

Organic Radical Reactions Associated with Nitrogen Monoxide

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Jens Hartung took his diploma degree in 1987 with Klaus Hafner and his Ph.D. with Bernd Giese in 1990 at the Technische Hochschule Darmstadt, Germany. He spent a postdoctoral year with K. Barry Sharpless at MIT and joined in 1992 the cardiovascular division of Hoechst AG (today Sanofi-Aventis). In 1994 he moved as lecturer to the Bayerische Julius-Maximilians-Universität Würzburg. He completed his habilitation in 1998 and was promoted in 2003 to the first Chair of Organic Chemistry at the Technische Universität Kaiserslautern. His research interests include the chemistry of reactive intermediates, in particular oxygen-centered radicals, transition metal-catalyzed oxidations, the chemistry of vanadium-dependent bromoperoxidases, static and dynamic stereochemistry, heterocyclic synthesis, and marine natural products.

an independent chemical entity. This discovery clearly marked chapter 1 in the chemistry of nitrogen monoxide. Following the beginnings of chemistry as an independent scientific discipline, researchers began to deduce from their experiments numerous fundamental material properties, spectroscopic data, and information concerning the structure and bonding of nitrogen monoxide.⁹ In other laboratories, the transition metal chemistry of 'NO began to evolve.^{10–12} This picture was supplemented by a wealth of reactivity data from gas phase reactions between nitrogen monoxide and organic compounds, such as hydrocarbons and organic free radicals.¹³ The information accumulated from these studies provided a cornerstone for the development of atmospheric models, to address environmental concerns more adequately. It finally was the quest for a transient that induces relaxation of vascular muscle tone (endothelium derived relaxing factor – EDRF) which uncovered an entirely unexpected role of nitrogen monoxide—its property to serve as secondary messenger in physiology.^{14,15} The impact of this discovery was enormous. It stimulated numerous approaches to therapeutically apply nitrogen monoxide regulation and still continues to do so.¹⁶

Nitrogen monoxide constitutes the simplest radical that exists at room temperature as a neat substance. It forms an integral part of interstellar molecular clouds in star-forming regions^{17–19} and is a trace component of several planetary

1. Introduction

...beginning with the solution of brass, on the fourth of June 1772, I first found this remarkable species of air; one effect of which, though it was casually observed by Dr. Hales, he gave but little attention to; and which, as far as I know, has passed altogether unnoticed since his time, insomuch that no name has been given to it...¹

It probably was the natural philosophers in the time between the Renaissance and the Enlightenment who were the first to prepare from *aqua fortis* (HNO₃) and available metals, such as copper, a compound that probably like no other would have one day the potential to exemplify the alliance between all scientific disciplines, including the field of medicine.^{2–8} Approximately a further 150 years had to pass before it became possible to interpret and rationalize results from those early experiments on the basis of material transformations. It was his knowledge gained from pioneering studies on composition of gases¹ which finally allowed Priestley to comprehend *nitrous air* (nitrogen monoxide) as

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atmospheres. The lower atmosphere of Mars, for instance, contains 1.7 ppb of $\cdot\text{NO}$. Concentrations of 5.5 ± 1.5 ppb of $\cdot\text{NO}$ were detected in altitudes of 60 km above Venus' surface.^{20–23} The averaged nitrogen monoxide level of Earth's atmosphere varies depending on geographical site and atmospheric layer. In nonindustrialized areas, for instance above the pacific ocean, the nitrogen monoxide lifetime progressively increases from the boundary layer via the troposphere (averaged nitrogen monoxide lifetime of 57–600 s) to the stratosphere.^{28,24} The largest amounts of atmospheric $\cdot\text{NO}$ originate from gas phase reactions between O_2 and N_2 that are induced by lightning discharges [$(\sim 1.0\text{--}4.2) \times 10^7$ t y^{-1}],²⁵ biomass burning [$(\sim 0.4\text{--}2.5) \times 10^7$ t y^{-1}], and fossil fuel combustion [$(\sim 4.0\text{--}4.6) \times 10^7$ t y^{-1}].^{26–28} Notable quantities of $\cdot\text{NO}$ are furthermore released from marine and freshwater sedimentary environments, fertilized temperate and tropical agricultural fields, tropical savanna, and woodlands, with global soil emissions estimated to be 4.5×10^7 t of $\cdot\text{NO}$ per year.^{26,29–31}

Under physiological conditions,^{32–34} $\cdot\text{NO}$ is formed in mammalian tissue in concentrations that decrease from $\sim 10^{-6}$ M at the site of production to $\sim 10^{-9}$ M at the site of action.³⁵ An increase in cellular nitrogen monoxide level above these values generally is taken as evidence for pathophysiological conditions.^{34,36,37} The mean diffusion path of the radical *in vivo* measures $\sim 10\text{--}30$ times the average diameter of a cell ($\sim 200\text{--}600$ μm).³⁸ This mobility allows $\cdot\text{NO}$ to play an important role in cellular communication, as hormone, neurotransmitter, or paracrine substance.^{3,4,39,40} Nitrogen monoxide also occurs as metabolite in invertebrates,⁴¹ insects,⁴² and plants,^{43–46} where it regulates important functions for maintaining homeostasis in its producing organism.

Due to its significance to many scientific areas, common aspects of nitrogen monoxide chemistry were reviewed in monographs, edited books, and comprehensive articles.⁴⁷ Specialized journals exist for communicating important new developments (e.g., *Nitric Oxide: Biology and Chemistry*). In view of this background, it is surprising that the progress in nitrogen monoxide chemistry associated with hydrocarbon transformations has not been summarized within the past decades in a timely review. To organize synthetic and mechanistic aspects of organic nitrogen monoxide chemistry on the basis of five characteristic free radical elementary reactions, with a focus on hydrocarbon transformations, therefore constitutes the major aim of this article. Emphasis was laid on principles and diversity rather than on completeness, with respect to existing examples related to developments dating from 1970 to late 2008. Earlier aspects were partly summarized in an excellent book chapter dealing with nitrogen oxide chemistry in general.⁴⁸ Important physical properties of nitrogen monoxide necessary for rationalizing its radical reactivity, principle methods of *in situ* generation, and selected aspects dealing with oxyl radical reactions were included for tutorial reasons. For biochemical,^{49–52} medicinal,^{3–5,16} atmospheric,^{28,24} coordination chemical,^{53–58} combustional, and surface scientific aspects of nitrogen monoxide chemistry,^{59–61} the reader is referred to existing specialized literature. The same should be done for reactions resulting in a change of oxidation state at nitrogen (oxidation, reduction)^{2,6–8} and for those dealing with van der Waals-molecule formation,^{62,63} excited state reactions,^{64,65} reactions with polymers,⁶⁶ and transformations starting from reagents that typically are classified as inorganic compounds.^{6–8,67}

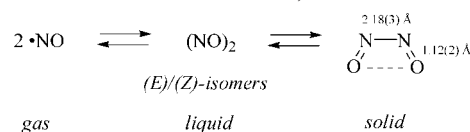
2. General Aspects

Nitrogen monoxide [$\cdot\text{NO}$, IUPAC: oxidonitrogen(\cdot)] forms under standard conditions a colorless paramagnetic gas.^{68,69} The solubility of $\cdot\text{NO}$ in oxygen-free water is small (1.9×10^{-3} mol L^{-1} at 1.013 bar and 25 °C) and independent from proton concentration in the pH range between 2 to 13 due to its low dipole moment (0.53×10^{-30} C m, microwave spectroscopy).⁷⁰ Nitrogen monoxide solubility in organic media is approximately 1 order of magnitude higher, showing a slight increase along the series of solvents EtOH (1.1×10^{-2} mol L^{-1}) < C_6H_6 (1.3×10^{-2} mol L^{-1}) < CCl_4 \sim CH_3CN (1.4×10^{-2} mol L^{-1}) < AcOEt (1.6×10^{-2} mol L^{-1}) < cyclohexane (1.9×10^{-2} mol L^{-1}) < Et_2O (2.3×10^{-2} mol L^{-1}), as extrapolated from vapor pressure measurements.⁷¹

Nitrogen monoxide is heavier than air ($M_r = 30.01$; $\rho_{\text{NO}} = 1.34$ kg m^{-3} compare to $\rho_{\text{air}} = 1.185$ kg m^{-3} ; 25 °C, $p = 1.013$ bar). It condenses at -151.8 °C to a colorless liquid and at -163.6 °C to a colorless solid ($p = 1.013$ bar). The triple point of $\cdot\text{NO}$ is located at 109.49 ± 0.05 K and 219.15 ± 0.01 mbar.^{72,73}

Paramagnetism gradually decreases in going from gaseous via liquid to crystalline nitrogen monoxide.⁷² This change is caused by an association equilibrium (Scheme 1). It is

Scheme 1. State Dependency of Nitrogen Monoxide Aggregation and Presentation of Diagnostic Bond Lengths for the Dimer in the Solid State (for the Role of the Dimeric $\cdot\text{NO}$ in Diazeniumdiolate Formation, See Section 5.3.2)^{72,74,75}

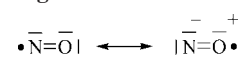


shifted in the gas phase almost entirely to the side of the monomeric radical. The dissociation energy of $(\text{NO})_2$ is small (8.32 ± 0.05 kJ mol^{-1}). Liquid nitrogen monoxide is almost entirely composed of $(\text{NO})_2$ molecules. Its degree of dissociation gradually decreases from $\sim 2.7\%$ at -160 °C to 5% at -150 °C.⁷²

The crystal structure of nitrogen monoxide is composed of $(\text{NO})_2$ molecules that form C_{2v} -symmetric equilateral trapezoids.^{75,76} The N,N bond [$2.18(3)$ Å (-164 °C)] exceeds the mean value for a standard single bond between two planar nitrogens [$1.40(2)$ Å].⁷⁷ The O,O distance [$2.63(3)$ Å] falls short of the sum of associated van der Waals radii [3.04 Å].⁷⁸ According to molecular orbital (MO) theory, the bond order for the connectivity between N and O in nitrogen monoxide is 2.5.^{69,79} This value correlates with experimental data for the N,O distance [1.151 Å via infrared spectroscopy,⁸⁰ $1.12(2)$ Å via X-ray diffraction]⁷⁵ and the observed red shift of IR-absorptions for the N,O-stretching mode in the series of compounds NO^+ (2377 cm^{-1}), $\cdot\text{NO}$ (1875 cm^{-1}), and NO^- (1470 cm^{-1}).^{81,82}

The largest spin density in $\cdot\text{NO}$ (see Scheme 2 for the

Scheme 2. Mesomeric Formula for the Valence Bond Description of Bonding in $\cdot\text{NO}$ ^{68,69,79}



mesomeric formula) is located at nitrogen ($\sim 65\%$; EPR).⁸³ According to theory, the singly occupied molecular orbital (SOMO) has π^* -symmetry, thus classifying $\cdot\text{NO}$ as a π -type radical. The magnetic moment of gaseous and therefore

(i) Combination of a carbon radical with $\cdot\text{NO}$ provides a nitroso compound. This reaction consumes two radical equivalents and therefore requires efficient ways to generate transient radicals in a separate step. In order to avoid additional nitrogen monoxide-consuming side reactions, only those procedures are considered useful which provide carbon radicals under neutral and nonoxidative conditions. In the past years, haloalkanes, xanthates, azo compounds, thiohydroamic acid derivatives, and organocobalt compounds were preferentially used for this purpose.^{108–111} In particular, organocobalt reagents nowadays play an important role in carbon radical-mediated C-nitrosation. The compounds liberate upon visible light photolysis carbon radicals without interfering $^4\Pi$ -excitation of $\cdot\text{NO}$, which otherwise would convert the trapping reagent into a strongly H-atom abstracting intermediate.⁶⁵ In addition to carbon radical trapping, combinations of $\cdot\text{NO}$ with oxygen-centered radicals have attracted notable attention over the past decades. Such reactions are relevant for atmospheric science^{24,112} and an understanding of the complex interplay between reactive nitrogen and oxygen species.^{113,114} A selection of oxyl radical reactions with $\cdot\text{NO}$ therefore was included in this article.

(ii) Nitrogen monoxide is able to homolytically displace carbon and oxygen radicals from suitable precursors, for instance alkanes,¹¹⁵ alkenes,¹¹⁶ dihydropyridines,¹¹⁷ alkyl nitrites,¹¹⁸ or phenols.¹¹⁹ Since strong bonds are broken and weaker ones are formed (Table 2), homolytic substitution associated with nitrogen monoxide requires in most instances elevated temperatures. Radicals generated in the latter step should to be trapped in strongly exothermic reactions, in order to provide an adequate driving force for the overall process.

(iii) Nitrogen monoxide adds to strong nucleophiles, for instance to carbanions or ylides, but not to carbonyl groups ($\text{C}=\text{O}$) or neutral alkenes ($\text{C}=\text{C}$). Earlier reports on successful reactions between $\cdot\text{NO}$ and olefins referred to transformations that were evoked by contaminants, in particular $\cdot\text{NO}_2$. Nitrogen dioxide has a strong affinity for addition to nonactivated olefins, to yield α -substituted nitro compounds.¹²⁰ Transformations of this type are, for reasons clarified above, not covered in this article.

(iv) Pericyclic reactions between nitrogen monoxide and 1,3-dienes afford nitroxyl radicals ($[4 + 1]$ -cycloaddition; chelotropic reactions). Nitroxyl radicals are valuable intermediates for EPR-spectroscopic nitrogen monoxide detection and quantification.¹²¹

(v) Electron transfer converts $\cdot\text{NO}$ into the nitrogen monoxide cation [NO^+ ; oxidonitrogen(+1); oxidation] or NO^- [oxonitrate(1-); reduction].¹²² Both transformations are strongly solvent and pH-dependent. For the $\text{NO}^+/\cdot\text{NO}$ -couple, a standard reduction potential (vs NHE) of $E^\circ = +1.2$ V (in H_2O) was reported.¹²³ Oxidation of $\cdot\text{NO}$ to NO^+ therefore requires drastic conditions, which generally are not relevant for application in modern organic radical chemistry. For reduction of $\cdot\text{NO}$ to NO^- , values of -0.8 ± 0.2 V (formation of $^3\text{NO}^-$; ground state) and -1.7 ± 0.2 V were determined (generation of $^1\text{NO}^-$; excited state; both values refer to H_2O as solvent).^{124–126} Electron transfer provides ions that show a distinctively different chemical behavior in comparison to $\cdot\text{NO}$. Examples dealing with redox chemistry in this article (section 5.5) therefore were restricted to oxidations, in which the role of $\cdot\text{NO}$ for selective C-radical transformation was unambiguously clarified.

The elementary reactions summarized in sections i–v (*vide supra*) served as the basis for development of sophisticated qualitative and quantitative nitrogen monoxide analysis in solution.^{127,128} Trapping with appropriate 1,3-dienes and thus nitroxyl radical formation (pericyclic reaction) allows EPR-spectroscopic detection of $\cdot\text{NO}$ in concentrations down to $\sim 10^{-2}$ μM .^{121,129} More specialized electrochemical techniques using, for instance, modified carbon fiber electrodes¹³⁰ or porphyrinic microsensors (electron transfer reactions)^{131,132} are adequate for nitrogen monoxide analysis from the micromolar range to the ~ 10 nM level.¹³³ Analysis in the range of 10–0.6 nM of $\cdot\text{NO}$ is feasible via spectrofluorimetric analysis of, e.g., [1H]-naphthotriazole-6,8-disulfonic acid, which is formed in a selective reaction between $\cdot\text{NO}/\text{O}_2$ and 5,6-diamino-1,3-naphthalene disulfonic acid.¹³⁴

4. Nitrogen Monoxide Generation

Nitrogen monoxide is an endergonic compound ($\Delta G^\circ_f = +86.9$ kJ mol⁻¹) that is formed from the elements, for instance within plasma channels of lightning discharges ($\sim 30\,000$ K) or as side product from fossil fuel combustion in an atmosphere of N_2 and O_2 .^{25,28} In vivo, $\cdot\text{NO}$ is generated via enzymatic metabolism of L-arginine,^{135–139} via nitrite reduction,⁴⁶ or from so-called exogenic $\cdot\text{NO}$ donors,^{140–142} such as iron(III) nitrosyl complexes,^{143,144} furoxans,^{145–147} sydnone imines,^{148,149} or alkyl nitrates.¹⁵⁰ Most of the reagents are not suited for nitrogen monoxide generation in organic synthesis, thus requiring alternatives.

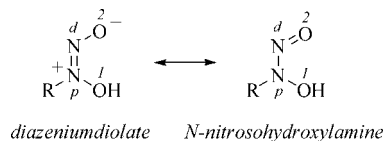
Nitrogen monoxide is a commercial product that is sold in gas cylinders. Depending on age and initial degree of purity, commercial $\cdot\text{NO}$ generally contains $\cdot\text{NO}_2$, N_2O , N_2O_3 , and N_2 as contaminants, resulting from disproportionation and subsequent redox reactions.^{151–153} In particular, $\cdot\text{NO}_2$, which is considerably more reactive toward the majority of organic substrates, needs to be thoroughly removed, e.g., by low temperature distillation (<100 K), chromatography on SiO_2 as a stationary phase at <200 K for absorbing oxides of nitrogen that are less volatile than $\cdot\text{NO}$, or passing commercial $\cdot\text{NO}$ through beads of high surface area KOH.^{10,154–157} Results from experiments using nitrogen dioxide-contaminated $\cdot\text{NO}$ led to notable confusion about nitrogen monoxide reactivity toward, e.g., olefins and conjugated dienes (see sections 5.3 and 5.4). Since $\cdot\text{NO}$ reacts instantaneously with O_2 to $\cdot\text{NO}_2$, exclusion of air is a prerequisite for maintaining a high level of nitrogen monoxide purity throughout a reaction.^{158,159}

Purified $\cdot\text{NO}$ is added via a gas buret as neat compound to reaction mixtures (standard procedure) or after dilution with an appropriate inert gas (e.g., CO_2 for carbon radical trapping in the absence of amines).¹⁶⁰ If a synthesis or a mechanistic study requires continuous release of the reagent in low concentration, either in organic or aqueous solution, established photochemical or thermally induced procedures need to be applied (*vide infra*). Nitrogen monoxide generation in aqueous solutions requires the use of a liquid/liquid two-phase system with the organic transformation occurring in the non-water miscible phase.

4.1. From Diazeniumdiolates

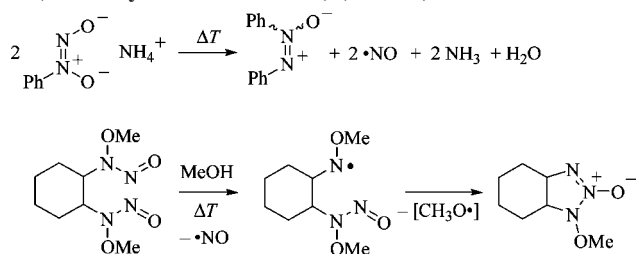
The rate of nitrogen monoxide liberation from diazeniumdiolates (*N*-nitrosohydroxylamine, Scheme 5) depends on the nature of the proximal nitrogen (N^p)- and the O^1 -bound

Scheme 5. Mesomeric Formula and Heteroatom Notation for the Diazeniumdiolate/Nitrosohydroxylamine Structure (p = proximal, d = distal)¹⁶¹

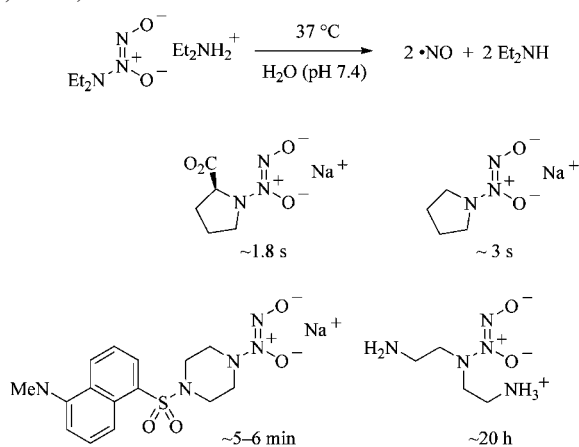


substituent, as well as reaction parameters (Schemes 6 and 7).¹⁶¹ Enzyme-catalyzed oxidation, for instance, furnishes

Scheme 6. Generation of Nitrogen Monoxide via Thermal Decomposition of Cupferron (Top) and a Bis(*l*-O-methyldiazeniumdiolate) (Bottom)^{164,161}



Scheme 7. Decomposition of *N*-Diazeniumdiolates in Aqueous Solutions (Figures Refer to Half Lifetimes at pH 7.4, 37 °C)^{161,165–168}



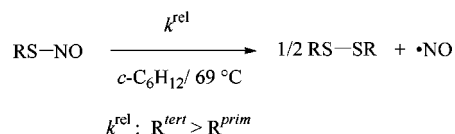
nitrogen monoxide from *N*-aryl-substituted diazeniumdiolates (e.g., Cupferron), at room temperature in aqueous media, while the reaction in organic media in the absence of peroxidases requires notable thermal activation.^{162,163} The activation energy for nitrogen monoxide formation may be lowered by alkyl substitution at O¹. Cyclohex-1,2-diyl-bis(*l*-methyldiazeniumdiolate), for instance, reacts in methanol solution to furnish a 4,5-dihydro-1,2,3-triazole (Scheme 6). The yield of decomposition product thereby gradually increases with the temperature from traces (20 °C) to ~76–92% (boiling point of methanol).

N-Diazeniumdiolates (Drago complexes)¹⁶⁵ decompose in neutral to weakly acidic aqueous solutions via first order kinetics. Half-life times depend on the substitution pattern and vary from seconds to minutes to hours (Scheme 7).^{161,166–168} Diazeniumdiolates were prepared from cross-linked polyethyleneimine. Films, coated microspheres, gels, powders, and moldable resins were formed from this material, thus allowing sustained nitrogen monoxide release for ~5 weeks at 37 °C in buffered solution (pH 7.4).¹⁶⁹

4.2. From Nitrosothiols

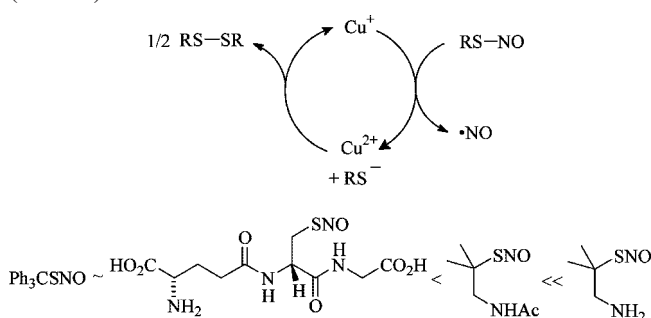
Nitrosothiols^{170,171} selectively decompose via S,N homolysis upon photoexcitation (~350 or ~550 nm) or thermal activation, for instance in boiling cyclohexane under anaerobic conditions.^{172,173} The rate of nitrosothiol decomposition thereby increases along the series of substituents at sulfur from phenyl via primary to tertiary alkyl, thus reflecting a combination of polar and strain effects (Scheme 8).^{174,175}

Scheme 8. Nitrogen Monoxide Generation via Thermally Induced S,N Homolysis of *S*-Nitrosothiols ($R^{prim} = n\text{-C}_6\text{H}_{13}$, PhCH_2 ; $R^{tert} = \text{Ph}_3\text{C}$, Me_3C)¹⁷⁴



In aqueous media, nitrogen monoxide release from nitrosothiols is efficiently catalyzed by Cu(I) salts. The rate of S,N homolysis correlates with the ability of the nitrosothiol to bind to Cu(I). β -Amino-substituted nitrosothiols are thus considerably faster decomposed than *N*-acylated or sterically demanding derivatives thereof (Scheme 9).¹⁷⁶

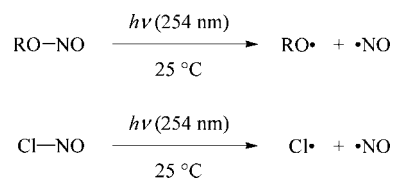
Scheme 9. Key Steps for Nitrogen Monoxide Liberation via Cu(I)-Catalyzed Nitrosothiol Cleavage (Top) and Stability Progression of Selected Nitrosothiols under Such Conditions (Bottom)¹⁷⁶



4.3. From Alkyl Nitrites and Nitrosyl Chloride

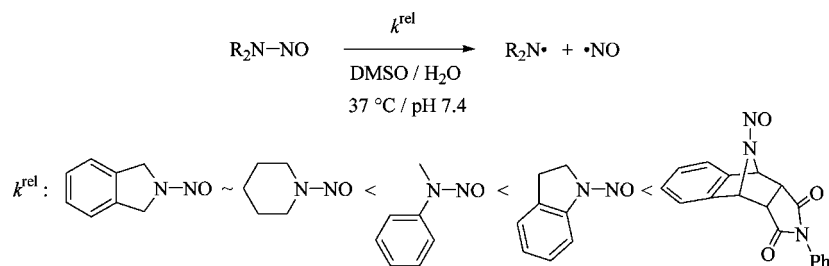
UV-excited alkyl nitrites (Scheme 10) fragment into •NO

Scheme 10. Photochemical N,O Homolysis for Nitrogen Monoxide Generation from Alkyl Nitrites and Nitrosyl Chloride^{177,180}



and alkoxy radicals.¹⁷⁷ Since alkoxy radical trapping in organic media occurs with rate constants that significantly exceed the majority of nitrogen monoxide radical reactions,⁹³ alkyl nitrite photolysis constitutes a valuable method for nitrogen monoxide generation in mechanistic or spectroscopic investigations.^{178–183} Although alkyl nitrites exhibit absorptions in the range of ~320–380 nm caused by $n \rightarrow \pi^*$ transitions,¹⁸⁴ the use of shorter wavelength UV-light for achieving effective N,O homolysis via $\pi \rightarrow \pi^*$ excitation generally is recommended.¹⁷⁷

Nitrosyl chloride (NOCl) forms at ambient temperature a yellowish orange gas that may be condensed to a reddish

Scheme 11. Structural Dependence of Relative Reactivity for N,N-Bond Homolysis for Nitrogen Monoxide Generation from N-Nitrosamines^{104,187}


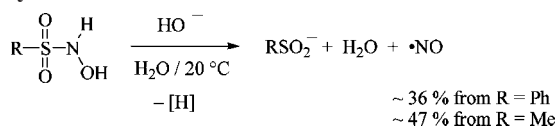
liquid (bp -6.4°C) or a red crystalline solid (mp -59.6°C). It serves as a useful alternative to alkyl nitrites for photolytic nitrogen monoxide generation.¹⁸⁵ Nitrosyl chloride is commercially available and fragments upon visible light photoexcitation into a chlorine atom and $\cdot\text{NO}$ (Scheme 10). The inherent high reactivity of $\text{Cl}\cdot$ in combination with its low selectivity for distinguishing between primary ($k^{\text{rel}} = 1.0$), secondary (3.6), and tertiary (4.2) aliphatic C,H bonds,¹⁸⁶ however, restricts application of the reagent to more specialized instances.

4.4. From N-Nitroso Compounds

N-Nitrosamines decompose in thermally induced reactions into aminyl radicals and $\cdot\text{NO}$ (Scheme 11).^{104,187} A general guideline states that the rate of nitrogen monoxide liberation gradually increases as the barrier to rotation about the N,N bond decreases. This effect was correlated with a decrease of N-nitroso resonance, thus facilitating homolytic breaking of the N,NO bond.

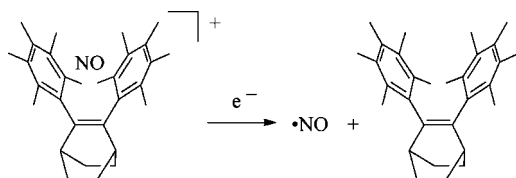
4.5. From Miscellaneous Sources

Sulfhydroxamic acids [Scheme 12, R = Ph or CH_3 (e.g.)]

Scheme 12. Nitrogen Monoxide Generation from Sulfhydroxamic Acids¹⁹⁰


undergo heterolysis of the S,N bond in aqueous media to leave a sulfinate anion and HNO. Arylsulfhydroxamic acids require stronger basic conditions, whereas their aliphatic congeners decompose at physiological pH.^{188,189} It is assumed that HNO release in the initial step is followed by one electron oxidation, to provide $\cdot\text{NO}$ in yields between 36 and 47% as determined via an $\cdot\text{NO}$ -electrode.¹⁹⁰

Adducts composed of radical cations of sterically demanding substituted 1,2-diarylethenes or calix[4]arenes and nitrogen monoxide quantitatively dissociate into $\cdot\text{NO}$ and the organic fragment upon electrochemical reduction (Scheme 13).¹⁹¹⁻¹⁹³ Binding is reversible upon olefin oxidation and

Scheme 13. Liberation of π -Trapped $\cdot\text{NO}$ via Electrochemical Reduction¹⁹³


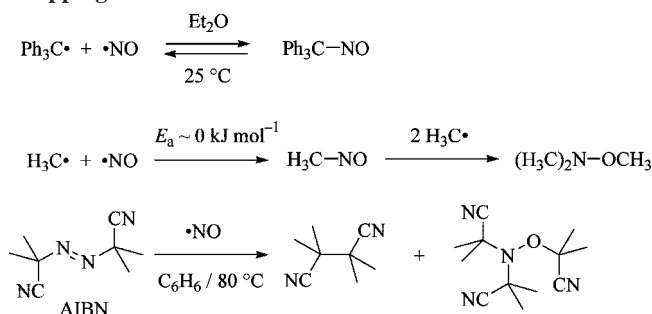
nitrogen monoxide loading of the radical cation.

5. Elementary Reactions and Their Application in Organic Transformations

5.1. Combination

5.1.1. Alkyl Radical Trapping

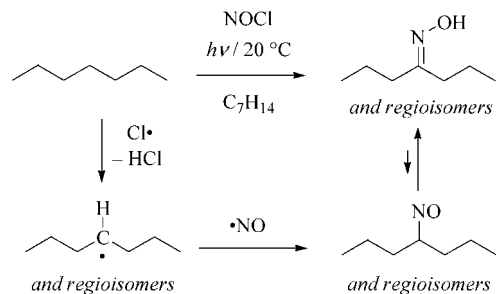
Combinations of alkyl radicals with $\cdot\text{NO}$ occur close to the diffusion limit ($k \sim 10^{10} \text{ M}^{-1} \text{ s}^{-1}$).¹⁹⁴ A transient or prevailing blue color is diagnostic for C-nitroso compound formation, whereas a gradual decolorization is indicative either of nitroso compound dimerization or tautomerization to the corresponding oxime. Since homocoupling between two molecules of $\cdot\text{NO}$ at 25°C is inherently slow, C-nitrosation of the carbon radical in nitrogen monoxide-containing organic solutions ($c_{\text{NO}} \sim 10^{-3} \text{ M}$) becomes the major radical consuming process, if the stationary alkyl radical concentration in solution remains below $\sim 10^{-4} \text{ M}$. If stabilized radicals, for instance the trityl radical, are subjected to nitrogen monoxide trapping, combinations may become reversible (Scheme 14, top).¹⁹⁵ Since C-nitroso

Scheme 14. Formation of C-Nitroso Compounds and N,N,O-Substituted Hydroxylamines from Alkyl Radical Trapping with $\cdot\text{NO}$ ^{160,195,196,198,199}


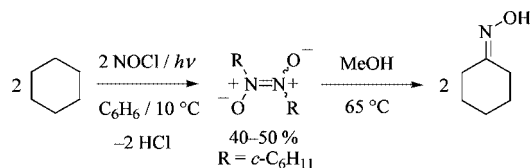
compounds are excellent radical traps themselves, N,N,O-substituted hydroxylamines are frequently obtained as major products, particularly if carbon radical precursors, e.g. $\text{Hg}(\text{CH}_3)_2$, $\text{H}_3\text{CN}=\text{NCH}_3$, or AIBN (α,α -azobisisobutyronitrile) are used in notable excess (Scheme 14, center and bottom).¹⁹⁶⁻¹⁹⁹

For technical application of alkyl radical generation and subsequent C-nitrosation, NOCl often is used as a combined chlorine atom and nitrogen monoxide source. Since the selectivity of C,H-abstraction by the chlorine atom is inherently low,¹⁸⁶ this method in most instances is restricted to functionalization of symmetric compounds (Scheme 15),^{185,200} for instance as the key step of the Toray process, i.e. the photonitrosation of cyclohexane (Scheme 16).²⁰¹ This sequence provides cyclohexanone oxime as starting material for ϵ -caprolactame and thus polyamide fiber production. Mechanistic studies indicated that NOCl can be replaced in

Scheme 15. C,H-Activation and Subsequent C-Radical Trapping in the Synthesis of Dipropylketoxime from Heptane and NOCl^{185,200}

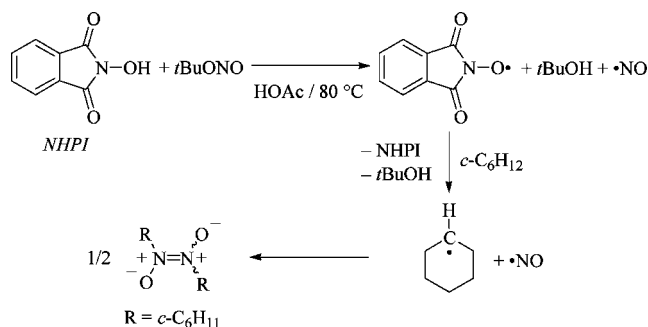


Scheme 16. Synthesis of the Nitrosocyclohexane Dimer and Its Transformation into Cyclohexanone Oxime^{201,202}



this process by a 8/1 (*v/v*) $\bullet\text{NO}/\text{Cl}_2$ mixture. In nonpolar media, for instance in benzene solution, the nitrosocyclohexane dimer is obtained as the major product. It may be recrystallized without decomposition. Tautomerization requires the use of polar protic solvents, e.g. MeOH, and elevated temperatures (~ 60 °C) in order to effectively occur.²⁰² An increase in yield of the nitrosocyclohexane dimer to 64% was obtained by replacing NOCl with a combination of *tert*-butyl nitrite and *N*-hydroxyphthalimide (NHPI) in hot acetic acid (80 °C). The mechanism of the latter reaction seems to closely follow that of the general photonitrosation pathway (Scheme 17), with the Cl-atom being replaced as

Scheme 17. Proposed Mechanism of Nitrosocyclohexane Dimer Formation from *tert*-Butyl Nitrite and *N*-Hydroxyphthalimide (NHPI; for the Structural Formula See Scheme 28)²⁰³



H-atom abstracting intermediate by the phthalimidyl-*N*-oxyl radical.²⁰³

The advent of alkylbis(dimethylglyoximate)(pyridine)cobalt(III) complexes [alkylcobaloximes(III), $\text{RCo}(\text{dmgH})_2\text{py}$]²⁰⁴ as selective carbon radical source^{205,206} constituted a significant improvement for homolytic C-nitrosation (Table 3).^{207,208} Primary and secondary alkylcobaloximes are accessible in considerable structural diversity from the highly nucleophilic cobaloxime(I), upon treatment with epoxides, alkenes, alkyl halides, or -sulfonates according to well established procedures.¹¹¹ While allyl- and benzylcobaloximes react at ~ 20 °C spontaneously with $\bullet\text{NO}$, photoactivation with an intense visible light bulb is necessary for C-nitrosation starting from primary and secondary alkyl

Table 3. Synthesis of Oximes from Alkylcobaloximes(III) [$\text{RCo}(\text{dmgH})_2\text{py}$] and $\bullet\text{NO}$ ²⁰⁸

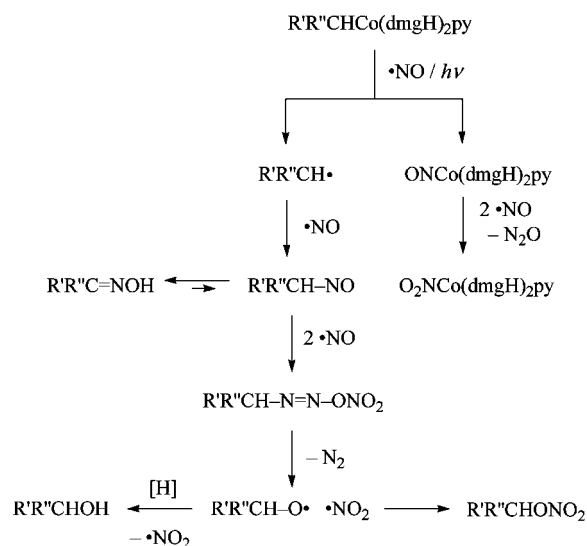
entry	R'	R''	R'R''C=NOH/%	R'R''CHONO2/%	R'R''CHOH/%
1	CO ₂ Et	Et	96	<i>a</i>	<i>a</i>
2	CO ₂ CH ₂ Ph	Me	87	<i>a</i>	<i>a</i>
3	Ph	Me	74 ^b	14	6
3	CH ₂ CH ₂ Ph	H	<i>a</i>	52	12
4	(CH ₂) ₃ Ph	H	<i>a</i>	55	28

^a Not detected. ^b Additional product: 2% of benzaldehyde.

derivatives (Table 3). Although the existing reports describe oximes as sole products, it is expected on the basis of mechanistic studies that nitroso compounds are formed as initial products.²⁰⁹ The cobaloxime(II), which is left from the radical generating step, is converted by $\bullet\text{NO}$ into nitrocobaloxime. Reduction of this material in an atmosphere of hydrogen or with a suitable hydride donor affords hydridocobaloxime(III) or the derived cobaloxime(I) nucleophile, depending on the pH of the solution. Addition of $\text{HCo}(\text{dmgH})_2\text{py}$ to an olefin or substituting an appropriate leaving group of an alkylating reagent with the cobaloxime(I) anion allows use of the cobalt fragment either for a second reaction cycle (catalysis) or in another reaction.¹¹¹

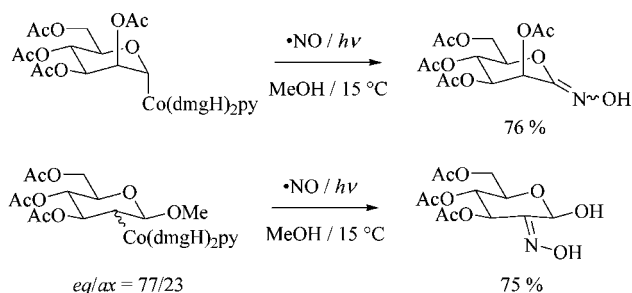
Whereas α -acceptor substituted alkyl radicals selectively afford oximes in their reactions with $\bullet\text{NO}$, C-nitrosation of alkyl- or aryl-substituted carbon radicals gives notable amounts of alcohols and nitrates. These selectivities were attributed to differences in rate constants of oxime formation from the nitroso compound. Slow tautomerizations favor nitroso compound accumulation and thus increase the rate of diazonitrate formation via nitrogen monoxide addition. Diazonitrates, in turn, decompose via an alkoxy radical pathway into alcohols and nitrates (Scheme 18).²⁰⁸

Scheme 18. Proposed Mechanism for Product Formation from Alkylcobaloximes(III) [$\text{R}'\text{R}''\text{CHCo}(\text{dmgH})_2\text{py}$] and $\bullet\text{NO}$ ^{205,206,208}



Carbohydrate-derived cobaloximes provide sugar oximes in ~75% yield, if photolyzed in a saturated solution of $\cdot\text{NO}$ in MeOH. The compounds were applied in short and efficient deoxyaminomonosaccharide syntheses (Scheme 19).^{210,211}

Scheme 19. Synthesis of Carbohydrate-Derived Oximes from Cobaloximes and $\cdot\text{NO}$ ²¹¹



Reduction of chlorocobaloxime(III) [$\text{ClCo}(\text{dmgH})_2\text{py}$] in alcoholic media affords derived hydridocobaloxime, which adds to aryl- or acceptor-substituted π -bonds with Markownikow-type regioselectivity.¹¹¹ Visible light photolysis of in situ prepared, e.g., secondary benzylic cobaloximes in the presence of $\cdot\text{NO}$ furnishes substituted acetophenone oximes (Table 4).²¹² The overall sequence corresponds to HNO

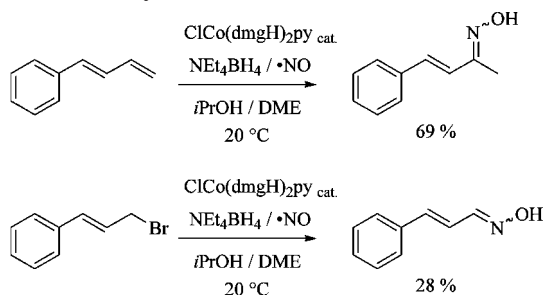
Table 4. Formation of Substituted Acetophenone Oximes via Cobaloxime-Catalyzed Nitrosation of Styrenes²¹²

entry	R	yield/%
1	<i>p</i> -OCH ₃	55
2	<i>o</i> -CH ₃	37
3	<i>p</i> -CH ₃	68
4	H	68
5	<i>o</i> -Cl	68
6	<i>p</i> -Cl	69
7	<i>m</i> -NO ₂	41

addition across an olefinic π -bond, which is not feasible in the absence of cobaloxime catalysis.

Nitrosation of 1-phenylbuta-1,3-diene and cinnamyl bromide using chlorocobaloxime catalysis under reductive conditions provides conjugated oximes in 28–69% yield (Scheme 20).²¹²

Scheme 20. Regio- and Chemoselectivity in Cobaloxime-Catalyzed Nitrosations²¹²

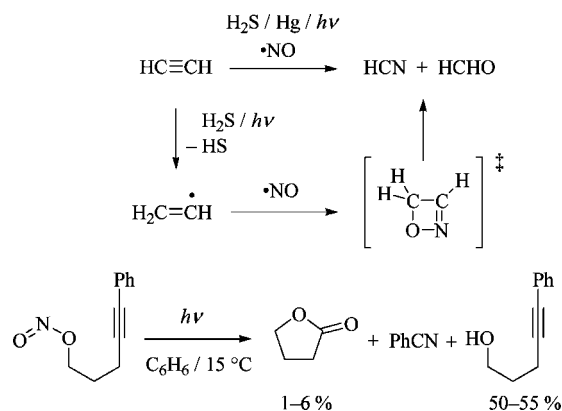


5.1.2. Vinyl Radical Trapping

The rate constant for vinyl radical combination with $\cdot\text{NO}$ is $9.6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ at 20 °C.²¹³ The reaction furnishes an adduct that rearranges into a cyclic intermediate and subse-

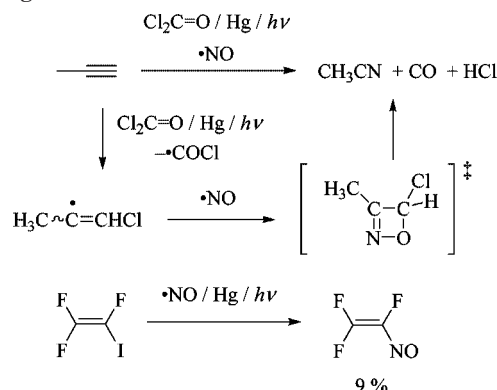
quently decomposes into formaldehyde and HCN (Scheme 21, top).^{213,214} In a similar fashion, photolysis of 5-phenyl-

Scheme 21. Triple Bond Fragmentation in Nitrogen Monoxide-Mediated Reactions^{213–215}



pent-4-en-1-yl nitrite affords γ -butyrolactone and benzonitrile in minor yields (Scheme 21, bottom). The vinyl radical intermediate in this sequence is considered to originate from 5-*exo*-dig ring closure of an alkinoxyl radical (not shown).²¹⁵ Formation of the main product, i.e. 5-phenylpent-4-en-1-ol, was attributed to H-atom trapping of the intermediate 5-phenylpent-4-en-1-oxyl radical. Propyne undergoes in a similar way breaking of the C,C-triple bond to provide acetonitrile, carbon monoxide, and HCl, if treated with phosgene and $\cdot\text{NO}$ (Scheme 22).²¹⁶ On the other hand, no

Scheme 22. Selectivity in the Chemistry of Vinyl Radical Trapping with $\cdot\text{NO}$ ^{216,217}



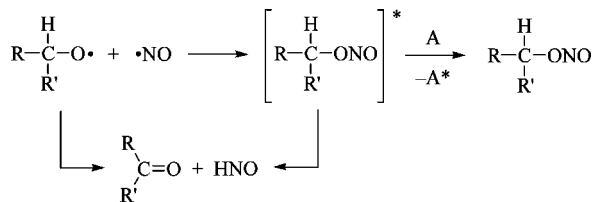
products of C,C fragmentation were reported for the reaction between $\cdot\text{NO}$ and the perfluorovinyl radical. The low mass balance of the latter reaction, however, requires attention.²¹⁷

5.1.3. Oxyl Radical Trapping

Alkoxy radicals react with $\cdot\text{NO}$ to afford alkyl nitrites (combination) and carbonyl compounds (H-atom abstraction).²¹⁸ Products of homolytic displacement originate either from direct H-atom abstraction or fragmentation of a thermally excited alkyl nitrite (Scheme 23). The partitioning factor, i.e. the ratio between H-atom abstraction and combination scaled by the number of abstractable H-atoms, remained within the series of radicals $\text{MeO}\cdot$ via $\text{EtO}\cdot$ to $i\text{PrO}\cdot$ approximately constant (~ 0.16) and was independent from the reaction temperature.²¹⁸ Activation energies gradually decreased from primary via secondary to tertiary alkoxy radicals from -0.6 to -3 kJ mol^{-1} .^{219–221} The overall rates for alkoxy radical reaction with $\cdot\text{NO}$ (combination and

H-atom abstraction taken together) varied only marginally with the size of the alkyl residue ($k \sim 2.0 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$).²²⁰ Aryloxy radical reactions with $\bullet\text{NO}$ ($k \sim 2.0 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) were approximately 1 order of magnitude slower than those with their alkoxy congeners. Although kinetics of

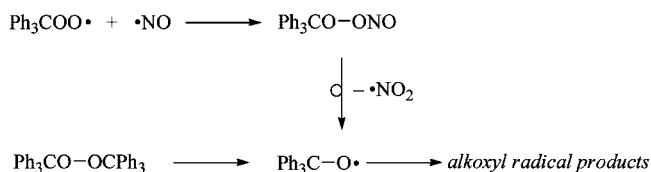
Scheme 23. Schematic Presentation of Alkoxy Radical Combination with $\bullet\text{NO}$ and Competing H-Atom Abstraction (R and R' = H, CH₃, C₂H₅; A = Collision Partner; * Marks an Excited State)^{218,220}



phenoxy radical²²² and tyrosyl radical²²³ trapping with $\bullet\text{NO}$ (not shown) were investigated in detail due to their relevance to atmospheric science and *in vivo* 3-nitrotyrosine formation, details of transformations that follow the radical combination are not yet fully understood.²²⁴

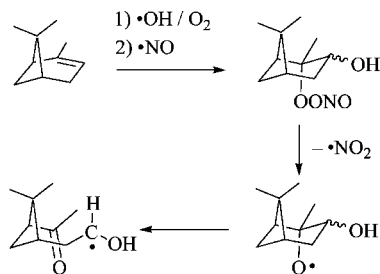
Reactions between peroxy radicals and $\bullet\text{NO}$ afford peroxy nitrites, which undergo fast rearrangement into alkyl nitrates (not shown), or fragment into $\bullet\text{NO}_2$ and alkoxy radicals (Scheme 24).^{93,225–227} Alkylperoxy radicals are formed in

Scheme 24. Alkoxy Radical Generation from a Peroxy Radical and $\bullet\text{NO}$ in Comparison to Its Independent Generation from a Peroxide Source^{93,225}



large amounts from addition of atmospheric hydroxyl radicals and molecular oxygen to terpenes, for instance (+)- α -pinene or isoprene. These olefins are released in vast quantities into the lower atmosphere from plants in the course of their vegetation processes (Scheme 25).²⁴ Combination of peroxy

Scheme 25. Initial Steps of Nitrogen Monoxide-Assisted Atmospheric (+)- α -Pinene Degradation²⁴



and alkoxy radical chemistry with nitrogen monoxide reactivity furnishes low molecular weight water-soluble products from volatile nonmethane organic compounds (often referred to as NMOCs) and therefore constitutes an integral part of the atmospheric carbon cycle.²⁴

5.2. Homolytic Substitution

5.2.1. Carbon Radical Substitution

Homolytic substitution of alkyl or acyl radicals by $\bullet\text{NO}$ is endothermic by 155–210 kJ mol⁻¹ because C(sp³),H-bond

dissociation energies (BDEs) of attacked organic compounds are not compensated by the enthalpic contribution from the newly formed H,N bond in HNO [nitroxyl, nitrosyl hydride, hydrogen oxynitrate (IUPAC), monomeric hyponitrous acid] (Tables 2 and 5). In view of small positive entropy effects,

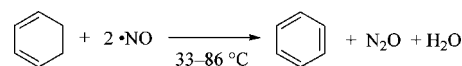
Table 5. Reaction Enthalpies and Activation Energies Associated with Nitrogen Monoxide-Mediated H-Atom Abstraction from Hydrocarbons, Dimethyl Ether, and Acetaldehyde^{228–230}

R-H	$\Delta_R H / (\text{kJ mol}^{-1})$	$E_a / (\text{kJ mol}^{-1})$
C ₂ H ₆	210	218
nC ₅ H ₁₂	197	218
iC ₅ H ₁₂	193	189
neoC ₅ H ₁₂	202	202
(H ₃ C) ₂ O	185	181
CH ₃ CHO	155	164

the rate of H-atom abstraction by $\bullet\text{NO}$, which is insignificant at 20 °C, is accelerated as the temperature is raised to pyrolysis conditions ($T > 500$ °C). These findings were used to explain an inhibitory effect of $\bullet\text{NO}$ in autocatalytic hydrocarbon transformations at elevated temperatures.^{116,228–231}

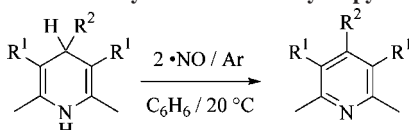
NO is able to abstract allylic H-atoms from olefins on heating due to inherent low C(sp³),H bond dissociation energy of such connectivities ($345 \pm 8 \text{ kJ mol}^{-1}$ for pent-1-ene).^{98,232} Lower reaction enthalpies of, e.g., 149 kJ mol⁻¹ for homolytic displacement of a stabilized allylic radical upon H-atom abstraction from pent-1-ene with $\bullet\text{NO}$ are partly reflected in smaller activation energies of the process. This reactivity was correlated with the propensity of $\bullet\text{NO}$ to induce geometrical and positional isomerization of, for instance, pentenes in the temperature range between ~ 115 and 335 °C. The enhanced reactivity of cyclohexa-1,3-diene for dehydrogenation using $\bullet\text{NO}$ as reagent is similarly explicable on the basis of the thermochemical parameter. C(sp³),H homolysis from the diene (BDE = 311 kJ mol⁻¹) furnishes a highly stabilized cyclic pentadienyl radical. The latter intermediate is rapidly converted under such conditions into benzene, thus providing a notable driving force for the two sequential homolytic displacements (Scheme 26). The fate of HNO was not entirely clarified

Scheme 26. Stoichiometry of Cyclohexa-1,3-diene Dehydrogenation with $\bullet\text{NO}$ ¹¹⁶



because N₂O and H₂O balances remained erratic. The hydrocarbon mass balance in the series of experiments was satisfactory.¹¹⁶

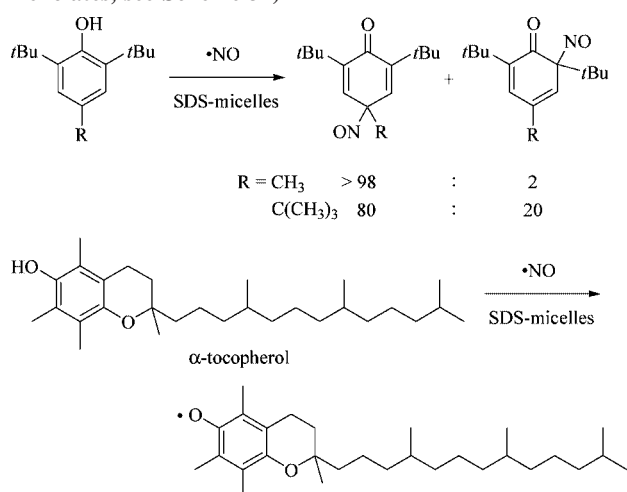
1,4-Dihydropyridines are almost quantitatively dehydrogenated, if treated at 20 °C in benzene solution with $\bullet\text{NO}$. The effectiveness of the process is guided by groups attached to position 4, leading to a gradual decrease of rates along the series of 4-substituents H > Ph > Me \sim *i*Pr (Table 6).²³³ Since N,H bond strengths in Hantzsch-type dihydropyridines ($361\text{--}388 \text{ kJ mol}^{-1}$)²³⁴ significantly exceed C(sp³),H bond dissociation energies of cyclohexa-1,4-diene ($\sim 318 \text{ kJ mol}^{-1}$),²³⁵ it is expected that $\bullet\text{NO}$ preferentially abstracts the H-atom attached at C4, which is followed by N,H-homolysis and pyridine formation.

Table 6. Formation of Pyridines from Dihydropyridines^{233,235}


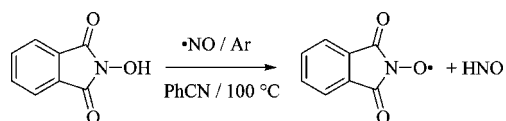
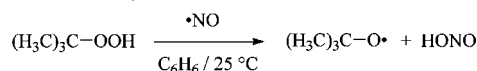
entry	R ¹	R ²	equiv of [•] NO	solvent	yield/%
1	CO ₂ Et	H	2	C ₆ H ₆	98
2	CO ₂ Et	CH ₃	13	C ₆ H ₆	91
3	CO ₂ Et	CH(CH ₃) ₂	13	C ₆ H ₆	99
4	CO ₂ Et	Ph	4	C ₆ H ₆	95
5	CN	CH(CH ₃) ₂	3	CH ₃ CN	98

5.2.2. Oxyl Radical Substitution

Donor-substituted phenols liberate aryloxy radicals, if treated with [•]NO, for instance in sodium dodecyl sulfate micelles, as evident from EPR-spectroscopic detection of the α -tocopherol-derived oxyl-radical or formation of nitroso-substituted cyclohexadienones (Scheme 27).^{119,236}

Scheme 27. Chemistry of Phenols in the Presence of [•]NO (SDS = Sodium Dodecyl Sulfate; for Reaction of [•]NO with Phenolates, see Scheme 34)^{119,236}

Nitrogen monoxide reacts rapidly with *tert*-butyl hydroperoxide (TBHP) at 25 °C (Scheme 28, top). The reaction

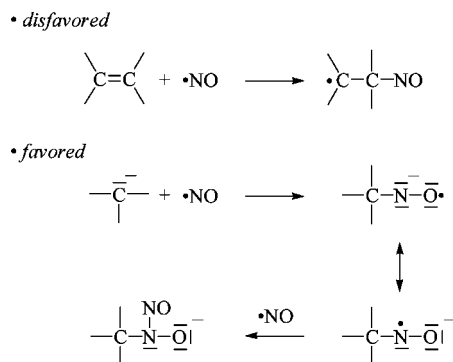
Scheme 28. Oxyl Radical Generation from *tert*-Butyl Hydroperoxide (TBHP) (Top) and *N*-Hydroxyphthalimide (Bottom) and [•]NO (for Application of NHPI in C,H Activation Prior to NO-Mediated C-Radical Oxidation, Refer to Section 5.5)^{237,238}

was interpreted in terms of *tert*-butoxyl radical generation, as evident from control experiments starting from *m*-chloroperbenzoic acid and *tert*-butyl hypochlorite.²³⁷ The former sequence thus poses a useful method for *t*BuO[•] formation under nonphotolytic conditions at ambient temperatures. Substitution of the phthalimidyl-*N*-oxyl (PINO) radical from *N*-hydroxyphthalimide (NHPI) with [•]NO requires elevated temperatures, for example, 100 °C in solutions of PhCN, in order to significantly occur (Scheme 28,

bottom).²³⁸ The PINO radical is an important intermediate for aliphatic C,H-functionalization.

5.3. Addition

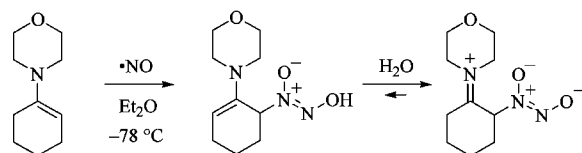
Nitrogen monoxide does not add under standard conditions to aryl- or alkyl-substituted olefins because the energy gained from the newly formed C,NO bond (Table 2) neither balances the π -bond dissociation energy (247–272 kJ mol⁻¹)^{239,240} nor compensates the unfavorable reaction entropy. Nitrogen monoxide therefore can be stored in neat olefins of the type mentioned above without additions taking place.²⁴¹ Earlier reports on [•]NO additions to nonactivated olefins referred to transformations that were initiated by contaminants, in particular [•]NO₂.¹²⁰ Enamines,²⁴² aci-nitronates,²⁴³ σ -bound organometallics,²⁴⁴ ylides,²⁴⁵ or delocalized π -type carbanions,²⁴⁶ on the other hand, are strong carbon nucleophiles that readily add [•]NO. This step furnishes nitroxyl radicals which exhibit sufficient lifetime to be converted by a second nitrogen monoxide molecule into an alkyldiazoniumdiolate (Scheme 29). This sequence is the preferred mode of nitrogen

Scheme 29. Intermediates Associated with Nitrogen Monoxide Addition to Olefins (Top) and Carbon Nucleophiles (Bottom)

monoxide addition to strongly nucleophilic reagents, as long as nitroxyl radical fragmentation remains insignificant. The mechanism is furthermore able to explain major product formation from amines^{161,165} and alkoxides.²⁴⁷ Starting from straight chain secondary amines, *N*-diazoniumdiolate salts are obtained in synthetically useful yields, while nitrogen monoxide addition to primary alkoxides provides labile *O*-bound diazeniumdiolates that decompose into an aldehyde, nitrous oxide, and hydroxide in a Cannizzaro-type reaction (not shown).

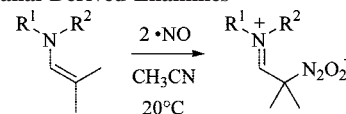
5.3.1. Formation of Nitrogen Carbon Bonds

Enamines are strong carbon nucleophiles that add 2 equiv of [•]NO in etheral solutions at –78 °C in exothermic reactions, to provide alkyldiazoniumdiolates. Tautomerization of the *N*–OH form into a corresponding 2-fold zwitterion may be slow in polar aprotic solvents (e.g., CD₃CN) but can occur with a notable rate in H₂O (Scheme 30). The generality of

Scheme 30. Conversion of a Morpholine-Derived Enamine into a Diazoniumdiolate²⁴²

the sequence was probed by studying iminium salt formation (33–75%) from a series of 2-methylpropanal-derived enamines (Table 7).²⁴²

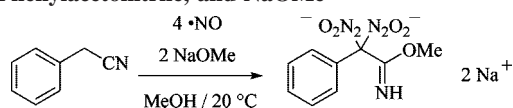
Table 7. Synthesis of Diazeniumdiolate Iminium Betaines from 2-Methylpropanal-Derived Enamines²⁴²



entry	R ¹	R ²	yield/%
1	–(CH ₂) ₂ –O–(CH ₂) ₂ –		41
2	–(CH ₂) ₅ –		45
3	–(CH ₂) ₄ –		60
4	C ₆ H ₅	CH ₃	33
5	<i>p</i> -H ₃ C–C ₆ H ₄	CH ₃	33
6	<i>p</i> -H ₃ CO–C ₆ H ₄	CH ₃	75

Nitrogen monoxide adds to benzylic anions, formed for instance *in situ* via NaOMe-mediated deprotonation of phenylacetonitrile (Scheme 31). The sequence affords bis-

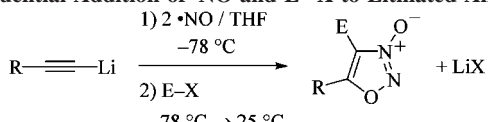
Scheme 31. Bis(diazeniumdiolate)imide Synthesis from [•]NO, Phenylacetonitrile, and NaOMe²⁴⁶



(diazeniumdiolate)imides which are stable under basic conditions but decompose vigorously in acidic media into [•]NO and N₂O.²⁴⁶

Lithiated alkynes add [•]NO at low temperature to furnish metalated 1,2,3-oxadiazole 3-oxides, which may be trapped with electrophiles, such as the proton (from H₂O), the deuteron (from D₂O), or Me₃Si⁺ (from Me₃SiCl) (Table 8,

Table 8. Formation of Disubstituted 1,2,3-Oxadiazole 3-Oxides via Sequential Addition of [•]NO and E–X to Lithiated Alkynes²⁴⁴

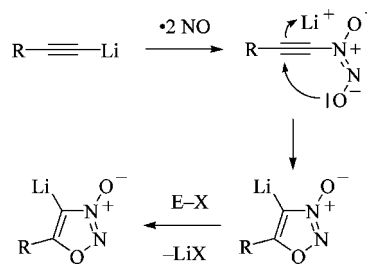


entry	R	E–X	yield/%
1	<i>n</i> C ₈ H ₁₇	H–OH	84
2	<i>n</i> C ₈ H ₁₇	D–OD	82
3	<i>n</i> C ₈ H ₁₇	Me ₃ Si–Cl	88
4	C ₆ H ₅	Me ₃ Si–Cl	78
5	(CH ₂) ₃ OCH ₂ C ₆ H ₅	Me ₃ Si–Cl	80

entries 1–3). The significance of this quite general heterocycle synthesis (e.g., Table 8, entries 3–5) was related to the utility of the 1,2,3-oxazole framework in medicinal chemistry.²⁴⁴ The proposed mechanism is based on the propensity of two molecules of [•]NO to add in sequential steps to carbon nucleophiles, to furnish an alkynyldiazeniumdiolate. 5-*endo*-dig cyclization of the intermediate is assumed to afford a lithiated 1,2,3-oxazole, which allows functionalization at position 4 with a broad range of electrophiles E⁺ (from E–X; see Scheme 32).

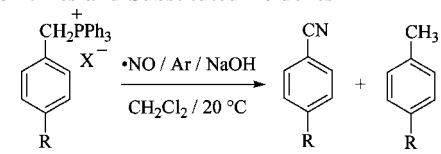
Wittig-reagents afford arylcarbonitriles and triphenylphosphine oxide, if treated under anaerobic conditions at 25 °C with [•]NO, preferentially in solutions of THF.²⁴⁵ Substituted toluenes, i.e. products of reductive C,P disconnection, are formed as side products. The product selectivity depends on the nature of the substituent. A gradual decrease in arylcarbonitrile formation was noted along the series of *p*-substit-

Scheme 32. Mechanistic Rationale for 1,2,3-Oxadiazole 3-Oxide Synthesis via Nitrogen Monoxide Addition to Lithiated Alkynes²⁴⁴



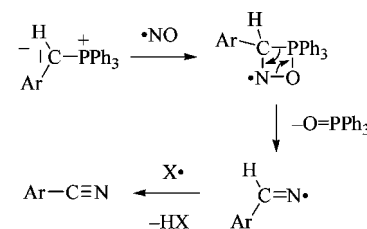
uents NO₂ > H ~ CN > CH₃ > OC₂H₅ > Cl. No clear-cut trend in terms of linear free energy relationship was obvious from the presented data (Table 9, entries 1–6). The proposed mechanism (Scheme 33) follows the general sequence for

Table 9. Conversion of Benzylic Wittig-Reagents with [•]NO into Arylcarbonitriles and Substituted Toluenes²⁴⁵



entry	R	<i>p</i> -RC ₆ H ₄ CN/%	<i>p</i> -RC ₆ H ₄ CH ₃ /%
1	OC ₂ H ₅	65	32
2	CH ₃	72	25
3	H	80	15
4	Cl	55	40
5	CN	78	20
6	NO ₂	95	5

Scheme 33. Key Steps in Arylcarbonitrile Synthesis from C,P-Ylides²⁴⁵



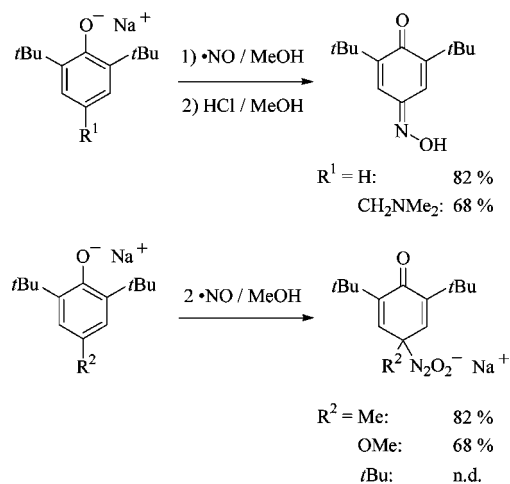
C-nucleophile addition to [•]NO (Scheme 29) but diverges as the proximity of oxygen and phosphorus allows oxazaphosphetane formation. This intermediate was proposed to extrude triphenylphosphine oxide according to the general scheme of the Wittig reaction. The iminyl radical that is left probably undergoes β-C,H-fragmentation to furnish an arylcarbonitrile.²⁴⁵

Phenolates are ambident nucleophiles, that add [•]NO in the *p*-position to provide cross conjugated π-systems (Scheme 34).²⁴⁸ Oximates are formed, if a H-atom or a CH₂NMe₂ substituent is located in the *p*-position. *p*-Methyl or methoxy substitution leads to diazeniumdiolate formation, presumably due to the poor leaving group abilities of the latter two substituents. No nitrosation occurred upon treatment of *p*-(*tert*-butyl)-substituted phenolates with [•]NO.

5.3.2. Formation of Nitrogen Nitrogen Bonds

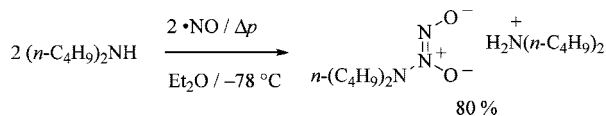
Nitrogen monoxide adds to sterically unencumbered amines, such as symmetrical straight chain secondary amines, or saturated heterocyclic derivatives, such as pyrrolidine,

Scheme 34. *N*-Functionalization of Substituted Phenolates (n.d. = not detected; for Reactions of $\cdot\text{NO}$ with Phenols, see Scheme 27)²⁴⁸



piperidine, or piperazine, preferentially in Et_2O at low temperature (e.g., $-78\text{ }^\circ\text{C}$), to furnish *N*-diazoniumdiolates (Drago complexes, Schemes 7 and 35).^{161,165} Neutral *N*-

Scheme 35. *N,N*-Di(*n*-butylammonium) *N,N*-Di(*n*-butyl)aminoazaniumdiolate Formation from $\cdot\text{NO}$ and Di(*n*-hexyl)amine¹⁶⁵

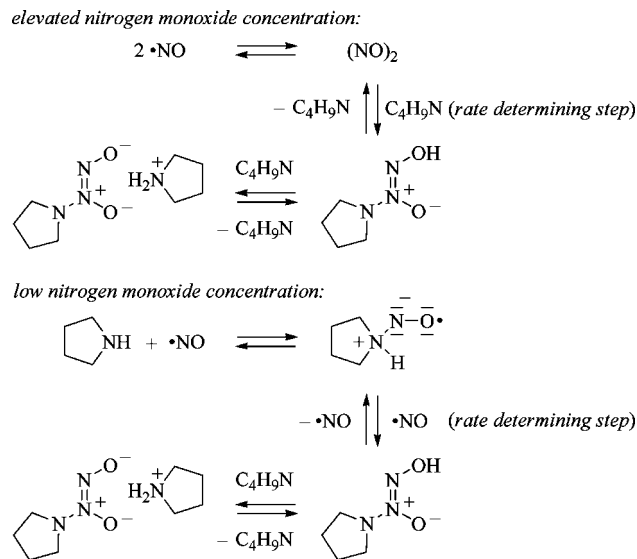


diazoniumdiolates and diazeniumdiolates formed from sterically hindered amines generally are not stable at ambient temperature (e.g., Scheme 7). Ammonium salts of diazeniumdiolates frequently are hygroscopic substances that require cation metathesis for being stored without deterioration. If primary amines serve as substrates, *N*-alkylammonium *N*-alkylaminodiazoniumdiolate stability gradually increases in the homologous series of amines from methyl- via ethyl-, 1-propyl-, to 1-butylamine. The stability of the 1-pentylamine-derived diazeniumdiolate was surprisingly similar to that of the methylamine adduct. The latter decomposed spontaneously at $-10\text{ }^\circ\text{C}$ or above. Isopropylamine and cyclohexylamine adducts to $\cdot\text{NO}$ were for unknown reasons more stable than those of straight chain primary amines. The reaction between $\cdot\text{NO}$ and secondary amines bearing secondary alkyl substituents, such as diisopropylamine or diisobutylamine, furnished dialkylammonium nitrites in low yields (not shown) but no *N*-diazoniumdiolates. Similarly, attempts to obtain a *tert*-butylamine-derived diazeniumdiolate failed. Experiments directed to convert aniline and nitrogen monoxide into the derived *N*-phenylaminodiazoniumdiolate resulted in vigorous explosion. Differences in amine reactivity were attributed to variation in basicity and steric congestion at nitrogen, which in turn affects electron delocalization from the amino nitrogen toward the N_2O_2 entity (see Scheme 5).¹⁶⁵

The reaction between $\cdot\text{NO}$ (3.44 bar) and dipropylamine in a solution of Et_2O at $25\text{ }^\circ\text{C}$ ($c_{\cdot\text{NO}} = 0.02\text{ M}$) occurred with a pseudo-first-order rate constant ($k = 9 \times 10^{-5}\text{ s}^{-1}$).²⁴⁹ The rate law showed a strong solvent dependence, changing from first order, if the reaction was conducted in pyridine or 1-methylimidazole, to second order in $\cdot\text{NO}$, if performed in the neat amine. In Et_2O , the reaction order gradually changed from first to second order in $\cdot\text{NO}$, as the reactant

concentration was raised from $c_{\cdot\text{NO}} = 0.01$ to 0.06 M . These data were interpreted in terms of two competing reactions that operate, being in favor of amine addition to $(\text{NO})_2$, at elevated $\cdot\text{NO}$ concentrations (Scheme 36, top), whereas

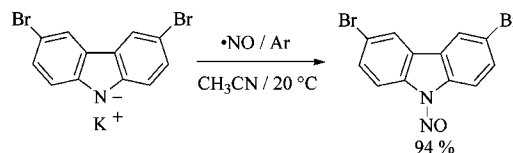
Scheme 36. Mechanistic Interpretation of Kinetic Data for *N*-Diazoniumdiolate Formation from Pyrrolidine and $\cdot\text{NO}$ at Different Reactant Concentrations ($\text{C}_4\text{H}_9\text{N}$ = Pyrrolidine; for Validation of *Elevated* and *Low* Nitrogen Monoxide Concentration, See Text)²⁴⁹



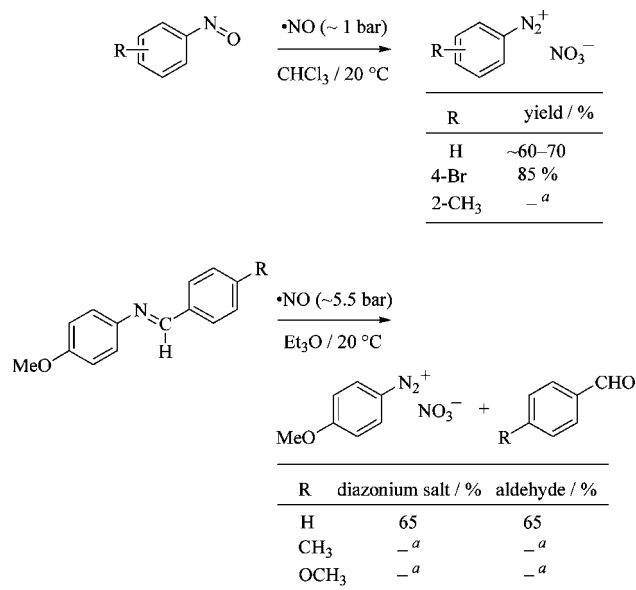
stepwise nitrogen monoxide addition and heteroatom radical-combination with $\cdot\text{NO}$ were proposed to dominate at low nitrogen monoxide levels (Scheme 36 bottom).²⁴⁹

N-Nitrosation of the amino group generally does not occur under anaerobic conditions in neutral solutions.^{250,251} Amides formed from aromatic *N*-heterocycles on the other hand, such as substituted carbazoles add one molecule of $\cdot\text{NO}$ to afford products of *N*-nitrosation in the absence of additional oxidants. It was assumed that an *in situ* formed *N*-nitroso radical anion (not shown) was oxidized by $\cdot\text{NO}$ to afford the target compound (Scheme 37).²⁵²

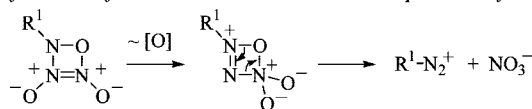
Scheme 37. *N*-Functionalization of an Carbazole-Derived Anion²⁵²



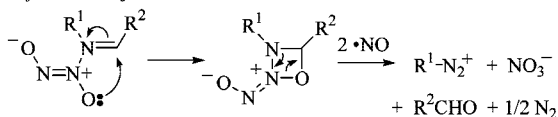
Nitrosoarenes²⁵³ and Schiff-bases prepared from *p*-methoxyaniline and aryl carbaldehydes²⁵⁴ form aryldiazonium nitrates in 60–85% yield, if treated with nitrogen monoxide under conventional conditions ($20\text{ }^\circ\text{C}$, $\sim 1\text{ bar}$ —for nitroso arenes) or elevated pressure ($\sim 5.5\text{ bar}$ —for imines; Scheme 38). Mechanistic details for both transformations were not provided. In extension to the general reactivity scheme, $\cdot\text{NO}$ is expected to add to the most nucleophilic site, which is O in a nitroso compound and N in an imine. Addition of a second equivalent of $\cdot\text{NO}$ provides opportunity for strained heterocycle formation (Scheme 39) from underlying diazeniumdiolate betaines (e.g., Scheme 39, bottom). Anionotropic O shift and subsequent nitrate extrusion offer an explanation for benzenediazonium salt formation from a nitrosoarene and an excess of $\cdot\text{NO}$ (Scheme 39, top). A

Scheme 38. Formation of Aryldiazonium Salts from $\cdot\text{NO}$ and Nitroso Arenes (Top) and Imines (Bottom) (a No Yields Reported)^{253,254}

Scheme 39. Mechanistic Proposal for Diazonium Salt Formation from Nitrogen Monoxide Adducts to Nitrosoarenes (Top) and Imines (Bottom; R¹, R² = Phenyl or Substituted Aryl)

transformation of nitrosoarene-derived adduct to 2 equivalents of $\cdot\text{NO}$



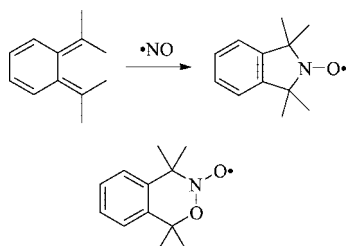
transformation of imine-derived *N*-diazoniumdiolate



multistep sequence starting with benzaldehyde extrusion of an iminodiazoniumdiolate-derived heterocycle was proposed to operate for *p*-methoxybenzenediazonium nitrate formation (Scheme 39, bottom).²⁵⁴

5.4. Pericyclic Reactions

Substituted *o*-quinodimethanes undergo rapid and selective [4 + 1]-cycloaddition with $\cdot\text{NO}$ (Scheme 40).¹²¹ The che-

Scheme 40. Spin Adduct Formation via Cheletropic Reaction between $\cdot\text{NO}$ and Tetramethyl-*ortho*-quinodimethane and the Chemical Formula of a Contaminant Formed from Nitrogen Dioxide-Trapping (See Text)¹²¹


leotropic reaction furnishes isoindolin-2-oxyl radicals, as evident from characteristic three-line EPR spectra due to ¹⁴N

hyperfine splittings. Trapping with other 1,3-dienes, for instance substituted butadienes²⁵⁵ and anthracenes,²⁵⁶ was comparatively slow, thus allowing multistep reactions to occur, resulting in C-nitrosation and subsequent alkyl radical trapping.²⁵⁷ The overall sequence in the latter cases provided nitroxyl radicals that were distinctively different from those obtained by direct cheletropic reaction between a 1,3-diene and $\cdot\text{NO}$. Another aspect that requires attention while interpreting EPR spectra from cheletropic nitrogen monoxide trapping relates to spin adduct formation caused by nitrogen dioxide contamination. Trapping of $\cdot\text{NO}_2$ is notably faster than the competing reaction between the *o*-quinodimethane and $\cdot\text{NO}$. Nitroxyl radicals obtained from the two nitrogen oxides can be distinguished on the basis of their *g* values and nitrogen hyperfine splittings, as shown in cycloadditions starting from 7,7,8,8-tetramethyl-*o*-quinodimethane [1,2-bis(*exo*-isopropylidene)cyclohexa-3,5-diene: $g = 2.00565(1)$, $a_N = 2.712(5)$ mT for the nitrogen dioxide trapping product (Scheme 40, bottom) and $g = 2.00589(1)$, $a_N = 1.452(3)$ mT for the 1,1,3,3-tetramethylisoindolidin-2-oxyl radical, i.e. the product of nitrogen monoxide cycloaddition (Scheme 40, top)].

The rate of cycloaddition with 7,7,8,8-tetramethyl-*o*-quinodimethane in solutions of pentane, hexane, or acetonitrile ($C^{\cdot\text{NO}} \sim 10^{-2}$ to 4×10^{-5} M) was sufficiently high to detect $\cdot\text{NO}$ release from Kupffer cells (i.e., macrophages) from the liver of male Wistar rats.¹²¹ The known metabolic rate of nitrogen monoxide production by the cells was used to estimate a trapping efficiency of 6% for $\cdot\text{NO}$.

o-Quinodimethanes are chemically labile compounds [half-lifetime for 7,7,8,8-tetramethyl-*o*-quinodimethane (Scheme 40) ~ 9 min at 20 °C] that generally are prepared via photodecarbonylation of 1,1,3,3-substituted 2-indanones (in Table 10 not shown). Stopped-flow kinetic investigations

Table 10. Rate Constants of *o*-Quinodimethane Trapping with NO^{258}

entry	R ¹	R ²	solvent	$k/(\text{M}^{-1} \text{s}^{-1})$ (23 °C)
1	OMe	OMe	CH ₃ CN	10 ± 1
2	OMe	OMe	C ₆ H ₆	20 ± 5
3	Ph	OMe	CH ₃ CN	60 ± 15
4	OCH ₂ CO ₂ Et	OCH ₂ CO ₂ Et	CH ₃ CN	230 ± 15
5	Me	Me	C ₆ H ₆	2140 ± 460
6	Ph	Me	C ₆ H ₆	4140 ± 390

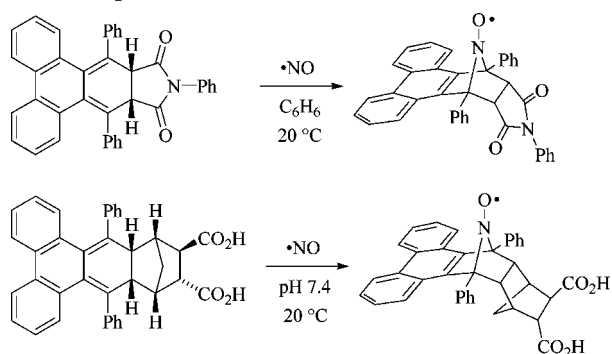
indicated that nitrogen monoxide trapping starting from solutions of photolysate obtained from 2-indanone decomposition containing an *o*-quinodimethane of interest and the product of electrocyclic ring closure, i.e. the corresponding benzocyclobutene, occurred in two phases.²⁵⁸ A swift intensity increase of the isoindolin-2-oxyl radical EPR signal was attributed to direct nitrogen monoxide trapping with the *o*-quinodimethane. The rate constants were dependent on the chemical nature of substituents R¹ and R² and solvent polarity (Table 10). A succeeding significantly slower increase of nitroxyl radical EPR signal intensity, being correlated with rate constants between 4.0×10^{-3} and $7.5 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ (23 °C), was attributed to an *a priori* electrocyclic ring-opening of the 7,7,8,8-tetrasubstituted benzocyclobutene and thus *in situ* generation of additional *o*-quinodimethane.

On a kinetic scale, rate constants of $\sim 300 \text{ M}^{-1} \text{ s}^{-1}$ for the [4 + 1]-cycloaddition with a 1,3-diene were proposed to

suffice for detecting nitrogen monoxide release from cells that typically produce the metabolite in approximately nanomolar concentrations. Nitroxyl radical formation via chelotropic nitrogen monoxide trapping using the existing probes, however, may be too slow for tracing generation of the metabolite from low-level producing sources, such as the brain (\sim pM). In the latter instance, alternative modes of nitrogen monoxide consumption, such as oxidation, are expected to notably interfere.²⁵⁸

For specialized applications, *o*-quinodimethanes were designed that allow quantitative analysis of spin adducts in a combination of fluorescence and EPR spectroscopy (Scheme 41). The use of fluorescence spectroscopy allows a decrease

Scheme 41. Formation of Fluorescent Nitrogen Monoxide-Spin Adducts²⁵⁹

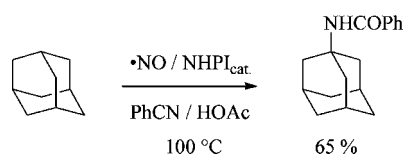


of the detection limit to 10 nM of \cdot NO for transformations in organic media ($k = 134 \pm 12$, for $T = 20$ °C, Scheme 41, top) or in phosphate buffered solution ($k = 60 \pm 8$, for $T = 20$ °C, Scheme 41, bottom).²⁵⁹

5.5. Electron Transfer

Hydrocarbons react in benzonitrile solution at 100 °C with \cdot NO under anaerobic conditions in the presence of catalytic amounts of NHPI via selective benzamidation (Scheme 42).²³⁸ This radical version of the Ritter-reaction starts with

Scheme 42. Use of *N*-Hydroxyphthalimide (NHPI) and \cdot NO for C,H-Activation in Adamantane²³⁸



homolytic substitution of, e.g., the 1-adamantyl radical via in situ-formed PINO (Schemes 28 and 41).^{238,260} Oxidation of the 1-adamantyl radical by \cdot NO leaves the 1-adamantyl cation, which reacts with one molecule of the solvent and an *O*-nucleophile, such as HOAc or H₂O, furnishing after workup *N*-(1-adamantyl)benzamide besides 6% of 1-nitroadamantane, 7% adamantane-1-ol, 2% adamant-1-yl-acetate, and 2% adamantane-2-one (in Schemes 42 and 43 not shown).

Selective functionalization of alkyl benzyl ethers with the reagent combination of \cdot NO/NHPI provides arylcarbaldehydes. Conversions and yields were dependent on the chemical nature of the ether substituent and gradually increased with the cationic leaving group ability along the series of alkyl groups Me < Et < *t*Bu (Table 11, entries 1–3).²⁶⁰ The reactivity effect of the aryl substituent was small

Scheme 43. Mechanistic Rationale for C,H-Activation in a \cdot NO/NHPI-Mediated Reaction [for Generation of the Phthalimidyl-*N*-oxyl Radical (PINO), Refer to Scheme 28]^{238,260}

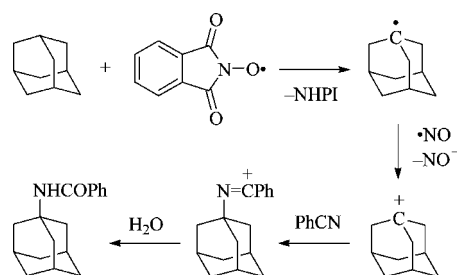
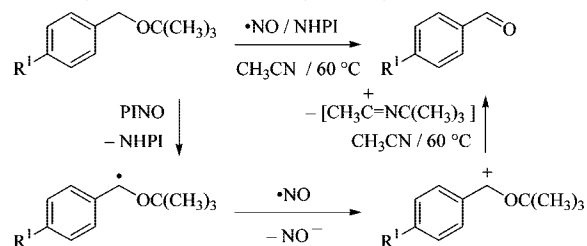


Table 11. Selective Oxidation of Benzyl Ethers with the Combination \cdot NO/*N*-Hydroxyphthalimide (NHPI)²⁶⁰

entry	R ¹	R ²	conversion/%	yield/%
1	Me	Me	56	50
2	Me	Et	70	60
3	Me	<i>t</i> Bu	90	72
4	H	<i>t</i> Bu	80	70
5	Cl	<i>t</i> Bu	95	84
6	<i>t</i> Bu	<i>t</i> Bu	83	74

(Table 11, entries 3–6). The mechanism was interpreted in terms of phthalimidyl-*N*-oxyl (PINO) radical formation from *N*-hydroxyphthalimide (NHPI) and \cdot NO. The PINO radical was proposed to abstract a benzylic H-atom, which would be followed by oxidation of the newly formed benzylic radical with \cdot NO (Scheme 44). A subsequent solvent-induced

Scheme 44. Mechanism for Rationalization of Aryl Carbaldehyde Formation from Benzylic Ethers in \cdot NO/NHPI-Mediated Reactions (for Structural Formula of PINO and NHPI, Refer to Scheme 28; for R¹, see Table 11)

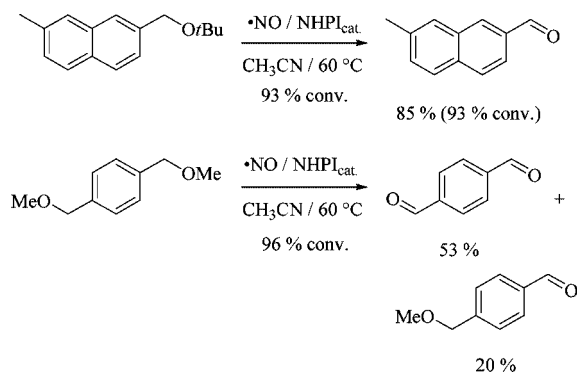
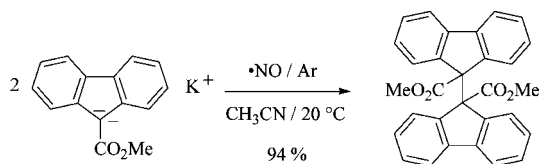


C,O bond heterolysis offered an explanation for aryl carbaldehyde formation.²⁶⁰ The procedure was further developed toward dialdehyde synthesis, although conversion of mono- into dialdehydes did not occur quantitatively (Scheme 45).

Sterically demanding, highly delocalized carbanions, for instance the monoanion of methyl 9-fluorenylcarboxylate, react with \cdot NO not via diazeniumdiolate formation but via one electron oxidation to provide a stabilized π -type radical that slowly combines to the derived dimer (Scheme 46).²⁵²

6. Concluding Remarks

Application of carbon radicals in modern organic synthesis generally takes profit from kinetically controlled exothermic elementary reactions that proceed via early, i.e. reactant-like, transition states. The sequence is terminated in most instances via homolytic substitution, leaving the target product and a chain-propagating radical.^{108,261–264} Organic synthesis with

Scheme 45. Formation of Aryl Carbaldehydes in $\cdot\text{NO}$ /NHPI-Mediated Reactions²⁶⁰

Scheme 46. Oxidation of a Substituted Fluorenyl Anion with $\cdot\text{NO}$ ²⁵²


$\cdot\text{NO}$ does not follow this general scheme, which is a tribute to a π^* -type SOMO, where location of highest spin density coincides with the most electrophilic position.

The organic radical chemistry associated with nitrogen monoxide is dominated by combinations, which occur close to the diffusion limit. It is a terminating sequence that consumes 2 equiv of radicals and leaves a C-nitroso compound. Since the chemical properties of the nitroso and the carbonyl group in many ways are quite similar, a wide range of synthetically useful carbon carbon bond forming reactions or functional group interchanges may follow C-nitrosation. Its moderate electrophilicity restricts nitrogen monoxide addition to reactions with strong nucleophiles such as carbanions, ylides, enamines, or amines. Additions to nonactivated π -bonds, one of the most important carbon radical reaction, do for thermochemical reasons not occur.

Nitrogen monoxide always has had the potential to surprise and probably will continue to do so. New chapters will be added as the pursuit of reactivity and selectivity of nitrogen monoxide in organic radical reactions is being continued. It is a chemistry of marvelous simplicity and impressive complexity. It is probably best reflected by summarizing one of its important discoveries as follows: *During the course of some experiments with nitrosyl chloride the writer, by request, prepared a saturated solution of this gas in normal heptane.... The solution so prepared was accidentally set in the sunlight for a day. When next observed the reddish brown color had changed to blue and there was a precipitate of white feathery crystals....*¹⁸⁵

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