Synthesis of 1,1-Dialkyhydrazines and their Hydroxyl Radical Degradation in Aqueous Environments

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SYNTHESIS OF 1,1-DIALKYLHYDRAZINES AND THEIR HYDROXYL RADICAL DEGRADATION IN AQUEOUS ENVIRONMENTS

by

Benjamin F. Strong

A Thesis
Submitted to the
Faculty of the Graduate College
in partial fulfillment of the
requirements for the
Degree of Master of Science
Department of Chemistry
Advisor: James J. Kiddle, Ph.D.

Western Michigan University
Kalamazoo, Michigan
August 2012
THE GRADUATE COLLEGE
WESTERN MICHIGAN UNIVERSITY
KALAMAZOO, MICHIGAN

Date June 21, 2012

WE HEREBY APPROVE THE THESIS SUBMITTED BY

__________________________
Benjamin F. Strong

ENTITLED Synthesis of 1,1-dialkylhydrazines and their Hydroxyl Radical Degradation in Aqueous Environments

AS PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF Master of Science

Chemistry

(Department)

Chemistry

(Program)

James J. Kiddle
Thesis Committee Chair

Elke Schitffers
Thesis Committee Member

Andre Venter
Thesis Committee Member

APPROVED

__________________________
Dean of The Graduate College

__________________________
Date August 2012
SYNTHESIS OF 1,1-DIALKYLHYDRAZINES AND THEIR HYDROXYL RADICAL DEGRADATION IN AQUEOUS ENVIRONMENTS

Benjamin F. Strong, M.S.
Western Michigan University, 2012

Determination of hydroxyl radical rate constants are essential to ensure adequate degradation of contaminants in wastewater. Hydrazines are an important class of organic contaminants and are the focus of this research. Ten 1,1-dialkylhydrazines are synthesized by the zinc reduction of the corresponding N-nitrosamines. Their hydroxyl radical rate constants are determined using the linear accelerator at the Notre Dame Radiation Laboratory at pH 4, 7, and 10.

Their rate constants are found to depend on the protonation state of the molecule. At pH 4 the molecules are fully protonated and hydrogen atom abstraction is favored from the alkyl chains. At pH 7 the molecules exist in both the protonated and freebase forms and their rate constants are a sum of the rate constants at pH 4 and 10. In the fully freebase form at pH 10 hydrogen atom abstraction occurs from amine hydrogens. A NMR study was also done to fully characterize a series of N-nitrosamines. Interesting results including a splitting of $^{15}$N NMR signals for N-alkylbenzylnitrosamines were observed.
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CHAPTER I

INTRODUCTION

Statement of the Problem

As our population grows so do the demands we place on our environment. With more people comes a greater requirement for water, and consequently more waste water being generated. In addition to growing in quantity, the contaminants requiring removal from waste water are changing as technology advances. While many regions of the world currently enjoy ample supplies of clean water, some areas are already beginning to feel the weight of this problem. This poses a challenge to come up with new and improved methods for treating the waste water to ensure adequate water supplies for the future.

This issue is especially apparent in the Western United States where limited water resources are being strained by a growing population. Currently the common ways to purify and treat water are collectively known as advanced oxidation processes (AOP’s). The primary oxidative mechanism used to purify waste water of its contaminants is degradation via hydroxyl radicals. These radicals can be produced in a variety of ways including combinations of ozone, peroxide and ultraviolet light (Figure 1). Hydroxyl radicals generally react with non aromatic molecules by abstracting a proton to form water and a carbon centered radical.
Figure 1. Advanced oxidation processes which use the hydroxyl radical as the main method of oxidation.2

The rates of these reactions differ for every molecule so determining the rate constant for each compound you want to remove is essential to ensure total degradation. If a contaminant in the waste water has a slow rate constant it would require either a high concentration of radicals or a long reaction time. Conversely some molecules which have very fast rate constants can be removed quickly and long reaction times in this instance would be wasteful. Determining the rate constant is therefore essential to help find a balance between fully purifying the waste water and over treatment.

It is essential to determine the rate constants for the reaction with hydroxyl radicals at differing pH’s. This is especially important for the hydrazines given the acid base properties of these molecules. Wastewater can vary widely in pH depending on location and the types of contaminants. The EPA mandates that water treatment facilities adjust the pH of their effluent to between 5 and 10 before it can be released into the environment.3

After carbon, hydrogen, and oxygen, nitrogen is one of the most prevalent atoms found in organic molecules. One particularly interesting configuration is the nitrogen-nitrogen single bond. There are three important classes of compounds with nitrogen-
nitrogen single bonds that occur depending on the oxidation state of the molecule. Hydrazines are the fully reduced form of a nitrogen-nitrogen single bonds, nitrosamines are the intermediate oxidation state, and nitramines the fully oxidized species (Figure 2).

![Figure 2. The structures of hydrazines, nitrosamines, and nitramines.](image)

Of the three groups of nitrogen-nitrogen single bonded compounds hydrazines have the most widespread applications. Unsymmetrical dimethyl hydrazine (UDMH) is used as a rocket fuel. Many pesticides also have the hydrazine functionality such as diaminozide, whose concentration in apple products in the late 1980’s caused a public outcry. Hydrazines are also commonly found in medicines such as isoniazid which is a common treatment for tuberculosis, a deadly and widespread disease which killed 1.7 million people in 2009. In addition to being widespread hydrazines are also very toxic. They have been shown to be hepatotoxic, neurotoxic, mutagenic, and carcinogenic. Some of this toxicity is due to the disruption of the N-aminotransferase enzymes in the body.

Nitrosamines are not as industrially significant as hydrazines, but there are many indirect sources of exposure. One of the chief exposure routes is through sodium nitrite which is a preservative used to prevent the growth of *Clostridium Botulinum* in canned products which is a harmful bacteria. The Food and Drug Administration (FDA) now limits the levels of sodium nitrite and mandates the use of nitrosamine inhibitors such as ascorbic acid. Nitrosamines such as nitrosodiethanolamine are also found in cosmetics.
and personal care products. Researchers have shown that inorganic pigments have the ability to cause nitrosation of diethanolamine present in cosmetics.\(^8\)

Another important source of nitrosamines exposure is through tobacco and tobacco smoke. Tobacco specific nitrosamines (TSNA’s) such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N-nitrosonornicotine (NNN) are the carcinogens present in the highest concentration in unburned tobacco.\(^9\) Nitrosamine exposure levels due to TSNA’s can be two orders of magnitude higher than nitrosamines from other sources.\(^10\)

Nitrosamines were determined to be toxic and extremely carcinogenic by the work of Barnes and Magee.\(^11\) One nitrosamine of particular concern is \(N\)-nitrosodimethylamine (NDMA) which was added to the environmental protection agency’s (EPA’s) emerging contaminants list due to its toxicity and miscibility with water.\(^12\)

Nitramines are perhaps the most widespread of the nitrogen-nitrogen bonded compounds due to their explosive properties. Two nitramines that are very important in particular are Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) (1) and Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) (2) (Figure 3). The production of RDX in the United States peaked between 1969 and 1971 at a rate of 15 million pounds per month.\(^13\)

![Figure 3. The Structures of RDX and HMX.](image)
It has been shown that RDX degrades rapidly in soil under anaerobic conditions and its degradation byproducts include hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine, hexahydro-1,3-dinitroso-5-nitro-1,3,5-triazine, and hexahydro-1,3,5-trinitroso-1,3,5-triazine. Hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine were also found from the microbial degradation of RDX.14

**Goal of the Project**

Hydrazines have been found in waste water streams throughout the country, and have been previously determined to be highly toxic and carcinogenic.6 Removal of these toxins from wastewater is therefore a very important issue. One of the chief ways of removing these pollutants is to use advanced oxidation treatment methods which rely on the oxidizing power of the hydroxyl radical. The reaction rates of hydroxyl radicals with contaminants vary depending on their structure. While it is impossible to determine the rate constants for every single possible pollutant, structure activity relationships can be found and used to extrapolate rate constants to molecules containing similar structures. This work has been done previously for both nitrosamines1 and nitramines,13 so determining the rate constants for 1,1-dialkylhydrazines will complete the research into the reactivity nitrogen-nitrogen single bonded molecules with the hydroxyl radical.

The purpose of this research was to determine hydroxyl radical rate constants for a series of 1,1-dialkylhydrazines, and use this information to find a structure activity relationship. Ten 1,1-dialkyl hydrazines representing every straight chain 1,1-dialkyl hydrazine up to and including dibutyl were the focus of these experiments. This set of molecules would allow us to determine how small changes in the size of alkyl substituents affect the rate constant. As many of these compounds were not
commercially available it was necessary to develop a method to synthesize and purify them. This data can then be used to extrapolate hydroxyl radical rate constants for other hydrazine molecules and ensure waste water contaminated with hydrazines are adequately treated.

Also, as a large number of nitrosamines have been synthesized previously, another goal of this project was to compile (\textsuperscript{1}H, \textsuperscript{13}C, and \textsuperscript{15}N) NMR data for these molecules. This data has never been tabulated before, perhaps due to the difficulty in taking \textsuperscript{15}N spectra.

Background

Hydrazine was first discovered by Theodor Curtis who published his discovery in 1887.\textsuperscript{16} It possesses a characteristic ammonia like odor, and has the appearance of a clear oily liquid.\textsuperscript{17} Hydrazine plays an important part in organic chemistry such as in the Wolf-Kishner reduction which converts aldehydes and ketones to alkanes (Scheme 1).\textsuperscript{18}

\[ \text{R}^1\text{R}^2 \text{KOH} \rightarrow \text{R}^1\text{R}^2 \]

Scheme 1. The Wolf-Kishner reduction of a ketone.

Since their discovery hydrazines have been found useful in a wide variety of roles including as rocket fuels, pesticides, and medicines. Unsymmetrical dimethyl hydrazine (3) is one of the most commonly used rocket fuels forming a hypergolic mixture with nitrogen tetroxide. Isonicotinohydrazide (4), marketed as Isoniazid, is a very effective medicine in treating tuberculosis infections which occur in up to one third of the world’s population and killed 1.7 million in 2009.\textsuperscript{5} Because of the widespread nature of the infection Isoniazid is taken daily by millions of people. Once ingested the hydrazine
nitrogens are oxidized by a catalase peroxidase enzyme called KatG producing nitric oxide, \(^1\) and an acyl radical responsible for cellular damage (Figure 4).

Diaminoazide (5), also known as Alar, was developed by the Uniroyal Chemical Company and was approved for use by the EPA in 1963 as a plant growth regulator (Figure 4). \(^4\) In 1984 Alar was placed under special investigation by the EPA because it and its breakdown product unsymmetrical dimethyl hydrazine were found to be carcinogenic. \(^6\) After the investigation, and a public outcry over the levels of Alar found in apple products the EPA revoked its use on food products in March 1990. \(^4\)

![Figure 4. The structures of 1,1-dimethylhydrazine, Isoniazid, and Alar.](image)

Hydrazine (7) was also first synthesized by Theodor Curtius in 1887. His synthesis involved the treatment of ethyl diazoacetate (6) with concentrated sodium hydroxide followed by adding dilute acid (Scheme 2). \(^1\)

![Scheme 2. Curtius synthesis of hydrazine.](image)

While this method is successful in generation of hydrazine it would not be practical on an industrial scale. Instead hydrazine is produced commercially using the Raschig synthesis. \(^2\) This process involves the reaction between chloramine (9) generated via the oxidation of ammonia by sodium hypochlorite to yield hydrazine. \(^2\) Ammonia in
this reaction is added in excess to ensure the chloramine generated reacts with it, and not
the hydrazine. Substituted amines, such as diethyl amine (8), can also be used to generate
the corresponding 1,1-dialkylhydrazine (10) by this method (Scheme 3).  

![Scheme 3. Raschig synthesis of unsymmetrical diethyl hydrazine.](image)

One of the advanced oxidation processes commonly used in the treatment of
waste water employs chloramines in the disinfection process. Chloramine has been
shown to react with dimethylamine in waste water to produce unsymmetrical dimethyl
hydrazine (UDMH) which can then be oxidized to \(N\)-nitrosodimethylamine (NDMA).  
Two drinking water wells in California were taken out of service in 2000 because the
level of NDMA after treatment of wastewater with chloramines was found to exceed
California standards.  
NDMA has also been shown to form in high concentrations from
direct contamination of ground water supplies with UDMH. Concentrations of up to
400,000 ng/L NDMA were detected in groundwater contaminated with UDMH at a
rocket testing facility in California.  

Because of their oxidation/reduction relationship another method of synthesizing
1,1-dialkylhydrazines is through the reduction of nitrosamines. Many reagents have been
used for this purpose, with one of the most common being lithium aluminum hydride
(LAH). Given the extreme reducing power of this reagent it is also possible to over
reduce directly to the free amine. In one of their attempts at producing 1,1-
diphenylhydrazine (12) from diphenylnitrosamine (11) Poirnier and Benington found that
nearly 20% of their product was the secondary amine (13) (Scheme 4).
Scheme 4. Reduction of diphenylnitrosamine with LAH.

Direct alkylation of hydrazine is also possible, but generally difficult to control without some form of amine protecting group. A number of protecting groups have been used to gain better control over the substitution of hydrazine during alkylation. One of these compounds is tert-butyloxy-carbonyl (t-Boc) which was shown to be an effective protecting group for the alkylation of 1,2-diprotected hydrazines. By using two t-Boc groups mono alkylated (16) and 1,2-dialkylhydrazines were synthesized after the removal of the protecting groups via acid cleavage (Scheme 5). Unfortunately 1,2-diprotection would not allow the synthesis of 1,1-dialklyhydrazines.

N-aminophthalimide offers another pathway to produce substituted hydrazines. This compound allows the facile formation of 1,1-disubstituted hydrazines. In this reaction the substituted aminophthalimide (18) is first generated by the reaction of phthalic anhydride and hydrazide (17) followed by the addition of N-N’-dicyclohexylcarbodiimide (DCC) and then triethylammonium acetate under refluxing conditions (Scheme 6).
The alkoxy carbonyl hydrazines are then alkylated using the Mitsunobu protocol to yield the disubstituted hydrazines (20) (Scheme 7).\textsuperscript{26} While this work was used to produce disubstituted hydrazines these were not the dialkyl hydrazines we required for comparison to the corresponding nitrosamines.

Another possible synthetic method for the production of 1,1-dialkyl hydrazines is to use hydroxyl amine-O-sulfonic acid (21). This reaction can occur with either primary or secondary amines (22) to yield the corresponding alkyl or 1,1-dialkyl hydrazine (3) respectively (Scheme 8).\textsuperscript{27} Sisler carried out the reaction by diluting dimethylamine in diglyme at -78°C followed by the addition of hydroxyl amine-O-sulfonic acid in diglyme, and stirring for one hour, followed by addition of KOH and distillation to give 1,1-dimethyl hydrazine.\textsuperscript{27}
As mentioned above, N-nitrosamines are the closely related to hydrazine differing only in the oxidation state of one nitrogen. Despite their similarities, and widespread interest in hydrazines, N-nitrosamines received very little attention from the scientific community until they were discovered to be highly toxic by the pioneering research of Barnes and Magee. After the discovery of the toxicity and carcinogenicity of N-nitrosodimethylamine, many other nitrosamines were screened for cancer activity, and most were determined to be carcinogenic. Scientists began searching for nitrosamines in everyday life which lead to their discovery in a wide array of common foods such as beer and bacon. Other sources of nitrosamine exposure include cosmetics, tobacco, pesticides, and cutting fluids. Due to their extremely hazardous nature, nitrosamines are not used industrially, and exposure is predominantly through contaminated sources such as those mentioned above.

The nitrosamines found in tobacco are collectively known as tobacco specific nitrosamines (TSNA’s) as they are found nowhere else. Nitrosamine formation occurs both during curing and smoking of the tobacco from the reaction of nicotine and nitrite which are both found in tobacco leaves after harvest. Nitrosonomicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are the two most important tobacco specific nitrosamines and both have been shown to be pulmonary carcinogens (Figure 5). Animal studies have shown that injections of NNK caused an increase of lung cancer in lab animals while injections of NNN caused tumors predominately in either the nasal cavity or the esophagus.
Of all the carcinogens present in unburned tobacco TSNA’s are present in the greatest concentration and can be two orders of magnitude higher than nitrosamine levels found in other consumer products.\textsuperscript{9,10}

![Figure 5. Structure of NNN and NNK.]

The presence of nitrosamines in bacon and other cured meats is due to the addition of sodium nitrite as a preservative. Inorganic pigments have been shown to form nitrosamines in personal care products, and exposure of malt to nitrogen oxides during the drying process is responsible for their presence in beer.\textsuperscript{8,19}

Sodium nitrite in cured meats is used to prevent the growth of \textit{Clostridium Botulinum}, the bacteria responsible for botulism food poisoning.\textsuperscript{7} Since the discovery of its role in nitrosamine formation the level of sodium nitrite has been regulated by the FDA to 120ppm, and inhibitors of nitrosamine formation such as ascorbic acid have been included in cured meats.\textsuperscript{7} When sodium nitrite reacts with acids it is converted to nitrous acid (Scheme 9). This acid is then protonated, and the loss of water forms the nitrosonium ion which is then able to react with amines to form nitrosamines.
Nitrosamines can be synthesized by electrophilic attack of the nitrosonium ion on a secondary amine. One of the ways this allows nitrosamines to be synthesized is through the use of sodium nitrite, hydrochloric acid, and a secondary amine in a method similar to what occurs \textit{in vivo} after sodium nitrite ingestion. An example, of this method is described by Hatt who used this to synthesize $N$-nitrosodimethylamine for later reduction to form the hydrazine.$^{33}$ Potassium nitrosodisulphonate (25) also known as Fremy’s salt is another option for use in the synthesis of nitrosamines. When secondary amines (8) are combined with Fremy’s salt, and sodium carbonate the corresponding nitrosamines (26) were produced in low to moderate yields (Scheme 10).$^{34}$ This reaction allows nitrosamines to be synthesized under milder conditions than the highly acidic conditions required for sodium nitrite nitrosation.$^{33}$
Recently, a novel nitrosation technique was reported with nitromethane acting as the source of nitrosonium ions. In this reaction a secondary or tertiary amine with one aryl or benzyl substituent (27) is stirred with two equivalents of o-iodoxybenzoic acid (IBX) and tetrabutylammonium fluoride (TBAF) in nitromethane at 70°C. This reaction produced the corresponding nitrosamines (28) in high yield and requires a relatively short (~3h) reaction time compared to Fremy’s salt (Scheme 11).33

![Scheme 11. Synthesis of alkyl aryl nitrosamines via nitrosation and dealkylation.](image)

Since the main goal of this project required us to have a series of 1,1-dialkylhydrazines, and the literature is full of synthetic methodologies for the synthesis of these compounds, it became a matter of testing these methods to identify one that would fit our needs. The methods we attempted and the outcome of these results are reported in the results and discussion section.
RESULTS AND DISCUSSION

Synthesis of 1,1-dialkylhydrazines

The first attempt to synthesize a 1,1-dialkylhydrazine was through reduction of \(N\)-nitrosodibutylamine using lithium aluminum hydride (LiAlH\(_4\)). 1,1-Dibutylhydrazine was selected as the model compound due to a large amount of it having been synthesized, as well as for the hydrophobicity provided by its long alkyl chains which aided in purification (Scheme 12).

\[
\begin{align*}
\text{N} & \equiv O \\
\text{N} & \equiv \text{H}
\end{align*}
\]

Scheme 12. The reduction of \(N\)-nitrosodibutylamine with lithium aluminum hydride.

After the solvent was removed an NMR of the crude reaction mixture failed to show any 1,1-dibutylhydrazine. To increase the chance of success the reduction reaction was run again with two modifications. The amount of LiAlH\(_4\) was increased from two to three equivalents and the reaction was also allowed to reflux overnight. Increasing the amount of LiAlH\(_4\) used was an attempt to compensate for any degradation of the reducing agent that might have occurred with age. Not knowing the rate of this reaction both heat and additional reaction time were used to accomplish the reduction. This reaction mixture was worked up and again failed to show formation of the desired 1,1-dialkylhydrazine by NMR. Given the high reactivity of LiAlH\(_4\) with water it was thought that moisture might be destroying the reductant prior to the reaction with the nitrosamine.
Since the LiAlH₄ reduction failed to provide the desired product a modified Raschig synthesis was attempted. In this method chloramine is generated *in situ* by the reaction of ammonia with sodium hypochlorite. Direct nucleophilic attack by the ₂° amine would then produce the corresponding 1,1-dialkylhydrazine (Scheme 13).

The chloramination of dibutylamine failed to produce the desired 1,1-dibutylhydrazine. This may have been due to the low solubility of dibutylamine in water, 4.3g/L at 30°C, which would prevent interaction with the chloramine generated *in-situ*. Since both direct nucleophilic attack of a secondary amine on an electrophilic amine and the hydride reduction failed to produce the hydrazine product an attempt was made to identify a milder method of reduction. One example of a milder reduction method is the Clemmensen reduction which uses Zn/Hg amalgam with HCl to reduce carbonyls to alkanes. While not precisely the reaction required to convert a nitrosamine to a hydrazine, a search of Zn mediated reduction reactions yielded a method using zinc dust, ammonium carbonate, and ammonium hydroxide to convert nitrosamines to their corresponding 1,1-dialkylhydrazine (Scheme 14).

Scheme 13. The synthesis of 1,1-dibutyl hydrazine by chloramines.

Scheme 14. Zinc reduction of nitrosamine.
The NMR of the crude reaction mixture showed both signals for 1,1-dibutylhydrazine shown in Figure 7a as well as signals for N-nitrosodibutylamine Figure 7b. The $^1$H NMR spectra of all N-nitrosamines exhibit proton signals for each alkyl substituent as compared to the corresponding hydrazine.

Figure 6. The resonance structure of N-nitrosamines.

Figure 7. Proton NMR spectra for a) 1,1-dibutylhydrazine and b) N-nitrosodibutylamine.
Figure 6 shows the resonance structures of a symmetric dialkyl nitrosamine. Like amides, the nitrosamine resonance form containing a nitrogen-nitrogen double bond predominates producing a restricted rotation around this bond, and signals for the protons in each alkyl chain. Signals for the protons on the alkyl chain syn to the oxygen anion appear further downfield than the protons anti to the oxygen. However, in nitrosamines with asymmetric alkyl chains the less bulky group will reside syn to the oxygen anion. Having shown the zinc reduction to be effective in reducing a nitrosamine to the desired 1,1-dialkylhydrazine, reaction conditions were then optimized to increase the yield.

The reaction time was increased to improve the yield of hydrazine while simultaneously reducing the amount of nitrosamine present. While longer reaction times reduced the amount of starting material present it also lead to the 1,1-dialkylhydraines being reduced to the corresponding secondary amines. Balancing of reaction time to fully reduce the nitrosamine without undergoing further reduction to the secondary amine proved difficult. Aggregation of zinc precipitate and the changing of the solution from yellow to clear were used as indicators of reaction completion. Also, it was found that nitrosamines with shorter alkyl chains underwent faster reduction to both the 1,1-dialkylhydrazine and secondary amines compared to nitrosamines with longer alkyl chains.

Instead of attempts to identify an optimal reaction time for each reduction, solvent extraction was considered for hydrazine purification. Short reaction times were used to prevent over reduction of the starting material to the corresponding amine, and ensure that only nitrosamine and 1,1-dialkylhydrazine were present in the reaction mixture. The pKₐ of the hydrazine primary amine is between 7 and 8 therefore
protonation of the NH$_2$ on the hydrazine was thought to occur more readily than protonation of either nitrosamine nitrogen. This would allow for both the 1,1-dialkylhydrazine and starting nitrosamine to be extracted from the reaction mixture simultaneously, followed by precipitation of the hydrazine from the organic phase as a salt.

The hydrazines are easier to protonate than their corresponding nitrosamines. The pK$_a$ of NDMA is between 12 and 13$^{39}$ which is significantly higher than the 7.21 for 1,1-dimethylhydrazine.$^{38}$ The synthesis of hydrazine hydrochloride salts had been attempted earlier by the addition of HCl/ether to the crude hydrazine reaction mixtures following reduction. A halogen salt was preferred to other anions because hydrazine salts are more stable than the neutral molecules and the halogen anion would not react with the radicals produced in the planned kinetics experiments. Unfortunately the hydrochloride salts of dialkyl hydrazine were found to be hygroscopic yielding only viscous liquids even after drying at reduced pressure for $\sim$72h.

Initial solvent extraction work focused on the removal of excess nitrosamine from the acidified crude reaction mixture. Due to the hygroscopic nature of hydrazine hydrochlorides difficulty in removing water using a traditional solvent extraction with an organic and an aqueous layer was not ideal. Methanol and n-hexane showed some promise as an immiscible non-aqueous solvent extraction pair.$^{40}$ Following the methanol/hexane extraction the hexane layer was dried via MgSO$_4$ and the solvent removed under reduced pressure. Crude NMR showed the hexane layer contained only the nitrosamine. However this process was not satisfactory for the isolation of the hydrazines because it left some of the nitrosamine in the methanol layer. It is possible
the nitrosamine could have been protonated given the highly acidic conditions, which would explain the inability to separate it by the hexane. With the failure of the non-aqueous extraction ether was instead used as the organic phase for work up of the nitrosamine reductions.

Given the hygroscopic nature of the hydrochloride salts of 1,1-dialkylhydrazines alternative counter ions were considered to improve separation from the residual nitrosamines. Troyan has published a detailed account of the solubility of 13 hydrazine salts in water.\textsuperscript{41} Based on this detailed account oxalate was chosen as an alternative to the chloride anion. Oxalate salts of the 1,1-dialkylhydrazines did not show the same hygroscopic character as the hydrochloride salts which made their storage and manipulation easier. In addition, both the 1,1-dialkylhydrazines and the oxalic acid were soluble in ether, the resulting salts precipitate from the solution offering a direct method for isolation. This allowed direct isolation of the 1,1-dialkylhydrazines from the crude reaction mixture by the addition of oxalic acid in ether to the combined ether extracts from the solvent extraction after filtration. The final rinsing of the filtrate with ether conveniently removed any residual nitrosamine as well as any excess oxalic acid.

Unfortunately oxalate reacts with the hydroxyl radical, unlike the chloride anion, so the hydrazine oxalates could not be used directly for the planned kinetic studies. Therefore the oxalate anion needed to be replaced again by the chloride anion. This was accomplished by solvent extraction with ether/bicarbonate to neutralize the oxalate salts and addition of HCl/ether to the organic phase followed by azeotropic distillation. The samples were then weighed and diluted with HPLC water to produce solutions for kinetic analysis.
As described previously the project requires 1,1-dialkylhydrazines of chain lengths from one to four carbons. Unfortunately the solubility of hydrazines with water increases as the carbon chain lengths decrease. The increase in hydrophilicity made direct ether extractions problematic for the hydrazines with smaller alkyl groups. Therefore an alternative strategy was necessary for these hydrazine compounds. Hydrazones, synthesized from an aldehyde and hydrazine, are insoluble in water and could be extracted from the crude reaction mixture. Because of the poor water solubility of the hydrazone the purification of short chain hydrazines was attempted using benzaldehyde (Scheme 15).

![Scheme 15. Hydrazone formation with benzaldehyde.](image)

After extraction from the reaction the hydrazone was hydrolyzed using aqueous HCl that both decomposed the hydrazone and formed the hydrazine hydrochloride salt for kinetic analysis. Using these two methods nine 1,1-dialkylhydrazine were synthesized to study their degradation kinetics with the hydroxyl radical.

**Synthesis of N-nitrosamines**

With a process in place to efficiently reduce nitrosamines to their corresponding 1,1-dialkylhydrazine there was a need to synthesize a series of nitrosamines for hydrazine
production. To accomplish the synthesis of these nitrosamines a commonly employed reaction method was used (Scheme 16).

\[
\begin{align*}
\text{H} & \text{N} \\
\text{R}^1 & \text{R}^2 \\
\text{HCl} & \text{NaNO}_2 \text{(aq.)} \\
\text{H}_2\text{O, }0^\circ\text{C} & \text{H}^\cdot\text{O} \\
\text{R}^1 & \text{R}^2
\end{align*}
\]

Scheme 16. The general synthesis of nitrosamines.

As with the hydrazines longer alkyl chains generally required longer reaction times. Most of the nitrosamines produced were viscous yellow oils with the exception of diisopropyl and dibenzyl nitrosamine which were solids and also required heating to complete the reaction.

**Hydroxyl Radical Degradation**

Many of the advanced oxidation processes mentioned in the introduction produce the hydroxyl radical to degrade contaminants. Examples of these processes include the use of ozone,\(^1\) UV/ozone,\(^1\) and UV/H\(_2\)O\(_2\)\(^1\) that produce only the hydroxyl radical and systems like TiO\(_2\),\(^1\) sonolysis,\(^1\) or electron beam degradation\(^1\) which produce both solvated electrons and hydroxyl radicals.\(^1\) Hydroxyl radicals are extremely reactive with a redox potential of 2.8 V.\(^{42}\) They quickly react via two main pathways, to either abstract a hydrogen atom or add to an aromatic ring to form a phenol. To determine the rate constants for the hydroxyl radical degradation of the hydrazines we used the linear accelerator (Linac) at the Radiation Laboratory on the campus of The University of Notre Dame. Determining these rate constants allows a quantitative assessment of the number of hydroxyl radicals necessary to treat these compounds without over treatment.
In pulse radiolysis a 8MeV electron pulse produced by the Linac energy strikes a sample cell containing the analyte and water and is analyzed by UV/Vis spectroscopy. The energy from the electrons beam is used to cleave the bonds in water generating a predictable set of products including the hydroxyl radical, atomic hydrogen, solvated electrons, hydrogen gas, hydrogen peroxide, and protons. The bracketed values are the relative ratios of each species produced by a given amount of energy (Scheme 17).

\[
\text{H}_2\text{O} \rightarrow [0.28] \cdot \text{OH} + [0.06] \text{H} + [0.27] \text{e}^- \text{(aq.)} + [0.05] \text{H}_2 + [0.07] \text{H}_2\text{O}_2 + [0.27] \text{H}^+
\]

Scheme 17. Equation for the radiolysis of water.

Based on reaction conditions it is possible to select for a specific reactive species for study. To select for the hydroxyl radical the solutions are bubbled with nitrous oxide that reacts with both the solvated electron (Eq. 1) and hydrogen atoms (Eq. 2) to produce additional hydroxyl radicals.

\[
\begin{align*}
\text{e}^- + \text{N}_2\text{O} + \text{H}_2\text{O} & \rightarrow \text{N}_2 + \cdot \text{OH} + \text{OH}^- \quad k_1 = 9.1 \times 10^9 \text{M}^{-1}\text{s}^{-1} \\
\cdot \text{H} + \text{N}_2\text{O} & \rightarrow \text{N}_2 + \cdot \text{OH} \quad k_2 = 2.1 \times 10^6 \text{M}^{-1}\text{s}^{-1}
\end{align*}
\]

Unfortunately the 1,1-dialkylhydrazines did not show an absorption within the range of the spectrophotometer so the reaction products could not be observed directly. Therefore, the rate constants had to be determined by competition kinetics to indirectly measure the reaction rates. Potassium thiocyanate was used as our reporter molecule which reacts with hydroxyl radicals and forms a radical ion dimer that has a strong absorption at 475nm (Eq. 3).

\[
\cdot \text{OH} + \text{SCN}^- (+\text{SCN}^-) \rightarrow \text{OH}^- + (\text{SCN})_2^- \quad k_3 = 1.96 \times 10^8 \text{M}^{-1}\text{s}^{-1}
\]
The addition of the hydrazine compound causes the hydroxyl radicals to be partitioned between the thiocyanate and analyte producing a decrease in the absorbance. Knowing the rate constant for the reaction of thiocyanate with hydroxyl radicals it is then possible to determine the rate constant for the reaction of the dialkyl hydrazines.

(Figure 8) is an overlay of four different absorption spectra at varying concentrations of 1,1-dimethylhydrazine. As the concentration of hydrazine increases the hydroxyl radical partitions between the two species producing less thiocyanate radical dimer. The reduction of hydroxyl radicals leads to a lower production of the observable thiocyanate radical dimer and consequently a lower overall absorbance.

\[
\frac{[\text{SCN}^2-]_0}{[\text{SCN}^2-]} = 1 + \frac{k [R^1R^2N-NH_2]}{k [\text{SCN}^-]}
\]

Scheme 18. The equation for the calculation of the hydrazine rate constant.

Using the equation above and knowing the initial absorbance, final absorbance, and the rate constant for the reaction of thiocyanate with the hydroxyl radical, rate
constants for the nine 1,1-dialkylhydrazines were calculated. A plot of absorbance verses concentration of the hydrazines produces a plot where the slope of the line is the second order rate constant.

![Graph](image)

**Figure 9.** The ratios of absorbances plotted against the ratios of concentrations for 1,1-dimethylhydrazine at pH 10.

Using this method we determined the rate constant for each of the 1,1-dialkyl hydrazine from dimethyl to dibutyl at three different pH values (Table 1). The pH values were selected to represent the fully protonated (pH 4) fully free base (pH 10) and a mixture of both (pH 7) hydrazine species.

![Chemical Structures](image)

**Figure 10.** The structures of fully protonated and fully freebase hydrazines at pH 4 and 10.
Table 1. The hydroxyl radical rate constants for 1,1-dialkylhydrazines in acidic, neutral, and basic conditions.

$$\text{NH}_2\overset{[\cdot\text{OH}]}{\underset{R^1-N-R^2}{\rightarrow}}\text{products}$$

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>pH 4 ($M^{-1}s^{-1}$)</th>
<th>pH 7 ($M^{-1}s^{-1}$)</th>
<th>pH 10 ($M^{-1}s^{-1}$)</th>
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</thead>
<tbody>
<tr>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>$(0.83 \pm 0.04) \times 10^9$</td>
<td>$(4.42 \pm 0.08) \times 10^9$</td>
<td>$(10.3 \pm 0.3) \times 10^9$</td>
</tr>
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<td>CH$_2$CH$_3$</td>
<td>$(0.44 \pm 0.03) \times 10^9$</td>
<td>$(1.94 \pm 0.03) \times 10^9$</td>
<td>$(7.43 \pm 0.11) \times 10^9$</td>
</tr>
<tr>
<td>CH$_2$CH$_2$CH$_3$</td>
<td>CH$_2$CH$_2$CH$_3$</td>
<td>$(1.72 \pm 0.12) \times 10^9$</td>
<td>$(2.83 \pm 0.04) \times 10^9$</td>
<td>$(7.53 \pm 0.17) \times 10^9$</td>
</tr>
<tr>
<td>CH$_2$CH$_3$CH$_2$CH$_3$</td>
<td>CH$_2$CH$_2$CH$_2$CH$_3$</td>
<td>$(3.49 \pm 0.11) \times 10^9$</td>
<td>$(4.98 \pm 0.12) \times 10^9$</td>
<td>$(9.06 \pm 0.40) \times 10^9$</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>$(0.42 \pm 0.01) \times 10^9$</td>
<td>$(2.89 \pm 0.10) \times 10^9$</td>
<td>$(7.40 \pm 0.24) \times 10^9$</td>
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<td>$(0.89 \pm 0.02) \times 10^9$</td>
<td>$(3.01 \pm 0.04) \times 10^9$</td>
<td>$(7.40 \pm 0.24) \times 10^9$</td>
</tr>
<tr>
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<td>$(2.75 \pm 0.15) \times 10^9$</td>
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<td>$(6.03 \pm 0.54) \times 10^9$</td>
</tr>
<tr>
<td>CH$_2$CH$_3$</td>
<td>CH$_2$CH$_3$</td>
<td>$(0.66 \pm 0.04) \times 10^9$</td>
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<td>$(7.07 \pm 0.23) \times 10^9$</td>
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<tr>
<td>CH$_2$CH$_2$CH$_3$</td>
<td>CH$_2$CH$_2$CH$_2$CH$_3$</td>
<td>$(2.63 \pm 0.11) \times 10^9$</td>
<td>$(5.54 \pm 0.23) \times 10^9$</td>
<td>$(9.58 \pm 0.38) \times 10^9$</td>
</tr>
</tbody>
</table>

The reaction of 1,1-dialkylhydrazines with the hydroxyl radical occurs via hydrogen atom abstraction. In theory as the number of hydrogen atoms in the 1,1-dialkylhydrazines increases, there should be a corresponding increase in the rate constant. In previous work a dependence upon alkyl chain length was shown for the reaction of nitrosamines with the hydroxyl radical. A similar trend can be observed in the experiments done at pH = 4 where the slowest rate constants are hydrazine possessing fewer carbon atoms.

Within the pH = 4 data there are two distinct trends where increases in alkyl chain length correspond to faster rate constants. The first trend occurs in the symmetrical 1,1-dialkylhydrazines and the second when $R^1$ is a methyl group. For the symmetrical 1,1-dialkylhydrazines ($R^1=R^2$) hydrogen atom abstraction occurs from the thermodynamically more favorable methylene carbons as expected and the rate constant increases with an increase in the number of CH$_2$ groups (Figure 11).
A similar trend can be seen for the 1-methyl-1-alkylhydrazines where the majority of the reactivity is at the alkyl chain due to the thermodynamics of hydrogen atom abstraction from the methylene carbons over the methyl groups (Figure 12).
At neutral pH, there is an increase in the rate constants for each 1,1-dialkyhydrazine. At pH 7 the hydrazines exist in equilibrium between the acid and base forms in solution. Therefore the rate constants for the hydrazines at pH 7 should correspond to a sum of the rate constants for the protonated and the free base form of the hydrazines.

To confirm this it should be possible to calculate the theoretical rate constant for a hydrazine with the hydroxyl radical knowing the rate constants at pH 4 and pH 10 as well as the pKₐ. The experimentally determined pKₐ of dimethyl hydrazine is 7.21, and the fraction of acid versus base species can then be calculated using the Henderson-Hasselbalch.

Solving the Henderson-Hasselbalch equation for 1,1-dimethylhydrazine shows that 62% of the 1,1-dimethylhydrazine should be in the acid form. Multiplying this value by the experimentally determined rate constants for the reaction with the hydroxyl radical at pH 4 and pH 10 respectively yields a calculated value of $4.46 \times 10^9$ M⁻¹s⁻¹ for pH 7. This value shows an excellent correlation with the experimentally determined value ($4.42 \pm 0.08 \times 10^9$ M⁻¹s⁻¹) in Table 1.

It is also worth noting that the range of rate constants, which was nearly an order of magnitude at pH 4, has decreased by a factor of two at pH 7. The decrease in rate constant can be attributed to a change in mechanism for the reaction with the hydroxyl radical.

It has been shown that 1,1-dialkylhydrazines increase in basicity as alkyl chain length increases. For example, 1,1-dimethylhydrazine has a pKₐ of 7.21 while the pKₐ of 1,1-diethylhydrazine is 7.71. If a similar calculation is carried out for 1,1-diethyl
hydrazine it is found that there is a greater amount in the acid from (81%). Thus for 1,1-dimethylhydrazine in going from pH 4 to pH 7 38% of the hydrazine molecules are now in their base form compared to 1,1-diethylhydrazine where only 20% of the hydrazine molecules are in the base form. This explains the compression of rate constants in going from pH 4 to pH 7, but also indicates a change to a single mechanism for the reaction of the base forms of the 1,1-dialkylhydrazines.

At pH 10 the range of rate constants decreases again and becomes independent of chain length. This data is supported by previous work that showed hydroxyl radicals prefer hydrogen atom abstraction from the amine nitrogen atom or the α-methylene carbons in the base form of the secondary amines. At pH 10 all of the hydrazines are in their base form and would suggest that abstraction from the hydrazine amine nitrogen or a methylene carbon would be favored, like the amines. This hypothesis is supported by the data for the 1,1-dialkylhydrazines at pH 10.

![Figure 13. Correlation between hydroxyl radical rate constant, pH, and number of methylene groups.](image)

R² = 0.0343  
R² = 0.2021  
R² = 0.5894

<table>
<thead>
<tr>
<th>pH 4</th>
<th>pH 7</th>
<th>pH 10</th>
</tr>
</thead>
<tbody>
<tr>
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</table>
Figure 13 illustrates a compilation of all the data for the reaction rate constants with the hydroxyl radical at each of the pH's studied versus the number of methylene groups. As noted previously there is a larger correlation with methylene C-H bonds at pH 4 where no reaction at the protonated amine group occurs. Therefore the hydroxyl abstracts a hydrogen atom from one of the carbons in the alkyl chains.

As noted before there is no correlation between alkyl chain length and hydroxyl radical rate constant at pH 10 suggesting that abstraction must occur from functionality common to all the 1,1-dialkylhydrazines structures. This would suggest a conserved mechanism that is now occurring primarily by hydrogen atom abstraction from the amine or α-methylene carbon atoms, as these would be the most reactive sites in the base form. This data indicates that in real world applications it will not only be important to have knowledge of the contaminants in the waste stream, but also the acidity since in the case of the 1,1-dialkylhydrazines this has a clear impact on their degradation.

Compilation of Nitrosamine NMR Data

Over the past five years numerous nitrosamines have been synthesized in the laboratory including many for the construction of the hydrazines for this project. Since multinuclear NMR data for these compounds is sparse, especially nitrogen and carbon NMR, it was decided to produce a compilation of relevant multinuclear NMR data for these compounds. Thirty-three nitrosamines were chosen for the study that comprised six classes based on both structure and biological activity.

$^1$H, $^{13}$C and $^{19}$F are common NMR nuclei that are routinely used for characterization of organic molecules. However the nitrogen NMR data for these classes
of nitrosamines present certain experimental challenges, and explains why $^{15}$N NMR values had not been reported for a majority of these compounds. Nitrogen has two stable NMR active nuclei, $^{14}$N and $^{15}$N, each presenting their own challenges. $^{14}$N NMR is a quadrapolar nucleus with 99.64% abundance which allows for quick acquisitions, but produces broad signals. Convesely $^{15}$N is a spin $\frac{1}{2}$ nucleus, like $^1$H and $^{13}$C which produce well resolved peaks, but has an abundance of only 0.365% which requires longer acquisition times.

$^{15}$N was chosen for its resolution characteristics that provided good signals in overnight runs. NMR samples were prepared at concentrations ranging from [1.7M] to [4M] based on nitrosamine structure in deuterated nitromethane. Nitromethane was chosen because all the nitrosamines are soluble in it, but also because it is a common reference standard in $^{15}$N NMR (0ppm). Most nitrosamines exhibit spectra with two peaks in $^{15}$N NMR, one shifted downfield from the nitroso-nitrogen and one upfield for the amine nitrogen with respect to the nitromethane reference peak. The $^{15}$N NMR data is reported in Table 2, the remaining multinuclear NMR data for each nitrosamine is reported in the experimental section.
Table 2. $^{15}$N NMR values for acyclic nitrosamines.

Any change in substituent structure of the nitrosamine should have a larger effect on the $^{15}$N NMR of the amine nitrogen that is directly bonded to it rather than the nitroso-nitrogen that is one bond farther away. This is clearly indicated for the nitroso-nitrogens with the greatest difference being between $t$-butylmethyl nitrosamine (entry 8) at 153.80 ppm and $N$-nitroso-2,2,2-trifluoroethylamine (entry 24) at 178.45 ppm. This would be the

Any change in substituent structure of the nitrosamine should have a larger effect on the $^{15}$N NMR of the amine nitrogen that is directly bonded to it rather than the nitroso-nitrogen that is one bond farther away. This is clearly indicated for the nitroso-nitrogens with the greatest difference being between $t$-butylmethyl nitrosamine (entry 8) at 153.80 ppm and $N$-nitroso-2,2,2-trifluoroethylamine (entry 24) at 178.45 ppm. This would be the

<table>
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<tr>
<th>Entry</th>
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</table>
result as expected as the alkyl groups provide a large shielding of the nitrogen, while the electronegative fluorine atoms provide strong deshielding due to their high electronegativity.

Between the most shielded and deshielded there are some other trends observed in the chemical shifts of the nitroso-nitrogen values. All of the n-alkyl nitrosamines show very similar chemical shifts which are also shared by the alkyl benzyl and dibenzyl compounds. This is not surprising considering that all of these molecules contain only methyl or methylene carbons adjacent to the amine nitrogen (entries 1-7, 9, 10, 12, 18-22). The aromatic ring in the benzyl structures are too far away from the nitroso-nitrogen to have an appreciable effect on its chemical shift as evidenced by entries (18,19, and 21) not differing significantly from entries (2-4). The presence of an aromatic ring on the amine nitrogen produces a deshielding effect on the nitroso-nitrogen signal moving it further downfield as compared to those with only sp\(^3\) carbons attached.

Another interesting phenomenon is observed in the acyclic nitrosamine \(^{15}\text{N}\) NMR’s when \(R^1 = \text{Benzyl}\). Both the nitroso-nitrogen and the amine nitrogen each show two signals in the \(^{15}\text{N}\) NMR from conformational isomers of the nitrosamine. In the Z-isomer the oxygen atom of the nitroso-group is over the face of the aromatic ring producing a deshielding effect that does not occur in the E-isomer (Figure 14).

Most of the trends observed for the nitroso-nitrogen are consistent with those observed for the amine nitrogen. However, because the amine nitrogen is directly bonded to the carbon chains the \(^{15}\text{N}\) NMR signals should be more sensitive to changes in these structures.
The $^{15}\text{N}$ NMR chemical shift values for the amine-nitrogen range over 51 ppm compared to 24 ppm for the nitroso-nitrogen. This sensitivity is illustrated by a distinct difference in chemical shifts between methyl and methylene groups bonded adjacent to the nitrogen with the methyl groups having much greater shielding. While the 2,2,2-trifluoroethyl group provided deshielding to the nitroso-nitrogen it is the most shielded of all of the amine nitrogen’s. The highly deactivating nature of the CF$_3$ group is withdrawing electron density from the oxygen causing the deshielding effect on the nitroso-nitrogen and an increase in electron density around the amine-nitrogen producing its increase in shielding.

Similar trend can be observed in the cyclic and tobacco specific nitrosamines like those described for the acyclic, benzyl, and phenyl nitrosamines.
Table 3. The $^{15}$N NMR values for cyclic and tobacco specific nitrosamines.

<table>
<thead>
<tr>
<th>Nitrosamine</th>
<th>N=O $\delta$(ppm)</th>
<th>R$^{1}$-N-R$^{2}$ $\delta$(ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Nitrosamine 1" /></td>
<td>153.83</td>
<td>-121.84</td>
</tr>
<tr>
<td><img src="image2" alt="Nitrosamine 2" /></td>
<td>151.27</td>
<td>-130.88</td>
</tr>
<tr>
<td><img src="image3" alt="Nitrosamine 3" /></td>
<td>155.99</td>
<td>-125.41</td>
</tr>
<tr>
<td><img src="image4" alt="Nitrosamine 4" /></td>
<td>156.23</td>
<td>-125.33</td>
</tr>
<tr>
<td><img src="image5" alt="Nitrosamine 5" /></td>
<td>161.59 157.74 -60.56 -61.09 -111.28 -113.65</td>
<td></td>
</tr>
<tr>
<td><img src="image6" alt="Nitrosamine 6" /></td>
<td>152.87</td>
<td>-139.6625</td>
</tr>
<tr>
<td><img src="image7" alt="Nitrosamine 7" /></td>
<td>156.84</td>
<td>-136.0111</td>
</tr>
</tbody>
</table>
CHAPTER III

CONCLUSIONS

Nine 1,1-dialkyl hydrazine molecules were synthesized by the reduction of the corresponding nitrosamines. These molecules were determined to be of high purity by NMR spectroscopy. Using the Linac at Notre Dame rate constants were determined for the reaction of hydroxyl radicals with each hydrazine at pH 4, 7, and 10. At pH 4 there was a correlation between the number of methylene carbons and the rate constants. However at pH 10 there was a change in mechanism for the reaction with the hydroxyl radical and there was no correlation between rate constant and the number of methylene carbon atoms.

Our findings are reinforced by previous work showing both amines and hydrazines having slower rate constants when the nitrogen is protonated which was attributed to unfavorable interaction between the positive nitrogen center and electrophilic hydroxyl radical. At pH 4 the reactivity was shifted towards the alkyl chains producing a correlation between rate constant and number of methylene groups. Raising the pH to 10 caused the removal of the unfavorable interaction between the hydroxyl radicals and nitrogen center, which allowed hydrogen atom abstraction from the nitrogen to become the dominant reaction pathway. As the NH$_2$ structure was conserved among all hydrazines studied the rate constants converged and became independent of alkyl chain length. Finally, the values of the rate constants at pH 7 were shown to be a sum of the rate constants of the protonated and free base hydrazines.
In addition, 33 N-nitrosamines spanning six different classes were analyzed by $^1$H, $^{13}$C, $^{19}$F, and $^{15}$N NMR. Many of these values, especially the $^{15}$N values are reported here for the first time. While most compounds showed two signals in $^{15}$N NMR, one for the nitroso-group and a second for the amine, the alkyl benzyl nitrosamines showed an additional set of signals. This was attributed to conformational interactions between the lone pair of electrons on the nitroso-nitrogen atom and the aromatic ring of the benzyl group.
CHAPTER IV

EXPERIMENTAL

General Method for the Preparation of $N$-nitrosamines

Diethyl amine was added to a 100ml round bottom flask (4g, 54.67mmol) and placed in an ice bath and a magnetic stir bar was added to the flask. 6.25mL of concentrated HCl was then added dropwise to the flask. A solution of sodium nitrite (7.9g, 114.5mmol in 60mL of deionized water) was then added dropwise over 15 minutes via an addition funnel. After the addition was complete the reaction was gradually allowed to warm to room temperature and stirred for 12h. The solution was then extracted with 3x50ml portions of ether followed by the washing of the organic fractions with saturated sodium chloride solution. The ether solution was further dried by the addition of magnesium sulfate which was then removed by gravity filtration. The product was concentrated under reduced pressure yielding the nitrosamines as viscous yellow oils.

\[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\]

$N$-Nitrosodiethylamine 4.15g, 74.2% $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.14 (q, $J = 7.32$ Hz, 2H), 3.59 (q, $J = 7.32$ Hz, 2H), 1.39 (t, $J = 7.32$ Hz, 3H), 1.09 (t, $J = 7.32$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 46.98, 38.42, 14.13, 11.32.
$N$-Nitrosodimethylamine $^1$H NMR (400 MHz, CDCl$_3$) δ 3.78 (s, 3H), 3.05 (s, 3H); $^{13}$C
NMR (100 MHz, CDCl$_3$) δ 39.90, 32.15.

$N$-Nitrosodipropylamine 1.55g (75.4%) $^1$H NMR (400 MHz, CDCl$_3$) δ 4.02 (t, $J = 7.32$
Hz, 2H), 3.49 (t, $J = 7.68$ Hz, 2H), 1.76 (sextet, $J = 7.32$ Hz, 2H), 1.52 (sextet, $J = 7.32$
Hz, 2H), 0.95 (t, $J = 7.32$ Hz, 3H), 0.87 (t, $J = 7.32$ Hz, 3H); $^{13}$C NMR (100 MHz,
CDCl$_3$) δ 54.19, 45.53, 21.72, 19.54, 11.66, 11.13.

$N$-Nitrosodibutylamine 8.62g (88.0%) $^1$H NMR (400 MHz, CDCl$_3$) δ 4.06 (t, $J = 7.32$
Hz, 2H), 3.53 (t, $J = 7.32$ Hz, 2H), 1.72 (pentet, $J = 7.32$ Hz, 2H), 1.45 (pentet, $J = 7.32$
Hz, 2H), 1.36 (sextet, $J = 7.32$ Hz, 2H), 1.27 (sextet, $J = 7.68$ Hz, 2H), 0.97 (t, $J = 7.32$
Hz, 3H), 0.92 (t, $J = 7.32$ Hz, 3H); $^{13}$C NMR (100 MHz, CD$_3$NO$_2$) δ 51.76, 43.08, 29.95,
27.86, 20.12, 19.48, 12.73, 12.63.

$N$-Nitroso-$N$-ethyl-$N$-methylamine 2.87g (96.2%) $^1$H NMR (400 MHz, CDCl$_3$) δ 4.18 (q, $J = 7.32$ Hz, 2H), 3.73 (s, 3H), 3.63 (q, $J = 7.32$ Hz, 2H), 3.04 (s, 3H), 1.37 (t, $J = 7.36$
Hz, 3H), 1.08 (t, J = 7.32 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 48.75, 39.86, 38.40, 30.95, 13.67, 10.59.

\[
\begin{array}{c}
N\text{-Nitroso-}N\text{-methyl-}N\text{-propylamine} \\
1.28g (86.6\%) \\
\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 4.09 \\
(t, J = 7.32 Hz, 2H), 3.73 (s, 3H), 3.54 (t, J = 7.36 Hz, 2H), 3.03 (s, 3H), 1.75 (sextet, J = 7.32 Hz, 2H), 1.52 (sextet 7.72 J = Hz, 2H), 0.94 (t, 7.68 J = Hz, 3H), 0.86 (t, 7.68 J = Hz, 3H); \\
\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 55.35, 46.54, 39.17, 31.39, 21.37, 19.13, 11.47, 10.92.
\end{array}
\]

\[
\begin{array}{c}
N\text{-Nitroso-}N\text{-butyl-}N\text{-methylamine} \\
5.22g (78.4\%) \\
\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 4.14 (t, J = 6.96 Hz, 2H), 3.73 (s, 3H), 3.58 (t, J = 7.68 Hz, 2H), 3.04 (s, 3H), 1.71 (quintet, J = 7.32 Hz, 2H), 1.47 (quintet, J = 6.96 Hz, 2H), 1.35 (sextet, J = 7.68 Hz, 2H), 1.27 (sextet, J = 7.32 Hz, 2H), 0.96 (t, J = 7.68 Hz, 3H), 0.91 (t, J = 7.36 Hz, 3H); \\
\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 53.48, 44.78, 39.13, 31.41, 30.00, 27.73, 20.29, 19.60, 13.66, 13.57.
\end{array}
\]

\[
\begin{array}{c}
N\text{-Nitroso-}N\text{-tert-butyl-}N\text{-methylamine} \\
\text{H NMR (400 MHz, CD}_3\text{NO}_2\text{) } \delta 3.05 (s, 3H), 1.52 (s, 9H); \\
\text{C NMR (100 MHz, CD}_3\text{NO}_2\text{) } \delta 61.74, 27.75, 27.24.
\end{array}
\]
$N$-Nitroso-$N$-ethyl-$N$-propylamine 1.88g (80.7%) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.12 (q, $J = 7.32$ Hz, 2H), 4.04 (t, $J = 6.96$ Hz, 2H), 3.58 (q, $J = 7.32$ Hz, 2H), 3.51 (t, $J = 7.68$ Hz, 2H), 1.77 (sextet, $J = 7.32$ Hz, 2H), 1.52 (sextet, $J = 7.32$ Hz, 2H), 1.39 (t, $J = 7.32$ Hz, 3H), 1.09 (t, $J = 7.32$ Hz, 3H), 0.97 (t, $J = 7.32$ Hz, 3H), 0.88 (t, $J = 7.68$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 53.68, 47.37, 45.01, 38.79, 21.72, 19.60, 14.09, 11.61, 11.21, 11.08.

$N$-Nitroso-$N$-butyl-$N$-ethylamine 6.94g (89.9%) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.12 (q, 2H), 4.07 (t, 2H), 3.59 (q, 2H), 3.54 (t, 2H), 1.72 (quintet, 2H), 1.46 (quintet, 2H), 1.38 (m, 5H), 1.27 (sextet, 2H), 1.09 (t, 3H), 0.96 (t, 3H), 0.91 (t, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 51.77, 47.33, 43.22, 38.77, 30.41, 28.23, 20.49, 19.78, 14.13, 13.70, 13.63, 11.27.

$N$-Nitroso-$N$-tert-butyl-$N$-ethylamine $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.57 (q, $J = 6.96$ Hz, 2H), 1.53 (s, 9H), 1.09 (t, $J = 6.96$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 61.41, 37.03, 28.88, 12.62.
$N$-Nitrosodiisopropylamine $^1$H NMR (400 MHz, CDCl$_3$) δ 5.00 (septet, $J = 6.80$ Hz, 1H), 4.23 (septet, $J = 9.69$ Hz, 1H), 1.47 (d, $J = 6.96$ Hz, 6H), 1.14 (d, $J = 6.96$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 50.75, 44.94, 23.64, 19.03.

$N$-Nitroso-$N$-butyl-$N$-propylamine 2.14g (85.5%) $^1$H NMR (400 MHz, CDCl$_3$) δ 4.05 (m, 4H), 3.51 (m, 4H), 1.77 (sextet, $J = 7.32$ Hz, 2H), 1.71 (quintet, $J = 7.32$ Hz, 2H), 1.51 (sextet, $J = 7.36$ Hz, 2H), 1.46 (m, 2H), 1.37 (sextet, $J = 7.72$ Hz, 2H), 1.27 (sextet, $J = 7.32$ Hz, 2H), 0.96 (m, 3H), 0.90 (t, $J = 7.32$ Hz, 3H), 0.88 (t, $J = 7.32$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 54.02, 52.15, 45.34, 43.57, 30.41, 28.17, 21.75, 20.51, 19.81, 19.58, 13.72, 13.65, 11.68, 11.15.

$N$-Nitroso-$N$-methylaniline $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54 (m, 2H), 7.48 (m, 2H), 7.37 (m, 1H), 3.46 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 142.40, 129.56, 127.41, 119.29, 31.60.
N-Nitroso-N-ethylaniline $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.53 (m, 2H), 7.47 (m, 2H), 7.36 (m, 1H), 4.07 (q, $J = 6.96$ Hz, 2H), 1.17 (t, $J = 7.32$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.48, 129.60, 127.41, 126.27, 119.63, 39.31, 11.80.

N-Nitroso-N-propylaniline $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.53 (m, 2H), 7.47 (m, 2H), 7.35 (m, 1H), 4.01 (t, $J = 7.68$ Hz, 2H), 1.57 (sextet, $J = 7.32$ Hz, 2H), 0.89 (t, $J = 7.36$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.71, 129.57, 127.40, 119.76, 45.44, 20.00, 11.54.

N-Nitroso-N-butylaniline $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.53 (m, 2H), 7.47 (m, 2H), 7.36 (m, 1H), 4.02 (t, $J = 7.72$ Hz, 2H), 1.53 (quintet, $J = 7.68$ Hz, 2H), 1.31 (sextet, $J = 7.68$ Hz, 2H), 0.90 (t, $J = 7.32$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.70, 129.58, 127.41, 119.77 43.80, 28.57, 20.38, 13.70.
N-Nitrosodiphenylamine $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50 (m, 3H), 7.42 (m, 4H), 7.33 (m, 1H), 7.09 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 142.61, 136.86, 129.90, 129.62, 129.43, 127.50, 127.11, 119.78.

N-Nitroso-N-benzyl-N-methylamine 1.88g (75.4%) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 (m, 3H), 7.31 (m, 3H), 7.26 (m, 2H), 7.12 (m, 2H), 5.28 (s, 2H), 4.79 (s, 2H), 3.67 (s, 3H), 2.93 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 134.41, 129.17, 129.01, 128.71, 128.46, 128.16, 57.78, 47.99, 38.65, 31.21.

N-Nitroso-N-benzyl-N-ethylamine 1.81g (74.5%) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (m, 3H), 7.29 (m, 5H), 7.12 (m, 2H), 5.26 (s, 2H), 4.81 (s, 2H), 4.11 (q, $J$ = 7.32 Hz, 2H), 3.51 (q, $J$ = 7.32 Hz, 2H), 1.35 (t, $J$ = 7.36 Hz, 3H), 0.96 (t, $J$ = 7.32 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 134.87, 134.28, 129.08, 128.91, 128.61, 128.27, 128.19, 127.90, 55.88, 46.74, 45.86, 38.44, 14.01, 11.05.
$N$-Nitroso-$N$-benzyl-$N$-propylamine $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (m, 4H), 7.30 (m, 4H), 7.13 (m, 2H), 5.25 (s, 2H), 4.79 (s, 2H), 4.00 (t, $J$ = 7.36 Hz, 2H), 3.40 (t, $J$ = 7.68 Hz, 2H), 1.74 (sextet, $J$ = 7.32 Hz, 2H), 1.41 (sextet, $J$ = 7.36 Hz, 2H), 0.92 (t, $J$ = 7.32 Hz, 3H), 0.80 (t, $J$ = 7.32 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 134.95, 134.33, 129.07, 128.89, 128.58, 128.25, 127.88, 56.25, 53.29, 46.04, 44.77, 21.56, 19.41, 11.63, 11.14.

$N$-Nitroso-$N$-benzyl-$N$-butylamine .99g (83.9%) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 (m, 3H), 7.28 (m, 5H), 7.11 (m, 2H), 5.25 (s, 2H), 4.79 (s, 2H), 4.04 (t, $J$ = 7.32 Hz, 2H), 3.43 (t, $J$ = 7.68 Hz, 2H), 1.69 (quintet, $J$ = 7.36 Hz, 2H), 1.34 (m, 5H), 1.21 (sextet, $J$ = 8.08 Hz, 2H), 0.91 (t, $J$ = 7.36 Hz, 3H), 0.84 (t, $J$ = 6.96 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 134.86, 134.27, 129.07, 128.90, 128.60, 128.28, 128.24, 127.90, 56.26, 51.41, 46.10, 43.02, 30.13, 27.94, 20.39, 19.76, 13.66, 13.61.

$N$-Nitrosodibenzylamine .92g (72.2%) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (m, 3H), 7.29 (m, 3H), 7.25 (m, 2H), 7.05 (m, 2H), 5.20 (s, 2H), 4.66 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 134.55, 133.94, 129.11, 128.91, 128.64, 128.58, 128.45, 127.97, 55.05, 44.95.
$N$-Nitrosodiethanolamine $^1$H NMR (400 MHz, CDCl$_3$) δ 5.32 (t, $J = 5.52$ Hz, 2H), 4.94 (t, $J = 5.48$ Hz, 2H), 4.83 (t, $J = 5.88$ Hz, 2H), 4.71 (t, $J = 5.88$ Hz, 2H); $^{13}$C NMR (100 MHz, CD$_3$NO$_2$) δ 60.35, 58.78, 56.08, 48.46.

$N$-Nitroso-bis-(2,2,2-trifluoroethyl)amine $^1$H NMR (400 MHz, CDCl$_3$) δ 4.91 (q, $J = 8.04$, 2H), 4.31 (q, $J = 8.44$, 2H) $^{13}$C NMR (100 MHz, CDCl$_3$) δ 52.01 (q, $J = 34.41$ Hz), 41.82 (q, $J = 35.17$); $^{19}$F NMR (376 MHz, CDCl$_3$) δ $-XX.XX$ (q, $J = XX$ Hz)

$N$-Nitrosodicyanaomethylamine $^1$H NMR (400 MHz, CDCl$_3$) δ 5.30 (s, 2H) δ 4.50 (s, 2H) $^{13}$C NMR (100 MHz, CDCl$_3$) δ 113.05, 111.56, 39.50, 30.02.

$N$-Nitroso-bis-(2-chlorodiethyl)amine 3.10g (55.8%) $^1$H NMR (400 MHz, CDCl$_3$) δ 4.58 (t, $J = 6.24$ Hz, 2H), 3.92 (t, $J = 6.24$ Hz, 2H), 3.88 (t, $J = 6.24$ Hz, 2H), 3.61 (t, $J = 5.84$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 54.85, 47.09, 41.86, 39.44.
$N$-Nitrosopyrrolidine $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.21 (t, $J = 6.96$ Hz, 2H), 3.52 (t, $J = 7.72$ Hz, 2H), 2.00 (m, 4H); $^{13}$C NMR (100 MHz, CD$_3$NO$_2$) $\delta$ 49.58, 44.90, 23.60, 22.24.

$N$-Nitrosopiperidine $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.17 (t, $J = 5.48$ Hz, 2H), 3.76 (t, $J = 5.84$ Hz, 2H), 1.76 (m, 4H), 1.54 (quintet, $J = 6.2$ Hz, 2H); $^{13}$C NMR (100 MHz, CD$_3$NO$_2$) $\delta$ 50.61, 39.48, 26.28, 24.62, 23.79.

$N$-Nitrosohexamethyleneimine $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.33 (t, $J = 5.48$ Hz, 2H), 3.64 (t, $J = 5.88$ Hz, 2H), 1.87 (quintet, $J = 5.48$ Hz, 2H), 1.77 (quintet, $J = 6.24$ Hz, 2H), 1.58 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 52.18, 46.37, 29.40, 28.73, 28.13, 24.59.
$N$-Nitrosoheptamethyleneimine $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.20 (t, 2H), 3.65 (t, 2H), 1.94 (quintet, 2H), 1.75 (quintet, 2H), 1.64 (quintet, 2H), 1.41 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 53.49, 45.77, 26.38, 26.07, 25.60, 24.61, 24.45.

$N$-Nitrosomorpholine $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.24 (t, 2H), 3.83 (m, 4H), 3.61 (t, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 67.32, 65.92, 50.03, 40.43.

$N$-Nitrosomorpholine $^1$H NMR (400 MHz, CD$_3$NO$_2$) $\delta$ 8.56 (d, $J$ = 2.2 Hz, 2H), 8.52 (m, 2H), 8.42 (m, 1H), 8.37 (m, 1H), 7.66 (m, 2H), 7.45 (m, 1H), 7.36 (m, 2H), 7.27 (m, 1H), 5.63 (t, $J$ = 6.6 Hz, 2H), 5.17 (t, $J$ = 7.32, 1H), 4.61 (m, 1H), 4.44 (m, 1H), 3.82 (m, 2H), 3.76 (m, 2H), 2.53 (m, 3H), 2.08 (m, 6H); $^{13}$C NMR (100 MHz, CD$_3$NO$_2$) $\delta$ 149.16, 148.56, 148.37, 147.62, 137.09, 136.16, 134.40, 133.23, 123.73, 123.53, 62.76, 58.78, 50.91, 46.18, 33.30, 33.04, 22.53, 20.74.
Dinitrosopiperazine $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.54 (s, 2H), 4.38 (t, $J = 4.76$, 2H), 4.02 (t, $J = 5.52$ Hz, 2H), $\delta$ 3.80 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 49.65, 47.15, 40.59, 37.83.

**General Method for the Preparation of 1,1-dialkylhydrazines**

1.5g of $N$-Nitroso-$N$-methyl-$N$-ethylamine was weighed into a 100ml round bottom flask and a stir bar was added. 3.41g of Zn dust was then added followed by 6.64g of NH$_4$CO$_3$ in 65ml of H$_2$O and the solution was placed in an ice bath. 17.80 ml of NH$_4$OH was then added dropwise over 10min, followed by stirring in the ice bath for 1h.

After stirring the zinc was removed by gravity filtration and the mixture was worked up in one of two ways.

**Workup A:** The reaction mixture was first extracted with 3x50ml of ether. The ether was then dried with MgSO$_4$ and filtered to remove the solid. A solution containing 1.5 equivalents of oxalic acid dissolved in ether was then added to the organic extracts and a white precipitate formed. This precipitate was then isolated from the ether via gravity filtration and recrystallized with 95% ethanol. The hydrazine oxalate was then neutralized with saturated NaHCO$_3$ and again extracted with 3x50ml portions of ether.

The organic layer was then dried with MgSO$_4$ and the volume was reduced under vacuum.
Workup B: After filtration benzaldehyde (1.5 eq) was added to the reaction mixture to form the corresponding hydrazone, and the reaction mixture was also extracted with 3x50ml portions of ether. The organic phase was removed under vacuum and aqueous HCl was added to the flask to hydrolyze the hydrazone. After hydrolysis was complete the reaction was extracted with ether to remove the benzaldehyde and the water was removed by rotary evaporation. As in workup A, azeotropic distillation with methanol and benzene was used to remove excess water before the sample was dried under reduced pressure to remove any excess organic solvent.

\[
\text{YH}_2\cdot\text{HCl}
\]

\(\text{N-Ethyl-N-methylhydrazine hydrochloride: Worked up according to general procedure B to give 1.12g (59.6%).}^{1}H\text{ NMR (400 MHz, CD}_3\text{OD) }\delta 3.18 \text{ (q, } J = 7.32 \text{ Hz, 2H), 2.93 (s, 3H), 1.31 (t, } J = 7.36 \text{ Hz, 3H).}
\]

\[
\text{YH}_2\cdot\text{HCl}
\]

\(\text{Diethylhydrazine hydrochloride: Worked up according to general procedure B yielding 1.12g (45.9%).}^{1}H\text{ NMR (400 MHz, CD}_3\text{OD) }\delta 3.25 \text{ (q, } J = 7.32 \text{ Hz, 2H), 1.35 (t, } J = 7.32 \text{ Hz, 2H).}
\)
Af-Methyl-A-propylhydrazine hydrochloride: Worked up according to general procedure B to give 0.47g (34.3%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 3.10 (t, $J = 7.68$ Hz, 2H), 2.94 (s, 3H), 1.75 (sextet, $J = 7.68$ Hz, 2H), 1.00 (t, $J = 7.32$ Hz, 3H).

Af-Ethyl-A-propylhydrazine hydrochloride: Worked up according to general procedure B. $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 3.23 (q, $J = 7.32$ Hz, 2H), 3.12 (t, $J = 8.08$ Hz, 2H), 1.79 (sextet, $J = 7.36$ Hz, 2H), 1.33 (t, $J = 7.32$ Hz, 3H), 1.01 (t, $J = 7.68$ Hz, 3H).

Af-Butyl-Af-methylhydrazine hydrochloride: Worked up according to general procedure A. $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 3.12 (t, $J = 8.04$ Hz, 2H), 2.93 (s, 3H), 1.69 (quintet, $J = 8.08$ Hz, 2H), 1.41 (sextet, $J = 7.32$ Hz, 2H), 0.98 (t, $J = 7.32$ Hz, 3H).

Dipropylhydrazine hydrochloride: Worked up according to general procedure A. .90g (36.7%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.42 (t, $J = 7.32$ Hz, 2H), 1.55 (sextet, $J = 7.68$ Hz, 2H), 0.90 (t, $J = 7.32$ Hz, 3H).
Hydroxyl Radical Degradation

The hydrazines used in this research are not commercially available and were synthesized by the reduction of the corresponding nitrosamines. All of the hydrazines prepared were determined to be of high purity by NMR. Solutions of approximately 100mM were made by the dilution of 1mM of the corresponding hydrazine hydrochloride in 10mL of deionized water. The hydroxyl radical degradation experiments were done...
N-Butyl-N-ethylhydrazine hydrochloride: Worked up according to general procedure A.  
$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 3.24 (q, $J = 7.36$ Hz, 2H), 3.16 (t, $J = 8.08$ Hz, 2H), 1.75 (quintet, $J = 7.68$ Hz, 2H), 1.41 (sextet, $J = 7.68$ Hz, 2H), 1.34 (t, $J = 7.32$ Hz, 3H), 0.99 (t, $J = 7.36$ Hz, 3H).

N-Butyl-N-propylhydrazine hydrochloride: Worked up according to general procedure A.  
$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 3.13 (m, 4H), 1.76 (m, 4H), 1.41 (sextet, $J = 7.32$ Hz, 2H), 0.99 (m, 6H).

Dibutylhydrazine: Worked up according to general procedure A.  $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.44 (t, $J = 7.72$ Hz, 2H), 1.51 (quintet, $J = 7.32$ Hz, 2H), 1.32 (sextet, $J = 7.32$ Hz, 2H), 0.91 (t, $J = 7.32$ Hz, 3H).

**Hydroxyl Radical Degradation**

The hydrazines used in this research are not commercially available and were synthesized by the reduction of the corresponding nitrosamines. All of the hydrazines prepared were determined to be of high purity by NMR. Solutions of approximately 100mM were made by the dilution of 1mM of the corresponding hydrazine hydrochloride.
in 10mL of deionized water. The hydroxyl radical degradation experiments were done using the linear accelerator (linac) electron-pulse radiolysis system on the campus of Notre Dame University.

Stock solutions were prepared by diluting ~.0389g (400uM) KSCN and 5.6784g (40mM) of phosphate buffer in 4L of highly pure water. The high purity water was filtered through a Millipore Milli-Q charcoal filter and subjected to UV illumination to maintain organic contaminants below 13 μg L⁻¹. These samples were adjusted to the appropriate pH either with perchloric acid or sodium hydroxide before being saturated with N₂O using handmade bubblers. The function of the N₂O was to remove the solvated electrons and molecular hydrogen from solution leaving only the hydroxyl radicals. The measurements were taken in a continuous flow system using a 1cm path length quartz sample cell.

Each sample run consisted of a blank followed by 4 additions of ~250uL portions of hydrazine solutions. The absorbance measurements were taken at 475nm where the radical anion dimer (SCN₂)⁻ was observed. Each reported absorbance was produced from the average of 12 absorbance measurements, and three absorbances were reported for each dilution. All runs were taken at room temperature (21±2 °C).

NMR Experiment

All NMR spectra were taken on a JEOL Eclipse 400 MHz nuclear magnetic resonance spectrometer. NMR solvents were purchased from Sigma Aldrich with purities of >95%. All NMR samples were either run in CDCl₃ or CD₃NO₂ as noted with the exception of the hydrazine hydrochloride salts which were all run in CD₃OD and the
were needed to produce a good signal to noise ratio for the $^{15}$N NMR as it has a very low natural abundance of 0.365%.
REFERENCES


$^1$H and $^{13}$C NMR spectra of N-nitrosodimethylamine
$^1$H and $^{13}$C NMR spectra of $N$-nitroso-$N$-methyl-$N$-ethyamine
$^1$H and $^{13}$C NMR spectra of N-nitrosodiethylamine
$^1$H and $^{13}$C NMR spectra of N-nitroso-N-methyl-N-propylamine
$^1$H and $^{13}$C NMR spectra of N-nitrosodipropylamine
$^1$H and $^{13}$C NMR spectra of $N$-nitrosodibutylamine
$^1$H and $^{13}$C NMR spectra of $N$-nitroso-$N$-butyl-$N$-methylamine
$^1$H and $^{13}$C NMR spectra of $N$-nitroso-$N$-butyl-$N$-ethylamine
$^1$H and $^{13}$C NMR spectra of $N$-nitroso-$N$-butyl-$N$-proylamine
$^1$H and $^{13}$C NMR spectra of N-nitrosodiphenylamine
$^1$H and $^{13}$C NMR spectra of N-nitrosodibenzylamine
$^1$H and $^{13}$C NMR spectra of $N$-nitroso-$N$-methyl-$N$-benzylamine
$^{1}H$ and $^{13}C$ NMR spectra of $N$-nitroso-$N$-ethyl-$N$-benzylamine
$^1$H and $^{13}$C NMR spectra of N-nitroso-N-butyl-N-benzylamine
$^1$H and $^{13}$C NMR spectra of $N$-nitroso-$N$-methylaniline
$^1$H and $^{13}$C NMR spectra of $N$-nitroso-$N$-ethylaniline
$^{1}$H and $^{13}$C NMR spectra of N-nitroso-N-propylaniline
$^{1}H$ and $^{13}C$ NMR spectra of $N$-nitroso-$N$-butylaniline
$^{1}H$ and $^{13}C$ NMR spectra of $N$-nitroso-$N$-tert-butyl-$N$-ethylamine
$^1$H and $^{13}$C NMR spectra of N-nitrosodiisopropylamine
$^{1}H$ and $^{13}C$ NMR spectra of $N$-nitrosopyrrolidine
$^1$H and $^{13}$C NMR spectra of $N$-nitrosopiperidine
$^1$H and $^{13}$C NMR spectra of N-nitrosomorpholine
$^1$H and $^{13}$C NMR spectra of N-nitrosohexamethyleneimine
$^1$H and $^{13}$C NMR spectra of $N$-nitroso-bis-(2-chloroethyl)amine
$^{1}H$ and $^{13}C$ NMR spectra of $N$-nitroso-bis-(2,2,2-trifluoroethyl)amine
$^1$H and $^{13}$C NMR spectra of $N$-Nitrosonornicotine
$^1$H and $^{13}$C NMR spectra of N-Nitrosodicyanomethylamine
$^1$H and $^{13}$C NMR spectra of N-Nitrosodiethanolamine
$^1$H and $^{13}$C NMR spectra of N-Nitroso-N-benzyl-N-propylamine
$^1$H and $^{13}$C NMR spectra of N-Nitrosoheptamethyleneamine
$^1$H and $^{13}$C NMR spectra of $N$-dinitrosopiperazine
$^1$H and $^{13}$C NMR spectra of $N$-Nitroso-$N$-tert-buty1-$N$-methylamine
$^1$H and $^{13}$C NMR spectra of $N$-Nitroso-$N$-ethyl-$N$-propylamine