# *An Organic Chemist's Guide to N -Nitrosamines: Their Structure, Reactivity, and Role as Contaminants*

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# An Organic Chemist's Guide to *N*-Nitrosamines: Their Structure, Reactivity, and Role as Contaminants

Jessica C. Beard and Timothy M. Swager*

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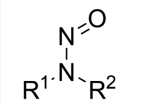
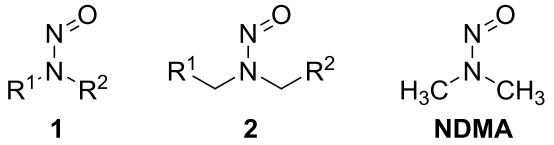
**ABSTRACT:** *N*-Nitrosamines are a class of compounds notorious both for the potent carcinogenicity of many of its members and for their widespread occurrence throughout the human environment, from air and water to our diets and drugs. Considerable effort has been dedicated to understanding *N*-nitrosamines as contaminants, and methods for their prevention, remediation, and detection are ongoing challenges. Understanding the chemistry of *N*-nitrosamines will be key to addressing these challenges. To facilitate such understanding, we focus in this Perspective on the structure, reactivity, and synthetic applications of *N*-nitrosamines with an emphasis on alkyl *N*-nitrosamines. The role of *N*-nitrosamines as water contaminants and the methods for their detection are also discussed.



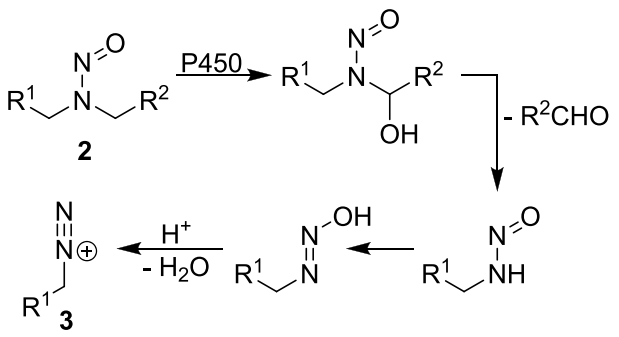

- *Ground State Reactivity*
- *Photochemistry*
- *Environmental Formation, Remediation, and Detection*

*N*-Nitrosamines (or simply "nitrosamines") are a class of compounds sharing the general structure **1** (Chart 1), where the amine moiety may be derived from any organic secondary amine. Many nitrosamines, particularly those with structure **2** (e.g., *N*-nitrosodimethylamine [NDMA], Chart 1), are known to be carcinogenic to animals and are reasonably anticipated to be human carcinogens.[1−3] Scheme 1 shows the mechanism of carcinogenicity for **2**. Nitrosamine **2** first undergoes enzymatic $\alpha$-hydroxylation with cytochrome P450 and subsequently forms the dealkylated primary nitrosamine. The unstable primary nitrosamine further decomposes to diazonium **3**, a DNA alkylating agent.[2,4,5] The resulting DNA damage can lead to cancer.

**Chart 1. Some *N*-Nitrosamines**




**Scheme 1. Transformation of Nitrosamine 2 into Diazonium 3 via Enzymatic $\alpha$-Hydroxylation**




In recent years, nitrosamines have drawn increased attention after several popular medications were discovered to contain unacceptable levels of nitrosamines, resulting in recalls[6] and new regulatory guidance.[7] However, concern over nitrosamine exposure is much older than these latest recalls. Although now used only as a research chemical, NDMA was previously used for a number of industrial applications.[3,8] NDMA initially only drew concern for its high toxicity,[9] but in 1956 it was reported to be carcinogenic to rats[10] and scrutiny soon turned toward other nitrosamines. Now, we know that many nitrosamines are carcinogenic[1−3] and they can be found throughout the human environment, from air, water, and soil to foods, drinks, and drugs.[2,7,8] Those new to the problem of nitrosamines will find a number of quite recent reviews on nitrosamines as contaminants (particularly NDMA in water),[11−15] but scarce discussion of nitrosamines *as organic chemicals*. However, an understanding of the chemistry of nitrosamines will be essential to addressing many of the challenges of nitrosamine contamination, especially with regard to detection and remediation. Herein, we address nitrosamines from an organic chemistry perspective with an emphasis on alkyl nitrosamines (i.e., **2**) since those are generally more likely to be carcinogenic.[1,2] We discuss first the structure and reactivity

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of nitrosamines, and then briefly cover their role as water contaminants and the methods for their detection.

## THE STRUCTURE OF NITROSAMINES

Although nitrosamines are typically depicted as structure **1a**, their actual structures and chemical reactivity are heavily influenced by the zwitterionic resonance structure **1b** (Figure 1). Rotation about the N−N bond is hindered as a result of its

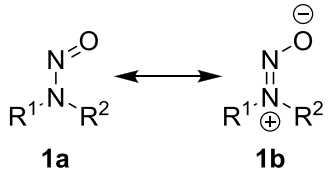



**Figure 1.** Two major resonance contributors of nitrosamines.

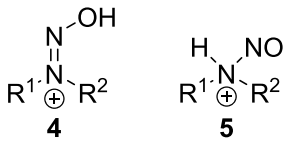
significant double bond character, with a barrier of ∼23 kcal/mol for NDMA and other acyclic dialkylnitrosamines.[16−18] This is slightly higher than the barrier to rotation about the analogous C−N bond of *N*,*N*-dimethylformamide (DMF) in water (22 kcal/mol).[19] This hindered rotation and the planarity of the $C_\alpha C_\alpha NNO$ moiety[20,21] result in magnetic nonequivalence of the *N*-substituents in symmetric nitrosamines (e.g., NDMA).[16,22] For the simplest dialkylnitrosamine, NDMA, the N−N and N−O bond lengths are 1.344 and 1.235 Å in the gas phase, respectively.[20] In single crystals of NDMA at low temperature, intermolecular interactions stabilize increased polar character (e.g., **1b**), resulting in a shortened N−N bond (1.320 Å) and an elongated N−O bond (1.260 Å).[21]

## REACTIONS OF NITROSAMINES IN THE GROUND STATE

Although *N*-nitrosamines are not commonly employed in organic synthesis, their reactivity has been studied both for synthetic applications and for understanding the mechanisms of their carcinogenicity. Herein, we describe some reactions and synthetic applications of nitrosamines. While we particularly focus on chemistry relevant to alkyl nitrosamines, much of it is also applicable to other nitrosamine derivatives.

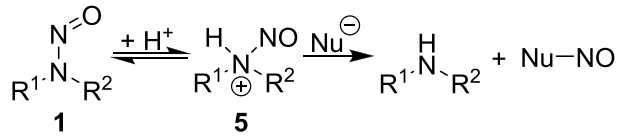
**Protonation and Protolytic Denitrosation.** Consistent with the resonance contributors in Figure 1, nitrosamines are most basic at oxygen.[23,24] For NDMA and other dialkylnitrosamines, the $pK_a$ is less than 1 for the *O*-protonated species (**4**, Chart 2).[25] Hydroxydiazenium salt **4** is the only protonated

**Chart 2. *O*-Protonated (4) and *N*-Protonated (5) Isomers of the Nitrosamine Conjugate Acid**




form seen in NMR spectra of nitrosamines in acid,[22,24] and it is predicted to be more stable by 16 kcal/mol (for $R^1 = R^2 = Me$) than the amino-*N*-protonated isomer (**5**, Chart 2).[26] The *N*-protonated species **5** has not been directly observed, although it may occur in kinetically relevant amounts at pH 1−2.[27] **5** is sometimes evoked to explain reactions of nitrosamines in acid.[5] One such reaction is the denitrosation of nitrosamines in acidic conditions, yielding the corresponding secondary amines.[22,28,29] A common mechanism for this decomposition is shown in Scheme 2, wherein **5** is formed and subsequently

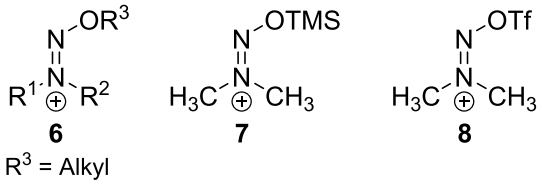
**Scheme 2. Proposed Mechanism for Nitrosamine Denitrosation in Acid via the *N*-Protonated Conjugate Acid (5)**




denitrosated by attack of a nucleophile.[5] Protolytic denitrosation can be accelerated by the addition of nucleophiles such as bromide, thiocyanate, and thiourea to the reaction.[29,30]

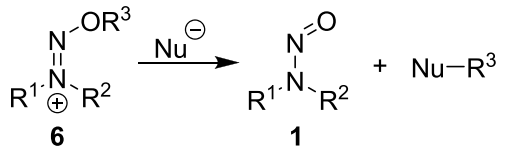
**Reactions with Electrophiles: Synthesis and Reactivity of Alkoxydiazenium Salts.** Nitrosamines can react through their oxygen with various electrophiles to form *O*-substituted hydroxydiazenium salts (i.e., *O*-substituted derivatives of **4**). The electrophile is most commonly an alkylating agent, forming alkoxydiazenium **6**,[31−34] but *O*-trimethylsilyl (**7**) and *O*-triflyl (**8**) derivatives of NDMA have also been prepared (Chart 3).[35] Trialkyloxonium salts,[31−33] dimethyl

**Chart 3. *O*-Alkyl (6), *O*-Trimethylsilyl (7), and *O*-Triflyl (8) Hydroxydiazenium Derivatives**




sulfate,[31,36] alkyl fluorosulfonates,[34] and alkyl halides with silver perchlorate[32,35] have all been used to *O*-alkylate nitrosamines. These cations **6**−**8** are themselves electrophilic and generally the parent nitrosamine is recovered after nucleophilic attack (e.g., *O*-dealkylation of **6**, Scheme 3),[33−35] although in a few cases *N*-dealkylation[34,35] or attack

**Scheme 3. *O*-Dealkylation of Alkoxydiazenium 6**




at the *O*-attached nitrogen occur instead.[36−38] *O*-Triflyl derivative **8**, formed from NDMA and triflic anhydride, undergoes *N*-dealkylation to methylate toluene and give a mixture of xylenes.[35] Curiously, 3,4-dichlorothiophenol with either the *O*-methylated salt of *N*-nitrosodiethylamine (**6a**) or the *O*-ethylated salt of *N*-nitrosomethylethylamine (**6b**) in organic solvent resulted in the same product distribution, indicating both *O*- and *N*-dealkylation had occurred (Scheme 4), whereas aniline and 3,4-dichloroaniline only gave *O*-dealkylation products, and thiophenol and phenol showed no reaction at all.[34] The mechanism is unclear, particularly for the formation of nitrosamine products after *N*-dealkylation.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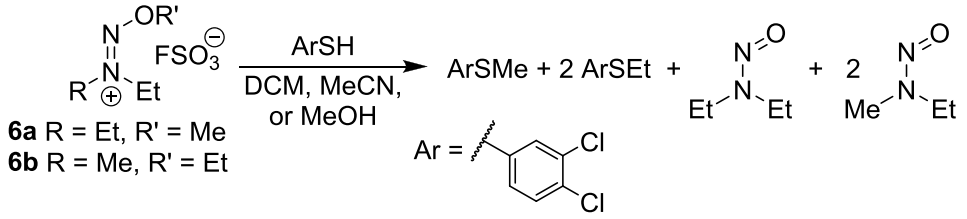
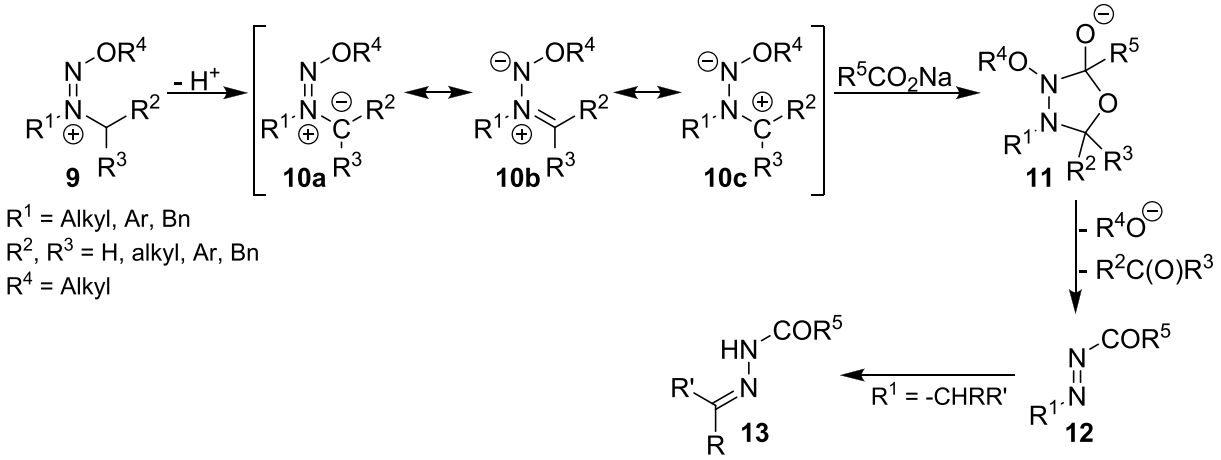
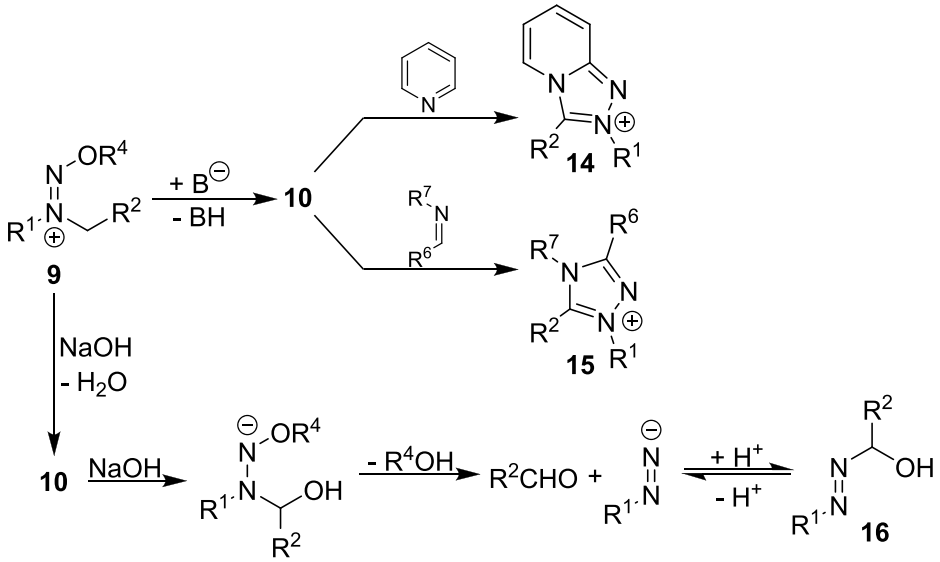
**Scheme 4. Reaction of Alkoxydiazenium Salts 6a,b with 3,4-Dichlorothiophenol**




**Scheme 5. Deprotonation of Alkoxydiazenium 9 and Subsequent Reaction with a Carboxylate**




**Scheme 6. Formation of 1,2,4-Triazolium or *trans*-α-Hydroxydialkyldiazene Products from Alkoxydiazenium 9**




For alkoxydiazeniums of form **9** (a subset of **6**), some reactions are proposed to begin with deprotonation of the α-position, giving zwitterion **10** (Scheme 5), which behaves as structures **10b** or **10c** in subsequent reactions.[33] Those reactions are reviewed in detail elsewhere,[33] but as that review is in German, we will discuss the chemistry here briefly. Reaction of **9** with carboxylates passes through cyclic species **11** and produces either carbonylazo compound **12** ($R^1$ = aryl, *tert*-butyl) or acylhydrazone **13** ($R^1$ = Me, Et, *i*-Pr, Bn, etc.) (Scheme 5).[39,40] Fused 1,2,4-triazolium cations (e.g., **14**) are formed from the cyclization of **10** ($R^3$ = H) and nitrogen heterocycles, while cyclization with Schiff bases produces **15** (Scheme 6).[41,42] Treatment of **9** ($R^3$ = H) with sodium hydroxide yields *trans*-α-hydroxydialkyldiazene **16**.[43,44] In that transformation, the migration of $-CH(OH)R^2$ likely occurs through decomposition and intermolecular recombination of intermediate species (Scheme 6).[44]

**α-Lithiated Nitrosamines.** The α-protons of nitrosamines are more acidic than those of the corresponding secondary amines,[45] allowing them to be easily lithiated at the α-position with lithium diisopropylamide (LDA).[46] These α-lithiated nitrosamines **17** can be utilized in reactions with various electrophiles as synthetic equivalents of secondary amine α-carbanions (Figure 2).[46,47] Seebach and co-workers have reported a one-pot procedure for the α-substitution of secondary amines via formation of the nitrosamines. In it,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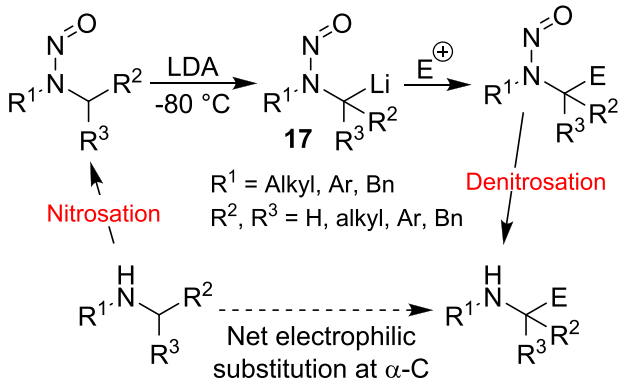
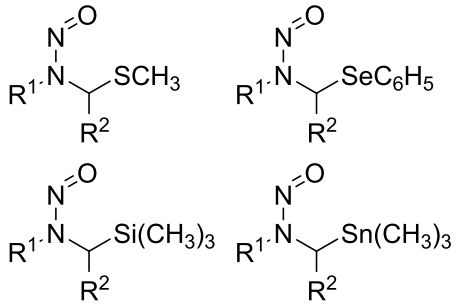



**Figure 2.** Lithionitrosamines **17** can react with various electrophiles. Denitrosation reveals the $\alpha$-substituted secondary amine.

the secondary amine is nitrosated with ethyl nitrite, lithiated with LDA, reacted with the desired electrophile, and then denitrosated by either Raney nickel-catalyzed hydrogenolysis alone[48,49] or reduction with lithium aluminum hydride (LAH) followed by hydrogenolysis with Raney nickel.[50] Other procedures recover the substituted amine via denitrosation in acid.[51−53] After the first addition of electrophile, the lithiation−substitution sequence can be repeated without an intervening workup.[52,54]

A variety of electrophiles can be added to lithionitrosamines (**17**). Reactions with alkyl halides, aldehydes, ketones, and a variety of carboxylic acid derivatives work well.[47,51,54,55] The product of **17** and $\alpha,\beta$-unsaturated ketones depends on the structure of the ketone. The 1,2-adduct is produced with cyclohexenone, while reaction with chalcone yields a mixture of the 1,2- and 1,4-adducts.[46] Heteroatom-substituted products can be obtained from reaction of **17** with disulfides, diselenides, trimethylsilyl chloride, and trimethyltin chloride (Chart 4).[56] Reaction of **17** ($R^3$ = H) with aryl nitriles gives

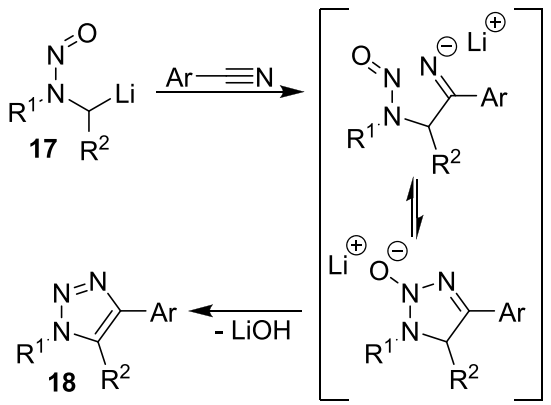
**Chart 4. Heteroatom-Substituted Nitrosamines**



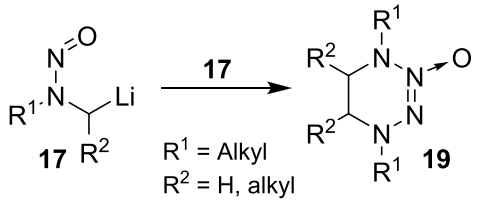

cyclization to form 1,2,3-triazoles **18** (Scheme 7),[57] wherein the highest yields are obtained using a twofold excess of **17**.[58] Tetrahydro-1,2,3,4-tetrazine oxides **19** are produced by the dimerization of lithiated dialkylnitrosamines (Scheme 8),[46,59,60] and a radical mechanism has been proposed.[60] Oxides **19** can be reduced to the corresponding tetrahydrotetrazines with trimethyl phosphite.[46,59,60]

**Reactions with Organolithium and Grignard Reagents.** *N*-Nitrosamines are weakly electrophilic at the nitroso-nitrogen and are susceptible to nucleophilic attack at that site by organolithium and Grignard reagents ($R^3M$, M = MgX or Li).[61−64] The initial product is an unstable oxyhydrazine (**20**), which undergoes elimination to form either

**Scheme 7. Cyclization of Aryl Nitriles and 17 to Give 1,2,3-Triazoles 18**




**Scheme 8. Dimerization of Dialkyl 17**




hydrazone **21** ($R^3 = -CH_2R$ only)[61,62,64] or azomethine imine **22** (Scheme 9).[63,64] Elimination from **20a** (M = MgX) can occur before quenching with protic solvent.[64] Because **22** is susceptible to further nucleophilic attack, $\alpha$-substituted hydrazine **23** is often isolated after workup when Grignard reagents are used (Scheme 9).[64] When the Grignard reagent used is phenylmagnesium bromide, *N*-phenyl hydrazine **24** is produced by a formal reduction of **20a** (Scheme 9).[61,62,64] In reactions with phenyllithium or *tert*-butyllithium, elimination from **20b** (M = Li) only occurs after quenching with protic solvent.[63] When **20b** is quenched with water, the only product observed is the head-to-tail dimer of **22** (**25**, Scheme 9). When ethanol is used, the solvent adduct **26** (Scheme 9) is briefly observable by NMR, but it is in equilibrium with **22** and ultimately decomposes to **25**.[63] Similar to other azomethine imines,[65] **22** can undergo 1,3-dipolar cycloadditions with dipolarophiles.[63]

**Reduction to 1,1-Disubstituted Hydrazines.** NDMA was once used as a starting material in the industrial manufacture of 1,1-dimethylhydrazine, a rocket fuel.[66] The reduction of nitrosamines (**1**) to 1,1-disubstituted hydrazines (**27**, Figure 3) has been known since the late 19th century[67] and can be effected with a wide variety of reaction conditions.[68] Reduction of nitrosamines with zinc dust in acetic acid is perhaps the oldest method,[67] and dialkyl **27** can be isolated as the hydrochloride salt in fair yields by this method.[69] Catalytic hydrogenation was of interest for industrial purposes, and Pd/C, Pt/C, and Rh/C all yield the corresponding hydrazines, although the yield of **27** is strongly dependent on reaction conditions and the identity of **1**.[70,71] The yield of **27** by catalytic hydrogenation is improved by the inclusion of a salt (e.g., $NH_4OAc$, $CaCl_2$) in the reaction mixture.[71] Hydride reduction using LAH generally provides fair to good yields of 1,1-dialkyl or 1,1-alkylaryl **27**,[50,72−74] but diarylnitrosamines are easily over-reduced to give the parent amine and ammonia[73] unless the reaction conditions are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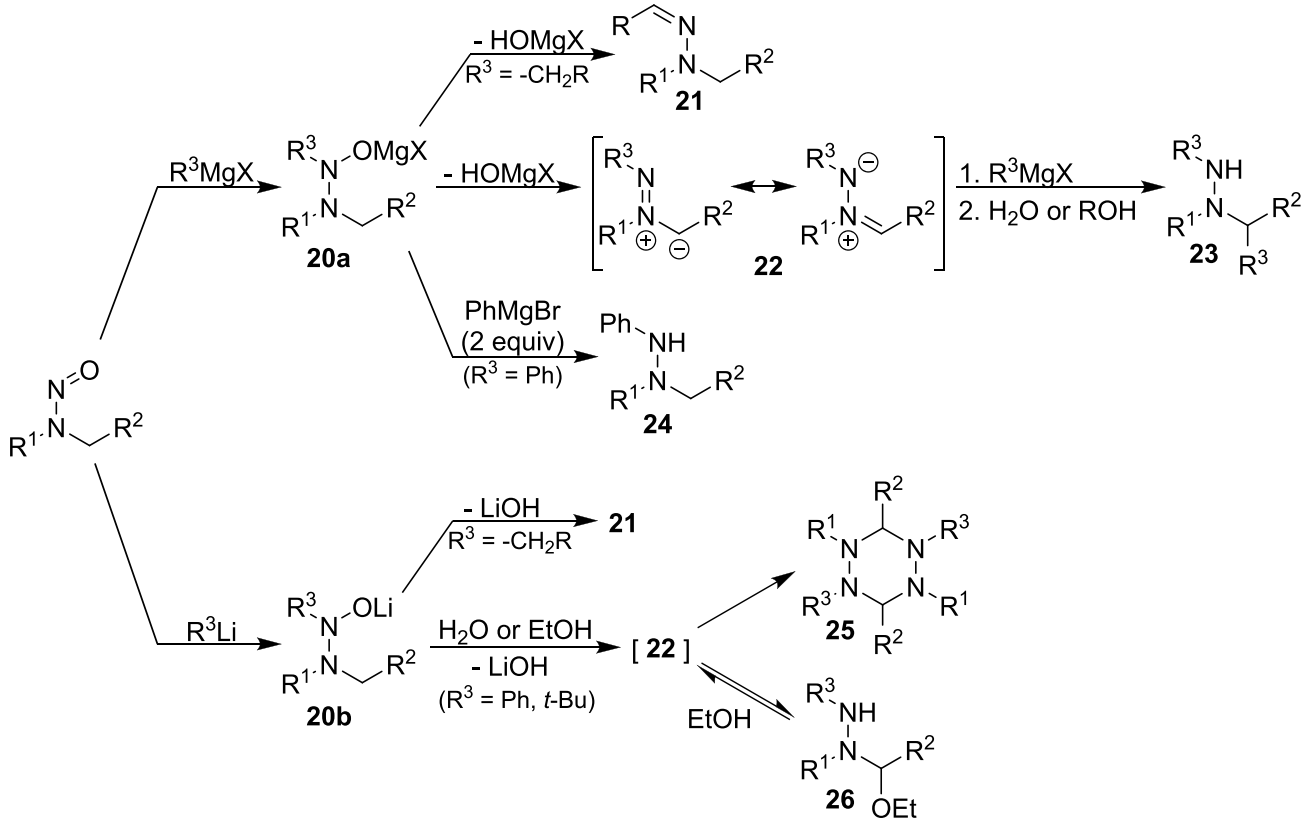
**Scheme 9. Nucleophilic Attack at the Nitroso-N by Organometallic Reagents and Subsequent Reactions**



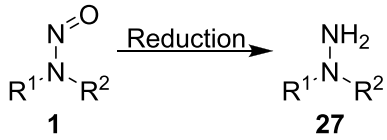




**Figure 3.** Reduction of nitrosamines (**1**) to hydrazines (**27**).

carefully controlled.[75] Reduction of **1** can be effected with sodium metal in either absolute ethanol or ethanol in liquid ammonia, but the yield is lower than with LAH for many substrates.[72] $TiCl_4$ with magnesium powder in dichloromethane/diethyl ether solution forms a reducing Ti(II) reagent that reduces a variety of nitrosamines to hydrazines in excellent yields (>90% typically), though the reagent must be made fresh for each reaction.[76] Electrolytic reduction of dialkylnitrosamines proceeds smoothly in acidic ethanol, but much lower yields were obtained with nitrosamines bearing aryl substituents.[77] In all of these conditions, denitrosation to the parent amine is also observed.

**Other Reactions of Nitrosamines.** Nitrosamines can be oxidized to their corresponding nitramines. The nitramine (**28**) can be obtained in good yield after treatment of **1** with either nitric acid[78] or peroxytrifluoroacetic acid,[79] although by different mechanisms. Peroxytrifluoroacetic acid oxidizes the existing nitroso moiety (Scheme 10a), while nitric acid effects the exchange of the nitroso and nitro groups (Scheme 10b).[80]

We have focused this section on the chemistry of alkyl nitrosamines. The reactions of *N*-nitrosamines bearing other substituents (e.g., *N*-nitrosoenamines) or having additional reactive moieties are outside the scope of this review, but such reactions have been reviewed previously.[81] Nitrosamine-metal complexes have also been reviewed elsewhere,[82] and Chart 5

**Scheme 10. Oxidation of $^{15}$N-Labeled Nitrosamine 1 to (a) Labeled Nitramine 28 with Peroxytrifluoroacetic Acid and (b) Unlabeled 28 with Nitric Acid**

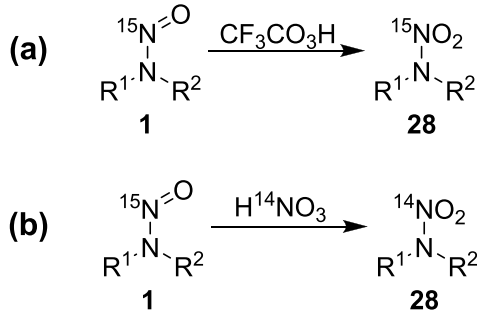
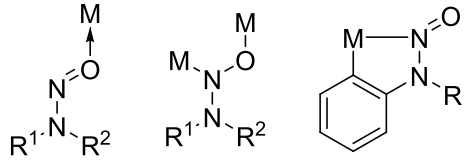



**Chart 5. Metal-Binding Modes between Nitrosamines and Metals (M)**



shows possible binding modes in such complexes. Through the formation of cyclic *ortho*-metalated complexes (Chart 5, right), the *N*-nitroso moiety can act as an easily cleavable directing group in metal-catalyzed C−H activation of *N*-nitrosoaniline derivatives.[83−89] For completeness, we mention here the Fischer−Hepp rearrangement of aryl nitrosamines because it is relevant to *N*-aryl-*N*-alkyl nitrosamines. In acidic conditions, aryl nitrosamines (e.g., *N*-nitrosoaniline **29**) undergo rear-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rangement to the corresponding *p*-nitroso products (e.g., **30**, Figure 4).[90] The exact mechanism of the Fischer–Hepp

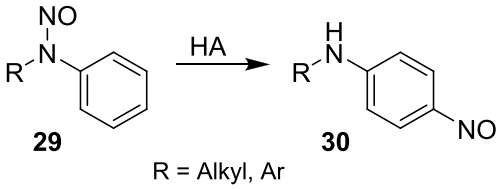


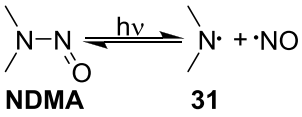

**Figure 4.** Fischer–Hepp rearrangement.

rearrangement is unknown, and both inter- and intramolecular mechanisms have been proposed.[5] Because the rearrangement is performed in acidic conditions, denitrosation is increasingly competitive with increasing acidity.[91] The rearrangement occurs with a variety of aromatic substituents.[5]

## PHOTOCHEMISTRY

**Photolysis.** Since the 1930s, it has been known that UV irradiation of NDMA and other *N*-nitrosamines induces fragmentation of their N–N bond.[92] Excitation of NDMA to a singlet excited state by either its $\pi \rightarrow \pi^*$ ($S_0 \rightarrow S_2$) or n $\rightarrow$ $\pi^*$ ($S_0 \rightarrow S_1$) transition leads to photolytic cleavage, although it can be reformed by recombination of the produced nitric oxide (NO) and dimethylamino radical **31** (Scheme 11).[93,94]

**Scheme 11. Photolysis of NDMA by N–N Bond Homolysis and the Thermal Recombination Back Reaction**




For NDMA in water, the $\pi \rightarrow \pi^*$ and n $\rightarrow$ $\pi^*$ transitions appear in the absorption spectrum as bands at $\lambda_{max}$ = 228 nm ($\varepsilon$ = 7378 $M^{-1}cm^{-1}$) and 332 nm ($\varepsilon$ = 109 $M^{-1}cm^{-1}$), respectively, and other dialkylnitrosamines have similar characteristics.[95,96] Photolysis of gaseous NDMA displays a fragmentation quantum yield of 1,[93] whereas the quantum yields for nitrosamines in solution are much lower ($\Phi \leq 0.3$), presumably as a result of solvent cages that promote the back reaction shown in Scheme 11. The reported solution-phase quantum yields vary and can be affected by solution pH, the presence of oxygen, and the initial nitrosamine concentration.[96−100] The variations arise, at least in part, from the effect of photolysis conditions on the multiple mechanistic pathways involved in nitrosamine photolysis, which as a result of their complex environmental dependence are not fully understood. We describe below the range of mechanisms and the products of NDMA, which is the most studied *N*-nitrosamine and serves as a general guide for the expected reactivity of other dialkyl analogues.

The proposed pathways of nitrosamine photolysis in solution are depicted for NDMA in Figure 5, and for simplicity some secondary reactions have been excluded. In contrast to the gas phase wherein photolytic breakdown proceeds by a mechanism analogous to path A (homolysis) in Figure 5,[93,94] in the solution phase NDMA* can also be protonated (**33***) and decomposed by nucleophilic nitrite attack (path B)[98,101] or water (hydrolysis, path C).[26,102] Alternatively, **33*** can rearrange (path D) to the unstable *N*-protonated isomer (**34**), which then homolytically fragments.[26,102,103] Fragmentation of **34** is very different from what is observed in path A, wherein NO and **31** can recombine to regenerate NDMA.[23,99] Specifically, this homolysis is effectively irreversible because the recombination of NO and aminium radical **35** would produce high-energy species **34**, which is energetically unfavorable.[26,103] Thus, the decomposition of **33*** (via paths B–D) is not expected to lead to significant reformation of NDMA.[103]

Paths A–D are consistent with experimental observations of the effect of pH on photolysis. Although the rate of nitrosamine photolysis increases with decreasing pH in aqueous solutions in air,[95,104,105] the quantum yield of NDMA decomposition by photolysis is constant ($\Phi \approx 0.3$) over an extended range of acidity, pH 2–8.[100,101] However, the decomposition quantum yields drop precipitously to below 0.1 between pH 8–9 and continue to slowly decrease with increasing alkalinity above pH 9.[101] This pH dependence suggests that the p$K_a$ of **33*** is 8–9, above which point decomposition from NDMA* dominates.[101] Additionally, the quantum yields obtained above pH 9 in water are similar to those obtained in neutral aprotic solvent for other dialkylnitrosamines, which also decompose from the neutral excited state (e.g., NDMA*).[99,106] A dependence on the initial nitrosamine concentration has also been observed in aprotic solvent. This feature is expected for decomposition by path A: at higher initial concentrations, **31** has an increased probability of hydrogen atom abstraction from unreacted NDMA rather than recombination with NO.[99] In contrast to aqueous solutions, the photolysis quantum yields in aprotic solutions are significantly improved by the addition of acid,[23,106,107] presumably because paths B–D become accessible.

Path E in Figure 5 illustrates how NDMA* and **33*** can decompose through single-electron transfer to $O_2$ with subsequent fragmentation of the oxidized species.[101] This mechanism was proposed as part of an explanation to account for differences in quantum yield between solutions photolyzed under $O_2$ and those under $N_2$. In accord with this branch point in the mechanistic possibilities, a distinct decrease in quantum yield is observed with increasing pH under $N_2$ atmosphere.[101] The decreased decomposition quantum yield when photolysis is run under inert atmosphere has been noted earlier for solutions in acetonitrile but was attributed to $O_2$ reacting with radicals in path A to hinder reformation of the nitrosamine under air and not investigated further.[99] The difference between air and inert atmosphere vanishes when only the $S_0 \rightarrow S_1$ (~332 nm, n $\rightarrow$ $\pi^*$) transition is excited;[96,101] our analysis is that this is likely the result of electron transfer and/or other reactions stemming from a longer lived $T_1$ state that can result from intersystem crossing from the $S_2$ state. Superoxide radical ($O_2^{\bullet-}$)[101] and a species with hydroxyl radical-like reactivity (suggested to be peroxynitrite, $ONOO^-$)[105] have been detected in the photolysis of aqueous NDMA. These results are consistent with the occurrence of path E, however additional investigation is still needed to confirm the existence of this pathway and identify the secondary decomposition reaction products. There are also other oxygen reaction pathways in addition to path E. In particular, irradiated nitrosamines have been found to undergo oxygen-atom exchange with dissolved $O_2$ and to also produce the corresponding nitramines. These transformations plausibly occur via the formation and collapse of a nitrosamine peroxide intermediate.[108,109]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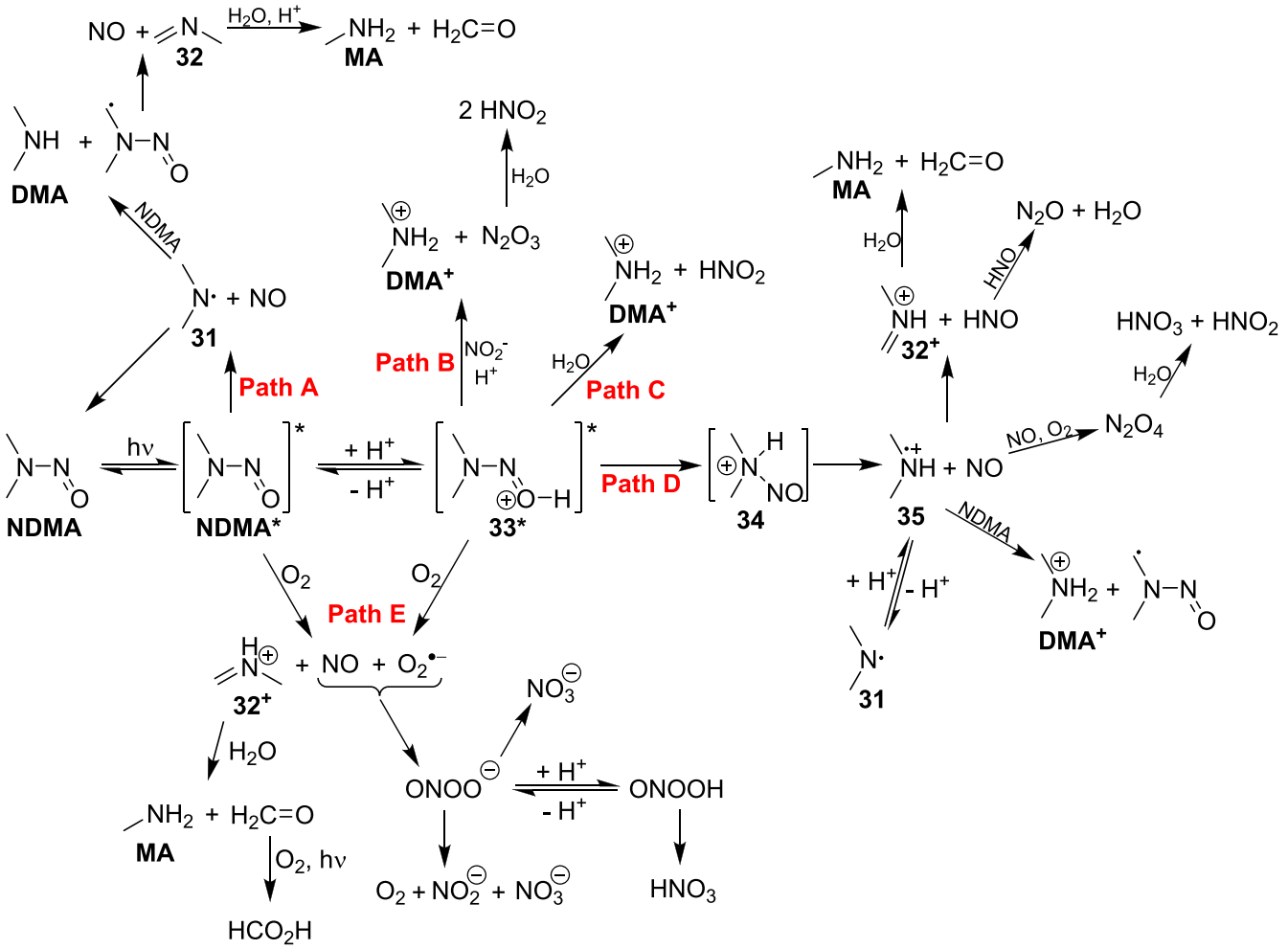
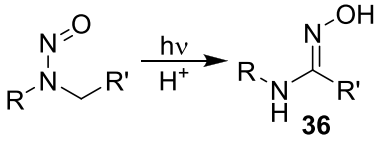



**Figure 5.** Proposed mechanisms of *N*-nitrosamine photolysis in solution using NDMA as a representative nitrosamine.

Although the initial products of the photolysis pathways in Figure 5 differ, a number of the secondary reactions result in similar final products. In aqueous solutions of NDMA, the major products are methylamine (MA), dimethylamine (DMA), nitrite, nitrate, formaldehyde, and formic acid.[95,98,101] MA and formaldehyde are produced by the hydrolysis of imine **32** (**32**$^+$), and the latter is oxidized to formic acid. In nonaqueous solutions without acid, the imine is observed instead of its hydrolysis products.[23,110] In acidic solutions with relatively high concentrations of nitrosamine (≥~50 mM), the corresponding amidoxime (**36**, Scheme 12) is also obtained.[23,110,111] Although there is no single agreed-upon mechanism for **36**'s formation,[101,111] there is evidence that this amidoxime is produced by an intermolecular reaction rather than an intramolecular rearrangement.[110] The amidoxime product is not typically observed in more modern product studies of nitrosamine photolysis, which are often conducted in dilute aqueous solutions (≤1 mM nitrosamine).[95,96,98] However, an amidoxime has been proposed as an intermediate in the formation of *N*-methylformamide during NDMA photolysis at low concentrations in water.[101]

**Scheme 12. Formation of an Amidoxime (36) during Nitrosamine Photolysis**




In aqueous solutions, the solution pH and initial concentration of NDMA significantly affect the distribution of photolysis products. In neutral and acidic conditions, DMA is the favored product when the initial concentration of NDMA is greater than $10^{-4}$ M,[95] but MA is increasingly favored at lower, more environmentally relevant concentrations (≤$10^{-5}$ M).[96,98] DMA and nitrite formation are both maximized at approximately pH 4, and the product distribution can be diverted toward DMA at other pHs by the addition of nitrite.[98,101] This is consistent with the occurrence of path B in Figure 5, which both consumes and produces nitrite (through the decomposition of $N_2O_3$) and is favored by higher concentrations of nitrite in solution (a consequence of higher initial NDMA concentration). Higher initial NDMA concentrations also facilitate DMA production by hydrogen abstraction from unreacted NDMA (or another species) by **31** and **35**. Hydrogen abstraction from NDMA also leads to MA formation by hydrolysis of **32** (**32**$^+$). In alkaline aqueous solutions, MA is the major amine product.[98,101] Under nitrogen atmosphere, formation of *N*-methylformamide has been observed in solutions at pH > 5, although as mentioned this product is presumed to be generated from decomposition of *N*-methylformamidoxime (**36** where R = $CH_3$, R′ = H).[101]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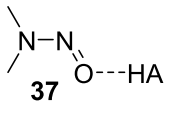
Photolysis of nitrosamines in acidic aqueous conditions produces more nitrite than nitrate and in alkaline conditions the ratio is reversed.[101,105] Photolysis of acidic solutions initially produces both nitrite and nitrate, however the nitrate production quickly tapers off while nitrite formation continues.[95,98,105] In alkaline solutions, both are produced throughout the reaction progression, but nitrate is formed at a faster rate.[105] The relative amounts of nitrate and nitrite produced by photolysis of neutral solutions are less clear, and studies have reported that nitrite may be significantly favored,[95] slightly favored,[98] or slightly disfavored[101] relative to nitrate. Stefan and Bolton found that nitrate appeared to be primarily produced as a result of oxidation of nitrite at pH 7.[95] In contrast, a study by Lee and co-workers reports their simultaneous formation.[98] These differences may be a consequence of experimental conditions, which used different initial nitrosamine concentrations, solution buffer systems, and light sources for photolysis. The formation mechanisms of these ions in nitrosamine photolysis have been given much less attention than the organic products. A complete exploration of the relevant solution-phase $NO_X$ chemistry is beyond the scope of this review, but Figure 5 includes several key reactions that lead to their production.[101,105]

The kinetics of nitrosamine photolysis are concentration-dependent. Nitrosamine photolysis in water follows first-order kinetics for low initial concentrations (<0.1 mM).[95,96,100,104,112] Stefan and Bolton found that at higher initial NDMA concentrations (0.1 and 1 mM), zero-order kinetics were initially observed, followed by first-order kinetics after a significant amount of NDMA had already degraded.[95] Zero-order kinetics have also been observed for the photolysis of *N*-nitrosopiperidine (NPIP) in acidic aqueous methanol (1:1) at high initial concentrations.[111] It is unclear in the literature why zero-order kinetics are observed at these high concentrations, but it may be a consequence of poor transmission of UV light through concentrated solutions of nitrosamines. Typical studies focus on environmentally relevant concentrations in the first-order kinetics regime. For aqueous nitrosamine samples with low initial concentrations, higher rate constants are observed for more dilute solutions,[95,104] but this trend is reversed in acetonitrile.[99] As mentioned above, nitrosamine photolysis is faster in more acidic solutions than in neutral or basic solutions,[95,104,105] and is also accelerated in $O_2$-saturated solutions relative to $N_2$-saturated solutions when the $\pi \rightarrow \pi^*$ transition is excited.[101] The structure of the nitrosamine is also important. Dialkylnitrosamines have been found to decompose much more rapidly than diarylnitrosamines in aprotic solvents, which is likely because the latter are not susceptible to hydrogen abstraction from the $\alpha$ position.[108]

Lastly, it should be noted that although Figure 5 depicts NDMA as the species which is excited, early literature proposed that the photolabile species is in fact a hydrogen-bonded nitrosamine/acid complex (**37**, Figure 6) and not the nitrosamine itself.[23,107] This was consistent with the then-accepted (and now thoroughly disproven) photostability of the nitrosamines in neutral solvents[23,107] and the fact that nitrosamines are too weakly basic (conjugate acid $pK_a$ < 1)[25,113] for the *O*-protonated nitrosamine conjugate acid (**4**, e.g., ground-state **33**) to play a significant role under most conditions. Complex **37** had also been described previously to explain some observed effects of solution acidity on the UV−vis absorption spectra of nitrosamines.[25,114] In this view, when complex **37** is excited it behaves analogously to **33*** and produces the same products as depicted in Figure 5.[26,102,115] Formation of **37** is observed in cyclohexane solutions of dialkylnitrosamines with trichloroacetic acid at millimolar concentrations (~10 mM) by UV−vis spectroscopy.[114] Thus, it is plausible that such complexes are involved in nitrosamine photolysis in aprotic solvents in the presence of acid. However, the role of the evoked nitrosamine/acid complex **37** is unclear in neutral or alkaline aqueous solutions, wherein the nitrosamine is primarily engaged in weaker, but omnipresent, hydrogen bonding with water.[25] Dilute acids are also expected to be largely dissociated under these conditions and the hydronium ion does not appear to be a strong enough proton donor to produce a detectable spectroscopic signature for **37**. Specifically, the UV−vis absorption spectra of aqueous solutions of NDMA pH 2−8 do not contain features attributed to the strongly hydrogen-bonded complex **37**.[25,97,101] Thus, the formation of strongly H-bonded ground-state complex **37** must not be required for photolysis because quantum yields are consistent across pH 2−8[101] and hydrolysis (path C) occurs outside of acidic solutions.[102] Nevertheless, perhaps because many of the early solution-phase photolysis studies were done in weakly acidic nonaqueous conditions,[23,26,107,115] the nitrosamine/acid complex **37** is often evoked in modern literature descriptions of nitrosamine photolysis in aqueous solutions.



**37**

**Figure 6.** Strongly hydrogen-bonded NDMA/acid (HA) complex **37**.

**Synthetic Applications of Nitrosamine Photochemistry.** Although fewer investigations have focused on neutral conditions, the photochemical reactions of *N*-nitrosamines in acidic conditions were extensively explored by Chow and co-workers in the late 1960s through the 1980s.[26,103,115−127] Many of these reactions have been reviewed previously,[26,118] but are covered briefly here for completeness. Chow and co-workers found that the reactions of nitrosamines under photolytic conditions with various substrates are dominated by the reactivity of the produced aminium radical, and consequently require acidic conditions.[26] Upon photolysis of a nitrosamine under inert gas, the aminium radical and nitric oxide can add across unsaturated C−C bonds in a stepwise fashion to yield products bearing a tertiary amine and an adjacent *C*-nitroso moiety (Figure 7). These interesting products often undergo additional transformations, such as tautomerization to the corresponding oxime (Figure 7, middle and bottom).[26,118,127] When the photolysis is alternatively performed under air, the products contain a nitrate ester rather than a *C*-nitroso group (Figure 7, top).[26,120] An exception to these acidic reactions is the photoinduced nitrosation of polycyclic phenols (e.g., 1-naphthol **38**) by NDMA in neutral solutions under inert gas.[116] The nitrosated products undergo rearrangement and are isolated as the quinone monooximes (**39**, Figure 8). The authors proposed that acid was not required because the excited polycyclic phenol (e.g., **38**) undergoes a proton transfer reaction with NDMA, initiating fragmentation of NDMA to the reactive fragments.

Additional reactivity may be accessed in neutral solutions through the nitramine products of nitrosamine photolysis.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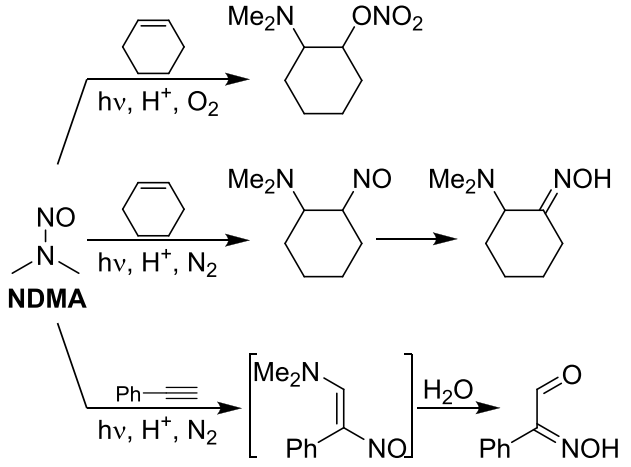


**Figure 7.** Examples of nitrosamine photoaddition across unsaturated C−C bonds.

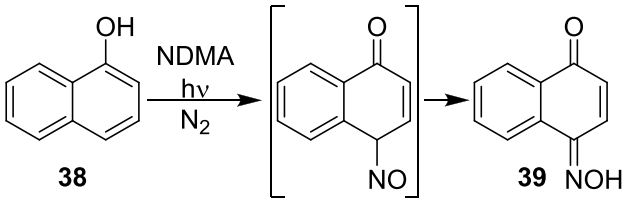


**Figure 8.** Acid-free photoinduced nitrosation of **38** by NDMA. The initial nitrosated product rearranges to **39**.

Analogous to nitrosamines, nitramines can photolyze by homolytic scission of the N−N bond to produce an amino radical (e.g., **31**) and a $NO_x$ species ($NO_2$ instead of NO in Scheme 11).[128] Photolysis in various solvents of *N*-nitroso-*N*-methylaniline (**40**) or the *p*-nitro derivative in air produced ring-nitrated products **42a,b** alongside the corresponding nitramine (**41**, Figure 9). The nitrated species were formed

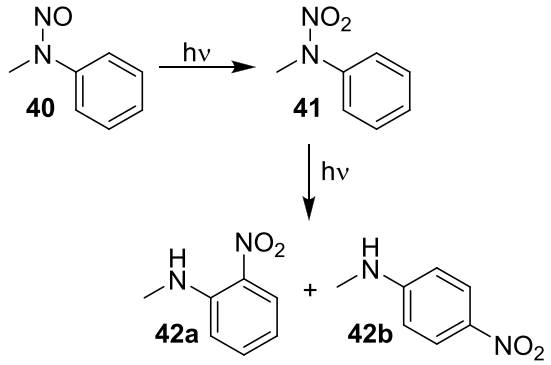


**Figure 9.** Irradiated *N*-nitrosoaniline **40** produces *N*-nitroaniline **41**, which gives ring-nitrated anilines **42a,b** with continued irradiation.

from photolysis of the initial nitramine product.[129] Photolysis of nitramine explosives like RDX can also effect nitration of electron-rich aromatic molecules (e.g., **43a**, Figure 10a)[130] and olefins[131] in solution. Under UV irradiation, RDX can also formally abstract hydride from 10-methyl-9,10-dihydroacridine (**43b**) to yield the corresponding *N*-methylacridinium (**44**, Figure 10b).[132] Although these reactions have not been explicitly explored for dialkylnitrosamines, related transformations may be possible.

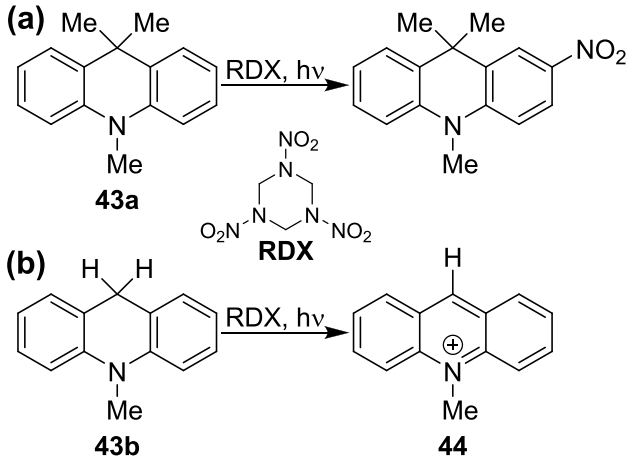


**Figure 10.** Photoinduced (a) nitration of **43a** and (b) hydride abstraction from **43b** with nitramine explosive RDX.

## ■ *N*-NITROSAMINES AS WATER CONTAMINANTS

*N*-Nitrosamines can be found throughout the environment, but it is their presence in water that has drawn the most concern. While nitrosamines may accumulate in indoor air, particularly at tanneries or manufacturing sites in the rubber and pesticide industries,[8] they are short-lived in outdoor air as a result of facile degradation by sunlight photolysis and other atmospheric reactions.[133,134] In water, however, NDMA and other nitrosamines are more persistent.[8] Although they may naturally decompose through photolysis, this is obviously limited to sunlight-exposed surface waters and can be hindered by light-screening by other dissolved matter.[96] As indicated in our above discussion of nitrosamine chemistry, they are unlikely to degrade by other reactions in the mild aqueous conditions expected in most natural or municipal waters. This stability is made all the more troubling by their formation as disinfection byproducts (DBPs) during common water treatment processes.[135] Consequently, and unsurprisingly, there is a vast and growing body of literature on the formation, remediation, and prevention of nitrosamines (particularly NDMA) in water, and a number of reviews have been published on this subject.[11−14] Here, we present a brief overview of nitrosamines as water contaminants, and direct readers to the cited reviews for detailed coverage of the topic.

**Formation.** Although nitrosamine production is not typically a desired outcome, there are numerous conditions which can lead to the unintentional formation of nitrosamines.[136] Thus, nitrosamines can be introduced into the environment through waste streams from industrial sites where they were inadvertently formed or they can form from precursors in the environment through various biological or chemical processes.[8] Much of the research on the occurrence of nitrosamines in water has focused on their formation during water disinfection. Of the disinfection methods, chloramination has received the most attention in large part due to the ubiquity of the requisite organic amine precursors in dissolved organic matter.[13,14] Although nitrosamine formation during chloramination has long been established to occur, the mechanism is not entirely understood and there is still some debate about whether monochloramine ($NH_2Cl$)[137−139] or dichloramine ($NHCl_2$)[135,140,141] is the species most responsible for nitrosamine formation. The importance of the latter is supported by evidence that minimizing dichloramine during


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chloramination reduces nitrosamine formation.[142,143] Figure 11 outlines the proposed formation pathways with each chloramine from a secondary amine as a model precursor. In short, the amine precursor attacks the electrophilic chloramine to produce an unsymmetrically substituted hydrazine derivative (**45** and **45-Cl**), which is subsequently oxidized to a nitrosamine.[135] A wide variety of amine precursors have been shown to form nitrosamines under chloramination conditions, including both secondary and tertiary amines.[13,14,135] In particular, dimethyl tertiary amines bearing a $-CH_2-$aryl moiety (e.g., benzyl, furfuryl) (**46**, Chart 6) have been identified as having especially high NDMA formation potential.[141,144] Notably, this group contains the pharmaceutical ranitidine (Chart 6),[138,145,146] which was pulled from shelves in late 2019 after multiple lots were found to contain NDMA.[6] Quaternary ammonium compounds can also contribute to nitrosamine formation, including components of consumer products[147] and quaternary ammonium polymers used as coagulants in wastewater treatment (e.g., polyDADMAC, Figure 12).[148,149] The quaternary ammonium cations can degrade to secondary and tertiary amines during chloramination, which can then go on to form nitrosamines.[135,147] Although they produce nitrosamines in substantially lower yields than secondary and tertiary amines,[147] quaternary ammonium compounds are potentially significant precursors because of their ubiquity in commercial products.

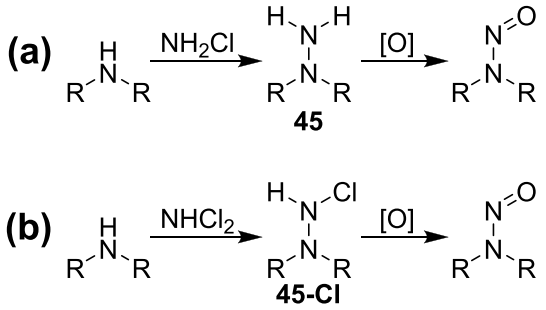
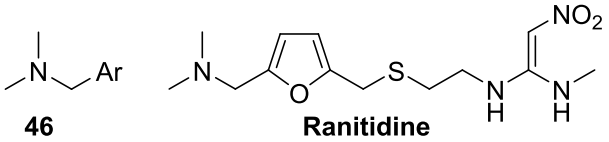



**Figure 11.** Nitrosamine formation during chloramination with either (a) monochloramine or (b) dichloramine as the reactive chloramine.

**Chart 6. Dimethyl Tertiary Amine Bearing a $-CH_2-$aryl Group (46) and Ranitidine, Which Contains the 46 Motif**



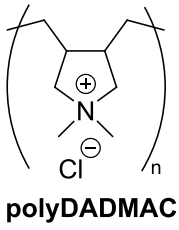
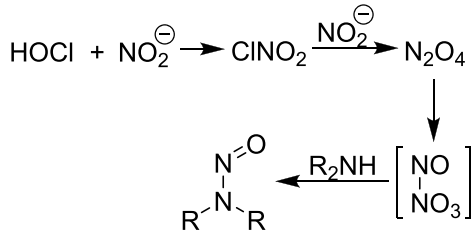




**Figure 12.** PolyDADMAC, a coagulant polymer.

Chlorination of nitrite-containing water can lead to the formation of nitrosating species and consequently result in the formation of nitrosamines during disinfection (Scheme 13).[150]

**Scheme 13. Formation of a Nitrosamine during Chlorination of Nitrite-Containing Water**




Both secondary[150] and tertiary[151,152] amines may serve as precursors. This pathway is relatively unimportant in drinking water, which typically has low nitrite concentrations, but may be significant in other water matrices with elevated amounts of nitrite and amine precursors.[135,153] Outside of chlorination, it has also been demonstrated that the nitrosation of aliphatic secondary amines in water can be catalyzed by micelles formed from cationic surfactants.[154] Cationic surfactants are common in a variety of consumer products and thus may often be present in municipal waste streams.

Disinfection of water via ozonation has also been tied to NDMA formation, but the yields of NDMA from most precursors are very low unless ammonia and bromide levels are also elevated.[14,155] During ozonation, ammonia can form hydroxylamine ($NH_2OH$) and, in the presence of bromide, brominated nitrogenous species like bromamines (e.g., $NH_2Br$). Analogously to the pathways depicted in Figure 11, these products can react with amines to form hydrazine derivatives which are oxidized to nitrosamines by ozone.[155] A narrow subset of precursors including dimethylamine-containing hydrazines[156] and, by a slightly different mechanism, sulfamides[157] are converted to nitrosamines in high yields during ozonation, but these precursors are not commonly present in significant concentrations.[13,14] Thus, in many water matrices, nitrosamine formation during ozonation is not expected to be significant, but in some waters (e.g., municipal wastewater) it can be quite high.[158] Similarly, while treatment with chlorine dioxide produces very little NDMA (<0.1% yield) from most precursors,[14] it produces considerably more from the plant regulator daminozide (~5%),[159] so nitrosamine formation by this pathway may primarily be a concern for waters impacted by agricultural runoff.

**Remediation and Mitigation.** Techniques for the remediation and mitigation of nitrosamines in water fall generally into one of three broad categories: destruction of nitrosamines, physical removal of nitrosamines (i.e., filtration), or prevention of nitrosamine formation. Of the first type, destruction of nitrosamines, irradiation with UV light was one of the earliest methods and it remains one of the most established.[11,14,95,96,100,102,160] Direct photolysis can be effective,[95,100] but the high UV fluence required for nitrosamine treatment can make this method costly.[13] Additionally, direct UV photolysis does little to destroy nitrosamine precursors, including the secondary amine produced by photolysis, and so subsequent reformation of nitrosamines remains a plausible issue in UV-treated waters.[13] This issue can be somewhat mitigated by the inclusion of an oxidant like ozone during UV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treatment ($UV/O_3$), which has been found to reduce the amount of secondary amine produced by photodegradation.[104] Some recent work suggests that including peroxodisulfate ($S_2O_8^{2-}$) during UV treatment ($UV/S_2O_8^{2-}$) may improve the efficiency of NDMA photodegradation,[160] though more work is needed to evaluate the product distribution and performance with other nitrosamines.

Other means of nitrosamine destruction exist, but none are as well-established as UV treatment. Treatment of contaminated waters with ozone/hydrogen peroxide ($O_3/H_2O_2$) is more effective at degrading nitrosamines than conventional ozonation, but this technique may have limited practical application as a result of the risk of carcinogenic bromate formation under these conditions.[161] Electrochemical oxidation[162] and reduction[163] of aqueous NDMA have been reported, and several metals have been demonstrated to catalyze the reduction of nitrosamines in water.[164−166] Various methods utilizing bioremediation (e.g., bacterial degradation) of nitrosamines in water have shown promise.[14] One such method, propane biosparging, has been demonstrated in the field for the in situ treatment of an NDMA-contaminated aquifer.[167] Propane-oxidizing bacteria are capable of degrading NDMA, so introducing additional propane via biosparging feeds these bacteria and promotes biodegradation of NDMA.[167,168]

The second strategy, physical removal of nitrosamines, is often challenging. Removal of nitrosamines from water through adsorption to materials such as activated carbon is typically ineffective due to the low hydrophobicity of many nitrosamines,[11] although removal does improve with increasing hydrophobicity of individual nitrosamines.[169] Sand and soil filtration are also ineffective.[11] Studies on the effectiveness of reverse osmosis (RO) for nitrosamine removal have found that membrane rejection of NDMA is often low and also highly variable with operating conditions, such as temperature.[170,171] Rejection is better for larger nitrosamines, though there is much less information about their removal by RO because most reports focus on NDMA.[170] In addition to size affecting removal by RO, nitrosamines' ability to hydrogen bond with the membrane materials appears to facilitate their diffusion through the membrane.[172] When tested with two different polyamide membranes, NDMA and *N*-nitrosomethylethylamine (NMEA) were rejected at a lower rate than both larger nitrosamines and also similarly sized non-nitrosamine structural analogs with reduced hydrogen bonding ability (e.g., their formamide analogs).[172] The rejection of nitrosamines by polyamide RO membranes can be greatly improved through methods such as heat-treating the membranes[173] or functionalizing the surface with graphene oxide,[174] but both of these modifications reduce water permeability which may limit their practical application. Physical removal techniques can be paired with destructive methods. In one example, powder-activated carbon was used to adsorb NDMA to a reactive membrane, where it was then electrochemically reduced.[163]

Given the difficulties and costs of remediating nitrosamine-contaminated water, the adage that an ounce of prevention is worth a pound of cure rings strikingly true here. Prevention of nitrosamine formation is arguably the most important aspect of long-term control of nitrosamine contamination in many situations. Considerable research has been dedicated to methods for removing precursors or for transforming them into species with reduced nitrosamine formation potential, and many of these strategies are analogous to those mentioned above for nitrosamines.[13,14] Although not particularly effective for nitrosamine removal, activated carbon can remove nitrosamine precursors and reduce the nitrosamine formation potential during chloramination.[175,176] Preoxidation to destroy potential precursors can significantly decrease nitrosamine production during chloramination.[177] However, a preoxidation step can itself increase the formation of other DBPs and so these trade-offs must be considered when choosing an oxidant.[178] Modification of water treatment conditions can also reduce nitrosamine formation. For example, purification of the coagulant polymer polyDADMAC (Figure 12) to remove lower molecular weight fractions has been shown to reduce NDMA formation during disinfection without harming polymer performance in water treatment.[179]

The most effective long-term strategies for controlling nitrosamines will combine methods of eliminating existing nitrosamines with tactics to prevent their formation in the first place. There is unlikely to be a single "best" solution to the problem of environmental nitrosamines because there is no single cause for their presence. Mitigation strategies that effectively control disinfection-related contamination might do very little to reduce nitrosamines originating from other sources, and more work is needed to understand what those sources may be. Additionally, research on aqueous nitrosamines has often focused on NDMA exclusively, and this is a significant problem for the field. It has long been known that numerous nitrosamines are carcinogenic to mammals[1,3,180] and there is evidence that NDMA may only make up a small fraction of the total nitrosamine content in drinking water,[181] and yet there is relatively little work focusing on those other nitrosamines. These other nitrosamines may respond very differently from NDMA to remediation strategies, have different origins, and/or have different effects on human health, and future work must fill this gap in our understanding. Essential to this work will be reliable, sensitive methods for detecting nitrosamines, which are discussed in the next section.

## ■ DETECTION AND SENSING OF *N*-NITROSAMINES

Our ability to understand how *N*-nitrosamines form and spread in our environment—not only in air and water, but also in our diets and drugs—is inherently limited by our methods for detecting these contaminants. In recent decades, particular attention has been paid to quantitative detection of nitrosamines in water, motivated in part by their occurrence as byproducts of manufacturing and disinfection processes. Although there are no federal regulations on nitrosamines in water in the United States, the US Environmental Protection Agency (EPA) has set a screening level of 0.11 ng/L (0.11 ppt, 1.5 pM) for NDMA in residential tap water based on a $10^{-6}$ cancer risk.[182] Similar screening levels were also set for other small dialkylnitrosamines. Several states have set their own drinking water guidelines for NDMA.[66] In some states, such as Massachusetts (10 ng/L guideline), the guidelines are as much based on how much NDMA can be practically detected as they are on the cancer risk.[183,184] Thus, analytical methods for aqueous nitrosamines must be highly sensitive for practical use.

At the simplest level, many of the common methods for adequately sensitive (ng/L) detection of aqueous nitrosamines are based on a similar concept: Extract the nitrosamines from water, greatly concentrate the sample in organic solvent, chromatographically separate the components, and then detect the components, often with mass spectrometry.[12,15,185] Naturally, there are numerous variations within this frame-


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Table 1. EPA Method 521 LODs[186] and Corresponding EPA Screening Levels for Residential Tap Water[182]

| *N*-nitrosamine | Method 521 LOD (ng/L) | screening level (ng/L) |
|---|---|---|
| *N*-nitrosodimethylamine (NDMA) | 0.28 | 0.11 |
| *N*-nitrosodiethylamine (NDEA) | 0.26 | 0.17 |
| *N*-nitrosomethylethylamine (NMEA) | 0.28 | 0.71 |
| *N*-nitrosodi-*n*-propylamine (NDPA) | 0.32 | 11 |
| *N*-nitrosodi-*n*-butylamine (NDBA) | 0.36 | 2.7 |
| *N*-nitrosopyrrolidine (NPYR) | 0.35 | 37 |
| *N*-nitrosopiperidine (NPIP) | 0.66 | 8.2 |

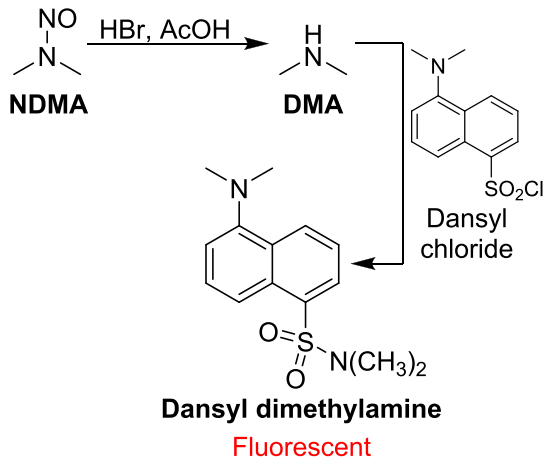
work, and these analytical methods for detection of aqueous nitrosamines have been reviewed elsewhere.[12,185] Additionally, *N*-nitrosamine detection methods were recently the subject of a review by Parr and Joseph.[15] Here, we will focus on those methods which leverage the chemistry of nitrosamines in their detection scheme to reduce sample preparation and instrumentation requirements.

For comparison purposes, we briefly describe here EPA Method 521, the standard EPA method for sensitive detection of volatile nitrosamines in drinking water.[186] In this method, analytes are extracted from 0.5 L of water via solid phase extraction (SPE) using a cartridge of coconut charcoal. The sample is then eluted/extracted with DCM and concentrated to less than 1 mL. After the addition of an internal standard, the volume is adjusted to 1.0 mL with DCM. This concentrated sample is then analyzed by gas chromatography−tandem mass spectrometry (GC−MS/MS). Method 521 can detect NDMA and six other volatile nitrosamines at low ng/L concentrations in drinking water, with limits of detection (LODs) ranging from 0.26 to 0.66 ng/L (Table 1). Notably, the LODs for NDMA (0.28 ng/L) and *N*-nitrosodiethylamine (NDEA, 0.26 ng/L)[186] are higher than their respective EPA screening levels for residential tap water (0.11 ng/L and 0.17 ng/L).[182] However, it may be possible to obtain lower LODs with this method than were reported in the original 2004 technical document with newer, more sensitive instrumentation.

GC may also be coupled with other detection methods, such as nitrogen−phosphorus detection and chemiluminescent nitric oxide detection, for determination of nitrosamine content.[12,187] Although EPA Method 521 and other GC-based methods can measure volatile nitrosamines with high sensitivity, they often struggle with nonvolatile or thermally unstable nitrosamines, such as *N*-nitrosodiphenylamine. Various liquid chromatography−mass spectrometry (LC−MS) methods, particularly LC−MS/MS, have been developed which are compatible with a wider range of nitrosamines.[15,185] However, as exemplified by EPA Method 521, the high sensitivity of GC−MS and LC−MS methods alike come at the cost of time-consuming sample preparation and expensive instrumentation.

The latter issue, instrumentation cost, is reduced in methods which couple high-performance liquid chromatography (HPLC) with detection by UV−vis absorption or emission, rather than mass spectrometry. In one such detection scheme, pre-column acidic denitrosation of NDMA and subsequent reaction with dansyl chloride gave the fluorescent dansyl amine (Scheme 14), which was then separated by HPLC and detected by fluorimetry.[188] Although choosing to perform the denitrosation and derivatization pre-column clearly risks interference by ambient dimethylamine, the authors reported that dimethylamine was only ineffectively adsorbed during SPE

Scheme 14. Acidic Denitrosation of NDMA and Subsequent Derivatization with Dansyl Chloride




of aqueous samples and thus was present in insignificant amounts during the later reaction with dansyl chloride. Rather than rely on the extraction step to remove likely interferents, HPLC-absorption/emission methods more often utilize nitrosamine reactivity *after* chromatographic separation. The reduction of tris(2,2′-bipyridyl)ruthenium(III) ($Ru(bpy)_3^{3+}$) by aliphatic amines generates chemiluminescence,[189] and this reaction was utilized in conjunction with post-column photolytic denitrosation to detect aliphatic nitrosamines.[190] The nitrite generated by nitrosamine photolysis has also been utilized in their detection: post-column UV irradiation and subsequent addition of Griess reagent (Figure 13a) allows for colorimetric measurement of nitrosamines.[191,192] This concept has been applied to nitrosamines in beer, gastric juices,[191] and water.[192] Positive responses to the online Griess test (Figure 13b) are obtained from both nitrosamines and nitramines, but these can be distinguished from each other by comparison of observed retention times to those of analytical standards.[192]

Although the above-described HPLC methods can detect low ng/L concentrations of nitrosamine, they all require significant preconcentration by SPE to achieve that sensitivity.[188,190−192] Even if the entire detection scheme from extraction to detection is fully automated, as in the case of the $Ru(bpy)_3^{3+}$ chemiluminescence method,[190] SPE is nevertheless time-consuming and consequently the analysis of a single sample often takes at least 1 h, and sometimes much longer.[192] Furthermore, activated carbon-based materials commonly used for SPE have been shown to catalyze the formation of nitrosamines from secondary amines under aerobic conditions, leading to potential errors in analysis.[193−195] Without preconcentration, none of the methods mentioned thus far can achieve ng/L detection limits, which makes the HPLC−photochemical reaction−chemilumines-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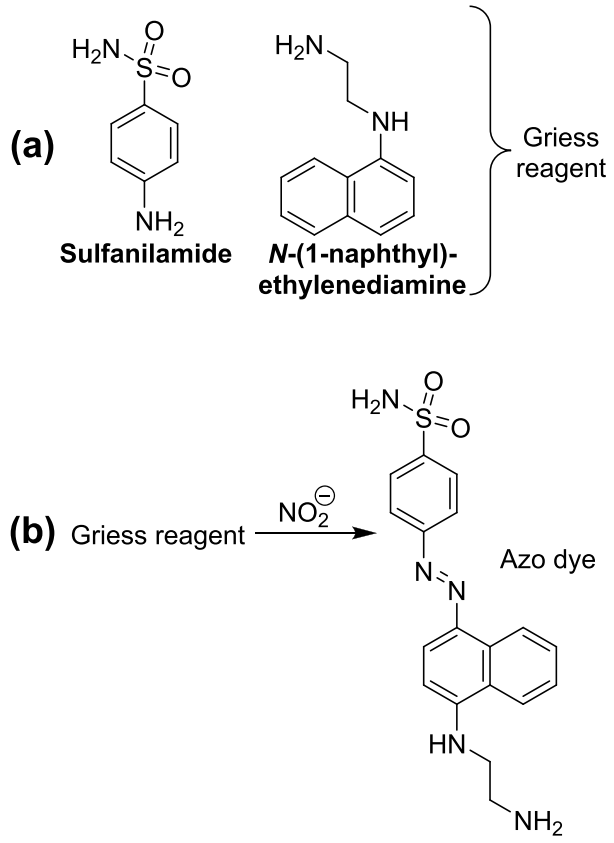


**Figure 13.** (a) Typical components of the Griess reagent and (b) their reaction with nitrite to produce a colorful azo dye. This is the basis of the Griess test for nitrite.

cence (HPLC−PR−CL) method[196] first reported by Kodamatani et al. in 2009 notable in the realm of HPLC-based methods of nitrosamine detection. In this method, a small volume (200 $\mu$L) of aqueous sample is directly injected for HPLC separation without preconcentration, followed by post-column photolysis to produce peroxynitrite ($ONOO^-$). Luminol is then added and reacts with the peroxynitrite, resulting in chemiluminescence that is measured by a standard chemiluminescence detector. The complete analysis takes minutes, rather than hours, and low-ng/L detection limits are achieved for NDMA and several other nitrosamines. Interference from hypochlorite, commonly found in reclaimed wastewater, could be eliminated by brief pretreatment of the sample with ascorbic acid, and interference from residuals in ultrafiltration-treated wastewater could be controlled by reducing the injection volume to 20 $\mu$L while still achieving a method detection limit of 2 ng/L for NDMA.[197] No interference is observed in the direct injection of reverse osmosis permeate, which has allowed this method to be used for online near real-time monitoring of NDMA in wastewater treated by reverse osmosis at pilot scale.[198] The method has been validated for the detection of four nitrosamines in several recycled water matrices[199] and performs comparably to SPE-GC−MS/MS methods.[197] However, although the sensitivity is impressive when detecting NDMA, NMEA, *N*-nitrosomorpholine (NMOR), and *N*-nitrosopyrrolidine (NPYR), the method's performance detecting NDEA and NPIP is disappointing (LODs > 15 ng/L).[199]

Although chromatography-based methods for nitrosamine detection are well established, the required instrumentation inherently restricts their use to specialized settings (e.g., laboratories). This limits the widespread accessibility of these methods, and hinders work requiring large numbers of water sources to be tested. Chromatography and mass spectrometry can be miniaturized, however portable devices are still highly expensive and complex to operate, and so a practical integrated device for in-field detection of these carcinogens is not possible by these current methods. The desire for a simple, rapid nitrosamine test is not new. Particularly in the 1960s and 1970s, a number of colorimetric and fluorimetric indicators were reported for the detection of nitrosamines.[200] Similar to the more modern methods described above, these methods typically cleaved the nitrosamine N−N bond and then added an indicator which reacted with either an $NO_x$ fragment (e.g., detection of nitrite by Griess reagent)[201,202] or the secondary amine (e.g., derivatization with dansyl chloride) to give colored or fluorescent product.[203] However, these methods often had high LODs and poor selectivity, even when used as thin-layer chromatography stains rather than as stand-alone indicators.[15,200] Other methods first reduced the nitrosamine to the corresponding hydrazine, which was then condensed with an aromatic aldehyde to give a colored or fluorescent hydrazone product.[204−206] Those methods are also incompatible with a portable in-field detection scheme, as they require harsh reagents like LAH to reduce the nitrosamine.[204]

Several more modern chromatography- and mass spectrometry-free detection methods also utilize cleavage of the N−N bond. In particular, there are several methods for quantifying total *N*-nitrosamine (TONO) content in water that subject samples to denitrosative conditions and then detect the released nitric oxide (NO) with a commercial NO detector.[207,208] This concept has also been used to measure TONO content in food, personal care products, and human bodily fluids.[209] Mitch and colleagues utilize acidic triiodide to cleave the N−N bond,[181,207] but these denitrosation conditions have been shown to produce the nitrosating agent nitrosyl iodide (NOI).[210] NOI may simply decompose to NO in solution, but conceivably it could also nitrosate species (e.g., amines) in the sample, reducing the observed NO yield. Furthermore, successive injections of nitrosamine samples into the acidic triiodide solution resulted in a gradual reduction of the measured NO, suggesting a degradation of the reagent solution.[208] Better signal reproducibility is obtained when, instead of chemical denitrosation, UV light is used to cleave the N−N bond.[208] Additionally, photolysis can be performed with only a small UV light source, and thus is more compatible than chemical denitrosation for use in a portable nitrosamine detector. However, both TONO methods share several drawbacks.[207,208] First, both chemical and photolytic denitrosation methods show differences in conversion efficiency among different nitrosamines, so the analysis accuracy may vary with nitrosamine composition. Second, *S*-nitrosothiols and nitrite also produce NO under either of these denitrosative conditions, and so pretreatment steps are required to eliminate these species prior to denitrosation. Third, without preconcentration, the detection limits of these methods are impractically high (~0.1 $\mu$M, or 7.4 $\mu$g/L as NDMA). The detection limit can be lowered with extraction and preconcentration, but extraction efficiencies can vary widely across nitrosamines of different polarities using any single extraction method.[207] Not only may this skew results by total nitrosamine composition, but also preconcentration is time-consuming and ill-suited for use in in-field analysis.


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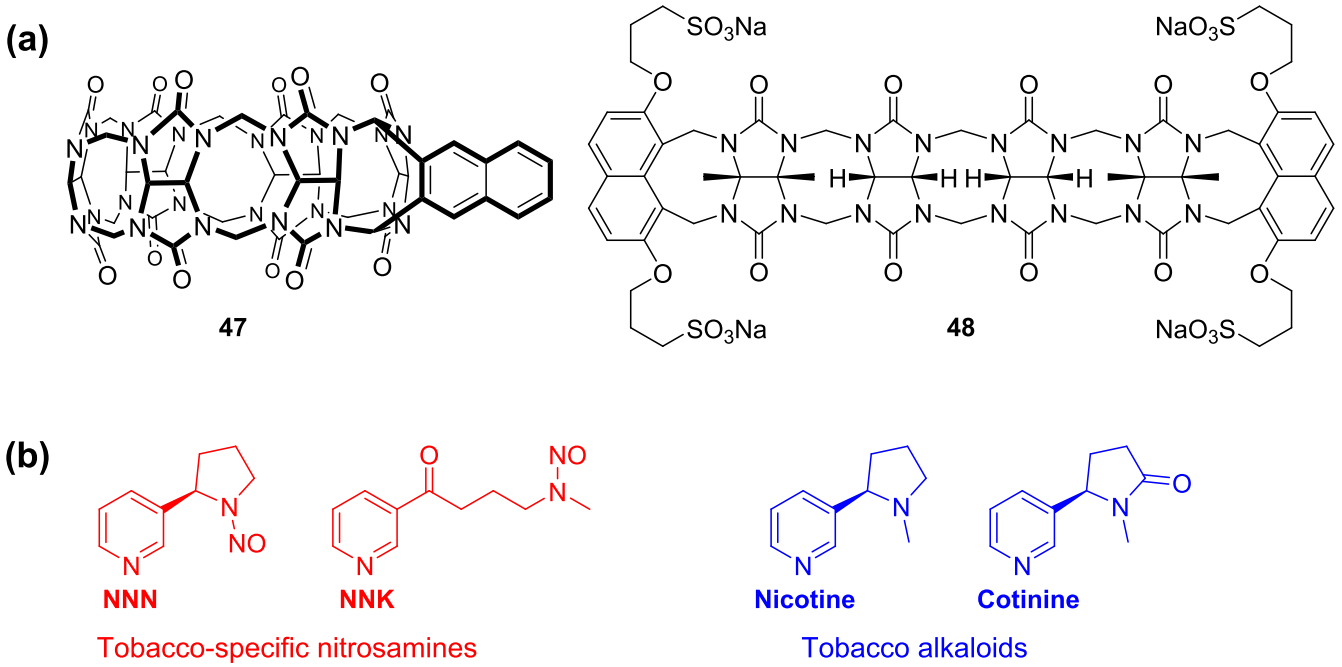


**Figure 14.** (a) Receptors in Anzenbacher and co-workers' two-probe fluorimetric assay, CB[6] derivative **47** and cucurbituril-like molecule **48**. (b) Tobacco-specific nitrosamines and tobacco alkaloids that could be differentiated by the assay.

To this point, we have almost exclusively discussed methods of nitrosamine detection that do not measure the nitrosamines directly, but rather detect one of the species produced by breaking the nitrosamine N−N bond. However, the products most often used to detect nitrosamines (e.g., nitrite, NO, and secondary amines) may be present independently of nitrosamines in complex samples such as environmental waters or wastewater. Products like nitrite and nitric oxide may also be formed from species other than nitrosamines under the implemented denitrosation conditions.[5] These interferents can be removed through sample preparation and/or chromatographic separation, but this increases the total cost and time required to perform the analysis. It thus would be advantageous to detect nitrosamines more directly. However, there are exceedingly few nonchromatographic methods of this kind for nitrosamines in any matrix, let alone for nitrosamines in water.

For detection of aqueous NDMA, Cetó et al. reported an impedimetric sensor consisting of molecularly imprinted polymer (MIP) particles made of cross-linked poly(methyl methacrylate) trapped in a polypyrrole matrix on a glassy carbon electrode.[211] The MIP particles were formed using NDMA as the template, so when exposed to aqueous solutions only NDMA is easily trapped near the electrode surface. The sensor showed significantly smaller responses to other structurally related molecules (e.g., DMF) and the presence of these related molecules in solution did not significantly affect the sensor's response to NDMA. Because no sample preparation is required, the entire analysis can be completed within 20 min, but a 30 min regeneration period to remove NDMA is required before the sensor can be reused. Although the speed and portability of this highly selective sensor are attractive, the LOD is only 0.85 $\mu$g/L (850 ppt) and so a preconcentration step would be needed to make this sensor practical for most water sources. A somewhat lower LOD was reported by Lin et al. for NDMA (10 nM, ∼ 740 ppt) and NDEA (10 nM, ∼ 1 ppb) in water through the use of surface-enhanced Raman scattering (SERS).[212] The SERS substrate consisted of a zwitterionic copolymer, poly(glycidyl methacrylate-*r*-sulfobetaine methacrylate) (PGMA-*r*-PSBMA), grafted onto hexagonal gold nanorods (Au NRs). When water evaporates from the sample on the substrate, the NDMA and NDEA are held near the Au NRs by association with PGMA-*r*-PSBMA, allowing the detection of these small molecules with SERS. Importantly, the report only demonstrates that it is possible to detect NDMA and NDEA with Raman spectroscopy, not that this is a quantitative detection method. However, a variety of hazardous chemicals can be detected with SERS-based methods, and on-site detection is possible with portable Raman spectrometers.[213,214] It is conceivable that further work could yield a sensitive and portable SERS-based nitrosamine sensor.

Although not proposed for water analysis, a conceptually interesting fluorescence-based sensor in aqueous solution was reported by Anzenbacher et al. which could recognize several nitrosamines.[215] Their sensor utilized two fluorescent receptors: cucurbit[6]uril (CB[6]) derivative **47** and cucurbituril-like acyclic molecule **48** (Figure 14a). When bound to a metal ion, their fluorescence is partially quenched, and displacement of the metal by another guest either recovers or further quenches the fluorescence, depending on the identity of the new guest. The differing sizes and flexibilities of **47** and **48** affect their respective affinities for guests, and their correspondingly different changes in emission intensity can be used together to identify guests. Using $Eu^{3+}$ as the metal ion, linear discriminant analysis was applied to the response of the two-probe assay and used to sort guests into one of three categories (biological amines, nitrosamines, and tobacco alkaloids). Most notably, the assay could differentiate between tobacco-specific nitrosamines *N*-nitrosonornicotine (NNN) and nicotine-derived nitrosamine ketone (NNK), and the structurally related tobacco alkaloids nicotine and cotinine (Figure 14b). This may be due to differences in protonation: the assay is performed at pH 3, which would protonate the alkaloids but not NNN and NNK, resulting in very different


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interactions with the probes. Although NDMA and NPIP were included in the two-probe qualitative assay, they were not included in the authors' efforts to use their sensor for quantitative measurements. Of the nitrosamines, only NNN and NNK were included for quantitative studies. This is likely because these studies were done only with probe **48**, which did not respond strongly to the smaller nitrosamines. The authors report LODs of 50 and 270 ppb for NNN and NNK, respectively. Although more rigorous selectivity studies are needed to evaluate the sensor, these detection limits are suitable for use with tobacco products.[216] Although it is unlikely this sensor will ever be practical for water testing, the concept itself is promising if receptors are developed which respond strongly to small dialkylnitrosamines like NDMA, preferably at circumneutral pH.

In the final sensor we will discuss, the ability of *N*-nitrosamines to bind to metal centers and form stable complexes[82] is leveraged for detection of dialkylnitrosamines in air.[217] This single-walled carbon nanotube (SWCNT)–based chemiresistive sensor, reported by Swager and co-workers, utilizes a cobalt(III) tetraphenylporphyrin (**49**, Figure 15a) as a selector for nitrosamines. The SWCNTs were

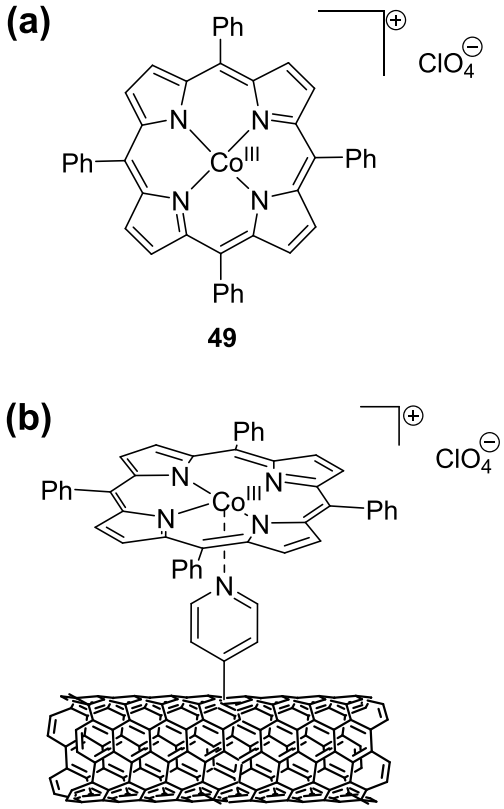


**Figure 15.** (a) Cobalt(III) tetraphenylporphyrin (**49**) used by Swager and co-workers as a selector for nitrosamines. (b) **49** anchored to the SWCNT through a 4-pyridyl group covalently attached to the nanotube's surface.

covalently functionalized with 4-pyridyl groups, which were used to anchor the metalloporphyrin (Figure 15b). Nitrosamines in the air can coordinate to the Co(III) center through their oxygen (e.g., Chart 5, left side) and this interaction produces an increase in resistance. The sensor was found to be highly selective for the tested dialkylnitrosamines (NDMA, NDEA, and NDBA) over common volatile organic compounds, which produced significantly smaller responses. Critical for real-world use, the sensor was not significantly affected by humidity. The potential utility of this sensor for distributed air monitoring was demonstrated by integrating the sensor device into a commercial sensing node, which enabled online detection of NDMA at ppb levels. The LOD was 1 ppb for all three nitrosamines. Although nitrosamines are not expected to significantly accumulate in outdoor air, 1 ppb is well below levels of nitrosamines that have been observed indoors in industrial settings.[218]

While selective, sensitive nitrosamine detection has been achievable in laboratory settings for many years through techniques such as GC–MS/MS, these methods are labor- and time-intensive and require expensive instrumentation. To facilitate on-site/in-field testing, more work is needed to leverage the chemistry of nitrosamines into robust, selective, and sensitive sensors, particularly for aqueous nitrosamines. Furthermore, sensors are needed which are inexpensive to produce and easy to use so that they may be used by nonscientists in communities affected by nitrosamine pollution (i.e., citizen science).

## FINAL REMARKS AND OUTSTANDING CHALLENGES

Here, we have provided a primer on the chemistry of nitrosamines, their role as water pollutants, and the methods for their detection. Although work has often focused on NDMA in recent years, it must be emphasized that nitrosamines are a diverse group of chemicals unified by a markedly simple structure, the N–N=O group. That diversity complicates both removal and detection efforts because individual nitrosamines can vary widely in terms of traits like size, shape, and hydrophilicity. However, their shared *N*-nitroso moiety is a challenging functional handle for practical applications because of its relative stability under mild conditions. That core N–N=O structure can be formed from a wide range of precursors under numerous different conditions, making the prevention of nitrosamines a multifaceted problem with no single solution. At the root of these different sides to the nitrosamine problem—prevention, removal, detection—is the chemistry of nitrosamines, and so an understanding of nitrosamine chemistry is essential to developing effective mitigation processes for environmental and public health. In particular, leveraging the chemical behavior of these carcinogens will enable the development of better sensors and better extraction materials.

## AUTHOR INFORMATION

### Corresponding Author

**Timothy M. Swager** – *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States;* orcid.org/0000-0002-3577-0510; Email: tswager@mit.edu

### Author

**Jessica C. Beard** – *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States;* orcid.org/0000-0003-3662-3042

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02774

### Notes

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## Biographies

Jessica C. Beard received her B.A. in chemistry from Northwestern University in 2017. Later that year, she joined the Swager group at the Massachusetts Institute of Technology, where she is currently a chemistry Ph.D. candidate. Her work focuses on the development of optically responsive indicators for the detection of aqueous contaminants.

Timothy M. Swager is a Professor of Chemistry at the Massachusetts Institute of Technology. He obtained his B.S. from Montana State University in 1983 and Ph.D. from Caltech in 1988, studying under Robert H. Grubbs. His research program is focused materials chemistry with emphasis on systems that advance analytical science.

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