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City University of New York, 1990

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NITROGEN-15 MAGNETIC RESONANCE SPECTROSCOPY OF COMPOUNDS CONTAINING THE NITROGEN-NITROGEN BOND

by

XIAOHUA HUANG

A dissertation submitted to the Graduate
Faculty in Chemistry in partial fulfillment
of the requirements for the degree of
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1990

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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ABSTRACT

Nitrogen-15 Magnetic Resonance Spectroscopy of Compounds Containing the Nitrogen-Nitrogen Bond

by

XIAOHUA HUANG

Advisor: Professor Theodore Axenrod

This dissertation is divided into four parts. The first part deals with a brief description of the nitrogen-15 NMR spectroscopy with a special emphasis on the theory and applications of chemical shifts and coupling constants in the investigation of structures of organic compounds. The second part covers the application of carbon-13 and nitrogen-15 NMR spectroscopy to the study of benzenediazonium ions, namely, the influence of aromatic ring-substituents, solvents and specific complexing agents such as crown ethers, on the structure and bonding in benzenediazonium ions. The use of one-bond carbon-nitrogen spin-spin coupling constants as a probe of the electronic structure and of the C_1-Nα bond order in the benzenediazonium ions with specific examples is included. Electron-donating groups on the benzenediazonium ions induce larger changes in the one-bond C_1-Nα and Nα-Nβ coupling constants whereas electron-withdrawing groups produce only small changes in the coupling. Further, both the electron-donating and electron-withdrawing groups do effect the bond order of the C_1-Nα.

Also, bulky substituents in the 3,5- positions in the ring affect differently the coupling constants. It is concluded that solvents with large donor numbers (DN) enhance the diazonium type structures in the benzenediazonium ions. Complexation of benzenediazonium ions with crown ethers causes an increase in the single bond character of the C_1-Nα. Further, the crown ethers with different cavity sizes seem to stabilize the benzenediazonium ions by different modes of interaction and the bulky ortho substituents do tend to destabilize the crown ether complex. The third part includes an investigation of hydrazine and its derivatives. It is demonstrated that the nitrogen-nitrogen one-bond coupling constants have an explicit dependence on the conformation of the adjacent lone-pair electrons. The last part of this thesis details the experimental procedures adopted in the synthesis of the various benzenediazonium ions and their precursors.

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CHAPTER 1. INTRODUCTION

1.1 Scope

The use of nuclear magnetic resonance (NMR) spectroscopy as an aid in the determination of structure and in the investigation of molecular properties began in 1950 with the discovery of the phenomenon of the chemical shift for hydrogen[1], fluorine[2] and nitrogen-14[3]. With the advent of modern FT instrumentation, natural-abundance nitrogen-15 spectroscopy is practical in many instances. The potential of ^{15}N-NMR spectroscopy is unique, largely due to the critical role the nitrogen atom plays in a wide variety of chemical compounds.

It is the purpose of this dissertation to investigate the molecular structure of compounds containing nitrogen-nitrogen bond by nitrogrn-15 and carbon-13 NMR spectroscopy. The thesis is organized as follows: Chapter 1 discusses the general theory of nitrogen NMR spectroscopy. The spectroscopy parameters which are related to the molecular and electronic structural properties of chemical compounds are illustrated in detail. This provides a basis for the interpretation of the experimental results in the subsequent chapters. In Chapter 2, the investigation of the electronic structure of benzenediazonium ions using one-bond nitrogen-carbon spin-coupling ($^1J_{^{13}C-^{15}N}$) is outlined. In Chapter 3, the relationship between the dihedral angle of the lone-pair electrons in different conformations and the nitrogen-nitrogen spin-coupling ($^1J_{^{15}N-^{15}N}$) in various hydrazines is examined. Detailed experimental procedures are presented in Chapter 4.

1.2 Nitrogen NMR Spectroscopy

For nitrogen, there exist two naturally occurring isotopes, ^{14}N (I=1) and ^{15}N (I=1/2), where I is the spin quantum number. Both nitrogen isotopes are magnetically active with resonance frequencies at 7.22MHz and 10.135 MHz in a polarizing field of 2.35T (100 MHz for Proton). Their magnetic moments, however, are inherently small. The magnetogyric ratios of ^{14}N and ^{15}N with respect to hydrogen (γ_N/γ_H) are 0.072 and -0.101, respectively. Therefore, their sensitivities in comparison to that of the proton are inherently low (0.00101 and 0.00194 for ^{14}N and ^{15}N respectively).

Since the relative sensitivities for both isotopes are comparable, an approximately 300-fold higher natural abundance of ^{14}N would seem to make it the nucleus of choice for nitrogen NMR spectroscopy. However, ^{14}N, like all nuclei with spin quantum number I>1/2, possesses an electric quadrupole moment that arises from a non-spherical electric charge distribution in the nucleus itself. When placed in an electric field gradient, a quadrupolar nucleus experiences random fluctuating electric fields. The characteristic frequencies of these fluctuating motions have components at the ^{14}N resonance frequency and hence afford an efficient relaxation mechanism. Since $T_1=T_2$ for ^{14}N in most molecules that are freely mobile in solution, ^{14}N line widths are correspondingly large, ranging from tens to thousands of hertz.

Consequently, small chemical shift differences in general are not resolvable and the splitting due to the spin-spin coupling with another ^{14}N isotope is not discernible. Thus, the usefulness of the ^{14}N chemical shifts and coupling constants for structure elucidation of molecules containing similar nitrogen atoms is limited.

Due to the absence of a quadrupole moment for ^{15}N (I=1/2), generally sharp resonance lines, approaching 1 Hz in width, are possible and the coupling to other nuclei can be readily measured. Unfortunately, the detection of ^{15}N resonances is more difficult due to its inherent lower natural abundance as well as due to their T_1 values being several orders of magnitude longer (85-170 sec)[11]. Furthermore, the nuclear Overhauser effect (NOE), advantageous for carbon-13 NMR spectroscopy, can in fact be a detriment for ^{15}N owing to the negative magnetogyric ratio. As a result, a maximum NOE, arising from the exclusive dipole-dipole relaxation, gives rise to an inverted signal with an intensity enhanced by a factor of four. When relaxation mechanisms other than the dipole-dipole mechanism intervene, the NOE is reduced. To avoid these problems, samples enriched in ^{15}N are usually employed.

Both the chemical shift and coupling constant of nitrogen-15 are related to that of nitrogen-14 by their respective magnetogyric ratios ($\gamma_{^{15}N}/\gamma_{^{14}N}$). The ratio $\gamma_{^{15}N}/\gamma_{^{14}N}$ was studied for molecules with a wide range of chemical shifts[13]. Based on the observed nitrogen resonances of the $^{15}NH_4^+$ and $^{14}NH_4^+$ ions at constant field strength, $\gamma_{^{15}N}/\gamma_{^{14}N}$ has been calculated to be 1.402547. It follows that the shielding constants of nitrogen isotopes for the isotopomers of the same molecule are the same, since

$$\nu_{^{15}N} = \gamma_{^{15}N}\,(1-\sigma_{^{15}N})\ \ H_0 \qquad (1.1)$$

and

$$\nu_{^{14}N} = \gamma_{^{14}N}\,(1-\sigma_{^{14}N})\ \ H_0 \qquad (1.2)$$

Thus if the ratio $\gamma_{^{15}N}/\gamma_{^{14}N}$ is constant, $\sigma_{^{15}N}=\sigma_{^{14}N}$ must hold. Likewise, the ratio of the coupling constants of isotopomers is constant[9].

$$J_{(^{14}N\text{-}X)} = -0.7129\ J_{(^{15}N\text{-}X)} \qquad (1.3)$$

This is particularly important since coupling constants measured easily for the isotopomer containing the ^{15}N nucleus can be used to calculate the coupling constants for the analogous ^{14}N isotopomer. In the latter case the direct measurement of the coupling constant is hindered by the quadrupole broadening.

1.3 Nitrogen NMR Parameters

In nitrogen NMR spectroscopy, one usually encounters the following parameters. The parameter σ describes nuclear shielding; J is nuclear spin-spin coupling; T_1 and T_2 are relaxation times which describe the relaxation processes encountered by the nuclei excited in the NMR experiment. Interpretation of these parameters provides a considerable amount of structural and reactivity information about the molecule. In the following sections, some of these parameters and their interpretation of the molecular properties are discussed.

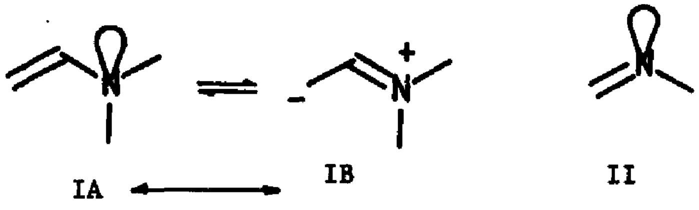
1.3.1 Nitrogen Chemical Shifts

According to quantum theory, nuclei with non-zero spins have magnetic moments proportional to their spins. The magnetization in an external magnetic field is quantized. Thus, the application of the proper amount of energy by an external source can induce nuclei to pass from one energy level to the other. This process is known as nuclear magnetic resonance (NMR). In molecules, the local magnetic field arising from electronic currents induced by the external magnetic field will differentiate one nucleus from another because of their local neighboring chemical environment. As a result, the resonance frequencies will vary according to the molecular structure and the shift in resonance frequency is termed the chemical shift. It is this chemical shift which forms the basis for using NMR as a probe to determine the structure of molecules. Quantitatively, chemical shift is described by the nuclear shielding (or screening), σ. The relationship between the shielding and the magnetic field, H_0, is as follows:

$$\nu = \frac{\gamma H_0 (1-\sigma)}{2 \pi} \qquad (1.4)$$

As indicated by this equation, the magnetic field experienced by a nucleus is not the applied field, but rather the difference between the applied field H_0 and the product of H_0 and σ. Like the other non-proton nuclei, nitrogen chemical shifts span a wide range, approximately 900 ppm. Thus, for nitrogen-15, neighboring effects can be neglected, since their magnitudes are insignificant with respect to its wider chemical shift range. In addition, nitrogen has some features that differentiate it from carbon, namely, the lone-pair of electrons present in neutral molecules. As a result, a nitrogen resonance line position may change in either direction when the nitrogen is protonated, and these changes may be characteristic of the type of nitrogen in the molecule.

In general, nitrogen is deshielded when the atom possesses an electron lone-pair that can be delocalized into an adjacent π system <u>I</u> (e.g., aniline) or when it is itself a part of an unsaturated system <u>II</u> (e.g., azines, pyridines). In the latter case the deshielding is associated with the presence of low-lying $n-\pi^*$ electronic states.



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However, protonation of the anilines and azines removes the deshielding contribution of the lone-pair in these compounds and thus effects the shielding in a way that compensates for, or outweighs, the influence of the positive charge generation.

1.3.2 Nitrogen Coupling Constants

The spin-spin coupling constant, J_{AB}, is a measure of the energy of interaction between the magnetic moments of nuclei A and B. Since the interaction is transmitted by a magnetic polarization of the electrons in the molecules, J_{AB} is intrinsically a second order property of the molecule which depends somewhat on the details of the electron distribution. It is therefore often convenient to define a reduced spin-spin coupling constant K_{AB}, independent of the magnetic moments of A and B

$$K_{AB} = \frac{{}^{n}J_{AB}\ 2\pi}{\gamma_A\ \gamma_B} \qquad (1.5)$$

where γ_A and γ_B are the magnetogyric ratios of nuclei A and B, respectively. The interaction energy, E_{AB}, between the nuclear magnetic moments is

$$E_{AB} = h\ J_{AB}\ I_A\ I_B \tag{1.6}$$

According to Ramsey's theory, E_{AB} arises from three types of interactions between electron and nuclear spins[16]. Thus, J_{AB} can be written as a sum of three contributions

$$^{n}J_{AB} = {}^{n}J_c + {}^{n}J_o + {}^{n}J_d \tag{1.7}$$

The first term on the right hand side of eq.(1.7), J_c, arises from relativistic effects, referred to as the "Fermi contact term"[11]; the J_o term is due to the interaction between the nuclear magnetic moments and the magnetic moments of the electrons; and the J_d term arises from the magnetic shielding of the direct interaction of nuclear spins by electron orbital motion. Both theoretical calculations and experimental data[8] have verified that for all couplings involving hydrogen, the contact term is dominant and the other terms may be neglected. For coupling not involving hydrogen, however, the other two terms may be important. In the latter case the couplings should obey completely different rules from that of the corresponding H-H and X-H couplings. For example, $^{1}J_{CN}$ of pyridine, calculations[12,13] show

J_c= -0.7 Hz, J_o= +1.6 Hz, and J_d= -0.3 Hz. J_o is much larger than J_c and J_d. Therefore, J_c alone, in this case, would be insufficient to be used to estimate $^1J_{CN}$ of pyridine.

It has been demonstrated[14] that single bond C-N couplings are usually dominated by the contact interaction, whereas the non-contact mechanisms normally control the multiple bond carbon-nitrogen couplings, such as in the case of pyridine, isocynaide, etc. This is consistent with the fact that only s-electron density contributes to the contact interaction, whereas p-, d-, etc. electrons produce the non-contact coupling contributions.

The coupling constant, J_{AB}, can be either positive or negative, depending on whether the lower or the higher of the two energy levels of the coupled spin pair corresponds to the antiparallel alignment of the two spins. If the coupling J_{AB} is positive, the spin states of spins A and B are opposite (i.e., $m_A+\frac{1}{2}$ $m_B-\frac{1}{2}$ or $m_A-\frac{1}{2}$, $m_B+\frac{1}{2}$) and will have lower energy than the state with parallel spins. If J_{AB} is negative, the converse is true. When at least three spins interact, the relative but not the absolute sign of the coupling may be determined from the spectrum. For spin systems characterized by a single constant or composed of sets of magnetically equivalent nuclei, the sign of the coupling does not influence its spectra. Therefore, from such spectra, only absolute value of coupling constant can be obtained. For more complicated spin systems, such as the "AMX" spin system, spectra do depend on the sign of the coupling constants, and the analysis of the spectra will give only their relative signs (see section 3.3).

Spin-spin couplings of nitrogen are usually dependent on various molecular parameters such as hybridization, electronegativity of substituents and geometries. In the following, a brief discussion of each of these effects is presented.

1. Hybridization effects

Because the nature of bonding can be understood by means of spin-spin coupling, especially when the contact term is of greatest importance, the hybridization effects have been investigated widely in the past[8]. It has been suggested[18] that the spin-spin coupling depends upon the amount of s character in the bond joining the nuclei. In fact, an empirical relationship between the coupling and the percentage of s character of the atomic orbitals forming the σ bond between the ^{15}N and ^{13}C nuclei has been proposed, viz.,

$$k \mid {}^{1}J_{({}^{13}C-{}^{15}N)} \mid = \% s_C \% s_N \qquad (1.8)$$

where $\%s_C$ and $\%s_N$ represent the percentages of s character in the bonding orbital of the carbon and nitrogen atoms respectively. k is a proportionality constant. FPT-INDO calculations[15] show that k should be 80 and the sign of the coupling should be negative. For sp^3, sp^2 and sp carbon or nitrogen hybridization, the $\%s_C$ or $\%s_N$ are calculated to be 25%, 33%, and 50%. It is clear that $^{1}J_{CN}$ value of a certain compound could be easily predicted from equation 1.8. For example, the predicted coupling constants of 7.8 Hz for methylamine, 13.6 Hz for N-phenylacetamide and 20.6 Hz for diazoquinone agree well with the experimentally observed coupling constants of 7.0 Hz, 13.3 Hz and 20.0 Hz, respectively.

2. Angular Dependence

It is well known that some types of coupling show an angular dependence, especially those over two bonds and three bonds. Since Karplus' prediction[16] from VB theory of a strong conformational dependence of vicinal H-H coupling, the relationship between the conformation and vicinal coupling of, amongst others, ethane derivatives, has received much attention. The dihedral angle (θ) dependence of vicinal spin-spin coupling for ethane is similar to that given by the Karplus relation:

$$^{3}J_{HH} = A + B\cos\theta + C\cos^{2}\theta \qquad (1.9)$$

Several Karplus-type relationships have also been invoked in explaining spin-spin coupling to nitrogen. The following equation is typical for a N-H three-bond coupling[23]:

$$^{3}J_{NH} = -4.6\cos^{2}\theta + 3.0\cos\theta + 0.8 \qquad (1.10)$$

θ is the N-(CO)-C-H dihedral angle specifically for a peptide linkage, R_2N-(CO)-HXY. Theoretical studies of hydrazine showed that, in compounds with s hybridized lone-pairs, the dominant Fermi contact contribution varies with the dihedral angle θ between the nitrogen lone-pairs according to the following relation[18]:

$$^{1}J_{NN} = a_0 + a_1\cos\theta + a_2\cos^2\theta \qquad (1.11)$$

3. Electronegativities or Hammett Constants of Substituents Effects

Although a complete breakdown of the electronic properties of a substituent is not possible, it can be shown that good correlations between $^{n}J_{NX}$ and electronegativity of the substituents exist in certain series of compounds. Since electronic effects are also well-defined by the Hammett parameter, σ, it is not surprising that reasonable correlations between $^{n}J_{NH} = f(\sigma)$ have been drawn corresponding to two different solvents for meta and para substituted anilines[19,20].

$$^{1}J_{NH} = 6.4\ \sigma + 82.3 \qquad \text{in DMSO} \qquad (1.12)$$

$$^{1}J_{NH} = 6.3\ \sigma + 78.4 \qquad \text{in CDCl}_3 \qquad (1.13)$$

A similar relationship, $^{1}J_{CN} = f(\sigma)$, for the same series of compounds has also been found[21]:

$$^{1}J_{CN} = 0.26\ \sigma + 26.5 \qquad \text{in DMSO} \qquad (1.14)$$

$$^{1}J_{CN} = 2.89\ \sigma + 11.95 \qquad \text{in CDCl}_3 \qquad (1.15)$$

CHAPTER 2. NMR STUDY OF BENZENEDIAZONIUM IONS

The physical properties and electronic structure of the benzenediazonium ion have been the subject of much work[22,24] since its discovery about a hundred years ago[23]. Recently, a variety of spectroscopic methods including infrared, ultraviolet, ^{1}H, ^{13}C and ^{15}N NMR[25] have been employed to assess the influence of aromatic ring substituents, solvents and specific complexing agents such as crown ethers[26,27] on the structure and the nature of the bonding in benzenediazonium ions. The ^{13}C and ^{15}N NMR techniques have been proven to be particularly sensitive probes of the electronic environments of the carbon and nitrogen nuclei, although the reports appearing in the literature to date have been essentially confined to the influence of the above phenomena on the respective chemical shifts of these nuclei. The instability and low solubility of uncomplexed benzenediazonium salts in most organic solvents, combined with the need for ^{15}N-enriched compounds, probably precluded the study of the ^{13}C-^{15}N and ^{15}N-^{15}N spin-spin couplings in these systems.

It is the aim of this Chapter to show that these difficulties can be overcome so that the electronic structure of benzenediazonium ion can be investigated. We have used special techniques such as synthesizing ^{15}N double-labeled compounds, reducing the sample temperature, using pure samples, and adding complexing reagents. A lot of potentially new information about C_1-Nα couplings in these systems has been obtained. The effects of substituents and solvents on the J_{CN} and J_{NN} one-bond spin-couplings of uncomplexed benzenediazonium ions as well as the changes in these couplings in the presence of crown ethers are presented. The significance of various resonance structures suggested for the ground state of benzenediazonium compounds is discussed. From the measured ^{13}C chemical shifts and J_{CN} couplings, together with various other spectroscopic results, the electronic structure and the bonding in benzenediazonium ions are assessed.

2.1 Substituent Effects in para-Substituted Benzenediazonium Fluoroborates

A series of para-substituted benzenediazonium fluoroborates with 95% ^{15}N-enrichment was prepared. The coupling constants J_{CN} and J_{NN} in these compounds were determined in dimethylformamide using approximately 0.2 molar solutions. These data are presented in Table 1. Assignments of the one-bond $^1J_{C_1N\alpha}$ coupling constants and two-bond $^2J_{C_1N\beta}$ coupling constants are based upon the comparison of the couplings in the single and double-labeled diazonium salts illustrated in Figures 2.1 and 2.2. The long-range $^nJ_{C_1N\alpha}$ coupling values are from the carbon-13 measurements reported by Elofson and co-workers[28]. Examination of the data in Table 1 reveals that the coupling J_{CN} over more than two bonds is unaffected when the substituent changes. But the one-bond couplings, $^1J_{CN}$ and $^1J_{NN}$, show a dependence on the nature of the para substituents. The magnitude of the change in $^1J_{NN}$ is smaller than in $^1J_{CN}$.

Table 1. $^{13}C_1$ Chemical Shifts, ^{13}C-^{15}N and ^{15}N-^{15}N Coupling Constants for para-substituted Benzenediazonium Fluoroborates-$^{15}N_2$[a]

		[c]			
Substituents	C-1[b]	$^{1}J_{C_1N\alpha}$	$^{2}J_{C_2N\alpha}$	$^{2}J_{C_1N\beta}$	$^{1}J_{N\alpha N\beta}$
$-N(CH_3)_2$	89.4	17.9	2.0	5.1	3.0
-OH	100.7	14.8	2.3	5.4	1.7
$-OCH_3$	103.7	14.4	2.0	5.3	1.6
$-CH_3$	111.9	11.6	2.0	5.6	1.4
-H	116.4	10.5	2.1	5.6	1.3
-Cl	115.0	12.1	2.4	5.7	d
-Br	115.4	12.1	2.3	5.6	1.2
-COOH	119.8	10.4	2.1	5.5	1.2
$-NO_2$	122.1	11.2	2.5	5.6	1.0
$-N(CH_3)_3^+$	118.8	11.5	2.4	5.7	1.2

[a] Measurements made at 5 °C using 0.20M solution in 93:7 w/w DMF:C_6D_6,

[b] From TMS in ppm,

[c] In Hz; the error in these measurements is estimated to be ±0.3 Hz,

[d] The measurement was not completed due to the decomposition of the sample.

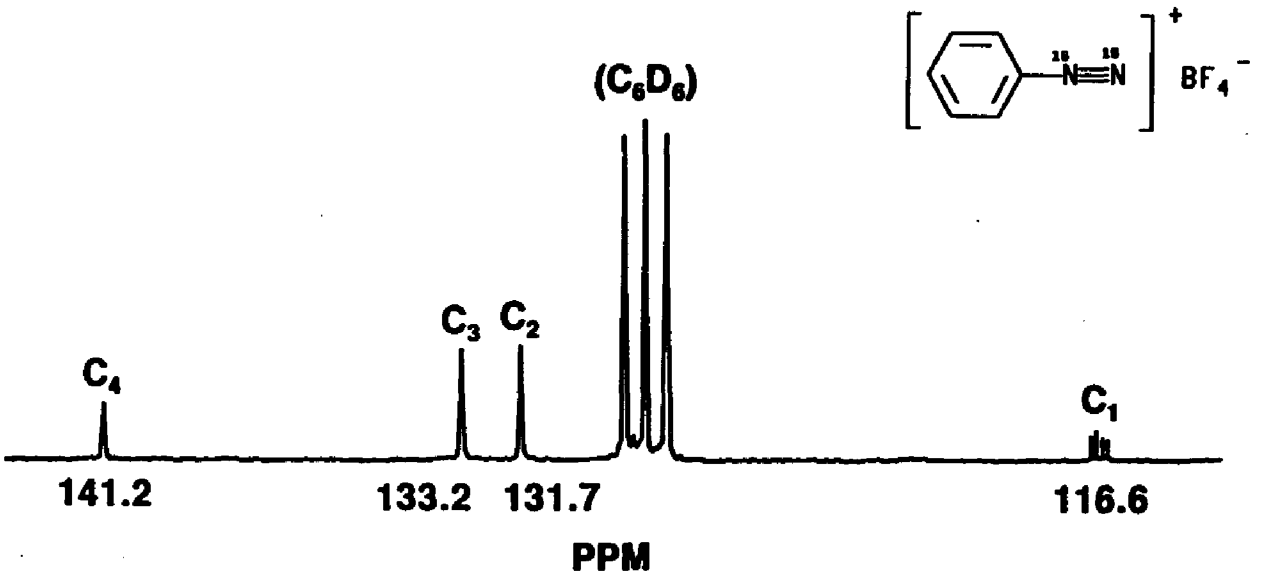


Figure 2.1 ^{13}C Spectrum of Benzenedizonium Fluoroborate-^{15}N$_2$

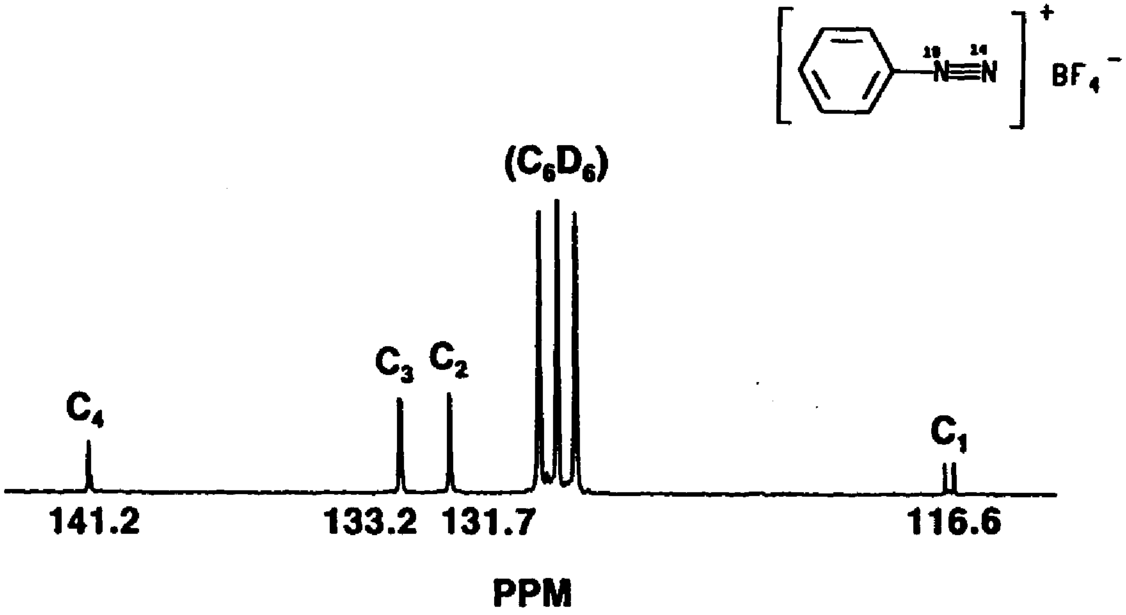
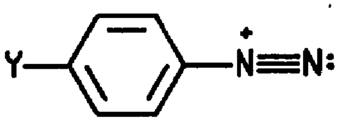


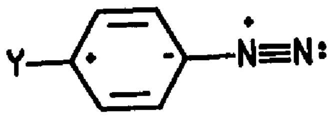
Figure 2.2 ^{13}C Spectrum of Benzenediazonium Fluoroborate-^{15}N$_1$

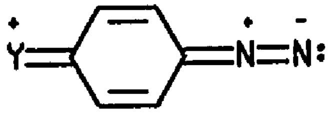
With electron-donating substituents, both $^1J_{CN}$ and $^1J_{NN}$ vary over a range of 7.4 Hz and 1.8 Hz, respectively. Much smaller changes are found for electron-withdrawing substituents. Curiously, the $^1J_{CN}$ and $^1J_{NN}$ do not correlate with either σ^+ or σ_p, but correlate well with $\sigma^+ \leq 0$ (electron-donating substituents), for $^1J_{CN}$. This is shown in Figure 2.3. The linear relationship between the Hammett substituent constant (only $\sigma^+ \leq 0$) and $^1J_{CN}$ can be described by the following equation:

$$^1J_{CN} = -4.46\sigma + 10.5 \qquad \text{corr. coeff.} = 0.995 \qquad (2.1)$$

In fact, a similar relationship has also been found by Roberts and co-workers[28] when the chemical shift of the terminal nitrogen in the bezenediazonium ion was plotted against σ^+ as shown in Figure 2.4. They suggested that with electron-donating substituents, diazo-type structures such as <u>IIIc</u> make a significant contribution to the ground state of the ion.


IIIa


IIIb


IIIc

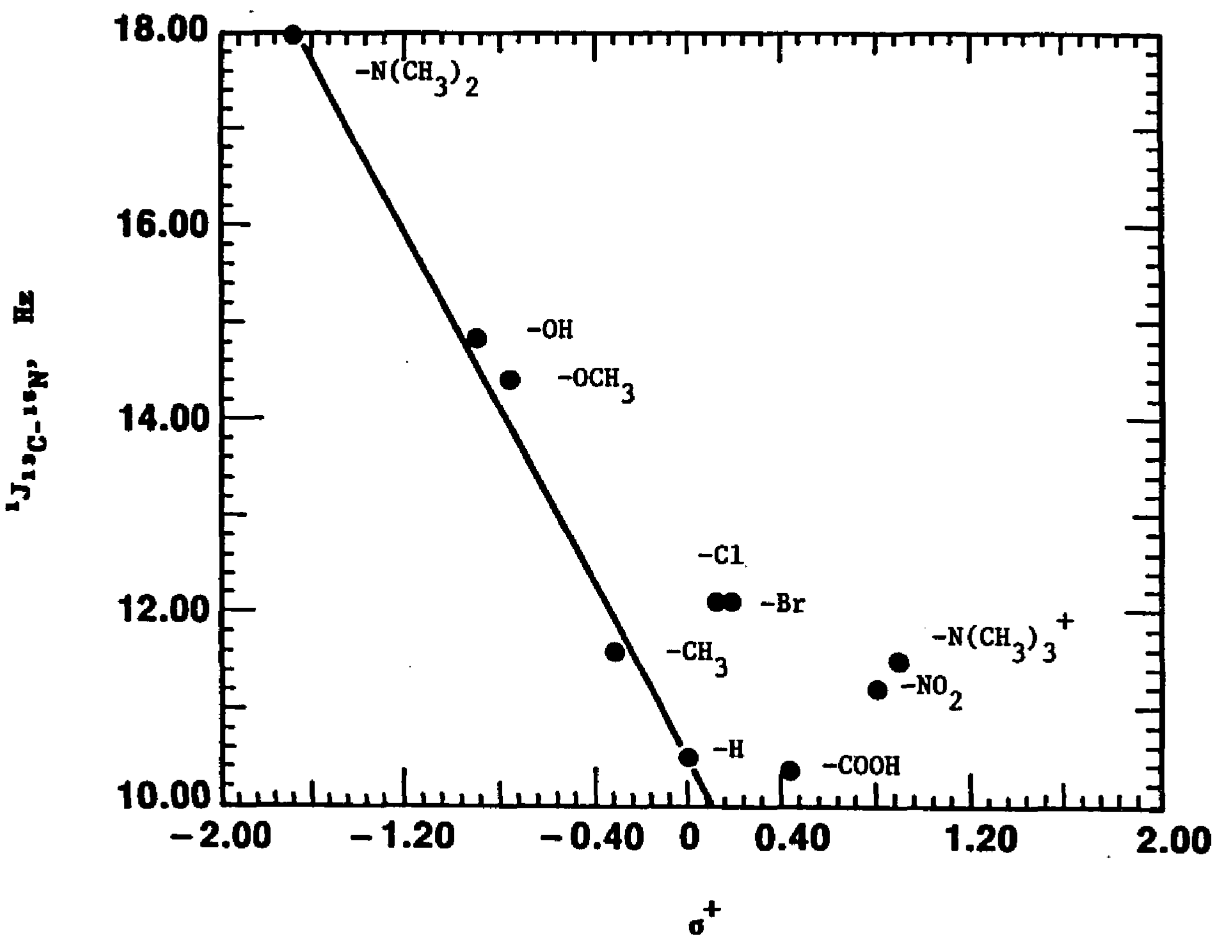


Figure 2.3 Correlation of One-Bond ^{13}C-^{15}N Coupling Constants in Ring Substituted Benzenediazonium Ions With Hammett Substituent Constants

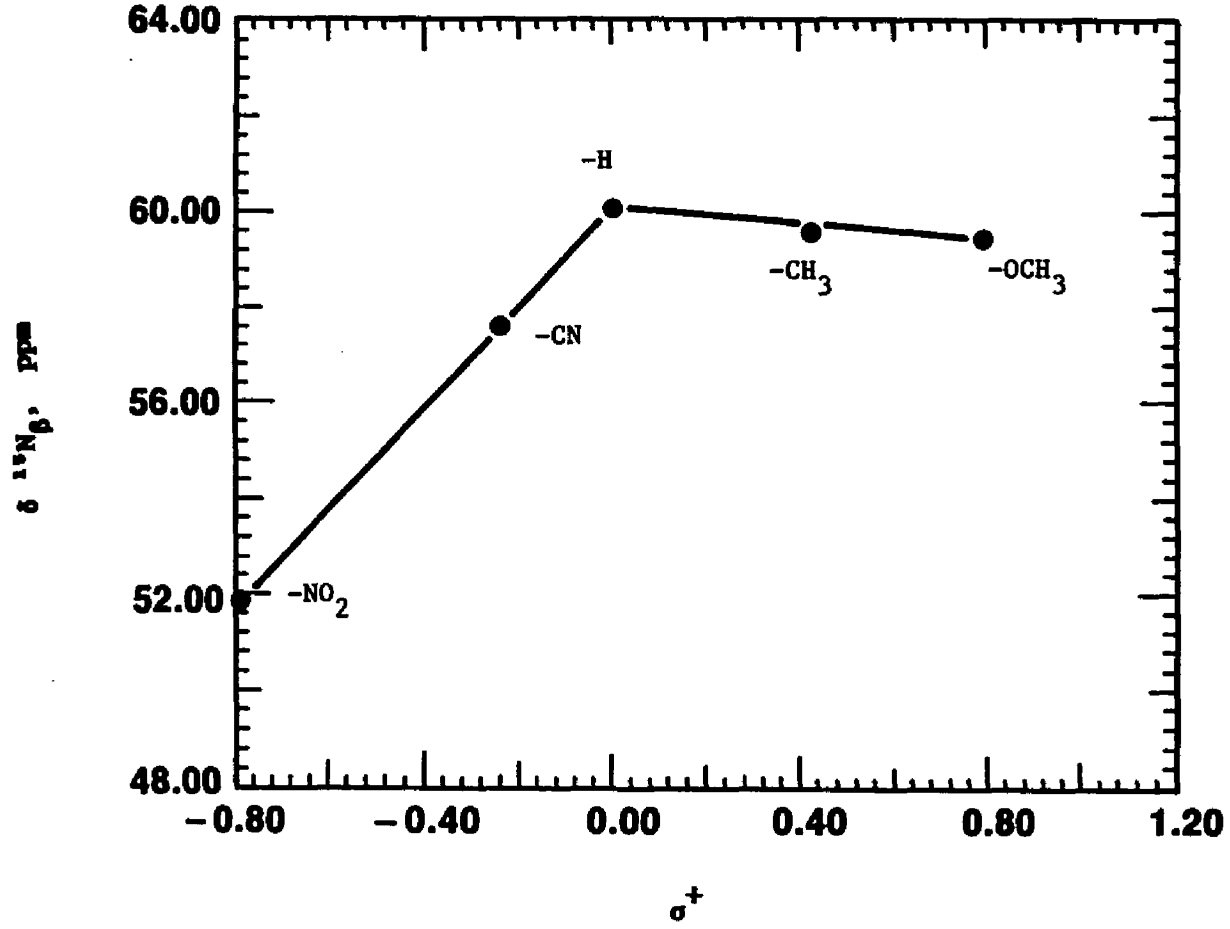


Figure 2.4 Correlation of ^{15}N Chemical Shifts of the Terminal Nitrogen in para-substituted Benzenediazonium Ions With Hammett Substituent Constants

Theoretically, some INDO-SOS-MO calculations of ${}^{1}J_{CN}$ for several para-substituted benzenediazonium ions were carried out by Axenrod et al.[30] The results are summarized in Table II. In terms of the Ramsey formulation[18] for the molecules considered, these data show that the one-bond coupling, ${}^{1}J_{C_1N\alpha}$, is dominated by contributions from the Fermi contact (J_{Fc}) term whereas the combined contributions to the overall coupling from the orbital (J_O) and spin-dipolar (J_D) terms are negligible. In addition, it is apparent that the expected sign of ${}^{1}J_{CN}$ is negative.

From Table II, we see that the agreement between the calculated and experimental data is fairly good. At the INDO-SOS level of approximation, the Fermi contact term depends on the s-electron distribution, while the orbital and dipolar terms are p-electron dependent. If the electron-withdrawing and donating groups largely affect the p-electron distribution rather than that of the s-electron, and the p-electron controlled terms J_O and J_D are not important for these molecules, then the correlation between ${}^{1}J_{CN}$ and the nature of the substituents seems reasonable. However, the empirical relationships (see section 1.3.2) that relate the observed ${}^{1}J_{CN}$ to the hybridization of the orbitals do not apply in this case despite Webb's calculation which shows the dominance of the Fermi contact term. Indeed, the coupling constant ${}^{1}J_{C_1N\alpha}$ changes with the nature of the substituent while the hybridization of two corresponding nuclei, C_1 and Nα, remain the same. But the bond order of C_1-Nα may be different.

Table II. Some INDO-SOS-MO Calculated Contributions to ${}^{1}J_{CN}$ for para-Substituted Benzenediazonium Fluoroborates and Experimental Values [a]

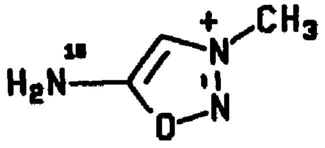
Substituents	J_{FC}	J_O+J_D	J_{Total}[b]	J_{Exp}
$-N(CH_3)_2$	-18.6	0.88	-17.7	17.9
$-OCH_3$	-14.7	0.89	-13.7	14.4
-H	-11.9	0.78	-11.1	10.5
$-NO_2$	-13.5	1.18	-12.3	11.2

---

[a] All the calculations were performed on the PRIME system at University of Surrey, using standard geometries [J.A. Pople and M.S. Gordon, J. Amer. Chem. Soc., 89, 4253 (1967)]. The details of the calculation procedure are described in "Theory of NMR Parameters" by I. Ando and G.A. Webb, Academic Press, London, (1983).

[b] $J_{Total} = J_{Fc} + J_O + J_D$

The uses of $^{1}J_{CN}$ values in structural investigations are numerous. For example, the large value of $^{1}J_{CN}$, 23.5 Hz, found[31] for the exocyclic NH_2 group of N-methylsydnonimine hydrochloride (IV) implies



IV

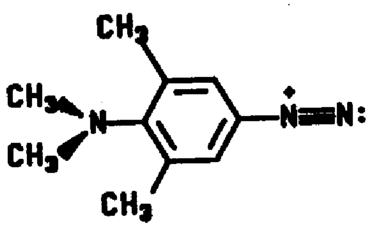
the planarity of NH_2 group and that the nitrogen lone-pair is delocalized into the conjugated system involving the ring π-electrons. A similar situation is reported for 2-phenylamino-2-thiazoline V[32]. The shift of the equilibrium towards the structure Va was suggested by the large $^{1}J_{CN}$ value. (Usually $^{1}J_{CN}$ for C-N single bond is about 9 Hz[33]).

Va

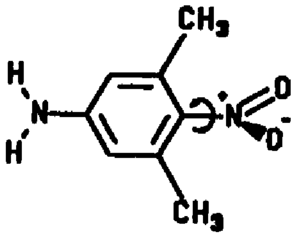
Vb

A consequence of a significant contribution from structures having diazo-character IIIc is the increased C-N bond order as reflected in the magnitude of $^1J_{CN}$. The validity of $^1J_{CN}$ as a probe of the nature of the C_1-Nα bond in benzenediazonium ions has been investigated further by examining the effect of the J_{CN} coupling (strong electron-donating group). The results are summarized in Table III along with comparable data for some model systems.

A large value of $^1J_{CN}$, 20 Hz, was observed for both diazomethane and diazoquinone. In these two molecules, the diazo-type structure IIIc is dominant[14]. The value of $^1J_{CN}$, therefore, may represent the limiting value for contributions from the diazo-type structures, IIIc. This value is very close to that observed in the case of the strong electron-donating substituent, 4-(N,N-dimethylamino)benzene-diazonium ion, 17.9 Hz. In the 3,5-dimethyl derivatives (compounds (4),(6),(7), in Table III), non-bonded interactions of the nitro-oxygens(4) or N,N-dimethyl(6) substituents with the adjacent methyl groups results in a structure with N,N-dimethyl moiety out of the plane of the benzene ring, as shown in VI;



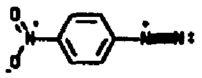
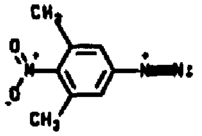
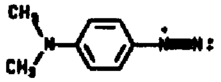
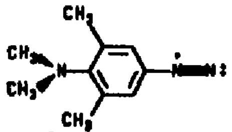
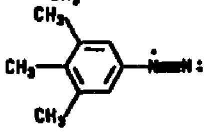
VI



VII

while for aniline VII it has been estimated[35] at 55°. This lack of co-planarity effectively prevents contributions of the type illustrated in structure IIIc, which exists in diazomethane (1) and diazoquinone (2).

Table III. One-Bond ^{13}C-^{15}N Spin-Coupling Constants and ^{13}C-1 Chemical Shifts in Bezenediazonium Fluoroborates and Some Related Model Compounds[a]

Numbers	Compounds	$^{1}J_{NC}$, Hz	δC-1, ppm
1		20.2[b]	
2		20.0	76.2
3		11.2	122.1
4		11.2	118.6
5		17.9	89.4
6		14.7	98.3
7		10.0	115.4

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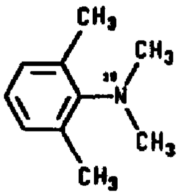
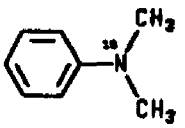
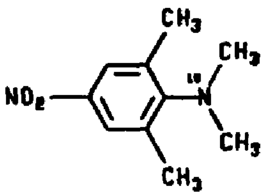
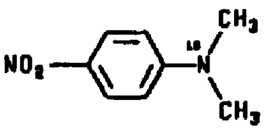
a Measurements were made under the same conditions as described in Table 1. b Data were taken from W. Runge and J. Firl in Z. Naturforsch., 31b, 1515 (1976).

Table IV. Some One-Bond ^{13}C-^{15}N Spin-Coupling Constants for N,N-dimethylanilines-^{15}N [a]

Compounds	$^{1}J_{CN}$, Hz
	14.2
	15.6
	12.9
	13.2

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[a] Data were taken from T. Axenrod et. al[36]. Samples were measured as 1M solutions in DMSO-d_6.

Table IV shows the ${}^{1}J_{CN}$ values for some 4-(N,N-dimethyl) anilines-^{15}N obtained previously in our laboratory[36]. The coupling constants, ${}^{1}J_{CN}$, in these molecules are also affected by the steric interactions of 3,5-dimethyl substituents in a manner similar to that observed in benzenediazonium ions.

From the data shown in Table III, the addition of two methyl groups in the 3,5- positions of the para-nitrobenzenediazonium ion(3) does not change the coupling constant ${}^{1}J_{CN}$, whereas a reduction in ${}^{1}J_{CN}$ of 3.2 Hz is observed for 3,5-dimethyl-4-(N,N-dimethyl-amino) benzenediazonium ion(6) as a result of the steric hindrance. From this it is concluded that there is little, if any, double bond character in the C_1-Nα bond, reflecting the absence of interaction between the 4-nitro group and the strongly electron-withdrawing diazonium group. On the other hand, the electron-donating dimethylamino group interacts substantially with the diazonium group. Moreover, when the dimethylamino group is distorted, as shown in <u>VI</u>, from the conformation necessary for optimum lone-pair π interaction, the C-1 resonance is shifted downfield by 9 ppm, whereas twisting of the nitro group causes a small 3.5 ppm upfield shift in the C-1 resonance.

2.2 Solvent Effects in Benzenediazonium Fluoroborates

The investigation of the interaction between benzenediazonium fluoroborate and polar aprotic solvents is described in this section. ^{13}C and ^{15}N NMR spectra of double-^{15}N-labeled benzenediazonium

Table V. Some One-Bond ^{13}C-^{15}N and ^{15}N-^{15}N Coupling Constants and $^{13}C_1$ $^{15}N\beta$ Chemical Shifts for Benzenediazonium Fluoroborate in Polar Aprotic Solvents with Different Donor Numbers[a]

Solvents	δC_1 [b]	$\delta N\beta$ [c]	$^1J_{CN}$	$^1J_{NN}$	DN [d]
Hexamethylphosphoramide	117.3	230.98	10.8	1.1	36.8
Dimethylsulfoxide	116.2	231.44	10.6	e	29.8
Dimethylformamide	116.4	231.43	10.5	1.3	26.6
Acetone	115.9	231.61	9.9	1.6	17.0
Acetonitrile	115.3	231.69	9.7	1.7	14.1
Nitromethane	114.0	231.74	9.1	2.1	2.7

[a] Measurements made at 5 °C using 0.20M solution and 2% deuteriobenzene for lock signal.

[b] Chemical shifts were measured with respect to deuteriobenzene (128.0ppm) and reported relative to TMS.

[c] Measured with respect to NH_4Cl (26.8ppm) and are reported relative to NH_3.

[d] DN values are from Gutmann[39]

[e] The signal was too broad to measure coupling.

fluoroborate in six solvents were examined. The chemical shifts of C_1 and the coupling constants $^1J_{CN}$ and $^1J_{NN}$ are listed in Table V. In general, the effects of solvents on the coupling constants (1.0 Hz in $^1J_{NN}$ and 1.7 Hz in $^1J_{CN}$) and chemical shift (3.3 ppm in C-1) are not too large. The results agree with the observation that only a small N-N stretching frequency change results with solvent variation[37] in IR spectrum of benzenediazonium chlorides.

Similar to predicting donor-aceptor (Lewis acid-base definition) reaction, donor numbers (DN) were developed to correlate the behavior of a solute (such as its solubility, redox potential or degree of ionization) in a variety of solvents with a given solvent's coordinating ability, i.e., its basicity or donicity. Donor number (DN) is also used to characterize a solvent's ability to donate electron density to an electron deficient center[38]. A relative measure of the basicity of solvent D is given by the enthalphy of its reaction with an arbitrarily chosen reference acid. For Gutmann's[39] scale, the reference acid is $SbCl_5$, and the negative heat of reaction of a dilute solution of the solvent and of $SbCl_5$ in 1,2-dichloroethane is called the donor number (DN) or donicity of the solvent. It was assumed (and graphically tested by plotting logK of D-$SbCl_5$ reaction vs DN) that entropy effects are constant and that 1:1 adducts are formed. Then the DN is a reflection of the inherent D-$SbCl_5$ bond strength. Therefore, the greater the DN, the more electron density is shifted from the solvent to the solute species and the easier it is to remove an electron from the solute. DN values have been measured for about 53 donor solvents by Gutmann[39]. Selected donor solvents with DN values are listed in Table V.

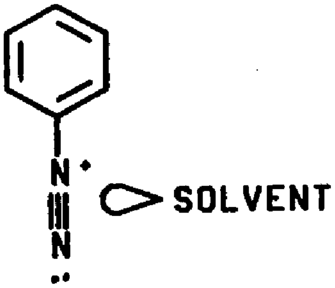
When we examine the data in Table V, it is quite interesting to note that the C_1 chemical shifts and coupling constants, $^1J_{CN}$ and $^1J_{NN}$, can be correlated with the solvent donor capacities, DN. (see Figure 2.5-2.7):

$$^1J_{CN} = 0.0498\ \mathrm{DN} + 9.0 \qquad \text{corr.coeff.} = 0.985 \qquad (2.3)$$

$$^1J_{NN} = 0.0281\ \mathrm{DN} + 2.1 \qquad \text{corr.coeff.} = 0.987 \qquad (2.4)$$

$$\delta C_1 = 0.084\ \mathrm{DN} + 114.0 \qquad \text{corr.coeff.} = 0.976 \qquad (2.5)$$

With an increase in DN of the solvent, the resonance of the terminal nitrogen (Nβ) shifts upfield and the resonance of the C_1 shifts downfield. These correlations indicate some type of Lewis acid interaction between the diazonium cation and the solvents, as depicted in VIII:



VIII

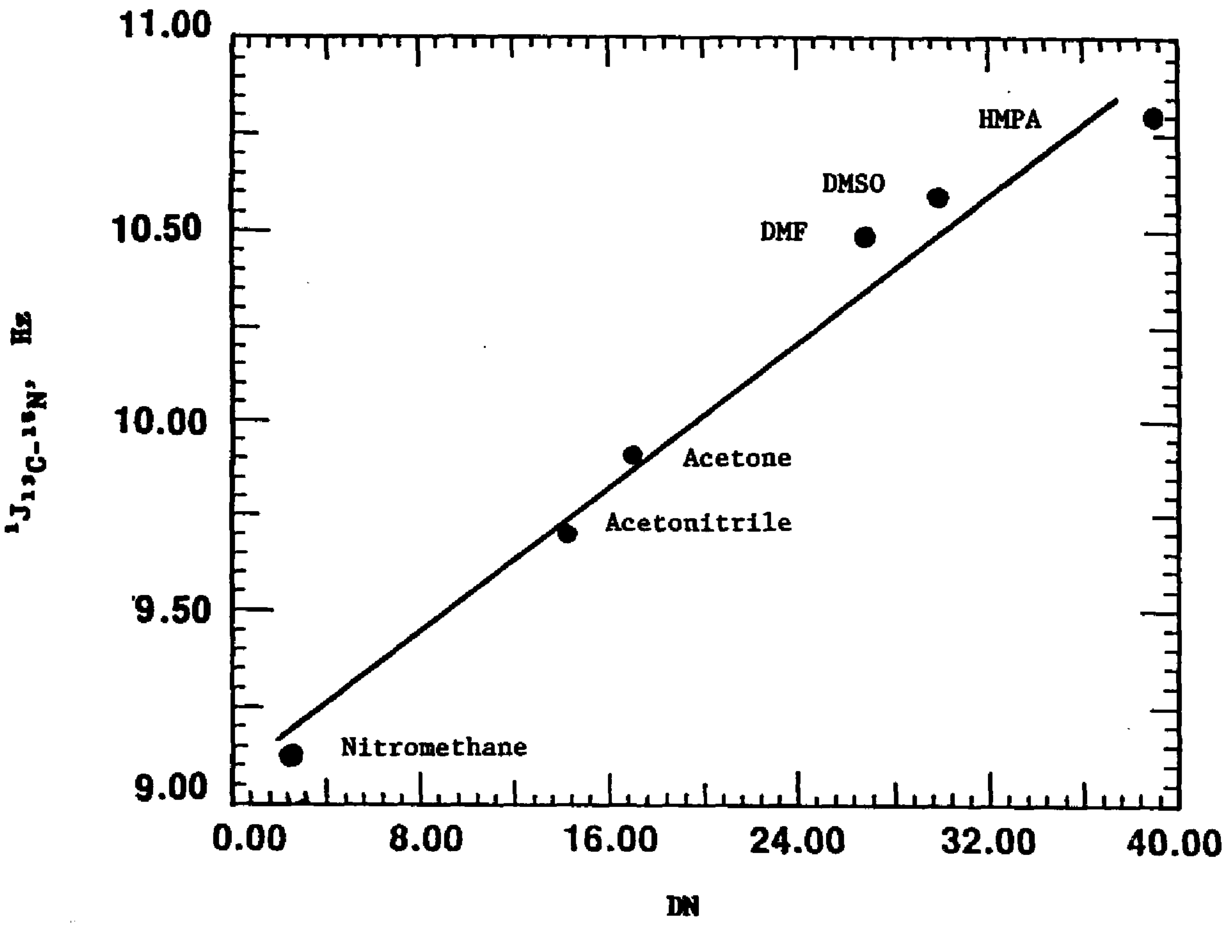


Figure 2.5 Correlation of One-Bond $^{13}C-^{15}N$ Coupling Constants in Benzenediazonium Ions With the Solvent Donor Numbers

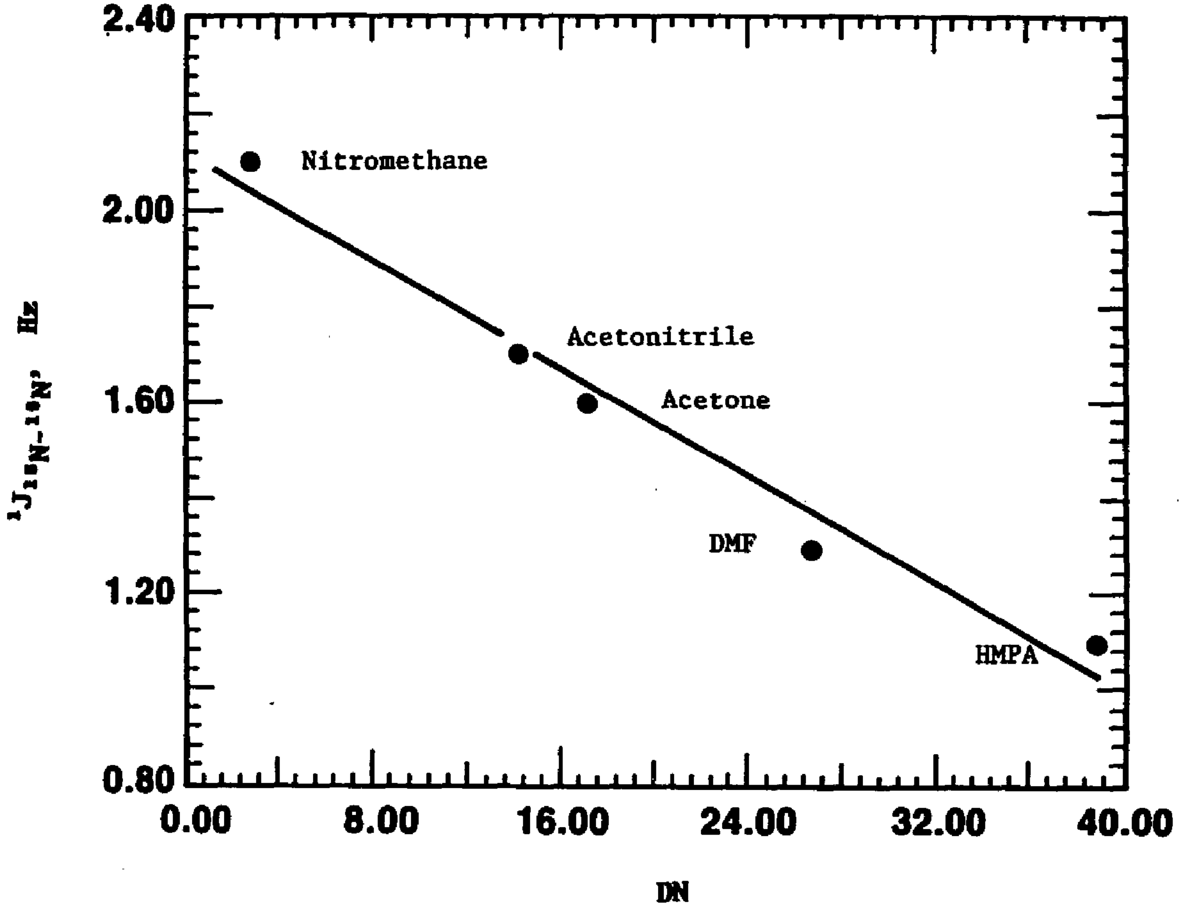


Figure 2.6 Correlation of the One-Bond ^{15}N-^{15}N Coupling Constants in Benzenediazonium Ions With the Solvent Donor Numbers

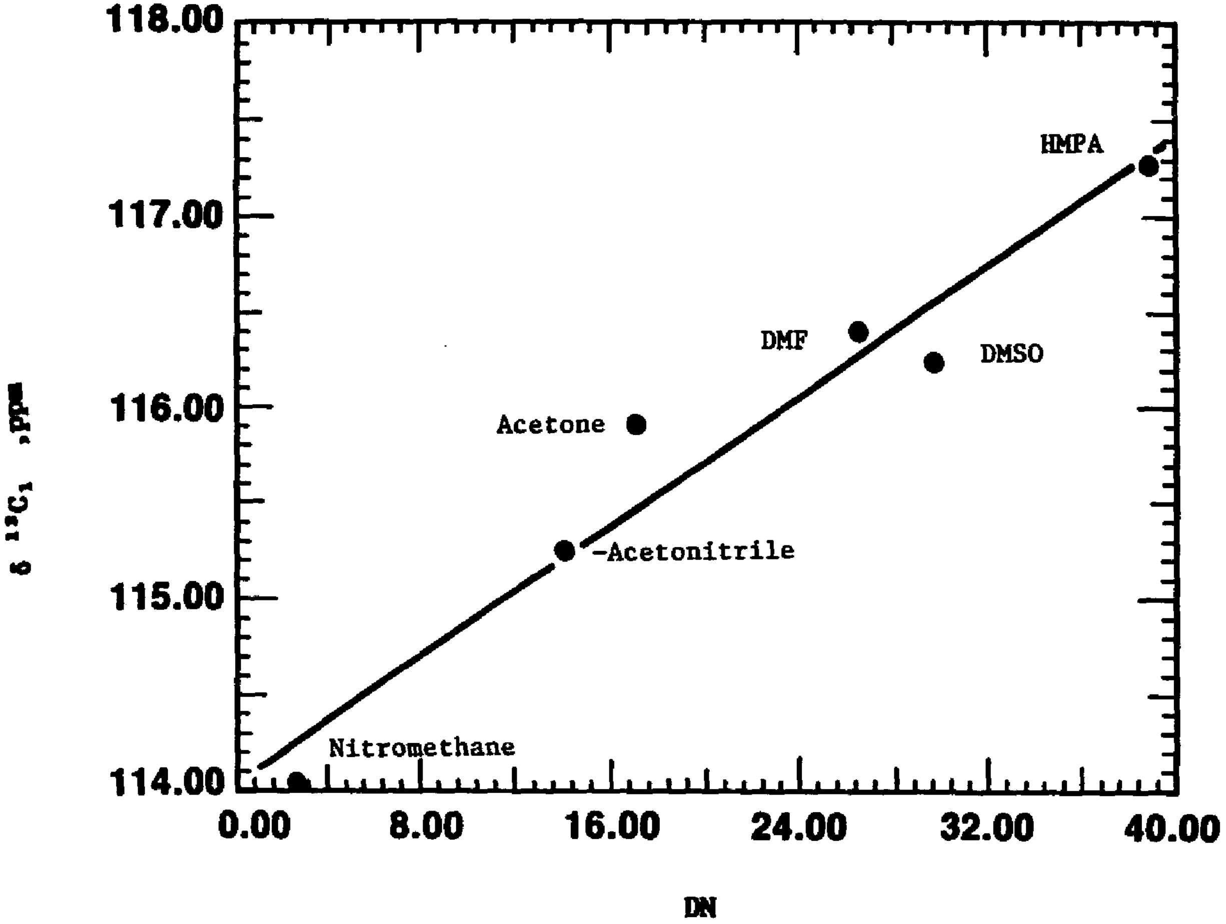


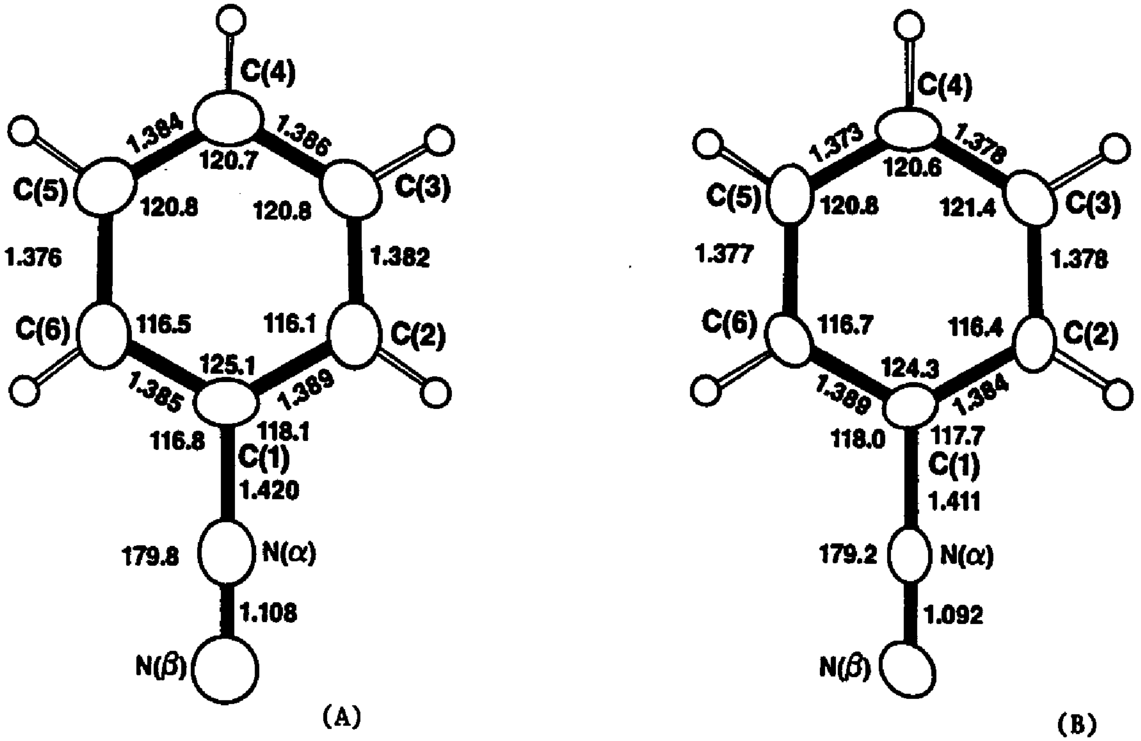
Figure 2.7 Correlation of the $^{13}C_1$ Chemical Shifts in Benzenediazonium Ions With the Solvent Donor Numbers

The downfield shift of C_1 is a reasonable consequence of a resonance interaction of C_1 with the diazonium group because part of the positive charge may be transferred to the solvent[40]. The interaction results in a reduction of electron delocalization in the system and the C_1 $N\alpha$ bond is rendered more like a single bond. Thus, it is suggested that the diazonium type structure is enhanced in solvents with larger DN values.

It is not too surprising that neither the chemical shift nor the coupling constant correlates with the dielectric constant, ε, although a good relation was found between $^1J_{CN}$ and ε in both isocyanides and cyanides[41]. This is because the electron transferring between the diazonium cation and the solvent is more important than the ionization effect.[40]

2.3 Crown Ether-Benzenediazonium Cation Complexation Effects

Since the original observation that benzenediazonium fluoroborates are solubilized[43] and stabilized[44,45] by crown ethers in nonpolar solutions, the nature of the stabilization has been of considerable interest. The proton NMR investigation by Gokel and Cram[43] provided the first evidence for solubilization and complexation of the benzenediazonium salt by crown ethers in chlorocarbon solvents. Within two years, Haymore, Ibers and Meek reported the isolation of the benzenediazonium-salt-crown-ether complex[46]. Correct elemental composition of a 1:1 complex of benzenediazonium hexafluorophosphate has been determined recently by low-temperature X-ray diffraction[47].



(A)

(B)

Figure 2.8 Structure of Uncomplexed(A) and 18-crown-6 Ether Compelexed(B) Benzenediazonium Ions

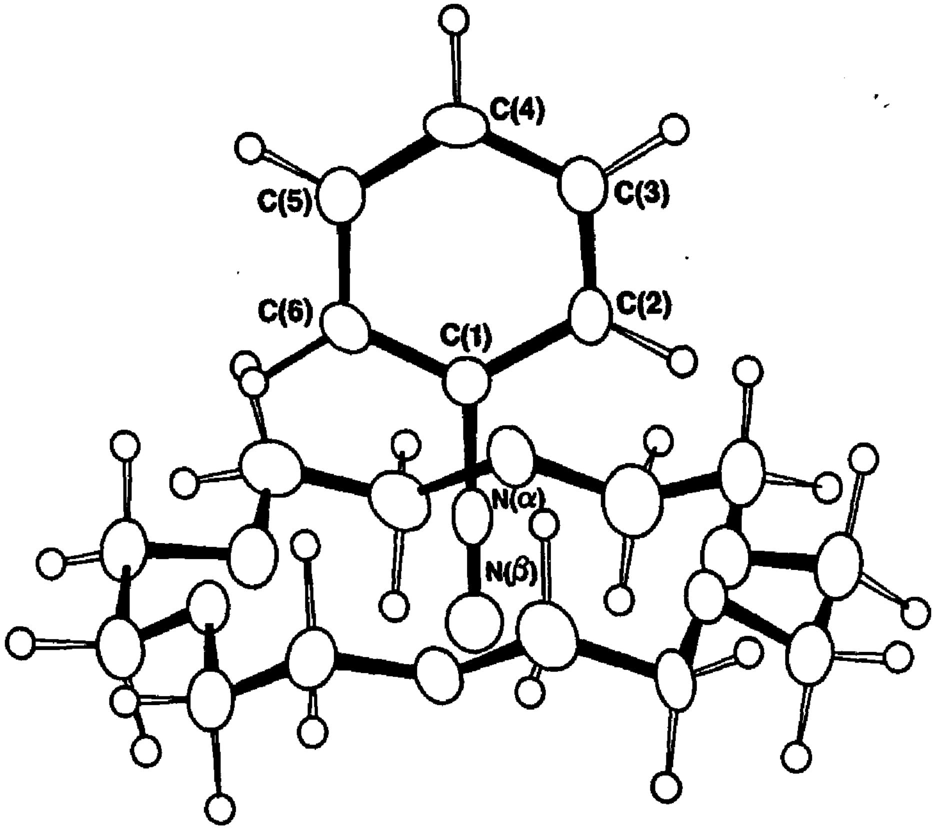


Figure 2.9 Structure of the Complex of Benzenediazonium Hexafluorophosphate with 18-crown-6 Ether

The three dimensional structure, Figures 2.8 and 2.9, shows that complexation involves insertion of the diazonium group into the crown ether cavity. The approximate plane formed by the crown ether oxygens roughly bisects the Nα-Nβ bond. Further insertion is prevented by steric repulsions between the ortho hydrogens of the benzenediazonium ion and methylene hydrogens of the crown ether ring. In this section we present a full investigation of the influence of crown ether complexation on the δC_1, $^1J_{CN}$ and $^1J_{NN}$ values of benezenediazonium ions. The chemical shifts and coupling constants of a series of benzenediazonium fluoroborates were measured in the presence of crown ethers.

2.3.1 Crown Ether Complexation Effects on para-Substituted Benzenediazonium Ions

The chemical shifts C_1 and coupling constants $^1J_{C_1N\alpha}$ of para-substituted benzenediazonium fluoroborates in the presence of 5.0 equivalents of 18-crown-6 are listed in Table VI. Five equivalents of crown ether is sufficient to fully complex the diazonium cation[48]. Indeed, ^{13}C NMR spectra of benzenediazonium fluoroborate with an excess of 18-crown-6 ether (up to 10 equivalents) have been measured and no difference has been found after more than three equivalents of 18-crown-6 ether was added. The influence of crown ether on the chemical shifts and coupling constants is substantial: C_1 shifts downfield, with a maximum of 4.8 ppm for the 4-(N-N-dimethyl)amino substituent, and $^1J_{CN}$ increases to 2.4 Hz for the 4-(N,N,N-trimethyl)-ammonium substituent. However, the determination of $^1J_{NN}$ becomes very

Table VI. $^{13}C_1$ Chemical Shifts and One-Bond ^{13}C-^{15}N Coupling Constants for para-Substituted Benzenediazonium Fluoroborates in the Presence of 5.0 Equivalents of 18-crown-6 Ether[a]

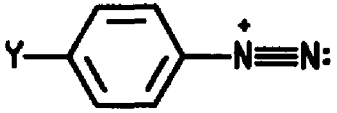
Substituent	δC-1,ppm	$^1J_{CN}$,Hz	J_{NN},Hz
$-N(CH_3)_2$	95.1	18.4	0.5
-OH	104.4	16.0	1.2
$-OCH_3$	106.6	15.7	1.3
$-CH_3$	113.8	13.3	1.7
-H	117.5	12.3	1.8
-Cl	116.2	14.1	2.0
-Br	115.7	14.2	2.1
-COOH	120.8	12.4	2.0
$-NO_2$	122.6	13.3	2.1
$-N(CH_3)_3^+$	119.7	13.3	2.4

---

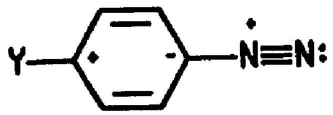
[a] All measurements were made at 5 °C using 0.2M solution in dimethylformamide containing five equivalents of 18-crown-6 ether.

difficult in the presence of crown ether, since $^1J_{NN}$ is smaller and the signal is broader than in the absence of crown ether.

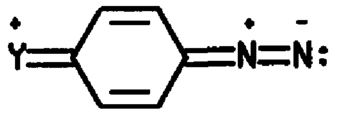
The C_1 chemical shift changes may be rationalized on the basis of the resonance theory argument[26]. The resonance hybrid for the benzenediazonium cation is comprised of contributions from the diazonium and diazo resonance forms (IIIa to IIIc). In the presence of crown ether, the contribution of the diazonium resonance form IIIa to the hybrid should be enhanced by interactions of the crown ether with the localized positive charge. Therefore, crown ether complexation should increase the amount of positive charge on the diazonium group and reduce the positive charge on the ortho- and para-carbons due to the decrease in charge dispersions by resonance.



IIIa



IIIb



IIIc

According to this, C_1 should be deshielded due to the increased positive charge on the diazonium group and should be shifted downfield. These predictions are in agreement with the experimental observations. The downfield chemical shift for C_1 caused by crown ether complexation is also consistent with the results of CNDO/2 molecular orbital calculations[49] that indicate the amount of positive charge on C_1 will increase in crown-ether-complex. Moreover, other spectroscopic measurements also fully support this rationalization. Infrared spectra[51] exhibit an increase in N-N character upon crown ether complexation indicating that the Nα-Nβ bond order of the diazonium ion is increased. Ultraviolet spectra reported by Bartsch and coworkers[40] show the shifting of the ultraviolet absorption maximum for benzenediazonium ion to shorter wavelengths in the presence of appropriate crown ethers.

These all lead to the view that crown ether complexation causes a localization of the π electron system of benzenediazonium ions. ^{15}N NMR chemical shift measurements for the two nitrogen atoms of benzenediazonium ions in the presence of 18-crown-6 ether[29] show an upfield shift for Nα and smaller downfield shift for Nβ. These results provide the evidence for an increase in the positive charge density on Nα with a concomitant decrease of positive charge on Nβ, resulting in more single bond character in the C_1-Nα bond.

It is interesting to note that the difference in one-bond C_1-Nα coupling constants ($^1J_{CN}$) in the presence and in the absence of 18-crown-6 ether for para-substituted benzenediazonium ions correlate with the Hammett substituent constant, σ, (see Figure 2.10) as follows:

$$^1J_{CN} = 0.68\sigma + 1.8 \qquad \text{corr. coeff.} = 0.973 \qquad (2.11)$$

This correlation implies a quantitative relationship between the crown ether complexation and the nature of the substitutents. A similar correlation has been reported by Izatt and his co-workers[50] by using a titration calorimetry method, in which logK is linear with the Hammett substituent constant, with $\rho = 0.65$.

$$\text{Log K} = 0.65\sigma + 2.52 \qquad (2.12)$$

Izatt's study shows that the extent of complexation was found to be highest for the 4-nitro substituent, an order of magnitude greater than that for the 4-methoxyl substituent. Therefore, the smaller influence of 18-crown-6 on $^1J_{CN}$ couplings for benzenediazonium ions bearing more electron-donating substituents, for example, 4-(N,N-dimethylamino) ($^1J_{CN}$ = 0.5 Hz), may arise from a lesser proportion of the benzene-

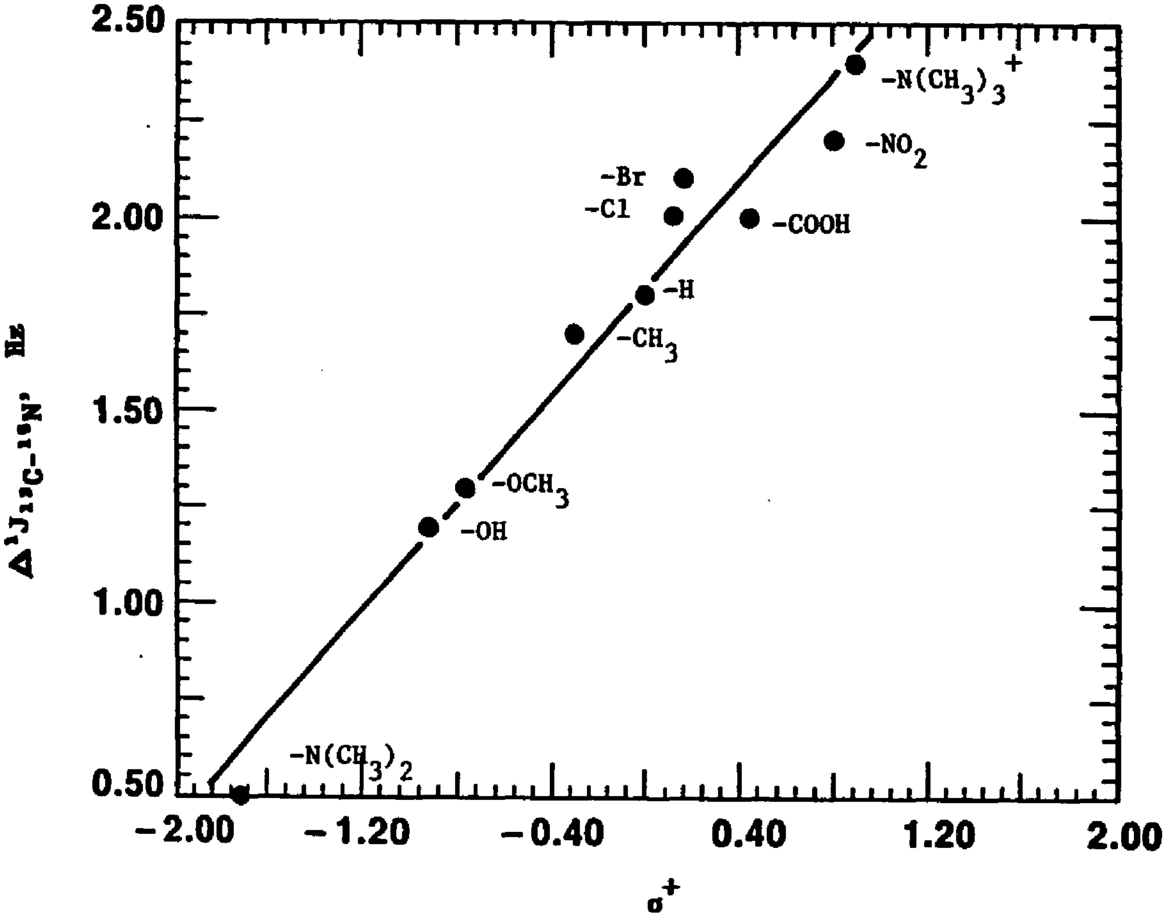


Figure 2.10 Correlation of Changes in ^{13}C-^{15}N One-Bond Coupling Constants With Hammett Substituent Constants for para-substituted Benzenediazonium Ions in the Presence of 18-Crown-6 Ether

diazonium salt being converted into the crown ether complexed form. The stronger electron-withdrawing substituent, 4-(N,N,N-trimethyl) ammonium-group, may have the strongest complexed form (with a largest Log K value), and in turn the largest coupling constant, ${}^1J_{CN}$ = 2.4 Hz.

2.3.2 Effect of Crown Ether Cavity Size

Limited information regarding the relationship between the cavity size of the crown ether and its ability to complex a benzenediazonium ion is provided by the solubilization studies of Gokel and Cram[43] and the kinetic study of Bartch and Juri[52]. These results suggest that a crown ether cavity size of approximately 2.7Å should be optimal because the estimated diameter of the benzenediazonium ion is 2.4Å[53]. The approximate cavity sizes for different crown ethers reported in the literature[52,53] are given in Table VII. The NMR spectroscopic studies in our laboratory provided additional evidence that the cavity size of crown ether affects the complexation as reflected by the magnitude of ${}^1J_{CN}$. The measured values of ${}^1J_{CN}$ in the presence of different crown ethers are listed in Table VIII. Neither 12-crown-4 nor 15-crown-5 ether measureably changes the magnitude of ${}^1J_{CN}$ from that observed in the absence of any complexing agent. These crown ethers' cavities apparently are too small to accommodate the diazonium group. For 18-crown-6 ether, there is a good match between the size of the diazonium group and that of the crown ether cavity. Thus, the largest change in coupling, ${}^1J_{CN}$ = 2.0 Hz, results. With 21-crown-7 ether, the change in ${}^1J_{CN}$ is smaller than in 18-crown-6 ether, although other

Table VII. Estimated Cavity Diameters for Different Crown Ethers[52]

Crown Ether	Cavity Diameter, Å
12-crown-4	1.2 - 1.5
15-crown-5	1.7 - 2.5
18-crown-6	2.6 - 3.2
21-crown-7	3.4 - 4.3

Table VIII. $^{13}C_1$ Chemical Shifts, ^{13}C-^{15}N and ^{15}N-^{15}N Coupling Constants for Benzenediazonium Fluoroborates in the Presence of Different Crown Ethers[a]

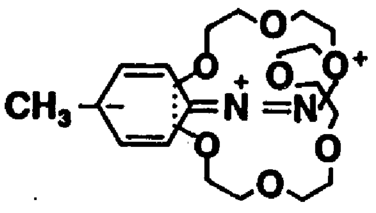
Crown ether(equiv.)	δC-1,ppm	$^1J_{CN}$,Hz	$^1J_{NN}$,Hz
none	116.4	10.5	1.3
	115.3	9.7	1.7[b]
12-crown-4 (4)	115.3	9.7	1.6[b]
15-crown-5 (1)	116.2	10.4	1.3
15-crown-5 (4)	116.2	10.4	1.3
16-crown-6 (1)	117.3	11.8	1.0
16-crown-6 (4)	117.5	12.3	c
21-crown-7 (1)	117.0	11.0	1.2[b]
21-crown-7 (4)	117.0	11.1	1.0[b]
	116.6	11.0	1.0
24-crown-8 (1)	116.1	10.4	1.3
24-crown-8 (4)	116.0	10.6	1.3

[a] All measurements were made at 5°C in 0.20M N,N-dimethylformamide solution containing 2% deuteriobenzene.

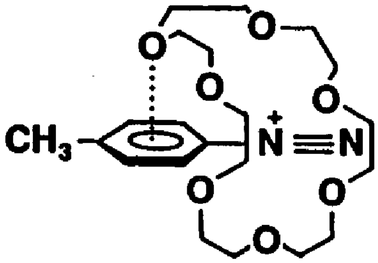
[b] Measurements were made at 5°C in 0.20M acetonitrile solution.

[c] Broad signals precluded the measurement of the coupling constant.

studies suggest that 21-crown-7 ether involves stronger complexation of the benzenediazonium cation.[52,55] Two possible models for the complex (IX and X) have been considered to explain the unusual behavior of 21-crown-7 ether.[55]



IX



X

Instead of completely and tightly surrounding the diazonium group, the crown ether nearly encircles the diazonium group and then uses the remaining donor atom either to solvate the terminal nitrogen atom IX or to interact as a base with the π-acidic aromatic ring X, providing additional stability. The mode by which 18-crown-6 ether solvates the diazonium ion may differ from that of 21-crown-7 ether. It is not possible without evidence to validate any one mode of stabilization of the complex as unique for a particular crown ether. We believe that the greater stabilization of benzenediazonium cation by 21-crown-7 ether compared to that provided by the smaller crown ether is probably due to a combination of (a) α-nitrogen solvation and (b) stabilization of either the electron deficient aromatic ring or the α-nitrogen at the same time by Lewis base donation from the crown oxygens used in collaring the Nα-Nβ group.

Although kinetic studies[52] show that the thermolysis rates of the diazonium salts in 18-crown-6 and 24-crown-8 ethers are about the same,

${}^1J_{CN}$ in the benzenediazonium ion with 18-crown-6 ether is larger than with 24-crown-8 ether. Further, the coupling constant in the presence of 24-crown-8 ether is essentially the same as the uncomplexed diazonium ion. It appears that the cavity of 24-crown-8 is too large for efficient complex formation with the diazonium group, and the greater ring flexibility may allow for relief of steric interactions between the orthohydrogens of the diazonium cation and the macrocyclic ring.

2.3.3 Effect of ortho-Substituents on Crown Ether-Benzenediazonium Ion Complexation

To test for steric interference due to the presence of substituent groups in the ortho positions, the chemical shift of C_1 and coupling constant, ${}^1J_{C_1N\alpha}$, of several ortho-substitued benzenediazonium ions in presence of 5.0 equivalents 18-crown-6 ether were studied. The results are listed in Table IX. The NMR spectral data from this study show that the complexation between 18-crown-6 ether and the various benzenediazonium ions is strongly dependent not only on the electronic effects (see section 2.2.1), but also on the steric effects. With ortho substituents, the presence of 18-crown-6 ether has no effect on either the C_1 chemical shift or the C-N coupling constant. This observation indicates that the chemical shift and coupling constant in the 18-crown-6 complex of benzenediazonium cation are very sensitive to steric interference from substituents in the ortho positions. This leads to the conclusion that bulky substituents in the ortho positions limit the collaring of the diazonium group and have a great

Table IX. $^{13}C_1$ Chemical Shifts and ^{13}C-^{15}N Coupling Constants for Some ortho-Substituted Benzenediazonium Fluoroborates in the Presence and Absence of 18-crown-6 Ether[a]

Substituents	- 18-Crown-6 Ether		+ 18-Crown-6 Ether	
	δC-1,ppm	$^1J_{CN}$, Hz	δC-1,ppm	$^1J_{CN}$, Hz
2,4,6-$(Br)_3$	120.6	19.8	120.6	19.9
2,4,6-$(CH_3)_3$	111.6	10.4	111.8	10.6
2-Br	118.8	14.5	118.8	14.7
2-Cl-4-NO_2	122.7	15.6	122.3	15.9

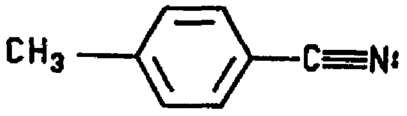
[a] All measurements were made at 5°C in 0.2M dimethylformamide solutions containing five equivalents of 18-crown-6 ether.

destablizing effect on the diazonium-crown-ether complex. This conclusion is also consistent with the prediction from steric consideration by Izatt et al[58] .

Several unsuccessful attempts were made to detect crown ether complexation of other species by NMR spectroscopy. Spectroscopic and chemical studies of diazoquinone XI and XII[34]

XI XII

indicate that resonance structure XI makes an important contribution to the ground state of the molecule. The possibility that diazonium-like nitrogen might be complexed by 18-crown-6 ether was negated by the ^{13}C and ^{15}N NMR measurements. The C_1-Nα and Nα-Nβ coupling constants for diazoquinone in dimethylsulfoxide (0.2M solution) were unaffected by the addition of five equivalents of 18-crown-6 ether. Similarly addition of up to five equivalents of 18-crown-6 ether to 0.25M solution of ^{15}N-labeled para-toluenenitrile XIII in chloroform did not show any evidence of complexation as indicated by the absence of a change in $^1J_{CN}$.



XIII

CONCLUSIONS:

The proton-proton and proton-carbon coupling constants have been been shown to be useful in the structure elucidation of organic compounds. In contrast, carbon-nitrogen and nitrogen-nitrogen coupling constants, which may provide more structure information in the molecules containing nitrogens, are less extensively employed and understood. The present dissertation lends support for the usefulness of carbon-nitrogen and nitrogen-nitrogen coupling constants in the evaluation of the bond order and the structure of the compound. Several conclusions and useful comparisons may be drawn from this dissertation study. First, the influences of aromatic ring-substituents, solvents and specific complexing agents such as crown ethers on the electronic structure and bonding in benzenediazonium ions have been examined. The values of J_{CN} and J_{NN} offered substantial information on the C_1-Nα bond order and the electronic structure in benzenediazonium ions. It is concluded that:

(1) Electron-donating groups on the benzenediazonium ions enhance the diazo-type structure and increase the bond order of C_1-Nα from single to double bond character.

(2) Solvents with large donor numbers enhance the diazonium-type structure for the benzenediazonium ions.

(3) Complexation of benzenediazonium ions with crown ethers cause an increase in the single bond character of C_1-Nα. Also, the bulky ortho-substituents tend to destabilize the crown ether complex. Therefore, the C_1-Nα bond order is not affacted by the complexation with the crown ether in the case of the ortho-substituted benzenediazonium ions.

CHAPTER 3 NMR STUDY OF THE CONFORMATIONAL STRUCTURE OF SOME HYDRAZINE DERIVATIVES

3.1 Theoretical Considerations

Comparison of $^1J_{NN}$, nuclear spin-spin coupling constants between directly bonded nitrogens has received little theroetical and experimental attention[56]. It is generally recognized[57] that both the sign and magnitude of nuclear spin coupling constants involving nitrogen are effected by the orientation of the lone-pair of electrons as well as other structural parameters.

Schulman.[59,60] extended the theoretical studies of the one-bond carbon-nitrogen spin-spin coupling constants[58] to nitrogen-nitrogen systems using a suitable molecule. Using hydrazine as a reference system, the effects of pyrimidization and protonation of one or both nitrogens and dihedral angle variation on $^1J_{NN}$ were calculated. They predicted a strong dihedral angle dependence of the coupling leading to the possibility of both positive and negative $^1J_{NN}$ values depending on conformation.

The structural aspects of hydrazine and its derivatives have been studied by a variety of techniques and much is known about the molecular geometry in these systems[61]. Depending on the nature of the substitution on nitrogen, hydrazine derivatives may be divided into three groups illustrated in Figure 3.1: bipyramidal <u>XIV</u>, where, as in the case of alkyl derivatives, the nitrogens are nearly tetrahedral;

XIV

XV

XVI

Figure 3.1 Three Conformations of Hydrazines

pyramidal-planar XV, where conjugation of the lone-pair on one nitrogen with an adjacent π system deforms its configuration towards a planar one; and biplanar XVI, where both nitrogen atoms are substantially flattened as a result of attachment of mesomerically electron-withdrawing groups.

The principal interaction determining the conformation in hydrazines is the adjacent lone-pair-lone-pair interaction which is strongly dependent on the dihedral angle, ϕ , between the lone-pairs. In the Schulman's incisive theoretical examination of ^{15}N-^{15}N spin coupling in model hydrazines, several intriguing but yet untested conclusions have been reached. In all cases considered, the overall coupling mechanism is found to be dominated by the Fermi contact term. Also, depending on the degree of pyramidization at the nitrogens, a strong dependence of the $^{1}J_{NN}$ values on the dihedral angle ϕ is predicted. For the bipyramidal configuration XV, where there are two s-hybridized lone-pairs, calculations indicate a reversal in the sign of coupling as a function of the dihedral angle with J_{NN} varying from -10.8 to +12.7 Hz as ϕ changes from 0 to 180°. This is illustrated graphically in Figure 3.2.

To evaluate these theoretical predictions, the determination of $^{1}J_{NN}$ in several specifically designed ^{15}N-labelled compounds was undertaken.

3.2 Present Investigation

In the experimental plan, several double ^{15}N-labelled, angle-constrained hydrazines including acyclic, cyclic and bicyclic

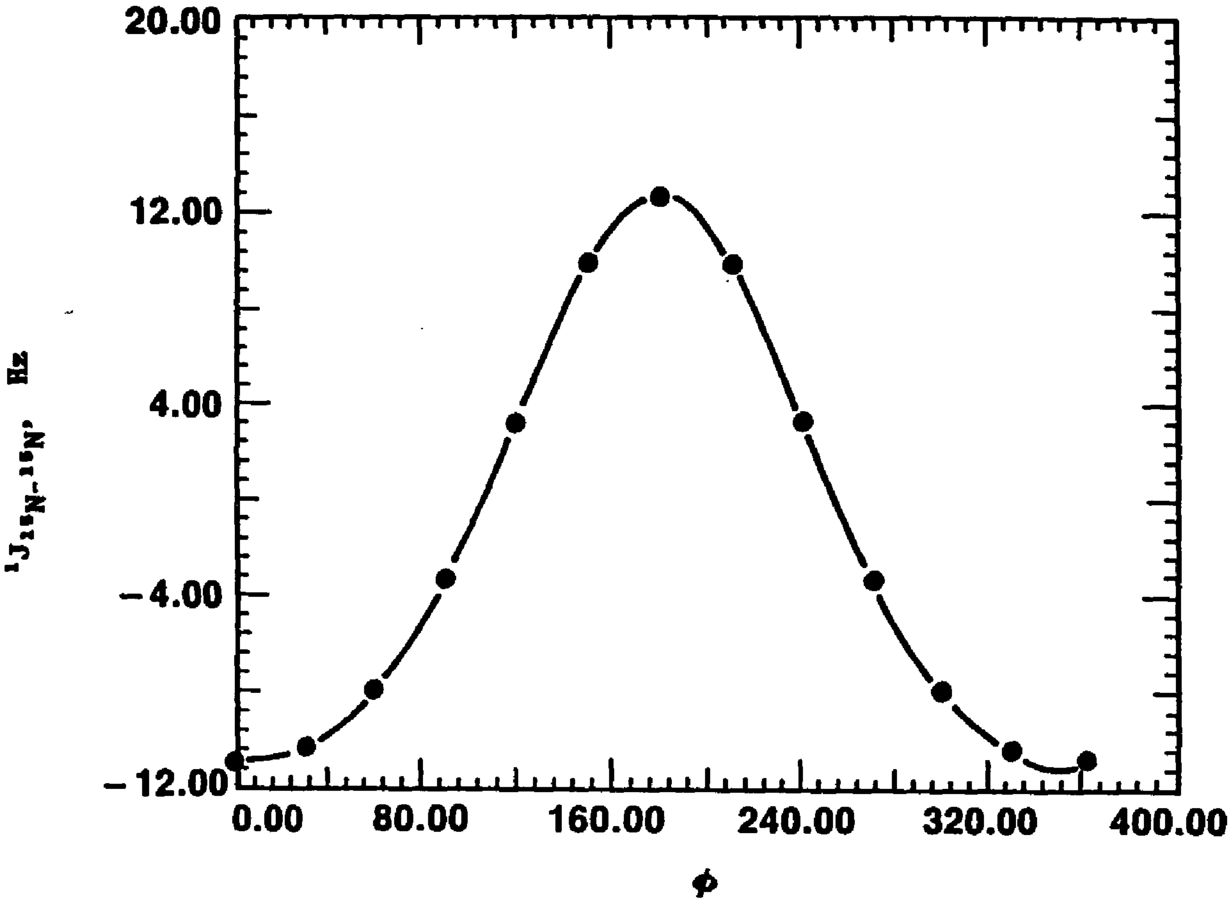
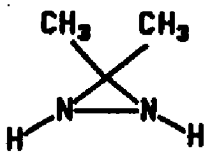


Figure 3.2 One-Bond ^{15}N-^{15}N Coupling Constants of Hydrazine as a Function of Dihedral Angle between Nitrogen Lone-pair Electrons

hydrazines were chosen to be investigated. The lone-pair dihedral angles are resonablly well-known for these compounds from other studies and cover a range of ϕ values from 0 to 180°.

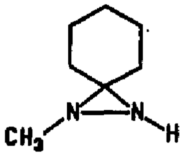
Simple acyclic hydrazines are essentially bipyramidal and electronically prefer and exist in $\phi=90°$ conformation. Support for this conformation comes from ab initio calculations[62], infrared[63], microwave[64] and photoelectron[65],[66] spectroscopies. The activation energy of conformation interchange for alkyl hydrazine also indicates a relatively stable conformation at ~ 90°.[66] Thus, N,N-dibenzylhydrazine was chosen since alkyl substitution in acyclic hydrazines appears to have only a negligible effect on ϕ suggesting that N,N-dibenzyl -hydrazine-^{15}N may also represent the $\phi=90°$ situation.

Diaziridines are small ring cyclic hydrazine compounds with severe ring strain. This steric strain forces the lone-pair electrons to exist with a dihedral angle different from 90°. From the photoelectron spectrum of 1,2-dimethyl diaziridine XVII, Rademacher and Koopmann[67] have estimated the dihedral angle between two lone-pairs to be 102°.

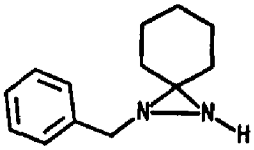


XVII

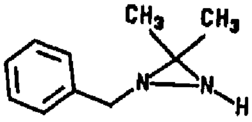
The chemical equivalence of the nitrogens in this compound precluded the observation of the $^{1}J_{NN}$ value. Three unsymmetrical diaziridines XVIII, XIX, XX were prepared and the coupling constants were measured.



XVIII

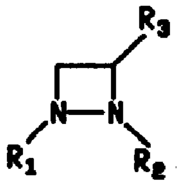


XIX



XX

Diazetidines are four member ring cyclic hydrazines which have structures similar to diaziridines. Based on photoelectron spectra, Rademacher and Koopmann[67] predicted a conformation with a dihedral angle of 154° between the nitrogen lone-pair orbitals for 1,2-dimethyl 1,2-diazetidine XXI. In this conformation both methyl groups occupy a quasi-equatorial position.

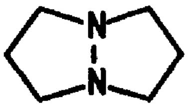


XXI $R_1 = R_2 = CH_3$, $R_3 = H$

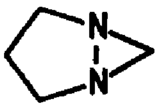
XXII $R_1 = H$, $R_2 = PhCH_2$, $R_3 = H$

A value of ϕ=149.6°, obtained from recent microwave and electron diffraction studies[68], is in excellent agreement with this structure. A diazetidine, having chemically non-equivalent nitrogens (XXII) was chosen to be prepared.

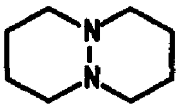
A bicyclic structure imposes additional conformational constraints which can force the nitrogens out of their preferred geometries. Hydrazines of this type are known covering the entire range[69]: from ϕ=0° XXIII, (1.5-diazabicyclo[3.3.0]-octane), ϕ=45° XXIV, (1,5-diazabicyclo-[3.1.0]-hexane) to ϕ=180° XXV,



XXIII

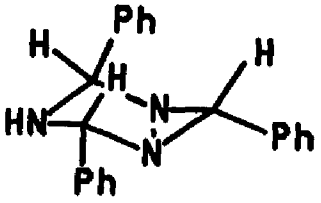


XXIV

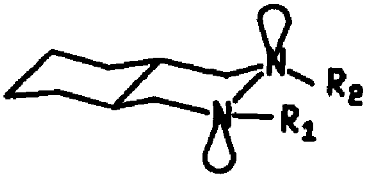


XXV

(1,6-diazacyclo[4.4.0]-decane). Unfortunately, the chemical equivalence of the nitrogens in these compounds precluded any observation of spin-coupling. However, several 2,4,6-trisubstituted-1,3,5-triazabicyclo[3.1.0]-hexanes produced in the Schmitz reaction between aldehydes, ammonia and chloroamine have been fully characterized by equilibration studies and ^{1}H and ^{13}C NMR spectroscopy[70]. Among these compounds, trans-exo-1,3,5-triazabicyclo-[3.1.0]-hexane XXVI was studied since it has similar structure to that of XXIII and the dihedral angle can be estimated to be between 0° and 45°. Similarly, X-ray[71] and photoelectron determinations[72] have shown the compound XXVII to have the electronically favorable (ϕ=180°) lone-pair conformation, namely, the asymmetrically nonequivalent nitrogens retaining the 180° lone-pair conformation.



XXVI



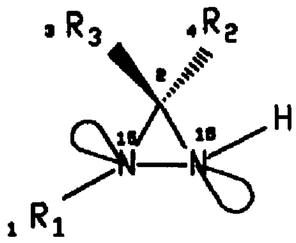
XXVII

$R_1 = H, \quad R_2 = PhCH_2$

3.3 Results and Discussion

Table X summarizes ^{13}C and ^{15}N chemical shifts in several diaziridines. The NMR spectral assignments of three diaziridines in Table X are based on the data reported by Radeglia[73] for N,N-dimethyldiaziridine. The assignments were also made by comparison of the observed chemical shifts and coupling constants of the labeled compounds with the unlabeled compounds. Figure 3.3 show a proton decoupled ^{13}C NMR spectrum of N-methyl-3,3-pentamethylene diaziridine (XVIIIA) as a typical example. The lowest field triplet in that spectrum was assigned to the quaternary carbon, C_1, attached to the nitrogens (deshielding effect on this carbon). The quaternary carbon coupled to both ^{15}N-labelled nitrogens should then yield a doublet of doublets signal in the carbon-13 spectrum. Since $^1J_{C_1N\alpha}$ and $^1J_{C_1N\beta}$ are the same (5.2 Hz), a triplet signal was observed. The overlapped

Table X . Carbon-13 and Chemical Shifts for Diaziridines[a]

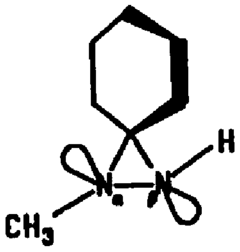


R_1	R_2	R_3	δC_1	δC_2	δC_3	δC_4	δN_α [b]	δN_β [b]
$PhCH_2$	CH_3	CH_3	57.5	57.4	28.1	17.4	94.5	90.0
CH_3	C_6H_{10}	C_6H_{10}	39.9	61.3	38.9	27.5	95.1	79.0
$PhCH_3$	C_6H_{10}	C_6H_{10}	56.5	61.7	38.7	28.0	93.9	91.5

---

[a] Measurements were made at room temperature using 0.10M in deuteriochloroform solution.

[b] Chemical shifts were measured with respect to saturated ^{15}NH4Cl aqueous solution, 26.8 ppm, (external) and reported relative to NH_3.



XVIIA

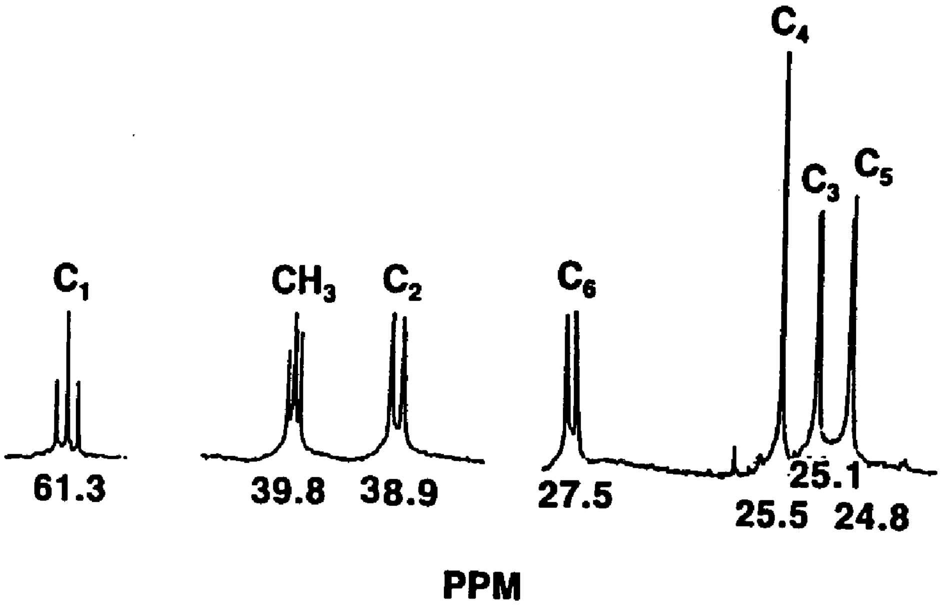
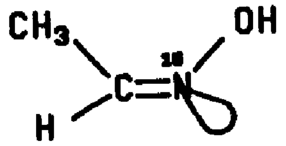
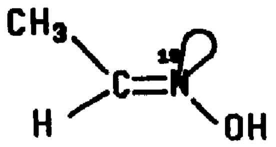


Figure 3.3 ^{13}C Spectrum of N-Methyl-3,3-pentamethylene-Diaziridine-$^{15}N_2$

doublets at 39.8ppm were assigned to the N-methyl- carbon, based on the assignment by Radegilia[73]. The two methylene carbons, C2 and C6, are expected to have different chemical shifts because the long-pair electrons on the two nitrogens have different influence on these carbons. It has been known that a nitrogen lone-pair orientation can markedly affect $^1J_{CN}$ and $^2J_{CN}$[74]. $^{13}C-^{15}N$ coupling constants are generally large and negative for those nuclei that are closer in space (synclinal) to the lone-pair, and are small and positive for those that are further removed (anticlinal) from the lone-pair. Typical data are given for acetaldoxime XXVIII[75] and acetophenone oximes XXIX.[76]

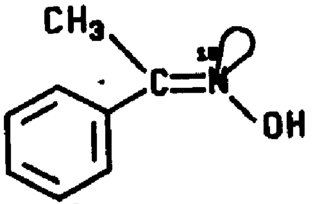


$^1J_{CN}$ = -2.3 Hz

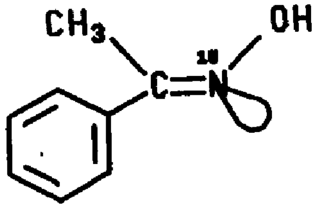


$^1J_{CN}$ = -4.0 Hz

XXVIII



$^2J_{CN}$ = -11.6 Hz



$^2J_{CN}$ = +1.0 Hz

XXIX

Structure XVIIIA shows that the distance between C_2 and Nβ lone-pair is shorter than between C_6 and Nα. Thus, the resonances at 38.9 and 27.5 ppm were assigned to C_2 and to C_6 respectively, based on the magnitude of $^2J_{CN}$: $^2J_{C_2N\beta} = 6.7$ Hz, $^2J_{C_6N\alpha} = 4.6$ Hz, respectively. All the other carbons on the cyclohexane ring were assigned using the same principle. The results are listed in Tables XI.

The ^{15}N NMR spectral assignments of compound <u>XVIIIA</u> are much simpler because there are only two nitrogens in this molecule. Owing to the negative magnetic moment of the ^{15}N nucleus, the nuclear Overhauser effect will result in a less intense signal and sometimes even a negative signal. Nβ bears one hydrogen atom and this will give rise to a less enhanced signal due to NOE. Thus the small doublet at 79.0 ppm is assigned to Nβ, whereas the other Nα does not bear any protons and hence shows an intense signal at 95.1 ppm (see Figure 3.4).

The experimental data of $^1J_{NN}$ (Table XII) values show some disagreement with the theoretical predictions, although the measurement of the sign of those coupling constants is not available. For example, $^1J_{NN}$ of N,N-dibenzylhydrazine-^{15}N was found to be 8.5 Hz, different from the predicted value of -3.4 Hz. For the three substituted diaziridines, the calculated and experimental $^1J_{NN}$ values are 3.3 Hz and 4.5 Hz, respectively. The experimental value of $^1J_{NN}$ for 2,4,6-triphenyl-1,3,5-triazabicyclo[3.1.0]-hexane is 11.0 Hz and the predicted value is -10.8 Hz.

The lack of known procedures and the high cost of labeled materials precluded the synthesis of the two compounds, diazatidine <u>XXV</u> and 3.4-substituted-3,4-diazabicyclodecane <u>XXIV</u>. As a result, further

Table XI . ^{13}C-^{15}N and ^{15}N-^{15}N Coupling Constants of Diaziridines-$^{15}N_2$

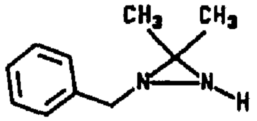
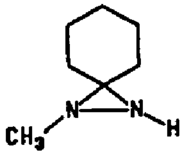
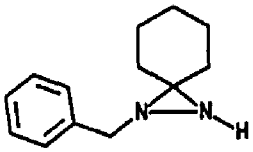
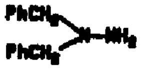
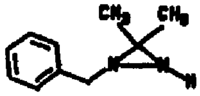
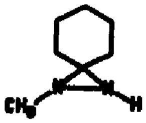
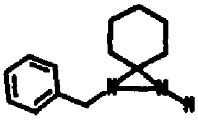
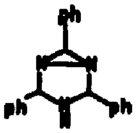
J(N-C)			
$^1J(N\alpha$-$N\beta)$	4.1	4.7	4.5
$^1J(N\alpha$-$C_1)$	3.0	2.9	3.0
$^1J(N\alpha$-$C_2)$	5.6	5.2	5.5
$^1J(N\beta$-$C_2)$	5.3	5.2	5.3
$^2J(N\beta$-$C_2)$	3.0	2.5	3.0
$^2J(N\alpha$-$C_3)$	5.8	6.7	4.9
$^2J(N\alpha$-$C_4)$	0.5	0.5	0.3
$^2J(N\beta$-$C_3)$	0.7	0.8	0.7
$^2J(N\beta$-$C_4)$	5.1	4.6	4.0

Table XII. Comparison of Experimentally Determined Absolute Values of One Bond ^{15}N-^{15}N Coupling Constants for Hydrazine Derivatives With the Expected Preferred Lone Pair Dihedral Angles[a]

Compounds	$^1J^{15}_{NN}$, Hz	Dihedral Angle (ϕ)
	| 8.5 |	~90°
	| 4.1 |	~102°
	| 4.5 |	~102°
	| 4.7 |	~102°
	| 11.0 |	~0-45°

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[a] Sample concentrations were ca. 0.10M in deuteriochloroform. The probe temperature was maintained at 30°C.

[b] Measurements are accurate to ± 0.3 Hz.

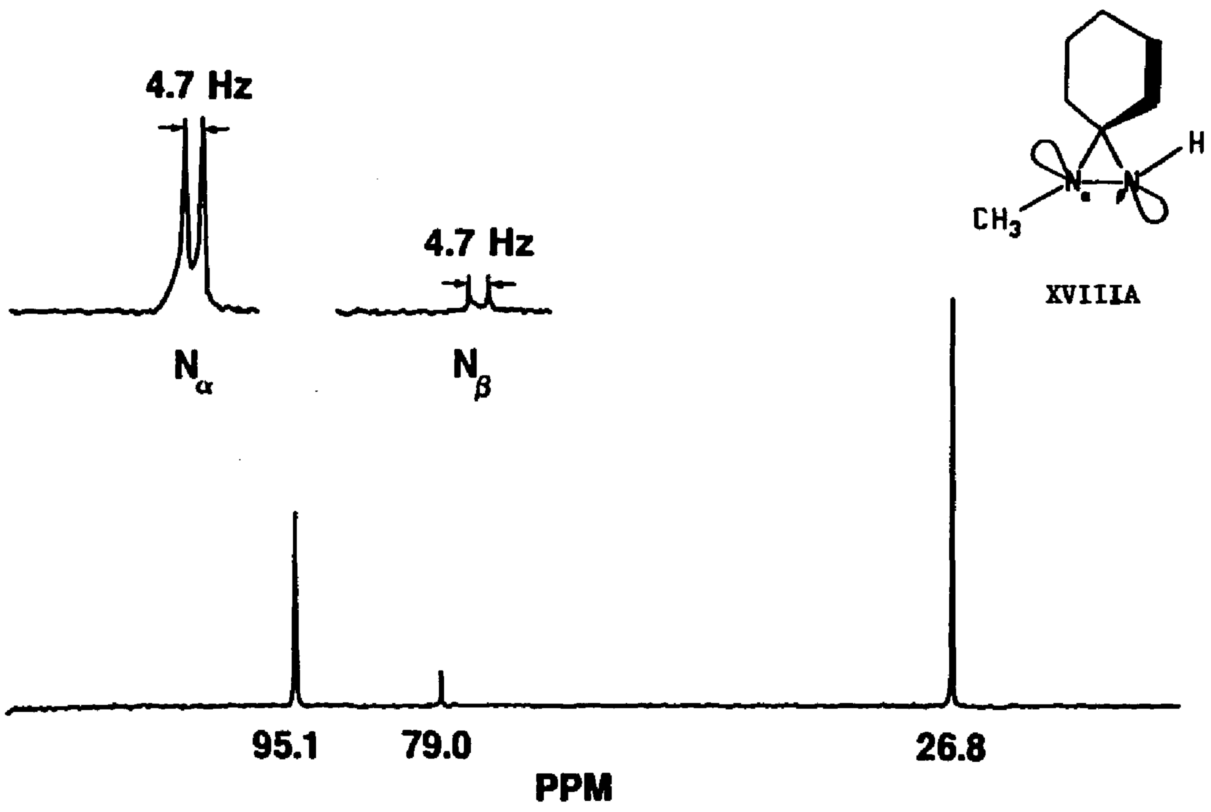
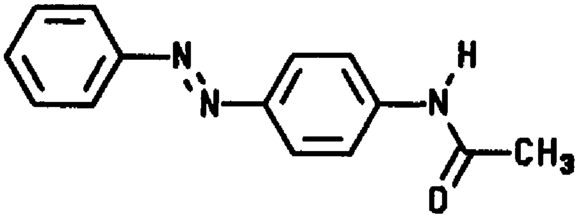


Figure 3.4 ^{15}N Spectrum of N-Methyl-3,3-pentamethylene-Diaziridine-$^{15}N_2$

study of the J_{NN} values in these systems could not be carried out.

In order to determine the sign of $^{1}J_{NN}$, triple resonance ^{13}C-{^{1}H(noise), ^{15}N(selective)} and ^{1}H-{^{1}H(selective), ^{15}N(selective)} experiments, similar to those reported by Kuroda et al[77]., must be performed. Although the determination of the sign of the $^{1}J_{NN}$ could protentially provide more information, these experiments could not be done in the present investigation due to the high cost of a selective ^{15}N and ^{1}H decoupler probe. Recently, Kuroda and co-workers have determined the sign of $^{1}J_{NN}$ of trans-diazene(4-acetyl-aminoazobenzene) <u>XXX</u>[78]



XXX

to evaluate the theoretical prediction[79] that $^{1}J_{NN}$ would be positive in sign when nitrogens have s-hybridized lone-pairs and take a trans conformation. The sign of trans-diazene was first determined relative to those of ^{13}C-^{15}N spin coupling constants, $^{n}J_{CN}$, by selective ^{15}N decoupling experiments and then finally referred to that of $^{1}J_{CH}$ in the benzene ring, which undoubledly bears a positive sign, by selective ^{15}N and ^{1}H decoupling experiments. It was found that the sign of $^{1}J_{NN}$ of trans-diazene is negative in contrast to the theoretical prediction. Kuroda believed that the discrepancy is attributed to the large negative contribution from the orbital-dipole term which was not correctly evaluated in previous calculations for the $^{1}J_{NN}$ coupling of the N=N bond[80].

CONCLUSIONS:

The dependence of nitrogen-nitrogen one bond coupling constants on the conformation of the adjacent lone-pair electrons of nitrogens in hydrazines have been demonstrated. The limited series of hydrazine derivatives studied in the present investigation showed that the J_{NN} coupling values change with the dihedral angles of the lone-pair of the nitrogens. The experimental data indicated some disagreement between the theoretical calculation and the experimental results. In addition, the effect of substituents on J_{CN} couplings in trans-N-benzylidene-aniline-N^{15} has also been investigated (see Appendix A). From the changes in the carbon-nitrogen coupling constants, it is concluded that steric compression by the ortho-substituent causes the aniline ring to rotate towards the planar conformation, bringing C-2 closer in space to the nitrogen lone-pair while simultaneously moving C-6 away.

CHAPTER 4. EXPERIMENTAL

4.1 Methods and Materials

The carbon-13 and nitrogen-15 NMR spectra presented in this thesis were obtained on a Bruker WP-200SY spectrometer operating at 50.233 MHz for ^{13}C and 20.279 MHz for ^{15}N. The spectrometer was equipped with a B-VT 1000 variable temperature controller. Nitrogen chemical shifts are reported with respect to liquid ammonia using 9.0M 90% $H^{15}NO_3$ (99.1% ^{15}N), or saturated $^{15}NH_4Cl$ (97.2% ^{15}N) aqueous solution as an external reference. Chemical shifts for carbon-13 NMR are expressed with respect to TMS as an internal reference.

The ^{13}C and ^{15}N chemical shifts and $^{n}J_{CN}$ coupling constants presented in Tables I to IX (except VII) were obtained by broad-band proton decoupling. The uncertainty in these coupling constants was estimated to be ±0.4Hz. The measurements were made at 5°C in order to slow down the rate of sample decomposition. Sample solutions were prepared in N,N-dimethylformamide containing 2% deuteriobenzene for frequency lock. The acquisition parameters for ^{13}C NMR spectra were: 30° pulse angle, 2000-5000 scans, 2.3 s acquisition time, 7200 Hz spectral width, 32K data points and 2-3 seconds delay between pulses, while ^{15}N NMR spectra were determined using 30° pulse angle, 400-1000 scans, 16K data points and a 4 second delay between pulses.

The chemical shifts and coupling constants listed in Tables X through XIV were obtained with proton decoupling at ambient temperature using ca. 10% w/v solutions in deuteriochloroform or deuteriodimethylsulfoxide. Typical parameters used are: 30° pulse angle; 5000 Hz spectral width; 1000-2000 scans and 32K data points for ^{13}C and 16K data points for ^{15}N.

All ^{1}H NMR spectra were obtained on a Varian EM-60 spectrometer. IR spectra were measured on a Perkin Elmer 247 spectrometer. Melting points were taken on a Thomas Hoover melting point apparatus. Melting points and decompositions points are uncorrected.

All starting materials, unless otherwise specified, were commercially available and were used without further purification. DMSO-d_6 and $CDCl_3$ NMR solvents were obtained from Norell Incorporated and benzene-d_6 was obtained from Diaprep Incorporated. Sodium nitrite (99.0 atoms% ^{15}N), and ammonium chloride (97.2 atom% ^{15}N), were supplied by Isomet, Inc., and aniline (97.8 atom% ^{15}N) and para-nitroaniline (48.6 atom% ^{15}N) were supplied by Junta De Energia Nuclear Madrid.

4.2 Preparation of Ring-substituted Benzamides-^{15}N

The following general procedure was adopted for the preparation of the ring-substituted benzamides-^{15}N[81]. A 25ml three-necked flask was equipped with a gas inlet adapter for dry nitrogen, a dropping funnel and a reflux condenser fitted with 10cm potassium hydroxide drying tube which was connected to a dry-ice trap by means of tygon tubing. A solution of ring-substituted benzoyl chloride in 65ml of anhydrous ether was placed in the dry-ice trap. After initiating the nitrogen flow and cooling the trap to dry-ice acetone temperature, ammonia^{15}N

was generated in the three-necked flask by the dropwise addition over a 20-minute period of a solution of ammonium-^{15} chloride (99.3 atom% ^{15}N) to a refluxing solution of sodium hydroxide. The aqueous solution was heated under reflux for 4 hours, then the oil bath was removed and the nitrogen flow was discontinued. The trap and its contents were left in the dry-ice bath overnight. The suspension formed in the trap was filtered and the crude was washed with acetone and the washings combined with the ethereal filtrate. Removal of the solvent at reduced pressure on a rotary eaporator gave the crude benzamide-^{15}N. The crude product was washed with hexane to remove any unreacted acid chloride and was then suction air-dried. Most of the benzamides-^{15}N obtained were of acceptable purity. The ammonium chloride-^{15}N recovered from the filter paper was re-used.

4-Bromobenzamide

From a reaction mixture of 4-bromobenzoyl chloride (0.4390g, 2.0 mmol), ammonium chloride-^{15}N (0.241g, 4.55 mmol, 99.0 atom% ^{15}N) and sodium hydroxide (1.000g, 25.0 mmol), 0.3460g (86.7%) of 4-bromobenzamide was obtained, m.p. 187-189° (Lit.[82], 190-193°).

4-Chlorobenzamide

4-chlorobenzamide (0.853g(96.6%)) was obtained, m.p. 175-177.5° (lit.[83],180°) from a reaction mixture of 4-chlorobenzoyl chloride (1.000g, 5.70 mmol), ammonium chloride-^{15}N (0.720, 1.30 mmol) and sodium hydroxide (3.500g, 87.00 mmol).

4-Methylbenzamide

A reaction mixture of 4-methylbenzoyl chloride (0.400g, 2.60 mmol), ammonium chloride-^{15}N (0.267g, 5.00 mmol) and sodium hydroxide (0.500g, 12.20 mmol), yielded 0.343g (98.0%) of 4-methylbenzamide, m.p. 157° (lit.[84],165°).

3,5-Dimethylbenzamide

From a solution of 3,5-dimethylbenzoyl chloride (0.420g, 2.50 mmol), ammonium chloride-^{15}N (0.34g 6.00 mmol) and sodium hydroxide (0.500g, 12.20 mmol), 0.359g(96.3%) of 3,5-dimethylbenzamide was obtained, m.p. 130-131° (Lit,[85],135°).

3,5-Dimethyl-4-nitrobenzamide

Reaction of 3,5-dimethyl-4-nitrobenzoyl chloride (0.294g, 1.38 mmol) and ammonium chloride-^{15}N (0.360g, 6.90 mmol) with sodium hydroxide (0.27g, 6.90 mmol) gave 0.203g(76.0%) of 3,5-dimethyl nitrobenzamide. m.p. 161-163° (Lit.[86],169-170°).

2-Chloro-4-nitrobenzamide

A good yield of 0.890g(88.4%) of 2-chloro-4-nitrobenzamide was obtained, m.p. 168-172°, from a mixture of 2-chloro-4-nitrobenzoyl chloride (1.100g, 5.00 mmol), ammonium chloride-^{15}N (0.562g. 10.30 mmol) and sodium hydroxide (0.400g, 11.00 mmol).

4.3 Preparation of Ring-substituted Anilines-^{15}N [81]

To a solution of sodium hydroxide in 4-5ml of water, cooled to 0°C, bromine was added dropwise with efficient stirring. The resulting solution was stirred at 0°C for a five-minute period and then it was added to the ring-substituted benzamide-^{15}N. The suspension was stirred at 0°C for an additional twenty minutes until a clear yellow solution was obtained. The solution was gradually heated in an oil bath to a temperature of 90-95°C and kept at that temperature for 2-3 hours. After heating, the mixture was cooled to room temperature and the organic layer was extracted with three 10ml portions of ether. The combined extract was dried over anhydrous sodium sulfate for one hour. Removal of the ether on a rotary evaporator gave the product. The purity of the liquid anilines-^{15}N was verified by comparison of the ^{1}H NMR spectra of the labeled aniline with that of its commercially available ^{14}N-isotopomer. The solid anilines-^{15}N were also verified by comparison of the melting point of the labeled anilines with that of the ^{14}N-anilines reported in the literature. Unsubstituted ^{15}N-aniline and 4-nitroaniline-^{15}N were obtained commercially.

4-Methylaniline

From 4-methylbenzamide-^{15}N (0.134g, 1.00 mmol), sodium hydroxide (0.280g, 7.00 mmol) and bromine(0.180g, 1.20 mmol), 0.0868g(81.1%) of 4-toluidine was obtained, ^{1}H NMR ($CDCl_3$): δ3.25(d, $^{15}NH_2$), δ6.56(q, ArH_4).

4-Bromoaniline

From a mixture of 4-bromobenzamide-^{15}N (0.240g, 1.20 mmol), sodium hydroxide(0.240g, 6.00 mmol) and bromine (0.210g, 1.3 mmol), 0.110g (54.7%) of 4-bromoaniline was obtained, m.p. 58-60°(lit.[88],66°).

4-Chloroaniline

A solution of 4-chlorobenzamide-^{15}N (0.428g,2.70 mmol), sodium hydroxide(0.450g, 11.20 mmol) and bromine (0.450g, 2.80 mmol) yielded 0.223g(67.2%) of 4-chloroaniline, m.p. 68-69.5° (Lit.[96], 70-71°). ^{1}H NMR (DMSO): δ5.03(d, $^{15}NH_2$), δ6.81 (q, ArH_4).

3,5-Dimethylaniline

By the reaction of the mixture of 3,5-dimethylbenzamide-^{15}N (0.280g, 1.90 mmol), sodium hydroxide (0.32g, 8.00 mmol) and bromine (0.336g, 2.10 mmol), 0.100g(43,5%) of 3,5-dimethylaniline was obtained. ^{1}H NMR ($CDCL_3$): δ2.15(s, CH_3), δ3.29(broad, $^{15}NH_2$), δ6.09(s, ArH_2), δ6.29(s, ArH_1).

3,5-Dimethyl-4-nitroaniline

From 3,5-dimethyl-4-nitrobenzamide-^{15}N (0.100g, 0.52 mmol), sodium hydroxide (0.093g, 2.30 mmol) and bromine (0.083g, 0.52 mmol), 0.067g (78.2%) of 3,5-dimethyl-4-nitroaniline-^{15}N was obtained, m.p. 128-130° (Lit,[35], 132-134°).

2-Chloro-4-nitroaniline

From a mixture of 2-chloro-4-nitrobenzamide-^{15}N (0.503g, 2.50 mmol), sodium hydroxide (0.500g, 12.50 mmol) and bromine(0.448g, 2.80 mmol), 0.351g(81.2%) of 2-chloro-4-nitroaniline-^{15}N was obtained, m.p. 97-100°(Lit.[89], 107°).

4.4 Preparation of 2,4,6-Trimethylaniline-^{15}N

2,4,6-Trimethylaniline-^{15}N was prepared by the reduction of the nitromesitylene-^{15}N using tin and hydrochloric acid. The nitromesitylene-^{15}N was prepared by the nitration of mesitylene.

4.4.1 Nitration of Mesitylene

Nitric acid (1.23ml, 37.7%, 99.5 atom% ^{15}N) was added dropwise to a solution of 4.5ml of acetic acid and 3.0ml acetic anhydride kept at a temperature below 10°C. This cold mixture of acids was added dropwise to a solution of mesitylene (0.360g, 3.00 mmol) in a mixture of acetic anhydride (0.75ml) and acetic acid (0.45ml) kept in an ice-water bath. The mixture was then stirred for one hour at room temperature followed by an addition of 1.5ml acetic anhydride. This mixture was then heated at 40-50°C for five hours and left at room temperature overnight. The resulting clear yellow liquid was poured into 100ml of ice-water. The light yellow solid was filtered and dried in air, to give 0.385g (77.8%) of nitromesitylene-^{15}N, m.p. 38-39° (Lit.[90], 44°). ^{1}H NMR ($CDCl_3$): δ2.21(s, $2CH_3$), δ2.25(s, CH_3), δ6.87(s, ArH_2).

4.4.2 Reduction of 4-Nitromesitylene

Reduction of nitromesitylene was carried out by a modification of the procedure described by Vogle[91]. Nitromesitylene-^{15}N (0.380g, 2.30 mmol) and tin(0.600g, 5.10 mmol) were placed in 5.0ml round-bottomed flask at room temperature. Then 0.8ml of concentrated hydrochloric acid was added dropwise. After completion of the addition of hydrochloric acid, the mixture was heated in a 100°C water bath for two hours and then allowed to stand at room temperature overnight. The milky mixture was poured into a beaker and then 10% sodium hydroxide solution was added till the dissolution of all the precipitate. The alkaline solution was extracted with ether. The extract was dried over sodium sulfate and evaporated on a rotary evaporator to give 0.227g (73.2%) of an orange liquid. ^{1}H NMR spectrum of this material confirmed the structure of 2,4,6-trimethylaniline-^{15}N and about 5% unreacted nitromesitylene. ^{1}H NMR ($CDCl_3$): δ2.03(s, 2CH_3), δ2.13(s, CH_3), δ3.20(d, $^{15}NH_2$), δ6.67(s, ArH_2).

4.5 Preparation of 2,4,6-Tribromoaniline-^{15}N

Tribromoaniline-^{15}N was prepared by the bromination of aniline-^{15}N. Bromine was added dropwise to a mixture of aniline (0.120g, 1.34 mmol, 97.5 atom% ^{15}N) and 0.5ml of water in an ice-water bath until the bromine color did not change. The white solid was isolated by filtration to give 0.435g(98.4%) of 2,4,6-tribromoaniline, m.p. 118° (Lit.[92], 120°). ^{1}H NMR ($CDCl_3$): δ4.59(d, $^{15}NH_2$), δ7.50(s, ArH_2).

4.6 Preparation of 4-Aminobenzoic Acid

4-Aminobenzoic acid ^{15}N was prepared by the oxidation of nitrotoluene-^{15}N followed by the reduction of 4-nitrobenzoic acid-^{15}N.

4.6.1 Oxidation of Nitrotoluene-^{15}N

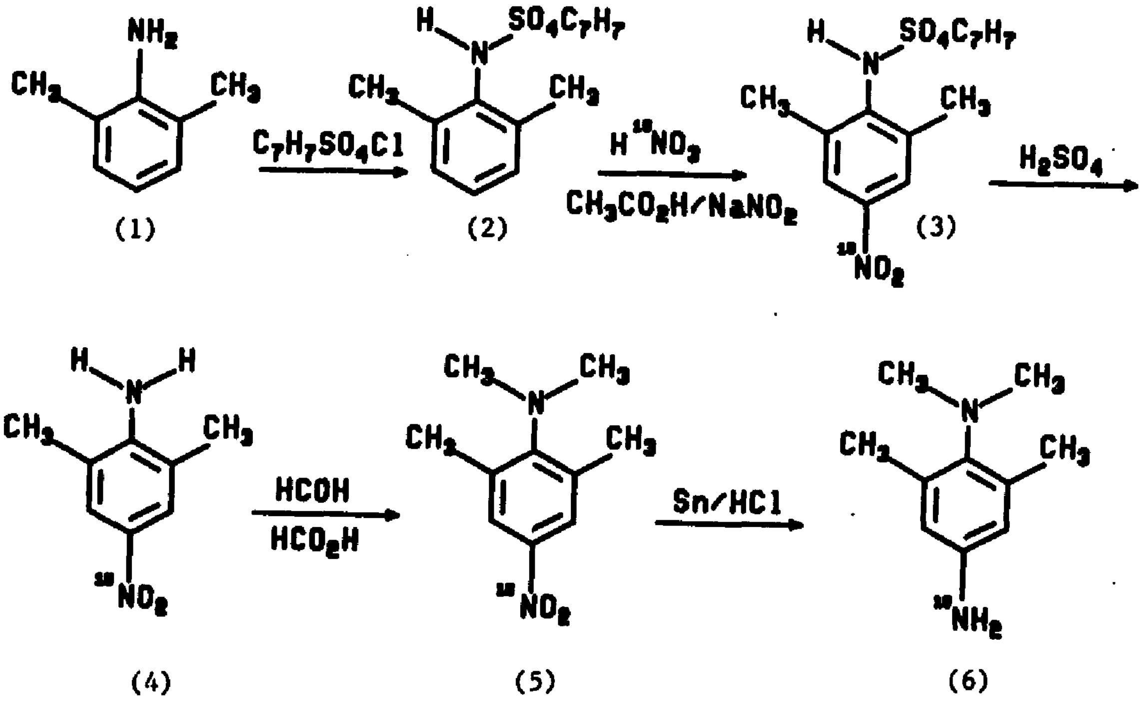
4-Nitrotoluene-^{15}N (0.290g, 2.10 mmol) and sodium dichromate (0.860g, 3.13 mol) were placed in 4.0ml of water in a 10ml round-bottomed flask. Concentrated sulfuric acid (1.20ml) was added to the mixture dropwise over a 2-minute period. When the addition of sulfuric acid was complete, the temperature of mixture was reduced and some solid precipitated out. This mixture was then immediately moved to a preheated oil bath and heated at 120°C for 1.5 hours. The resulting dark green mixture was cooled and carefully poured into 4 ml of ice water. The semi-white crude product was filtered and washed with water. The solid was transfered to a 20 ml beaker and 3 ml of 5% sulfuric acid was added. The mixture was digested on a 60°C water bath to remove the chromium salts. The solid was filtered again and treated with 5% sodium hydroxide until the liquid remained alkaline. The unreacted 4-nitrotoluene-^{15}N was removed by filtration and the alkaline solution was acidified with 15% sulfuric acid and then filtered to give 0.260g(74.3%) of 4-nitrobenzoic acid-^{15}N, m.p. 237-238° (Lit.[93], 239°).

4.6.2 Reduction of 4-Nitrobenzoic Acid-^{15}N

4-Nitrobenzoic acid-^{15}N (0.260g, 1.55 mmol) was placed in a 10 ml round-bottomed flask fitted with a reflux condenser. Granulated tin (0.610g, 5.10 mmol) and 1.3 ml of concentrated hydrochloric acid were introduced. The mixture was heated gently at 65°C for two hours. The cloudy suspension became a clear yellow solution. This solution was cooled and decanted into a 20 ml beaker. The residual tin was washed with water. The reaction mixture and the washings were combined and made alkaline with concentrated ammonium hydroxide. The white gel-like mixture was filtered and the solid hydrated tin oxide was washed with water. The washings were evaporated by heating until the volume had been reduced to 4 ml. The solution was acidified with glacial acetic acid in a cold water bath. Some white crystals were collected to give 0.17g(84.8%) of 4-amonibenzoic acid-^{15}N, m.p.190°(Lit.[94],192°).

4.7 Preparation of N,N,2,6-Tetramethyl- 1,4-Benzenediamine-^{15}N

N,N,2,6-Tetramethyl-1,4-benzenediamine-^{15}N (6)was prepared as outlined below: 2,6-Xylidine(1) was converted to 1-(4-toluenesulfonyl) amino-2,6-dimethylbenzene(2), and followed by the nitration of (2) to 1-(4-toluenesulfonyl)amino-2,6-dimethyl-4-nitrobenzene^{15}N(3), hydroxysis of (3) to 1-amino-2,6-dimethyl-4-nitrobenzene-^{15}N(4), methylation of (4) to 4-(N,N-dimethyl)amino-3,5-dimethyl nitrobenzene-^{15}N(5) and reduction of (5) to 4-(N,N-dimethyl)amino-3,5-dimethylaniline-^{15}N(6).



4.7.1 Conversion of 2,6-xylidine to 1-(4-toluenesulfonyl) amino-2,6-dimethylbenzene

2,6-Xylidine(1) was converted to 1-(4-toluenesulfonyl)amino-2,6-dimethylbezene(2) by the procedure of Wepster[95] and Hampson[96]. Para-toluenesulfonyl chloride (13.500g, 0.071 mol) was added to a solution of xylidine(7.80g, 0.064 mol) in 25 ml of pyridine in a 100 ml round bottomed flask. The mixture was heated under reflux for two hours and then it was poured, with stirring, into 250 ml of 2N HCl to give a crude product 17.50g (98.9%). This crude product was purified by two recrystallizations from 95% ethanol to give 12.28g of white 1-(4-toluenesulfonyl)amino-2,6-dimethylbenzene-^{15}N. ^{1}H NMR ($CDCl_3$): δ1.98(s, 2CH_3), δ2.32(s, CH_3), δ6.02(s, NH), δ7.20(m, ArH_4), m.p. 134-136°C.

4.7.2 Nitration of 1-(4-Toluenesulfonyl)amino-2,6-dimethylbenezene

The nitration of compound(2) was carried out by a modified procedure of that published by Wepster[95]. To a solution of 60.2% nitric acid(3.36 ml, 0.031 mmol, 95 atom% ^{15}N) were added the compound(2)(0.720g,2.60 mmol), 5 ml of glacial acetic acid and 20 mg of sodium nitrite. A clear yellow solution resulted after heating the mixture for one hour at 60-70°C. The solution was cooled and was added to 40 ml of ice-water. The precipitated semi-solid was purified by dissolution, with stirring, in 30 ml of 5% aqueous sodium hydroxide. The basic solution was filtered and the solid was washed twice with two 10 ml portions of water. The filtrate and the basic solution were combined and concentrated to about 40 ml by heating on a hot plate. The basic solution was made acidic by the addition of 50% HCl with cooling. The white precipitate formed was filtered to give a product(3) 0.620g(73.8%), m.p. 164-165° (Lit.[95], 165-166°).

4.7.3 Hydrolysis of 1-(4-Toluenesulphonyl)amino-2.6-dimethyl-4-nitrobenzene-^{15}N

Concentrated sulfuric acid (3.50 ml) was added to compound(3) (0.620g,1.9m mol) in a 125 ml Erlenmeyer flask. The mixture was left at room temperature for 24 hours. Ice water (40 ml) was added slowly to the brown liquid mixture with stirring. A yellow precipitate was formed. This cloudy mixture was made basic with concentrated ammonium hydroxide. The white solid was filtered and dried in the air to give 0.262g (81.5%) of 4-nitro-2,6-dimethylaniline-^{15}N, m.p. 160-163°C (Lit.[96], 163.5-164.4°C).

4.7.4 Methylation of 4-nitro-2,6-dimethylaniline-^{15}N

The methylation was carried out by the addition of formaldehyde 37.3% solution(0.048 ml, 5.90 mmol) to a warm (about 45°) solution of compound(4)(0.230g, 1.40 mmol) in 8.7 ml of 88% formic acid. The mixture was heated under reflux for two hours and then 0.05 ml of concentrated hydrochloric acid was added. The mixture was cooled to room temperature. The most of the acid was removed by 0.1 mmHg vacuum. The residual acid was diluted with 2 ml of water and then made alkaline with 10% sodium hydroxide solution. The yellow solid formed was filtered to give 0.200g(74.0%) of 4-(N,N-dimethyl)amino-3,5-dimethyl-1-nitrobenzene-^{15}N, m.p. 64-65°, (Lit[97], 67-68°).

4.7.5 Reduction of 4-(N,N-dimethyl)amino-3,5-dimethyl-1-nitrobenzene-^{15}N

The reduction of nitro compound(5) was carried out by placing 4-(N,N-dimethyl)amino-3,5-dimethyl-1-nitrobenzene^{15}N(4) (0.200g, 1.00 mmol) and granulated tin (0.400g, 3.30 mmol) in a 5 ml round-bottomed flask. Then 4 ml of 3M hydrochloric acid was added dropwise with stirring. After the addition was completed, the mixture was warmed for 4 hours at 100°C water bath. The excess homogeneous yellow solution was decanted into a beaker. The excess tin was washed three times with warm water and the solution was decanted. Aqueous sodium hydroxide solution(12M) was added to the mixture until all the tin hydroxide was completely dissolved. The basic solution was extracted with ether. The ether extract was dried over potassium hydroxide pellets. Removal of the solvent on a rotary evaporator gave 0.150g(88.7%) of a green liquid. The ^{1}H NMR and IR spectra (Figure 4.1) confirmed the structure of the green liquid to be 4-(N,N-dimethyl)amino-3,5-dimethyl-1-nitrobenzene-^{15}N. ^{1}H NMR ($CDC1^3$): δ2.19 (s, 2CH^3), δ2.74 (s, 2CH^3), δ3.27 (broad, $^{15}NH_2$), δ6.30 (s, ArH_5).

4.8.1 Preparation of 4-Nitrosophenol-^{15}N

4-Nitrophenol-^{15}N was prepared by using the method of Marvel[88]. In a 30ml round-bottomed flask was placed 1.22g (13mmol) of phenol dissolved in a solution of 0.54g (13mmol) of sodium hydroxide in 7.0ml of water. The solution was cooled to 0°C in an ice bath and 0.9g (13mmol) of sodium nitrite-^{15}N was added. With stirring, 8.0ml (0.25% aqueous solution) of sulfuric acid was added from a dropping funnel over a period of 15 minutes. Then the reaction was left for 1.25

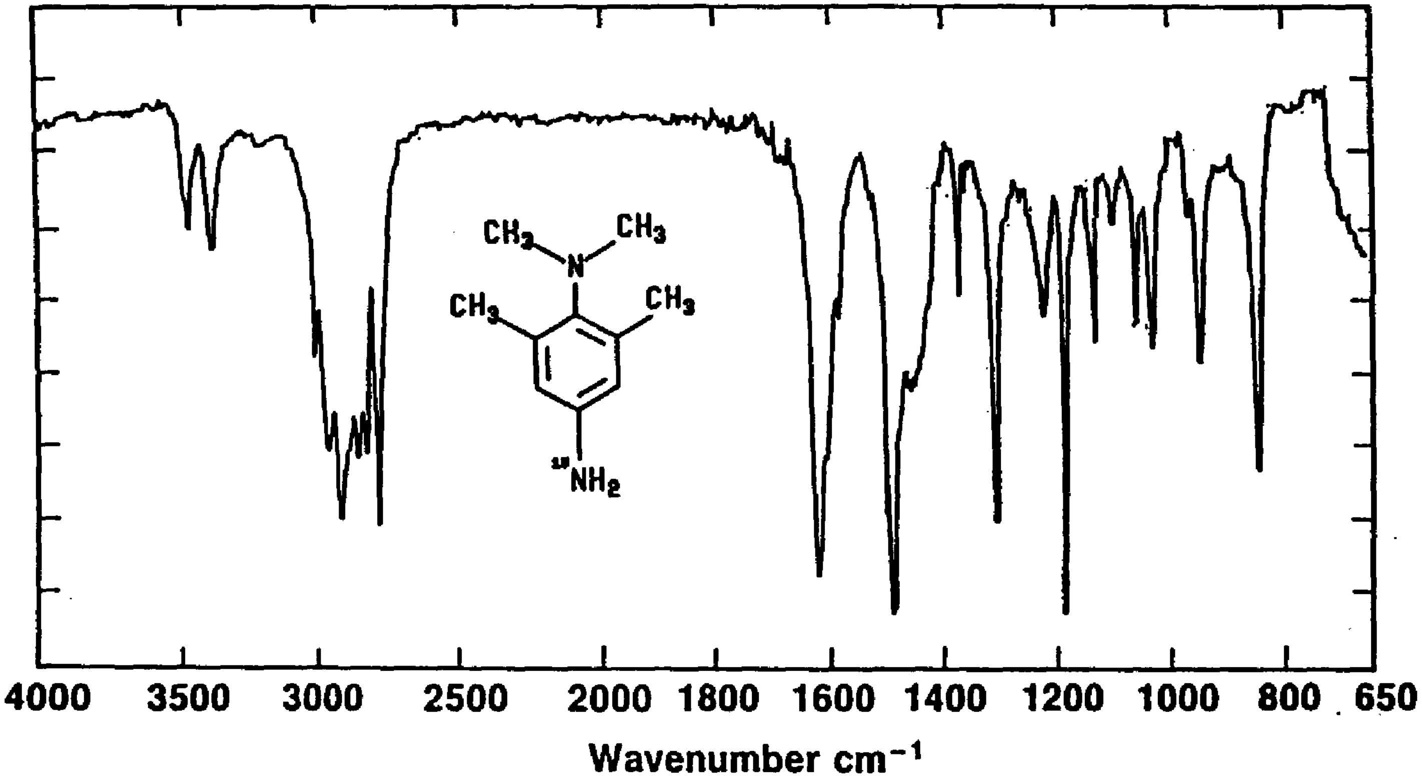


Figure 4.1 Infrared Spectrum of 4-(N,N-dimethyl)amino-3,5-dimethyl-1-nitrobenzene-^{15}N

hours. The product was filtered with suction and washed thoroughly with ice water. The yield of 4-nitrosophenol-^{15}N was 0.56g (43.1%). The melting point is 134 - 136° (Lit. 132 - 134°)

4.8.2 Preparation of 4-hydroxyanline-^{15}N

The procedure of Tufaro[30] was adopted for the preparation of 4-hydroxyaniline-^{15}N from 4-nitrosophenol-^{15}N.

4.9 Preparation of Isoamylnitrite-^{15}N

The procedure of Noyes[88] was employed with a slight modification. Over a period of 20 minutes, an aqueous solution of $Na^{15}NO_2$(0.440g, 6.30 mmol in 1.5 ml of H_2O) was added dropwise to a solution of isoamyl alcohol (0.440g, 5.0 mmol) in 20 ml of 50% sulfuric acid maintained in an ice-water bath. During the addition of $Na^{15}NO_2$, the mixture changed from colorless to light yellow in color and separated into two layers. The mixture was allowed to stand at 0°C for two hours. The top layer was carefully separated and dried in a calcium chloride desiccator at -10°C overnight to give 0.56g(96%) of a yellow liquid. The ^{1}H NMR spectral data confirmed the structure of isoamylnitrite ^{15}N.

^{1}H NMR($CDCl_3$): δ0.95 (d, $2CH_3$), δ1.65 (m, CH_2, CH_2), δ4.65 (t, CH).

4.10 Preparation of Ring-Substituted Benzenediazonium Fluoroborate-$^{15}N_2$

Most of the ring-substituted benzenediazonium fluoroborates -^{15}N were prepared by diazotization of ring-substituted anilines-^{15}N with sodium nitrite-^{15}N and fluoboric acid. The diazotization was carried out by a modified procedure of that reported by Roe[100] and Starkey[101]. For example, a substituted aniline-^{15}N was suspended in a small volume of 50% tetrafluoboric acid-water solution or sodium fluoroborate water solution in a 0-5°C ice-water bath. After stirring for 30 minutes, an aqueous sodium nitrite(95 atom% ^{15}N) solution was added dropwise to the mixture. The precipitate changed from a white solid to a fine brown solid. This mixture was allowed to stand in an ice-water for 30 more minutes. The liquid layer was withdrawn with a pipet and the precipitate was washed with small amounts of ethyl alcohol followed by ether. The product was purified by recrystalization from a mixture of acetonitrile and ether. The purities of all the benzenediazonium salts prepared by the above mentioned procedure were verified by the comparison of the melting or decomposition points with those reported in the literature. Some of the compounds have no reported literature values of melting or decomposition points. The structures of these materials were confirmed by comparision of the ^{13}C-NMR spectral data reported by Elofson[28] and Gruner[102].

4-Methoxybenzenediazonium Ion

From the reaction mixture of 4-methoxylaniline-^{15}N (0.130g, 1.05 mmol), hydrochoric acid (0.44 ml, 0.60N), sodium nitrite-^{15}N (0.085g, 1.12 mmol, 95 atom% ^{15}N) and sodium fluoroborate (0.160g, 1.45 mmol), 0.160g(68.4%) of 4-methoxybenzenediazonium ion was obtained, mp 137-140° decomp. (lit.[103], 142°).

4-Methylbenzenediazonium

The reaction of 4-methylaniline-^{15}N (0.08g, 0.64 mmol) with fluoboric acid (0.5 ml, 2.8 mmol) and sodium nitrite-^{15}N (0.070g, 1.01 mmol) yielded 0.09g(76.8%) of 4-methoxylbenzenediazonium ion dec.p. 107-108° (Lit.[103], 109-110°).

4-Hydroxybenzenediazonium Ion

4-hydroxybenzenediazonium ion 0.320g(60.4%) was obtained. m.p. 113-115° dec.p. 167° from the reaction mixture of 4-hydroxylaniline-^{15}N (0.280g, 2.54 mmol), isoamylnitrite-^{15}N (0.28 ml, 2.80 mmol) and 1 ml 54% fluoboric acid in ether solution. ^{13}C NMR (DMF): δ100.15 C_1, δ118.63 C_2, δ136.47 C_3, and δ152.56 C_4.

4-Hydrogenbenzenediazonium Ion

By reacting aniline-^{15}N (0.200g, 2.15 mmol) with fluoboric acid (1.5 ml, 8.2 mmol) and sodium nitrite-^{15}N(0.160g, 230 mmol) in 0.34 ml of water, 0.25g(62.9%) of benzenediazonium ion was obtained. dec.p. 104° (lit.[104], 104°).

4-Chlorobenzenediazonium Ion

From 4-chloroaniline-^{15}N (0.100g, 0.78 mmol), fluoboric acid (0.50 ml, 2.8 mmol) and sodium nitrite (0.055g, 0.80 mmol), 0.163g(92.1%) of 4-chlorobenzenediazonium ion was obtained. m.p. 118-119°, dec.p. 130-131° (Lit.[103], dec.p. 136-137°).

4-Bromobenzenediazonium Ion

A solution of 4-bromoaniline-^{15}N (0.200g, 1.16 mmol), fluoboric acid (1.0 ml, 5.60 mmol) and sodium nitrite-^{15}N (0.081g, 1.16 mmol) yielded 0.227g(72.3%) of 4-bromobenzenediazonium ion. m.p. 105° (lit.[103], 137-138°).

4-Carboxybenzenediazonium Tetrafluoroborate Ion

An yield of 0.12g(63.2%) of 4-carboxybenzene diazonium ion was obtained from a mixture of 4-aminobenzoic acid-^{15}N (0.100g, 0.73 mmol), fluoboric acid (0.50 ml, 2.80 mmol) and sodium nitrite (0.055g, 0.80 mmol). ^{13}C NMR (DMF): δ119.81 C_1, δ131.76 C_3, δ133.57 C_2 and δ141.48 C_4.

4-Nitrobenzenediazonium Ion

From a mixture of 4-nitroaniline-^{15}N(0.195g, 1.40 mmol), fluoboric acid (1.0 ml, 5.60 mmol) and sodium nitrite-^{15}N (0.108g, 1.54 mmol), 0.236g(70.7%) of 4-nitrobenzenediazonium ion was obtained, dec.p. 153-155° (Lit.[104], 157-158°).

2-Bromobenzenediazonium Ion

By reacting 2-bromoaniline-^{15}N (0.172g, 1.00 mmol, 98.8 atom% ^{15}N) with fluoboric acid (0.8 ml, 4.50 mmol) and sodium nitrite-^{15}N (0.069g, 1.00 mmol), 0.205g(75.6%) of 2-bromobenzenediazonium ion was obtained, m.p. 131°, dec.p. 142°.

2-Chloro-4-nitrobenzenediazonium Ion

From 2-chloro-4-nitroaniline-^{15}N (0.1g, 0.58 mmol) and fluoboric acid (0.4ml, 2.27mmol) and sodium nitrite-^{15}N (0.05g, 0.73mmol), 0.173g (79.8%) of 2-chloro-4-nitrobenzenediazonium ion was obtained. ^{13}C NMR (DMF): δ123.0 C_1, δ125.3 C_3, δ127.5 C_2 and δ154.3 C_4.

3,5-dimethylbenzenediazonium Ion

From 3,5-dimethylaniline-^{15}N (0.100g, 0.82 mmol), fluoboric acid (0.5 ml, 2.8 mmol) and sodium nitrite-^{15}N (0.090g, 130 mmol), 0.147g (81.1%) of 3,5-dimethylbenzenediazonium ion was obtained, m.p. 86°.

3,5-dimethyl-4-nitrobenzenediazonium Ion

3,5-dimethyl-4-nitroaniline-^{15}N (0.037g, 0.22 mmol) was reacted with fluoboric acid (0.30 ml, 1.70 mmol) and sodium nitrite-^{15}N (0.031g, 0.44 mmol) to yield 0.025g(43.0%) of 3,5-dimethylbenzenediazonium ion. m.p. 94-96°.

2,4,6-Trimethylbenzenediazonium Ion

From a solution of 2,4,6-trimethylaniline-^{15}N (0.226g, 1.37 mmol), fluoboric acid (0.8 ml, 4.50 mmol) and sodium nitrite-^{15}N (0.10g, 1.50 mmol), 0.298g(87.6%) of 2,4,6-trimethylbenzenediazonium ion was obtained. ^{13}C NMR(DMF): δ98.15 C_1, δ122.54 C_3, δ134.12 C_2 and δ133.22 C_4.

2,4,6-Tribromobenzenediazonium Ion

By reacting 2,4,6-tribromoaniline-^{15}N (0.435g, 1.34 mmol) with fluoboric acid (0.8 ml, 4.50 mmol) and sodium nitrite-^{15}N (0.093g, 134 mmol), 0.480g(86.3%) of 2,4,6-tribromobenzenediazonium ion was obtained. dec.p. 257-260°.

4.11 Preparation of 4-(N,N-dimethyl)amino-3,5-dimethyl benzenediazonium fluoroborate-^{15}N Ion

4-(N,N-Dimethyl)amino-3,5-dimethylbenzenediazonium fluoborate-^{15}N ion was prepared by a modified procedure of Piercey[105].4-(N,N-Dimethyl) amino-3,5-dimethylaniline-^{15}N (0.100g, 0.60 mmol) in 0.5 ml of dry ether was slowly added to nitrosoyl tetrafluoroborate suspended in 1.5 ml of dry ether in a dry ice-acetone bath. A light solid was formed. The mixture was allowed to stand in dry ice for another hour. The ether was evaporated with a stream of nitrogen gas. Since the complete removal of water was not possible, the resultant product has an unknown yield and melting point. ^{13}C NMR spectral data of this product in DMF: δ20.83, δ43.56, δ98.35, δ124.97, δ133.72 and δ134.40. To further confirm the sturcture of 4-(N,N-dimethyl)amino-3,5-dimethyl- diazonium salt, IR spectrum was run in fluorinated hydrocarbon. A weak, sharp signal at 2280 cm^{-1}, characteristic of the stretching mode of N-N bond, was observed.

4.12 Preparation of 4-(N,N,N-trimethyl)ammoniumbenzenediazonium Chloride-^{15}N

The procedure of Gruner[111] was employed with modifications. A solution of 1.0N trimethylamine (1.52 ml) in acetonitrile was added dropwise to 4-chlorobenzenediazonium fluoroborate-$^{15}N_2$ (0.343, 1.52 mmol) in acetonitrile (1.40 ml). The reaction mixture was kept at 0°C for one hour after the addition of the amine. The mixture was centrifuged and the liquid was discarded to leave behind a light brown solid. The solid was washed with acetonitrile and methylene chloride. The supernatant was removed with a pipet. The wet product was dried to give a light brown solid(0.06g, 13.7%), dec.p 105-106°. ^{13}C NMR spectrum of this material verified the structure of 4-trimethylammonium benzenediazonium chloride.

4.13 Preparation of 24-crown-8 Ether

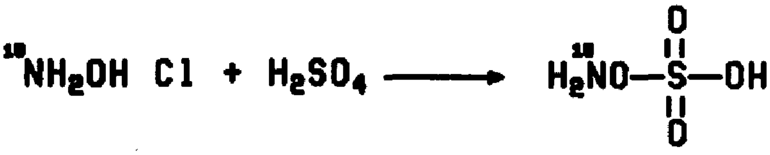
The procedure of Gokel[102] was employed. Tetraethylene glycol solution (116g, 0.60 mol) and tetraethylene glycol ditosylate (300g, 0.60 mol) in tetrahydrofuran (800 ml) were added to a slurry of sodium hydride (29.7g, 1.19 mol) in refluxing tetrahydrofuran(1.01) over 12 hour period. The reaction mixture was separated and purified by column chromatography (alumina oxide, 0-2% 2-propanol/hexane) 17.5g (yield 8%) of colorless 24-crown-8 ether was obtained. ^{1}H NMR($CDCl_3$): δ3.67(s, $6CH_2$); ^{13}C NMR ($CDCl_3$): δ70.39.

4.14 Preparation of Diazophenone-$^{15}N_2$

The procedure of Roedel[107] was employed. 4-hydroxylbenzene-diazonium salt-$^{15}N_2$ (0.150g, 0.72 mmol) was dissolved in 3.8 ml of absolute alcohol at 0°C and a slight excess of silver oxide (from 0.30g of silver nitrate and 0.056g sodium hydroxide) was added to the solution with stirring. After the mixture was stirred for three hours at 0°C protected from direct light, the silver chloride was then filtered. The alcoholic filtrate was concentrated on a rotary evaporator to yield the wet brown diazophenone along with other impurities. The mixture was dried and stored in a vacuum desiccator over phosphours pentoxide.

4.15 Preparation of Hydroxylamine-O-Sulphonic Acid-^{15}N

The preparation was carried out by the procedure of Schmitz[108].



$$^{15}NH_2OH\ Cl + H_2SO_4 \longrightarrow H_2{}^{15}NO-\overset{\overset{O}{||}}{\underset{\underset{O}{||}}{S}}-OH$$

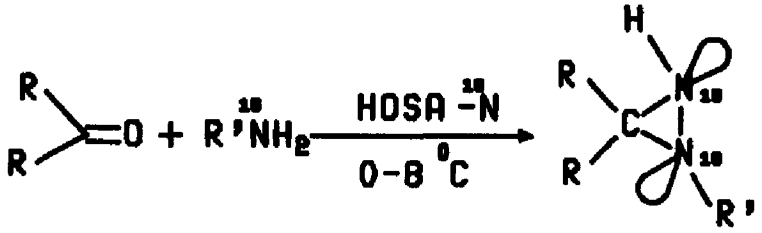
Oleum(30%, 0.8 ml) was added dropwise over an hour to hydroxylamine chloride-^{15}N (0.250g, 3.57 mmol, 96.2% atom ^{15}N) and the reaction mixture was stirred keeping the moisture out (exothermic reaction) by purging with nitrogen gas at room temperature. After further stirring for an hour, the thick paste was left overnight. Ether (5 ml) was added to the crude acid product and the mixture was cooled on ice. Filtration and subsequent washing with 10 ml ether to give 0.335g (88.1%) white solid hydroxylamine-o-sulphonic acid which was stored over $CaCl_2$. m.p. 206-209° (Lit.[108], 210-211°).

4.16 Preparation of Benzylamine-^{15}N

The procedure of Vogle[109] was employed with modification. 10 ml of ether was placed in a 50 ml three-necked flask while the $LiALH_4$ (0.411g, 11.0 mmol) was added slowly at 0°C. After the material was stirred for 15 minutes, benzamide (0.800g, 6.60 mmol, 98.6% atom ^{15}N) was added in aliquots. The mixture was stirred for another half hour in an ice-water bath and then transferred to an oil bath and heated to 60-70°C. The mixture was heated under reflux for 5 hours and left overnight at room temperature. The reaction was quenched carefully by the addition of 1 ml of water and 1 ml of 5% NaOH aqueous solution at 0.°C and left stirred for 15 minutes at room temperature. The mixture was filtered by suction and the residual salts were washed with three 20 ml portions of ether. The combined ether washings were dried over sodium sulfate for one hour. Removal of the solvent on a rotary evaporator gave 0.59g (84.0%) of benzylamine-^{15}N. ^{1}H NMR (CDCl$_3$: δ2.15 (s, CH$_2$), δ3.72 (d, ^{15}NH$_2$), δ7.32 (s, ArH$_5$).

4.17 Preparation of Diaziridines-^{15}N$_2$

The procedures for Ohme[110] and Schmitz[111] were employed.



A mixture of ketone and alkylamine-^{15}N in water solution was stirred in an ice-water bath. The temperature of the solution was maintained at 0-8°C while hydroxylamine-O-sulfonic acid-^{15}N(HOSA) was added in aliquots over a half hour period. The reaction mixture was stirred for two more hours and left at -10°C overnight. The precipitated solid was washed with four portions of dry ether. The ether extracts were dried over sodium sulfate and the solvent was removed on a rotarty evaporator to give diaziridines-^{15}N.

N-benzyl-3,3-pentamethylenediaziridine-^{15}N

From a solution of cyclohexanone (0.17g, 1.80 mmol), benzylamine-^{15}N (0.482g, 4.50 mmol) and HOSA-^{15}N (0.169g, 1.50 mmol), 0.251g (82.8%) of N-benzyl-3,3-pentamethylenediaziridine-^{15}N was obtained. ^{1}H NMR ($CDCl_3$): δ1.55(m, C_6H_{10}), δ2.20(broad, C_6H_{10}), δ5.55 (broad, ^{15}NH), δ7.30(m, ArH_5).

N-benzyl-3,3-dimethyldiaziridine-^{15}N

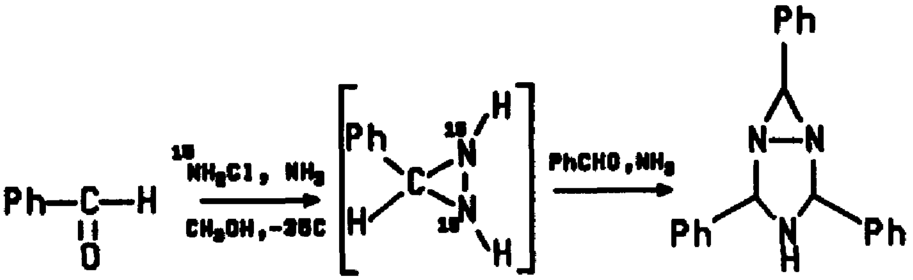
By reacting acetone (0.290g, 0.50 mmol) and benzylamine-^{15}N (0.107g, 0.1 mmol) with HOSA-^{15}N (0.085g, 0.75 mmol), 0.038g (76.5%) of N-benzyl-3,3-dimethyldiaziridine-^{15}N was obtained. ^{1}H NMR ($CDCl_3$): δ1.67 (s,CH_3), δ3.14 (d,^{15}NH), δ3.36 (s, CH_2), δ7.22 (s, C_6H_5).

N-methyl-3,3-pentamethylenediaziridine-^{15}N

From a mixture of cyclohexanone (0.111g, 1.14 mmol), methyl amine-^{15}N (0.188g, 0.57 mmol) and HOSA-^{15}N (0.136g, 1.20 mmol) 0.106g (56.3%) of N-methyl-3,3-pentamethylenediaziridine-^{15}N was obtained. ^{1}H NMR ($CDCL_3$): δ39.9 CH_3, δ61.3 C, δ38.9 CH_2 and δ27.5 CH_2.

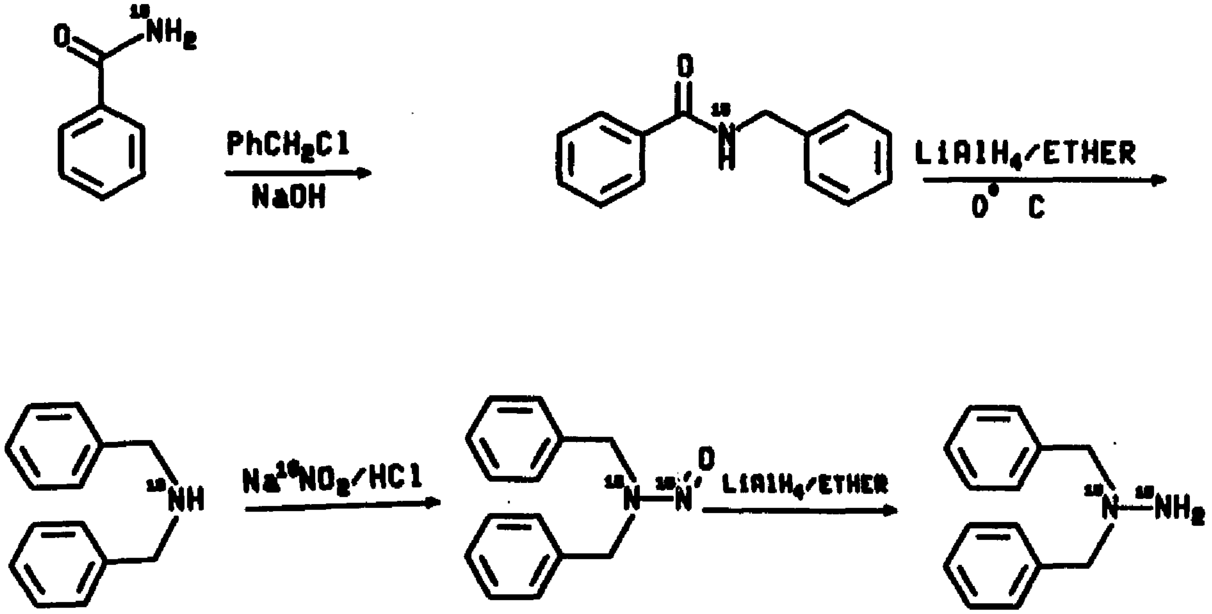
4.18 Preparation of 2,4,6-triphenyl-1,3,5-triazabicyclo-[3.1.0.]hexane-$^{15}N_2$

The procedure of Schmitz[112]was employed with slight modifications.



4.19 Preparation of N,N-Diphenylhydrazine-$^{15}N_2$

N,N-diphenylhydrazine-$^{15}N_2$ was prepared by benzoylation of benzylamine-^{15}N as outlined below. The reduction of benzylbenzamide-^{15}N followed by nitrosation of dibenzylamine-$^{15}N_2$ and and then a light reduction of N,N-diphenylnitrosoamine-$^{15}N_2$ gave the desired material.



4.19.1 Benzoylation of benzylamine-^{15}N

The procedure of Vogle[114] was employed. Benzylamine-^{15}N (0.705g, 6.58 mmol) was stirred at room temperature with 30 ml 5% sodium hydroxide solution while benzoylchloride (3.93g, 28.0 mmol) was added to the mixture dropwise over a half hour period. Stirring was continued for an hour during which time an additional 5 ml 5% sodium hydroxide was added to keep the reaction mixture basic. At the end of the time, bezoylchloride could not be detected by odor(24 hours). The resulting white suspended solid was extracted with 2x10 ml of chloroform. The chloroform layer was washed with 25 ml water and then dried over sodium sulfate. Removal of solvent on a rotary evaporator gave 0.987g (71.0%) of N-benzylbenzamide-^{15}N. m.p. 101-106° (Lit. 104-106).

4.19.2 Reduction of N-Benzylbenzamide-^{15}N

The same procedure that was used for the reduction of benzylamine (section 4.16) was employed for this compound. From a mixture of N-1 benzylbenzamide-^{15}N (0.903g, 4.25 mmol) and $LiAlH_4$ (0.359g, 9.44 mmol), 0.72g (86.4%) of dibenzylamine-^{15}N was obtained. ^1H NMR ($CDCl_3$): δ3.65 (broad, ^{15}NH), δ4.50 (s, $2CH_2$), δ7.25 (s, C_6H_5).

4.19.3 Nitrosation of dibenzylamine-^{15}N

The procedure of Overberger[115] was employed for the preparation of this compound. A mixture of 7 ml of water and 1.1 ml of concentrated hydrochloric acid was added to dibenzylamine-^{15}N (0.683g, 3.46 mmol) in a 25 ml round-bottomed flask equipped with a magnetic stirring bar.

The mixture was heated to 65°C and kept at this temperature while adding 7 ml of $Na^{15}NO_2$ (0.248g, 3.60 mmol) aqueous solution over a two hour period. The salts dissolved slowly to give a colorless solution and then the oil layer was separated out. Stirring at room temperature was continued for an additional hour. Then 15 ml of chloroform was added and the yellow chloroform layer was decanted. The aqueous layer was made alkaline with 10% sodium hydroxide solution and then was extracted with 25 ml chloroform. The combined organic layers were dried over sodium sulfate. Removal of solvent on a rotary evaporator gave 0.683g (87.4%) of orange solid N,N-dibenzylenenitrosoamine-$^{15}N_2$. m.p. 48-55°, ^1H NMR ($CDCl_3$): δ4.45 (s, $2CH_2$), δ7.05 (m, C_6H_5).

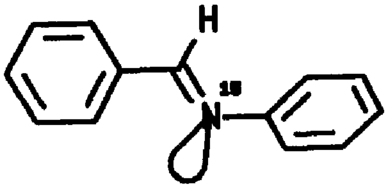
4.19.4 Reduction of N,N-Dibenzylnitrosoamine-$^{15}N_2$

A solution of N,N-dibenzylnitrosoamine-$^{15}N_2$ (0.110g, 0.49 mmol) in 10 ml of ether was added dropwise to a solution of $LiAlH_4$ (0.057g, 1.50 mmol) in 10 ml of ether in a 100 ml of three-necked flask. The resulting milky solution was stirred for 45 minutes at room temperature. Water (0.5 ml) was added slowly and the ether solution was filtered. The precipitated salt was washed with ether. The combined ether extracts were dried over sodium sulfate and the solvent was removed to give 0.088g (85.5%) of N,N-dibenzylhydrozine$^{15}N_2$. m.p. 50-56°.

APPENDIX A

SUBSTITUENT EFFECTS ON ^{13}C-^{15}N SPIN COUPLING AND ^{13}C CHEMICAL SHIFTS IN BENZYLIDENEANILINES

Considerable evidence[116] indicates that the preferred conformation of trans-N-benzylideneaniline <u>XXIX</u> and its derivatives has the benzylidene ring essentially coplanar with the imine double bond, while the aniline ring is twisted out of this plane by an estimated 30-50°



XXIX

(values depend on the experimental technique used and the physical state of the sample). The non-planarity of the aniline ring and the C=N bond has been attributed to the conjugation arising from the overlap of the nitrogen lone-pair of electrons with the π-system of the aniline ring [11]. The molecular conformations of benzylideneanilines have been extensively studied by ^{13}C NMR through the effects of substituents (2-Cl, 2-Br, 2-CH_3). The coupling $^{2}J_{C_2N}$ increases by 1 Hz or more, while coupling to the ortho carbon, $^{2}J_{C_6N}$, decreases of substituents on the ^{13}C-^{15}N couplings, but these latter studies have been limited to compounds containing substituents only in the benzylidene ring [11]. Previous studies in our laboratory[21,36] have shown that ^{13}C-^{15}N spin-coupling in anilines are subject to significant electronic and steric influences. It was therefore of interest to investigate compounds having substituents in the aniline ring and, in particular, at the ortho position where possible steric effects on the molecular conformation could be examined.

The ^{13}C chemical shifts and ^{13}C-^{15}N spin coupline constants are reported in Table XIII and XIV, respectively. Chemical shift assignments for the various carbon atoms were made by comparison of the observed chemical shifts and coupling constants with those for either known, or closely related, labeled and unlabled compounds that have been reported in the literature.

In general, it may be seen that the one-bond ^{13}C-^{15}N couplings and most of the other two- and three-bond couplings are fairly constant, despite the wide range of substituents that has been studied. The striking exception, however, is the effect that is observed when the aniline ring bears ortho-substituents. In these cases, the couplings change from 3 Hz to less than 0.4 Hz. These changes are also accompanied by an upfield shift in the resonance of the C_6 atom. One may speculate that steric compression involving the ortho substituent causes the aniline ring to rotate towards the planar conformation, bring C_2 closer in space to the nitrogen lone-pair while simultaneously moving C_6 away, and that this conformational change is responsible for the observed effects[11].

Table XIII. ^{13}C Chemical Shifts for Benzylideneanilines-^{15}N

Substituents	C_8	C_1	C_4	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{3'}$	$C_{5'}$	$C_{6'}$
2'-Cl	157.0	151.9	126.4	133.4	136.1	127.1	130.0	132.2	128.7
2'-OCH_3	156.5	152.8	125.7	124.9	159.6	111.2	132.7	120.9	127.5
2',6'-$(Cl)_2$	156.4	151.4	126.7	132.7	135.2	128.8	130.7	128.8	135.2
2',6'-$(NO_2)_2$	153.4	150.6	127.1	128.6	149.7	128.7	130.5	128.7	149.7
4'-NO_2	157.3	150.9	127.0	141.6	129.4	123.9	149.3	123.9	129.4
4'-Cl	158.8	151.7	126.2	134.7	130.0	129.1	137.4	129.1	130.0
4'-$N(CH_3)_2$	160.2	153.0	124.9	124.6	130.4	111.6	152.5	111.6	130.4
4'-OCH_3	159.7	152.4	125.5	129.4	130.5	114.2	162.3	114.2	130.5

	C_8	C_1	C_2	C_3	C_4	C_5	C_6	$C_{1'}$	C_4
2-Br	161.7	151.0	118.1	133.0	126.6	128.3	119.7	135.9	131.7
2-Cl	162.1	149.6	127.8	130.1	126.3	129.4	118.9	135.9	131.8
2-CH_3	159.4	151.2	131.9	130.3	125.6	126.7	117.6	136.6	131.2
3,5-$(CH_3)_2$4-NO_2	161.8	156.1	121.0	131.3	153.3	131.3	121.0	135.7	131.9
4-NO_2	162.7	157.9	121.2	125.0	145.4	125.0	121.2	135.4	132.4
4-H	160.4	152.1	120.9	129.2	125.9	129.2	120.9	136.3	131.4
4-CH_3	159.6	149.4	120.8	129.7	135.8	129.7	120.8	136.4	131.1
4-OCH_3	158.4	144.9	122.2	114.4	158.3	114.4	122.2	136.5	131.0

Table XIV. $^{13}C-^{15}N$ Coupling Constants for Benzylideneanilines-^{15}N

Substituents	$^1J_{C_8N}$	$^1J_{C_1N}$	$^2J_{C_2N}$	$^3J_{C_3N}$	$^3J_{C_5N}$	$^2J_{C_6N}$	$^2J_{C_9N}$	$^3J_{C_2N}$	$^3J_{C_6N}$
2'-Cl	7.5	1.3	2.9	1.5	1.5	2.9	7.3	2.5	3.7
2'-OCH_3	7.2	1.4	3.0	0.5	0.5	3.0	6.8	2.5	3.5
2',6'-$(Cl)_2$	7.2	1.4	2.9	1.4	1.4	2.9	6.3	1.4	1.4
2',6'-$(NO_2)_2$	8.1	0.9	2.9	1.5	1.5	2.9	7.4	<0.4	<0.4
4'-NO_2	7.4	1.4	3.0	1.6	1.6	3.0	7.1	3.1	3.1
4'-Cl	7.3	1.4	2.9	1.4	1.4	2.9	6.8	3.0	3.0
4'-$N(CH_3)_2$	7.0	1.6	2.9	1.4	1.4	2.9	6.6	2.8	2.8
4'-OCH_3	7.1	1.4	2.9	1.5	1.5	2.9	5.2	2.9	2.9
2-Br	7.1	2.7	4.9	1.0	<0.4	<0.4	7.0	3.0	3.0
2-Cl	7.3	2.5	4.0	<0.4	<0.4	<0.4	6.8	3.0	3.0
2-CH_3	7.3	1.5	4.6	1.3	<0.4	<0.4	6.8	2.7	2.7
3,5-$(CH_3)_2$,4-NO_2	7.2	1.0	3.0	1.5	1.5	3.0	6.1	2.9	2.9
4-NO_2	7.0	1.4	3.0	1.4	1.4	3.0	6.7	2.9	2.9
4-H	7.1	1.4	2.9	1.4	1.4	2.9	6.7	2.6	2.6
4-CH_3	7.3	1.7	3.1	1.5	1.5	3.1	6.8	2.6	2.6
4-OCH_3	7.2	1.9	3.3	1.7	1.7	3.3	6.8	2.9	2.9

^{13}C NMR spectra were recorded with broad band decoupling at ambient temperature at 50 MHz, using ca 10% w/v solutions in deuteriochloroform, on an Bruker WP-200SY spectrometer equipped with a multinuclear broad-banded probe. Typical parameters used were: pulse width, 30° flip amgle; spectral width, 5000 Hz; aquisition time, 3.3 s; number of accumulations, 1000-2000; number of data points, 32K. Chemical shifts were measured with respect to deuteriochloroform (77.0 ppm) and are reported relative to tetramethylsilane.

The benzyildeneanilines were prepared by condensation of the appropriately substituted benzaldehydes and anilines by standard procedures[116]. The synthesis of the required ^{15}N-labeled anilines (99% enriched) has been described elsewhere[11].

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