1974

Conformational Preferences in Some Bicyclic, Tricyclic, and Related Acyclic N-Nitrosamines.

David Ray Battiste

Louisiana State University and Agricultural & Mechanical College

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CONFORMATIONAL PREFERENCES IN SOME BICYCLIC, TRICYCLIC, AND RELATED ACYCLIC N-NITROSAMINES

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy in

The Department of Chemistry

by

David Ray Battiste
B.S., University of Florida, 1969

May 1974
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ABSTRACT

Nmr spectral data indicate that, in simple N-nitrosamines, there is a substantial energy barrier to rotation about the N-N bond. N-Nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (VIII), N-nitroso-2-azabicyclo[2.2.2]octane (XXII), N-nitroso-4-azatricyclo-[4.3.1.1^3,8]undecane (XIV), N-nitroso-7-azabicyclo[4.2.2]decane (XX), and N-nitroso-11-azabicyclo[4.4.1]undec-l-ene (XXIII) were synthesized and their structures were investigated by means of nmr techniques, including the use of europium shift reagent. Nitrosamines VIII and XXII are obtained as single compounds, with the nitroso oxygen anti to the adjacent bridgehead, and nitrosamines XIV, XX, and XXIII are obtained as mixtures of non-equilibrating stereoisomers. The size of the heterocyclic ring influences the geometry between the bridgehead hydrogen (or methyl) and the NNO moiety sufficiently to account for these differences.

Photoelectron (pes) spectra of a series of N-nitrosamines have been obtained and compared with the results of CNDO/2 and CNDO/S calculations; all observable pes bands have been assigned. The most energetic occupied molecular orbital is a \( \pi \) orbital, and the next most energetic occupied orbital is an \( n \) orbital localized on the nitroso oxygen. Bond orders, charge densities, and dipole moments determined by the calculations are presented and discussed. The calculated \( \pi \) charge densities indicate that the amino nitrogen is electron deficient; however, the calculated total charge densities indicate that the amino nitrogen is slightly electron rich. Barriers to syn-anti isomerization
of dimethylnitrosamine by means of both rotation around the N-N bond and inversion at the nitroso nitrogen have been calculated by means of the CNDO/2 method. The inversional barrier is four times greater than the rotational barrier. The calculated rotational barrier, 18.2 kcal/mol, is about the same as the experimentally determined barrier, 23 kcal/mol.

Conformational analyses of methylphenylnitrosamine and of diisopropynitrosamine have been made by means of the CNDO/2 method and have been compared with the analyses of previous investigations.
PART I

AN NMR STUDY OF STRUCTURE IN SOME BI-
AND TRICYCLIC N-NITROSAMINES

FOREWORD

Part I of this Dissertation is composed of three chapters. Chapter I contains background information on the nmr spectroscopy and structure of several acyclic N-nitrosamines. Chapter II provides the background to explain how lanthanide shift reagents are used to simplify the nmr spectra of a number of different kinds of organic compounds. In Chapter III, the results of the nmr and shift reagent studies of some bi- and tricyclic N-nitrosamines are presented and discussed.
Nuclear Magnetic Resonance Studies

The first definite conclusions regarding the structure of N-nitrosamines were made possible by means of nuclear magnetic resonance (nmr) studies.\(^1\)\(^-\)\(^3\) The nmr spectrum of N-nitrosodimethylamine consists of two equally-intense resonances, indicating that there is a substantial energy barrier to rotation around the N-N bond.\(^1\) The compound is conveniently represented by a zwitterionic structure (Ia).\(^1\) Two conformations (E and Z) of N-nitroso derivatives of unsymmetrical secondary

\[\text{CH}_3\text{N}-\text{NO}\rightarrow\text{CH}_3\text{N}^+\text{CH}_3\]

\[\text{CH}_3\text{CH}_2\text{N}-\text{NO}\rightarrow\text{CH}_3\text{CH}_2\text{N}^+\text{CH}_3\]

\[\text{I} \quad \text{Ia}

\[\text{I} \quad \text{Ia}

\[\text{II-E} \quad \text{II-Z}

\[\text{II-E} \quad \text{II-Z}
amines are possible (e.g., \( \text{II-E} \) and \( \text{II-Z} \)).\(^1\) Protons situated above or below the plane of the \( \text{C}^\alpha\text{C}^\alpha\text{NNO} \) group are shielded, whereas protons held in the plane are deshielded.\(^3\)

The room temperature 30 MHz nmr spectrum of \( \text{N-nitrosodimethylamine} \), \( \text{I} \), consists of two equally intense singlets separated by 19 Hz.\(^1\) The nonequivalence of the two methyl groups indicates a substantial barrier to rotation around the N-N bond.\(^1\) Discrete resonances for non-equivalent groups are observed if environmental exchange of the nuclei proceeds at an average rate of less than \( 1/\tau = \delta\omega/\sqrt{2} \);\(^1,4\) \( \delta\omega \) is the separation of the two resonances and \( \tau \) is the lifetime in either position. Only a single resonance located between the resonance positions of the two non-equivalent nuclei in a "slowly" changing environment is observed if the rate of environmental exchange is greater than \( \delta\omega/\sqrt{2} \).\(^1,4\) Thus, if rotation around the N-N bond of \( \text{N-nitrosodimethylamine} \) proceeds at a rate of \( 2\pi(19)/\sqrt{2} = 84 \text{ sec}^{-1} \) or more at room temperature only a single resonance would be observed.\(^1\) Because two resonances are observed in the nmr spectrum there must be a barrier that is large enough to reduce the rate of either inversion at the nitroso nitrogen or rotation around the N-N bond to less than 84 sec\(^{-1} \) at room temperature.\(^1\)
The magnitude of the energy barrier to inversion or rotation has been found to be 23 kcal/mol. The temperature dependence of the nmr spectrum (neat), shown in Figure 1, was used to find this barrier.

The numerical value of the barrier was found by means of the mathematical methods developed by Gutowsky and Holm. If the numbers of exchanging nuclei in the two environments are equal and the resonance line widths are small compared to the chemical shift between the nuclei in the two environments, the observed chemical shift, \( \delta \omega_e \), is given by the expression

\[
\delta \omega_e = \left(1 - \frac{2}{\tau \delta \omega^2}\right)^{\frac{1}{2}} \delta \omega
\]  

where \( \tau \) is the average time an exchanging nucleus spends in a given environment and \( \delta \omega \) is the separation in Hz between the signals of the nuclei in the two environments measured at temperatures at which the rate of exchange can be characterized as "slow", i.e., \( \tau \delta \omega \gg 1 \). Equation (1) applies to N-nitrosodimethylamine because the numbers of exchanging nuclei in the two environments are the same and because \( \delta \omega \) is much larger than the methyl line widths.

The reorientation process is assumed to behave as a typical rate process, and the rate equation is of the form

\[
k = v_0 \exp(-E_a/RT),
\]

where \( k \) is the rate constant, \( v_0 \) is the frequency factor, and \( E_a \) is the activation barrier energy. Because \( k = \frac{1}{\tau \delta \omega} \), equation (2) can be re-written as

\[
\log_{10}(1/\tau \delta \omega) = \log_{10}(2v_0/\delta \omega) - \frac{E_a}{2.3RT}.
\]

The slope of a plot of \( \log_{10}(1/\tau \delta \omega) \) vs. \( 1/T \) (Figure 2) yields a value
Figure 1. The temperature dependence of the nmr spectrum of dimethylnitrosamine.
Figure 2. Plot of $\frac{1}{\tau_0 \omega}$ (on log scale) vs. $\frac{1}{T}$ for dimethylnitrosamine.¹
of 23 kcal/mole for $E_a$, and the intercept yields a value of $7 \times 10^{12}$ sec$^{-1}$ for $v_0$.\textsuperscript{1}

The nmr evidence indicates a planar or nearly planar geometry for the \textit{N}-nitroso group, NNO.\textsuperscript{1} The planar structure indicated by resonance form 2 most readily accounts for the non-equivalence of the two methyl groups. Were the plane containing the NNO group perpendicular to the CNC plane, the methyl groups would be equivalent.\textsuperscript{1}

\begin{align*}
\text{H}_3\text{C} & \quad \text{N} - \text{N} \\
\text{CH}_3 & \quad \bigcirc
\end{align*}

The low field resonance was originally assigned to the methyl hydrogens \textit{syn} to the nitroso oxygen, and the resonance at higher field was assigned to the methyl hydrogens \textit{anti} to oxygen.\textsuperscript{1} These assignments were based on the assumption that the methyl hydrogens \textit{syn} to oxygen would be more greatly affected by the field effect of the electron rich oxygen than would the methyl hydrogens \textit{anti} to oxygen. They were shown, however, to be incorrect.\textsuperscript{2,3}

The first report that reversed the methyl assignments was published by H. W. Brown and D. P. Hollis.\textsuperscript{2} By means of an nmr study of several unsymmetrically substituted \textit{N}-nitrosamines, these workers predicted that as alkyl group $R_1$ becomes sterically more bulky, the more favored conformation of the nitrosamine becomes $\text{III-}E$, the one in which $R_1$ is \textit{anti} to the oxygen atom.\textsuperscript{2}
Table I shows the results of their study of the nmr spectra of dimethyl-, methylpropyl-, methylisopropyl-, and methyl-sec-butyl nitrosamines.²

In the above cases studied by Brown and Hollis, both conformers were present, and the conformational equilibrium was determined by nmr integration ratios.² Note that the higher values of K indicate a preference for conformer III-E, in which the more bulky branched alkyl group is anti to the oxygen atom.² Further, note that the methyl group syn to oxygen is now assigned the higher field resonance, and the methyl group anti to oxygen is assigned the lower field resonance.²

G. J. Karabatsos and R. A. Taller later in 1964 reported the findings of their nmr study of thirteen N-nitrosamines.³ These workers corroborated the chemical shift assignments of Brown and Hollis. Karabatsos and Taller discovered that the chemical shifts of N-nitrosamines and R₁R₂C=NG (G = -NHX where X may be CH₃ or C₆H₅) compounds behave almost identically; protons syn to G resonate upfield from protons anti to G.³ Thus these workers assumed that the anisotropic effects of NNO and C=NG are qualitatively similar.³ Their studies
TABLE I
THE EFFECT OF STERIC BULK ON THE CONFORMATIONAL RATIOS
OF SOME UNSYMMETRICALLY SUBSTITUTED N-NITROSAMINES\textsuperscript{2}

<table>
<thead>
<tr>
<th>N-Methyl Proton Shift, $\delta$</th>
<th>( K^a \frac{\text{syn-Me}}{\text{anti-Me}} )</th>
<th>Nitrosamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti</td>
<td>syn</td>
<td></td>
</tr>
<tr>
<td>3.8</td>
<td>3.1</td>
<td>1.0</td>
</tr>
<tr>
<td>3.8</td>
<td>3.0</td>
<td>3.6</td>
</tr>
<tr>
<td>3.7</td>
<td>3.0</td>
<td>8.4</td>
</tr>
<tr>
<td>3.7</td>
<td>3.0</td>
<td>11.0</td>
</tr>
</tbody>
</table>

a. \( K \) is the ratio of the areas of the absorptions of the hydrogens syn and anti to oxygen.

b. In the unsymmetrical N-nitrosamines considered in this table the preferred position of the more bulky alkyl groups is anti to oxygen; thus, the preferred position of the methyl group is syn to oxygen. Therefore, the ratio of the area of the methyl syn to oxygen to the area of the methyl anti to oxygen should be one or greater than one in the compounds shown. In analogous fashion, the ratio of the area of the alkyl group anti to oxygen to the area of the alkyl group syn to oxygen should be one or greater than one. The two ratios are equivalent.
showed that the region in the C=NG plane is deshielded with respect to the region above and below the plane.\textsuperscript{3}

In contrast to α-methyl and α-methylene protons which resonate at higher fields when \textit{syn} rather than when \textit{anti} to the oxygen atom, α-methine protons resonate at lower fields when \textit{syn} to the nitroso oxygen rather than when \textit{anti} to it.\textsuperscript{3} Because of steric interactions between the bulky β substituents (e.g., CH\textsubscript{3} in Figure 3) of the \textit{syn}

![Figure 3](image)

Figure 3. The preferred conformation of an isopropyl group \textit{syn} to oxygen

isopropyl group and the oxygen, the \textit{syn} α-methine proton spends more time in or nearly in the deshielding plane of the N-nitroso group.\textsuperscript{3}

The \textit{syn} α-methine was shown to be further downfield than the \textit{anti} α-methine by benzene solvent shifts in the nmr spectrum.\textsuperscript{3}

When benzene is added to a carbon tetrachloride solution of an N-nitrosoamine (or to the neat liquid N-nitrosamine), the \textit{anti} protons shift upfield to a greater extent than do the \textit{syn} protons.\textsuperscript{3} A regiospecific collision complex (Figure 4) was proposed to account for this observation.\textsuperscript{3} When R\textsubscript{1} and/or R\textsubscript{2} increase in steric bulk (Me < Et < 1-Pr < 1-Bu), the shift becomes smaller because of a decrease in the
The regiospecific complex formed between benzene and an N-nitrosamine. The equilibrium constant for formation of the complex.\textsuperscript{3} Thus, the use of benzene-induced shifts of the resonances confirmed the NMR assignments of syn and anti protons.

In order to learn more about the anisotropy of the nitrosamino group, Y. L. Chow and coworkers studied a series of 4-substituted N-nitrosopiperidines.\textsuperscript{5,6} These workers found that the long-range diamagnetic effects of the nitrosamino group could be qualitatively represented by the drawing reproduced in Figure 5.\textsuperscript{6} Thus, above and below

The shielding cones derived from the C\textsuperscript{α}-N single bond and the N-N-O partial double bonds are regarded as being fused together to form a semicircular shielding zone curved toward the syn side.\textsuperscript{11}
the Cα-N-N-O plane diamagnetic shielding is expected. The above semi-
circular shielding zone indicates that there is more shielding on the
syn side of the nitroso group than on the anti side. However, the de-
shielding zone which is in the plane of the Cα-N-N-O bond is expected
to be nearly equal in magnitude in both directions. Electric field
effects of the electron-rich oxygen cause protons in this plane and
syn to the oxygen to be slightly further downfield than similar protons
anti to the oxygen.

**Electron and X-Ray Diffraction Studies**

The planarity of the Cα-Cα-NNO group, postulated by nmr studies,
has recently been confirmed by means of an electron diffraction study on
N-nitrosodimethylamine and an X-ray diffraction study on its copper-
(II) chloride complex. The bond lengths and bond angles of N-
nitrosodimethylamine and of N-nitrosodimethylaminocopper(II) chloride,
(CH₃)₂N-NO·CuCl₂, are shown in Table II. No significant deviation from
a planar skeleton was exhibited by either molecule. The N-
nitrosamine coordinates with copper(II) chloride through the oxygen
atom.
TABLE II

EXPERIMENTAL BOND LENGTHS AND BOND ANGLES OF
N-NITROSODIMETHYLAMINE AND N-NITROSODIMETHYLAMINE COPPER(II) CHLORIDE

<table>
<thead>
<tr>
<th>Bond Lengths (Å)</th>
<th>IVa</th>
<th>IVb</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-O</td>
<td>1.255</td>
<td>1.21</td>
</tr>
<tr>
<td>N-N</td>
<td>1.344</td>
<td>1.26</td>
</tr>
<tr>
<td>C-N</td>
<td>1.461</td>
<td>1.48</td>
</tr>
<tr>
<td>C-H</td>
<td>1.129</td>
<td>1.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond Angles (Degrees)</th>
<th>IVa</th>
<th>IVb</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-N-O</td>
<td>115.6</td>
<td>117.3</td>
</tr>
<tr>
<td>C'-N-N</td>
<td>120.5</td>
<td>120.0</td>
</tr>
<tr>
<td>C''-N-N</td>
<td>116.4</td>
<td>120.6</td>
</tr>
<tr>
<td>N-C-H</td>
<td>109.6</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER II

LANTHANIDE SHIFT REAGENTS

Discovery and Usefulness

Nuclear magnetic resonance spectroscopy is a powerful tool through which one can derive structural information about organic compounds. One appropriate example is the demonstration of a barrier to rotation about the N-N bond of N-nitrosodimethylamine by means of its temperature dependent nmr spectrum (Figure 1). The principle requirement in structural and stereochemical studies of organic compounds using nmr parameters such as coupling constants, chemical shifts, and nuclear ratios to determine the stereochemistry of a compound is complete resolution of the spectrum. A number of techniques have been used to simplify complex nmr spectra: deuterium substitution, spin-decoupling experiments, derivatization, and the use of higher frequency (100, 220, or 300 MHz) spectrometers. Another technique to simplify a complex nmr spectrum, the use of a solvent shift reagent, has been discussed in a previous chapter. Because most organic molecules contain some type of functional group to which a shift reagent could complex, the use of this type of shift reagent for simplifying a complex nmr spectrum is quite attractive.

It has long been known that such paramagnetic complexing reagents as nickel(II) and cobalt(II) bis(acetylacetonates) cause shifts in the nmr spectrum of certain organic compounds. However, these shifts are very small in magnitude, and line broadening of the peaks is
extensive. An ideal shift reagent would cause large shifts, would not cause severe line broadening, and would be extremely soluble in common nmr solvents (CCl₄ and CDCl₃).¹³,¹⁴

C. C. Hinckley first discovered the usefulness of lanthanide complexes as "chemical shift" reagents.¹³ He found that the dipyridine adduct of bis(dipivalomethanato)europium(III), Eu(dpm)₃ · 2py, induces substantial downfield shifts of the proton resonances in cholesterol and causes very little line broadening. Larger downfield shifts are observed when the pyridine-free adduct of Eu(dpm)₃ is used; however, the solubility of the pyridine-free lanthanide complex in nmr solvents decreases drastically.¹⁵,¹⁶ The praseodymium complex, Pr(dpm)₃, induces upfield shifts which are three times as large as the downfield shifts of Eu(dpm)₃; however, the bands are significantly broadened. These lanthanide shift reagents coordinate in Lewis acid-base fashion to a number of organic functional groups such as alcohol, amine, epoxide, ester, ketone, oxime, and N-nitrosamine. The induced chemical shifts vary linearly with shift reagent concentration over a shift reagent:substrate molar ratio range of 0.1-0.5:1.¹¹ Because only one set of peaks for the organic substrate is observed in the presence of shift reagent, the observed chemical shift is the weighted average of the shifts of the complexed and uncomplexed substrates.¹¹ Induced shifts are usually reported as values extrapolated linearly to a molar ratio of 1.0 or are reported as the gradient [ppm/mol Eu(dpm)₃/mol substrate] of the linear portion of the induced shift vs. molar ratio plot.¹¹

The magnitude of the induced shifts depends on the type of coordination site (Table III), the nature of the shift reagent, the position of the magnetic nuclei in relation to the lanthanide ion, and
TABLE III
THE DEPENDENCE OF THE MAGNITUDE OF INDUCED SHIFT ON THE TYPE OF FUNCTIONAL GROUP

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Ppm/mol of Eu(dpm)₃ per mol of substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCH₂NH₂</td>
<td>150</td>
</tr>
<tr>
<td>RCH₂OH</td>
<td>100</td>
</tr>
<tr>
<td>RCH₂NH₂</td>
<td>30-40</td>
</tr>
<tr>
<td>RCH₂OH</td>
<td>20-25</td>
</tr>
<tr>
<td>RCH₂COR'</td>
<td>10-17</td>
</tr>
<tr>
<td>RCH₂CHO</td>
<td>19</td>
</tr>
<tr>
<td>RCH₂CHO</td>
<td>11</td>
</tr>
<tr>
<td>RCH₂OCH₂R</td>
<td>10</td>
</tr>
<tr>
<td>RCH₂CO₂Me</td>
<td>7</td>
</tr>
<tr>
<td>RCH₂CO₂Me</td>
<td>6.5</td>
</tr>
<tr>
<td>RCH₂CN</td>
<td>3-7</td>
</tr>
</tbody>
</table>
certain experimental conditions. Table III shows that the preferred order of coordination for the various functional groups studied is: amines > alcohols > oximes > aldehydes, ketones > ethers > esters > nitriles. Also, it has been found that the europium(III) complex with the ligand 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione, Eu(fod)₃, is a better Lewis acid than Eu(dpm)₃ and is more soluble in carbon tetrachloride than is Eu(dpm)₃. The presence of water in the nmr sample severely reduces the shifting ability of the lanthanide shift reagents; water associates more strongly with the shift reagent than does the organic substrate. Even traces of acid present in some nmr solvents cause reduced shifts because of the decomposition of the lanthanide complex. Thus, in order to maximize the usefulness of the shift reagents, the characteristics listed above must be considered.

Theoretical Considerations

The magnitude of the induced shifts (Δδ) may be expressed by equation (4):

\[ Δδ = K(3\cos^2φ - 1)r^{-3} \]  

(4)

where K is a constant for a particular complex at a given temperature, φ is the proton-lanthanide ion coordination site internuclear angle, and r is the straight line distance between the proton and the metal ion. In a number of examples the dependence of the induced chemical shift on the angle φ may be neglected; the size of the induced shift for the hydrogens in a given molecule would then depend on the reciprocal of the cube of the distance between the metal ion and the proton. The \((3\cos^2φ - 1)\) term is positive for \(0° < φ < 54.74°\) and \(125.26° < φ < 180°\),
but it is negative for $54.75^\circ < \phi < 125.26^\circ$.\textsuperscript{11} When the $(3\cos^2\phi - 1)$ term is positive, Eu(dpm)$_3$ and Eu(fod)$_3$ will induce downfield shifts, while Pr(dpm)$_3$ and Pr(fod)$_3$ will cause upfield shifts. However, when the angle term is negative the direction of the shift is reversed; the europium(III) complexes cause upfield shifts, and the praseodymium(III) complexes cause downfield shifts. Thus, the size and direction of the induced shifts depend on the geometry of the shift reagent-organic substrate complex.

There are two mechanisms which may be used to describe the effects of paramagnetic species on the nmr resonances of organic compounds: the contact shift mechanism and the pseudocontact shift mechanism.\textsuperscript{16} In the contact mechanism, interaction between nuclear and electron spins produces an internal magnetic field at the resonating nucleus which either adds to or subtracts from the applied field and thereby leads to a resonance shift. The spin density of the unpaired electron on the paramagnetic species is transferred through the bonding structure to the resonating nucleus. The pseudocontact shift is similar to the contact shift except that in this case the shift is caused by the combined effects of the electron spin-orbit, electron orbit-nuclear spin, and electron spin-nuclear spin couplings.\textsuperscript{16} These forces generate a shift that is related to the geometry of the complex species. There is no transfer of unpaired electron spin density. Correlations of induced chemical shifts ($\Delta\delta$) with $r^{-3}$ and $\phi$ for the lanthanide complexes have established the predominant role of the pseudocontact mechanism.\textsuperscript{11,16}

The lanthanide shift reagents have been very successfully applied to stereochemical and structural problems. The shift reagent may be used merely to separate overlapping chemical shifts in order to
obtain a first order spectrum for analysis. In another method, the geometry or configuration of a substrate nucleus is related to an observed induced chemical shift; of course, both the distance \( r^{-3} \) and the angle \( \phi \) dependence must be considered. Thus, the substrate geometry may be deduced from the particular substrate-complex geometry which is most consistent with the observed variation of the induced shift as a function of \( r^{-3} \) and \( \phi \). This approach is especially useful when supporting data from other techniques are available.

In summary, the important features of the use of lanthanide shift reagents in nmr spectroscopy have been discussed in the foregoing paragraphs. Where applicable, lanthanide shift reagents have tremendous advantages over other techniques used for simplifying a complex nmr spectrum; these advantages are ease of use, low cost of the reagent, and the speed of the analysis. The lanthanide shift reagents played an important role in the analysis of the nmr spectra of the N-nitrosamines reported in this Dissertation.
CHAPTER III

RESULTS AND DISCUSSION

Synthesis of N-Nitrosamines

N-nitrosamines are easily prepared from secondary amines by the addition of the amine hydrochloride to an aqueous solution of sodium nitrite.\(^1\) The N-nitroso derivatives of diisopropylamine (VII), dimethylamine (I), and the bicyclic amines were prepared in this manner. N-nitroso-N-methylaniline (VII) was prepared by means of the reaction of nitrosyl chloride with N-methylaniline and was also obtained from a commercial supplier; there was no difference between the two samples. N-nitrosodiethylamine (V) was inherited from an earlier worker, M. T. Yang, in this Laboratory. Both V and VII were purified before use by means of vacuum distillation. The acyclic N-nitrosamines, I, V, and VI were used as models for the shift reagent studies used to determine the preferred conformation of the bicyclic N-nitrosamines. The synthesis of the appropriately substituted bicyclic amines was accomplished by means of known pathways. The bicyclic amine, 7-azabicyclo[4.2.2]decane (XIV), is a new compound synthesized as a part of this investigation.

The synthetic scheme used to prepare N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX) is shown below:
Piperitenone (VII) was stirred in aqueous ammonia for five days to yield 1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one, (VIII). Then VIII was converted to the N-nitroso derivative, IX, by treatment with nitrous acid.

The preparation of N-nitroso-4-azatricyclo[4.3.1.1^3,8]-undecane by means of a four-step process is shown below:
Commercially available 2-adamantanone (X) was converted to its oxime (XI) and the oxime was transformed into 4-azatricyclo[4,3,1,1<sub>3,8</sub>]undecan-5-one (XII) by means of a Beckman rearrangement.\textsuperscript{20,21} The amide (XII) was reduced with lithium aluminum hydride (LAH) to 4-azahomoadamantane (XIII).\textsuperscript{22} Treatment of XIII with aqueous HCl/NaNO<sub>2</sub> gave the N-nitroso derivative (XIV).\textsuperscript{18}

N-Nitroso-7-azabicyclo[4.2.2]decane (XX) was prepared from cyclooctatetraene (XV) by means of the five-step synthesis shown below:

Chlorosulfonyl isocyanate reacted with XV to yield the N-(chlorosulfonyl) lactam (XVI);\textsuperscript{23a} hydrolysis of this initial 1,4-cycloadduct with sodium hydroxide in aqueous acetone yielded the 7-azabicyclo[4.2.2]deca-2,4,9-trien-8-one (XVII);\textsuperscript{23b} hydrogenation of the unsaturated amide over 5% palladium on carbon in methanol yielded 7-azabicyclo[4.2.2]decan-8-one (XVIII);\textsuperscript{24} reduction of XVIII with LAH in tetrahydrofuran yielded the 7-azabicyclo[4.2.2]decane (XIX),\textsuperscript{22} isolated as its crystalline
hydrochloride; and the N-nitrosamine $XX$ was prepared in the usual manner. The properties of the newly-synthesized bicyclic amine, $XIX$, and its N-nitroso derivative ($XX$) are described in greater detail in the Experimental Section of this Dissertation.

2-Azabicyclo[2.2.2]octane ($XXI$), precursor of N-nitroso-2-azabicyclo[2.2.2]octane ($XXII$), was obtained as a gift from Dr. Frank J. Villani, Schering Corporation. 25 11-Azabicyclo[4.4.1]undec-1-ene ($XXIII$), precursor of N-nitroso-11-azabicyclo[4.4.1]undec-1-ene ($XXIV$), was obtained from Ronald R. Lilienthal, another worker in this Laboratory. 26

**Shift Reagent Studies of Acyclic N-Nitrosamines**

Benzene has been used as a solvent shift reagent in the analysis of the nmr spectra of symmetrical and unsymmetrical acyclic N-nitrosamines. However, as in the case of most solvent shift reagents, the induced shifts are small. This shift reagent also depends on the formation of a regiospecific collision complex, the stability of which might be unpredictable for structurally complex N-nitrosamines. Thus, the discovery of the lanthanide shift reagents by Hinckley greatly enhanced the prospects for an easier and more straightforward analysis of the nmr spectra of a variety of complex compounds, including N-nitrosamines.

Because no data existed on the use of lanthanide shift reagents with N-nitrosamines, shift studies of dimethyl-, diethyl-, and diisopropyl nitrosamine were undertaken. The shift reagents were Eu(fod)$_3$ and Eu(dpm)$_3$.11 These reagents coordinate with the electron rich oxygen atom of the N-nitrosamine and cause downfield shifts of the hydrogens _syn_ and _anti_ to the oxygen. The shift of _syn_ hydrogens is
expected to be greater than the shift of \textit{anti} hydrogens because the \textit{syn} hydrogens are closer to the side of complexation.\textsuperscript{11} This behavior was found to hold in the cases of the acyclic, bicyclic, and tricyclic N-nitrosamines reported in this Dissertation. In the plots of chemical shift vs. the europium:N-nitrosamine molar ratio, the slopes of the lines for the hydrogens closer to the coordination site are steeper. The plots for these three compounds are shown in Figures 6, 7, and 8.

In the case of dimethylnitrosamine (Figure 6), the slope of the line for the methyl hydrogens \textit{syn} to oxygen is steeper than the slope of the line for the methyl hydrogens \textit{anti} to oxygen. This shift study corroborates the earlier nmr studies (Brown and Hollis; Karabatsos and Taller) of N-nitrosamines which assigned the high field singlet (\textit{\delta} 2.96) to the methyl group \textit{syn} to oxygen and the low field singlet (\textit{\delta} 3.76) to the methyl group \textit{anti} to oxygen.\textsuperscript{2,3}

Diethylnitrosamine (Figure 7) exhibits shift behavior similar to that of dimethylnitrosamine. The methylene hydrogens \textit{syn} to oxygen generate a slope which is steeper than both that for the methylene hydrogens \textit{anti} to oxygen and that for the methyl hydrogens \textit{syn} to the oxygen.

The much greater magnitude of the shifts of proton resonances by means of lanthanide shift reagents in comparison with the magnitude of shifts by means of solvent shift reagents allows one to assign nmr resonance bands with more confidence. For diisopropyl nitrosamine, Karabatsos and Taller postulated that the methine hydrogen \textit{syn} to oxygen resonates at lower field than the methine hydrogen \textit{anti} to oxygen.\textsuperscript{3} This ordering of the \textit{syn} and \textit{anti} methine resonances is opposite to the ordering of the corresponding methyl and methylene resonances. Because
Figure 6. Shift reagent study of dimethylnitrosamine (1) with Eu(fod)₃. The slope is reported in units of ppm/mol Eu(fod)₃/mol 1⁻.
Figure 7. Shift reagent study of diethylnitrosamine ($\psi$) with Eu(fod)$_3$. The slope is reported in ppm/mol Eu(fod)$_3$/mol $\psi$. 

- $\text{syn CH}_3$: 3.92
- $\text{anti CH}_3$: 2.08
- $\text{syn CH}_2$: 6.66
- $\text{anti CH}_2$: 3.41
Figure 8. Shift reagent study of diisopropylnitrosamine (VI) with Eu(dpm)$_3$. 
the greatest area of deshielding by the nitroso group is in its plane and on the side syn to oxygen, the methine hydrogen syn to oxygen must occupy a position in or nearly in the plane of the nitroso group.³

The shifted nmr spectra and the shift reagent plots (Figure 8) both give clear evidence for the assignment of the low field resonance in the spectrum of diisopropylnitrosamine to the methine syn to oxygen. Note that in the shifted spectra of dimethylnitrosamine the absorption for the higher field, syn methyl approaches that of the methyl anti to oxygen and eventually passes it toward the low field end of the spectrum as the shift reagent:substrate ratio increases. The methylene hydrogens and methyl hydrogens of diethylnitrosamine behave in an entirely analogous manner, the resonances of the hydrogens syn to oxygen shift toward the low field part of the spectrum to a greater extent than do those of the corresponding hydrogens anti to oxygen. The shift reagent plots show the intersection point.

In diisopropylnitrosamine, the absorption for the methyl hydrogens syn to oxygen (originally the high field resonance) shifts to lower field to a greater extent than does the absorption for the methyl hydrogens anti to oxygen. Because of the relative chemical shift of the syn methyls in the uncomplexed nitrosamine, the shift reagent plot shows an intersection point. However, the shift reagent plot for the methine hydrogens does not show an intersection point. This result is entirely consistent with the methine syn to oxygen being in or nearly in the plane of the nitroso group

An important factor to consider in the use of lanthanide shift reagents for the determination of the structure of N-nitrosamines is whether or not complexation by the reagent may promote rapid
equilibration and averaging of the nitrosamine conformers. The nmr spectrum of each of the three acyclic N-nitrosamines in the presence of the shift reagent shows only one set of peaks for each syn or anti group. Thus, the association-dissociation of N-nitrosamine with the shift reagent occurs in the fast exchange limit, and the chemical shifts of protons in the N-nitrosamines are the weighted average of their chemical shifts in the uncomplexed and complexed species. The three symmetrically substituted N-nitrosamines, I, V, and VI, have shown that groups syn to oxygen shift to lower field when treated with europium- (III) shift reagent to a greater extent than groups anti to oxygen.

Thus, rapid equilibration of the conformers upon complexation with shift reagent may be ruled out because only one resonance for the two methyl groups would then be observed rather than two.

Because of the efficacy of the lanthanide shift reagent in analysis of the nmr spectra of simple acyclic nitrosamines, this reagent was used to assist analysis of the spectra of a series of bi- and tricyclic N-nitrosamines.

Nmr and Shift Reagent Studies of Bi- and Tricyclic N-Nitrosamines

The most characteristic feature in the nmr spectrum of N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX), (see Figures 31 and 32) is the presence of only three methyl singlets. The bridgehead methyl group attached to C-1 resonates at δ 1.71, the endo methyl group attached to C-3 is assigned to the resonance at δ 1.40, and the exo methyl group is assigned to the peak at δ 1.24. The bridgehead methyl group at C-3 is expected to be deshielded with respect to the other two methyls, because it lies in the deshielding zone of the
planar N-nitroso group. The two methyls at C-3 lie above and below the plane of the \(C^1(C^3)\text{NNO}\) group and in the shielding cone of the N-nitroso group. Furthermore, the exo methyl lies in the shielding cone of the C-5 carbonyl group and is therefore more shielded than the endo methyl group.

The two nonequivalent hydrogens on C-6 have different splitting patterns and chemical shifts. Examination of Dreiding molecular models shows the appropriate geometry for \(W\) coupling between the \textit{syn} hydrogen on C-6 and the \textit{endo} hydrogen on C-7, but no such coupling seems possible for the \textit{anti} hydrogen. Therefore, the hydrogen on the same side (\textit{syn}) of the bicyclic ring as the N-nitroso group is assigned to the doublet of doublets (\(J_{\text{gem}} = 18.5\ \text{Hz}, J_W = 1.8\ \text{Hz}\)) centered at \(\delta\ 2.46\), whereas the hydrogen on the opposite side (\textit{anti}) is assigned to the doublet (\(J_{\text{gem}} - 18.5\ \text{Hz}\)) centered at \(\delta\ 2.24\) (see Figure 32 and Figures 32a-c).

The nmr spectrum of IX suggests that there is only one conformational isomer present. If both conformers of the \(N\)-nitrosamine were present, there should be six singlets for the methyl groups: one singlet each for \textit{syn} and \textit{anti} bridgehead methyl, one singlet each for
syn and anti exo methyl and one singlet each for syn and anti endo methyl. However, only three singlets for the methyl groups are observed. A consideration of Dreiding molecular models and the conformational equilibria displayed by methylethyl-, methylisopropyl- and methyl-tert-butyl nitrosamines lead to the prediction that the more abundant conformer would be the one in which the nitroso oxygen is anti to the C-1 (bridgehead) methyl group. Thus, the C-1 methyl resonance is predicted to be the most downfield resonance because it lies in the deshielding zone of the nitroso group. The endo C-3 methyl is predicted to be at higher field than the C-1 methyl because it lies in the shielding zone of the nitroso group, and the exo C-3 methyl is predicted to be the most upfield methyl group because of its position in the shielding zones of both the nitroso group and the carbonyl group. Evidence confirming the NMR assignments and the conclusion that only one conformation is present was obtained from the shift reagent study (see Figure 9 and Table XVIII).

For IX the shift reagent plot for the anti methyl group on C-1 has a lower slope than that for the two syn methyls on C-3. Also, the slope of the plot for the exo syn methyl is steeper than the slope of the plot for the endo syn methyl. The difference in the slope of the line for these two methyls occurs because the exo syn methyl is closer to a second site of coordination. The C-5 carbonyl oxygen, the resonance assignment for each methyl is thus confirmed, and the conformational preference is established. Furthermore, the shift reagent plot makes possible the assignment of the C-6 methylene hydrogens. The hydrogen closer to the two coordinating groups is expected to have the steeper slope. Because the doublet (J = 1.7 Hz) at δ 2.6 shifts
Figure 9. Shift reagent study of N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX) with Eu(fod).

The slope is reported in ppm/mol Eu(fod)/mol IX.
downfield faster (steeper slope) than the singlet at δ 2.58, this resonance is assigned to the methylene hydrogen syn to the N-nitroso group, H₅; the singlet at δ 2.58 is thus assigned to the anti hydrogen H₆.

The above example follows the well-known observation that the preferred conformer of any N-nitrosamine is the conformer in which the nitroso oxygen is anti to the sterically more bulky substituent.2,3 However, that idea is carried one step further in that the C-1 methyl is locked in the plane of the nitroso group while the methyls on C-3 are locked above and below that plane. In order to determine whether a bridgehead hydrogen is sterically bulky enough to affect the conformer ratio in the same way, the parent bicyclic N-nitrosamine, XXII, was prepared.

The nmr spectrum of N-nitroso-2-azabicyclo[2.2.2]octane (XXII), (see Figure 33), consists of a broad five-line multiplet at δ 4.82, which is assigned to the (bridgehead) hydrogen on C-1. The doublet (J = 2.9 Hz) at δ 3.58 is assigned to the methylene hydrogens on C-3, while the remaining hydrogens are included in the envelope from δ 2.90-1.50. The presence of only one absorption peak for the C-1 bridgehead hydrogen and only one for the C-3 methylene hydrogens indicates that again in this case only one conformer exists. Also, there is no change in the nmr spectrum of XXII upon cooling the solution to -40°C. Investigation of molecular models reveals that the C-1 hydrogen would have a dihedral angle of 0° with the planar N-nitroso group. This hydrogen in the plane of the N-nitroso group destabilizes the conformation in which the oxygen is syn to the C-1 hydrogen; the model internuclear distance is only 2.5 Å. Thus, the preferred conformer of XXII, as shown below, has the oxygen syn to the methylene hydrogens.
The shift reagent plot for resonances of XXII is shown in Figure 10 (see also Table XIX). The line for the C-3 methylene doublet has a steeper slope than the line for the C-1 bridgehead hydrogen. Thus, the preferred conformer has the oxygen syn to the C-3 methylene hydrogens. Again, no change was observed in the conformational preference of the bicyclic N-nitrosamine as the shift reagent:substrate molar ratio was increased. The pseudo-allylic $A^{(1,3)}$ strain mechanism, cf. infra page 45, appears to be important in both IX and XXII, even though the C-1 substituent is methyl in IX but only hydrogen in XXII.

The nmr spectrum of N-nitroso-4-azahomoadamantane (XIV), (see Figure 34) is described below. In this compound, the N-nitroso group is incorporated into a seven-membered ring, but the substitution pattern of the carbon atoms is the same as seen before. Unlike the previous examples, however, two isomers are revealed by the nmr spectrum. The multiplet centered at $\delta 5.22$ is assigned to the syn and anti bridgehead hydrogens.
Figure 10. Shift reagent study of N-nitro-2-azabicyclo-[2.2.2]octane (XXII) with Eu(fod)₄. The slope is reported in ppm/mol Eu(fod)/mol XXII.
The doublet \((J = 3.9 \text{ Hz})\) at \(\delta 4.43\) is assigned to the methylene hydrogens \textit{anti} to the oxygen, and the doublet \((J = 3.9 \text{ Hz})\) at \(\delta 3.65\) is assigned to the methylene hydrogens \textit{syn} to the oxygen. The remaining hydrogens are assigned to the envelope between \(\delta 1.40-2.60\). The two doublets immediately indicate that both diastereomers of the \(N\)-nitrosamine exist in \(\text{XIV}\). Thus, by use of the integration ratios of the two doublets, the diastereomer ratio \(\text{XIVa:XIVb}\) was found to be \(87:13\).

![Diagram XIVa](image1.png)

![Diagram XIVb](image2.png)

The first indication of the importance of ring size on the \(N\)-nitrosamine diastereomer ratio is demonstrated in \(\text{XIV}\). The C-3 bridgehead hydrogen is sufficiently bulky to make the \textit{anti} isomer, \(\text{XIVa}\), the more favored configuration. The \textit{pseudo-allylic} \(A^{(1,3)}\) strain mechanism\(^{28a,b}\) still applies; however, the seven-membered ring system is more flexible than the six-membered ring in \(\text{XXII}\). In \(\text{XXII}\), twisting of the two-atom bridge, \(C^3-N\), could give a dihedral angle of only \(10-15^\circ\) between the C-1 bridgehead hydrogen and the \(N\)-nitroso group. On the other hand, twisting of the two atom bridge, \(C^5-N\), in \(\text{XIV}\) could yield a dihedral angle between \(35\) and \(40^\circ\). Thus, this ease of twisting in the model of \(\text{XIV}\) indicates added flexibility in the two atom bridge which may account for the presence of the \textit{syn} conformer \(\text{XIVb}\).
The shift reagent plots of the four resonances of XIV are shown in Figure 11 (see also, Table XX). The upfield doublet at $\delta 3.65$ gives a plot with a steeper slope than does the downfield doublet at $\delta 4.43$. Thus, the assignment of the doublet at $\delta 3.65$ to the syn conformer is correct. The slope of the shift reagent plot of the C-3 bridgehead hydrogen syn to oxygen is greater than the slope of the shift reagent plot of the C-3 bridgehead hydrogen anti to oxygen. Because the absorption of the C-3 bridgehead hydrogen syn to oxygen is buried under the multiplet centered at $\delta 5.22$ which is assigned to the C-3 bridgehead hydrogen anti to oxygen, the exact position of this hydrogen in the uncomplexed N-nitrosamine is not known. If one extrapolates the shift reagent plot of the C-3 bridgehead hydrogen syn to oxygen to zero concentration of the shift reagent the value obtained would be at higher field than the chemical shift observed for the C-3 bridgehead hydrogen anti to oxygen. The resonance of the C-3 bridgehead hydrogen syn to oxygen at higher field than the resonance of the C-3 bridgehead hydrogen anti to oxygen would mean that the C-3 bridgehead hydrogen syn to oxygen is slightly in the shielding zone of the nitroso group and not exactly coplanar with the NNO group. This type of geometric arrangement would help account for the existence of conformer XIVb. Because extrapolation of the shift reagent plot of the C-3 bridgehead hydrogen syn to oxygen gives a value of the chemical shift in the uncomplexed nitrosamine which is at higher field than the whole multiplet assigned to the two C-3 bridgehead protons, a more detailed analysis than presented in this work is needed to confirm the assignment of the C-3 bridgehead hydrogen syn to oxygen.

The next compound in the series, N-nitroso-7-azabicyclo-[4.2.2]decane (XX), has the N-nitroso group incorporated into an eight
Figure 11. Shift reagent study of N-nitroso-1-azahomoadamantane XIV with Eu(fod)₃.
membered ring. The nmr spectrum of this compound (see Figure 35) is particularly noteworthy, because it shows not only signals for the two configurations of the N-nitroso group, but also signals for the two possible conformations of the eight-membered ring. The four possible diastereomers are shown below.

The peak assignments were made with the aid of europium(III) shift reagent studies and double resonance experiments.

The nmr spectrum of XX (see Figure 35) is very complex. The absorptions are described in succession from those most downfield to those most upfield. The broad multiplet at lowest field, \( \delta \ 5.04 \), is assigned to the \textit{anti} C-6 bridgehead hydrogen of XXa and XXc. The broad multiplet at higher field, \( \delta \ 4.56 \), is attributed to the \textit{syn} C-6 bridgehead hydrogens of XXb or XXd. The resonance pattern next in line at higher field is a doublet of doublets which is partly obscured by the multiplet centered at \( \delta \ 4.56 \). However, by means of shift reagent studies (see Figure 12 and Table 21) the doublet of doublets pattern becomes visible. This resonance pattern is centered at \( \delta \ 4.46 \) \((J_{\text{gem}} = 13.8 \text{ Hz}, J_{\text{vic}} = 4.0 \text{ Hz})\) and is assigned to the \textit{anti} C-8 methylene hydrogens of either XXb or XXd. The next pattern is also a doublet of doublets centered at \( \delta \ 4.09 \) \((J_{\text{gem}} = 15.8 \text{ Hz}, J_{\text{vic}} = 4.0 \text{ Hz})\), and it is
Figure 12. Shift reagent study of N-nitroso-γ-azabicyclo[4.2.2]decane (XX) with Eu(fod)$_3$. 

- **Chemical Shift (ppm)**
  - 6.00
  - 5.80
  - 5.60
  - 5.20
  - 4.00
  - 3.80

- **Shift Reagent:Substrate Molar Ratio (x 10$^2$)**
  - **Slope**
    - syn CH$_2$(A) --- 10.2
    - anti CH$_2$(A) --- 6.0
    - syn CH ---- 10.7
    - anti CH ---- 8.5
    - syn CH$_2$(B) --- 8.6
    - anti CH$_2$(B) ---- 6.7
assigned to the anti C-8 methylene hydrogens of either 111b or 111d. The next pattern consists of two spikes with small splitting of each spike and is centered at $\delta$ 3.86 ($J_{gem} = 16.0$ Hz). This pattern is assigned to the syn C-8 methylene hydrogens of either 111a or 111c. Next, one comes to the doublet of doublets centered at $\delta$ 3.18 ($J_{gem} = 16.0$ Hz, $J_{vic} = 6.0$ Hz); this resonance pattern is assigned to the syn C-8 methylene hydrogens of either 111a or 111c. Finally, the remaining hydrogens are assigned to the envelope between $\delta$ 2.70-1.00.

The conformational ratio of the eight-membered ring and the configurational ratio of the N-nitrosamine may be determined by comparing integration ratios. There appears to be a 1:1 mixture of the ring conformers because the integration areas of the two absorptions at $\delta$ 3.86 and $\delta$ 3.18 (syn C-8 methylenes) are equal. However, comparison of the integration areas at $\delta$ 4.09 (anti C-8 methylene hydrogens) and at $\delta$ 3.18 (syn C-8 methylene hydrogens) reveals that the diastereomers 111a and 111c predominate over 111b and 111d by a margin of 58:42%. Once again the more stable isomer has the oxygen anti to the C-6 bridgehead hydrogen.

Even though the model internuclear distance between the oxygen and the C-6 bridgehead hydrogen is still 2.5 $\AA$, the model dihedral angle between the hydrogen and the N-nitroso group is now about 20°. That is, the four carbon bridge, $-C^2-C^3-C^4-C^5-$, causes the C-6 bridgehead hydrogen to occupy a position about 20° below the $C^6C^3NNO$ plane. This 20° angle places the C-6 bridgehead hydrogen in the shielding cone of the N-nitroso group with the result that this hydrogen resonates at higher field when syn to the oxygen instead of at the more downfield position found in acyclic N-nitrosamines.
The shift reagent study (see Figure 12 and Table XXI) shows that the broad multiplet at δ 4.56 shifts downfield faster than does the broad multiplet at δ 5.04. The δ 4.56 absorption must therefore belong to the syn C-6 bridgehead hydrogen, and the δ 5.04 absorption must belong to the anti C-6 bridgehead hydrogen. The large shift downfield of the multiplet at δ 4.56 reveals clearly the doublet of doublets centered at δ 4.46. The signals for syn methylenes, δ 3.86 and δ 3.18, shift downfield further than those for the anti methylene hydrogens, δ 4.46 and δ 4.09. Finally, all of the syn and anti methylene patterns are shown to be coupled to the same hydrogen by means of a double irradiation experiment. This hydrogen is presumably the C-1 bridgehead hydrogen.

N-Nitroso-ll-azabicyclo[4.4.1]undec-l-ene, XXIV, has two features which make it different from the other bicyclic N-nitrosamines in this series: (1) the amino nitrogen is attached to two bridgehead carbons and (2) one of those bridgehead carbons is unsaturated. The nmr spectrum (see Figure 36) consists of two triplets, one centered at δ 5.88 (J = 6.0 Hz) and the other centered at δ 5.73 (J = 6.0 Hz); a broad multiplet centered at δ 5.05; and a large envelope region at δ 1.00-2.90. The observation of two triplets for the vinyl hydrogen on C-2 suggests the presence of both configurations of the nitrosamine. Indeed, integration of the nmr signals indicates the multiplet (δ 5.05) to be two hydrogens. The two possible isomers are shown below:
The triplet at $\delta 5.88$ is assigned to H-2 of \textit{XXIVb}, and the triplet at $\delta 5.73$ is assigned to H-2 of \textit{XXIVa}. The resonance for H-6 of \textit{XXIVa} is expected to be at higher field than the resonance for H-6 of \textit{XXIVb} because the dihedral angle between H-6 and the nitroso group is $0^\circ$ in the untwisted model and can be altered by only about $10^\circ$ by twisting of the bicyclic ring structure. The resonance of H-6 in \textit{XXIVb} is at approximately $\delta 5.15$, while the resonance of H-6 in \textit{XXIVa} is at about $\delta 5.02$. The predominance of \textit{XXIVa} indicates that again the position and steric bulk of the bridgehead hydrogen causes the more stable isomer to be the one in which the nitroso oxygen is \textit{anti} to it.

The existence of both diastereomers of \textit{XXIV} is indicated by the two triplets for the vinyl hydrogen. The addition of shift reagent causes the multiplet enclosed in the downfield edge of the broad multiplet centered at $\delta 5.05$ to shift downfield a greater distance than the remainder of the multiplet (see Figure 13 and Table XXII). The steeper slope for the shift reagent plot and the initial chemical shift of this resonance identifies this hydrogen as the \textit{syn} C-6 bridgehead hydrogen.
Figure 13. Shift reagent study of N-nitroso-11-azabicyclo[4.4.1]undec-1-ene (XXIV) with Eu(fod)...
Integration of the shifted peaks gives a ratio of \( \text{XXIV}_a : \text{XXIV}_b = 60:40 \); the major isomer has the oxygen \textit{anti} to the C-6 bridgehead hydrogen.

\textbf{Pseudo-Allylic }\textit{A}^{(1,3)}\textit{ Strain}

Steric interference in allylic and \textit{pseudo}-allylic systems was first described by Johnson and Malhotra.\textsuperscript{28b} The steric interaction between substituents on the 1 and 3 positions of an allylic system was defined as \( A^{(1,3)} \) strain.\textsuperscript{28b} For example, consider the two conformers \textit{XXV} and \textit{XXVI} in Figure 14, which contain the \( \text{-C}_3=\text{C}_2=\text{C}_1 \) system. The dihedral angle between \( \text{-C}_3\text{R}' \) and the double bond (\( \text{C}_2 = \text{C}_1 \)) is zero, which means that \( \text{R}' \) and \( \text{R} \) must lie in the same plane. Thus, even when \( \text{R}' \) and \( \text{R} \) are only moderate in size, steric interference between them will be significant. This interference is greater in magnitude than 1,3-axial interaction between the same groups on the cyclohexane ring, and relief of this strain in the above example may be obtained by means of a ring.
flip from XXV to XXVI.\textsuperscript{28b} In this case, conformer XXVI is more stable than XXV.\textsuperscript{28b}

The value of the above model is that the A\textsuperscript{(1,3)} strain mechanism holds for allylic systems containing atoms other than carbon.\textsuperscript{28a} When the system contains atoms other than carbon (for example, cyclic ketones, imines, and enamines), the effect is termed \textit{pseudo}-allylic A\textsuperscript{(1,3)} strain.\textsuperscript{28a} There are several examples in the literature of A\textsuperscript{(1,3)} strain involving N-nitrosamines.\textsuperscript{28a} Nmr evidence indicates that the preferred isomer of the N,N′-dinitroso-2,3,5,6-tetramethylpiperazine shown in Figure 15 is XXVIII in which all methyl groups are axial.\textsuperscript{28a}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {XXVII};
\node (B) at (2,0) {XXVIII};
\draw[->] (A) -- (B);
\end{tikzpicture}
\end{center}

\textit{Figure 15.} Steric interference in a \textit{pseudo}-allylic system.

\textbf{Summary}

In summary, all of the bi- and tricyclic N-nitrosamines in this study exhibit \textit{pseudo}-allylic A\textsuperscript{(1,3)} strain. The rigidity of the carbon ring skeletons of these N-nitrosamines bars relief of strain by
means of ring inversion. However, relief of strain can be attained by means of rearrangement of the N-N partial double bond and twisting of the carbon bridge. These compounds show that the in-plane position of the substituent on atom 3 in the pseudo-allylic system is more important than the size of that substituent.
Part II of this Dissertation contains three chapters. The energy-minimized geometries of the nitrosamines studied are given in Chapter IV. The conformational analysis of diisopropyl- and of methylphenylnitrosamine is presented in Chapter V. The third chapter is primarily concerned with photoelectron spectroscopy, but it also includes a discussion of bond orders, charge densities, and barriers to rotation and inversion in the nitrosamines studied.
CHAPTER IV

STRUCTURES AND GEOMETRIES

General

The procedure used to obtain the calculated ionization potentials involved several steps. First, the experimental bond lengths and bond angles of dimethylnitrosamine, obtained by means of an electron diffraction study, were used in the CNDO/2 calculation of the binding energy. Then the bond lengths and bond angles were varied, the CNDO/2 calculation was repeated, and the geometry giving the minimum binding energy for dimethylnitrosamine was considered to be the geometry of the same group in the other nitrosamines in the series. The exceptions are described later. Finally, the CNDO/S program, which utilized the energy-minimized geometry found by means of the CNDO/2 method, was run.

The CNDO/2 and CNDO/S calculations were carried out for the series of N-nitrosamines shown in Table IV by means of an IBM 360/65 digital computer. The CNDO/2 program written by Pople and Dobosh was used. The CNDO/S method was originally developed by Del Bene and Jaffe; their later reparameterization was used in this work. The Fock matrix averaging technique suggested by King was employed to accelerate convergence.

Energy-Minimized Structures

Since the C$_2$N$_2$O atoms of dimethylnitrosamine have been shown by X-ray and electron diffraction to have a planar geometry, a
<table>
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<tr>
<td>V</td>
<td><img src="image" alt="Structure V" /></td>
<td>N-nitrosodiethylamine</td>
</tr>
<tr>
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<td>N-nitrosodisopropylamine</td>
</tr>
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<td>N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one</td>
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planar model of the $\text{C}_2\text{N}_2\text{O}$ framework of the molecule was used. Further, it was assumed that (a) the bond angles in the methyl group are tetrahedral, (b) all of the C-H bond lengths are the same, (c) the two C-N bond lengths are identical, and (d) the methyl hydrogens are oriented in the manner shown in IA'.

With these assumptions, the calculations gave the energy-minimized bond lengths and bond angles of dimethylnitrosamine that are presented in Table V. This Table includes the experimental bond lengths and bond angles based upon electron diffraction results. The agreement between calculations and experiment is quite good; the calculated bond lengths are slightly shorter than the experimental ones.

Bond lengths and bond angles within the ethyl and isopropyl groups of $\text{V}$ and $\text{VI}$ were taken to be those given by Pople and Beveridge. With the phenyl group of $\text{XXIX}$, the carbon-carbon bond lengths were taken to be $1.395 \, \text{Å}$, the carbon-hydrogen bond lengths to be $1.084 \, \text{Å}$, and all carbon-carbon-carbon and carbon-carbon-hydrogen bond angles to be $120^\circ$. The energy-minimized bond length of the phenyl-nitrogen bond was found to be $1.41 \, \text{Å}$ for both a completely planar molecule and for
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<td>1.235</td>
<td>1.20</td>
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<tr>
<td>N-N</td>
<td>1.344</td>
<td>1.31</td>
</tr>
<tr>
<td>C-N&lt;sub&gt;syn&lt;/sub&gt;</td>
<td>1.461</td>
<td>1.41</td>
</tr>
<tr>
<td>C-N&lt;sub&gt;anti&lt;/sub&gt;</td>
<td>1.461</td>
<td>1.41</td>
</tr>
<tr>
<td>C-H</td>
<td>1.129</td>
<td>1.12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (deg.) Electron Diffraction</th>
<th>Angle (deg.) (Calculated) This Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNO</td>
<td>113.6</td>
<td>115.0</td>
</tr>
<tr>
<td>CNN&lt;sub&gt;syn&lt;/sub&gt;</td>
<td>120.4</td>
<td>120.0</td>
</tr>
<tr>
<td>CNN&lt;sub&gt;anti&lt;/sub&gt;</td>
<td>116.4</td>
<td>120.0</td>
</tr>
<tr>
<td>CNC</td>
<td>123.2</td>
<td>119.0</td>
</tr>
<tr>
<td>NCH</td>
<td>109.6</td>
<td>109.5° (assumed)</td>
</tr>
</tbody>
</table>
several conformations that have various angles of twist between the planar phenyl and planar NNO groups.

Compounds XXII and IX were assumed to have standard C-C and C-H bond lengths of 1.54 Å and 1.07 Å, respectively. All C-C-C and C-C-H bond angles in the methyl groups and in the bicyclic ring structures were assumed to be tetrahedral. The geometry of the NNO group was kept the same as that in the energy-minimized structure of dimethylnitrosamine. However, the bond angles and bond lengths associated with the CNC position of the molecule were varied in order to find the minimum energy geometry. The resultant geometry has angles at the carbons α to the ring nitrogen which are slightly smaller than the normal tetrahedral angles of the ring structure, C-N bond lengths that are greater than the 1.41 Å energy-minimized value for dimethylnitrosamine, and a C-N-C bond angle near 120°. The compressed ring angles at the α-carbons and the C-N bond distances, lengthened with respect to those of dimethylnitrosamine, are the structural features that were adjusted to accommodate the nitrosamine group into the bicyclic ring system.
The energy-minimized geometry of compound XXII is shown in XXIIA. The geometry of the bicyclic ring of compound IX was the same as that of compound XXII except that the C\textsuperscript{4}C\textsuperscript{5}C\textsuperscript{6} angle (see Table IV, compound IX) was increased slightly from tetrahedral to a value approaching 120° and the C\textsuperscript{4}-C\textsuperscript{5} and C\textsuperscript{5}-C\textsuperscript{6} bond lengths were decreased from 1.54 Å to 1.52 Å. These changes were made to lessen the strain in the C\textsuperscript{α}-C\textsuperscript{α}O group. The C=O bond length was assumed to be 1.22 Å.\textsuperscript{33}
Conformational Analysis of Diisopropylnitrosamine

An analysis of the preferred conformation of the anti isopropyl group of diisopropylnitrosamine by means of a comparison of the nmr spectra of diisopropylnitrosamine with methylisopropyl nitrosamine was reported by Karabatsos and Taller. The important points of this analysis are considered before the results of the calculation of the binding energy of diisopropyl nitrosamine conformations are shown.

Karabatsos and Taller considered the conformations shown below in their analysis of the preferred conformation of groups anti to oxygen. They showed that when R is methyl, \( \text{XXXIII} \) is favored over \( \text{XXXIV} \), and that the ratio \( [\text{XXXIII}]:[\text{XXXIV}] \) decreases when R is changed from methyl to isopropyl.

![Chemical Structures](A) R N N + R   (B) R N N + R
\[
\begin{align*}
\text{XXXII} & \quad \text{XXXIII} & \quad \text{XXXIV}
\end{align*}
\]

They considered the conformations of methyl-tert-butyl nitrosamine, \( \text{XXXV} \), methylisopropyl nitrosamine, \( \text{XXXVI} \) and \( \text{XXXVII} \), \( \text{XXXVII} \) is twice as probable as \( \text{XXXVI} \) and methylethyl nitrosamine \( \text{XXXVIII} \) and
XXXIX, (XXXVIII is twice as probable as XXXIX) (see Figure 16). Chemical shifts of the anti-β-methyls could not be explained by assuming that energetically XXXVI=XXXVII and XXXVIII=XXXIX. However, they assumed that XXXVI is less energetic than XXXVII and that XXXVIII is less energetic than XXXIX. Thus, they predicted that there should be a methyl group at position A in methyl-tert-butynitrosamine 100% of the time, at position A in methylisopropynitrosamine 66% of the time, and at position A in methylethylnitrosamine 33% of the time. Because the anti-β-methyls spend progressively less time in the deshielding zone of the nitroso group, the chemical shift of the anti-β-methyls in methylisopropyl- and methylethylnitrosamines should be at higher field than the chemical shift of the corresponding protons in methyl-tert-butynitrosamine. This reasoning is supported by the nmr data.

Karabatsos and Taller considered the conformations of diisopropynitrosamine to be XXX and XXXI. Because of the more severe interactions of the methyl groups in XXX than in XXXI, they predicted the ratio [XXXI]:[XXX] to be larger than the ratio [XXXVII]:[XXXVI]. (1) If XXXI predominates over XXX, then the anti-α-methine should resonate at
Figure 16. The conformations of the groups anti to oxygen in some N-nitrosamines
higher field than that of methylisopropylnitrosamine. Indeed, the anti-α-methine in diisopropylnitrosamine resonates 0.59 ppm upfield from that in methylisopropylnitrosamine. (2) The anti-β-methyls in diisopropylnitrosamine would be expected to resonate downfield from those in methylisopropylnitrosamine; the shift is -0.1 ppm. (3) The magnitude of the solvent shift for the anti-α-methine in diisopropylnitrosamine should be larger than for that in methylisopropylnitrosamine, and the data corroborate this prediction. (4) Finally, the magnitude of the solvent shift of the anti-β-methyls should decrease to a greater extent than that of the syn-β-methyls on going from methylisopropyl to diisopropylnitrosamine. This difference is found to be the case.

The conformational analysis by Karabatsos and Taller is lacking in that only two conformations of the anti isopropyl group were considered, and estimates of the binding energies were not available. Thus, in this study, two more possible conformations were considered, the binding energies were calculated, and the adherence of the conformation to criteria 1-4 was tested. The conformations of diisopropylnitrosamine that were considered are shown in Figure 17 along with their binding energies. In each of the four conformations, interactions between methyl group hydrogens syn and anti to oxygen were minimized. The isopropyl group syn to oxygen was maintained in the same spatial arrangement in each of the four conformations because nmr evidence indicates that α-methine hydrogens resonate at lower fields when they are syn than when they are anti to the oxygen. This arrangement required the methine hydrogen to be in the plane or very nearly in the plane of the nitroso group. By comparison of the nmr chemical shift of the anti methine resonance in methylisopropylnitrosamine and diisopropylnitrosamine,
### Conformation

<table>
<thead>
<tr>
<th>Conformation</th>
<th>Binding Energy (Hartrees)</th>
<th>Binding Energy (Kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXX</td>
<td>-9.0448</td>
<td>-5675.3</td>
</tr>
<tr>
<td>XXXI</td>
<td>-9.0547</td>
<td>-5681.5</td>
</tr>
<tr>
<td>XXXXX</td>
<td>-9.2221</td>
<td>-5786.5</td>
</tr>
<tr>
<td>XXXXI</td>
<td>-9.1532</td>
<td>-5743.3</td>
</tr>
</tbody>
</table>

*Figure 17. Binding energies of various conformers of diidopropynitrosamine*
Karabatsos and Taller\(^3\) showed that the anti methine in the latter compound must spend more time in the shielding zone of the nitroso group than does that in the former compound. Thus, conformation XXX is ruled out, and these workers assigned the preferred conformation of diisopropyl nitrosamine to conformation XXXI of Figure 17. However, conformation XXXXI is calculated to be only 6.2 kcal/mol more stable than the most strained conformational possibility, XXX. Conformation XXXXI is calculated to be about 62 kcal/mol more stable than XXXI. The most stable conformation is XXXXX, and its stability may be attributed to the minimization of hydrogen-hydrogen interactions between the isopropyl group syn to oxygen and the one anti to oxygen. However, XXXXX would be expected to violate criterion 2 above. Conformation XXXXI does conform to the four criteria considered above, and the calculations demonstrate it is energetically more stable than XXXXI. Figure 18 shows that the two conformations (XXX and XXXXI) considered by Karabatsos and Taller\(^3\) are predicted by means of the CNDO/2 calculation to be the least stable ones. Thus, the present work elucidates the effects of the hydrogen-hydrogen interactions between the two isopropyl groups on the conformational preference of diisopropyl nitrosamine.

**Structural Variation in Methylphenyl Nitrosamine**

Both methylphenyl nitrosamine (XXIX) and diisopropyl nitrosamine (XXX) provide an opportunity to use the binding energy calculated by means of the CNDO/2 method along with other data to predict the preferred conformation of the groups attached to the carbon atoms \(\alpha\) to nitrogen. The binding energies of a number of different conformations of XXIX were calculated.
Figure 18. Binding energies of diisopropylnitrosamine conformations. XXX, XXXI, XXXX, and XXXXI are illustrated in Figure 17. Curve is approximate because only the maxima and minima were calculated.
Nmr spectroscopy indicates that the only configurational isomer present in XXIX has the methyl group syn to oxygen. Two conformational arrangements of the methyl hydrogens which should be important in determining the preferred geometry are XXIXa and XXIXb. Tables VI and VII present the binding energy as a function of the C-N bond distance and the dihedral angle between the phenyl plane and the nitrosamine plane. For both XXIXa and XXIXb the energy-minimized C-N bond distance for each dihedral angle is 1.41 Å. Also, conformation XXIXb, which has the two methyl hydrogens gauche to an ortho phenyl hydrogen, has in each case a lower binding energy than conformation XXIXa, which has two methyl hydrogens gauche to oxygen.

In order to obtain more reliable data on the effect of phenyl dihedral angle and methyl hydrogen configuration, the binding energies of a number of varied conformations were computed. The binding energies, calculated as a function of phenyl dihedral angle and methyl hydrogen dihedral angle (the angle between H* and the nitrosamine plane), for conformation XXIXc are shown in Table VIII. The conformation having the lowest binding energy has a phenyl dihedral angle of 0° and an orientation of the methyl hydrogens gauche to the phenyl ortho-hydrogen, H0.

Because the binding energy was affected by the methyl hydrogen conformation and because only a small number of all the possible methyl hydrogen conformations were calculated, the methyl conformations were averaged to give a representative binding energy for each angle of phenyl twist. The averaging formula employed was

\[
\text{Binding Energy} = \frac{\sum_{i=1}^{n} B_i e^{-\frac{(B_i - E_0)}{RT}}}{\sum_{i=1}^{n} e^{-\frac{(B_i - E_0)}{RT}}};
\]


**TABLE VI**

**THE DEPENDENCE OF BINDING ENERGY ON C(\(\phi\)) N BOND LENGTH AND PHENYL CC(\(\phi\))NNO DIHEDRAL ANGLE**

<table>
<thead>
<tr>
<th>Phenyl/NNO Dihedral Angle (degrees)</th>
<th>C((\phi))N Bondlength ((\text{\AA}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.37</td>
</tr>
</tbody>
</table>

a. The preferred C(\(\phi\))N bond distance is 1.41 \(\text{\AA}\) for each angle of twist.

b. The angle of phenyl twist having the lowest binding energy is at 30° (-9.14348 Hartrees); C(\(\phi\))N = 1.41 \(\text{\AA}\).

c. The binding energies are all negative; units are Hartrees.
TABLE VII
THE DEPENDENCE OF BINDING ENERGY ON C(\phi)N BOND LENGTH
AND PHENYL CC(\phi)NNO DIHEDRAL ANGLE

![Chemical Structure]

<table>
<thead>
<tr>
<th>Phenyl/NNO Dihedral Angle (degrees)</th>
<th>C(\phi)N Bondlength (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.37</td>
</tr>
</tbody>
</table>

a. The preferred C(\phi)N bond distance is 1.41 Å for each angle of phenyl twist.
b. The angle of phenyl twist having the most negative binding energy is at 0° (-9.14616 Hartrees); C(\phi)N = 1.41 Å.
c. The binding energies are all negative; units are Hartrees.
TABLE VIII

THE BINDING ENERGIES OF METHYLPHENYLNITROSAMINE FOR A
NUMBER OF CONFORMATIONS OF THE METHYL AND PHENYL GROUPS

![Methylphenylnitrosamine structure]

<table>
<thead>
<tr>
<th>Phenyl/NNO Dihedral Angle (degrees)</th>
<th>Methyl Hydrogen Dihedral Angle (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

a. The C(\(\sigma\))N bond length is in all cases 1.41 Å.

b. The binding energies are all negative; units are Hartrees.
where $B_i$ is the binding energy for one particular methyl conformation, $E_0$ is the binding energy of the most stable methyl group conformation for a given phenyl angle of twist, $T$ is room temperature, and the sum extends over all methyl conformations which were calculated for each angle of phenyl twist. Note that the formula weights each contributing methyl conformation by a Boltzmann factor which gives its relative importance in the overall distribution of conformations. Table IX presents the binding energy as a function of the angle between the phenyl group and the nitrosamine group after the averaging has been done. Note that the most stable conformation has a value of the phenyl/nitrosamine angle of planes of about ten degrees.

The binding energy of the unstable conformer of methylphenyl-nitrosamine ($XXIXd$) shown below was calculated. The energy-minimized

![Diagram](image)

$C\_6-N$ bond distance for $XXIXd$ was 1.41 Å. The phenyl/nitrosamine dihedral angle was varied and the calculated binding energies are shown in Table X. The difference in binding energy between $XXIXd$ and the more stable $XXIXb$ is approximately 7.8 kcal/mol. The steric interaction of the phenyl ortho-hydrogen, $H'_o$, with the nitroso oxygen in $XXIXd$ causes the conformer with phenyl anti to oxygen to be the only one observed.
<table>
<thead>
<tr>
<th>Phenyl Angle (degrees)</th>
<th>Binding Energy (Hartrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-9.14567</td>
</tr>
<tr>
<td>10</td>
<td>-9.14568</td>
</tr>
<tr>
<td>20</td>
<td>-9.14532</td>
</tr>
<tr>
<td>30</td>
<td>-9.14458</td>
</tr>
<tr>
<td>40</td>
<td>-9.14345</td>
</tr>
<tr>
<td>50</td>
<td>-9.14207</td>
</tr>
<tr>
<td>60</td>
<td>-9.14069</td>
</tr>
<tr>
<td>70</td>
<td>-9.13956</td>
</tr>
<tr>
<td>80</td>
<td>-9.13884</td>
</tr>
<tr>
<td>90</td>
<td>-9.13859</td>
</tr>
</tbody>
</table>
TABLE X
THE DEPENDENCE OF BINDING ENERGY ON C(\phi)N BOND LENGTH
AND PHENYL/NITROSAMINE DIHEDRAL ANGLE

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Phenyl Dihedral Angle (degrees)</th>
<th>C(\phi)N Bond Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.37</td>
</tr>
<tr>
<td>30</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

a. Because the C(\phi)N bond length of 1.41 Å is the preferred bond length for each angle of phenyl twist from 0° to 20°, only that bond length was used for the phenyl dihedral angles of 30° to 70°.

b. The binding energies are all negative; units are Hartrees.
CHAPTER VI

PHOTOELECTRON SPECTROSCOPY

Qualitative Interpretation of Photoelectron Spectra

One method of interpreting photoelectron spectra is to compare the spectrum of the sample molecule with the assigned spectrum of a similar molecule. A more rigorous treatment is to subject the molecule under consideration to a full molecular orbital calculation and to assign the bands in the spectrum by means of the calculated orbital energies. Both of these techniques were used to assign the molecular orbital energies of the N-nitrosamines studied in this work.

The molecular orbital calculations were performed using the CNDO/2 and CNDO/S computer programs. Larry P. Davis, a fellow graduate student who collaborated on this portion of the study, provided the knowledge to obtain and interpret the results of the computer calculations. An excellent discussion of the calculational methods is contained in his Ph.D. Dissertation. Two topics, the qualitative interpretation of photoelectron spectra and the use of the CNDO calculations to assign orbital energies, are presented in the following paragraphs.

The qualitative approach to the interpretation of photoelectron spectra involves the assignment of spectral features to certain molecular characteristics. A few of these characteristics are the electronegativity of a substituent, the inductive effect of a substituent, the presence of lone pairs of electrons, and the perfluoro
Because the spectra of a great many compounds have been correlated with these factors, generalizations about shifts in peak positions in a series of compounds and about lone-pair and $\pi$-orbital bands are particable. This method of band identification depends on the following two assumptions:35

1. Changes in the energies of molecular orbitals can be correlated specifically with changes in the substitution pattern of the molecule.
2. Molecular orbitals can often be treated as being localized on an atom (e.g., a lone pair orbital) or between a relatively small number of atoms, e.g., a $\pi$-orbital.

The electronegativity of a substituent may be used in the interpretation of the photoelectron spectrum of a molecule in two ways. First, as the electronegativity of the substituent increases, the ionization potential of the orbitals of the other atoms in the molecule increases. Second, substituent atoms may be identified by means of electronegativity-orbital ionization potential correlations. For example, the ionization potentials of halogen lone-pair orbitals vary linearly with electronegativity; the higher the electronegativity, the higher the ionization potential.35

The inductive effect, well-known in organic chemistry, also influences photoelectron spectroscopy. For example, in the series

$$\text{CH}_2=\text{CH}_2, \text{CH}_3-\text{CH}=\text{CH}_2, \text{C}_2\text{H}_5-\text{CH}=\text{CH}_2, \text{C}_3\text{H}_7-\text{CH}=\text{CH}_2,$$

the greater inductive effect of the longer chain alkyl substituents causes the ionization potential of the $\pi$ orbital to decrease; the values are, respectively, 10.51, 9.74, 9.61, and 9.51 eV.35 Correlation of orbital ionization potentials with the Hammett constant, $\sigma^*$, also reveals that a more highly branched substituent lowers the ionization potential of a particular orbital.35
Not only is the position of a band in the photoelectron spectrum important but its shape is also important. Ionization from lone-pair orbitals produces sharp bands in the photoelectron spectrum, while ionization from \( \pi \)-orbitals usually gives rise to broader peaks having more vibrational fine structure. The most energetic occupied lone-pair orbitals having very little bonding character are especially sharp, and these bands may show spin-orbit splitting. However, lone-pair orbitals which contribute to the bonding molecular orbitals are broad and contain little fine structure.

In the case of aliphatic compounds, it is possible to distinguish \( \sigma \)- from \( \pi \)-orbitals by means of the perfluoro effect. The ionization potentials of the molecules' \( \sigma \)-orbitals are increased when fluorine is substituted for hydrogen, but the ionization potential of the \( \pi \)-orbitals is not affected.

The above discussion is limited to generalizations concerning band positions and shapes in photoelectron spectroscopy. It has been found that, in the main, ionization potentials increase in the order: lone-pairs of I, S, P < aromatic \( \pi \) (usually two to three associated peaks) \( \sim \pi \) aliphatic < lone pairs of Br, Cl, O, N < \( \sigma \)-C-O, C-Cl, C-C < lone-pair F < \( \sigma \)-

Even though the methods described above are helpful in assigning pes bands, a more accurate technique involves the use of molecular orbital calculations. Koopman's approximation equates the negative of the molecular orbital energy with the molecular ionization potentials. This approximation does not take into account geometrical reorganization upon ionization, nor does it allow alteration of the wave functions describing the remaining electrons. Thus, the calculated ionization
potentials in the CNDO/2 case are about four electron volts higher than experimental ones. 37.

Finally, it is common practice to compare the pes bands of a sample molecule with the previously assigned spectrum of an isoelectronic or similar molecule. The assignment methods discussed in this section all suffer some inaccuracies. Application of the appropriate techniques, however, should lead to correct assignments.

Results and Discussion

Ionization Potentials

Table XI presents the four most energetic occupied molecular orbitals and the orbital energies produced by both CNDO/2 and CNDO/S calculations for compounds I, V, VI, XXIX, XXII, and IX. In each case, the occupied molecular orbital with the highest energy is predicted to be a \( \Pi \) orbital that is denoted \( \Pi_1 \) and is essentially localized on the nitroso group. The orbital is quite similar to the most energetic occupied \( \Pi \) orbital of allyl anion and has large electron density on the oxygen and the amino-nitrogen. There is practically a node on the nitrogen bound to oxygen. In each case, except that of XXIX, the next most energetic occupied orbital is predicted to be an in-plane orbital which has major electron density on the oxygen atom and some delocalization onto both nitrogens. This orbital has been designated to be an n orbital because most of its electron density is on the oxygen atom. Both of these occupied orbitals become more energetic and consequently less stable as the alkyl groups attached to N become more complex.

The energetic order of the remaining occupied orbitals varies from molecule to molecule, and CNDO/2 and CNDO/S methods give different
### TABLE XI

**IONIZATION POTENTIALS**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type</th>
<th>Orbital</th>
<th>CNDO/2 Calc'd (-3.0eV)</th>
<th>CNDO/S Calc'd (-2.0eV)</th>
<th>Observed (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (CH₃)₂NNO</td>
<td>Π₁</td>
<td>8.99</td>
<td>9.21</td>
<td>9.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>10.23</td>
<td>10.35</td>
<td>9.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Π₂</td>
<td>15.39</td>
<td>15.54</td>
<td>11.54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>σ</td>
<td>13.48</td>
<td>12.84</td>
<td>12.90</td>
<td></td>
</tr>
<tr>
<td>V (CH₂CH₂)₂NNO</td>
<td>Π₁</td>
<td>8.69</td>
<td>8.93</td>
<td>8.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>9.92</td>
<td>10.21</td>
<td>9.39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Π₂</td>
<td>13.81</td>
<td>12.53</td>
<td>11.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>σ</td>
<td>12.34</td>
<td>11.15</td>
<td>12.30</td>
<td></td>
</tr>
<tr>
<td>VI (i-Pr)₂NNO</td>
<td>Π₁</td>
<td>8.29</td>
<td>8.60</td>
<td>8.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>9.65</td>
<td>9.85</td>
<td>9.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Π₂</td>
<td>13.74</td>
<td>12.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>σ</td>
<td>11.65</td>
<td>11.11</td>
<td>11.60</td>
<td></td>
</tr>
<tr>
<td>XXIX φCH₃NNO</td>
<td>Π</td>
<td>8.24</td>
<td>7.59</td>
<td>9.01</td>
<td></td>
</tr>
<tr>
<td>(planar</td>
<td>Π₀</td>
<td></td>
<td></td>
<td>8.19</td>
<td></td>
</tr>
<tr>
<td>conformation)</td>
<td>n</td>
<td>10.03</td>
<td>10.05</td>
<td>9.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Π₀₂</td>
<td>11.28</td>
<td>10.22</td>
<td>10.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>σ</td>
<td>11.30</td>
<td>10.60</td>
<td>11.50</td>
<td></td>
</tr>
<tr>
<td>XXII</td>
<td>Π₁</td>
<td>8.40</td>
<td>8.70</td>
<td>8.72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>9.62</td>
<td>10.01</td>
<td>9.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Π₂</td>
<td>11.32</td>
<td>10.42</td>
<td>10.97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>σ</td>
<td>10.72</td>
<td>10.32</td>
<td>11.37</td>
<td></td>
</tr>
<tr>
<td>IX</td>
<td>Π₁</td>
<td>8.20</td>
<td>8.57</td>
<td>8.63</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>9.07(NNO)</td>
<td>8.98(c=0)</td>
<td>9.29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>9.55(c=0)</td>
<td>9.40(NNO)</td>
<td>9.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>σ</td>
<td>10.94</td>
<td>10.57</td>
<td>10.80</td>
<td></td>
</tr>
</tbody>
</table>
relative and absolute values. In the cases if the nitrosamines I, V, VI, and XXII, the calculations indicate that there are one or two σ orbitals at lower energy than that of the n orbital. Only the more energetic σ is given in Table XI. A nitroso π orbital, π₂, occurs at lower energy than does the first σ orbital in the cases of I, V, VI, and XXII. The π₂ orbital has major electron density on the nitrogen and the oxygen of the nitroso group, but does not have a node on the nitrosoamino group. In the case of IX, which contains a carbonyl group, the CNDO/2 and CNDO/S methods yield opposite orders for the energies of the two n orbitals below the most energetic occupied orbital; the CNDO/2 calculation places the NNO n orbital at higher energy, but the CNDO/S calculation places the CO n orbital at higher energy.

The ordering of the occupied orbitals of methylphenylnitrosamine (XXIX) depends upon both the conformation chosen and the calculational method used. The results of the CNDO/2 and CNDO/S calculations on two representative conformations are shown in Table XII.

The CNDO/2 method predicts the two most energetic molecular orbitals to be the nitroso π orbital, π₁, and the nitroso n orbital. The energetic order of these two orbitals does not change upon twisting the phenyl group or rotating the methyl hydrogens. However, the phenyl localized π orbital, π₄, becomes less energetic in the twisted models than in the planar model.

The CNDO/S method predicts the most energetic occupied orbital of the planar form to be the nitroso π orbital, π₁. However, in contrast to the CNDO/2 method, the next most energetic occupied orbital is predicted to be π₄. The two remaining orbitals to lie above the most energetic occupied orbitals are the nitroso n orbital and a π
### Table XII
Orbital Energies and Assignments

#### CNDO/2

<table>
<thead>
<tr>
<th>Energy (eV)</th>
<th>Orbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>-11.24</td>
<td>$\pi_1$</td>
</tr>
<tr>
<td>-13.03</td>
<td>$\pi_{NNO}$</td>
</tr>
<tr>
<td>-14.28</td>
<td>$\pi_\phi$</td>
</tr>
<tr>
<td>-14.30</td>
<td>$\sigma$</td>
</tr>
<tr>
<td>-14.62</td>
<td>$\sigma$</td>
</tr>
<tr>
<td>-15.29</td>
<td>$\pi_{mixed}$</td>
</tr>
</tbody>
</table>

#### CNDO/S

<table>
<thead>
<tr>
<th>Energy (eV)</th>
<th>Orbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>-9.59</td>
<td>$\pi_1$</td>
</tr>
<tr>
<td>-10.19</td>
<td>$\pi_\phi$</td>
</tr>
<tr>
<td>-12.05</td>
<td>$\pi_{NNO}$</td>
</tr>
<tr>
<td>-12.22</td>
<td>$\pi_{mixed}$</td>
</tr>
<tr>
<td>-12.60</td>
<td>$\sigma$</td>
</tr>
<tr>
<td>-13.12</td>
<td>$\sigma$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Energy (eV)</th>
<th>Orbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>-9.58</td>
<td>$\pi_1$</td>
</tr>
<tr>
<td>-10.20</td>
<td>$\pi_\phi$</td>
</tr>
<tr>
<td>-12.02</td>
<td>$\pi_{mixed}$</td>
</tr>
<tr>
<td>-12.29</td>
<td>$\pi_{NNO}$</td>
</tr>
<tr>
<td>-12.67</td>
<td>$\sigma$</td>
</tr>
<tr>
<td>-13.16</td>
<td>$\sigma$</td>
</tr>
</tbody>
</table>
orbital which is delocalized over the entire molecule, \( \pi_{\text{mixed}} \). When the phenyl group is twisted out of the plane the two most energetic occupied orbitals retain the same ordering. The \( \pi_{\text{mixed}} \) orbital, however, becomes more energetic than the nitroso \( n \) orbital. The CNDO/2 calculation indicates that this \( \pi_{\text{mixed}} \) orbital is at lower energy than either of the two \( \sigma \) orbitals.

**Charge Densities, Bond Orders, Dipole Moments**

These CNDO/2 and CNDO/S calculations also produced charge densities, bond orders, and, in the case of the CNDO/2 calculations, dipole moments. Bond orders have been defined to be the square of the density matrix element for the out-of-plane \( p \) orbitals on the two atoms between which the bond is made.\(^{38,39}\) Since the phenyl and carbonyl groups in compounds XXIX and IX did not appreciably change the bond orders and charge densities for the nitrosamino group of the compounds in Table IV, only the results from the calculations of these quantities for the nitrosamino group of compound I will be given. Table XIII presents the \( \pi \) bond orders, \( \pi \) charge densities (relative to the formal structure \( \text{N-N}^\equiv \text{O} \)), and overall charge densities of dimethylnitrosamine. Note the similarity between the CNDO/2 and CNDO/S results. The N-O \( \pi \) bond order is slightly less than one, the N-N \( \pi \) bond order is about 0.2, and the \( \pi \) charge densities give two electron-deficient nitrogens and an electron-rich oxygen. However, the overall charge densities predict an alternating distribution of charge in which the oxygen is electronegative, the nitroso nitrogen electropositive, the amino nitrogen electronegative, and the methyl carbons electropositive. This predicted alternating charge distribution for polar molecules has been pointed out by Pople and Beveridge.\(^{41}\)
Table XIII
Bond Orders and Charge Densities for Dimethylnitrosamine

![Molecular structure diagram](image)

<table>
<thead>
<tr>
<th>Bond</th>
<th>$\pi$ Bond Order</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CNDO/2</td>
</tr>
<tr>
<td>N-O</td>
<td>0.773</td>
</tr>
<tr>
<td>N-N</td>
<td>0.198</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atom</th>
<th>$\pi$ Charge Densities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CNDO/2</td>
</tr>
<tr>
<td>$N_1$</td>
<td>+0.126</td>
</tr>
<tr>
<td>$N_2$</td>
<td>+0.253</td>
</tr>
<tr>
<td>$O_4$</td>
<td>-0.312</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall Charge Densities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atom</td>
</tr>
<tr>
<td>$N_1$</td>
</tr>
<tr>
<td>$N_2$</td>
</tr>
<tr>
<td>$C_3$</td>
</tr>
<tr>
<td>$O_4$</td>
</tr>
<tr>
<td>$C_5$</td>
</tr>
<tr>
<td>$H_6$</td>
</tr>
<tr>
<td>$H_7$</td>
</tr>
<tr>
<td>$H_8$</td>
</tr>
<tr>
<td>$H_9$</td>
</tr>
<tr>
<td>$H_{10}$</td>
</tr>
<tr>
<td>$H_{11}$</td>
</tr>
</tbody>
</table>
The experimental dipole moments of compounds I and XXIX are 3.98 D and 3.62 D, respectively. The dipole moments calculated for these compounds by means of the CNDO/2 method are 2.99 D and 2.72 D for XXIX and are smaller than the observed values. However, the calculated values fall in the same order as the observed ones, and little significance should be attributed to the quantitative results because neither CNDO method is parameterized to give good dipole moments. Nevertheless, the calculations may be underestimating the charge separation and contributions of canonical forms such as IA.

The bond orders for the planar CN=O portion of compound XXIX are shown in Table XIV. Note that the N-C=N bond order is very small, and thus only a small amount of formal conjugation between the phenyl group and the nitrosamino group is predicted. In the case of compound IX, the overall charge density (CNDO/2) of the carbonyl oxygen and carbon are -0.271 and +0.253, respectively. One interesting result in the case of compound IX is that C-3, the methylene carbon α to the carbonyl, is predicted to carry a slight negative charge and its attached hydrogens are predicted to be significantly electropositive.

This charge results from the reinforcement of the negative charge on C-3 by the alternating charge distributions from both the

<table>
<thead>
<tr>
<th>Bond</th>
<th>CNDO/2</th>
<th>CNDO/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-N</td>
<td>0.1871</td>
<td>0.2014</td>
</tr>
<tr>
<td>N-O</td>
<td>0.7804</td>
<td>0.7616</td>
</tr>
<tr>
<td>N-C=N</td>
<td>0.0788</td>
<td>0.0574</td>
</tr>
</tbody>
</table>
carbonyl oxygen and the nitroso oxygen. Because of the predicted electropositive character and the expected enolizable nature of these hydrogens, easy exchange with dilute NaOD/D$_2$O was anticipated. Indeed, both of these hydrogens undergo replacement by deuterium under mild conditions.

**Barriers to Rotation and Inversion**

The CNDO/2 method was used to calculate the barrier to rotation around the N-N bond and the barrier to inversion of the nitroso-group of dimethylnitrosamine. Two transition states were employed: (a) One was a 90° rotated form in which the N-N-O plane is perpendicular to the C-N-N plane; this transition state is the one for rotation about the N-N bond. (b) The other was a N-N-O linear transition state; this transition state is the one for inversion at the nitroso nitrogen. In each case the approximate barrier was calculated to be the difference between the binding energy of the transition state and the binding energy of the planar form. In the case of the rotational transition, N-O and N-N distances and the NNO angle were energy-minimized. For this conformation, both NNC angles were assumed to be 120°, and all C-H bond lengths were taken to be 1.10 Å. The energy-minimized parameters calculated were: N-O distance, 1.18 Å; N-N distance, 1.34 Å; and NNO angle, 115°. Note (see Table V) that the N-O distance is predicted to be shorter and the N-N distance to be longer than their corresponding values in the planar form. These facts are consistent with the idea that rotation destroys the N-N partial π bond. In the case of the linear transition state, the same assumptions concerning the NNC angle and the C-H distances were made. The N-N and N-O distances were energy-minimized, and the resultant
values were 1.29 Å and 1.16 Å, respectively. Note (see Table V) that both of these distances are shorter than the corresponding distances in the planar form. The calculated energy barriers to rotation and inversion are 18.2 kcal/mole and 73.3 kcal/mole, respectively.

**Photoelectron Spectroscopy**

The photoelectron spectra of I, V, VI, XXIX, XXII, and IX are shown in Figures 19 and 20. The shapes of the bands in the spectra of the series are similar; the first band is a broad, low intensity band, but the second band is much sharper and more intense. Table XI lists the observed and predicted ionization potentials and includes the molecular orbital assignment of each ionization potential.

The assignment of molecular orbitals to certain ionization potentials is based on the CNDO/2 and CNDO/3 predictions and also on the assignment of molecular orbitals in dimethylformamide XXXXII. This compound is not only isoelectronic with dimethylnitrosamine, but it also exhibits hindered rotation around the C-N partial double bond. Thus, its electron distribution should be similar to that of dimethyl-nitrosamine (I → IA).

![Diagram of XXXXII and XXXXII A](image-url)
Figure 19. Photoelectron spectra of four N-nitrosamines
Figure 20. Photoelectron spectra of two N-nitrosamines
In dimethylformamide the occupied orbital that has the highest energy is a \( \Pi \) orbital and has an ionization potential of 9.25 eV. The next most energetic occupied orbital is an \( n \) orbital that has an ionization potential of 9.77 eV. The corresponding bands in the photoelectron spectrum of dimethylnitrosamine (I) occur at 9.09 eV and 9.69 eV, respectively. Further, the separations between the two bands are in good agreement; the value is 0.52 eV in the case of dimethylformamide, and 0.60 eV in that of dimethylnitrosamine.

The results of the CNDO/2 and CNDO/S calculations compare very well with the observed ionization potentials when their values are reduced by 3.0 eV and 2.0 eV, respectively.\(^{37}\) The calculations display the same trend in orbital stability as that observed experimentally. That is, as the \( \alpha \) substituents become more complex, Me < Et < \( i \)-Pr, the \( \Pi \) and \( n \) orbitals become more energetic.

In the case of methylphenylnitrosamine (XXIX) the CNDO/S calculations predicted two \( \Pi \) orbitals very close in energy to be the two most energetic occupied orbitals. Analysis of the pes spectrum shows that the first broad band which has been assigned to the \( \Pi_1 \) orbital is, at half-height, twice as broad as the \( \Pi_1 \) band for any of the other \( N \)-nitrosamines. The \( n \) band has approximately the same width at half-height as those of the other nitrosamines. This breadth indicates that the two bands predicted by the calculations to originate from two \( \Pi \) orbitals may appear as one broad band in the observed spectrum.

The two limiting resonance forms for dimethylnitrosamine (I and \( IA \)) were shown on page 2. Resonance form \( IA \) accounts nicely for the \( N-N \) partial double bond character, and it indicates a positive charge on the amino nitrogen and a negative charge on the oxygen. The \( \Pi \)
charge densities calculated by both CNDO/2 and CNDO/S methods that are shown in Table XIII agree with this picture. However, the overall charge densities calculated by both methods predict that the amino nitrogen is slightly negative, the nitroso nitrogen slightly positive, and the oxygen very negative. These results point out that (a) resonance form IA is limited to representation of the charge distribution in the $\pi$ system and (b) that the $\sigma$ system readjusts the electron distribution of the nitroso group largely by removing electron density from the $\alpha$ carbons.

**Summary**

The pes spectra and both calculation methods indicate that the $\pi$ molecular orbital is higher in energy than the $n$ molecular orbital in all the $N$-nitrosamines studied. As the substituents on the $\alpha$ carbons of the simple dialkynitrosamines I, V, and VI become more complex, both $\pi$ and $n$ orbitals become more energetic. Both CNDO/2 and CNDO/S calculations show this same trend.

The charge densities obtained from the CNDO/2 and CNDO/S calculations require a clarification of the interpretation of the standard resonance form that is usually drawn for $N$-nitrosamines. Note that the $\pi$ charge densities in Table XIII indicate an electronegative oxygen and two electropositive nitrogens; the amino-nitrogen is the more electropositive. However, the overall charge densities obtained by means of the calculations show an electronegative oxygen, an electropositive nitroso-nitrogen, and a slightly electronegative amino-nitrogen. These charge densities present a perplexing problem in the interpretation of the significance of the resonance form. A full double bond between
the two nitrogens would require a positive charge on the amino nitrogen. A partial double bond between the two nitrogens would involve the redistribution of the lone pair of electrons on the amino-nitrogen toward the nitroso-nitrogen, and a deficiency of electron density on the amino-nitrogen would then occur. Thus, the standard resonance form would appear to be satisfactory. However, the molecule's σ electrons may redistribute themselves and indeed the electropositive character of the α carbon atoms indicate that this redistribution has taken place. Therefore, the standard resonance form should be classified as the limiting case for the Π electron system.

The calculated energy barrier, 18.2 kcal/mol, for rotation around the N-N partial double bond agrees well with the experimentally determined barrier, $E_a = 23$ kcal/mol. Because the calculated barrier for inversion of the nitroso-nitrogen, 73.3 kcal/mol, is about four times larger than the calculated barrier for rotation, the inversion process for making the two methyl groups of dimethylnitrosamine equivalent may be ruled out.

This work demonstrates the successful application of CNDO/S and CNDO/2 calculational methods for predicting physical and structural properties of N-nitrosamines.
PART III

EXPERIMENTAL DETAILS AND DATA

FOREWORD

Part III of this Dissertation includes the experimental details of the preparation of the bi- and tricyclic N-nitrosamines, the tables of data for the europium(III) shift reagent studies of the series of N-nitrosamines, mass spectral data of some of the compounds synthesized in this work, a table of structures and key numbers of the compounds investigated, and the nmr spectra of the compounds prepared, including some of the europium(III) shifted spectra.
EXPERIMENTAL

General

All anhydrous solvents were dried over lithium aluminum hydride or Vitride,\textsuperscript{42} distilled, and stored over molecular sieves in a nitrogen atmosphere. Boiling points and melting points are uncorrected. Infrared spectra were obtained by means of a Perkin-Elmer Infracord Model 137 spectrophotometer. The samples were prepared as neat films or as solid solutions in anhydrous potassium bromide pellets. Nmr spectra were obtained by means of a Varian A-60A or a Varian HA-100 spectrometer; David LaTour assisted in obtaining the 100 MHz spectra. All nmr chemical shifts are expressed in parts per million downfield from internal tetramethyldisilane. Ultraviolet spectra were obtained by using a Cary Model 14 spectrophotometer. All mass spectral data were obtained by means of a Hitachi Perkin-Elmer Model RMS-4 spectrometer with the assistance of Paula Boyd. Microanalytical data were obtained in these laboratories by Ralph Seab and from Galbraith Laboratories, Inc.

Preparation of N-Nitrosodiisopropylamine

To 9 ml of an ice-cold 3 M-hydrochloric acid solution were added 5.20 g (7.2 ml, 0.052 mol) of diisopropylamine. The amine hydrochloride solution was added dropwise to 4.14 g (0.06 mol) of sodium nitrite in 10 ml of water at room temperature. The mixture was distilled rapidly at atmospheric pressure until the water was removed. The residue was taken up in hot petroleum ether, and the nitrosamine crystallized on cooling; mp = 46\textsuperscript{\textdegree} - 47\textsuperscript{\textdegree} (lit \textsuperscript{1} 46\textsuperscript{\textdegree}); nmr (CCl\textsubscript{4}) \delta 4.79 (m,
1, J = 7.0 Hz, \textit{syn} CH) 4.23 (m, 1, J = 6.5 Hz, \textit{anti} CH), 1.42 (d, 6, J = 6.5 Hz, \textit{anti} C(CH\textsubscript{3})\textsubscript{2}), 1.08 (d, 6, J = 7.0 Hz, \textit{syn} C(CH\textsubscript{3})\textsubscript{2}).

\textbf{Preparation of N-Nitrosodimethylamine}

Dimethylamine (45.1 g, 66.3 ml, 1 mol) was cooled to -78º in a Dry Ice/acetone bath. Then 85.0 ml of concentrated hydrochloric acid was cautiously added dropwise to the cold amine. The hydrochloride solution was then added dropwise to an ice-cold aqueous slurry of 69.0 g (1 mol) sodium nitrite in 40 ml of water over a period of 20 minutes. This solution was allowed to warm to room temperature over 12 hours. The solution was extracted with chloroform, dried (MgSO\textsubscript{4}), and concentrated by means of distillation to yield 55.7 g (75.5%) of \textit{N}-nitrosodimethylamine, bp 152º (lit 1 bp 149-150º); nmr (CCl\textsubscript{4}) δ 3.76 (s, 3, \textit{anti} CH\textsubscript{3}), 2.96 (s, 3, \textit{syn} CH\textsubscript{3}).

\textbf{Preparation of N-Methyl-N-Nitrosoaniline}

\textit{N}-Methylaniline (53.6 g, 0.5 mol) was dissolved in 80 ml of ethyl ether, placed in a 300 ml three-necked, round bottom flask, cooled to -30º, and magnetically stirred. The flask was equipped with a reflux condenser and gas inlet tube. Nitrosyl chloride (32.7 g, 29.0 ml, 0.54 mol) was condensed in a cold trap at -30º and added slowly to the stirred amine. Vacuum distillation yielded the \textit{N}-nitroso derivative, bp 115-116º (12 mm) [lit 1 bp 77º (0.8 mm)]; nmr (CCl\textsubscript{4}) δ 7.50 (envelope, 5, C\textsubscript{6}H\textsubscript{5}), 3.38 (s, 3, \textit{syn} CH\textsubscript{3}).
The Synthesis of N-Nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one

Purification of Piperitenone

The crude piperitenone (10.0 g), obtained as a gift from Dr. J. J. Beereboom, Pfizer Inc., was added to a stirred solution of 16.5 g of sodium sulfite in 80 ml of water at 80-90°. The reaction was monitored with a Beckman Zeromatic pH meter during the 30-minute dropwise addition of piperitenone. The pH was kept at 8.0-9.0 by simultaneous dropwise addition of acetic acid (approx. 7 ml). When the pH remained stable over a period of five minutes, the aqueous mixture was cooled in ice to room temperature and extracted with three 30-ml portions of ethyl ether. This organic extract was discarded. Then the pH of the aqueous mixture was adjusted to 12, and this solution was extracted with four 30-ml portions of ether. The ethereal extract was dried (MgSO₄), concentrated, and distilled, and gave 2.51 g (25%) of piperitenone: bp 90-95° (10 mm); [lit.₄₃ bp 90-125° (10 mm)]; ir (neat) 6.0 μ (C=O) and 6.2 μ (C=C); nmr (CCl₄) δ 5.85 (m, 1, C=CH-C=O), 2.85-1.65 (broad m, 4, CH₂CH₂), 2.08 (s, 3, CH₃), 1.92 (s, 5, CH₃), 1.85 (s, 3, CH₃).

1,3,3-Trimethyl-2-azabicyclo[2.2.2]octan-5-one

To 27 ml of 28.7% aqueous ammonia magnetically stirred and cooled to 4° were added 1.40 g (9.1 mmol) of piperitenone. The mixture was stirred at 2-4° C for 120 hours. Sodium chloride was added to the aqueous mixture, and the saturated solution was extracted with ethyl ether. The ethereal extract was treated with 15 ml of 6 M hydrochloric acid, and the layers were separated. The acidic solution was made basic
(pH 11-12) and extracted with two 20-ml portions of ether. This ethereal extract was dried (MgSO₄), concentrated, and distilled, and gave 394 mg (26%) of 1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one: bp 80-83°C (0.3 mm) [lit 19 bp 50-52°C (0.01 mm)], ir (neat) 2.5 μ (N-H); 5.80 μ (C=O); 7.25 μ, 7.30 μ (gem-dimethyl).

N-Nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one

To 257.7 mg (1.55 mmol) of 1,3,3-trimethyl-2-azabicyclo[2.2.2]-octan-5-one was added 0.17 ml of concentrated hydrochloric acid. Then with a syringe the amine hydrochloride solution was added dropwise to a stirred ice-cold solution of 139.7 mg (2.0 mmol) of sodium nitrite in 2 ml water. After stirring at 0°C for 0.5 hour, the mixture was allowed to reach room temperature and was then heated to 45-50°C for two hours. After the reaction mixture had cooled, it was extracted with two 3-ml portions of carbon tetrachloride. The carbon tetrachloride was removed in vacuo, and 114.3 mg of N-nitrosamine (38%) were obtained; mp 125.5-126.5°C; nmr (CCl₄) 6 2.46 (dd, 1, J₉ = 18.5 Hz, J₉ = 1.8 Hz, syn H₉ C₆C = 0), 2.24 (d, 1, J₉ = 18.5 Hz, anti H₉ C₆C = 0); 2.13-1.65 (m, 4, C₇H₂C₉H₂), 1.71 (s, 3, anti C₃CH₃), 1.40 (s, 3, endo syn C₃CH₃), 1.24 (s, 3, exo syn C₃CH₃). Anal. Calcd. for C₁₉H₂₈N₂O₂: C, 61.2; H, 8.2; N, 14.3. Found: C, 60.9; H, 8.3; N, 14.5.

The Synthesis of N-Nitroso-2-azabicyclo[2.2.2]octane

To a magnetically stirred solution of 2.42 g (2.2 mmol) of 2-azabicyclo[2.2.1]octane (obtained from Dr. F. J. Villani, Schering Corp.) in 1.8 ml of concentrated hydrochloric acid and 0.9 ml water at
75-80° was added dropwise a solution of 1.79 g (2.6 mmol) of sodium nitrite in 3 ml of water. The mixture was stirred at 75-80° for 3 hrs and then allowed to cool to room temperature. The product was filtered and air-dried; 1.78 g (62%); mp 138.5-141.5° (lit 44 mp 140-142°); nmr (CCl₄) δ 4.82 (broad m, 1, anti C₁CH), 3.45 (d, 2, J = 3.0 Hz, syn C₃CH₂), 2.34-1.50 (envelope, 9).

The Synthesis of N-Nitroso-4-azatricyclo[4.3.1.1³,8]undecane

2-Adamantanone

About 20 g of hydroxylamine hydrochloride were dissolved in 120 ml of water; 80 ml of 10% sodium hydroxide solution and 8.0 g of 2-adamantanone were then added. Because the ketone is insoluble in water, just sufficient ethanol was added to the mixture to give a clear solution; 300 ml of hot ethanol was required. The mixture was warmed on a steam bath for 10-15 minutes. After 100 ml of solvent had been removed by distillation,²⁰ the reaction mixture was allowed to cool to room temperature. The product crystallized out of solution as long white needles, mp 164.5-165.5 (lit 21 mp 164-165.5°); yield, 7.3 g (85%).

4-Azatricyclo[4.3.1.1³,8]undecan-5-one

To a 100-ml 3-neck, round bottom flask equipped with reflux condenser, CaSO₄ drying tube, constant addition dropping funnel, magnetic stirrer, and heating mantle were added 1.74 g (2.87 mmol) of 2-adamantanone oxime and 20 ml of hydrocarbon-stabilized chloroform. Next, 20 g of polyphosphate ester ⁴⁵ (PFE, prepared according to the procedure in M. Fieser and L. Fieser, Reagents for Organic Synthesis, Vol. 3) was
added over a period of 15-30 minutes. A vigorous exothermic reaction took place without added heat; the evolution of heat was evidenced by the spontaneous refluxing of the chloroform. After addition of the PPE was complete, the reaction mixture was heated to maintain reflux for an additional 15 minutes. The mixture was allowed to cool to room temperature, 35 ml of water was added, and the two phase system was stirred for 12 hours. The two layers were separated, and the chloroform layer was washed with two 20-ml portions of 10% hydrochloric acid, dried (MgSO₄), and concentrated in vacuo to yield 2.9 g (61%) of the 4-azatricyclo[4.3.1.1³,8]undecan-5-one, mp 299-300° (lit21 mp 298-300°).

4-Azatricyclo[4.3.1.1³,8]undecane (4-Azahomoadamantane)

In a 100-ml 3-neck, round bottom flask equipped with magnetic stirrer, reflux condenser, constant addition dropping funnel, and nitrogen inlet were placed 4.0 ml of a solution of lithium aluminum hydride (LAH) in ethyl ether (about 3.9 M in LAH). To this mixture was added 25 ml of anhydrous tetrahydrofuran (THF). A solution of 2.0 g (1.21 mmol) of 4-azatricyclo[4.3.1.1³,8]undecan-5-one in 25 ml of anhydrous THF was added dropwise to the stirred LAH solution. The mixture was refluxed for 24 hours; the excess LAH was decomposed with 2.0 ml of 10% sodium hydroxide solution. The precipitated salts were removed by filtration, the THF solution was dried (MgSO₄), and the anhydrous solution was placed in a 100-ml 3-neck, round bottom flask equipped with magnetic stirrer, CaSO₄ drying tube, thermometer, gas inlet tube, and an ice bath. Anhydrous hydrogen chloride gas was bubbled into the cold stirred THF solution. A white precipitate formed immediately and yielded, after filtration and drying (P₂O₅), 1.26 g
(56%) of 4-azahomoadamantane hydrochloride, mp > 300°, (lit\textsuperscript{21} mp > 300°), nmr (CDCl\textsubscript{3}) δ 9.4-9.2 (s, 2, NH\textsubscript{2}Cl), 4.05-3.85 (broad s, 1, C\textsuperscript{3}HN\textsuperscript{+}H\textsubscript{2}Cl), 4.6-4.3 (broad s, 2, C\textsuperscript{5}HN\textsuperscript{+}H\textsubscript{2}Cl), 2.40-1.50 (envelope, 13).

**N-Nitroso-4-azatricyclo[4.2.1.1\textsuperscript{3,8}]undecane**

In a 15-ml one-neck round bottom flask were placed 166.7 mg (2.41 mmol) of sodium nitrite and one ml of water. The 4-azahomoadamantan-tane hydrochloride, 400.3 mg (2.14 mmol), was dissolved in 2.0 ml of water; 5-6 drops of 6 M hydrochloric acid were added to aid dissolution and to make the solution slightly more acidic. Then this solution was added dropwise to the magnetically stirred sodium nitrite solution. A reflux condenser was attached to the reaction flask, and the reaction mixture was heated to 50-60° for one hour. A fluffy white solid precipitated from solution and resulted in yielding, after filtration and drying over phosphoric anhydride in vacuo, 250 mg (65%) of nitrosamine; mp 214-214.5°; nmr (CDCl\textsubscript{3}) δ 5.32 (m, 2, syn and anti C\textsuperscript{3}CH), 4.43 (d, 2, J = 3.8 Hz, anti C\textsuperscript{5}H\textsubscript{2}), 3.65 (d, 2, J = 3.5 Hz, syn C\textsuperscript{5}H\textsubscript{2}), 2.60-1.35 (envelope, 26).

**Synthesis of N-Nitroso-7-azabicyclo[4.2.2]decane**

8-Azabicyclo[4.2.2]deca-2,4,9-trien-7-one\textsuperscript{46}

Into a 100-ml 3-neck, round bottom flask equipped with a magnetic stirrer, a constant addition dropping funnel, and a reflux condenser capped with a CaSO\textsubscript{4} drying tube were placed 5.2 g (5.0 mmol) of cyclooctatetraene. The stirred hydrocarbon was heated to 50°, and 5.7 g (4.0 mmol) of chlorosulfonyl isocyanate\textsuperscript{47} was added dropwise
over 45 minutes. The temperature of the reaction mixture was kept at 50-55°C. The reaction mixture was then warmed at 50°C for a total of 7 hrs. Upon cooling to room temperature, the dark mixture solidified.

The mixture was dissolved in 15-20 ml of acetone, and this solution was added dropwise to a mixture of 20 ml of water and 10 ml of acetone while the pH was maintained at 7 by concurrent dropwise addition of 4 M sodium hydroxide solution. A pH meter was used to monitor the pH closely. The resulting solution was extracted with three 50-ml portions of dichloromethane, dried (MgSO₄), and concentrated in vacuo to yield 3.61 g (49%) of 8-azabicyclo[4.2.2]deca-2,4,9-trien-7-one; mp 137-138°C (lit²⁵ mp 139-140°C).

8-Azabicyclo[4.2.2]decan-7-one

In a Parr hydrogenation bottle were placed 3.5 g (2.36 mmol) of 8-azabicyclo[4.2.2]deca-2,4,9-trien-7-one, 150 ml of methanol, and 0.34 g of 5% palladium-on-carbon catalyst. The mixture was shaken for 8 hrs (initial pressure, 40 psig) during which time 7.14 mmol of hydrogen was taken up. The catalyst was removed by filtration, and the methanol was removed by means of rotary evaporation to yield 2.86 g (79%) of 8-azabicyclo[4.2.2]decan-7-one; mp 70-71°C (lit²⁴ mp 73°C).

7-Azabicyclo[4.2.2]decane

To a 3-neck, 100-ml round bottom flask equipped with magnetic stirrer, reflux condenser, pressure equalizing constant addition dropping funnel, and nitrogen inlet were added 4.0 ml of an ether solution of lithium aluminum hydride (LAH, about 3.9 M, supplied by Foote Mineral
Company). Anhydrous tetrahydrofuran (THF, 45 ml) was added to the LAH solution. A solution of 1.024 g (6.79 mmol) of 8-azabicyclo[4.2.2]decan-7-one in 5 ml of anhydrous THF was added dropwise to the stirred LAH solution over 30 minutes. The reaction mixture was then heated at reflux for 24 hrs. Aqueous sodium hydroxide solution (10%, 5 ml) was added to the ice-cooled solution. The inorganic solids were removed by filtration, and the organic layer was dried (MgSO₄) and concentrated. The light yellow liquid which remained was dissolved in 40 ml of ethyl ether. The ether solution was placed in a 100-ml 3-neck, round bottom equipped with magnetic stirrer, gas inlet tube, and CaSO₄ drying tube. The solution was cooled in an ice bath, and anhydrous hydrogen chloride was bubbled into the stirred solution. The hygroscopic white solid which precipitated was dried in vacuo over phosphoric anhydride to yield 443.7 mg (58%) of the amine hydrochloride. Anal. Calcd. for C₉H₁₄N: C, 61.5; H, 10.4. Found: C, 61.5; H, 10.3.

N-Nitroso-7-azabicyclo[4.2.2]decane

In a 5-ml single neck, round bottom flask, equipped with magnetic stirrer were added 82.0 mg (1.19 mmol) of sodium nitrite and a solution of 100 mg of 7-azabicyclo[4.2.2]decane hydrochloride in 1.0 ml of water. A reflux condenser was attached to the flask, and the reaction mixture was heated at 50-60°C for one hour and then stirred overnight at room temperature. The white solid that precipitated was filtered and dried in vacuo over phosphoric anhydride; yield, 74.5 mg (68%); mp 168-170°C; nmr (CCl₄) δ 5.40 (m, 2, anti (C₆H₂)), 4.56 (m, 2, syn (C₆H₂)), 4.46 (dd, 2, J₈₁₂ = 13.8 Hz, J₁₂ = 4.0 Hz, anti C₆H₂), 4.09 (dd, 2, J₈₁₂ = 13.8 Hz, J₁₂ = 4.0 Hz, anti C₆H₂), 3.86 (d, 2H,
**Preparation of N-Nitroso-ll-azabicyclo[4.4.1]undec-l-ene**

ll-Azabicyclo[4.4.1]undec-l-ene, which was prepared by R. R. Lilienthal, a former worker in these laboratories, was purified before use by means of distillation; bp 79-80° (5 mm) [lit 26, 48 bp 79-81° (3 mm)]. To a 5-ml, one-neck round bottom flask equipped with a magnetic stirrer and cooled in an ice bath were added 421 mg (2.13 mmol) of ll-azabicyclo-[4.4.1]undec-l-ene. To the stirred ice-cold amine was added 0.2 ml of concentrated hydrochloric acid. After five minutes, 167 mg (2.42 mmol) of sodium nitrite dissolved in 2 ml of distilled water were added drop-wise. A brown solid immediately precipitated from the solution, and, after the reaction mixture had warmed to room temperature, 233 mg (61%) of crude nitrosamine were isolated. The nitrosamine was purified by means of preparative layer chromatography on silica gel with 2:1 cyclohexane:ethyl acetate; mp 65-67°; nmr (CCl₄) δ 5.88 (t, 1, J = 6.0 Hz, anti C¹=C²H), 5.73 (v, 1, J = 6.0 Hz, syn C¹=C²H), 5.15 (shoulder, 1, syn C⁶H), 5.02 (bm, 1, anti C⁶H), 2.90-1.00 (envelope, 28).

**Nmr Shift Reagent Studies**

In this study, europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione), Eu(fod₃), was the shift reagent. The Eu(fod)₃ was dried for at least 24 hrs. in vacuo over phosphoric anhydride. Both carbon tetrachloride and (²H)chloroform were stored in brown bottles and dried over linde 4A molecular sieves.
In a typical study, the N-nitrosamine was weighed, dissolved in 0.3 ml of either carbon tetrachloride or (2H)chloroform, and transferred to a clean, dry nmr tube. A solution of Eu(fod)₃ in the same solvent that was used for dissolution of the N-nitrosamine was then prepared. After the spectrum for the uncomplexes N-nitrosamine had been recorded, incremental amounts of the shift reagent solution were introduced into the sample tube by means of a microliter syringe. The sample was mixed thoroughly by shaking the tube, and the spectrum was again recorded. The addition of the shift reagent and the recording of the spectra were continued in this manner throughout each shift reagent study.
| Eu(fod)$_3$ & Eu(fod)$_3$ & Molar & syn CH$_3$ & anti CH$_3$ |
|---|---|---|---|---|
| a x 10$^{-6}$ | mmol x 10$^{-3}$ | Ratio Eu:NNO | Hz | Hz |
| 0 | 0 | 0.000 | 178.5 | 226.5 |
| 5 | 5.2 | 0.128 | 227.2 | 253.2 |
| 10 | 10.4 | 0.253 | 269.5 | 276.1 |
| 15 | 15.7 | 0.382 | 312.0 | 299.5 |
| 20 | 20.9 | 0.509 | 354.2 | 322.0 |
| 25 | 26.1 | 0.636 | 394.0 | 343.5 |
| 30 | 31.3 | 0.763 | 437.0 | 367.0 |
| 35 | 36.5 | 0.890 | 474.0 | 386.5 |
| 40 | 41.8 | 1.010 | 507.0 | 405.0 |

a. The concentration of the Eu(fod)$_3$ solution was 1.044 M; solvent CCl$_4$.

b. All of the nmr solutions contained 0.041 mmol of dimethylnitrosamine dissolved in CCl$_4$.

c. All of the nmr spectra were taken on the Varian A-60A spectrometer and the resonances are reported in Hz downfield from internal TMS.
<table>
<thead>
<tr>
<th>Eu(fod)$_3$ x 10$^{-6}$</th>
<th>Eu(fod)$_3$ mmol x 10$^{-3}$</th>
<th>Molar Ratio $^{b}$</th>
<th>CH$_2$ (Hz)$^{a}$</th>
<th>CH$_3$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0.000</td>
<td>210.2</td>
<td>63.0</td>
</tr>
<tr>
<td>5</td>
<td>5.2</td>
<td>0.101</td>
<td>248.0</td>
<td>84.0</td>
</tr>
<tr>
<td>10</td>
<td>10.4</td>
<td>0.202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>15.7</td>
<td>0.304</td>
<td>340.8</td>
<td>143.2</td>
</tr>
<tr>
<td>20</td>
<td>20.9</td>
<td>0.405</td>
<td>382.0</td>
<td>169.9</td>
</tr>
<tr>
<td>25</td>
<td>26.1</td>
<td>0.506</td>
<td>419.2</td>
<td>191.0</td>
</tr>
<tr>
<td>30</td>
<td>31.3</td>
<td>0.607</td>
<td>454.0</td>
<td>212.2</td>
</tr>
<tr>
<td>35</td>
<td>36.5</td>
<td>0.707</td>
<td>489.5</td>
<td>234.0</td>
</tr>
<tr>
<td>40</td>
<td>41.8</td>
<td>0.810</td>
<td>522.0</td>
<td>254.0</td>
</tr>
<tr>
<td>45</td>
<td>47.0</td>
<td>0.914</td>
<td>555.0</td>
<td>273.6</td>
</tr>
</tbody>
</table>

$^{a}$ Spectra were taken on the Varian A-60A spectrometer and are recorded in Hz downfield from internal TMS.

$^{b}$ All spectra contain 0.052 mmol of diethylnitrosamine.

$^{c}$ The Eu(fod)$_3$ solution is 1.044 M; solvent CDCl$_3$. 

**TABLE XVI**

SHIFT REAGENT STUDY - (CH$_3$CH$_2$)$_2$NNO with Eu(fod)$_3$
### TABLE XVII

**SHIFT REAGENT STUDY - DIISOPROPYLNITROSAMINE WITH Eu(dpm)$_3$**

<table>
<thead>
<tr>
<th>Eu(dpm)$_3^a$ mg</th>
<th>Eu(dpm)$_3$ mmol</th>
<th>Molar Ratio Eu:NNO</th>
<th>$\text{syn (CH}_3)_2$ Hz$^b$</th>
<th>$\text{anti (CH}_3)_2$ Hz</th>
<th>$\text{syn CH}$ Hz</th>
<th>$\text{anti CH}$ Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.000</td>
<td>0.000</td>
<td>113.5</td>
<td>151.0</td>
<td>484.5</td>
<td>420.0</td>
</tr>
<tr>
<td>3.86</td>
<td>0.006</td>
<td>0.009</td>
<td>163.0</td>
<td>181.0</td>
<td>589.5</td>
<td>466.0</td>
</tr>
<tr>
<td>13.36</td>
<td>0.019</td>
<td>0.029</td>
<td>306.0</td>
<td>268.0</td>
<td>879.5</td>
<td>595.0</td>
</tr>
<tr>
<td>22.48</td>
<td>0.032</td>
<td>0.050</td>
<td>458.0</td>
<td>359.0</td>
<td>1186.0</td>
<td>730.0</td>
</tr>
<tr>
<td>34.04</td>
<td>0.048</td>
<td>0.075</td>
<td>597.5</td>
<td>444.0</td>
<td>1474.0</td>
<td>858.0</td>
</tr>
</tbody>
</table>

---

*a. The indicated amounts were added to each of four samples containing 0.636 mmol of diisopropyl nitrosamine in 0.4 ml of CCl$_4$.

*b. All nmr spectra were taken on the Varian HA-100 spectrometer, and the resonances are reported in Hz downfield from internal TMS.*
**TABLE XVIII**

**SHIFT REAGENT STUDY OF**

N-NITROSO-1,3,3-TRIMETHYL-2-AZABICYCLO[2.2.2]OCTAN-5-ONE

**WITH Eu(fod)$_3$**

<table>
<thead>
<tr>
<th>Eu(fod)$_3$ x 10$^{-6}$</th>
<th>Eu(fod)$_3$ mmol x 10$^{-3}$</th>
<th>Molar Ratio $^{ab}$</th>
<th>CH$_3$ exo syn Hz$^d$</th>
<th>CH$_3$ endo syn Hz</th>
<th>CH$_3$ anti Hz</th>
<th>C$_6$H$_5$ syn Hz</th>
<th>C$_6$H$_5$ anti Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.00</td>
<td>0.0000</td>
<td>85.0</td>
<td>95.0</td>
<td>104.0</td>
<td>154.0</td>
<td>154.0</td>
</tr>
<tr>
<td>2.0</td>
<td>1.26</td>
<td>0.0168</td>
<td>88.0</td>
<td>97.5</td>
<td>105.5</td>
<td>169.0</td>
<td>167.5</td>
</tr>
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<td>4.0</td>
<td>2.52</td>
<td>0.0262</td>
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<td>104.5</td>
<td>109.4</td>
<td>175.2</td>
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<td>6.0</td>
<td>3.78</td>
<td>0.0398</td>
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<td>109.9</td>
<td>112.1</td>
<td>181.5</td>
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<td>0.0525</td>
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<td>142.7</td>
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<td>22.0</td>
<td>13.86</td>
<td>0.1241</td>
<td>146.8</td>
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<td>136.1</td>
<td>208.2</td>
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<td>16.38</td>
<td>0.1700</td>
<td>156.9</td>
<td>160.1</td>
<td>141.6</td>
<td>217.0</td>
<td>210.5</td>
</tr>
<tr>
<td>30.0</td>
<td>18.90</td>
<td>0.1968</td>
<td>166.9</td>
<td>169.0</td>
<td>147.0</td>
<td>226.0</td>
<td>218.2</td>
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<td>34.0</td>
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<td>230.0</td>
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<td>272.0</td>
</tr>
</tbody>
</table>

---

**a.** Spectra were taken on the Varian A-60A spectrometer and resonances are recorded in Herz downfield from internal TMS.

**b.** All nmr solutions contain 0.096 mmol of nitrosamine in CCl$_4$.

**c.** The Eu(fod)$_3$ solution was 0.65 M.

**d.** The protons H$_S$ and H$_A$ are not distinguishable in the 60 MHz spectrum, but are separated in the 100 MHz spectrum. These resonances do separate in the 60 MHz spectrum as the concentration of Eu(fod)$_3$ increases.
### TABLE XIX

**SHIFT REAGENT STUDY OF**

**N-NITROSO-2-AZABICYCLO[2.2.2]OCTANE WITH Eu(fod)₃**

<table>
<thead>
<tr>
<th>Eu(fod)₃ mmol x 10⁻³</th>
<th>Eu(fod)₃ x 10⁻⁸</th>
<th>Molar Ratio Eu:NNo</th>
<th>anti C¹H Hz</th>
<th>syn C³H₂ Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0.0000</td>
<td>290.0</td>
<td>214.0</td>
</tr>
<tr>
<td>10</td>
<td>6.7</td>
<td>0.0241</td>
<td>293.0</td>
<td>221.0</td>
</tr>
<tr>
<td>20</td>
<td>13.4</td>
<td>0.0462</td>
<td>299.0</td>
<td>232.0</td>
</tr>
<tr>
<td>30</td>
<td>20.1</td>
<td>0.0693</td>
<td>304.0</td>
<td>245.0</td>
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<td>40</td>
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</tr>
<tr>
<td>50</td>
<td>33.5</td>
<td>0.1155</td>
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<tr>
<td>70</td>
<td>46.9</td>
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<td>90</td>
<td>60.3</td>
<td>0.2080</td>
<td>342.5</td>
<td>328.0</td>
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</table>

a. All spectra were taken on the Varian A-60A spectrometer and resonances are reported in Hz downfield from internal TMS.

b. All nmr solutions contain 0.290 mmol of N-nitroso-2-azabicyclo[2.2.2]octane in 0.30 ml CDCl₃.

c. The Eu(fod)₃ solution is 0.07 M; solvent CDCl₃.

d. The change in chemical shift from the original resonance.
**TABLE XX**

SHIFT REAGENT STUDY OF

\( N\)-NITROSO-4-AZATRICYCLO[4.3.1.1^5,8]UNDECANE

WITH Eu(fod)_3

<table>
<thead>
<tr>
<th>Eu(fod)_3</th>
<th>Eu(fod)_3</th>
<th>Molar Ratio</th>
<th>syn C^6H_2</th>
<th>anti C^6H_2</th>
<th>syn C^4H</th>
<th>anti C^4H</th>
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</thead>
<tbody>
<tr>
<td>x 10^{-6}</td>
<td>mol x 10^{-3}</td>
<td>Eu:Nno</td>
<td>Hz</td>
<td>Hz</td>
<td>Hz</td>
<td>Hz</td>
</tr>
<tr>
<td>0.0</td>
<td>0.00</td>
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<tr>
<td>18.0</td>
<td>10.98</td>
<td>0.193</td>
<td>503.5</td>
<td>693.6</td>
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<tr>
<td>22.0</td>
<td>13.42</td>
<td>0.235</td>
<td>532.9</td>
<td>737.5</td>
<td>621.2</td>
<td></td>
</tr>
</tbody>
</table>

a. The Eu(fod)_3 solution is 0.01 M; 189.29 mg (0.182 mmol) of Eu(fod)_3 dissolved in 0.30 ml of CDCl_3.

b. All of the nmr solutions contain 10.25 mg (0.057 mmol) of N-nitrosamine (NNO) dissolved in 0.3 ml CDCl_3; 0.189 M.

c. All of the nmr spectra were taken on the Varian HA-100 spectrometer and the resonances are reported in Hz downfield from internal TMS.
TABLE XXI

SHIFT REAGENT STUDY OF
N-NITROSO-7-AZABICYCLO[1.2.2]DECANE
WITH Eu(fod)$_3$

| Eu(fod)$_3$ x 10$^{-8}$ | Eu(fod)$_3$ x 10$^{-3}$ | Molar Ratio | CH$_2$ CH$_2$ CH CH CH$_2$ CH$_2$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 0</td>
<td>0</td>
<td>318.0</td>
<td>409.0</td>
</tr>
<tr>
<td>2.0 1.19 0.0076</td>
<td>319.0 409.5 504.0 459.0 387.5 446.0</td>
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<td></td>
</tr>
<tr>
<td>4.0 2.39 0.0152</td>
<td>325.0 413.2 505.0 468.0 394.8 450.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.0 3.58 0.0228</td>
<td>333.0 418.8 510.5 479.0 404.0 455.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.0 4.76 0.0303</td>
<td>341.0 423.5 516.0 490.0 413.2 460.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.0 5.97 0.0380</td>
<td>349.2 430.0 520.0 502.0 423.0 466.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.0 7.14 0.0455</td>
<td>357.0 434.2 514.4 471.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.0 8.36 0.0532</td>
<td>364.5 438.8 441.0 476.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.0 9.55 0.0608</td>
<td>373.5 444.2 451.5 481.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.0 10.75 0.0685</td>
<td>380.0 448.2 539.0 460.0 485.0</td>
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<td></td>
</tr>
<tr>
<td>20.0 11.94 0.0761</td>
<td>388.5 453.2 557.0 540.0 469.8 490.0</td>
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</tr>
<tr>
<td>22.0 13.13 0.0836</td>
<td>397.0 458.2 568.0 544.0 479.8 495.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.0 14.33 0.0913</td>
<td>405.9 464.0 580.0 550.0 490.0 500.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. The Eu(fod)$_3$ solution contained 185.45 mg (0.179 mmol) of Eu(fod)$_3$, dissolved in 0.50 ml of CCl$_4$, 0.597 M.

b. All of the nmr solutions contained 26.55 mg (0.157 mmol) of N-nitrosamine (NNO).

c. All of the nmr spectra were taken on the Varian HA-100 spectrometer and resonances are reported in Hz downfield from internal TMS.
TABLE XXII
SHIFT REAGENT STUDY OF
N-NITROSO-11-AZABICYCLO[4.4.1]UNDEC-1-ENE
WITH Eu(fod)₃

<table>
<thead>
<tr>
<th>Eu(fod)₃ ₁₀⁻⁶ M</th>
<th>Eu(fod)₃ mmol x 10⁻³</th>
<th>Molar Ratio Eu:NNO</th>
<th>syn C₆H Hz</th>
<th>anti C₆H Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>0.0000</td>
<td>514.0</td>
<td>502.0</td>
</tr>
<tr>
<td>1.5</td>
<td>0.945</td>
<td>0.0074</td>
<td>522.0</td>
<td>505.0</td>
</tr>
<tr>
<td>2.5</td>
<td>1.575</td>
<td>0.0117</td>
<td>530.0</td>
<td>506.0</td>
</tr>
<tr>
<td>5.0</td>
<td>3.15</td>
<td>0.0233</td>
<td>545.0</td>
<td>510.0</td>
</tr>
<tr>
<td>10.0</td>
<td>6.30</td>
<td>0.0466</td>
<td>526.0</td>
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</tr>
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<td>15.0</td>
<td>9.45</td>
<td>0.0700</td>
<td>615.0</td>
<td>539.0</td>
</tr>
<tr>
<td>25.0</td>
<td>15.75</td>
<td>0.1169</td>
<td>680.0</td>
<td>565.0</td>
</tr>
</tbody>
</table>

a. The concentration of the Eu(fod)₃ was 0.63 M; solvent CDCl₃.
b. All of the nmr solutions contained 24.30 mg (0.135 mmol) of N-nitrosamine (NNO) dissolved in 0.10 ml CDCl₃; micro nmr tube used.
c. All of the spectra were taken on the Varian HA-100 spectrometer and the resonances are reported in Hz downfield from internal TMS.
MASS SPECTRAL DATA FOR
SOME SELECTED COMPOUNDS SYNTHESIZED IN THIS STUDY

IX

Mass spectrum (70 eV) m/e (rel. intensity) 193(36), 179(4), 166(5), 149(19), 124(15), 117(95), 69(89), 55(61), 43(100).

XIX

Mass spectrum (70 eV) m/e (rel. intensity) 139(23), 138(4), 124(21), 110(22), 96(31), 82(100), 68(27).

XX

Mass spectrum (70 eV) m/e (rel. intensity) 168(40), 151(23), 138(93), 95(25), 67(38), 55(100), 41(19).

XXII

Mass spectrum (70 eV) m/e (rel. intensity) 140(47), 118(8), 117(100), 110(14), 74(28), 44(55).

XXIV

Mass spectrum (70 eV) m/e (rel. 180(12), 150(100), 148(10), 134(12), 122(30), 70(31), 41(48).
Figure 21. Nmr spectrum of piperitenone (VII), 60 MHz. The sample was dissolved in carbon tetrachloride.
Figure 22. Nmr spectrum of 1,5,5-trimethyl-2-azabicyclo[2.2.2]octan-5-one (VIII), 100 MHz. The sample was dissolved in deuteriochloroform.
Figure 23. Nmr spectrum of 2-azabicyclo[2.2.2]octane (XXI), 60 MHz. The sample was dissolved in carbon tetrachloride.
Figure 24. Nmr spectrum of L-azatricyclo[4.3.1.1\textsuperscript{3,8}]undecane hydrochloride (XIII), 60 MHz. The sample was dissolved in deuterochloroform.
Figure 25. Nmr spectrum of 7-azabicyclo[4.2.2]decan-8-one (XVIII), 60 MHz. The sample was dissolved in carbon tetrachloride.
Figure 26. Nmr spectrum of 7-azabicyclo[4.2.2]decane (XIX), 100 MHz. The sample was dissolved in deuteriochloroform.
Figure 27. Nmr spectrum of 11-azabicyclo[4.4.1]undec-1-ene (XXIII), 60 MHz. The sample was dissolved in carbon tetrachloride.
Figure 28. Nmr spectrum of dimethylnitrosamine (I), 60 MHz. The sample was dissolved in carbon tetrachloride.
Figure 28a. Nmr spectra of dimethylnitrosamine shifted with Eu(fod)$_3$, 60 MHz. The sample was dissolved in CCl$_4$. The numbers on the spectra indicate the volume ($\mu$l) of Eu(fod)$_3$/CCl$_4$ solution added.
Figure 28b. Nmr spectra of dimethylnitrosamine shifted with Eu(fod)$_3$, 60 MHz. The sample was dissolved in CC1$_4$. The numbers on the spectra indicate the volume (ul) of Eu(fod)$_3$/CC1$_4$ solution added.
Figure 29. Nmr spectrum of diethylnitrosamine (V), 60 MHz. The sample was dissolved in carbon tetrachloride.
Figure 29a. Nmr spectra of diethylnitrosamine (V) shifted with Eu(fod)$_3$, 60 Mhz. The sample was dissolved in CCl$_4$. The numbers on the spectra indicate the volume in µl of Eu(fod)$_3$/CCl$_4$ solution added to the sample.
Figure 29b. Nmr spectra of diethylnitrosamine (V) shifted with Eu(fod)$_3$, 60 MHz. The sample was dissolved in CCl$_4$. The numbers on the spectra indicate the volume in µl of Eu(fod)$_3$/CCl$_4$ solution added to the sample.
Figure 29c. Nmr spectra of diethylnitrosamine (6) shifted with Eu(fod)$_3$, 60 MHz. The sample was dissolved in CCl$_4$. The numbers on the spectra indicate the volume in µl of Eu(fod)$_3$/CCl$_4$ solution added to the sample.
Figure 30. Nmr spectrum of diisopropyl nitrosamine (VI), 100 MHz. The sample was dissolved in carbon tetrachloride.
Figure 30a. Nmr spectra of diisopropyl nitrosamine (VI) shifted with Eu(dpm)$_3$, 100 MHz. The sample was dissolved in CCl$_4$. The numbers on the spectra indicate the volume in μl of Eu(dpm)$_3$/CCl$_4$ solution added to the sample.
Figure 30b. Nmr spectra of diisopropylnitrosamine (VI) shifted with Eu(dpm)$_3$, 100 MHz. The sample was dissolved in CCl$_4$. The numbers on the spectra indicate the volume in µl of Eu(dpm)$_3$/CCl$_4$ solution added to the sample.
Figure 31. Nmr spectrum of N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX), 60 MHz. The sample was dissolved in deuteriochloroform. The zero on the spectrum indicates no shift reagent has been added to the sample.
Figure 31a. Nmr spectra of N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX) shifted with Eu(fod)$_3$, 60 MHz. The sample was dissolved in CDCl$_3$. The numbers on the spectra indicate the volume in $\mu$l of Eu(fod)$_3$/CDCl$_3$ solution added to the sample.
Figure 3lb. Nmr spectra of N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX) shifted with Eu(fod)$_3$, 60 MHz. The sample was dissolved in CDCl$_3$. The numbers on the spectra indicate the volume in µl of Eu(fod)$_3$/CDCl$_3$ solution added to the sample.
Figure 3lc. Nmr spectra of N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX) shifted with Eu(fod)$_3$, 60 MHz. The sample was dissolved in CDCl$_3$. The numbers on the spectra indicate the volume in $\mu$L of Eu(fod)$_3$/CDCl$_3$ solution added to the sample.
Figure 32. Nmr spectrum of N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX), 100 MHz. The sample was dissolved in carbon tetrachloride.
Figure 52a. Nmr spectra of N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX) shifted with Eu(fod)$_3$, 100 MHz. The sample was dissolved in CCl$_4$. The numbers on the spectra indicate the volume in µl of Eu(fod)$_3$/CCl$_4$ solution added to the sample.
Figure 32b. Nmr spectra of N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX) shifted with Eu(fod)₃, 100 MHz. The sample was dissolved in CCl₄. The numbers on the spectra indicate the volume in μl of Eu(fod)₃/CCl₄ solution added to the sample.
Figure 32c. Nmr spectra of N-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (IX) shifted with Eu(fod)$_2$, 100 MHz. The sample was dissolved in CCl$_4$. The numbers on the spectra indicate the volume in ul of Eu(fod)$_2$/CCl$_4$ solution added to the sample.
Figure 33. Nmr spectrum of N-nitroso-2-azabicyclo[2.2.2]octane (XXII), 60 MHz. The sample was dissolved in deuteriochloroform.
Figure 33a. Nmr spectra of N-nitroso-2-azabicyclo[2.2.2]octane (XXII) shifted with Eu(fod)$_3$, 60 MHz. The sample was dissolved in CDCl$_3$. The numbers on the spectra indicate the volume in $\mu$l of Eu(fod)$_3$/CDCl$_3$ solution added to the sample.
Figure 33b. Nmr spectra of N-nitroso-2-azabicyclo[2.2.2]octane (XXII) shifted with Eu(fod)$_3$, 60 MHz. The sample was dissolved in CDCl$_3$. The numbers on the spectra indicate the volume in $\mu$L of Eu(fod)$_3$/CDCl$_3$ solution added to the sample.
Figure 34. Nmr spectrum of N-nitroso-4-azatricyclo[4.3.1.1^{3,8}]undecane (XIV), 100 MHz.
The sample was dissolved in deuteriochloroform.
Figure 5.4a. Nmr spectra of $\text{X-nitroso-azatricyclo[4.4.0.0^{3,7}]undecane (XIV)}$ shifted with Eu(fod)$_2$, 100 MHz. The sample was dissolved in CDCl$_3$. The numbers on the spectra indicate the volume in $\mu l$ of Eu(fod)$_2$/CDCl$_3$ solution added to the sample.
Figure 5.4b. NMR spectra of N-nitroso-L-azatricyclo[3.3.1.1^2,6]undecane (XIV) shifted with Eu(fod)$_3$, 100 MHz. The sample was dissolved in CDCl$_3$. The numbers on the spectra indicate the volume in µl of Eu(fod)$_3$/CDCl$_3$ solution added to the sample.
Figure 35. Nmr spectrum of N-nitroso-7-azabicyclo[4.2.2]decane (XX), 100 MHz.
The sample was dissolved in carbon tetrachloride.
Figure 35a. Nmr spectra of N-nitroso-7-azabicyclo[4.2.2]decane (XX) shifted with Eu(fod)$_3$, 100 MHz. The sample was dissolved in CCl$_4$. The numbers on the spectra indicate the volume in µl of Eu(fod)$_3$/CCl$_4$ solution added to the sample.
Figure 35b. Nmr spectra of N-nitroso-7-azabicyclo[4.2.2]decane (XX) shifted with Eu(fod)$_3$, 100 MHz. The sample was dissolved in CCl$_4$. The numbers on the spectra indicate the volume in µl of Eu(fod)$_3$/CCl$_4$ solution added to the sample.
Figure 36. Nmr spectrum of $\text{N}$-nitroso-$\text{ll}$-azabicyclo[4.4.4]undec-1-ene (XXIV), 100 MHz. The sample was dissolved in acetone-$d_6$. 
Figure 37. Nmr spectra of N-nitroso-11-azabicyclo[4.4.1]undec-1-ene (XXIV) shifted with Eu(fod)₃.
The sample was dissolved in carbon tetrachloride. Only the portion of the spectrum containing
the C-C bridgehead hydrogens is shown. The numbers on the spectra indicate the
volume in µl of Eu(fod)₃/CCl₄ solution added to the sample.
GENERAL SUMMARY

The structure of a number of bicyclic, tricyclic, and related acyclic N-nitrosamines has been investigated by means of nmr techniques and by means of quantum chemical techniques. The principle finding in all three cases is that the geometric arrangements of the alkyl portions of these compounds greatly affects the conformer ratio. In fact, the bi- and tricyclic N-nitrosamines studied in this work represent the first clear evidence that a hydrogen, substituted on atom 5 of the pseudo-allylic system (see Figure 14), is sterically bulky enough to cause a rearrangement around the N-N partial double bond to put the oxygen anti to this substituent. Ring size and flexibility also play an important role in the conformer ratio.

The photoelectron spectra show that the $\pi$ molecular orbital is higher in energy than the $n$ molecular orbital in the N-nitrosamines studied.

This area of study offers great potential for further investigations. The bicyclic N-nitrosamines containing a one-carbon and three-carbon bridge should be synthesized, and their structures should be determined. Also an attempt should be made to substitute a bulky group for first one and then both of the methylene hydrogens in order to see if the conformer ratio changes. Finally, more lanthanide shift studies could be done in an effort to more accurately extrapolate some of the chemical shifts which are not easily followed because the bands are hidden under complex multiplets.
REFERENCES


36. T. Koopmans, Physica (Utrecht), 1, 104 (1933).


42. Vitride is the trade name for a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene. Vitride was purchased from Eastman Chemical Company.


46. T. J. Barton, Iowa State University, personal communication, 1972.

47. Chlorosulfonyl isocyanate was purchased from the Aldrich Chemical Company and used without further purification.


49. Eu(fod)₃ and Eu(dpm)₃ are commercial materials purchased from Norell Chemical Company.
SELECTED BIBLIOGRAPHY

VITA

David Ray Battiste was born in Mobile, Alabama, October 15, 1946, to James M. and Mildred B. Battiste. He attended public school in Mobile and graduated from Murphy High School in May of 1964. He attended Auburn University, Auburn, Alabama, for one year, 1964-65, and transferred to the University of Florida, Gainesville, Florida, where he received the Bachelor of Science Degree in Chemistry (accredited by the American Chemical Society) in June of 1969. In that same month, he entered Louisiana State University, Baton Rouge, Louisiana. On August 23, 1969, he was married to Constance Louise Turner of Gainesville, Florida. He was awarded the DuPont Teaching Award in 1971, and he was elected as an associate member of the Society of the Sigma Xi in April of 1973.

Mr. Battiste is presently a candidate for the Doctor of Philosophy degree with a major in organic chemistry from Louisiana State University, Baton Rouge, Louisiana.