Chemistry of the Nitric Oxide-Releasing Diazeniumdiolate ("Nitrosohydroxylamine") Functional Group and Its Oxygen-Substituted Derivatives

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I. Introduction

This is a review of the chemistry of the atomic grouping of two nitrogens and two oxygens arranged as shown in resonance structures **1** and **2** (Figure 1) which is bonded to any other atom or molecule (X) through a single bond to one of the nitrogens from the perspective that this represents a rarely recognized organic functional group (which we shall also describe by the line designations $-N(O)=NO^-$ and $-N_2O_2^-$ as well as $-N_2O_2H$ for the protonated form). Included in the review are all oxygen-substituted derivatives (i.e., **3** and **4**), but nitrogen-substituted compounds (such as nitroso dimers, RN(O)=N(O)-NR′) are not considered since they exhibit a different chemistry.

Despite the fact that the formation of inorganic salts containing this atomic grouping was first observed two centuries ago[1] and organic compounds thereof have been known for almost 150 years,[2] it was not until 1969 that Woodward and Wintner first recognized that it represented a distinct organic functional group which they called the methoxazonyl group.[3] Unfortunately neither the name nor the designation as a functional group was adopted, and

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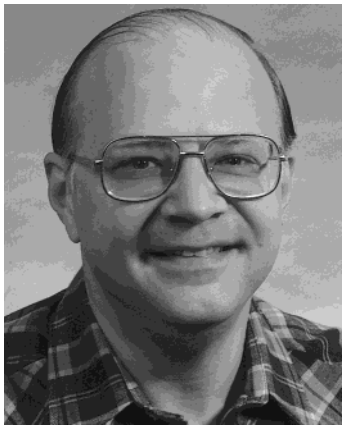
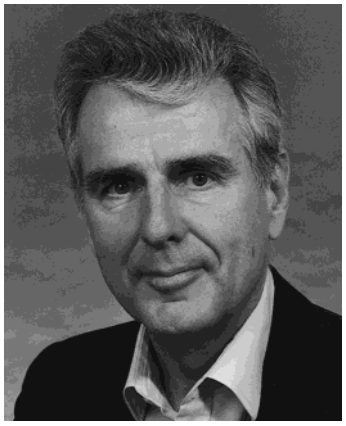


Joseph A. Hrabie received his entire education in the New York City public school system, including his Ph.D. degree in Chemistry (1981) under the guidance of Professor William F. Berkowitz at Queens College of the City University of New York. After postdoctoral research with Professor Herbert O. House at the Georgia Institute of Technology, he moved to the National Cancer Institute at Frederick and is currently a Senior Scientist with SAIC–Frederick, the primary NCI contractor at the site. In addition to many scientific publications, his continuing interest in nitric oxide chemistry has resulted in 15 U.S. patents.



Larry K. Keefer received his B.A. degree from Oberlin College and his Ph.D. degree in Chemistry (1965) under the guidance of Professor Gloria G. Lyle at the University of New Hampshire. He held research positions at the Chicago Medical School and the University of Nebraska College of Medicine before coming to the National Cancer Institute in 1971. He and his colleagues in the NCI's Chemistry Section, Laboratory of Comparative Carcinogenesis, are intensively studying the chemistry and pharmacology of the diazeniumdiolates as nitric oxide sources for biomedical applications.

the practice of naming these compounds as if they represented combinations of various other functional groups (see section II) continues to this day. There has thus never been a comprehensive review of the chemistry of this functional group, which is now of great interest due to its potential to serve as a source of nitric oxide (NO) under a wide variety of conditions. Obviously, it would be impossible to reference every paper published in the 200 year history to be encompassed by the present effort. Fortunately, there have been several minireviews which, although written from different perspectives, will be cited to help present as complete a picture as possible. Thus, the aim of this review is to present a comprehensive summary of the chemistry of this functional group coupled with a discussion of past and present nomenclature sufficient to guide the reader through the diverse literature with the hope that this will result in the long-overdue awarding of functional group

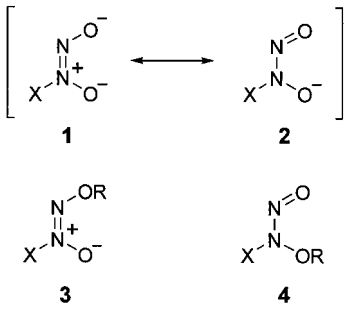


Figure 1. Possible bonding of resonance forms and tautomers or derivatives of the diazeniumdiolate functional group attached to a generic atom "X" (for clarity, only the *cis*-oxygen orientation is shown).

status to this atomic arrangement, lead to the adoption of a common nomenclature, and provide a resource to those conducting future research on this subject.

II. Nomenclature

A. The Modern ("Contemporary") Diazeniumdiolate System

As we shall see, early confusion in the nomenclature for these compounds can be directly linked to uncertainties in their structures. Numerous studies of these materials by X-ray crystallography and other modern techniques (see sections III.F and IV.G) have removed this excuse, and yet, remarkably, names for nonexistent structures continue to be popular. Still other names in recent use do not adequately represent the true nature of the simple conjugated π system and common chemistry of compounds containing this functional group. This situation is as chaotic and counterproductive as that which would exist if ketones were all named as hydroxy alkenes merely because some of them have an enol form or if carboxylic acids were called hydroxycarbonyls! Accordingly, as the use of these compounds in biomedical research increased, Koppenol and Traynham[4] proposed IUPAC names for several of the key substances. We[5,6] and others[7] have recently expanded the scope of this nomenclature, which also seems to have gained some degree of acceptance in the pharmaceutical literature.[8−10]

Figure 1 shows the possible structural formulas of the diazeniumdiolate functional group. The anionic form can exist as a hybrid of resonance forms **1** and **2**. Overwhelming evidence to be described in section III.F, including many X-ray crystallographic studies, supports structure **1** as the predominant determinant of its physicochemical properties. This is the bonding which gives rise to the group's name. "Diazen" represents the N═N linkage and "ium" the formal positive charge, and "diolate" includes the two negatively charged oxygens. The point of attachment to the additional substituent (X) is considered position 1, so the full name becomes "diazen-1-ium-1,2-diolate" for the anions. Substitution on the oxygens gives rise to either the O^2-substituted diazeniumdiolates (**3**) or the O^1-substituted diazeniumdiolates (**4**). Special notice must be taken of the fact that structures **2** and **4** can be named as nitrosohydroxyl-

amines. This is not incorrect, and indeed we have referred to **2** as the nitrosohydroxylamine resonance form of the diazeniumdiolates.[5] However, this is the minor form and thus should not dictate the name of the functional group just as the enolic form of ketones does not dictate their names. Similarly, while the use of the name "nitrosoalkoxylamine" to describe compounds with structure **4** is correct, the chemistry of these compounds only vaguely resembles that of the nitrosoamines.

B. Historical Designations

Historically, diazeniumdiolates have suffered numerous nomenclatural injustices. This has not only hidden their functional group status but has made it extremely difficult to find and interpret literature on the subject. A brief review of the history of the *C*-diazeniumdiolates (**1**, X = C) will illustrate this nicely. Soon after their initial preparation, with the structure still in doubt, organic compounds containing the diazeniumdiolate functional group were known as isonitramines if prepared by reaction of NO with carbanions (the so-called "Traube compounds")[11] and as nitrosohydroxylamines if prepared by nitrosation.[12] The term "isonitramines" acknowledges the fact that the compounds are isomeric with the nitramines (NNO_2) without assigning an absolute structure. While this was most useful during the early structural debates (a minireview is available[13]), the name has persisted into the 1980s,[14] causing some confusion since a family of alkaloids was given the same name in the 1970s.[15] Even more confusing is the fact that the term "isonitramine" has long been used to refer to the tautomeric form of primary nitramines (RN═N(O)OH) and its O-alkylated derivatives.[16] The origin of the term "nitrosohydroxylamine" is somewhat more satisfying since at least in this case the existence of structure **1** as one (as it turned out the predominant) tautomeric form was recognized soon after the name came into favor.[17] The O^1-alkylated diazeniumdiolates (**4**) are correctly named nitrosoalkoxylamines, and as we shall see, they more closely resemble nitroso compounds than any others in this review, but there is evidence that even these exhibit a strong contribution from the dipolar form containing a nitrogen−nitrogen double bond.[18]

Not surprisingly, this chaotic situation has prompted many authors to seek alternate ways to describe diazeniumdiolates. One system that has received extensive use is to name them as azoxy (N═N−O) compounds,[19] a tactic which was initially popular for describing oxygen derivatives whose second oxygen is contained in a well-known organic group such as tosylate[19] or triflate.[20] This was then extended using the more formal designation of azoxy compounds as diazene *N*-oxides so that the alkylated diazeniumdiolates were called "alkoxydiazene *N*-oxides", a name particularly favored in the Russian literature.[21] Application of this method to the *N*-diazeniumdiolates has resulted in names derived from the "alkoxytriazene oxide" root.[22] Such nomenclature is much more closely in agreement with IUPAC rules than is desirable for practical day-to-day usage and gives the unfortunate impression of dividing the C- and N-bound diazeniumdiolates into different chemical groupings.

An interesting way to sidestep the nomenclature issue has its origins in the use of NO as a reagent in preparations of some of these compounds. The first *N*-diazeniumdiolates were described[23] as "NO adducts", and the *C*-diazeniumdiolates produced via reaction of metal alkyls with NO[24] have been called "NO complexes". This type of name has proven to be a popular designation for many of the newer NO-releasing *N*-diazeniumdiolates.[25,26]

Thus, several protocols have been used in the past to name compounds containing the diazeniumdiolate functional group, and only one (isonitramines) seems to have slowly faded away. Additionally, as will be described in the individual sections of this review, the often used organic chemists' practice of naming compounds using the surname of the discoverer of the first example has further complicated the history of this group. It is for these reasons that we favor the adoption of the diazeniumdiolate nomenclature.

III. C-Bound Diazeniumdiolates (Including Nitrosohydroxylamines)

There are more examples of the diazeniumdiolate group being bound to carbon than to any other element. One of the first chemical properties of this functional group to be discovered was the ability of Cupferron (**5**) to complex metal ions,[27] which has led to its extensive use in analytical chemistry.[28] While technically the name only applies to the ammonium salt of phenyldiazeniumdiolate, many similar compounds are described by invoking the Cupferron name.[29,30] Complexes form between *C*-diazeniumdiolates and a wide range of metal ions.[29−31] Such complexes have even been used in the purification of plutonium,[32] and while a review of their chemistry is long overdue, a complete discussion of these materials is not included here since it is beyond the intended scope of this work. All other aspects of *C*-diazeniumdiolate chemistry are included in this section.

Two partial reviews of *C*-diazeniumdiolates have appeared as sections of larger works dealing with functional groups to which they have been linked by nomenclature as described above. A comprehensive review of the early literature, including a valuable listing of all *C*-diazeniumdiolates prepared through 1912, was included in a review of the nitramines.[33] More recently, a review of the formation of azoxy compounds included a good discussion of the early structural debates and some chemical studies that appeared prior to 1976.[34] Readers are urged to refer to these reviews since the current effort will only repeat references as required to present a firm platform of knowledge for future research to build upon.

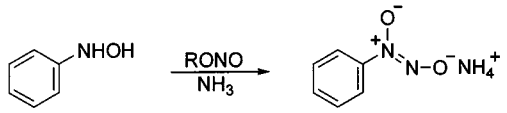
A. Reactions Leading to the Formation of Unsubstituted *C*-Diazeniumdiolates

This section contains a description of reactions that are used preparatively as well as those that do not

have synthetic value. Only representative references are provided for the most widely used reactions.

1. Nitrosations

The most common precursors to the *C*-diazeniumdiolates are the organohydroxylamines. Since some of the *C*-diazeniumdiolates are acid sensitive, the best general preparative methods have been neutral or basic reactions as illustrated by an early preparation of Cupferron (**5**) via nitrosation of phenylhydroxylamine with amyl nitrite/ammonia[35] or methyl nitrite/ammonia[36] (eq 1). Recent applications of this method



(1)

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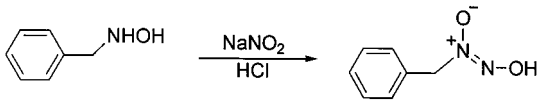
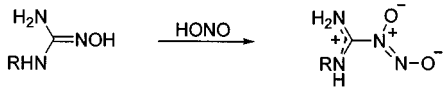
have resulted in the preparation of a variety of Cupferron derivatives[37] as well as 11 aliphatic *C*-diazeniumdiolates as the ammonium salts.[38] Organic nitrites can also be used under acidic conditions to produce the "free acid" (O^2-protonated) form of the diazeniumdiolate directly,[39] although this is usually accomplished via reaction with acidified inorganic nitrite as first demonstrated by Behrend and König[12] (eq 2) and in an alternate early preparation of Cupferron.[40] Acidified nitrite can successfully produce



(2)

diazeniumdiolates in the presence of free hydroxyls[41] and primary amines.[42] Nitrosyl chloride and nitrosylsulfuric acid can also serve as the nitrosating agents.[43]

The nitrosation of oximes can also serve to produce *C*-diazeniumdiolates. The acidified nitrite procedure has been applied to oximes derived from terpenes[44] and (recently) to hydroxyguanidines[45] (eq 3), although some α,β-unsaturated oximes are converted into pyrazole-1,2-dioxides.[46] The use of alkyl nitrites



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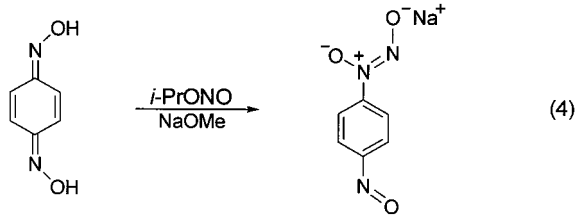
under basic conditions has produced interesting results. Quinone dioximes yield only monodiazeniumdiolates[47] (eq 4), while simple aliphatic oximes



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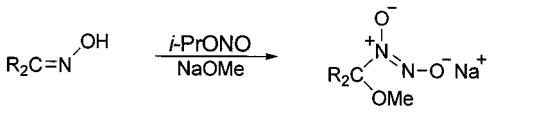
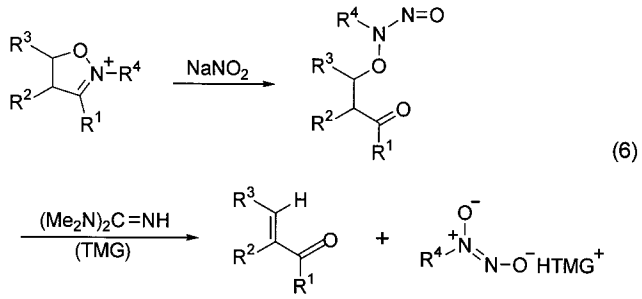
give products resulting from addition to the imine double bond[48] (eq 5). Treatment of oximes with



(5)

nitrosyl chloride does not lead to the isolation of diazeniumdiolates[49] and will be discussed later. However, nitrosyl chloride can be employed in the preparation of diazeniumdiolates via reaction with Grignard reagents.[50,51]

While the direct preparation of O-alkylated diazeniumdiolates and their reactions will be described later, an interesting synthesis of α,β-unsaturated ketones via base-catalyzed elimination of β-diazeniumdiolated ketones formed by nitrosation of dihydroisoxazolium salts (eq 6) is a novel method of preparing unsubstituted diazeniumdiolates.[52]



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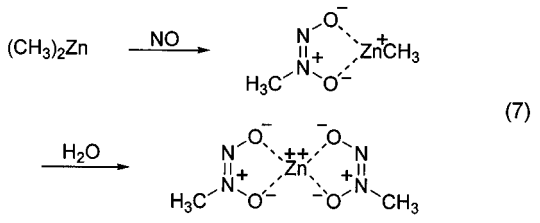
2. Insertions of Nitric Oxide into Metal–Carbon Bonds

The first observations of *C*-diazeniumdiolates were made by reacting NO with dimethylzinc,[2] although the true nature of the product was not known for over 100 years (eq 7).[53] Although not all organometallics



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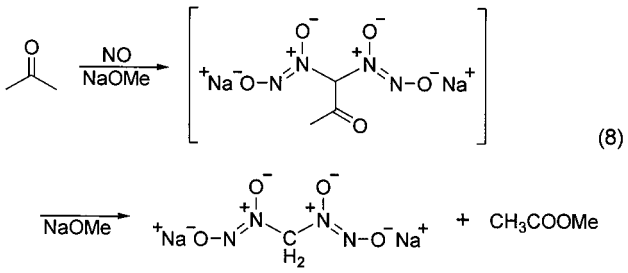
react with NO in this way, the reaction occurs with some frequency and is included in a review of reactions of NO coordinated to transition metals.[54] Several studies that have appeared after this review further illustrate the potential complexity of the reaction.[55−58] A special case is the reaction of NO with Grignard reagents[59] ($RMgX + 2NO \rightarrow RN_2O_2MgX \rightarrow RN_2O_2H$) which has been used preparatively.[50,60,61]

3. Reactions of Nitric Oxide with Carbanions or Their Equivalents

Over 100 years ago, Traube described the reaction of a variety of compounds containing acidic protons with NO in the presence of strong base,[62] as represented in eq 8. This work was largely ignored as a preparative method until a Russian group extended



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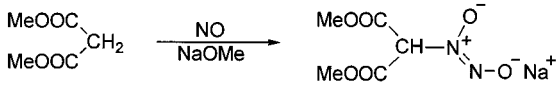
it to include the preparation of diazeniumdiolates of malonate esters[63−65] (eq 9) and a variety of ketones not originally included.[66−68] A recent reexamination



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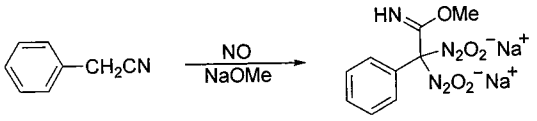
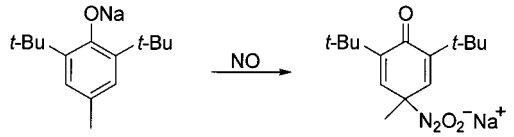
showed that benzyl cyanide produced an interesting imidate derivative[69] (eq 10).



(10)

While direct reaction of phenolic antioxidants such as BHT (2,6-di-*tert*-butyl-4-methylphenol) with NO under neutral conditions results in scavenging of the potentially harmful NO via radical reactions,[70] under basic conditions sodium phenolate undergoes a Traube-type reaction at the ortho position to produce a Cupferron derivative.[71] When the ortho positions are sterically blocked and the para position does not bear a proton, cyclohexadienone diazeniumdiolates may be formed[7] as shown in eq 11. Enamines, neutral



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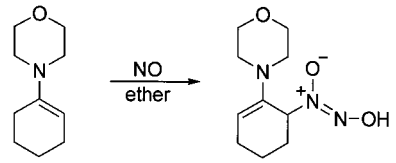
compounds that serve as carbanion equivalents, have also been shown to undergo Traube-like reactions[5] (eq 12).



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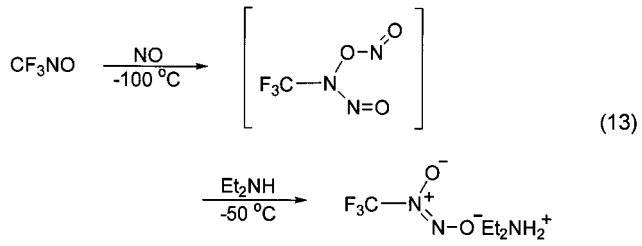
4. Other Nitric Oxide Reactions

An important recurring theme in the reactions of nitric oxide which will be described in more detail later is the radical addition of two molecules of NO across the nitrogen−oxygen double bond of nitroso compounds to produce *O*[1]-nitrosodiazeniumdiolates (for example, the intermediate in eq 13) which are highly unstable and can produce a variety of products. If the reaction is conducted in the cold, *C*-diazeniumdiolates may be produced as their alkylammonium salts[72] (eq 13), copper complexes,[72] sodium salts,[73] or protonated forms.[74] When the NO



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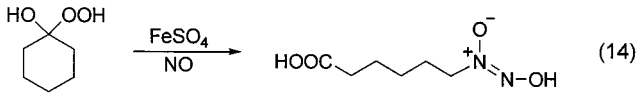
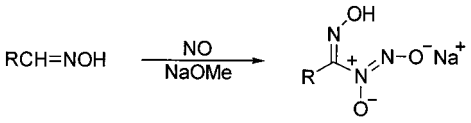
supply is not in large excess, the intermediate radical formed via addition of a single NO to the nitrogen ultimately generates a product that can be detected by ESR, and this forms the basis of a spin-trapping experiment used in biomedical research.[75,76] A similar mechanism probably governs the production of diazeniumdiolates from the reaction of NO with radicals generated from organic peroxides in the presence of iron sulfate as shown in eq 14.[77] Oxaziridines can also



(14)

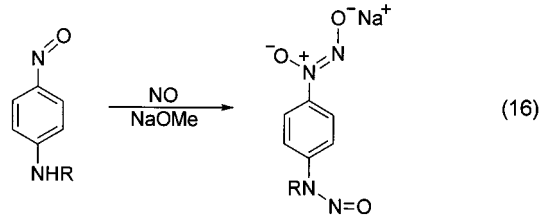
serve as the radical source for this reaction[78] as can arylamines (via the Sandmeyer-type reaction of diazonium salts).[79]

A related series of reactions seems to be involved in the production of diazeniumdiolates from oximes. Aliphatic oximes appear to react with NO via addition of NO across the imine double bond[80] (eq 15).



(15)

The formation of the bisdiazeniumdiolated analogue of Cupferron from benzoquinone dioxime by treatment with NO[80] as well as the preparation of nitrosoaniline derivative as shown in eq 16[81] suggest 1,6-addition of NO across a multiple bond system.



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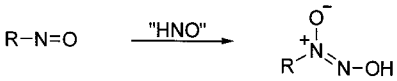
5. Transformations of C-Nitroso Compounds

Nitroxyl (HNO) generated in a variety of ways can add to N═O bonds to form diazeniumdiolates as shown in eq 17. In a recent direct example, nitroxyl

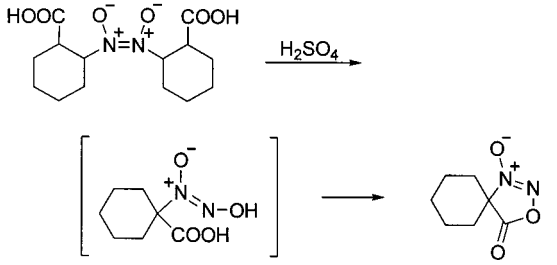


(17)

derived from Angeli's salt ($Na_2N_2O_3$, an *O*-diazeniumdiolate, see later) was trapped by nitrosobenzene to produce Cupferron.[82] The reaction also explains the production of diazeniumdiolates in the photolysis of *N*-nitrosoamines in the presence of olefins[83−85] (via addition of HNO formed from the *N*-nitrosoamine to the *C*-nitroso compound formed by addition of the

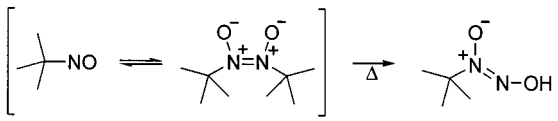
N-nitrosoamine to the olefin) and in the reaction of monoalkylhydroxylamines with nitric oxide.[86]

Conversion of *C*-nitroso dimers to diazeniumdiolates was first reported in 1895.[87] An interesting variation of this reaction (eq 18) affords an α-diazeniumdiolated carboxylic acid as an intermediate which appears to form an anhydride having the rarely observed E configuration.[88,89] The reaction is



(18)

also a complication in the use of 2-methyl-2-nitrosopropane (MNP) as a spin trap for NO, and solutions of this *C*-nitroso dimer have been found to produce *tert*-butyldiazeniumdiolate (eq 19) during gamma irradiation,[90,91] heating,[92] and ultraviolet irradiation.[92,93]



(19)

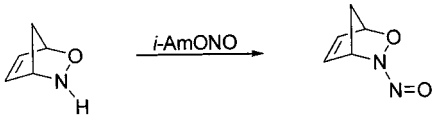
6. Miscellaneous

Several early preparations of Cupferron appear to have no modern applications but may be of value. They include treatment of nitrobenzene with hydroxylamine,[16] heating of aqueous solutions of phenylnitrosohydrazine ($PhN(NO)NH_2$),[94] and hydrogen peroxide oxidations of benzenediazoate[95] and *N*-nitrosoacetanilide.[96]

B. Reactions Leading to O-Substituted *C*-Diazeniumdiolates

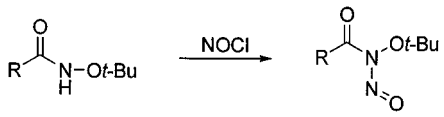
1. Nitrosations

The O^1-alkylated diazeniumdiolates (**4**) have been called nitrosoalkoxylamines because they can be prepared by direct nitrosation of N-substituted alkoxylamines[97,98] using acidified inorganic nitrite, but in reality, the relative instability of these compounds prevents widespread applicability of this method. Isoamyl nitrite could be used to produce an interesting bicycloheptene derivative[99] (eq 20). Nitrosyl



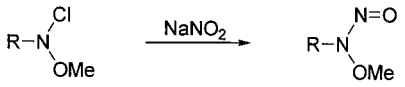
(20)

chloride can be used at lower temperatures to produce the benzoyl[100] and acetyl[101] diazeniumdiolates as their O^1-*tert*-butyl derivatives as shown in eq 21, even though these are not stable at room temperature.



(21)

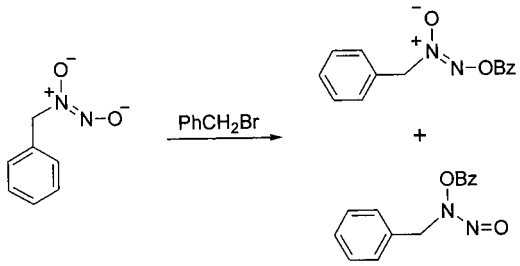
The substrate need not be confined to an alkoxylamine. Under nitrosating conditions, chloramines may be converted into O^1-alkyldiazeniumdiolates[102] (eq 22) and, as previously described, dihydroisoxazolium ions can also yield O^1-substituted diazeniumdiolates[52] (eq 6).



(22)

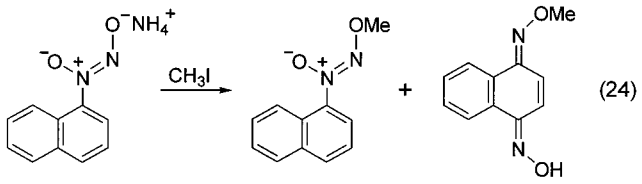
2. Alkylations of Unsubstituted *C*-Diazeniumdiolates

The best method of preparing O^2-alkylated diazeniumdiolates is via direct alkylation of previously prepared unsubstituted analogues, as demonstrated over 100 years ago[12,103] (eq 23). Alkylation is not



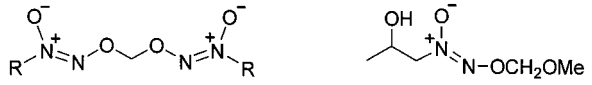
(23)

regiospecific, but the O^1-substituted (nitroso) compounds are frequently unstable[104] and usually do not interfere with the isolation of the terminally (O^2) alkylated products. While we choose not to give references, readers are cautioned that several reports of O^1-alkylated compounds are incorrect assumptions based on the mistaken belief that the O^1-oxygen is the more nucleophilic site. A considerable number of reports have appeared in the Russian literature describing extensive variation of both the diazeniumdiolate structure and the nature of the alkylating agent. This work has been reviewed[105] (including presentation of a tabular listing), and only the key features are summarized here. The diazeniumdiolate may be employed as its sodium,[106] silver,[106,107] copper,[107] halomagnesium,[61] or tetraethylammonium[107] salt, although the silver salts seem somewhat superior.[107] The alkylating agents may be alkyl halides,[106−109] dimethyl sulfate,[61,110] acid halides[111,112] (including *p*-toluenesulfonyl chloride[19,113]), *N*,*N*-dibenzylcarbamoyl chloride,[114] and epoxides.[115] Alkylation of Cupferron has received particular attention since under some conditions mixtures of products form,[116] while it is also possible to prepare exclusively O^2-alkyl derivatives.[117] An interesting recent study[118] verified that O^1-alkylation was a side reaction in the preparation of O^2-alkyl neocupferron derivatives by isolation of the *O*-alkylnaphthoquinone bisoxime byproduct (eq 24). Other interesting recent variations on the alkylation theme include the use of dihalom-



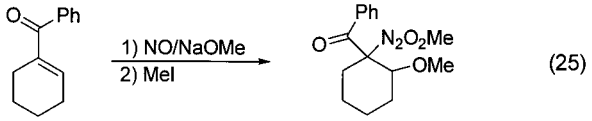
(24)

ethanes to produce formals such as **6**[119,120] and reaction with chloromethyl methyl ether to form methoxymethyl derivative **7**[121] (the thioether also works well). Alkylation may be used to trap the



6 **7**

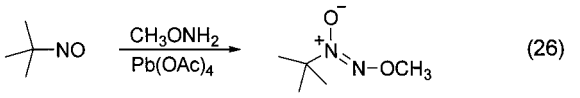
otherwise unstable diazeniumdiolate formed in a Traube-like reaction of NO with vinyl ketones[21] (eq 25). Another variation leading to diazeniumdiolates is the recently reported dialkylation of hyponitrite silver salt.[122]



(25)

3. Miscellaneous

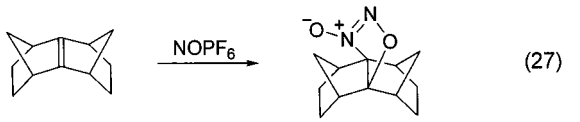
One truly regiospecific preparation of O^2-alkylated diazeniumdiolates is the coupling of nitrenes formed by oxidation of alkoxylamines with the nitrogen of a nitroso compound[123] as shown in eq 26. Similar



(26)

results are obtained using dimethoxylamines.[124]

Two fascinating, unexplained, and probably unique reactions leading to this functional group are the reaction of nitrosyl hexafluorophosphate with a bridgehead olefin[125] (eq 27) and the oxidation of glucopy-



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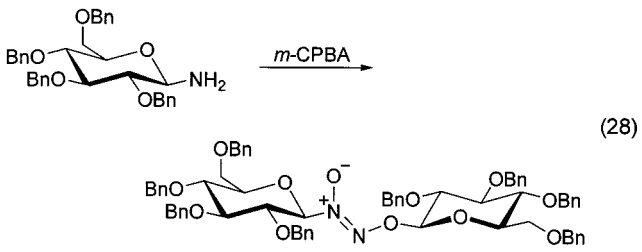
8

ranosylamine with peracid[126] (eq 28). The trans

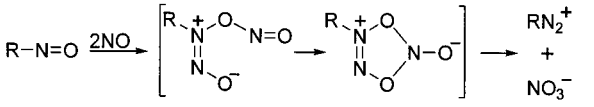


(28)

orientation of the oxygens in **8** is particularly interesting and to our knowledge has never been observed in acyclic compounds (see later).

C. *C*-Diazeniumdiolated Intermediates

The first observation of a reaction of NO which can be explained by the formation of a diazeniumdiolated intermediate was Bamberger's conversion of nitrosobenzene to phenyldiazonium nitrate.[127] Reaction of aliphatic nitroso compounds with NO results in the isolation of products derived from the unstable diazonium salts[128,129] formed by addition of two NO radicals across the N=O bond to produce an O^1-nitroso-*C*-diazeniumdiolated intermediate (**9**) as shown in eq 29. The same reaction may be used to produce



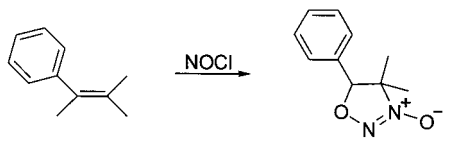
(29)

9

3-diazopyrrole from 3-nitrosopyrrole,[130] and a similar mechanism may be involved in the nitrosation of phenols to yield *p*-diazonium salts.[131]

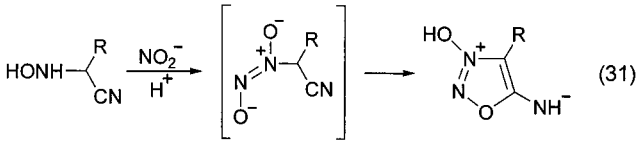
While rigorously purified NO does not react with simple olefins,[132] the slightest impurity can result in the production of a complex mixture of products which can be partly explained by the formation of O^1-nitroso-*C*-diazeniumdiolates.[132,133] Many of these reactions appear to produce yields of nitroalkanes far in excess of the traces of oxygen or nitrogen dioxide present, and this may be explained by the formation of nitrogen dioxide from compounds such as **9**.[132−134]

Many seemingly unexplainable products of nitrosation reactions can be rationalized by invoking unsubstituted *C*-diazeniumdiolates as intermediates. Perhaps the most interesting (because they suggest the presence of the E configuration about the diazene bond!) are the formation of cyclized products on reaction of nitrosyl chloride with certain styrene[135] (eq 30) and vinyl alcohol[136] derivatives. Isolation of



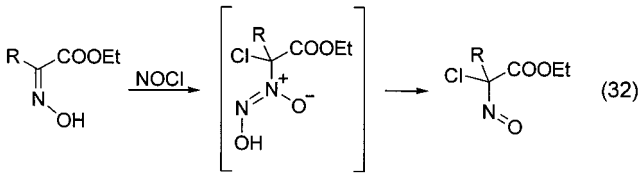
(30)

a nitroso dimer intermediate in the latter case proves that the diazeniumdiolate forms via the reaction described in section A.5 above. A similar cyclization forms the basis of a synthesis of 3-hydroxysydnone imines shown in eq 31.[137]



(31)

Nitrosation of certain oximes also produces reactive *C*-diazeniumdiolates which are not isolated. These include the reaction of α-oximino esters with nitrosyl chloride[138] (eq 32) and the nitrosation of various α,*β*-



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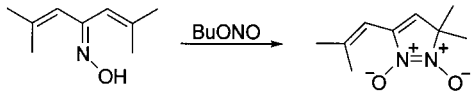
unsaturated oximes with sodium nitrite[139,140] or butyl nitrite[141] (eq 33). Some of these reactions are included



(33)

in a review of oxime chemistry.[142] Related intermediates explain the conversion of diphenylacetylene to tetrafluorodiphenylethane on treatment with hydrogen fluoride/pyridine and nitrosonium tetrafluoroborate.[143] The nitrosation of hydroxamate esters shown earlier in eq 21 may be used to produce ^{18}O-labeled hydroperoxides via rearrangement of the diazeniumdiolate to a hyponitrite as described in section E.1 below.[144]

Diazeniumdiolates are also proposed intermediates in the reaction of sydnones with oxygen[145] and in the thiol-induced NO release from 3,4-dihydrodiazete 1,2-dioxides[146] and may also be involved in the conversion of olefins to carbonyl compounds via reaction with nitrosonium ethyl sulfate.[147]

D. *C*-Diazeniumdiolated Natural Products

Diazeniumdiolates have not been frequently detected in nature. Those which have been isolated to date are all C-bound analogues, and their structures are shown in Figure 2. The most widely known compound is the antitumor antibiotic[42] alanosine, **10**, a fermentation product[148] which has a vast literature that has been reviewed.[149] Dopastin (**11**) was first isolated due to its ability to inhibit dopamine β-hydroxylase.[150] Compound **12** was isolated independently in a soil screen for antibiotics (nitrosofungin[151]) and in a search for a treatment against apple canker (propanosine[152]). Fragin, **13**, was originally isolated as a plant growth inhibitor[153] and has since been found in numerous bacterial cultures.[154] Homoalanosine, **14**, also displays herbicidal activity.[155] Three lipoxygenase inhibitors isolated from the same soil microbe fermentation have been named nitrosoxacins A, B, and C (structures **15**−**17**, respectively),[156] and stromelysin inhibitor nitrososstromelin (**18**) has been isolated from a related *Streptomyces* culture.[157]

The recent isolation of poecillanosine, **19**, from a marine sponge[158] represents a possible new source of naturally occurring diazeniumdiolates. Further work is clearly warranted since these materials show a variety of interesting biological activities including, for example, the ability of alanosine and synthetic analogues to inhibit reproduction of the common house fly.[159]

E. Reactivity of *C*-Diazeniumdiolates

Some reactions have inevitably been described in preceding sections. Transformations of well-characterized compounds that contain C-bound diazeniumdiolates are described in this section.

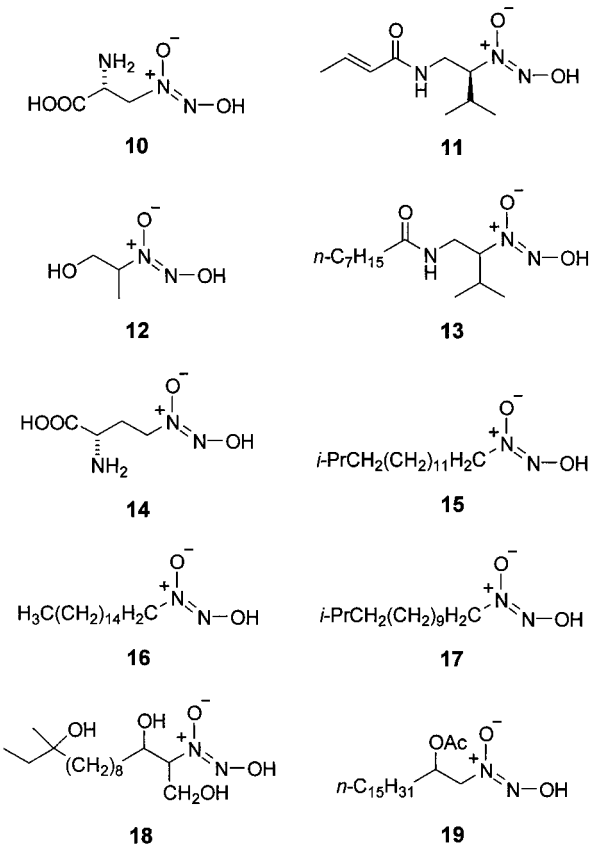
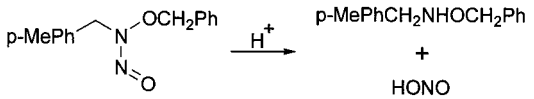


Figure 2. Diazeniumdiolated natural products.

1. Reaction with Nucleophiles (Including Hydrolysis/Solvolysis)

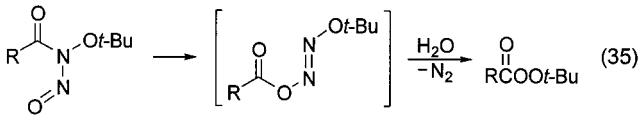
While introduction of a simple aliphatic group at O^2 produces a compound stable to aqueous acid and base (structure **3** in Figure 1),[160] all other *C*-diazeniumdiolates are susceptible to hydrolysis and appropriate O^2-derivatives also render these materials vulnerable as well. The predominant hydrolysis endpoint is the formation of nitroxyl (HNO) [which dimerizes to form nitrous oxide (N_2O)] and a *C*-nitroso compound. These products are formed from both aryl-[161] and alkyl-bound[51] unsubstituted diazeniumdiolates as well as O^1-alkylated derivatives.[160] Studies of the solvolysis of O^1-alkyl derivatives are complicated by their tendency to decompose via competing radical pathways,[162] but the O^1-benzyl derivatives are unique in that they hydrolyze back to the original synthetic precursors[163] (eq 34). The



(34)

mode of decomposition of O^1-alkylated diazeniumdiolates bound to carbonyls is also exceptional because they can undergo a rearrangement to hyponitrites before decomposition[164] (eq 35).

The O^1-acyl diazeniumdiolates are very unstable and rapidly decompose even at dry ice temperatures



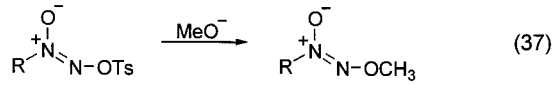
(35)

to generate nitrous oxide and the ester (eq 36).[165−168]

(36)

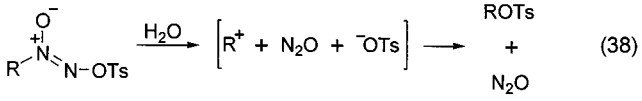
The O^2-acyl derivatives are equally unstable and yield analogous decomposition products.[111]

The O^2-tosyl diazeniumdiolates are quite stable and are the most studied derivatives.[19] Solvolysis in sodium methoxide solution generates the alkylated diazeniumdiolate (eq 37),[19] while under more neutral conditions a reaction analogous to that of the acyl compounds (above) occurs. The added stability of the



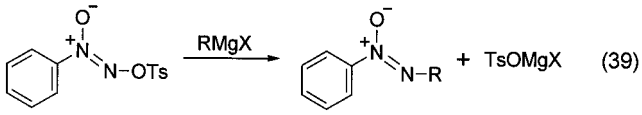
(37)

tosylates has enabled labeling studies,[169] which have shown that these reactions are probably initiated by migration of the acyl and tosyl groups to O^1, although similar recent studies of tosylated adamantane diazeniumdiolate[170] suggest that this does not occur in this case. This finding allows the nitrous oxide-forming reaction to be explained as shown in eq 38.[170]



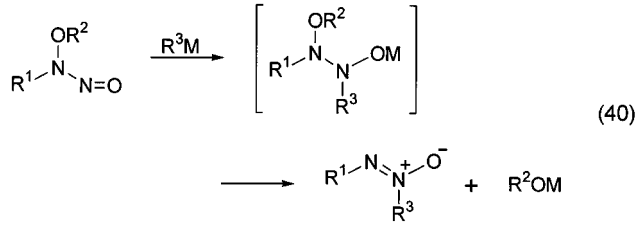
(38)

The reaction of Grignard reagents with O^2-alkyl diazeniumdiolates was correctly reported to produce azoxy compounds even before the true structure of the starting materials was known.[171] Stevens[19] later perfected the preparation of azoxy compounds from the O^2-tosylated acyl diazeniumdiolates (eq 39), although radical side reactions can interfere in some solvents[172] (but apparently not in all cases[173]). Inter-



(39)

estingly, the O^1-alkyl diazeniumdiolates, reacting via their nitrosohydroxylamino form, produce azoxy compounds with the oxygen on the opposite nitrogen from those above with excellent regiospecificity (eq 40), and alkyllithium reagents may also be used.[174]



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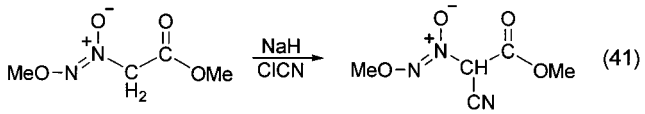
2. Reaction as Nucleophiles

Oxygen alkylation reactions have been described in the synthesis section above, but the carbon bearing the diazeniumdiolate is also a potential nucleophilic site since both the unsubstituted and alkylated versions of this functional group stabilize a negative charge on an adjacent carbon.[3] Thus, protons on carbons adjacent to diazeniumdiolates are acidic and in the presence of base these sites can be alkylated,[3,63,65,68] halogenated,[175,176] and cyanated (eq 41).[176] Carbanions derived from diazeniumdiolates



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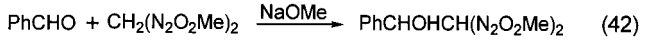
can also undergo the Knoevenagel[3] (eq 42) and



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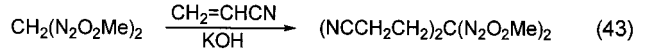
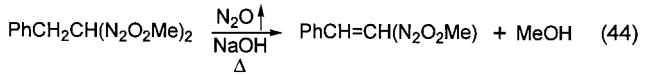
Michael[177] (eq 43) reactions. Under suitable condi-



(43)

tions, β-substituted diazeniumdiolates can undergo elimination to yield products derived from the olefin[21,178] and, in a related reaction, bis(diazeniumdiolates) can undergo elimination of one N_2O_2R group to produce olefins[3,179] (eq 44).



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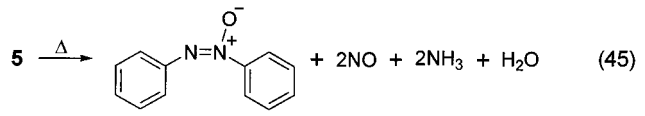
3. Reactions Leading to Nitric Oxide Release

Most *C*-diazeniumdiolates are not NO donors since they break down to produce nitrous oxide directly via a mechanism described above and recently generalized[180] in terms of electron flow away from the atom to which the $N_2O_2^-$ group is attached. However, carefully selected compounds can serve as NO donors under physiological conditions via alternate reaction pathways. Many Cupferron analogues release NO via enzymatic oxidation[181,182] as do O^1-alkylated diazeniumdiolates.[183] Thermal or photochemical release of NO may also occur via a bimolecular reaction[184] (eq 45), and this is probably the reaction that is implied when Cupferron derivatives are described as "spontaneous NO donors". Two groups have prepared

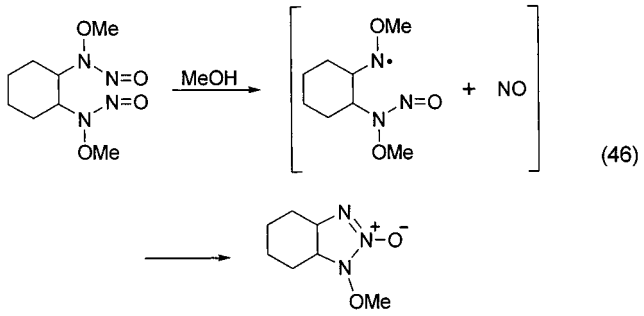


(45)

numerous Cupferron analogues containing substituents on the phenyl ring and concluded that electron-donating para substituents[185] and a variety of ortho substituents[37] can facilitate NO release.

Recently, several novel types of NO-releasing C-bound diazeniumdiolates have been prepared. These new preparative methods have been described in earlier sections. The precursors are enamines (eq 12),[5] phenolates (eq 11),[7] nitriles (eq 10),[69] and *N*-hydroxyguanidines (eq 3).[45] While some empirical rationalization for NO (as opposed to N_2O) release has been offered[5] and the reversal of electron flow

postulated for other materials[180] also seems applicable, the mechanism(s) of these NO-releasing reactions appear to be different than the simple solvolysis described above, and a stoichiometric amount of NO is not detected. While O^2-alkylation produces stable derivatives which do not release NO (until removal of the "protecting" group),[117,118] O^1-alkylation produces compounds that can still generate NO via a radical pathway[186] involving homolytic cleavage of the N−N bond. This radical formation has also been implicated in the release of NO during the formation of triazoles from vicinal bisdiazeniumdiolates[187] (eq 46).



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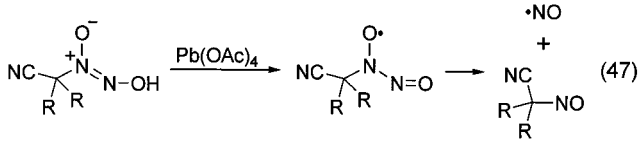
4. Chemical Oxidations

Bamberger[188] found that oxidation of Cupferron with either potassium permanganate or sodium hypochlorite produced nitrosobenzene and nitrite, while others report that some diazeniumdiolates are oxidized all the way to nitro compounds.[80,134] The early result has been verified by the conversion of neocupferron (2-naphthyldiazeniumdiolate) to 2-nitrosonaphthalene,[189] so there appears to be the possibility of selecting the outcome by controlling the conditions. Oxidation with lead tetraacetate produces the O-radical[190] which cleaves to the nitroso compound and NO (eq 47).[191] In contrast to these, O^2-alkylated

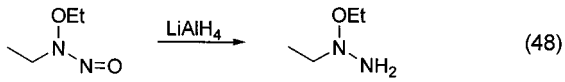


(47)

diazeniumdiolates appear capable of surviving chromic acid oxidation unaltered.[115]

5. Chemical Reductions

Reduction of either Cupferron or its O^2-methyl derivative with sodium amalgam produces phenylhydrazine, while the use of aluminum to reduce O^2-methyl Cupferron affords methyl benzenediazoate.[188] Hydrogenations over either platinum in acetic acid[97] or Raney nickel[77] go all the way to the amine. The diazeniumdiolate functional group appears to survive reductions using sodium borohydride[115] if alkylated on O^2, but an O^1-ethyl analogue was partly reduced to an ethoxyhydrazine[192] (eq 48) by lithium aluminum hydride. Reduction of Cupferron with ferrous sulfate affords benzenediazoate ion.[193]



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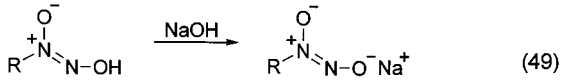
F. Structural and Physicochemical Characteristics

1. Analytical Chemistry

The diazeniumdiolate functional group is a monobasic acid (eq 49) which is also unstable in acidic solutions. This has created some difficulties in mea-



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(49)

suring its properties. The aromatic compounds (Cupferron analogues) have pK_a values between 3.5 and 4.4 in water solutions,[30,31] while the pK_a values of aliphatic derivatives range from 5.1 for nitrosofungin (**12**)[151] to 6.4 for fragin (**13**).[194]

Historically, the O^1- and O^2-derivatives have been differentiated using the Liebermann test.[195] This test is based on the fact that any nitrosating agent will react with phenol in acid solution to produce an intensely colored dye. The unsubstituted diazeniumdiolates[196] as well as the O^1-derivatives[12] give positive Liebermann tests, but the O^2-derivatives do not react.[80] Unfortunately, this type of wet chemical test is not very specific and is of little value in modern chemistry. The most characteristic spectroscopic properties of the diazeniumdiolates are their ultraviolet (UV) spectra. The acid forms (**20**) have an intense UV absorption at 229−232 nm in water or alcohol solutions which undergoes a bathochromic shift to 244−258 nm on deprotonation with sodium hydroxide (**21**, eq 49) accompanied by a slight increase in the molar extinction coefficient (which rises from 6.0−7.0 mM^{-1} cm^{-1} to 7.5−8.7 mM^{-1} cm^{-1}).[6,151,153,158,194,197−200] Alkylation produces a similar but smaller bathochromic shift[6,7,13,199,200] (λ_{max} = 237−242) regardless of which oxygen is derivatized, but if O^1 is alkylated, the resulting "nitrosoalkoxylamine" shows an additional weak absorption at 370−380 nm (ϵ = 0.1 mM^{-1} cm^{-1}).[6,7,13,200]

The infrared spectra of diazeniumdiolates exhibit three distinct bands[6,13,106,115] of which two are due to N−O stretching (1470−1510 cm^{-1} and 1270−1315 cm^{-1}) and one is due to N−N stretching at 1000−1060 cm^{-1} (which is weaker).

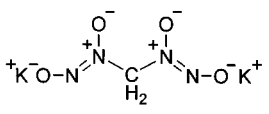
Nuclear magnetic resonance (NMR) spectroscopy of diazeniumdiolates has rarely received attention. Aliphatic protons on the carbon to which the N_2O_2 group is attached are shifted downfield by 2−3 ppm as might be expected by analogy to the carboxylates[61,201] and that carbon generally appears at 58−62 ppm in carbon NMR spectra[202] if no other influences are present. Most useful is a study of the ^{15}N NMR spectra of several diazeniumdiolates including C-, N-, O-, and S-bound compounds[203] (the latter two are inorganic salts, see below), but since only one of each type of compound was included, the data are not repeated here. ^{14}N NMR spectroscopy may also be useful since the *N*-oxide nitrogen signal of O^2-alkylated diazeniumdiolates has been reported to be

relatively sharp (ca. −65 to −70 ppm relative to nitromethane).[204] The ^{15}N chemical shifts of the N−O[1] nitrogens of several selectively labeled analogues are reported to be 320−360 ppm relative to ammonia.[205]

Additional analytical studies of great interest but limited scope include photoelectron spectroscopy,[205,206] ESR,[190] polarography,[207] and cyclic voltammetry.[185]

2. Structural Studies

The debate about the structure of these compounds was not truly ended until an X-ray crystal structure of the dipotassium analogue of Traube's salt (see eq 8) showed its structure to be as shown by **22** with two nearly equal N−O bond lengths[208] (a similar result was later obtained for the disodium salt[14]). The



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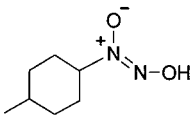

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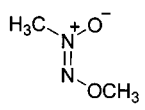
structure of the free acids that had falsely become known as "nitrosohydroxylamines" was finally proven when crystal structures of Cupferron free acid and a cyclohexyl analogue (**23**) were obtained.[209] Due perhaps to the limited stability of these compounds as the free acids, only five other O-unsubstituted structures have been determined by X-ray crystallography[5−7,45] and all show the tendency of the negative charge to exist predominantly on the terminal (O^2) oxygen. Crystal structures of O^2-derivatized Cupferron analogues[118,210,211] and numerous O^2-derivatized aliphatic diazeniumdiolates all show the same structural characteristics.[26,126,212−218]

These studies all show that the $-N_2O_2^-$ functional group is essentially planar and that the oxygens are in the syn configuration (i.e., on the same side) with respect to the diazene double bond, an arrangement designated the *Z* isomer by IUPAC rules. Indeed, even in the gas phase[206] the simplest possible O^2-alkylated diazeniumdiolate (O^2-methyl 1-(methyl)-diazeniumdiolate, **24**) exists predominantly in the *Z* conformation, and the barrier to rotation to the *E* conformer has been estimated by NMR as ca. 15 kcal/mol.[219] As might be expected, the O^1-alkyl diazeni-



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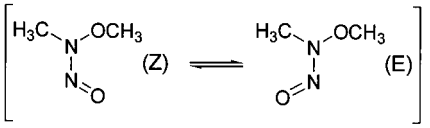

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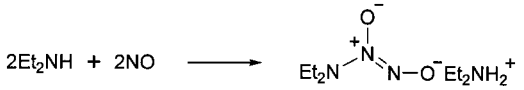
umdiolates (**25**), like most nitrosoamines, show evidence of an equilibrium between the *E* and *Z* conformers due to restricted rotation at low temperature.[18,160] Such evidence is lacking for any other unsubstituted or O^2-derivatized acyclic diazeniumdiolate reported so far, presumably due to the overwhelming preference for the *Z* conformer for any group larger than methyl (even the small change of substituting an ethoxy group for the methoxy group of **24** causes only the *Z* conformer to be observable[160]). Nevertheless, cyclization reactions such as those shown in eqs 18, 27, 30, and 31 suggest that rotation to the *E* conformer is possible for many diazeniumdiolates.

IV. N-Bound Diazeniumdiolates

The first reported N-bound diazeniumdiolate was the NO adduct of diethylamine (DEA/NO, **26**, eq 50)[220] prepared in the laboratories of Russell Drago[220] (hence the common name "Drago complexes") in 1960, although simultaneous work by Edward Reilly at DuPont would soon appear as a patent[221] which had the distinction of reporting the first O-alkylated derivatives. Since these materials are thus over 100



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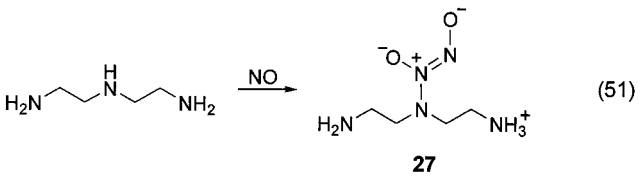
years "younger" than their C-bound analogues, there is much less chemistry reported. Furthermore, they were virtually ignored until this past decade when the need for NO donors arose,[222] and the work conducted since has been directed mainly toward this goal. Many of these compounds are now widely used as NO donors in biomedical research, and a simple method for naming the individual substances has gained popularity. As shown above for **26**, a simple, unambiguous designation can often be devised by interposing a virgule (backslash) between an abbreviation for the amine portion and the letters "NO" that stand for "nitric oxide adduct". This system is clearly superior to names based on either the "NONOate" or "NOC" designations that have previously been employed.[222]

A. Preparation of *N*-Diazeniumdiolates

The amine diazeniumdiolates are in general less stable than their carbon analogues, and so have never been isolated in their protonated forms. Direct reaction of NO with an amine remains the only useful method of preparation. Soon after their initial synthesis, it was discovered that the ammonium salts are quite hygroscopic and that the sodium salts (prepared either by metathesis[223] or directly by the use of added base in the reaction mixture[224]) were more stable. An early attempt to demonstrate that the reaction mechanism involves the sequential addition of NO rather than a single addition of NO dimer is unfortunately not very convincing due to misleading spectral interpretation,[225] although the sequential addition mechanism is assumed by analogy to the formation of certain *C*-diazeniumdiolates described previously. Early confusion over the structure of diazeniumdiolated diamines[224] was resolved years later when the zwitterionic nature of the polyamine/NO adducts (for example, **27** in eq 51, the diethylenetriamine/NO adduct often called "DETA/NO") was demonstrated[25] and the influence of reaction conditions on the nature of the products formed was described.[226] The reaction of polyamines with NO can also be used to prepare diazeniumdiolated solid



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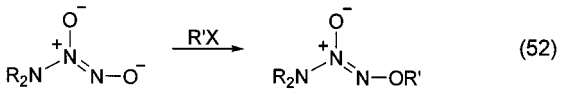
polymers by simple exposure of a slurry of poly(ethylenimine) in suitable solvents to NO gas.[227,228] Only one other method of preparing *N*-diazeniumdiolates exists based on the coupling of *O*-nitrenes with the nitroso nitrogen bond of *N*-nitrosoamines (the N-analogue of the reaction shown in eq 26).[22]

B. Alkylations of *N*-Diazeniumdiolates

In contrast to their C-bound cousins, the *N*-diazeniumdiolates have not, at least as yet, been induced to form stable O^1-derivatives, although the first O^2-alkylated products[221] were misidentified as a result of the same confusion regarding the nitrosohydroxylamine structure that has been described above for the carbon-based compounds. This situation has proven particularly advantageous since numerous O^2-alkylated compounds have been prepared more easily than would have been possible if mixtures of isomers were produced. The simple O^2-alkylated *N*-diazeniumdiolates are generally stable compounds, and many have been prepared with the goal of using the alkyl group as a protecting group that can be removed selectively to regenerate the *N*-diazeniumdiolate so that it can then release its NO.[26] These features will be described later. The O^2-alkylations may be accomplished using simple alkyl halides[26] (eq 52), epoxides,[26] alkyl sulfates,[26] and aryl halides.[229,230] Recently, more highly functionalized alkyl halides[231−233] have been employed.



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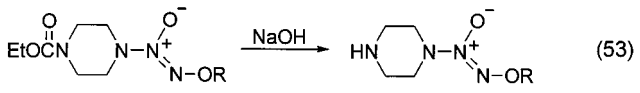
C. Synthetic Manipulations of O^2-Protected *N*-Diazeniumdiolates

Since little variation of the actual *N*-diazeniumdiolate synthesis reaction is possible, simpler molecules containing this functional group must serve as building blocks for larger derivatives. Several strategies have evolved to achieve this goal.

1. Modifications to the Amine Portion

Most O^2-derivatized as well as the underivatized diazeniumdiolates are stable to basic reagents and can survive many reactions conducted in the presence of base even if they involve acidic reagents. This was exploited in the preparation of a range of monodiazeniumdiolated piperazine derivatives[234] (**28**, eq 53).



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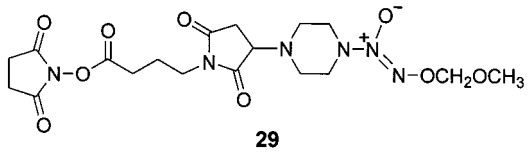
Reactions at the free amine could then be used to introduce the diazeniumdiolate functional group into other molecules. Reaction of **28** as a nucleophile with alkyl halides such as 6-chloropurine riboside, nicotinyl chloride, and poly(vinyl chloride) (PVC) produced the diazeniumdiolated nucleoside, vitamin, and polymer analogues, respectively.[234] Michael reaction of **28** with maleimides was used to produce a diazeniumdiolated derivative of the traditional protein cross-linking reagent GMBS (**29**) which can be used to derivatize the lysines in proteins.[235] Displacement of the sulfate groups in heparin by **28** (R = CH_2OCH_3) formed a diazeniumdiolated material that has been used to produce thromboresistant polymeric films.[236]



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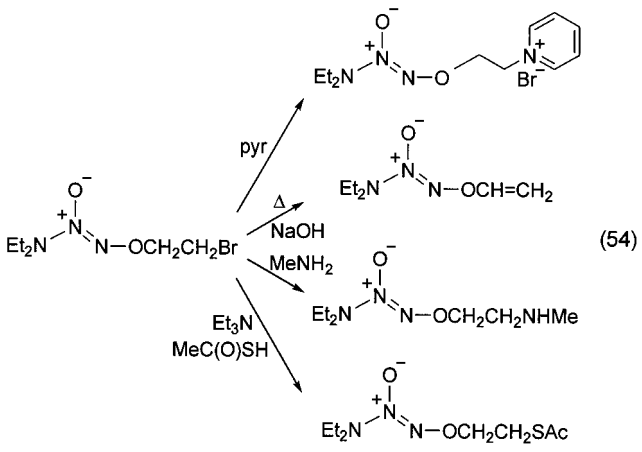
While the above procedures all involve O^2-protected compounds, unprotected diazeniumdiolate **28** (R = Na^+) can also react with heparin preferentially at the free amine to produce a product that can inhibit and even reverse platelet aggregation.[237] Various unprotected polyamine diazeniumdiolates have also been bound to dextran at their free nitrogen using cyanogen bromide as a cross-linking reagent.[238]

2. Modifications to the Oxygen Substituents

While direct alkylation has been used to introduce a variety of substituents at O^2 to modify the NO-releasing properties of molecules containing the diazeniumdiolate functional group and these will be detailed later, it has also proven possible to perform synthetic manipulations on several already existing O^2-substituted compounds without disturbing the diazeniumdiolate group. Halogens on side chains can undergo nucleophilic displacement by amines[26] or thiolates[231] and can be dehydrohalogenated[26] (eq 54).



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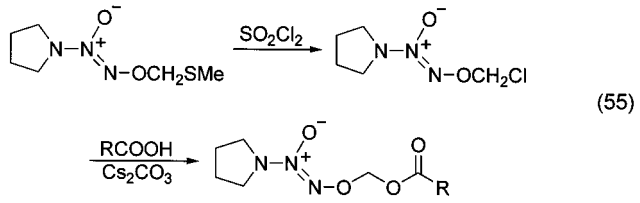
Recent work[232] shows that the functional group is inert toward sulfuryl chloride as well as cesium carbonate (eq 55) and forms the basis for a method of linking the diazeniumdiolates to proteins through an oxygen substituent (a complement to the use of **29**). Acetylated O^2-glycosylated diazeniumdiolates

may be deacetylated without destruction using sodium methoxide.[233]



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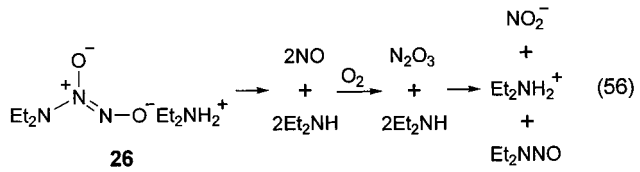
D. *N*-Diazeniumdiolated Intermediates

One of the earliest observations of *N*-diazeniumdiolates was as a consequence of the industrial preparation of nitrosoamines via a high-pressure reaction of NO with amines in the absence of oxygen.[221,239] Reilly[221] isolated the intermediate diazeniumdiolates but did not explain the pathway to nitrosoamines. In the presence of oxygen, decomposition to NO and its subsequent conversion to a nitrosating species (N_2O_3) by oxygen has been shown to be the operative mechanism[240] (eq 56). This has



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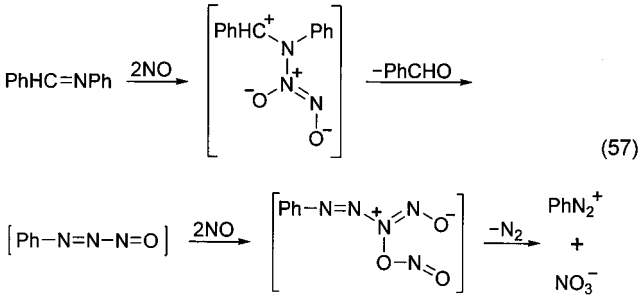
significant implications for the medicinal use of the diazeniumdiolates because many nitrosoamines are potent carcinogens. The mechanism of the industrial process remains a mystery. *N*-Diazeniumdiolates may also be intermediates in NO-based nitrosations induced by either Cu(I)[241,242] or oxygen[243] and in the reductive nitrosylation of a manganese complex.[244]

O[1]-Nitroso *N*-diazeniumdiolates formed by addition of NO across the N=O bond of an intermediate nitroso diazene (a reaction analogous to the one described in section III.C, see eq 29) are postulated intermediates in the reaction of NO with Schiff bases to produce diazonium nitrates[245] (eq 57).



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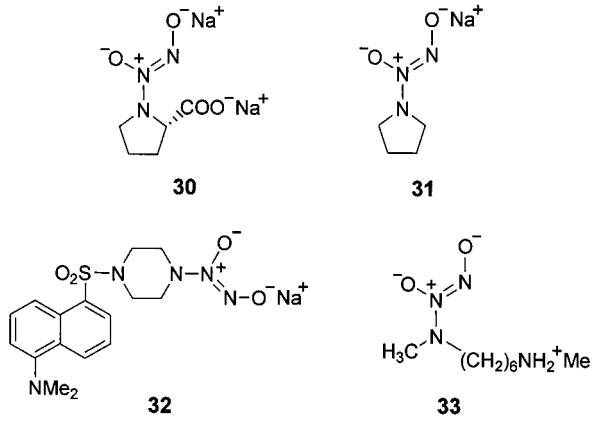
N-Diazeniumdiolates are probably also intermediates in the reductive deamination of aniline derivatives to substituted benzenes[246] since the primary amine adducts that would be formed in the reaction of NO with aniline have never been isolated. A similar situation exists in the oxidation of thiols to disulfides by NO (see later in this review).[247]

E. Nitric Oxide Release from *N*-Diazeniumdiolates

The initial finding that DEA/NO (**26**, eq 56) decomposed to regenerate its progenitors (diethylamine and NO)[23] as well as the subsequent finding that this was accelerated by acid and inhibited by base[240] attracted no attention until the central role of NO in physiology began to emerge. Chemical research aimed at influencing this NO-releasing process only began in earnest with the appearance of the first report correlating the NO-releasing properties of three structurally very different *N*-diazeniumdiolates with their vasorelaxant effects.[248]

1. Unsubstituted *N*-Diazeniumdiolates

Drago and Karstetter[223] found that the diazeniumdiolates of primary amines are far less stable than those of secondary amines, and thus, most further work has used the latter compounds. It has been found that the rate of NO release from *N*-diazeniumdiolated secondary amines varies greatly with the structure of the substrate. Simple monoamines have relatively rapid release rates that vary from 1.8 s for PROLI/NO (**30**)[249] and 3.0 s for PYRRO/NO (**31**)[250] to 5−6 min for GLO/NO (**32**)[234] as measured at pH 7.4 in phosphate buffer at 37 °C (the biologist's favorite conditions). While the "ultrafast" NO donors



such as PROLI/NO can be used in experiments to localize the activity of the NO released,[249] these compounds are most useful as their O^2-substituted derivatives to be discussed below.

The polyamine diazeniumdiolates exhibit a truly remarkable degree of variation in the rate of NO release with relatively minor structural change.[25] The half-lives of 16 of these compounds at room temperature have been summarized in a table,[25] and some have been determined at 37 °C in pH 7.4 phosphate buffer.[251] They range from 1 min for MAHMA/NO (**33**) to 20 h for DETA/NO (**27**, eq 51). DETA/NO has the distinction of having the longest half-life of any simple water-soluble diazeniumdiolate yet prepared (although certain insoluble fatty acid-substituted diazeniumdiolates are reported to have longer half-lives measured under different conditions,[252−254] these should probably be more closely compared to the polymeric materials). Incorporation of polyamine-type diazeniumdiolates into various polymers [236,255] can lead to extended NO generation at their surfaces not directly traceable to a simple hydrolysis half-life. Among the soluble biopolymers, a bovine serum albumin derivative whose diazeniumdiolate groups are O^2-methoxymethylated exhibits extended NO

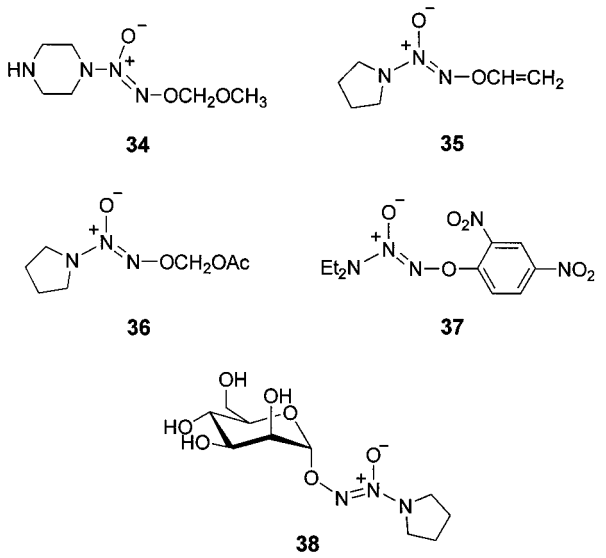


Figure 3. Selected O^2-protected diazeniumdiolates.

release,[235] while a diazeniumdiolated heparin bearing ionic $N_2O_2^-$ groups does not have a half-life longer than the piperazine diazeniumdiolate from which it is made.[237]

Kinetic studies of the decomposition of *N*-diazeniumdiolates, including determination of the pH dependence of the reaction, reveal that the reaction is initiated by protonation of the amine nitrogen bearing the $N_2O_2^-$ group but that in the case of the polyamines, protonation at other nitrogens adds additional complexity at lower pH values.[256] The dissociation reactions follow simple pseudo-first-order rate laws[256,257] but in some cases have been found to be influenced significantly by self-association to form bimolecular complexes at higher concentrations and by the presence of metal ions.[256]

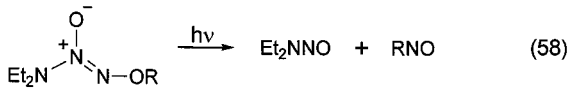
2. O^2-Substituted N-Diazeniumdiolates

Simple O^2-alkylated *N*-diazeniumdiolates are stable compounds which can be chromatographed, distilled, and/or recrystallized. They hydrolyze only slowly even in acid solutions.[26] This has prompted the design of O^2-substituents which would themselves react under a variety of conditions to regenerate the unsubstituted diazeniumdiolate, thus initiating its dissociation to produce NO as described above. A selection of these compounds is shown in Figure 3. Compounds such as the acetal MOM-PIPERAZI/NO (**34**) have an extended half-life of NO release (~17 days at pH 7.4 in phosphate buffer) due to the need for the alkyl group to hydrolyze to a mixture of the free diazeniumdiolate, methanol, and formaldehyde before NO release can begin.[234] V-PYRRO/NO (**35**) and AcOM-PYRRO/NO (**36**) are novel enzyme-selective NO donors that are activated by hepatocytes in the liver[250] and various esterases,[231] respectively. A series of O^2-aryl compounds (e.g., **37**) are activated by nucleophilic aromatic substitution (S_NAr) reactions, including by attacking the thiolate of the zinc finger portion of an HIV nucleocapsid protein.[230] Quite recently, a new series of O^2-glycosylated diazeniumdiolates (e.g., **38**) has been shown to generate NO after activation by glycosidases.[233]

F. Other Reactivity of *N*-Diazeniumdiolates

Few modes of reaction of the *N*-diazeniumdiolates other than those directly associated with NO release (described above) have been identified. As might be expected by analogy with Cupferron, they act as bidentate chelators and form complexes with a variety of transition metal ions.[258,259] Complexes can be quite unusual as shown by the formation of a sandwich-type structure containing both bi- and trinuclear components.[260] Suitable choice of the other ligands can lead to the formation of complexes in which the diazeniumdiolate acts as a monodentate ligand coordinated to Cu(II) at O^2 only.[261]

The *N*-diazeniumdiolates are quite photosensitive. Studies of various O^2-substituted compounds, both alkyl and aryl, revealed a primary photochemical reaction involving cleavage of the N═N bond to yield a nitrosoamine and an O-substituted nitrene which rearranges to a *C*-nitroso compound (eq 58), the latter often isolated as the oxime.[262] A minor pathway



involves the extrusion of nitrous oxide with cogeneration of amine and alkoxy radicals. Subsequent photolytic cleavage of the nitrosoamines does technically render the diazeniumdiolates photoreleasing NO donors,[262] although not via the pathways first envisioned.[229] Unsubstituted compounds such as PROLI/NO (**30**) also photolyze via cleavage of the N═N bond, in this case producing NO^- which ultimately leads to the production of nitrate under aerobic conditions.[262]

G. Structural and Physicochemical Characteristics

1. Analytical Chemistry

As noted previously, the diazeniumdiolate functional group is a monobasic acid. Since the N-bound compounds are quite sensitive to acids themselves, the O-protonated *N*-diazeniumdiolates have never been isolated. However, it has proven possible to determine the pK_a values for a number of these compounds because protonation causes a hypsochromic shift in the UV absorption maxima from ca. 250 to ca. 230 nm (see below).[256] These spectrally determined pK_a values range from 3.1 for DETA/NO (**27**) to 4.6 for MAHMA/NO (**33**).[256]

The UV spectra are the best method for characterization of *N*-diazeniumdiolates, and they have considerable resemblance to those of the C-bound compounds described earlier. In addition to protonation, O^2-alkylation also produces the characteristic red shift.[26] Typical UV spectra of unsubstituted diazeniumdiolates, measured in basic solution, show an absorption maximum at 250 nm with molar extinction coefficients in the range from 7.2 to 9.4 $mM^{-1}\,cm^{-1}$, while O^2-alkylation shifts the absorption to ca. 235 nm with a similar range of molar extinction coefficients.[26]

A detailed discussion of the vibrational spectroscopy of an N-bound diazeniumdiolate has recently been presented.[6] The infrared spectra of the unsubstituted compound exhibits three characteristic bands of which two may be attributed to N−O stretching (1225−1210 and 1187−1155 cm^{-1}) and one is attributed to N−N stretching (1131−1129 cm^{-1}).[220] An extensive analysis of the vibrational modes of the N_2O_2 grouping as a unit, which explains other infrared absorptions, is provided in the recent paper.[6]

Specific NMR study of N-bound diazeniumdiolates has been limited to a single report[203] of the ^{15}N NMR of DEA/NO (**26**), which reports chemical shifts of 215 and 386.5 ppm (relative to ammonium chloride reference) for the two nitrogens of the functional group. A limited amount of photoelectron spectroscopy has also been reported (see the next section).[205]

2. Structural Studies

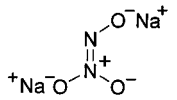
Structural studies of the *N*-diazeniumdiolates include X-ray crystal structures of DEA/NO (**26**) as its ammonium salt,[6] sodium salt,[6] and in copper complexes[259−261] as well as O^2-alkyl[26] and O^2-aryl[230] derivatives. These verify that the functional group has the same features when bound to nitrogen as when attached to a carbon. The most remarkable feature continues to be the *Z* (syn) configuration of the oxygens with respect to the N═N bond, and no evidence has ever been reported for the presence of the *E* (anti) configuration (even in solution). Analogy to the C-bound structures is not surprising given the fact that all the spectroscopic evidence given above[6] as well as a study of the photoelectron spectra of several O^2-alkylated *N*-diazeniumdiolates[205] shows virtually no interaction between the N_2O_2 functional group and the lone pair of electrons possessed by the nitrogen to which it is attached. Inspection of the literature referenced in this review reveals that no evidence of hindered rotation about the N−N single bond has ever been observed by NMR spectroscopy. Quantum mechanical calculations[263] show the thermodynamic stability of this configuration and also confirm the importance of the diazeniumdiolate resonance form relative to the nitrosohydroxylamine-type structures.

V. Diazeniumdiolates Attached to Other Elements

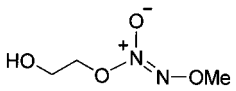
Most of the other compounds containing the diazeniumdiolate functional group are inorganic salts. These substances all seem to prefer to generate nitrous oxide in solution (although in the presence of oxidants this can change in some cases, see below) and so have limited application in the development of NO donor chemistry. This review will only present a brief overview of these diazeniumdiolates.

A. *O*-Diazeniumdiolates

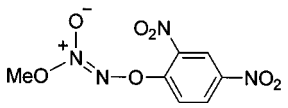
The predominant O-bound diazeniumdiolate is the inorganic salt **39** which is known as Angeli's salt in honor of its first preparer.[264] Although it is possible to prepare alkylated versions such as **40**[265,266] and **41**,[267] which are essentially diazeniumdiolated alcohols, few studies have been done in this area. The



39



40



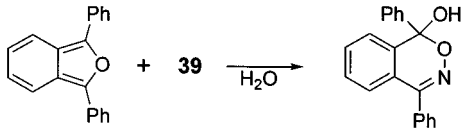
41

inorganic ion has also been known as trioxodinitrate,[268] oxyhyponitrite,[268] hyponitrate,[269] and OXI/NO.[251] Angeli's salt is prepared by treatment of hydroxylamine with an alkyl nitrate in the presence of sodium ethoxide[270] or sodium hydroxide.[271] Its ultraviolet spectrum (UV λ_{max} = 237 nm in pH 7.4 phosphate buffer[251]) first led to the suspicion of a diazeniumdiolate structure,[270] although a vigorous debate continued until an X-ray crystal structure[272] settled the issue. A crystal structure of a derivative of diazeniumdiolated alcohol **40** shows the expected syn configuration of the oxygens, although the proton and carbon NMR spectra of **41** show small amounts of a second (presumably anti) conformer.[267] It should be mentioned that even though these *O*-diazeniumdiolates have the same structure as the C- and N-bound compounds, the IUPAC designation reverses itself because it uses the atomic weights of the attached nuclei when specifying configurations about double bonds. Thus, technically, **40** and **41** are *E*-configured diazeniumdiolates, although the fundamental structure of the atomic grouping has not changed. Thus, yet another reason to begin to associate a common nomenclature with the functional grouping described in this review is that the syn configuration can be considered implicit in the name except in the few rare circumstances described in this review!

While decomposition of Angeli's salt in very dilute[248] or highly acidic[273] solution has been reported to produce NO directly, under all other conditions the reaction produces nitroxyl (HNO) and nitrite (NO_2^-).[268] Nitroxyl rapidly dimerizes and dehydrates to produce nitrous oxide,[268] but in the presence of a one-electron oxidant such as ferricyanide,[274] it can be converted to NO before dimerization. Indeed, the observation of the hypotensive properties of Angeli's salt in rats, one of the first such observations for any diazeniumdiolate, was explained in terms of formation of NO although it was not very potent.[275] Subsequent study revealed the conversion of NO^- to NO by physiological oxidants,[276] and as a result, Angeli's salt is often used as a source of NO^- in biological research.[277] Recent results suggest that copper ions are very efficient catalysts of the oxidation of NO^- to NO[278] but that some hydroxyl radical may form during hydrolysis of Angeli's salt,[279] so the use of this compound in biomedical research is clearly subject to considerable complexity. An interesting early review of the aqueous solution chemistry of nitrogen in low positive oxidation states is available.[280] Photochemical decomposition of Angeli's salt solutions

in the presence of oxygen can lead to the formation of peroxynitrite ($ONOO^-$).[281]

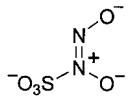
Angeli's salt is a bidentate chelator and has been shown to form complexes with manganese, iron, cobalt, and nickel.[282] Crystal structures have been reported for zinc and cobalt complexes.[283] Despite the predominance of the diazeniumdiolate resonance form, the salt has been found to undergo cycloaddition reactions via its nitrosohydroxylamine resonance form[284] (eq 59).



(59)

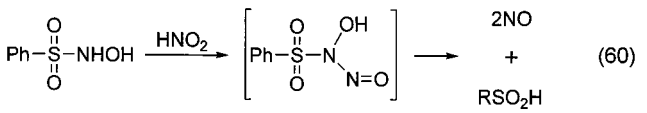
B. *S*-Diazeniumdiolates

The only known isolable sulfur diazeniumdiolate is **42**, whose formation was first observed by Davy,[1] although the dipotassium salt is known as Pelouze's salt since he has been given credit for determining its composition.[285] The dianion is also called dinitrososulfite,[286] nitrosohydroxylaminesulfonate,[286] and SULFI/NO.[251] The salts are prepared by passing NO into a basic solution of potassium sulfite,[287] although hydroxylamine-*N*-sulfonate may also serve as a precursor via nitrosation[288] or air oxidation.[289,290] The UV spectrum of the dianion has an absorption maximum at 259 nm in phosphate buffer,[251] but just as with all the other diazeniumdiolates, X-ray structural studies were required to establish the bonding. Structures have been determined for the dipotassium salt[291,292] and its bis-ammonium analog[6,293,294] and are fully consistent with the representation shown in the drawing of **42**.



42

Acid-catalyzed decomposition of SULFI/NO (**42**) has been extensively studied in solutions at various pH values.[295−297] Under all conditions, the reaction leads to the formation of nitrous oxide and sulfate ion without formation of either NO or NO^-, and this has led to a lack of interest in the salts in the biomedical research community. Nevertheless, a recent report that nitrosation of Piloty's acid (**43**) might lead to the formation of NO via an *S*-diazeniumdiolated intermediate (eq 60) may revive interest.[298] The oxidation of thiols to disulfides by reaction with NO is known to be accompanied by formation of nitrous oxide[247] and probably involves *S*-diazeniumdiolated intermediates.



(60)

43

C. Diazeniumdiolates of Other Elements

Reaction of NO with trialkylboranes has been reported to yield O-alkylated *B*-diazeniumdiolates[299,300] which decomposed to nitrous oxide. A variety of cobalt complexes can also be considered as O^2-cobalt derivatives of cobalt diazeniumdiolates,[301,302] although these are looked upon as binuclear complexes containing a bridging hyponitrite ligand.

VI. Conclusion

The diazeniumdiolate grouping occurs in a wide range of compounds and is involved in a broad range of chemistry. Strict adherence to nomenclature protocols makes effective communication difficult, and the chaotic system that has developed is a significant impediment to future research. This grouping of atoms deserves recognition as a valid organic functional group, and it is to be hoped that this presentation will prompt increased interest among chemists for this "orphaned" functional group which has been adopted by the biomedical research community for its NO-donating abilities.

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