274(8) 1.255(8)	128.8(4) 129.1(4)	63
		1.340(3)	1.460(3) 1.425(3)	1.252(2) 1.264(2)	120.5(2) 118.3(2)	64
	monomer		1.419(5)	1.213(5)	113.8(5)	65
	monomer		1.41(2)	1.23(1)	114.7(12)	66

[a] The data in ref 37 supersedes the data in ref 44. [b] Two molecules in the unit cell. [c] Data obtained from the Cambridge Structural Database. [d] Metrical data not reported. [e] Major component (83%). [f] Minor component (17%).

respectively. Monomeric aromatic ArNO compounds display υ_{NO} in the 1488−1513 cm^{-1} range: PhNO (1506 cm^{-1}), *p*-FC_6H_4NO (1511 cm^{-1}), and *p*-IC_6H_4-NO (1488 cm^{-1}). However, exceptions exist as seen in the case of the *p*-amino-substituted compound *p*-$Me_2NC_6H_4NO$, where the υ_{NO} has been determined to be at 1363 cm^{-1} based on isotopic substitution studies (the IR spectra are discussed in ref 97). Gowenlock and co-workers used IR spectroscopy to distinguish between cis and trans isomers of dimeric RNO compounds by examining their characteristic bands including υ_{NO} and υ_{NN}.[98] In general, *trans*-dimers show characteristic single strong absorptions due to υ_{NO} in the 1176−1290 cm^{-1} range for aliphatic RNO dimers and in the 1253−1299 cm^{-1} range for aromatic ArNO dimers.[2,3,96] The *cis*-dimers, on the other hand, show two bands in the 1323−1344 and 1330−1420 cm^{-1} ranges for aliphatic RNO dimers

Table 3. Structural Data for Ionic *C*-Nitroso Compounds

compound	C−N (Å)	N−O (Å)	C−N−O (°)	ref
		anionic		
	1.3402(13)	1.3031(11)	117.1(1)	67
	1.27(3)	1.18(3)	122(2)	68
	1.3589(13)	1.2823(12)	117.2(1)	69
	1.351(6) 1.357(6)	1.268(6) 1.261(6)	117.2(6) 116.8(6)	70
	1.336[a] 1.329[a]	1.278[a] 1.290[a]	119.20[a] 119.33[a]	71
	1.336[a]	1.280[a]	118.12[a]	72
	1.346[a]	1.280[a]	117.33[a]	73
	1.338(2)	1.290(2)	117.75(15)	74
		nitrosodicyanomethanide		
$[(NC)_2CNO]^-\ {}^1/_2Ba^{2+}$	1.313(5) 1.313(5)	1.286(4) 1.298(4)	117.4(3) 117.3(3)	75
$[(NC)_2CNO]^-\ NH_4^+$	1.314(2)	1.286(2)	116.39(13)	75
$[(NC)_2CNO]^-\ K^+$	1.324(2)	1.287(1)	115.9(1)	76
$[(NC)_2CNO]Ag$[b]	1.44(3)	1.18(3)	112(2)	77
		nitrosolato		
$Ph_4SbON{=}C(Me)N{=}O$	1.387 1.386	1.275 1.247	106.2 109.6	78
		cationic		
	1.316(3)	1.374(3)	111.7(2)	79
 [Ir] = $(PPh_3)_2(CO)(Cl)Ir$	1.21(9)	1.40(7)	104(6)	80

[a] Data obtained from the Cambridge Structural Database. [b] Contains both Ag−O and Ag−N interactions.

Table 4. Structural Data for Other *C*-Nitroso Compounds

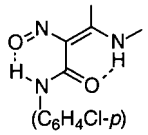
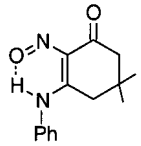
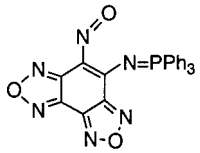
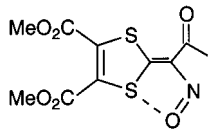
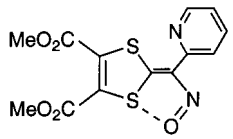
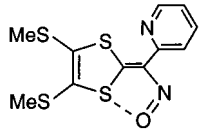
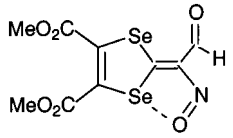
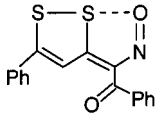
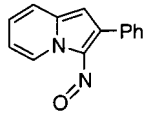
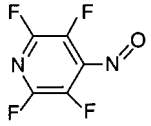
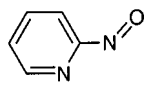
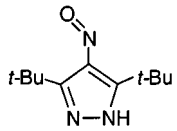
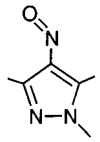
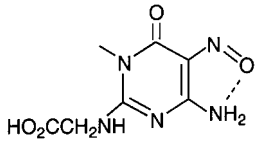
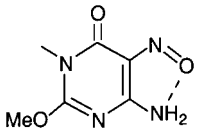
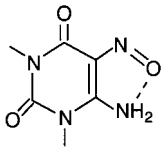
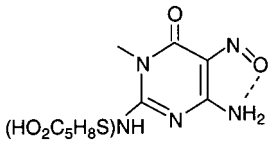
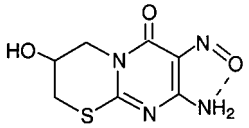
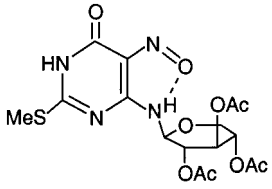
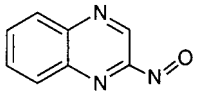
compound	C−N (Å)	N−O (Å)	C−N−O (°)	ref
	1.344(3)	1.290(3)	119.9(2)	81
	1.337(2)	1.301(2)	118.3(1)	81
	1.358(9)	1.265(8)	116	82
	1.357(3)	1.264(3)	114.7[a]	83
	1.345(5) 1.336(5)[b]	1.266(4) 1.288(4)[b]	115.3[a] 115.5[a,b]	83
	1.345(2)	1.276(2)	115.7[a]	83
	1.37(1)	1.244(13)	116(1)	84
	1.315(7)	1.312(6)	112.7(3)	85
	1.335(6)	1.281(7)	117.1(5)	86
	1.447(3)[c]	1.250(3)[c]	121.5(2)[c]	61a
	1.468(4)[d] 1.444(3)[d]	1.260(4)[d] 1.274(3)[d]	119.0(3)[d] 119.0(3)[d]	61b
	1.394(3) 1.391(4)[e]	1.053(10) 1.048(11)[e]	130.7(11) 134.1(13)[e]	87
	1.401(12)	1.209(6)	116.5(10)	87

Table 4 (Continued)

compound	C−N (Å)	N−O (Å)	C−N−O (°)	ref
	1.316(3)	1.296(2)	117.6(2)	88
	1.3518(24)	1.2663(24)	117.80(16)	89
	1.342(5)	1.281(4)	119.1(3)	90
	1.321(3)	1.309(3)	116.0(2)	91
	1.345(5)	1.279(4)	116.0(3)	92
	1.360(10)	1.288(9)	116.2(6)	93
	1.461(7)[f] 1.449(7)[f]	1.259(6)[f] 1.264(6)[f]	118.7(1)[f] 119.0(1)[f]	94

[a] Data obtained from the Cambridge Structural Database. [b] Data for the second molecule. [c] Compound is present as a *trans*-dimer with N−N = 1.320(4) Å. [d] Compound is present as a *cis*-dimer with N−N = 1.325(4) Å. [e] Second, minor, component based on NO orientation. [f] Compound is present as a *cis*-dimer with N−N = 1.328(6) Å.

and in the 1389−1397 and ∼1409 cm^{-1} regions for aromatic ArNO dimers. Nitrosoalkenes $R_2C{=}C(NO)R$ show υ_{NO} bands in the 1420−1485 cm^{-1} range,[99] and the υ_{NO} for $CH_3(CH_2)_3C{\equiv}CNO$ has been reported to be at 1580 cm^{-1}.[12]

Orrell and co-workers used solution variable-temperature NMR spectroscopy to study various substituted nitrosobenzenes.[100,101] They showed that at ambient temperature, the monomers were the major species in solution. However, lower temperatures favored the formation of the RNO dimers, with the *cis*-dimer being favored over the *trans*-dimer. They also obtained thermodynamic data for the dimer−monomer equilibria of substituted nitrosobenzenes and obtained solution $\Delta H°$ values of ∼38−55 and ∼25−42 kJ/mol for the dissociation of the *cis*-dimer and *trans*-dimer, respectively.[102] $^{14,15}N$ and ^{17}O NMR spectra of nitrosobenzenes have also been obtained,[16a,103,104] and the reader is encouraged to consult the contribution by Joan Mason in this issue for an in-depth discussion of nitrogen NMR spectroscopy.

B. Metal Complexes

In this section we will briefly cover (i) the methods to prepare metal−RNO compounds, (ii) the structures of the metal−RNO moieties, and (iii) the reactions displayed by the metal−RNO complexes. The coordination chemistry of nitronyl and other nitroxides[105−108] and amine and aromatic *N*-oxides[109,110] have already been described in the literature and will not be discussed here.

The coordination chemistry of *C*-nitroso compounds up to 1990 was the subject of an excellent review by Cameron, Gowenlock, and Vasapollo.[111]

1. Synthesis

(1) Addition of RNO. Metal−RNO complexes can readily be prepared by the addition of preformed

RNO compounds to metal complexes, and a few examples are shown in eqs 6−8.

$$W(CO)_5(pip) + (t\text{-}BuNO)_2 + h\nu \rightarrow (CO)_5W(t\text{-}BuNO)^{112} \quad (6)$$

$$(PPh_3)_2Pt(C_2H_2) + PhNO \rightarrow (PPh_3)_2Pt(\eta^2\text{-}ONPh)^{113} \quad (7)$$

$$CpMn(CO)_3 + (t\text{-}BuNO)_2 + h\nu \rightarrow CpMn(CO)_2(t\text{-}BuNO)^{112} \quad (8)$$

(2) Addition of Hydroxylamines. In some cases, hydroxylamines react with metal complexes to produce the metal−RNO derivatives (eqs 9−11).

$$(TPP)FeCl + \text{excess } i\text{-}PrNHOH \rightarrow (TPP)Fe(i\text{-}PrNO)(i\text{-}PrNHOH)^{114} \quad (9)$$

$$(L)Mo(O)_2(MeOH) + PhNHOH \rightarrow (L)Mo(O)(\eta^2\text{-}ONPh)^{115} \quad (10)$$

(H_2L = *S*-methyl 3-(2-hydroxyphenyl)methylenethiocarbazate)

$$[Fe(CN)_5(H_2O)]^{3-} + 2PhNHOH \rightarrow [Fe(CN)_5(PhNO)]^{3-} + PhNH_2 + 2H_2O^{116} \quad (11)$$

(3) NO Insertion into Metal−Carbon Bonds. On occasion, the insertion of NO into a metal−carbon bond has been observed to produce a bound RNO ligand. Examples for W,[117] Co (R = alkyl),[118−120] Fe (Cp′ = Cp[121] or Cp*[122]), and Ru[123] are shown in eqs 12−15.

$$Cp^*W(NO)Ph_2 + \Delta \rightarrow Cp^*W(=NPh)(Ph)\{\eta^2\text{-}ONPh\} + \text{other products} \quad (12)$$

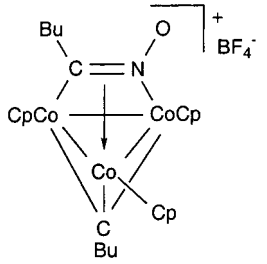
$$CpCo(NO)R + PPh_3 \rightarrow CpCo(PPh_3)\{\eta^1\text{-}N(O)R\} \quad (13)$$

$$Cp^*Ru(NO)Ph(Et) + PPhMe_2 \rightarrow Cp^*Ru(PPhMe_2)(Ph)\{\eta^1\text{-}N(O)Et\} \quad (14)$$

$$CpFe(NO)Me_2 + PMe_3 \rightarrow CpFe(PMe_3)(Me)\{\eta^1\text{-}N(O)Me\} \quad (15)$$

Addition of NO^+ to $CpCr(NO)_2R$ complexes (R = Me, CH_2SiMe_3, Ph) leads to a formal insertion of NO^+ into the Cr−R bonds to give the $[CpCr(NO)_2\{\eta^1\text{-}N(O)R\}]^+$ cationic complexes.[124] In the case of $CpCr(NO)_2Me$, the nitrosomethane complex rearranges to the formaldoxime product $[CpCr(NO)_2\{\eta^1\text{-}N(OH)=CH_2\}]^+$, which was characterized by X-ray crystallography.[124] A related NO^+ insertion into a metal−R bond in a cobalt cluster compound was reported by Vollhardt and co-workers; the product was characterized in the solid state by X-ray crystallography (eq 16).[125] NO insertion reactions have been reviewed.[1,111,126,127]

$$(CpCo)_3(\mu_3\text{-}CBu)_2 + NOBF_4 \rightarrow \quad (16)$$



(4) From Organic Nitro Compounds. Aromatic $ArNO_2$ compounds may be deoxygenated in the presence of a metal complex to give metal−ArNO derivatives. The deoxygenation reaction of $ArNO_2$ by $Ru(dppe)(CO)_3$ to give $Ru(dppe)(CO)_2(\eta^2\text{-}ONAr)$ and CO_2 (eq 17; Ar = $C_6H_3(4\text{-}Cl)(2\text{-}CF_3)$) has been determined to be first order with respect to both $Ru(dppe)(CO)_3$ and nitroarene; electron-withdrawing substituents on the nitroarene and polar solvents increased the rate.[128,129] It was proposed that inner-sphere electron transfer to the nitroarene probably preceded O-atom transfer.

$$(dppe)Ru(CO)_3 + ArNO_2 \rightarrow (dppe)Ru(CO)_2(\eta^2\text{-}ONAr) + CO_2 \quad (17)$$

A similar deoxygenation by $Ru(CO)_3(PPh_3)_2$ to produce a chelated *o*-nitrosophenolate complex of structure **A6** (see Figure 3) has been reported.[130] Other examples are known, and two of these are shown in eqs 18−19.

$$Ni(PR_3)_4 + R'NO_2 \rightarrow (PR_3)_2Ni(\eta^2\text{-}ONR') + OPR_3 + PR_3^{131} \quad (18)$$

(R = Et, Ph; R′ = alkyl, aryl)

$$(TC\text{-}3,5)Hf(\eta^2\text{-}OC(CH_2Ph)_2) + PhNO_2 \rightarrow [(TC\text{-}3,5)Hf]_2(\mu\text{-}O)(\mu,\eta^2\text{:}\eta^2\text{-}ONPh)^{132} \quad (19)$$

(5) From Radiolysis. Hoffman and co-workers have shown that radiolysis of deoxygenated aqueous solutions of $[Fe(CN)_5NO]^{2-}$ and $[Ru(NH_3)_5NO]^{3+}$ in the presence of RH (e.g., *t*-BuOH, *t*-$BuNH_2$, *N*,*N*-dimethylacetamide, and other organic compounds) results in the formation of metal−N(O)R complexes; radiation-generated HO radicals react with RH to produce β-carbon R radicals which combine with the reduced metal−NO complexes according to eq 20.[133−135]

$$[M^{II}-NO^+] \xrightarrow{e^-} [M^{II}-\dot{N}O] \xrightarrow{\cdot R} [M^{II}-N(O)R] \quad (20)$$

(6) From Nitrene Complexes. Cenini and coworkers demonstrated that O-atom transfer to some

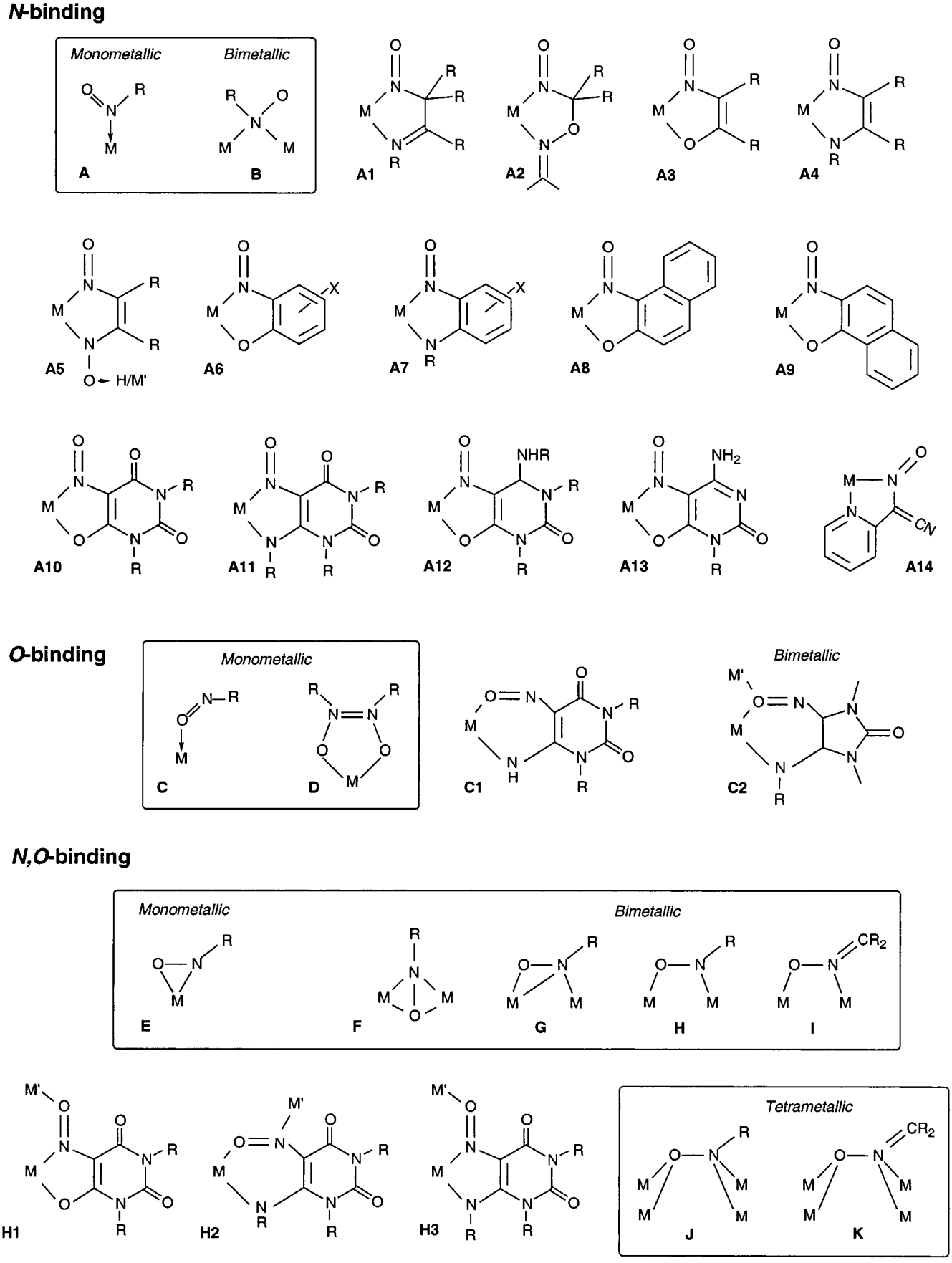


Figure 3. Binding modes in metal−RNO complexes established by single-crystal X-ray crystallography.

metal nitrene M=NR complexes gives metal−RNO derivatives (e.g., eq 21).[136,137]

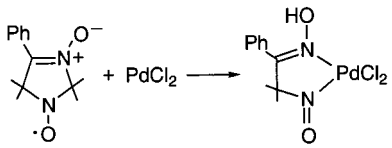
$$(PPh_3)_2Cl_3Re(NAr) + O_2 + \Delta \rightarrow (Ph_3PO)Cl_3Re(ArNO) + \text{other products} \quad (21)$$

Interestingly, deoxygenation of the ArNO ligand can be effected to give nitrene complexes (see later, eqs 31 and 32).[136]

(7) From Sulfinilamines. Sulfur dioxide is released when a rhenium oxo complex is reacted with the sulfinilamine RNSO (R = *p*-tolyl) as shown in eq 22.[136]

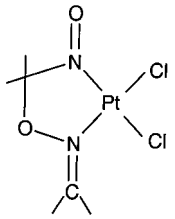
$$ReCl_3(O)(PPh_3)(SMe_2O) + RNSO \text{ (in benzene/}O_2) \rightarrow ReCl_3(RNO)(OPPh_3) + SO_2 + SMe_2O \quad (22)$$

(8) From Nitronyl Nitroxides. In what is a rather uncommon reaction, a nitronyl nitroxide heterocycle was destroyed in the presence of $PdCl_2$ to give the *N*,*N*-chelated nitrosooxime metal−RNO complex (structure determined by X-ray crystallography; υ_{NO} 1576 cm^{-1}) as shown in eq 23.[138]



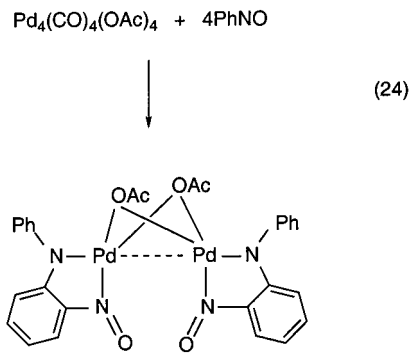
(23)

(9) From Ligand Coupling Reactions. Kukushkin and co-workers showed that *redox coupling of coordinated oximes* occurred when *cis*-$PtCl_4(Me_2C{=}NOH)_2$ was placed in aqueous acetone to give the product shown below (X-ray crystal structure obtained).[139]

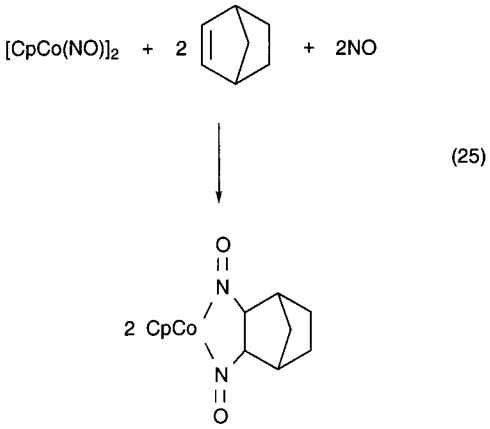


They also showed that *m*-chloroperoxybenzoic acid reacted with the platinum(II) compound *trans*-$PtX_2(ketoxime)_2$ to give metal−RNO compounds, and the solid-state X-ray crystal structure of the $PtCl_2$-$\{N(O)CC_5H_{10}ONCC_5H_{10}\}$ derivative was also obtained.[140]

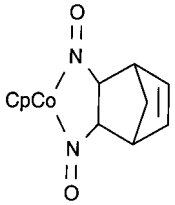
A remarkable *nitrene−nitrosoarene coupling* reaction occurs when $Pd_4(CO)_4(OAc)_4$ reacts with nitrosobenzene, presumably via an inner-sphere nitrene [Pd−NPh] insertion into the C−H bond of the phenyl ring of the coordinated PhNO, to give a chelating phenyl-*o*-nitrosophenylamide ligand characterized by X-ray crystallography (eq 24).[141,142]



Brunner and Loskot showed that a *dinitrosoalkane complex* (υ_{NO} 1357 cm^{-1}) formed in high yield when $[CpCo(NO)]_2$ was reacted with norbornene and NO at room temperature (eq 25).[143]



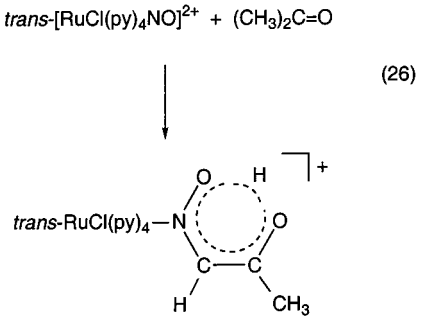
Derivatives containing substituted cyclic and noncyclic olefins have been generated in a similar fashion (υ_{NO} 1354−1435 cm^{-1});[143,144] the X-ray crystal structure of one of the derivatives (shown below) confirmed the formulation of a dinitrosonorbornene ligand.[145]



Bergman studied this reaction (eq 25) further, showed the intermediacy of the dinitrosyl complex $CpCo(NO)_2$, and developed a process for the net 1,2-diamination of alkenes; the dinitrosoalkane complexes reacted with $LiAlH_4$ to give the primary vicinal diamines.[144,146] Eisenberg and co-workers reported an NO−(η^3-allyl) intramolecular coupling reaction to produce an intermediate metal−nitrosopropene complex that underwent further reaction with CO to give acrolein oxime.[147]

(10) Reactions of Coordinated Nitrosyls with Nucleophiles. Carbanions react with some coordinated electrophilic nitrosyls to form metal-bound RNO species. For example, nitroprusside $[Fe(CN)_5NO]^{2-}$ reacts with a number of carbon-nucleophiles to form (sometimes transient) "$[Fe(CN)_5N(O)R]$" species.[148,149] Bottomley reported the reaction of *trans*-$[RuCl(py)_4(NO)]^{2+}$ with acetone in the pres-

ence of aqueous ammonia to give the product (characterized by X-ray crystallography as the PF_6 salt) shown in eq 26 and shown as the predominant "delocalized" tautomer.[150]



Meyer also reported the reaction of $[Ru(bpy)_2(NO)X]^{2+}$ (X = Cl, NO_2) with aromatic amines $C_6H_5N(R)Me$ (R = H, Me) in acetonitrile to give the *p*-nitrosoarene complexes (υ_{NO} ~1285 cm^{-1}) as shown in eq 27.[151−153]

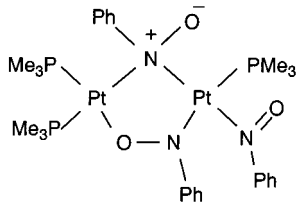
$$[Ru(bpy)_2(NO)X]^{2+} + C_6H_5N(R)Me \rightarrow [Ru(bpy)_2X\{N(O)C_6H_4N(R)Me\}]^{+} \quad (27)$$

Connelly, Geiger, and co-workers demonstrated a rather unique reaction of the bridging NO ligand in $[CpRh(CO)]_2(\mu\text{-NO})]^{+}$ with alkynes to generate coordinated RNO groups.[154]

2. Spectroscopy and Structure

There are nine main ways in which a *C*-nitroso compound may bind to metals. All these binding modes have been confirmed by single-crystal X-ray crystallography, and they are shown schematically in Figure 3. The mode in which the *C*-nitroso compound binds depends on a number of factors including the type, nature, and number of metal center(s) and the type of "R" group in the RNO compounds. The two main types of sole *N*-binding are shown as structures **A** and **B** in Figure 3 for the monometallic and bimetallic cases, respectively. Sole *O*-binding of the RNO group can also occur with the two main cases shown as structures **C** and **D** for the monomeric and dimeric RNO compounds. Both the N and O atoms of the RNO group may also be involved in binding to metals at the same time, and these are shown as **E**−**H** and **J** in the Figure 3. Tables 5−9 list the structural parameters for the various metal−RNO compounds characterized by X-ray crystallography.

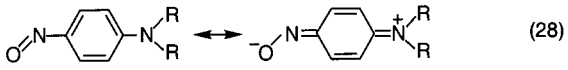
More than one binding mode may exist in the same complex, but this is not very common. A rather unique example of three binding modes in the same complex (shown below) was demonstrated in the X-ray crystal structure of $(PMe_3)_3Pt_2(PhNO)_3$.[159]



However, such cases are rare, and we will now consider each major binding mode separately.

(1) Sole N-Binding. This is the most common mode of RNO binding observed to date in crystallographically characterized metal−RNO compounds (Table 5). For monometallic non-porphyrin compounds, the N−O bond lengths fall in the 1.209−1.296 Å range. In the case of the *t*-BuNO complexes, the observed N−O lengths of 1.24 Å (for W; υ_{NO} 1415 cm^{-1}),[112] 1.234 Å (for Fe),[112] and 1.21−1.22 Å (for Pt)[158,160] are either within or are slightly longer than the 1.1−1.22 Å range observed for monomeric aliphatic RNO compounds (Table 1) but are shorter than that seen for the structurally characterized dimer $(t\text{-BuNO})_2$ (1.265 Å).[26] This is consistent with a long-held view that metals are involved in back-donation of electron density to the π^* orbitals of the NO moiety in the RNO ligand. Indeed, Geoffroy[112] and Richter-Addo[165] provided IR spectral evidence that the RNO ligands in $W(CO)_5(t\text{-BuNO})$ and (TTP)-Os(CO)(PhNO) are electron withdrawing. There is usually a (sometimes small) drop in υ_{NO} of the RNO ligand once bound to the metal center in the *N*-binding mode.[97,111,156] For example, the υ_{NO} of free PhNO (1506 cm^{-1}) drops to 1487−1495 cm^{-1} in a series of *trans*-$PtCl_2$(PhNO)L complexes.[158] Gowenlock and co-workers examined IR and NMR spectral data for a series of *N*-bound *C*-nitroso complexes of the form $K[PtCl_3(4\text{-}XC_6H_4NO)]$ and showed that the π-electrons of the −N=O bonds are only slightly altered when bound to metals in the *N*-binding mode.[192] Consistent with this is the observation of the slight fall in υ_{NO} (by 7−23 cm^{-1}) of the metal−RNO complex when compared with the υ_{NO} of the free ligand.[192]

A dinitrosoalkane compound, namely, $CpCo\{(ON)_2C_7H_8\}$ (similar to the product of eq 25), has also been characterized by X-ray crystallography.[145] The common mode of binding of RNO ligands to metalloporphyrins is the *N*-binding mode (Table 5), although *O*-binding has been accomplished in Fe^{III} and Mn^{III} complexes using *p*-substituted nitrosoarene ligands (see later; Figure 6),[161,171] presumably due to the contribution of the dipolar resonance form shown on the right of eq 28.



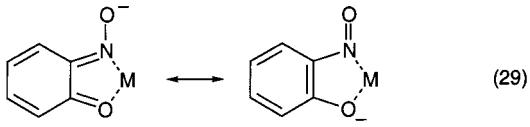
The *N*-binding mode **A** (Figure 3) is also seen in many chelating ligands containing the NO functionality, and these are shown as structures **A1**−**A14** in Figure 3. Structures **A1** and **A2** have the nitroso N-atoms bonded to an sp^3-hybridized carbon center, whereas **A3**−**A14** have the nitroso N-atoms bonded to sp^2-hybridized carbon centers. Examples [with NO bond distances shown in square brackets] are known for **A1** (Co [1.28−1.346 Å][193,194] and Pd [1.194 Å][138]), **A2** (Pt [1.24 Å]),[139] **A3** (Co [1.229−1.260 Å]),[195,196] **A4** (Ni [1.267 Å][197] and Cu [1.262 Å][198]), and **A5** (includes the dimethylglyoximato complexes; Co [1.278−1.342 Å][199,200] and Cu [1.359 Å][201]). Analysis of the charge distribution in **A6** and related structures has attracted great interest: the nitrosophenolate formulation (shown on the right of eq 29) in general

Table 5. Selected Structural Data for η^1-Bonded *C*-Nitroso Groups A and B from Figure 3

compound	C−N (Å)	N−O (Å)	C−N−O (°)	ref
		monometallic (**A**)		
$W(CO)_5(t\text{-BuNO})$	1.51(3)	1.24(3)	111(2)	112
$[CpFe(CO)(PPh_3)(t\text{-BuNO})]BF_4$	1.554(15)	1.234(10)	111.4(8)	112
$Cp^*Ru(PPhMe_2)(Ph)(EtNO)$	1.494[a]	1.257[a]	109.3[a]	123
$CoCl_2(ONC_6H_4NMe_2\text{-}p)_2$	1.356(6)	1.261(5)	118.6(4)	155
	1.363(6)	1.272(5)	117.8(4)	
$CpCo(PPh_3)(EtNO)$	1.484	1.282	109.9[a]	119,120
$RhCl(NBD)(ONC_6H_4Br\text{-}p)$	1.43(1)	1.23(1)	114.4(7)	156
trans-$PdCl_2(PhNO)_2$	1.411(3)	1.209(3)	118.2(2)	157
trans-$PtCl_2(t\text{-BuNO})_2$	1.56(2)	1.21(1)	116(1)	158
$(PMe_3)_2Pt(\mu\text{-PhNO})_2Pt(PMe_3)(PhNO)$	1.372[a]	1.296(14)	117.3(9)	159
$PtCl\{ON(t\text{-Bu}){=}CHCH_2\}(t\text{-BuNO})$	1.543[a]	1.22(2)	114.3[a]	160
		porphyrin complexes		
$(TPP)Fe(i\text{-PrNO})(i\text{-PrNH}_2)$[b]	1.55(2)	1.26(2)	117(1)	114
	1.54(2)	1.26(2)	115(1)	
$(TPP)Fe(PhNO)_2$	1.468(4)	1.237(3)	112.4(2)	161
	1.467(3)	1.227(3)	112.6(2)	
(TPP)Fe(py)(PhNO)	1.472(4)	1.249(4)	113.2(3)	162
$(TPP)Fe(py)(ONC_6H_4NMe_2\text{-}p)$	1.437(8)	1.252(6)	112.3(6)	162
(TPP)Fe(1-MeIm)(PhNO)[b]	1.444(9)−1.453(2)	1.254(8)−1.267(3)	109.9(3)−111.2(8)	162
(OEP)Fe(1-MeIm)(PhNO)[b]	1.448(6)	1.269(5)	111.7(4)	162
	1.454(6)	1.258(4)	110.1(3)	
$[(TPP)Co(ONC_6H_4NMe_2\text{-}p)_2]ClO_4$	1.35(2)	1.33(2)	109(2)	163
	1.38(2)	1.27(2)	112(2)	
$(OEP)Ru(ONC_6H_4NMe_2\text{-}p)_2$	1.453(7)	1.248(7)	115.9(5)	163
	1.468(6)	1.257(7)	116.7(5)	
(TPP)Ru(py)(PhNO)	1.475(4)	1.259(3)	112.3(3)	164
$(TPP)Ru(PhNO)_2$	1.468(3)	1.243(3)	112.3(2)	164
	1.452(3)	1.248(3)	113.1(2)	
$(TPP)Os(PhNO)_2$	1.469(5)	1.249(4)	112.4(3)	165
	1.458(5)	1.259(6)	113.1(3)	
$(TTP)Os(PhNO)_2$	1.475(14)	1.298(13)	109.3(11)	165
	1.43(2)	1.278(12)	113.2(10)	
$(TMP)Os(PhNO)_2$	1.40(2)	1.31(2)	110.4(12)	165
	1.45(2)	1.252(12)	112.5(9)	
(TTP)Os(CO)(PhNO)	1.39(3)	1.26(2)	120(2)	165
$(OEP)Os(o\text{-tolNO})_2$	1.481(14)	1.273(13)	108.8(9)	165
	1.441(14)	1.219(12)	116.9(10)	
		nitrosodicyanomethanide complexes		
$Ir(CO)(PPh_3)_2\{ONC(CN)_2\}$	1.342(21) av.	1.264(16) av.	118.2(13) av.	166
$Re(CO)_5\{ONC(CN)_2\}$	1.35(1)	1.26(1)	117.0(8)	167
		bimetallic (**B**)		
$Pt_2(PMe_3)_3(PhNO)_2(PhNO)$	1.459[a]	1.428(27)	106.6(15)	159

[a] Data obtained from the Cambridge Structural Database. [b] Two molecules in the unit cell.

is favored over the quinone oxime (shown on the left of eq 29).[202]



(29)

Examples of **A6** are known for Fe (e.g., ferroverdin and analogues; X = 5-C(O)$OC_6H_4CH{=}CH_2$; [1.20−1.28 Å]),[203−205] Ru ([1.246 Å]; υ_{NO} 1340 cm^{-1}),[130] Cu [1.18−1.31 Å],[206−212] Hg [1.21−1.32 Å],[213] and Ni [1.27 Å].[214] Palladium complexes containing the structure **A7** [1.24−1.272 Å] have been reported.[141,142,215]

Structures **A8** and **A9** differ in the placement of the nitroso group relative to the naphthol group. Thus, **A8** is referred to as a 1-nitroso-2-naphthol (or 1,2-naphthoquinone-1-oxime) complex, and **A9** is the related 2-nitroso-1-naphthol complex. Several examples for **A8**, where the metal is Ru [1.22−1.28 Å],[184,216] Ir [1.274 Å],[217] or Cu [1.257−1.287 Å],[218,219] are known as are structures for **A9**, where the metal is Ru [1.19−1.26 Å][216] or Cu [1.262−1.266 Å].[220]

Many metal−RNO complexes containing the violurato **A10** and the uracil **A11** frameworks are known. In the case of structure **A10**, complexes that have been structurally characterized are those of Fe [1.25 Å],[221] Co [1.253−1.265 Å],[222,223] and Cu [1.218−1.259 Å].[224−226] Those for **A11** contain Cu [1.220−1.28 Å].[224,225,227−232]

The structure **A12** has been reported for Ni [1.272 Å],[233] whereas that for **A13** has been reported for Zn [1.251-1.276 Å].[234] A complex containing the **A14** structure has been reported for Tl [1.229 Å].[235]

The *N*-only bonding mode **B** (Figure 3) has been observed in only one complex, namely, $(PMe_3)_3Pt_2(PhNO)_3$, and has a rather long N−O bond (1.428 Å) with significant single-bond character.[159]

(2) Sole O-Binding. The *O*-binding of *C*-nitroso compounds is much less common (Table 6). Complexes of formulation **C** in Figure 3 are now known for monomeric compounds containing Sn[168] or Zn[169]

Table 6. Selected Structural Data for the *O*-Bonded *C*-Nitroso Groups C, D (from Figure 3) and Related Groups

compound	C−N (Å)	N−O (Å)	C−N−O (°)	ref
		nitrosoarene (**C**)		
$Cl_2Me_2Sn(ONC_6H_4NMe_2)_2$	1.398(6)	1.218(4)	112.9(4)	168
$Cl_2Zn(ONC_6H_4NMe_2)_2$	1.345(4)	1.305(4)	114.9(3)	169
	1.339(4)	1.304(4)	114.6(3)	
$[Ph_3Pb(ONC_6H_3(F)O)]_x$	1.31	1.33	112	170
$[(TPP)Fe(ONC_6H_4NEt_2)_2]SbF_6$	1.323(11)	1.157(6)	118.7(7)	161
	1.413(13)[a]	1.062(8)[a]	121.8(9)[a]	
$[(TPP)Mn(ONC_6H_4NEt_2)_2]SbF_6$	1.36(2)	1.057(10)	121.9(12)	171
	1.356(13)[a]	1.109(8)[a]	122.0(9)[a]	
		nitrosodicyanomethanide complexes		
$(TTP)Fe(ONC(CN)_2)$	1.300(8)	1.330(5)	113.6(5)	166
$[\{(Me_2N)_3PO\}_4Yb\{ONC(CN)_2\}_2]^+ [(NC)_2CNO]^-$	1.37(3)	1.20(2)	111(2)	172
	1.55(4)	1.05(3)	94(2)	
$\{(Me_2N)_3PO\}_4Nd\{ONC(CN)_2\}_3$	1.28(4)	1.29(2)	114(2)	173
	1.38(2)	1.28(2)	118(1)	
	1.59(4)	1.13(2)	96(2)	
		diazenedioxide form (**D**)		
$[Fe\{[PhNO]_2\}_3][FeCl_4]_2$ (N═N = 1.276(11) − 1.328(12) Å)	1.442(13)−1.490(14)	1.270(10)−1.299(11)	117.3(8)−120.6(8)	174, 175

[a] Data for the disordered component.

Table 7. Selected Structural Data for *N,O*-Bonded *C*-Nitroso Groups E and F from Figure 3

compound	C−N (Å)	N−O (Å)	C−N−O (°)	ref
		monometallic (**E**)		
$(L)Mo(O)(PhNO)$[b]	1.442(4)	1.386(3)	112.0(2)	115
$(L')Mo(HMPA)(O)(PhNO)$[b]		1.416(7)	112.6(4)	176
$[PPh_4]_2[(CN)_4Mo(O)(o\text{-tolNO})]$	1.471[a]	1.393(10)	112.5(7)	177
$Cp^*W(NPh)(Ph)(PhNO)$	1.435(7)	1.432(6)	111.0(4)	117
$(dppe)Ru(CO)_2\{ONC_6H_3(o\text{−}CF_3)(p\text{−}Cl)\}$	1.42(1)	1.412(9)	112.2(7)	128,129
$Pt(PPh_3)_2(PhNO)$	1.412(9)	1.410(7)	110.9(5)	113
		bimetallic (**F**)		
$[(Cp^*Rh)_2(\mu\text{-Cl})(\mu\text{-PhNO})]BF_4$	1.422(5)	1.422(4)	113.6(3)	178
$[(TC\text{-}3,5)Hf]_2(\mu\text{-O})(\mu\text{-PhNO})$	1.417(9)	1.500(7)	117.0(6)	132

[a] Data obtained from the Cambridge Structural Database. [b] H_2L = *S*-methyl 3-(2-hydroxyphenyl)methylenedithiocarbazate; L′ = tridentate pyridine 2,6-dicarboxylate.

Table 8. Selected Structural Data for the *N,O*-Bonded *C*-Nitroso Groups G, H, and I from Figure 3

compound	C−N (Å)	N−O (Å)	C−N−O (°)	ref
		bimetallic (**G**)		
$[(CO)_3Fe\{ONC_6H_3(o\text{-Me})(m\text{-Cl})\}]_2$	1.43(1)	1.40(1)	112.2(7)	179
$Os_3(CO)_{11}(ONC_6F_5)$	1.506(25)	1.437[a]	107.8[a]	180
$[CpCo(PhNO)]_2$	1.423(5)	1.385(4)	114.4(3)	181
$Cp^*Rh(\mu\text{-Cl})(\mu\text{-PhNO})Rh(Cl)Cp^*$	1.495(9)	1.432(9)	117.4(6)	178
	1.53(1)[b]	1.37(2)[b]	131(1)[b]	
$[\{P(t\text{-Bu})_3\}Pd(PhNO)]_3$	1.43(3)	1.35(1)	113(1)	182
		bimetallic (**H**)		
$Ru_3(CO)_7(NPh)_2(PhNO)_2$ (no Ru−Ru bond)	1.44(1)	1.334(9)	111.6[a]	183
$Ru_3(CO)_8(ONC_{10}H_6O)_2$[c] (no Ru−Ru bond)	1.33(2)	1.30(1)	120.9[a]	184
	1.38(2)	1.31(1)	115.4[a]	
$[\{Cp^*Ru(S(i\text{-Pr}))\}_2(PhNO)]OTf$ (Ru−Ru bond)	1.391(6)	1.353(5)	112.8(4)	185
$[\{Cp^*Rh(S(i\text{-Pr}))\}_2(PhNO)]BPh_4$ (no Rh−Rh bond)	1.391(8)	1.333(6)	109.3(6)	185
$[\{Cp^*Ir(S(i\text{-Pr}))\}_2(PhNO)]BPh_4$ (no Ir−Ir bond)	1.40(1)	1.339(8)	109.5(7)	185
$Pt_2(PMe_3)_3(PhNO)_2(PhNO)$ (no Pt−Pt bond)	1.357[a]	1.433(15)	116.1(9)	159
$(PEt_3)_2Pt(PhNO)Ge\{N(SiMe_3)_2\}_2$ (Pt−Ge bond)	1.381(7)	1.498(6)	109.8(4)	186
		related oximato $M_2(\mu\text{-O−N═CR}_2)$ (**I**)		
$Fe_2(CO)_6(NH^iPr)(ONCMe_2)$ (Fe−Fe bond)	1.278(7)	1.371(5)	115.5(4)	187
$Fe_2(CO)_6(NCMe_2)(ONCMe_2)$ (Fe−Fe bond)	1.291(7)	1.351(6)	115.1(5)	188
$Cp_2Co_2(NCPh_2)(ONCPh_2)$ (Co−Co bond)	1.299(8)	1.343(6)	118.4(5)	189

[a] Data obtained from the Cambridge Structural Database. [b] Data for the disordered component. [c] The NO group is part of a bidentate 1,2-naphthoquinone-2-oximato ligand (binding mode **A8** in Figure 3).

and for a polymeric complex of Pb.[170] The *O*-binding mode has also been observed in porphyrin complexes of Fe^{III} [161] and Mn^{III};[171] however, both these complexes display unusually short N−O bond lengths. Extensive crystallographic disorder makes their short N−O bond lengths not very reliable, and this apparent shortening needs to be investigated further. Hence, it might be premature to speculate on this apparent N−O bond shortening feature. We note, however, that unusually short N−O lengths of ∼1.05 Å have

Table 9. Selected Structural Data for the *N,O*-Bonded *C*-Nitroso Groups J and K from Figure 3

compound	C−N (Å)	N−O (Å)	C−N−O (°)	ref
	tetrametallic (**J**)			
$Fe_4(CO)_{11}(NEt)(ONEt)$	1.479[a]	1.446[a]	105.9[a]	190
	related oximato (**K**)			
$(NBu_4)_2[Mo_4O_{12}\{MeC(NH_2)NO\}_2]$	1.298(5)	1.420(4)		191
	1.328(5)	1.418(4)		
$\{MeC(NH_2)NHOH\}_2[Mo_4O_{12}\{MeC(NH_2)NO\}_2]$	1.328(7)	1.428(5)	109.8[a]	191
$(NBu_4)_2[W_4O_{12}\{MeC(NH_2)NO\}_2]$	1.33(1)	1.42(1)		191

[a] Data obtained from the Cambridge Structural Database.

also been observed in an organic nitrosopyrazole compound (Table 4).[87]

The difficulty in assigning IR ν_{NO} bands in *O*-bonded RNO complexes has been addressed in excellent commentaries by Gowenlock, Vasapollo, and coworkers.[97] Many of the problems have arisen due to previous incorrect assignments of the ν_{NO} bands of the organic RNO compounds.[97] Not unexpectedly, the nitrosodicyanomethanide ligand $[ONC(CN)_2]^-$ can also bind via the O-atom (Table 6) as does the ethylnitrosolato anion $[O{=}NC(Me){=}NO]^-$.[236,237]

Two variations of sole *O*-binding have been reported, and these are represented schematically by structures **C1** and **C2** in Figure 3. The first type, **C1** (a uracil derivative), has been observed as a disordered component in a complex of Cu [1.24 Å],[224] and the second type, namely, the bimetallic **C2**, has been observed in a complex where M/M′ = Cu/Ni [1.35 Å].[229]

Only one X-ray crystal structure of a complex containing structure **D** in Figure 3 (containing the bound RNO dimer) has been reported, namely, that of $[Fe\{[PhNO]_2\}_3][FeCl_4]_2$.[174,175] Such metal−$[RNO]_2$ complexes are known, however, for Sn, Ti, and Pb.[238−240]

(3) N,O-Binding. The attachment of both the N and O atoms of the nitroso group to metals increases the N−O bond distance (Table 7) and results in a lowering of the N−O bond order. For the attachment of both N and O atoms to single metal centers in these "metallooxaziridine" compounds (structure **E** in Figure 3), the N−O bond lengths range from 1.386 to 1.432 Å. A ν_{NO} of 973 cm^{-1} has been assigned in $Pt(PPh_3)_2(PhNO)$ (structure **E**).[113] Related compounds of Ni and Pd have ν_{NO}'s in the 1025−1040 cm^{-1} region.[241] A related side-on-bonded oximate ligand is present in the structurally characterized $Mo(acac)_2\{CH_3C(NH_2)NO\}NO$ complex.[242] For bimetallic complexes of structure **F**, the N−O lengths are in the 1.422−1.500 Å range. Similar lengthening of the N−O bonds is seen in structures **G** and **H** (Table 8), where the N−O bond lengths are in the 1.30−1.498 Å range. For structure **G**, a ν_{NO} of 1039 cm^{-1} is observed for the coordinated PhNO ligand in $[Pd(PhNO)(P(t\text{-}Bu)_3)]_3$, representing a large drop from 1506 cm^{-1} for free PhNO.[182] A similar ν_{NO} of 1047 cm^{-1} is observed for $[CpCo(PhNO)]_2$ containing the **G** structure.[181]

A transformation of structure **G** to **F** is seen in the reaction of $Cp^*_2Rh_2Cl_2(PhNO)$ (structure **G**) with $TlBF_4$ to give $[Cp^*_2Rh_2Cl(PhNO)]BF_4$ (structure **F**).[178]

Variations in structure **H** are known, and these are shown in Figure 3 as **H1**−**H3**; examples have been reported for **H1** (M = M′ = Cu; [1.305 Å]),[243] **H2** (M/M′ = Cu/Ni; [1.26 Å]),[229] and **H3** (M = M′ = Cu [1.296−1.303 Å];[233] M/M′ = Cu/Ni [1.27−1.30 Å][229,232]). Related μ-oximate ligands bonded through both N and O atoms of formulation **I** are known and listed in Table 8.

A tetrametallic complex displaying *N,O*-binding of structure **J** is known for Fe, and related oximate structures of type **K** have been reported; the N−O bonds are also long and in the 1.418−1.446 Å range (Table 9).

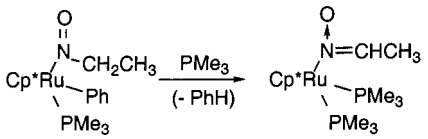
3. Reactions

In addition to simple displacement reactions whereby a coordinated RNO group dissociates from a metal center or is replaced by an added ligand, coordinated RNO groups can undergo a variety of transformations including isomerization, O-atom and/or nitrene transfer, reduction reactions, carbon−nitrogen bond cleavage, and coupling reactions with other reagents.

(1) Isomerization. Many organic *C*-nitroso compounds of the form $R_2CHN{=}O$ isomerize to the oxime $R_2C{=}NOH$ form, and this isomerization also occurs in the presence of metal centers. It has been calculated that formaldoxime $CH_2{=}NOH$ is ∼12 kcal/mol more stable than $CH_3N{=}O$[244] and that a metal cation such as Cu^+ catalyzes the isomerization reaction of nitrosomethane to formaldoxime in the gas phase.[244a] An alternate mechanism for the nitrosomethane to formaldoxime reaction in the gas phase, involving a free radical chain mechanism (e.g., initial C−N bond homolysis), has been suggested recently in light of the available experimental data.[245] An organometallic formaldoxime complex $[CpCr(NO)_2\{N(OH){=}CH_2\}]^+$ is the final product isolated when NO^+ inserts into the Cr−CH_3 bond of $CpCr(NO)_2CH_3$.[124]

An intermediate metal−nitrosopropene complex $[Ir(PPh_3)_2(CO)(\eta^3\text{-}ONCH_2CH{=}CH_2)]^+$ (formed via an intramolecular NO−allyl coupling reaction) isomerizes to the acrolein oxime derivative.[147]

Although not formally an isomerization reaction, the conversion of a nitrosoethane complex to its oximate derivative is worthy of mention in this section (eq 30):[123]



(30)

(2) O-Atom and/or Nitrene Transfer. La Monica and Cenini have shown that coordinated (*N*-bound) RNO ligands in some rhenium complexes can be deoxygenated by phosphines and by cyclohexyl isocyanide to give metal−nitrene products.[136] Examples are shown in eqs 31 and 32 (Ar = *p*-tol; R′ = Ph, Et).

$$ReCl_3(ArNO)(OPPh_3) + PR'_2Ph \rightarrow ReCl_3(NAr)(PR'_2Ph)_2 + OPR'_2Ph + OPPh_3 \quad (31)$$

$$ReCl_3(ArNO)(OPPh_3) + CNC_6H_{11} \rightarrow ReCl_3(NAr)(CNC_6H_{11})_2 + \text{organic products} \quad (32)$$

The side-on (*N*,*O*) bound nitroso ligand in Ni(PhNO)(*t*-BuNC)$_2$ is also deoxygenated when reacted with *t*-BuNC, PPh_3, or PhNO (e.g., eqs 33 and 34), although the proposed nitrene intermediates were not isolated.[241]

$$Ni(PhNO)(t\text{-}BuNC)_2 + PPh_3 \rightarrow Ni(PPh_3)_2(t\text{-}BuNC)_2 + t\text{-}BuNCO + OPPh_3 \quad (33)$$

$$Ni(PhNO)(t\text{-}BuNC)_2 + PhNO \rightarrow Ni(PhNO_2)(t\text{-}BuNC)_2 + PhN{=}N(O)Ph \quad (34)$$

In the case of the reaction with PhNO, a net formal O-atom transfer from one PhNO to another occurs.[241] It was found that Ni(*t*-BuNC)$_4$ catalyzes the related reaction of PhNO with isocyanide (eq 35).

$$PhNO + t\text{-}BuNC \rightarrow t\text{-}BuNCO + PhN{=}C{=}N(t\text{-}Bu) + PhN{=}NPh + (t\text{-}BuNH)_2CO \quad (35)$$

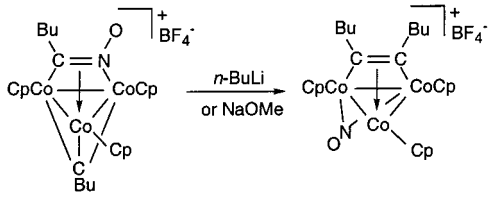
The deoxygenation of the η^1-*N*-bound nitroso groups in coordinated nitrosophenolates (of structure **A6** in Figure 3; M = Ni, Cu, Fe, Zn) by PPh_3 to give intermediate nitrene complexes has been reported.[246] The dimeric [Cp$_2$TiCl]$_2$ compound effects the deoxygenation of PhNO, presumably via initial *O*-coordination of PhNO, to give [Cp$_2$TiCl]$_2$(μ-O), PhN=NPh, and PhN=N(O)Ph.[247] The azoxybenzene product was also obtained from the related reaction with Fe(salen).[247] Nitrene intermediates were also proposed during the catalytic reduction of PhNO by CO using metal−PhNO complexes as catalysts (metal = Ru^{II}, Pd^{II}, Pt^{II}, Rh^{I}).[248] Similar metal−nitrene complexes were also proposed as intermediates during the transformation of nitrosoarenes and *t*-BuNO to the azo- and azoxy compounds by $Fe(CO)_5$ or $Cr(CO)_6$.[249] Carbon monoxide was also found to react with Rh nitrosobenzene complexes of structures **F** and **G** (Figure 3) to give phenyl isocyanate PhNCO and trace amounts of phenyl urea PhNHCONHPh.[178] Some RNO compounds react with some metal complexes to result in metal−nitrene formation.[250,251]

Srivastava and Nicholas demonstrated that the isolable azodioxide complex $[Fe\{[PhNO]_2\}_3]^{2+}$ (structure **D** in Figure 3) is capable of effecting the amination of alkenes (resulting in allylic amination) without the involvement of free PhNO.[174,175] However, a mechanism in which a direct "inner-sphere" transfer of a single PhNO unit to the alkene to produce the allylhydroxylamine was considered; the hydroxylamine was then chemically reduced to the allylamine in a subsequent reaction.[175] Nitrene −NR transfers from molybdooxaziridines (structure **E** in Figure 3) to give allylic amines have also been reported.[176]

(3) Reduction of Coordinated RNO. The coordinated PhNO groups in M(CO)$_5$(PhNO) (M = Cr, Mo, W) undergo facile reduction in THF to give the M(CO)$_5$(PhNH$_2$) compounds.[252] A similar reduction of W(CO)$_5$(*t*-BuNO) to W(CO)$_5$(*t*-BuNH$_2$) is known.[112] Becker and Bergman developed the $LiAlH_4$ reduction of the dinitrosoalkane ligands in cobalt complexes (e.g., those in eqs 25 and 37) to primary vicinal diamines.[144] The metal-ion-catalyzed reductions of RNO compounds continue to be studied under a variety of conditions.[253,254]

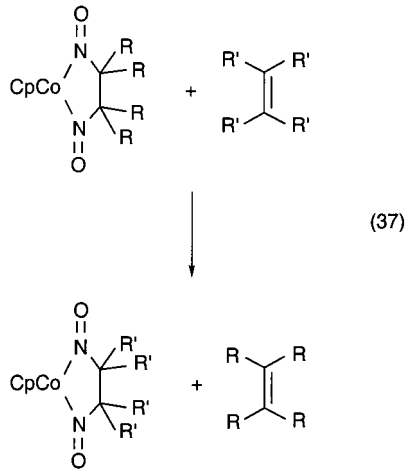
(4) Carbon−Nitrogen Bond Cleavage and Resultant Metal−NO Bond Formation. An early report describes the reactions of CF_3NO with Pt(PPh$_3$)$_4$ or Cp$_2$Ni to produce the nitrosyl complexes Pt(PPh$_3$)$_2$(NO)(CF$_3$) or CpNi(NO), respectively.[255] Later work with the Pt system resulted in the isolation of Pt(PPh$_3$)$_2$(η^2-ONCF$_3$) (the Pd analogue was also obtained similarly).[113]

Vollhardt and co-workers reacted an alkanenitrile oxide complex of Co with base to obtain the nitrosyl derivative (eq 36).[125]



(36)

Bergman reported that the alkene exchange reaction shown in eq 37 proceeds via initial carbon−nitrogen cleavage (alkene dissociation) to give the intermediate dinitrosyl CpCo(NO)$_2$ which recombines with alkene.[144,146]



(37)

Carbon−nitrogen bond cleavage is an essential feature in the conversion of L-arginine to citrulline and NO in this biological reaction catalyzed by the enzyme NO synthase (related carbon−nitrogen bond cleavages by cytochrome P450 have also been demonstrated).[256,257] Interestingly, some hydroxamates

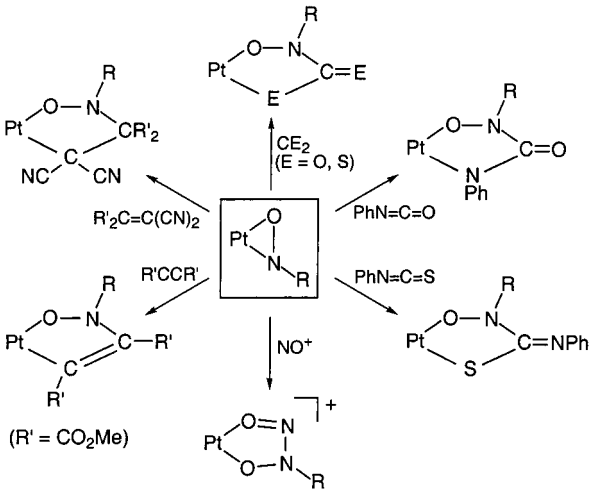


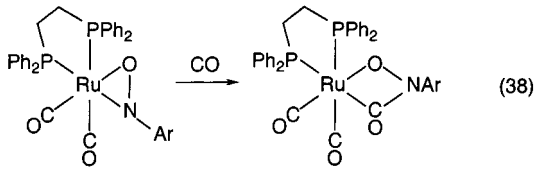
Figure 4. Reactions of the side-on-bonded RNO groups in Pt complexes.

have been shown to serve as net NO donors (from carbon−nitrogen bond cleavage) in their reactions with iron porphyrins.[258] Related NO donation by Ru coordination complexes of hydroxamic acids has been demonstrated[259] and by an amidoxime ligand in a Mo coordination complex.[242] Groves reported that (por)Fe(η^1-oximate) compounds are oxidized to generate (por)Fe(NO) via carbon−nitrogen bond cleavage.[260] The activation of guanylyl cyclase by hydroxamic acids (possibly by NO release) has also been reported,[259] and another report describes NO release via carbon−nitrogen bond cleavage in cyclohexanone oxime in vivo.[261]

(5) Coupling Reactions of Bound RNO. The side-on (*N*,*O*) bound RNO ligands in $Pt(PPh_3)_2(RNO)$ (R = Ph, *t*-Bu, CF_3) undergo a wide variety of coupling reactions with added reagents, and the range of such reactions is shown in Figure 4.[113,262−266]

Theoretical calculations on $Pt(PH_3)_2(CH_3NO)$ suggest a significant localization of negative charge (ca. −0.34) on the N-atom due to back-bonding from Pt into the π^*-orbital of the NO unit (thus giving the N-atom more sp^3 character), enabling it to engage in such coupling reactions.[267]

A related coupling of CO with a coordinated RNO ligand has been observed in a complex of Ru (eq 38; Ar = $C_6H_4CF_3$).[129]



A metal−PhNO complex of structure **H** (Figure 3) also displays coupling reactions of the PhNO group with added reagents to give addition products (some of which were characterized by X-ray crystallography) as shown in Figure 5 (L = PEt_3; R′ = $N(SiMe_3)_2$).[186]

The reactions of metal−RNO compounds continue to be explored. Some *C*-nitroso compounds and their metal complexes (M = Pt, Pd, Rh) have been used for the deposition of Langmuir−Blodgett films.[268−270]

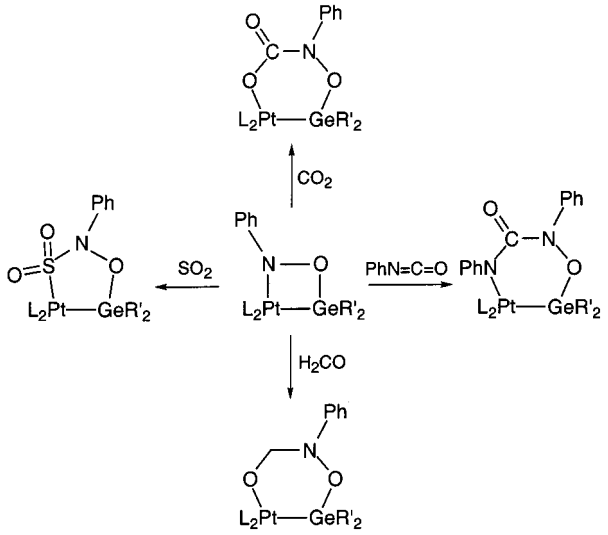


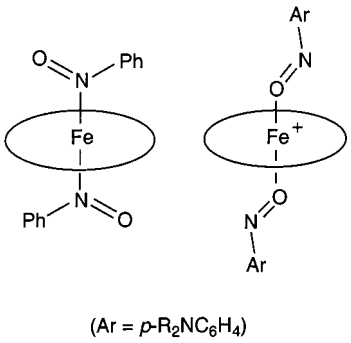
Figure 5. Reactions of the side-on-bonded RNO groups in Pt−Ge complexes.

4. Complexes with Heme and Heme Models

There is great interest in examining the products formed when metabolites of amines interact with heme biomolecules such as hemoglobin and cytochrome P450. The oxidation of amines to hydroxylamines or nitroso compounds and the reduction of the *N*-oxidized derivatives are known to occur in some biological environments.[271−279] The intermediate *C*-nitroso compounds can then bind to heme biomolecules or are involved in other reactions (such as metHb formation) in biological media.[280−282] Indeed, the study of the interactions of *C*-nitroso compounds with heme and heme models is motivated, in part, by the observation that various metabolites derived from amine oxidation or nitroaromatic reduction are involved in possible inhibition of enzymatic activity of P450 or cyclooxygenase and that such heme−RNO species are possible products in such processes.

The published literature on the interaction of nitrosoalkanes and nitrosoarenes with heme is reviewed in this section.

(1) Heme Model Complexes. *C*-Nitroso compounds interact with synthetic metalloporphyrins to form isolable adducts. Such metalloporphyrin−nitrosoalkane adducts were obtained by Mansuy and co-workers for Fe from the reaction of the ferric porphyrin with the precursor hydroxylamines; the X-ray crystal structure of (TPP)Fe(*i*-PrNO)(*i*-$PrNH_2$) revealed the *N*-binding mode of the nitrosoalkane ligand.[114] Richter-Addo and co-workers later demonstrated that the nature of binding of nitrosoarenes to iron porphyrins depended on a number of factors including the formal oxidation state of the iron center.[161] Thus, the solid-state structure of the formally *ferrous* complex $(TPP)Fe(PhNO)_2$ revealed an *N*-binding mode of the PhNO ligands (Figure 6, left), whereas the corresponding structure of the *ferric* complex $[(TPP)Fe(ONAr)_2]^+$ (Ar = *p*-amino-substituted benzene) revealed an *O*-binding mode of the nitrosarene ligands (Figure 6, right), presumably due to the contribution of the dipolar resonance form (eq 28).



(Ar = p-$R_2NC_6H_4$)

Figure 6. Nitrosoarene binding modes in ferrous (left) and ferric (right) porphyrins.

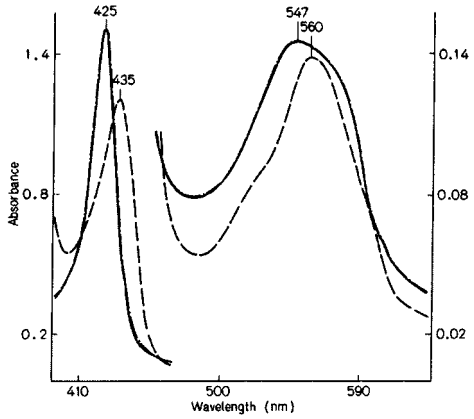


Figure 7. Visible spectra of myoglobin treated by nitroethane and dithionite: (- - -) 0.01 mM myoglobin and 0.02 M sodium dithionite in 0.1 M phosphate buffer, pH 7.4, (—) addition of 0.02 M nitroethane, (—·—) further 5 min CO bubbling.[289] (Reprinted with permission from ref 289. Copyright 1977 Blackwell Science.)

Metalloporphyrin complexes of Mn,[171] Fe,[114,162,283−286] Ru,[163,164,287] Os,[165] and Co[163] containing *C*-nitroso ligands have been reported. With the exception of two examples (Fe[161] and Mn[171]), all the structurally characterized complexes reveal the *N*-binding mode of the *C*-nitroso ligand (Table 5).

Iron phthalocyanine complexes containing nitrosoarene ligands, namely, (Pc)Fe(ArNO)($BuNH_2$) and (Pc)Fe(ArNO)(*N*-MeIm) (Ar = Ph, *p*-tol, *p*-C_6H_4-(*i*-Pr)), have been reported by Balch and co-workers.[288] Related (Pc)Fe complexes containing nitrosobenzene ligands have also been reported.[286]

(2) Myoglobin. The formation of nitroso*alkane* complexes of Mb has been observed by Mansuy and co-workers.[285,289,290] The reaction of a number of nitroalkanes (RNO_2; R = Me, Et, *i*-Pr, pentyl, hexyl) with Mb in the presence of dithionite (pH = 7.4, phosphate buffer) resulted in the formation of new complexes absorbing at 425 nm. Figure 7 shows an example for the specific case where R = Et.[289]

The rate and extent of formation of the 425 nm complexes were dependent on the structure of the RNO_2 reagent.[289] The 1° nitroalkane reagents all produced the 425 nm complexes rapidly (<3 min for R = Me, Et, but incomplete conversion even after 30 min when R = pentyl (98%) or hexyl (80%)). The 2° nitroalkanes were less reactive, and the 3° nitroalkanes did not produce the 425 nm derivatives (Figure 8).[289]

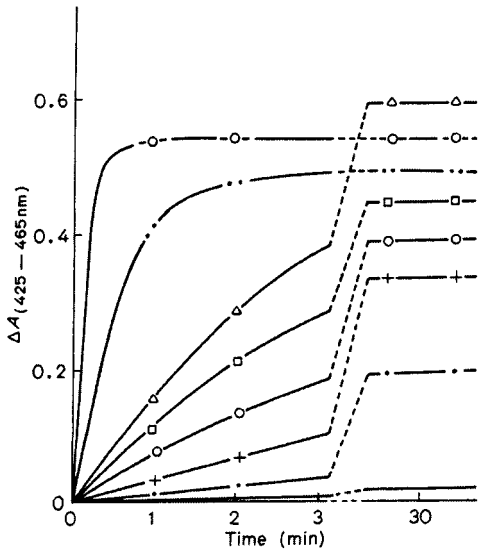


Figure 8. Reactions of various nitroalkanes with horse myoglobin in the presence of dithionite. Absorbance changes of solutions containing 0.01 mM myoglobin in phosphate buffer (pH 7.4) and 0.02 M sodium dithionite were monitored at 425 nm relative to the isosbestic point (465 nm) by dual-wavelength spectroscopy, after the addition of a nitroalkane half-diluted in methanol: (— - ○ - —) nitromethane, (—••—) nitroethane, (△—△) 2-nitropropane, (□—□) 1-nitropentane, (○—○) nitrocyclopentane, (+ — +) 1-nitrohexane, (—·—) nitrocyclohexane, (—) 2-methyl-2-nitropropane.[289] (Reprinted with permission from ref 289. Copyright 1977 Blackwell Science.)

The Mb nitrosomethane complex was stable in the pH 6−8.5 range and air-stable at 5 °C for several days. All the Mb nitrosoalkane complexes were stable to excess dithionite, but they decomposed in the presence of ferricyanide to give metMb. Their nitrosoalkane ligands in the (Mb)Fe^{II}−RNO complexes were not displaced by 1 atm of CO.

The reactions of nitrosoarenes with myoglobin are also known to give the (Mb)Fe^{II}−ArNO adducts directly. Gibson reported, in 1960, that PhNO and various nitrosotoluene isomers reacted with reduced myoglobin in borate buffer (pH 9.1) in a second-order reaction to give the nitrosoarene adducts with the rate generally independent of the nature of *o*/*m*/*p*-methyl substitution of the phenyl ring.[291] Mansuy also reported that ferrous deoxyMb reacted with PhNO at pH 7.4 to give the adduct (Mb)Fe^{II}−PhNO with λ_{max} 427 nm.[292] The same complex was obtained when metMb was used, although the reaction was slower. The products were unstable in the presence of dithionite or ferricyanide. In addition, PhNHOH was found to react with metMb to also produce the 427 nm-absorbing complex, and an analogous complex was also obtained when *p*-$ClC_6H_4NO_2$ was reacted with metMb in the presence of dithionite, although the latter complex was only observed as a transient species (it decomposed in <1 min).

Cho and co-workers confirmed the observation that either metMb or reduced Mb reacted with PhNO to produce the (Mb)Fe^{II}−PhNO complex (although the reaction with metMb was slower) and showed that the PhNHOH reagent is oxidized by air to PhNO which then binds the reduced iron and that NADPH also reduces free PhNO to PhNHOH.[283] Their results

helped to explain why the heme−nitrosoarene complexes (unlike their nitrosoalkane analogues) are not stable to dithionite, since the chemical reduction of the dissociated PhNO makes it unavailable for recombination with the heme.

(3) Hemoglobin. The reactions of *C*-nitroso compounds with Hb are quite complex due to the fact that four hemes are involved and the observation that the Cys93 residue from the protein β subunit (βcys93) may also partake in such reactivity. In this section, we will discuss the reactions of Hb with nitrosoalkanes followed by the reactions with nitrosoarenes.

Nitrosoalkane complexes of Hb (generally referred to as Hb(RNO) for convenience) have been generated by reduction of the precursor nitroalkane RNO_2 by dithionite in the presence of Hb. For example, Mansuy and co-workers studied the reaction of several nitroalkanes with human Hb in the presence of dithionite.[289,290] They found that for $MeNO_2$ and $EtNO_2$ compounds, the reaction to produce the Hb(RNO) complexes (λ_{max} 421 nm; R = Me, Et) was complete within a 3 min period. They proposed an *N*-binding mode of the RNO ligand based on resonance Raman spectroscopy.[289,293] When the R group was pentyl or *i*-Pr, they found only 60% and 42% conversion, respectively, to the Hb(RNO) complexes even after 30 min. No reaction occurred when R was cyclopentyl or cyclohexyl (in contrast with the reactions of Mb). Importantly, they also showed that the nitrosoalkane Hb(RNO) complexes did not exchange their RNO ligands with 1 atm CO, whereas Hb(PhNO) reacted with 1 atm CO to produce Hb(CO). They further showed that the Hb(RNO) complexes were stable to excess dithionite, whereas Hb(PhNO) was not.[289,292]

The interactions of nitrosoarenes (and other *N*-oxygenated amines) with Hb are more complex. The ability of *N*-oxygenated arylamines to react with Hb to produce metHb has been recognized for quite some time.[281,294−297] Interestingly, many substituted nitrosoarenes that are ligands to ferrous Hb also cause oxidative degradation of Hb in erythrocytes, and it was determined that binding of the nitrosoarenes to the metal center in Hb is not a necessary condition for nitrosoarene-induced hemolysis.[298] Indeed, absorption spectroscopy alone is usually not sufficient to completely discern the reactions of nitrosoaromatics with Hb, and in some studies radioactive labeling (e.g., the use of ^{131}I-labeled substituted nitrosoarenes)[299] or EPR spectroscopy of spin-labeled Hb (at the cysteine residue)[300,301] has been used to follow the reactions.

In general, nitrosoarenes can react with Hb at the heme iron and/or at reactive cysteine residues, as schematically shown in Figure 9 for nitrosobenzene.

It was recognized more than a century ago that nitrobenzene poisoning was associated with the formation of an adduct between a derivative of nitrobenzene and hemoglobin.[302,303] Heubner and coworkers also examined the reactions of PhNHOH with oxyHb and determined that metHb is eventually formed via a then-unknown intermediate complex.[304] In 1940, Jung reported that metHb reacted

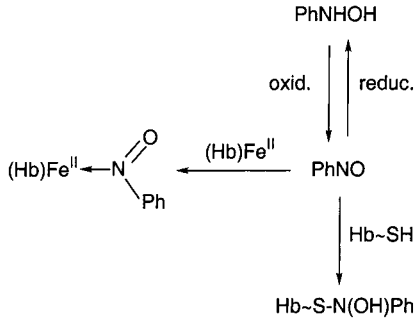


Figure 9. Reactions of nitrosobenzene with hemoglobin.

with PhNHOH to give either ferrous deoxyHb or the nitrosobenzene derivative of ferrous Hb and that the (Hb)Fe^{II}−PhNO complex slowly converted to metHb.[305,306] Both PhNHOH and PhNO had the same potency for metHb formation.[305,306] Furthermore, Jung showed that *p*-tolNO and *m*-$O_2NC_6H_4NO$, in addition to PhNO, reacted with oxyHb or Hb(CO) to form Hb(ArNO) adducts (neither *p*-$Me_2NC_6H_4NO$ or *p*-HOC_6H_4NO formed similar adducts).[307] Keilin and Hartree also reported that PhNHOH reacted with oxyHb or metHb to give a Hb−PhNO species and that the product was air-sensitive and destroyed by dithionite or ferricyanide.[308] Importantly, they reported that addition of authentic PhNO to deoxyHb produced an identical product (as ascertained by absorption spectroscopy). They reported that PhNHOH reacted with an alkaline solution of hematin to form a bright red heme−PhNO species and that the reaction was fast in the presence of air but that the heme−PhNO product decomposed in air or in the presence of dithionite or ferricyanide.[308]

Other reactions of Hb with substituted nitrosoarenes have been reported to generate Hb(ArNO) complexes.[291,309−310] Scheler observed the binding of PhNO to reduced Hb and determined that the PhNO:Fe ratio in the combination of PhNO with oxyHb was 1:1, although it was proposed that additional PhNO molecules could have interacted with the protein.[311]

Eyer and co-workers reexamined the competitive reactions of *para*-substituted nitrosoarenes with the heme iron and the cysteine residues of Hb.[312] They determined that when deoxy-Hb [60 μM] was reacted with PhNO, the stoichiometrically added PhNO all went to the heme iron. The measured affinity for PhNO by deoxyHb was very high, with a C_{50} value of less than 1 μM (C_{50} = concentration of free PhNO at one-half saturation). They also determined that the affinity of Hb for PhNO was 14 times higher than that for O_2 and that the maximum cooperativity during PhNO binding had an associated Hill coefficient n_{max} of 2.15 (cf., 2.23 for O_2). Furthermore, the relative affinity for substituted ArNO compounds decreased in the order *p*-ClC_6H_4NO > PhNO > *p*-tolNO > *p*-nitrosophenetole, suggesting that electron-donating substituents decreased the affinity to Hb, and a good Hammett ($\sigma_p^{\oplus}$) correlation was obtained. Reaction of ArNO with the cysteine residue(s) occurred when HS∼Hb(CO) (40−640 μM) was reacted with ArNO (20−80 μM); a decrease in [ArNO] was observed, although no iron-ligation occurred.[312] Indeed, reaction of ArNO with Hb containing *inactive*

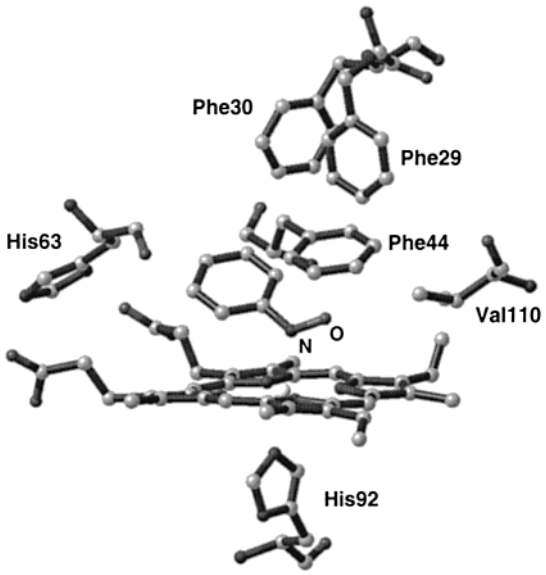


Figure 10. Heme site in the leghemoglobin−nitrosobenzene complex.[316] The Fe−N(O), Fe−N(His), and Fe−N(porphyrin) bonds are omitted for the sake of clarity. The X-ray coordinates were obtained from the Brookhaven Protein Data Bank.

cysteine groups (where the SH groups had been blocked with *N*-ethylmaleimide) showed no similar decrease in [ArNO]. The involvement of the cysteine SH groups in the reactions with ArNO was illustrated by the reaction of HS∼Hb(CO) with *p*-ClC_6H_4NO, which revealed the formation of a semimercaptal intermediate followed by rearrangement to the *para*-substituted cysteine *S*-oxide *S*-anilide derivative. The crystal structure of human hemoglobin modified by reaction with *N*-hydroxy-4-aminobiphenyl to give the hemoglobin sulfinamide adduct (via initial covalent bond formation between 4-nitrosobiphenyl and βCys93) has been reported.[313]

The reactions of the cysteine groups of Hb with nitrosochloramphenicol (NOCAP; a possible metabolite of chloramphenicol) have been demonstrated by radioactive labeling (e.g., the use of ^{14}C-labeled NOCAP).[314] It was shown that the heme group of Hb was a second site for NOCAP binding, although this heme−NOCAP binding was not very efficient probably due to steric reasons.

Eyer and co-workers have shown that $PhNH_2$, PhNHOH, PhNO, and $PhNO_2$ were all metabolized in vivo to yield the same metabolite phenylhydronitroxide radical (PhN(O$^\bullet$)H), which oxidizes the reactive SH group of Hb in rats in vivo, in red blood cells in vitro, and in purified oxyHb.[300] The resulting $^\bullet$S∼Hb radical could then be spin-trapped with 5,5-dimethyl-1-pyrroline-*N*-oxide and the adduct characterized by EPR spectroscopy. The reactions of nitrosoarenes with thiol SH groups and their biological relevance have been reviewed.[315]

(4) Leghemoglobin. The X-ray crystal structure of the ferrous (legHb)Fe^{II}−N(O)Ph adduct from *Lupinus luteus* has been obtained at 2.00 Å, and it reveals the *N*-binding mode of the PhNO ligand to the metal center (Figure 10).[316]

(5) Soluble Guanylyl Cyclase (sGC). The 425 nm-absorbing complex formed when ferrous sGC (pH 7.4, 10 °C) is reacted with $MeNO_2$ and dithionite under argon is attributed to a (sGC)Fe^{II}−MeNO complex (Figure 11).[317]

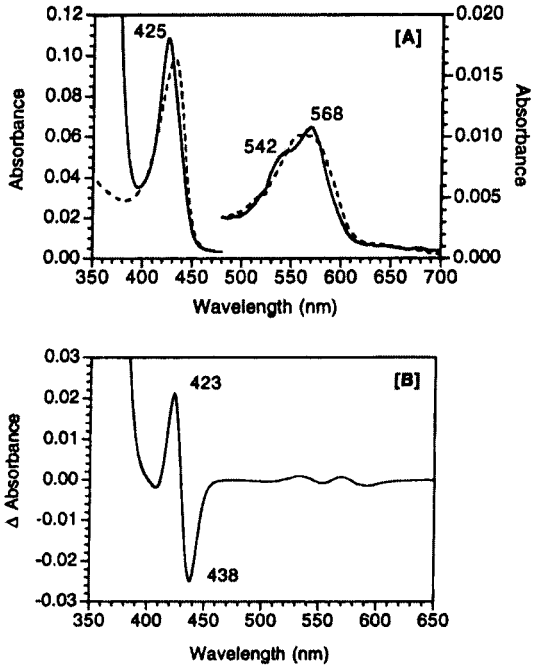


Figure 11. Spectral characterization of the nitrosomethane-sGC complex. (A) Electronic absorption spectrum of the nitrosomethane-sGC complex. sGC (0.9 μM heme) in 25 mM TEA, 50 mM NaCl, 5 mM DTT, and 20 mM nitromethane, pH 7.4, was placed in a septum-sealed cuvette under argon. Spectra were recorded in the presence (—) and absence (- - -) of 10 mM dithionite. (B) Electronic absorption difference spectrum for the binding of nitrosomethane to sGC. The electronic spectrum of ferrous sGC was subtracted from that of the nitrosomethane complex of sGC. The peak at 423 nm and the trough at 438 nm are due to the shifting of the Soret band as nitrosomethane binds to the heme.[317] [Reprinted with permission from ref 317. Copyright 1995 American Chemical Society.)

This complex was not very stable in solution and reverted to the five-coordinate ferrous sGC form within 30 min, suggesting a dissociation of the MeNO ligand (which is unstable in the free unligated form).

(6) Cytochrome P450. It has been known for quite some time that some organic *N*-containing compounds are capable of forming complexes (λ_{max} ∼455 nm) with cytochrome P450 during oxidative metabolism in microsomal systems, and there is the possibility that nitroso compounds (when capable of binding to heme iron) may inhibit P450 activity. An example of such a compound capable of forming a 455 nm complex is diethylaminoethyl 2,2-diphenylvalerate HCl (SKF 525-A; a known inhibitor of the metabolism of substrates of the hepatic microsomal mixed function oxidase system).[318] Similar "∼455 nm complexes" were observed by Estabrook,[319] Lindeke,[320] and Franklin[321−323] to form during the oxidative metabolism of amphetamine derivatives. Such a 455 nm complex formed rapidly (<1 min; in the presence of NADPH and O_2) during the P450-dependent metabolism of *N*-hydroxyamphetamine and was stable in the presence of dithionite but was destroyed by ferricyanide oxidation.[324] Further studies with amphetamine congeners suggested that

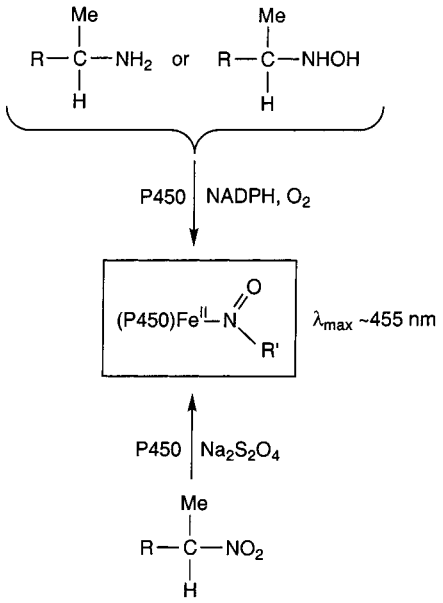


Figure 12. Formation of nitrosoalkane complexes of cytochrome P450 (R′ = RCH(Me)−).

oxidative metabolism involving the N-atom was implicated in the formation of the 455 nm complexes.[325] Interestingly, cytochrome P450 also formed a complex with a metabolite of *p*-chloroaniline (λ_{max} 448 nm), although this latter complex was unstable in the presence of dithionite.[326]

Ullrich observed that a ligand-binding spectrum (i.e., direct Fe−ligand binding) was obtained when 2-nitropropane was reacted with reduced P450.[327] Mansuy and co-workers studied the interaction of several 1° and 2° nitro RNO_2 compounds (R = Me, Et, *n*-pentyl, *n*-hexyl, cyclohexyl, cyclopentyl, benzyl (i.e., amphetamine)) with reduced P450 and found that the products were also 455 nm complexes.[290] Tertiary RNO_2 compounds did not produce the 455 nm complexes, presumably due to steric bulk of the R groups. They proposed that it was the nitroso metabolite (RNO; formed from reduction of the nitro compounds or after oxidation of the amines) that was the ligand in these 455 nm complexes (Figure 12).

The nitroso adduct was favored over its oxime (R″CH=NOH) isomer, since addition of free oxime to P450 did not produce any spectral change associated with binding.[290] Further studies also showed that aliphatic hydroxylamines formed ∼423 nm complexes with reduced P450 under anaerobic conditions, but these converted to the ∼455 nm complexes in the presence of dioxygen.[328] The results of these studies suggested that it was the nitroso metabolite of amphetamine or *N*-hydroxyamphetamine that was the ligand in the 455 nm complex with cytochrome P450 during hepatic microsomal oxidative metabolism.[324]

Jonsson and Lindeke reported their results on the interactions of amphetamines, other phenylalkylamines, and their *N*-oxygenated congeners with reduced P450.[329] Their observation of complex formation between 2-nitroso-1-phenylpropane and P450 in the presence of dithionite supported the earlier report by Mansuy and co-workers that the nitroso (RNO) metabolite was the likely ligand in the resulting 455 nm complexes during metabolism of the amines, although they also suggested that the nitroxide (RHNO) could be the ligand.

Mansuy and co-workers reported that arylnitroso (ArNO; Ar = Ph, *p*-chlorophenyl) complexes of NADPH-reduced liver microsomal P450 displaying λ_{max} 454 nm were also obtained by (i) direct interaction of the nitrosoarene under anaerobic conditions, (ii) reaction of the arylhydroxylamine (ArNHOH) under aerobic conditions, or (iii) reaction of the nitroarene ($ArNO_2$) under reducing (NADPH or dithionite) conditions.[292] Unlike the nitrosoalkane derivatives, these nitrosoarene complexes of P450 were unstable in the presence of dithionite and were also destroyed by addition of ferricyanide. They showed that a low concentration of phenylhydroxylamine (10 μM) produced a Type I spectrum with P450 (with no 454 nm peak) that shifted to a 454 nm spectrum after addition of NADPH. Cho and co-workers later examined the direct interaction of nitrosobenzene with ferric P450, and they found that the reaction of ferric P450 with PhNO without added reductant produced the $(P450)Fe^{II}$−PhNO adduct.[283] They also showed that the reaction of *N*-hydroxyaniline with ferric P450 produced the same $(P450)Fe^{II}$−PhNO adduct,[283] an observation consistent with the results of Mansuy and co-workers.[292] In addition, they showed that air-oxidation of *N*-hydroxyaniline gave PhNO, which then reacted with P450 to give the $(P450)Fe^{II}$−PhNO adduct. Indeed, the rate of complex formation between *N*-hydroxyaniline and ferric P450 increased drastically when air was introduced, presumably as a result of *N*-hydroxyaniline-to-nitrosobenzene oxidation. This concept was supported by studying the rate of complex formation of several *para*-substituted *N*-hydroxyanilines (p-XC_6H_4NHOH; X = CN, CF_3, Cl, F, Br, CH_3), where they found a positive correlation between the rate of $(P450)Fe^{II}$−ArNO formation and the rate of autoxidation of the *N*-hydroxyanilines.[283]

(7) Nitric Oxide Synthase. Nitrosomethane complexes of the oxygenase domain of NO synthase have been generated from the reaction of nitromethane ($MeNO_2$) and dithionite with recombinant $iNOS_{oxy}$ and $nNOS_{oxy}$ (pH 7.4, 50 mM HEPES).[330] The $(iNOS_{oxy})Fe^{II}$−MeNO complex (λ_{max} 448 nm) is formed quickly (<3 min; Figure 13), remains stable for at least 10 min, and does not exchange its MeNO ligand with CO but is oxidatively decomposed by ferricyanide to its ferric resting state with concomitant MeNO dissociation. Other $(NOS_{oxy})Fe^{II}$−RNO complexes were similarly produced from the reaction of nitroalkanes with $iNOS_{oxy}$ or $nNOS_{oxy}$ in the presence of dithionite (Table 10) but in the absence of tetrahydrobiopterin. The products formed at different rates depending on the size of the R group. Thus, the smaller RNO_2 compound (R = Me, Et) reacted to form the nitrosoalkane complexes within 3 min, whereas the larger RNO_2 compounds took longer (e.g., >10 min for R = *i*-Pr). In the case of PhNO, it was proposed that the $(NOS_{oxy})Fe^{II}$−PhNO product decomposed quickly due to the further reaction of the PhNO ligand with dithionite (as is observed with some other heme protein−PhNO complexes). Inter-

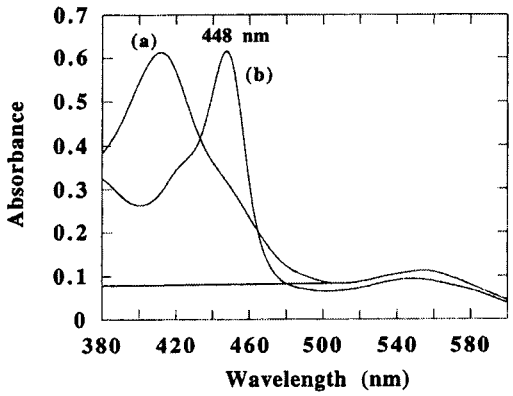


Figure 13. UV−vis spectra of the complex formed upon reaction of $iNOS_{oxy}$ with CH_3NO_2 in the presence of dithionite. (a) $iNOS_{oxy}$, 8 μM, in 50 mM HEPES buffer, pH 7.4, reduced by an excess of sodium dithionite. (b) Spectrum obtained 5 min after addition of 2.5 mM CH_3NO_2.[330] (Reprinted with permission from ref 330. Copyright 1998 American Chemical Society.)

Table 10. Formation of Nitrosoalkane Complexes of $iNOS_{oxy}$ and $nNOS_{oxy}$ after Reaction with Nitroalkanes ($R-NO_2$) and Dithionite

R	λ_{max} (nm)	$iNOS_{oxy}$[a]	$nNOS_{oxy}$[b]
methyl	448	0.72	0.40
ethyl	449	0.54	0.41
isopropyl	450	0.32	0.15
tert-butyl	no peak		
4-Cl-Ph-$CHCH_3$[c]	448	0.06	n.d.[d]
4-Cl-Ph-CH_2CHCH_3[c]	451	0.10	n.d.[d]
hexyl	452	0.18	0.09
cyclohexyl	450	0.10	0.04
phenyl	no peak		

[a] Initial rate of complex formation between 0.6 μM $iNOS_{oxy}$ and 2.5 mM nitroalkane in the presence of 10 mM sodium dithionite, expressed in nanomoles of complex (nmol of NOS^{-1}) min^{-1}. Calculations used an ϵ value identical for all complexes (45 ± 4.5 mM^{-1} cm^{-1}) assuming 100% complex formation in the case of CH_3NO_2. [b] As in footnote a but with 0.4 μM $nNOS_{oxy}$. [c] Due to limited solubilities of these two compounds, the final concentration was 1 mM. [d] Not determined. (Reprinted with permission from ref 330. Copyright 1998 American Chemical Society.)

estingly, in the absence of dithionite, it was observed that some of the RNO_2 reagents (R = hexyl, cyclohexyl) were able to interact with NOS_{oxy} by binding to a protein site close to the heme (rather than binding directly to the heme iron).

(8) Catalase. A (catalase)Fe^{II}−PhNO complex (λ_{max} 421 nm) has been proposed as a product when PhNHOH was reacted with bovine liver catalase.[331]

(9) Prostaglandin H Synthase (PGHS). The addition of *N*-hydroxyamphetamine (AmphNHOH; $PhCH_2C(Me)HNHOH$) to a microsomal suspension of sheep seminal vesicles under aerobic conditions in aqueous buffer (0.1 M Tris-HCl, pH 8.1) led to the formation of a product with λ_{max} 424 nm in the difference absorption spectrum (Figure 14).[331]

A similar reaction of purified reconstituted PGHS with AmphNHOH under aerobic conditions led to the formation of a similar product with λ_{max} 421 nm. Importantly, this product did not form in the absence of air (oxygen), and the reaction of the 421 nm-absorbing product with the oxidant $K_3Fe(CN)_6$ regenerated the resting ferric (PGHS)Fe^{III} compound.

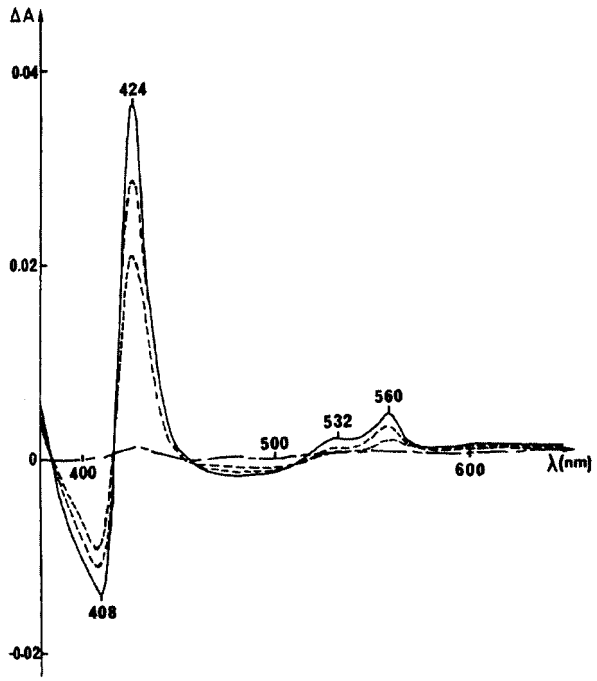
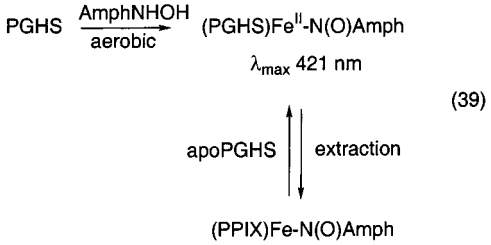


Figure 14. Difference spectra of microsomes from sheep seminal vesicles obtained after the addition of *N*-hydroxyamphetamine. The two cuvettes contained 4 mg of protein in 1 mL of 0.1 M Tris-HCl buffer, pH 8.1. *N*-Hydroxyamphetamine (1 mM) was added to the sample cuvette, and the spectra were recorded after 1, 5, and 9 min.[331] (Reprinted with permission from ref 331. Copyright 1991 American Chemical Society.)

A concentration of 68 μM AmphNHOH was needed to convert 50% of ferric PGHS (4 μM) to the nitrosoalkane derivative. A (PGHS)Fe^{II}−AmphNO complex was proposed for the 421 nm-absorbing species, since extraction with ethyl methyl ketone gave the non-protein (PPIX)Fe(AmphNO) species; the latter species was also generated independently (eq 39). Incorporation of authentic ferrous (PPIX)Fe(AmphNO) into apoPGHS also generated the (PGHS)Fe^{II}-(AmphNO) species.



(39)

Other *N*-substituted hydroxylamines such as *i*-PrNHOH and PhNHOH reacted with purified PGHS to form the analogous (PGHS)Fe^{II}−N(O)R complexes, although to different degrees. The (PGHS)Fe^{II}−N(O)*i*-Pr complex was prepared in higher yield by an alternate route: reduction of 2-nitropropane by 1 mM sodium dithionite in the presence of PGHS. This latter strategy was also used to prepare the methyl and ethyl derivatives (PGHS)-Fe^{II}−N(O)R (R = Me, Et). The latter complexes could not be prepared from their hydrophilic hydroxylamines. Although the nitrosoalkane complexes are stable to dithionite reduction, the nitrosobenzene

complex (PGHS)Fe^{II}−N(O)Ph is not stable in the presence of dithionite. It was suggested that perhaps the reversible dissociation of PhNO enables a facile reduction of free PhNO by dithionite, effectively depleting it from solution and hence hindering its rebinding to the heme.[331]

(10) Microperoxidase. Several nitrosoalkane complexes of microperoxidase 8 with λ_{max} ~414 nm containing the Fe^{II}−RNO group (R = Me, Et, Pr, *i*-Pr, hexyl, cyclohexyl, $PhCH_2CH(Me)$-, (p-ClC_6H_4)CH_2-CH(Me)−) have been reported to form from the reaction of microperoxidase 8 with the hydroxylamine precursors or from the reaction with the nitroalkane precursors under reducing conditions.[332]

III. N-Nitroso Compounds

A. Organic Compounds

1. Synthesis

Nitrosamines R_2NNO contain the *N*-nitroso functional group and are usually prepared by the *N*-nitrosation of amines and related compounds. Typical nitrosating agents (XNO) for these reactions include N_2O_4, ClNO, BuONO, NO^+, and acidified nitrite.[3,333,334]

$$R_2NH + XNO \rightarrow R_2NNO + HX \qquad (40)$$

Variations of the general reaction described by eq 40 continue to be explored for the syntheses of nitrosamines.[3,335−337] Under some conditions, 3° amines may be nitrosatively dealkylated (i.e., *N*-nitrosation-*N*-dealkylation) to give nitrosamines (e.g., eq 41).[3,338]

$$2R_2NCHR'_2 + 4HNO_2 \rightarrow 2R_2NNO + 2R'_2CO + N_2O + 3H_2O \qquad (41)$$

Such *N*-nitrosation−*N*-dealkylation reactions of 3° *N*,*N*-dialkyl aromatic amines by *n*-BuONO have been reported.[339]

Nitrosamine formation from their lithium amide precursors has been suggested as an alternate route for the preparation of some nitrosamines (eq 42).[340]

$$R_2NLi + NO \rightarrow R_2NNO \qquad (42)$$

Ohshima and co-workers studied the reaction of 2° amines with peroxynitrite and other reactive nitrogen oxides and showed that the reactions generate nitrosamines and *N*-nitramines (R_2NNO_2).[341a] Ohsawa and co-workers reported a related study on the reaction of 2° and 3° amines with NO in the presence of oxygen and showed that nitrosamines were products of these reactions.[341b] The reader is encouraged to consult the more extensive reviews related to the chemical reactivity of nitrosamines for an in-depth treatise of the subject.[3,333,334]

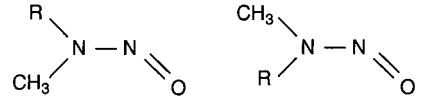
2. Spectroscopy and Structure

Nitrosamines can be written in two main forms, the second representing the commonly used 1,3-dipolar form with a formal N═N double bond (eq 43).


(43)

Nauman and co-workers obtained photoelectron and electronic absorption spectral data for a series of nitrosamines.[342] The charge densities of the NNO moieties obtained from their theoretical calculations (CNDO/2 and CNDO/S) revealed an electronegative O-atom, an electropositive nitroso N-atom, and a slightly electronegative amine N-atom; they also proposed an involvement and redistribution of the molecules' σ electrons. Thus, they suggested that the dipolar resonance form in eq 43 should be classified as the limiting case for the π-electron system; they calculated that the HOMO of R_2NNO is the nitroso π-orbital, with the second HOMO being an n orbital localized mostly on the O-atom.[342,343b] Wang and co-workers measured the HeI photoelectron spectra of the nitrosamines R_2NNO (R = Me, Et, *n*-Pr), performed ab initio SCF MO calculations (631*G basis sets), and suggested that the HOMO of R_2NNO is π in nature and largely localized in the NO group.[343] The UV−vis spectra of nitrosamines show absorptions in the 340−385 nm (ϵ ~100) and ~235 nm (ϵ ~7000) ranges assigned to n → π^* and π → π^* transitions, respectively.[2,344] The infrared spectra of aliphatic nitrosamines display bands in the 1425−1460 and 1030−1150 cm^{-1} ranges due to υ_{NO} and υ_{NN}, respectively.[345] In the case of aromatic nitrosamines, bands in the 1450−1500 cm^{-1} (υ_{NO}), 1160−1200 cm^{-1} (υ_{CN}), and 925−1025 cm^{-1} (υ_{NN}) ranges are usually observed.[345] These υ_{NO} bands are lower than those observed for *C*-nitroso compounds, and this observation is frequently used as evidence for the weakened N−O bond due to the dipolar contribution in eq 43. Substituent effects also affect the magnitude of υ_{NO}: for example, the υ_{NO} of $(CF_3CH_2)_2NNO$ is at 1550 cm^{-1}, whereas that of $(CH_3CH_2)_2NNO$ is at 1454 cm^{-1}.[96]

NMR spectroscopy is a well-recognized tool for studying the configurations of nitrosamines.[2] Consistent with the contribution of the dipolar form (eq 43) is the observation of hindered rotation about the N−N bond. In separate work, Karabatsos and Taller[346] and Brown and Hollis[347] assigned the configurations of several nitrosamines from the analysis of their NMR spectra, and their assignments were based on the assumption that the ratio of compounds **A**:**B** (shown below) increases as the R group gets bulkier (i.e., **B** is *less* stable if R is bulky).


A **B**

In general, the protons of the α-CH_3, α-CH_2, and β-CH_3 groups were found to be more shielded (by ~0.3−0.8 ppm) when positioned cis rather than trans to the nitroso O-atom.[346] Thus, the ^1H NMR spectrum of Me_2NNO showed two peaks at δ 3.02 ppm (Me cis to nitroso O-atom) and δ 3.77 ppm (Me trans to nitroso O-atom).[346] Rotational barriers of 18−23.5

Table 11. Structural Data for *N*-Nitroso Compounds R_2NNO, where R Groups Are Connected by sp^3-Hybridized Carbon Atoms

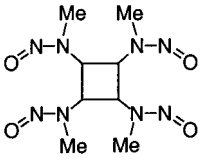
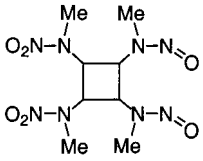
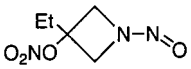
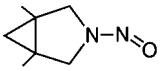
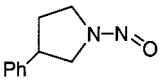
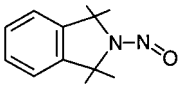
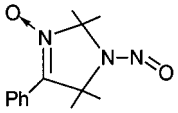
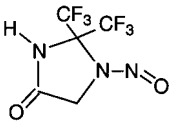
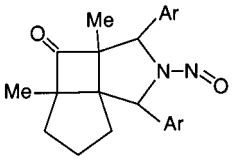
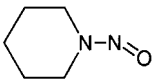
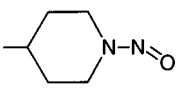
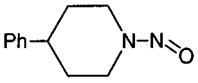
compound	N−N (Å)	N−O (Å)	N−N−O (°)	ref
Me_2NNO	1.320(6)	1.260(6)	114.3(3)	354
Me_2NNO[a]	1.344(2)	1.235(2)	113.6(2)	355,356
$H_2NC(O)CH_2N(Me)NO$	1.328(4)	1.223(3)	113.0(2)	357
	1.308(3)	1.237(4)	113.0(3)	
$(1\text{-adamantyl})_2NNO$	1.326(2)	1.245(2)	117.9(2)	348
$(1\text{-norbornyl})_2NNO$	1.326(3)	1.241(3)	115.7(2)	348
$(MeC(O)CH_2)_2NNO$	*b*	*b*	*b*	358
	1.307[c]	1.240[c]	114.8[c]	359
	1.312[c]	1.241[c]	114.9[c]	
	1.311[c]	1.239[c]	114.7[c]	
	1.309[c]	1.236[c]	114.8[c]	
	1.307[c]	1.248[c]	114.7[c]	359
	1.420[c]	1.229[c]	111.6[c]	
(HO)(Ph)CHCH(Me)N(Me)NO	1.302(8)	1.23(1)		360
	1.305[c]	1.223[c]	112.5[c]	361
	1.310(6)	1.231(6)	113.6(5)	362
(*complex with a chiral diol*)				
	1.378[c]	1.129[c]	104.5[c]	363
	1.292(4)	1.260(4)	116.6(3)	364
(*complex with DDQ*)				
	1.318(6)	1.118(5) [1.036(6)][d]	122.4[c]	365
	1.336[c]	1.234[c]	112.8[c]	366
	*b*	*b*	*b*	367
Ar = Ph or *o*/*o*′-difluorophenyl				
				
complex with cholic acid	1.315[c]	1.252[c]	115.2[c]	368
complex with deoxycholic acid	1.317[c]	1.252[c]	115.2[c]	368
	1.368[c]	1.184[c]	111.6[c]	368
(*complex with cholic acid*)				
	1.338[c]	1.232[c]	110[c]	369
(*complex with a chiral diol host*)				

Table 11 (Continued)

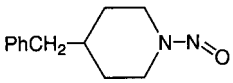
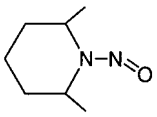
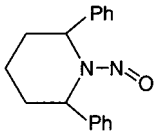
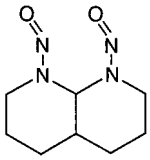
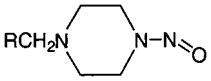
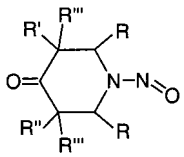
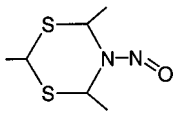
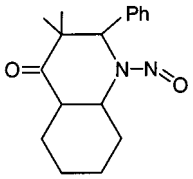
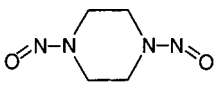
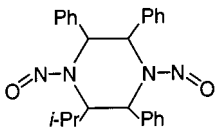
compound	N−N (Å)	N−O (Å)	N−N−O (°)	ref
	1.308(4)	1.135(4) 1.014(7)[d]	123.8(6) 123.3(8)[d]	362
complex with a chiral diol host	1.313(12) 1.36(5)[d]	1.163(10) 1.53(6)[d]	113.2(13)	362
complex with 2 chiral diol hosts	1.332(13) 1.46(4)[d]	1.220(14) 1.37(5)[d]	110.4(9) 103(3)[d]	362
				
complex with cholic acid	1.348[c]	1.240[c]	114.4[c]	368
complex with deoxycholic acid	1.347[c]	1.240[c]	114.3[c]	368
				
Form I	1.380(14) 1.378(13)	1.199(18) 1.257(25)	107.1(12) 100.9(13)	370
Form II	1.331(9) 1.324(34)	1.209(10) 1.219(48)	114.3(8) 112.7(32)	370
	1.322(6) 1.306(5)	1.222(6) 1.242(5)	113.8(5) 114.9(4)	371
	1.41(2)	1.34(3)	98(1)	372
R = 2-chloromercuri-4,4,6,6-tetramethyldehydropiperidine-5-oxyl				
				
R = furyl; R′ = R″ = Me; R‴ = H	1.320(5)	1.242(5)	115.1(4)	373
R = *o*-chlorophenyl; R′ = R″ = Me; R‴ = H	1.329(3)	1.233(2)	114.9(2)	374
R = Ph; R′ = R″ = Ph; R‴ = H	1.308[c]	1.179[c]	115.1[c]	375
R = Ph; R′ = *i*-Pr; R″ = R‴ = H	1.363[c]	1.222[c]	109.0[c]	375
R = Ph; R′ = Me; R″ = H (R‴ adjacent to R′ is Me; R‴ adjacent to R" is H)	1.326[c]	1.217[c]	114.8[c]	375
R = Ph; R′ = R" = R‴ = Me	1.332[c]	1.214[c]	114.1[c]	375
R = Ph; R′ = R″ = R‴ = H	*b*	*b*	*b*	375
	1.327(4)			376
	1.319[c]	1.239(2)	115.0(2)	377
	1.336(4)	1.202(4)	113.4(3)	378
	1.333(2) 1.320(2)	1.232(2) 1.244(2)	114.3(2) 114.8(2)	379

Table 11 (Continued)

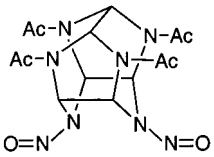
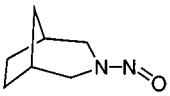
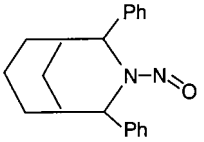
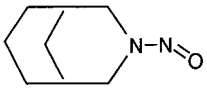
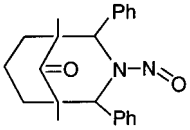
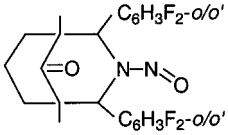
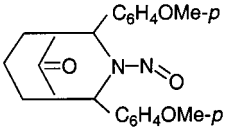
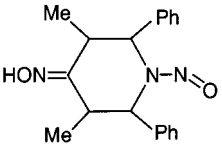
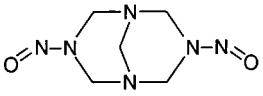
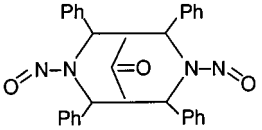
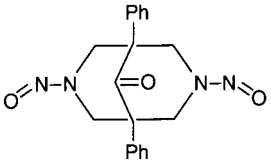
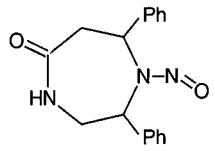
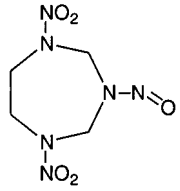
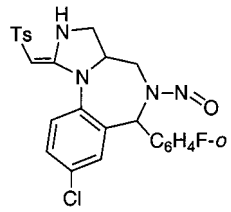
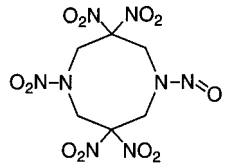
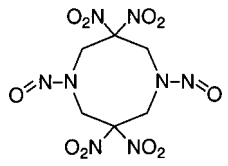
compound	N−N (Å)	N−O (Å)	N−N−O (°)	ref
	1.353[c] 1.338[c]	1.219[c] 1.222[c]	113.7[c] 114.8[c]	380
				
complex with a chiral diol	1.328(9) 1.319(10)	1.260(9) 1.257(10)	113.5(10) 114.9(12)	362
complex with a chiral diol	1.332(9) 1.321(10)	1.251(9) 1.250(10)	114.5(10) 116.4(12)	362
	1.542(8) 1.443(7)[e]	1.152(9) 1.167(7)[e]	93.8(5) 106.8(5)[e]	381
	1.322(3)	1.230(3)	115.1(2)	362
complex with a chiral diol	1.322(5)	1.225(5) 1.34(2)[d]	112.0(4) 119.3(10)[d]	362
	*b*	*b*	*b*	367
	1.343[c]	1.230[c]	115.2[c]	367
	1.359(6)	1.237(7)	112.5(4)	382
	1.343(4)	1.239(4)	113.8(3)	383
	1.392(6) 1.411(6)	1.179(6) 1.141(7)	115.9(4) 108.1(5)	384
	1.338[c] 1.353[c]	1.220[c] 1.227[c]	115.9[c] 112.8[c]	385
	1.382[c] 1.349[c]	1.185[c] 1.222[c]	108.9[c] 112.3[c]	386

Table 11 (Continued)

compound	N−N (Å)	N−O (Å)	N−N−O (°)	ref
	1.331(2)	1.231(2)	115.4(2)	387
	1.316(4) 1.315(4)[e]	1.237(4) 1.228(4)[e]	113.4(3) 114.6(3)[e]	388
	1.323[c]	1.237[c]	114.5[c]	389
	1.352(5)	1.213(5)	115.8(4)	390
	1.326(3)	1.195(3)	115.5(2)	390

[a] Determined by electron diffraction. [b] Metrical data not reported. [c] Data obtained from the Cambridge Structural Database. [d] Data for the disordered NO group. [e] Data for the second molecule.

kcal/mol have been determined for some R_2NNO compounds (R = Me, *i*-Pr, norbornyl, adamantyl).[348,349] Similar ranges were determined for substituted *N*-nitrosopiperidines (∼18−19 kcal/mol)[350] and for related cyclic and bicyclic nitrosamines (∼23−29 kcal/mol).[351]

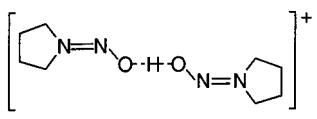
Ohwada and co-workers suggested, based on a study of 16 nitrosamines, that R_2NNO compounds with low N−N rotational barriers are the ones that are likely to engage in facile N−N(O) bond cleavage, releasing NO.[352] Cheng, Wang, and co-workers demonstrated that N−NO bond homolysis energies of some *N*-nitroso compounds are lower than the heterolysis energies (to give NO^+).[353] However, substituent effects need to be considered further in order to predict the preferred pathway of denitrosation of each nitrosamine.[353]

X-ray crystal structural data for organic R_2NNO compounds are listed in Tables 11 and 12. With the exception of a few cases, the N−N bond lengths in organic nitrosamines R_2NNO (where the NNO moiety is linked to two sp^3-hybridized carbon atoms; Table 11) fall in the 1.31−1.34 Å range. The N−N bond lengths for the structurally characterized nitrosoureas and other nitrosamines fall in the 1.30−1.37 Å range. These lengths are shorter than that expected for a N−N single bond (1.42 Å)[95] and are consistent with the contribution of the dipolar resonance form in eq 43. Most of the N−O bond lengths fall in the 1.21−1.26 Å range (Tables 11 and 12).

B. Metal Complexes

1. Reactions with Lewis Acids

Before we begin our discussion on the metal−nitrosamine interaction, we need to briefly examine the reactions of nitrosamines with Lewis acids. The nitroso O-atom of the nitrosamine group is basic and can be protonated to form $[R_2NNOH]^+$ species.[411−414] The X-ray crystal structure of the hydrogen-bonded binitrosamine cation shown below has been determined (N−N = 1.270(6) Å; N−O = 1.276(6) Å; N−N−O = 111.4(5)°).[411]



The nitroso O-atom can also be alkylated to form $[R_2NNOR']^+$ species.[415−422] Interactions of the nitroso O-atom with the Lewis acidic BF_3, BCl_3, and organoboranes have been documented.[423−425]

In an elegant study, Keefer and co-workers showed that the amino N-atom of the nitrosamine group can

Table 12. Structural Data for Other *N*-Nitroso Compounds

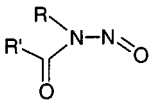
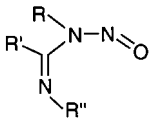
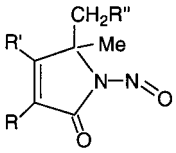
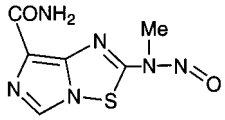
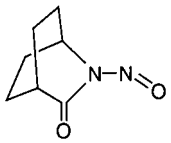
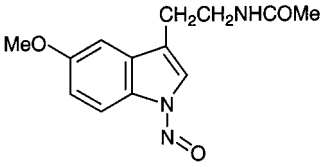
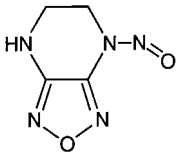
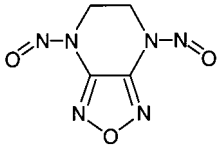
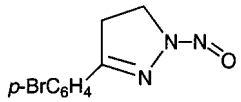
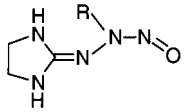
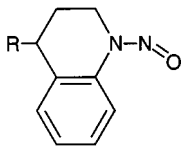
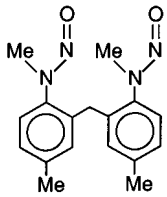
compound	N−N (Å)	N−O (Å)	N−N−O (°)	ref
				
R = Me; R′ = *p*-$C_6H_4NO_2$	1.352(5)	1.218(4)	113.8(4)	391
R = Me; R′ = NH_2	1.326(2)	1.231(2)	114.4(2)	391
R = Me; R′ = NHMe	1.332(2)	1.227(2)	113.9(2)	391
R = CH_2CH_2Cl; R′ = NHR″; R″ = *trans*−4-methylcyclohexyl	1.333(4)	1.218(4)	114.6(4)	392
R = *p*-C_6H_4OMe; R′ = NHMe	1.357(6)	1.219(5)	114.3(4)	393
R = *p*-tol; R′ = N(*i*-Pr)$_2$	1.327(2)	1.240(2)	114.0(1)	393
R = *o*-tol; R′= $N(CH_2Ph)_2$	1.345(5)	1.227(5)	114.5(3)	393
				
R = Me; R′ = NHMe; R″ = CN	1.343(4)	1.230(4)	113.7(2)	394
R = Me; R′ = $N(H)CH_2CH_2SCH_2\{C_4H_5N_2H^+\}NO_3^-$; R″ = CN	1.323(4)	1.228(4)	114.6(3)	395
R = Me; R′ = NH_2; R″ = NO_2				
monoclinic[c]	1.3415(13) 1.3596(14)	1.2276(14) 1.2187(16)	114.11(9) 114.01(10)	396
monoclinic[c]	1.346(8) 1.358(10)	1.235(8) 1.252(10)	113.3(6) 113.8(7)	397
orthorhombic	1.3521(10)	1.2195(10)	114.12(7)	396
R = Me; R′ = C(=NO^-)NO_2; R″ = $(CH_2)_2S\{C_8H_{12}ONH^+\}$	1.353(7)	1.231(6)	114.5(6)	398
				
R = $CH_2CH_2CO_2Me$; R′ = CH_2CO_2Me; R″ = $C_4NH(CH_2CO_2Me)(CH_2CH_2CO_2Me)(CO_2CH_2Ph)$	1.343[a]	1.225[a]	114.3[a]	399
R = $CH_2CH_2CO_2Me$; R′ = CH_2CO_2Me; R″ = $C_4NH(CH_2CO_2Me)(CH_2CH_2CO_2Me)(CO_2CHMePh)$	1.353[a]	1.211[a]	114.5[a]	400
	1.329[a]	1.225[a]	113.4[a]	401
	1.353(4)	1.227(5)	113.4(4)	391
	1.339(2)	1.221(2)	114.4(2)	402
	1.367[a]	1.177[a]	113.1[a]	403
	1.342(4) 1.364(4)	1.222(5) 1.204(5)	113.1(3) 113.7(3)	403

Table 12 (Continued)

compound	N−N (Å)	N−O (Å)	N−N−O (°)	ref
	1.300(16)	1.276(15)	111.2(12)	404
 ($R = CH_2C_6H_4Cl$-p)	1.300(14)	1.250(14)	114.8(11)	405
Ph_2NNO	1.344(5)	1.206(7)	114.9(4)	406
(2-pyridyl)$_2$NNO	1.342(6)	1.229(7)	114.4(5)	407
(p-ClC_6H_4)N(CH_2Ph)NO	1.339(5)	1.237(5)	114.4(4)	408
 R = CH(OH){$C_9H_{16}NH^+$}	1.35(1)	1.25(1)	112.4(9)	409
	1.326(4) 1.300(3)	1.208(5) [1.038(15)]^b 1.261(3)	117.2(3) [118.5(8)]^b 113.4(3)	410

^{a} Data obtained from the Cambridge Structural Database. ^{b} Data for the disordered NO group. ^{c} Two molecules in the unit cell.

be protonated.[412] It has been calculated by ab initio methods that *N*-protonation of H_2NNO to give $[H_3NNO]^+$ is a viable process if electron correlation effects are considered; these workers suggested that alkyl nitrosamines, however, generally favored *O*-protonation.[426]

2. Synthesis and Structure

Nitrosamines have been used as nitrosylating agents for the syntheses of metal−NO compounds.[1,427,428] In addition, nitrosoureas $H_2NC(O)N(CH_2R)NO$ and related compounds have been used for either nitrosylation or methylene "RCH" (or vinylidene) group transfer reagents in organometallic chemistry.[429,430] Some alkylnitrosoureas are also decomposed by bimetallic complexes of Rh to form metal−isocyanate derivatives.[431]

The complex formation between nitrosamines and metal compounds is also known, and this section deals specifically with the syntheses of such compounds. Three main kinds of binding modes have been established by single-crystal X-ray crystallography,[411,432−439] and Figure 15 and Table 13 illustrate these types.

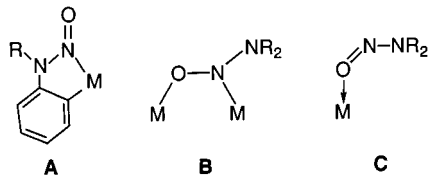


Figure 15. Binding modes in metal−nitrosamine complexes established by single-crystal X-ray crystallography.

Two main routes have been developed for the syntheses of metal−nitrosamine complexes. The first route involves adduct formation between a nitrosamine and a metal center, and the second involves the modification of coordinated ligands (usually the attack of *N*-nucleophiles at bound nitrosyl units).

(1) Adduct Formation. Brown and Coates reported the reaction of dialkylnitrosamines R_2NNO (R = Me, Et, *n*-Bu) with aqueous Na_2PdCl_4 to give *trans*-$(R_2NNO)_2PdCl_2$ and proposed an *O*-binding mode for the nitrosamines.[440] Schmidpeter reported that Me_2NNO formed adducts with the compounds MCl_2 (M = Pd, Cu, Ni, Co, Cd), $ZnBr_2$, $AlCl_3$, and also BF_3, $SbCl_5$, and PCl_5.[423] Constable, McDonald, and Shaw later showed that $(PhCH_2)(Me)NNO$ formed a similar adduct with Na_2PdCl_4, giving {$(PhCH_2)(Me)NNO$}$_2$-$PdCl_2$.[432] However, they demonstrated that *N*-methyl-*N*-nitrosoaniline Ph(Me)NNO was *cyclo*-(*ortho*-)-palladated by Na_2PdCl_4 to give a chloro-bridged complex (top right of Figure 16).

Reaction of the chloro-bridged complex with Lewis bases (L) such as PPh_3, PMe_2Ph, and py gave the monometallic complexes, the PPh_3 complex of which was characterized by X-ray crystallography.[432] Further reaction with L gave the Pd−aryl complexes containing an uncoordinated NNO group (bottom right of Figure 16; the X-ray structure was obtained for the bisphosphine derivative). Similar Pd complexes were obtained using Ar(R)NNO (Ar = p-C_6H_4-OMe, and R = Me; Ar = Ph, and R = Et) as were some Pt bisphosphine analogues.[432]

Albinati and co-workers extended the syntheses of related dimeric compounds of Pd to include a vast

Table 13. Selected Structural Data for Metal−Nitrosamines from Figure 15

compound	N−N (Å)	N−O (Å)	N−N−O (°)	ref
	structure **A**			
$Pd\{N(O)N(Me)C_6H_4\}Cl(PPh_3)$	1.276(19)	1.243(18)	117.8(11)	432
$Pd\{N(O)N(Me)C_6H_4\}_2$	1.301(7)	1.246(6)	117.4(4)	433
	1.331(6)	1.226(5)	116.6(4)	
$[Pd\{N(O)N(Me)C_6H_2(2\text{-}Cl)(5\text{-}Me)\}]_2(\mu\text{-}O_2CCF_3)_2$	1.328(11)	1.242(9)	118.1[a]	434
	structure **B**			
$(Me_2NNO)CuCl_2$	1.29(2)	1.22(2)	115.89(5)	435,436
$\{(CH_2)_5NNO\}CuCl_2$	1.288(3)	1.279(3)	114.9(2)	437
	structure **C**			
$[(N\text{-nitrosopyrrolidine})_2H]^+$	1.270(6)	1.276(6)	111.4(5)	411
$(Me_2NNO)SbCl_5$	1.262(5)	1.310(5)	112.0(3)	437
$[(TPP)Fe(ONNEt_2)_2]ClO_4$	1.276(10)	1.260(9)	113.9(7)	438,439
	1.288(9)[b]	1.285(8)[b]	113.6(7)[b]	
$(OEP)Ru(CO)(ONNEt_2)$	1.287(9)	1.243(8)	113.9(7)	438
$(TTP)Os(CO)(ONNEt_2)$	1.294(14)	1.241(13)	113.3(12)	438

[a] Data obtained from the Cambridge Structural Database. [b] Data for the second molecule.

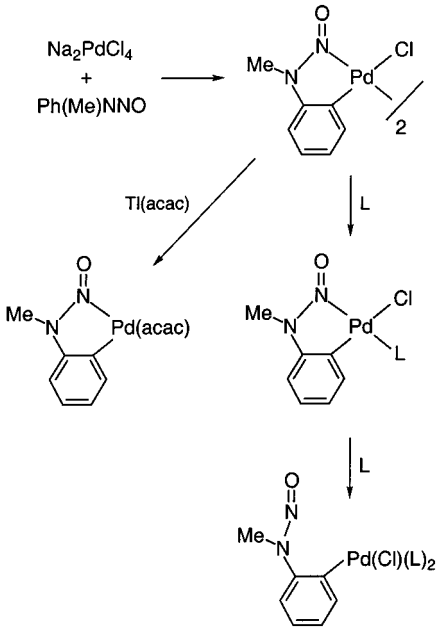
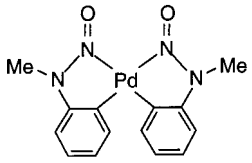


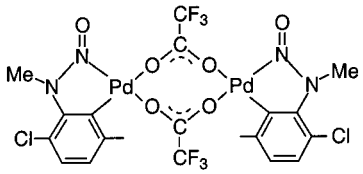
Figure 16. Formation and reactions of Pd−nitrosamine complexes.

number of Ar(Me)NNO compounds (Ar = *p*-C_6H_4-OMe, *p*-C_6H_4Me, Ph, *m*-C_6H_4Me, *p*-$C_6H_4NO_2$) with the acetate ion and iodide (Ar = Ph) as bridging groups.[433] They also isolated and characterized (by X-ray crystallography) the bisnitrosamine complex shown below.



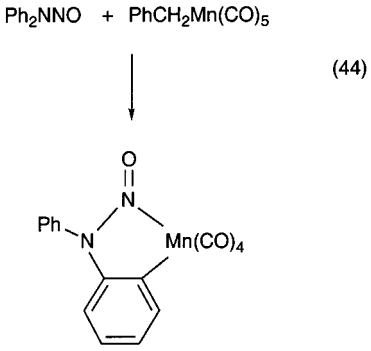
Klaus and co-workers reported the synthesis and X-ray crystal structure of the Pd bimetallic complex shown below, and this compound was isolated from the reaction of the arylnitrosamine with $Pd(OAc)_2$ and trifluoroacetic acid.[434,441]

The formulation of the structure was first suggested on the basis of ^{15}N NMR spectroscopy, which showed a shielding of the coordinated nitroso



^{15}N atom ~150 ppm relative to the uncoordinated ligand.[441]

A manganese complex containing a cyclometalated nitrosamine ligand has been obtained from the reaction of diphenylnitrosamine with $PhCH_2Mn(CO)_5$ in heptane as shown in eq 44.[442] The solid-state structure of the product was obtained from a single-crystal X-ray diffraction study.



The solid-state structures of two Cu−nitrosamine complexes have attracted a lot of attention due to the unique coordination mode of the nitrosamine ligands (**B** in Figure 15). The crystal structure of the complex $(Me_2NNO)CuCl_2$ revealed a formulation in which the Cu atoms are bridged by two chlorine atoms and the nitrosamine binding occurs via an *O*-binding mode to one Cu atom and an *N*-binding mode to another (Figure 17a).[435,436]

Nuclear quadrupole resonance spectroscopic studies of $(Me_2NNO)CuCl_2$ revealed a magnetic phase transition below 6 K, and magnetic susceptibility measurements indicated an antiferromagnetically ordered state below this temperature.[443] Studies on the magnetic properties of related compounds of the $(R_2NNO)CuX_2$ formulation (X = Cl, Br) have also been carried out.[444,445]

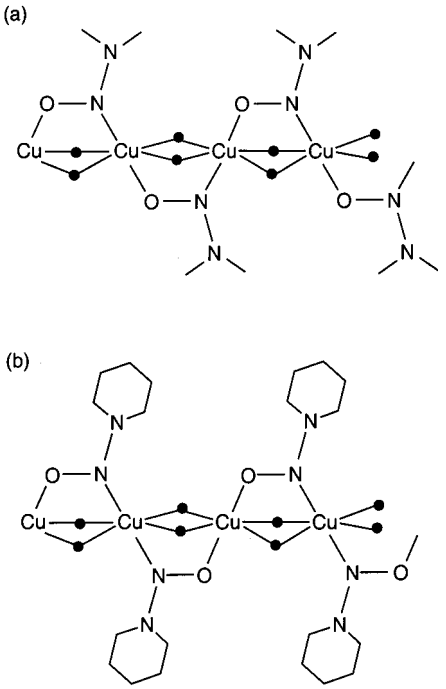


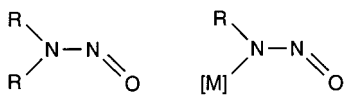
Figure 17. Schematic representation of the molecular structures of (a) $(Me_2NNO)CuCl_2$ and (b) $\{(CH_2)_5NNO\}CuCl_2$.

The X-ray crystal structure of the *N*-nitrosopiperidine complex $\{(CH_2)_5NNO\}CuCl_2$ has been reported and also consists of a $CuCl_2$ chain and *N*,*O*-bonded nitrosamine groups (Figure 17b).[437] Unlike the structure of the dimethylnitrosamine analogue, however, where all the Cu atoms are equivalent (each Cu atom axially bonded to one O-atom from one nitrosamine molecule and one N-atom from a second nitrosamine molecule), the Cu atoms in $\{(CH_2)_5NNO\}CuCl_2$ are not equivalent. One-half of the Cu atoms are axially bonded to two N atoms, and the other half are axially bonded to two O atoms.

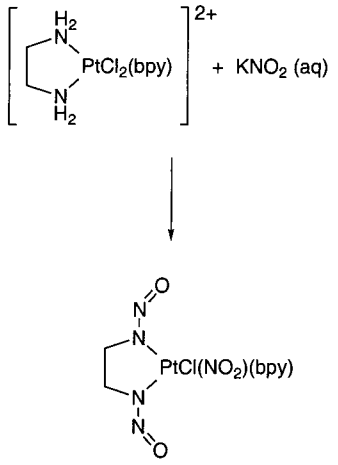
The sole *O*-binding mode for nitrosamines has been established from the X-ray crystal structures of some metalloporphyrin−nitrosamine complexes (see later) and in $(Me_2NNO)SbCl_5$.[437] The interactions of dialkylnitrosamines with the europium shift reagents $Eu(fod)_3$ and $Eu(dpm)_3$ are also proposed to occur via an *O*-binding mode.[446−448]

(2) Modification of Coordinated Ligands. Some metal nitrosyl compounds react with 1° and 2° amines to result in nitrosation of the amine, and a classic metal nitrosyl displaying this behavior is nitroprusside $[Fe(CN)_5NO]^{2-}$ (reviewed in refs 127 and 148). The reactions proceed, presumably, via attack of the *N*-nucleophiles at the coordinated NO group.[148,449−451]

Adrianova and co-workers pioneered the development of the "metallonitrosamine" (metal alkyldiazoate) chemistry of Pt.[454−467]



For example, they reported that the ethylenediamine ligand in $[Pt(en)_3]Cl_4$ could be *N*-nitrosated by aqueous KNO_2 to give complexes of the form $[Pt(en)_2\{N(NO)C_2H_4NH_2\}]^{3+}$, $[Pt(en)\{N(NO)C_2H_4NH_2\}_2]^{2+}$, and $[Pt\{N(NO)C_2H_4NH_2\}_3]^{+}$.[456] Freeman confirmed the solid-state structure of one such complex, namely, that of the product of eq 45 (N−N = 1.278(17) and



(45)

1.288(17) Å; N−O = 1.241(22) and 1.255(17) Å; N−N−O = 118.0(15)° and 115.9(14)°).[468] The X-ray crystal structures of several such compounds containing mono- and dinitrosated en ligands have been determined.[462,469−471]

Interestingly, Lalor and co-workers obtained a related Ni complex from the reaction of $CpNi(PPh_3)Cl$ with sodium *anti*-*p*-nitrobenzenediazoate.[472] The solid-state structure of the $CpNi(PPh_3)\{N(NO)C_6H_4NO_2\text{-}p\}$ product was determined by X-ray crystallography (N−N = 1.327(6) Å; N−O = 1.249(7) Å; N−N−O = 113.1(4)°).

3. Complexes with Heme and Heme Models

Nitrosamines are generally considered to be carcinogenic; however, they generally require chemical modification by cytochrome P450 to promote cancer. Several excellent reviews on the biochemistry and pharmacology of R_2NNO and related compounds are available.[473−479] This section will deal specifically with the direct metal−nitrosamine interaction as it applies to heme compounds and metalloporphyrins in general, and the reader is directed to the aforementioned reviews for a more complete description of nitrosamine biochemistry and pharmacology.

Appel and co-workers proposed (based on absorption spectroscopy) that some nitrosamines were capable of binding to liver microsomal cytochrome P450 either at the substrate pocket or at the metal center of the heme prosthetic group.[480] Saprin and co-workers also showed, by absorption and EPR spectroscopy, that nitrosamines were suitable ligands for direct binding to the metal center of heme in cytochrome P450.[481] Despite the observation of this direct binding to the metal site in heme, no well-defined complex formation between a nitrosamine and a metalloporphyrin had been reported prior to 1995. Furthermore, only a few reports at that time

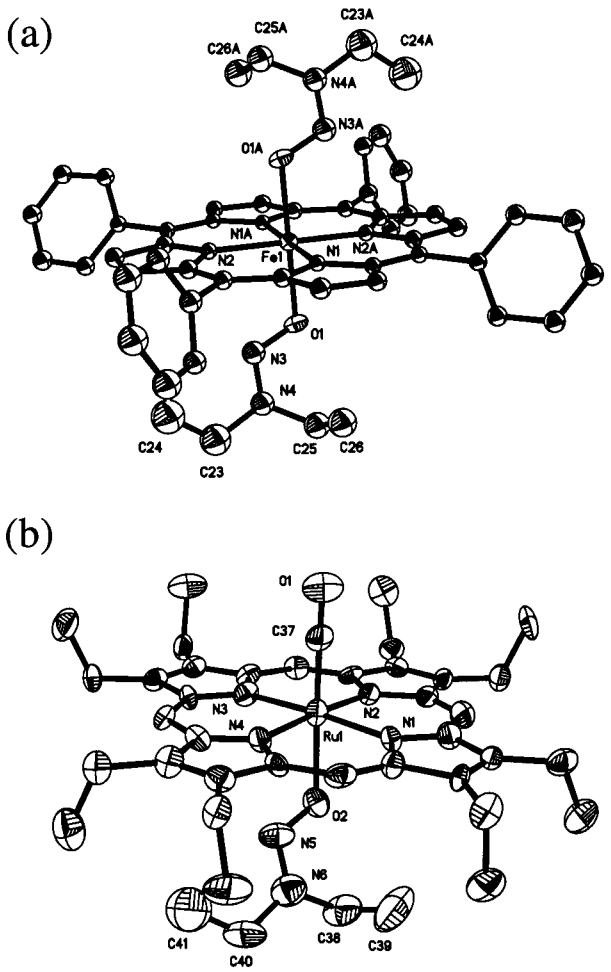


Figure 18. Molecular structure of (a) the $[(TPP)Fe(ONNEt_2)_2]^+$ cation and (b) $(OEP)Ru(CO)(ONNEt_2)$.

existed on the use of metalloporphyrins for the oxidative degradation of nitrosamines.[482−485] The reactions of iron nitrosyl porphyrins with amines to produce nitrosamines have been reported.[486]

The first isolable nitrosamine metalloporphyrin complex was prepared and characterized by single-crystal X-ray crystallography in 1995.[439] This compound was obtained by adduct formation between the nitrosamine and the ferric porphyrin (eq 46).

$$[(TPP)Fe(THF)_2]ClO_4 + \text{excess } Et_2NNO \rightarrow [(TPP)Fe(ONNEt_2)_2]ClO_4 \quad (46)$$

The molecular structure of the cation is shown in Figure 18a and displays a sole *O*-binding mode of the nitrosamine ligand.[438,439]

The structural parameters of the nitrosamine moiety (Table 13) suggest a significant contribution of the 1.3-dipolar resonance form in this complex (Figure 19).

Diethylnitrosamine complexes of Ru and Os have also been prepared.[438,487] The solid-state structures of $(OEP)Ru(CO)(ONNEt_2)$ (Figure 18b) and $(TTP)Os(CO)(ONNEt_2)$ were determined by X-ray crystallography and revealed a similar *O*-binding mode of the nitrosamine group.[438,487] These results demonstrated, for the first time, the ability of nitrosamines to function as *O*-donor ligands to the metal centers

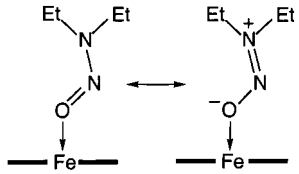


Figure 19. Contribution of the dipolar resonance form of diethylnitrosamine in its binding to ferric porphyrins.

in heme models. Whether this direct interaction has any significant role in the biological reactions of nitrosamines remains to be determined. However, it has been demonstrated that protonation of the bound nitrosamine in $(OEP)Ru(CO)(ONNEt_2)$ results in a net NO^+ release (the NO^+ is then trapped by unreacted $(OEP)Ru(CO)(ONNEt_2)$ to form the cationic $[(OEP)Ru(NO)(ONNEt_2)]^+$ species).[438]

IV. O-Nitroso Compounds

A. Organic Compounds

1. Synthesis

O-Nitroso compounds (alkyl nitrites) are generally prepared by nitrosation of the precursor alcohol. For example, alkyl alcohols can be nitrosated by various nitrosating agents XNO (e.g., HNO_2, nitrosyl halides, NO_2; eq 47).[3,488]

$$ROH + XNO \rightleftarrows RONO + XH \quad (47)$$

The reaction using HNO_2 appears to be the most common method for the preparation of alkyl nitrites. In the case of phenols, the reaction using HNO_2 commonly results in aromatic substitution to produce a *C*-nitroso compound instead of an *O*-nitrosation product.[3] Other methods include the reaction of cyclic alcohols with NO in aerated acetonitrile[489] or the reaction of alkyl halides with silver nitrite.[490]

O-Transnitrosation has also been used for the preparation of certain alkyl nitrites (eq 48).

$$RONO + R'OH \rightleftarrows ROH + R'ONO \quad (48)$$

2. Spectroscopy and Structure

RONO compounds generally display two υ_{NO} bands in the 1610−1685 cm^{-1} region due to the trans and cis isomers, with the trans isomer band at higher frequency.[96] As expected, the υ_{NO} bands are dependent on the nature of the R group. For example, MeONO shows bands at 1625 and 1681 cm^{-1}, amyl nitrite shows bands at 1613 and 1653 cm^{-1}, and trifluoroethyl nitrite shows bands at 1695 and 1736 cm^{-1}.[96]

The υ_{NO}'s of alkyl nitrites occur at higher wavenumbers than those of the corresponding alkyl thionitrites; for example, the υ_{NO} of *t*-BuONO was observed at 1620 cm^{-1}, whereas that for *t*-BuSNO was observed at 1490 cm^{-1}.[491]

Suter and Nonella performed quantum chemical investigations on EtONO and correlated their results with previous IR spectroscopic data on the stable rotamers of matrix-isolated EtONO.[492] They assigned the three υ_{NO} bands observed at 1659, 1609, and 1594

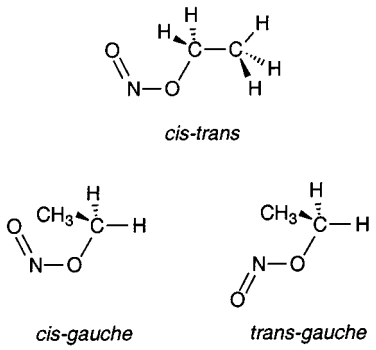


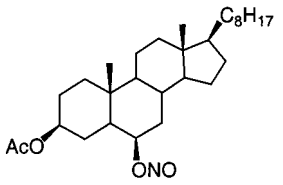
Figure 20. Various isomers of ethyl nitrite.[492]

cm^{-1} to the N=O groups of the *trans−gauche*, *cis−gauche*, and *cis−trans* conformers, respectively (Figure 20).[492]

Mäder and co-workers recently reported their FT microwave spectroscopic results on EtONO, and they also confirmed the presence of three rotational isomers for this molecule.[493]

NMR spectroscopy has been very useful in assigning cis or trans structures to alkyl nitrites.[347,494,495] NMR spectroscopic methods have been used to determine the gas-phase and liquid-phase thermodynamic ($\Delta H°$, $\Delta S°$, and $\Delta G°$) parameters for the *cis−trans* conformer interconversion for a series of primary and secondary alkyl nitrites.[494] It was found that the cis conformer is more stable for the smaller linear (C1−C4) alkyl nitrites, whereas the trans form predominates in the higher sterically hindered alkyl nitrites.[494] These results are consistent with an earlier proposal by Tarte.[496]

The single-crystal X-ray structure of 6β-nitrosooxy-5α-cholestan-3β-yl acetate shown below has been reported (O−NO = 1.41 Å, (O)N=O = 1.185 Å, and O−N−O = 110.3°).[497]



B. Metal Complexes

1. Metal Surfaces

The study of adsorbed alkyl nitrites on metal surfaces is important for at least two main reasons: understanding the NO desorption process and the production of adsorbed alkoxy radicals, which are possible intermediates in partial hydrocarbon oxidation reactions catalyzed by metal surfaces. The thermal activation of *t*-BuONO and MeONO on Pt(111) has illustrated the latter very well.[498−500] In these studies, dissociative chemisorption of RONO produced adsorbed alkoxy radicals and NO. Further reaction of the alkoxy species generated other species including alcohols, CO, H_2, and formaldehyde.

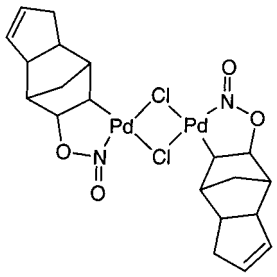
The photolysis of simple RONO compounds (in part generating NO) continues to attract research attention.[501−503] It has been shown that *t*-BuONO adsorbs reversibly on a Ag(111) surface.[504] The photodissociation of alkyl nitrites adsorbed on Ag(111) surfaces results in NO ejection and alkoxy radicals attached to the surfaces.[505−508] Photolysis of *t*-BuONO and *i*-BuONO physisorbed on a transparent insulating MgF_2 surface also results in desorption of NO.[509]

2. Coordination Compounds

Alkyl nitrites have been used as nitrosylating agents in coordination chemistry to generate metal−NO moieties.[510,511]

An intermediate complex $[(dmp)_2Cu\{N(O)OR\}]^+$, in which the RONO ligand is *N*-bound, has been proposed (based on kinetics experiments) to form during the reaction of the Cu^{2+}−ROH precursor with NO to give free RONO.[512,513] Nucleophilic attack of *O*-nucleophiles at the NO group of $[Fe(CN)_5NO]^{2-}$ is proposed to result in the formation of complexes of the form $[Fe(CN)_5\{N(O)OR\}]^{3-}$.[127,514] In the case of hydroxide attack (2 equiv), the nitro compound $[Fe(CN)_5NO_2]^{4-}$ is the final product, which undergoes subsequent hydrolysis to $[Fe(CN)_5(H_2O)]^{3-}$ and nitrite ion.

Perhaps the best evidence for metal−RONO complex formation comes from three reports in 1972 and in the 1980s. Reed and Roper reported the generation of isolable alkyl nitrite complexes $IrCl_3(RONO)L_2$ (R = Me, Et, Pr; L = PPh_3, $AsPh_3$) from the reaction of alcohols with $[IrCl_3(NO)L_2]^+$.[515] Also, Meyer and coworkers reported that isolable complexes of the form $[Ru(bpy)_2(py)\{N(O)OR\}]^{2+}$ (R = Me, Et, *n*-Bu, *i*-Pr) were obtained when the precursor complex $[Ru(bpy)_2(py)NO]^{3+}$ was reacted with alkoxide ions.[516] *N*-Bound RONO ligands were proposed based on IR spectroscopy (υ_{NO} ~1500 cm^{-1}). The complexes $[Ru(bpy)_2(Cl)\{N(O)OR\}]^+$ (R = Et, *i*-Pr) were obtained similarly from the attack of alkoxide ions on the precursor $[Ru(bpy)_2(Cl)NO]^{2+}$.[516] Andrews and co-workers reported the single-crystal X-ray structure of the *chelated* alkyl nitrite complex shown below (N=O = 1.19(2) and 1.18(2) Å; O−N = 1.36(2) and 1.40(2) Å; O−N=O = 113(1)°, υ_{NO} = 1612 cm^{-1}), which was obtained from the reversible alkene−nitro group coupling in the vicinity of the Pd center.[517]



3. Interactions of RONO with Heme Models

Alkyl nitrites react with metalloporphyrins of the form (por)M(CO) (M = Ru, Os) to give the formal *trans*-addition products (por)M(NO)(OR) as shown in Figure 21.[518−522]

IR spectroscopy studies suggest the intermediacy of the carbonyl alkoxide complexes (por)M(CO)(OR), formed from the proposed homolysis of the RO−NO bonds in the putative (por)M(CO)$\{\eta^1$-O(R)NO$\}$ adducts. Isoamyl nitrite reacted with ferric [(TPP)Fe-

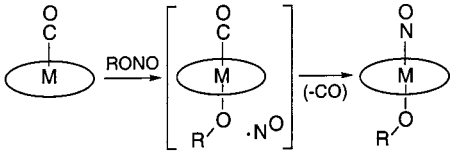


Figure 21. Proposed pathway for RONO addition to group 8 metalloporphyrins (M = Ru, Os) to generate nitrosyl alkoxide products.

$(THF)_2]^+$ to eventually yield the nitrosyl alcohol complex $[(TPP)Fe(NO)(HO\text{-}i\text{-}C_5H_{11})]^+$.[521]

V. S-Nitroso Compounds

A. Organic Compounds

The *S*-nitroso functional group in alkyl thionitrites (RSNO, *S*-nitrosothiols) is gaining widespread recognition as an important functional group in the biology of NO. Several reviews on RSNO compounds are available.[523−528]

1. Synthesis

S-Nitroso compounds are synthesized mostly from the reaction of thiols (RSH) with various nitrosating agents (X-NO) such as ClNO, N_2O_4, NO_2, N_2O_3, HNO_2, and RONO (eq 49).[3]

$$RSH + XNO \rightarrow RSNO + HX \qquad (49)$$

In many ways, these are similar to the formation of alkyl nitrites (RONO) from the corresponding alcohols, although one major difference between *O*- and *S*-nitrosation appears to be the essentially quantitative nature of RSNO generation.[3] Perhaps the most convenient routes utilize the reaction of RSH with N_2O_4 (excess N_2O_4 gives the $RSNO_2$ product), or alkyl nitrites (RONO) in aqueous solution or in organic solvents, or acidified nitrite.[491,526] Beloso and Williams noted, however, that *S*-nitrosation in acid solution is sufficiently reversible to allow the low thiol concentration (present at equilibrium) to reduce trace copper ions which will then decompose the RSNO products (see later).[529] The *S*-nitrosation in aqueous solution or in organic solvents using alkyl nitrites is especially useful (eq 50).[523,530−533]

$$RONO + R'SH \rightarrow ROH + R'SNO \qquad (50)$$

S-Nitrosation from alkyl nitrites might also have implications in biology, for example, in the reported microsomal formation of *S*-nitrosoglutathione.[534,535] *S*-Nitrosation of hemoglobin at the βCys93 residues was reported by Doyle in 1984, and this Hb(SNO) product was obtained from the reaction of Hb with alkyl nitrites.[536] The solid-state crystal structure of Hb(SNO) has been reported,[537] and mass spectral[538,539] and biochemical characterization[540] are also consistent with its formulation as an *S*-nitroso adduct. There have been reports that Hb(SNO) may play important roles in the regulation of blood flow.[541−544]

There are some reports of the direct reaction of RSH and NO; however, it is likely that other nitrogen oxides are the active nitrosating species. Sharma and co-workers have shown that at pH 7.0, NO by itself does not react with thiols *except in the presence of oxygen* and that the active nitrosating species is N_2O_3.[545] Furthermore, kinetics studies by Goldstein and Czapski suggest that the active nitrosating agents in the aerobic reaction of aqueous NO with thiols are NO_2 and/or N_2O_3 and that N_2O_3 was capable of nitrosating thiols with a rate constant $>6 \times 10^7$ M^{-1} s^{-1}.[546] It is now widely recognized that in the pure state, NO does not react with thiols but does so in the presence of trace oxygen.[528]

Other less common routes for the syntheses of RSNO include the photolytic reaction of disulfides (RSSR, to give $RS^{\bullet}$) and NO or the reaction of disulfides with N_2O_4 to give RSNO and other products.[3,526]

2. Spectroscopy and Structure

RSNO compounds are usually red (primary or secondary alkyl thionitrites) or green (tertiary alkyl thionitrites). Their UV−vis spectra show bands in the 330−350 nm ($\epsilon \sim 10^3$ M^{-1} cm^{-1}; $n_O \rightarrow \pi^*$) and 550−600 nm ($\epsilon \sim 20$ M^{-1} cm^{-1}; $n_N \rightarrow \pi^*$) regions.[528]

IR spectroscopy has been particularly useful for the identification of the *S*-nitroso group: for most RSNO compounds, the υ_{NO} generally occurs in the 1480−1530 cm^{-1} range.[523,528] Mason investigated the IR spectrum of CF_3SNO in the solid state at −196 °C and in the gas phase at room temperature. Bands at 1700 cm^{-1} (solid) and 1660 cm^{-1} (gas) were assigned to υ_{NO}, bands at 759 cm^{-1} (solid) and 757 cm^{-1} (gas) were assigned to υ_{NS}, and a band at 629 cm^{-1} (gas) was assigned to δ_{NO}.[547] ^{15}N-Isotope-sensitive bands in the IR spectra of Ph_3CSNO, SNAP, and GSNO at 1479−1514 and 650−670 cm^{-1} have been assigned to υ_{NO} and υ_{NS}, respectively.[548]

^{1}H and ^{13}C NMR spectroscopies have been used for the characterization of RSNO compounds;[491,523] *S*-nitrosation generally results in a deshielding (by ∼1 ppm) of the α-protons relative to the α-protons of the corresponding thiols or disulfides, and the α-carbons are also deshielded by ∼7−13 ppm (stronger deshielding for 3° RSNO compounds).[523] The ^{15}N NMR spectra of RSNO compounds such as Ph_3CSNO, CF_3SNO, EtSNO, *i*-PrSNO, and *t*-BuSNO have been reported.[548−550] Variable-temperature NMR spectroscopic (e.g., ^{15}N NMR) methods have been used to study the syn−anti orientation equilibria of a variety of RSNO compounds.[549]

Single-crystal X-ray crystallographic studies have been very useful in determining the orientations of the SNO groups in RSNO compounds. However, only a few solid-state structures of RSNO compounds are known,[537,548,549,551−554] and these are listed in Table 14.

Importantly, the structure of *S*-nitrosocaptopril reveals the syn nature of the SNO group,[549] whereas the structures of SNAP,[548,552,553] $ONSC(Me)_2CH_2NHC(O)Me$,[551] and Ph_3CSNO[548] reveal the anti orientation. The Ar_3CSNO compound (containing a sterically encumbered bowl-shaped trityl group), however, reveals both the anti and syn orientations in a 0.67:0.33 ratio (DFT calculations on Ph_3CSNO showed that the syn isomer was 0.15 kcal/mol more

Table 14. Metric Parameters for Structurally Characterized Alkyl Thionitrites

compound	N−O (Å)	S−N (Å)	C−S (Å)	S−N−O (°)	C−S−N (°)	ϕ^a	ref
$ONSC(Me)_2CH_2NHC(O)Me$	1.206(2)	1.754(2)	1.829(2)	114.9(2)	99.44(8)	178.51	551
S-nitroso-*N*-acetyl-penicillamine[b]	1.199(2)	1.763(2)	1.833(1)	113.99(11)	100.80(7)	176.3	552,553
S-nitroso-*N*-acetyl-penicillamine[c]	1.206(3)	1.762(3)	1.842	114.9(2)	96.56(8)	179.7	548
Ph_3CSNO	1.177(6)	1.792(5)	1.867(3)	114.0(4)	102.1(2)	175.7	548
S-nitrosocaptopril	1.206	1.766	1.800	117.7	103.7	0.68	549
Ar_3CSNO[d] (anti)	1.205 (6)	1.781(5)	1.841(4)	111.4(6)	104.2(3)	179.6	554
(syn)	1.189(12)			123.6(7)		7.3	554
S-nitrosohemoglobin[e]						87	537

[a] Defined as the O−N−S−C torsion angle. [b] Crystallized from methanol/water. [c] Crystallized from acetonitrile. [d] Ar = 3,5-bis(2,6-dimethylphenyl)phenyl, with *anti:syn* ratio of 0.67:0.33. [e] The SNO group was modeled after the SNO group of SNAP.

stable).[554] Theoretical calculations on RSNO compounds reveal a preferred syn orientation for CH_3SNO (4:1 over anti) and EtSNO (3:1 over anti) but a preferred anti orientation for *t*-BuSNO (6:1 over syn by ~1 kcal/mol).[549] The barrier to S−N bond rotation was determined to be ~11 kcal/mol.[548,549]

The X-ray crystal structure of Hb(SNO) has been obtained at 1.8 Å resolution.[537] It was determined that *S*-nitrosation of Hb results in a significant change in the tertiary structure of the carboxylic acid-terminal dipeptide of both β subunits. In this structure, the O−N−S−C torsion angle was 87° (i.e., neither syn or anti); however, the previously determined related structure of SNAP was used in the modeling of the SNO groups of Hb(SNO).

3. Reactions

(1) Thermal or Photolytic Decompositions. Thermal or photolytic decompositions of RSNO compounds produce the disulfide and NO, and these reactions continue to be studied in detail.[526] The photodissociation of jet-cooled methyl thionitrite has shown that NO dissociation is a direct process.[555] The interest in the use of RSNO compounds as NO donors[556] has placed increased importance to this general reaction (eq 51).

$$2RSNO \rightarrow RSSR + 2NO \qquad (51)$$

Wang and co-workers recently reported their results on the thermochemistry and computation of various RSNO compounds, and they concluded that S−N bond homolysis was found to require less energy than heterolysis by ~29 kcal/mol.[557] The electrochemical properties of some RSNO compounds have been studied by cyclic voltammetry and bulk electrolysis, and the data indicate an irreversible, diffusion-controlled reduction of RSNO which results in the release of NO.[548,558] Reduction peak potentials of −0.97, −0.98, and −0.91 V (vs Ag/AgCl) were obtained for SNAP, GSNO, and Glc-SNAP-1, respectively, and the authors found a correlation between the pK_a of the thiol (RSH) and the reduction peak potential of RSNO (the smaller the pK_a, the less negative the reduction peak potential).[558] In methylene chloride, Ph_3CSNO displayed a reduction peak potential of −1.36 V.[548]

(2) NO Transfer Reactions. The NO transfer reactions of RSNO compounds are especially intriguing. RSNO compounds are able to nitrosate amines to form the nitrosamines.[3,526,559] Interestingly, RSNO compounds are also able to engage in *S*-transnitrosation reactions with other thiols (eq 52).

$$RSNO + R'SH \rightleftarrows RSH + R'SNO \qquad (52)$$

These transnitrosation reactions have been shown to occur readily in aqueous solution at pH ≥ 7.4.[560,561] Williams and co-workers studied the transnitrosation reaction between $HOCH_2CH_2SNO$ and nine thiols, and they determined that these second-order reactions proceeded via the thiolate (RS^-) anions, as revealed by the dependence of the reactions on the pK_a of the thiol used.[560] They also showed (using the thiolate anion derived from *N*-acetylcysteine) that electron-withdrawing substituents in RSNO promote the transnitrosation reaction.

The reactions of RSNO with thiols to give unsymmetrical disulfides (RSSR′) were reported by Oae and co-workers.[562] It has also been shown that at high thiol concentrations, the reaction between RSNO and thiols (first order in both reactants) results in the formation of the disulfide and ammonia (not NO) as the principal final products, and the reaction was found not to be catalyzed by metal ions.[563,564]

The biological significance of *S*-transnitrosation was realized by Park in the report that *S*-nitrosoglutathione (GSNO) covalently modified thiol compounds to produce the mixed disulfide GS−SR′; for example, the reaction of GSNO with cysteine yielded GSSG, cystine, and GSScys.[565] Nagasawa and co-workers reported that RSNO reacts with thiols to give the disulfide and nitroxyl (HNO) as the primary products; secondary products from further reaction of HNO in the reaction mixtures are NO, sulfinamide, and hydroxylamine.[566] *S*-Transnitrosations between *S*-nitrosocysteine and glutathione (GSH) of red blood cells to form GSNO have also been reported,[567] as have other biologically relevant reactions involving proteins in general.[566,568−575]

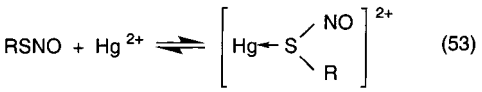
Some of the biological roles attributed to RSNO compounds are vasorelaxation and bronchodilation.[571,576−583] It has been proposed in some cases that metal-catalyzed release of NO from GSNO may be responsible for the RSNO activation of soluble guanylyl cyclase,[584] although in other cases the activation of sGC could not be explained by a simple NO release (from RSNO) pathway.[579]

Recently, the *S*-transnitrosation reaction was used to generate an RSNO-derivatized gold surface.[585] Other known reactions of RSNO compounds include reaction with anionic thiolates ($R'S^-$) to give the disulfides (RSSR′)[491] and reaction with oxygen to give the disulfides and N_2O_4.[526]

B. Metal Complexes

1. Mercury and Silver

Saville reported, in 1958, that a number of RSNO compounds underwent facile hydrolysis to HNO_2 in the presence of mercuric, silver, or cupric salts.[586] The reaction with Hg^{2+} has subsequently been widely used in the analytical determination of thiols, and an *S*-bound RSNO complex was proposed as an intermediate, whose weakened S−N bond was then attacked by (nucleophilic) water molecules to form $[Hg-SR]^+$ and $[H_2ONO]^+$ (eq 53).[586]



(53)

Williams and co-workers studied the Hg^{2+}/RSNO reaction in detail.[587,588] They determined that the reaction was essentially stoichiometric and first order in both reactants. They found that RSNO decomposition was $\sim 10^3$ faster when Hg^{2+}−nitrate was used instead of $HgCl_2$, since the latter was not completely dissociated in water to form Hg^{2+} ions. Importantly, the Hg^{2+} reaction does not result in the release of neutral NO but rather "NO^+".[587,588] They determined that Ag^+ reacted similarly in RSNO decomposition, although the decomposition was slower in this case and kinetically more complex (the rate depended on $[Ag^+]^2$ and not $[Ag^+]$).[587]

2. Nitroprusside

The reactions of nitroprusside with thiols and thiolates have presented an interesting research area for chemists over the years, especially since it was recognized that the vasorelaxant effect of nitroprusside was stimulated in the presence of thiols.[148] A generally accepted view is that the reaction proceeds via the nucleophilic attack of the thiolate anion (RS^-) on nitroprusside in a 1:1 stoichiometry in the absence of air to give an unstable red "Fe−N(O)SR" complex with $\lambda_{max} \sim 520-526$ nm (Figure 22).[127,148,589−594]

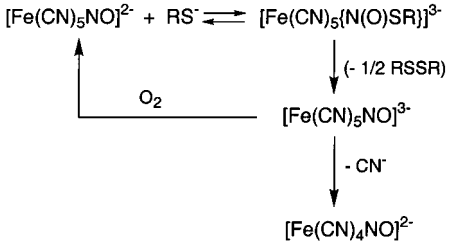


Figure 22. Reactions of nitroprusside involving proposed Fe−nitrosothiol intermediates.

The rate constants for the formation of the $[Fe(CN)_5\{N(O)SR\}]^{3-}$ complexes are generally on the order of 10^4 s^{-1} dm^3 mol^{-1}.[589] In the absence of air, the $[Fe(CN)_5\{N(O)SR\}]^{3-}$ complex decomposes via disulfide release to $[Fe(CN)_5NO]^{3-}$ which (i) converts to $[Fe(CN)_4NO]^{2-}$ in the absence of air or (ii) reconverts to $[Fe(CN)_5NO]^{2-}$ in aerated solvents.[589] The $[Fe(CN)_4NO]^{2-}$ complex then decomposes further, releasing neutral NO, or converts (in the presence of excess thiolate) to dinitrosyl complexes of the form $[Fe(NO)_2(SR)_2]^-$ or $Fe_2(SR)_2(NO)_4$.

3. Copper

Many initial kinetic studies of the decomposition of various RSNO compounds in aqueous solution did not yield consistent results, until it was reported by Williams, Butler, and co-workers that trace copper ions (even in distilled water) catalyzed the RSNO decomposition reaction.[588] This report explained the irreproducible kinetics results obtained previously, due to the fact that the copper ion concentration (e.g., 10^{-6} M $[Cu^{2+}]$ in distilled water) varied in different sample preparations. Thus, when the metal ion chelator EDTA was added to the sample preparations, the RSNO decomposition was essentially halted and the addition of excess Cu^{2+} reestablished the RSNO decomposition. Figure 23 shows the effect of Cu^{2+} on the decomposition of a typical RSNO compound SNAP.[528]

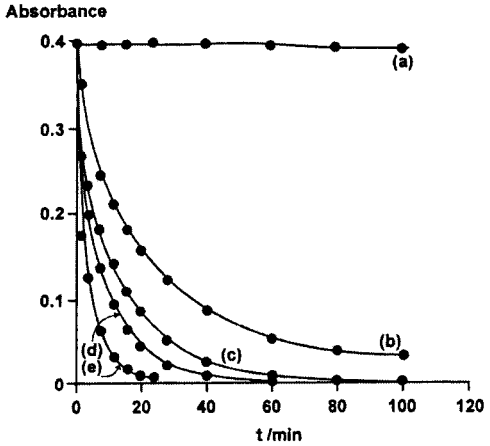


Figure 23. Effect of $[Cu^{2+}]$ on the decomposition of SNAP with (a) EDTA, (b) no added Cu^{2+}, (c) 5 μM Cu^{2+}, (d) 10 μM Cu^{2+}, and (e) 50 μM Cu^{2+}.[528] (Reprinted with permission from ref 528. Copyright 1999 American Chemical Society.)

Williams and co-workers also determined that Fe^{2+} (and Ag^+ to some extent) catalyzed the RSNO decomposition reaction; other metal ions such as Zn^{2+}, Ca^{2+}, Mg^{2+}, and Fe^{3+} did not catalyze the reaction.[588,595]

It has now been established that for the copper ion-catalyzed RSNO decomposition reaction, the active species is Cu^+, which is generated by the reduction of Cu^{2+} by thiolate anion (eqs 54 and 55).[528,596]

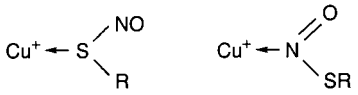
$$Cu^{2+} + RS^- \rightarrow Cu^+ + {}^1/_2RSSR \qquad (54)$$

$$Cu^+ + RSNO \rightarrow Cu^{2+} + RS^- + NO \qquad (55)$$

Further work by Williams and co-workers[527,597,598] and by others[599,600] has confirmed this view. The possible biological relevance of the Cu^+-induced decomposition of RSNO is evident in a study by Williams that shows that Cu^{2+} complexed to amino acids, peptides, and proteins can also partake in RSNO decomposition via initial reduction by thiolate to Cu^+.[601]

Further studies (of the copper ion-induced RSNO decomposition) with the selective and specific Cu^+ chelator neocuproine (2,9-dimethyl-1,10-phenanthroline) have confirmed the role of Cu^+ in RSNO decomposition kinetics and rat vascular smooth muscle relaxation.[602] Other copper chelators show similar effects on RSNO decomposition kinetics.[603]

The structures of the initially formed Cu^+−RSNO adducts (formed just prior to RSNO decomposition) are not known, and both *S*-bound and *N*-bound structures have been considered.[528]



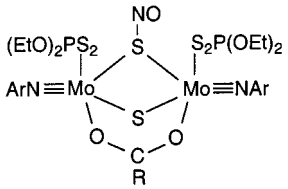
Interestingly, some RSNO compounds may also generate disulfide byproducts which may complex the Cu^{2+} ion (e.g., GSSG-Cu^{2+}) and make the RSNO decomposition kinetics dependent on the [RSNO]/[Cu^{2+}] ratio.[604−606] In some other cases, added thiol (as thiolate) is proposed to serve as a complexing agent for Cu^{2+}.[607]

It has recently been shown that addition of metal chelators to oxyHb preparations results in inhibition of βCys93 *S*-nitrosation by GSNO; in other words, *S*-nitrosation of the βCys93 residue of oxyHb (by GSNO) was found to require metal ions.[608]

4. Other Metals

Some RSNO compounds such as *S*-nitroso-*N*-acetylcysteine, Ph_3CSNO, and EtSNO have been used in inorganic chemistry as nitrosylating agents for metal−NO syntheses.[427,609−611] Complexes containing the "Fe−S(NO)" moiety have been proposed as intermediates in the CO substitution (by NO^+) reaction (Figure 24).[612,613]

Bridged "$Mo_2\{\mu$-S(NO)$\}$" functional groups (shown below) have been proposed to form from the reaction of the "$Mo_2(\mu$-$S)_2$" precursors with various nitrosating agents, and the unstable products (R = alkyl, Ar = aryl) were formulated as such based on characterization by ^1H, ^{31}P, and ^{15}N NMR spectroscopy.[614]



Hoff and co-workers proposed, on the basis of IR spectroscopy, that PhSNO is released when (phen)W(CO)$_2$(SPh)$_2$ reacts with NO to give (phen)W(CO)$_2$(NO)(SPh).[615]

5. Interactions of RSNO with Heme Models

In many ways, the reactions of RSNO compounds with metalloporphyrins resemble those of the corresponding alkyl nitrites. Thus, a formal net *trans*-addition of the RS and NO groups across the metal center occurs when RSNO compounds are reacted with (por)M(CO) (M = Ru, Os) as illustrated in Figure 25.[519−522,551,616−618]

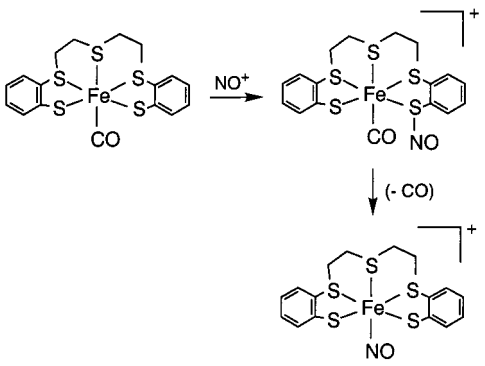


Figure 24. Proposed formation of an intermediate Fe−S−NO complex by nitrosation of a coordinated thiolate moiety.

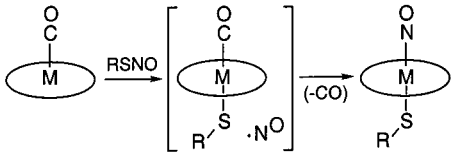


Figure 25. Proposed pathway for RSNO addition to group 8 metalloporphyrins (M = Ru, Os) to generate nitrosyl thiolate products.

The related reaction of RSNO with a ferrous heme model, namely, (TPP)Fe(THF)$_2$, resulted in a net NO transfer to the metal center to produce (TPP)Fe(NO) in high yield.[521] The possibility of direct NO transfer from RSNO to iron centers has implications in biology, and further research in this area is warranted. Interestingly, such a direct NO transfer from RSNO to non-heme iron complexes has been established recently.[619]

VI. Conclusions

In this review we have attempted to present and discuss the fundamental issues involved in the chemistry of organic nitroso compounds belonging to the *C*-nitroso, *N*-nitroso, *O*-nitroso, and *S*-nitroso classes. With the increased attention given to the chemistry and biochemistry of NO since its discovery as a natural product (from the enzymatic transformation of L-arginine to citrulline), it is likely that more biologically important roles of organic nitroso compounds will be discovered as a result of various nitrosation processes in vivo and in vitro. Consequently, their chemical behavior in the presence of metals is an important area that warrants continued investigation.

VII. Acknowledgments

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VIII. Abbreviations

acac	acetylacetonate
bpy	bipyridine
Cp	η^5-cyclopentadienyl
Cp*	η^5-pentamethylcyclopentadienyl
DFT	density functional theory
dmp	2,9-dimethyl-1,10-phenanthroline
dppe	1,2-bis(diphenylphosphino)ethane
EDTA	ethylenediamine tetraacetate
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
MeIm	methylimidazole
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NBD	norbornadiene
OEP	octaethylporphyrinato dianion
Pc	phthalocyanato dianion
pip	piperidine
por	porphyrinato dianion
PPIX	protoporphyrin(IX) dianion
py	pyridine
salen	*N*,*N*-ethylenebis(salicylideneiminato) dianion
SNAP	*S*-nitroso-*N*-acetyl-D,L-penicillamine
TC-3,5	tetradentate tetraazamacrocyclic tropocoronand
TMP	tetramesitylporphyrinato dianion
TPP	tetraphenylporphyrinato dianion
TTP	tetratolylporphyrinato dianion

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