NITROGEN-15 MAGNETIC RESONANCE SPECTROSCOPY

by

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A dissertation submitted to the
Graduate Faculty in Chemistry in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy,
The City University of New York.

1970

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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ACKNOWLEDGEMENTS

I would like to extend my gratitude to Dr. Theodore Axenrod for both his guidance and friendship during my tenure at the City College.

I would also like to thank Dr. William Milne of the National Institutes of Health for his helpful suggestions and his assistance in obtaining 100 MHz spectra. I would especially like to thank Dr. Edwin Becker of the National Institutes of Health for performing the double resonance experiments, necessary to obtain the nitrogen-15 chemical shifts.

I would like to thank my parents without whose foresight this thesis would have been impossible.

Especially, I would like to thank my wife, Carole. Her efforts, both in the typing of this thesis and in attempting to cope with its author, have contributed as much to this dissertation as have the author's efforts in the laboratory.

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INTRODUCTION

Scope

The advent of nuclear magnetic resonance spectroscopy as an aid in the determination of structure and 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] Theoretical considerations have related the amplitude of the nuclear magnetic resonance (nmr) signal for a given nucleus to the magnitude of the magnetic moment, μ. Consequently, it comes as no surprise that the early nmr investigations were confined primarily to those nuclei e.g., ^{1}H and ^{19}F, whose natural abundance and magnetic moments rendered them most amenable to the technique.

In this dissertation nitrogen-15 has been used to study molecular properties through a determination of its chemical shift and spin-coupling with neighboring protons. In Part I of this thesis the effect of structural changes on the ^{15}N-H coupling and the ^{15}N-chemical shift in a series of aniline-^{15}N derivatives has been investigated. In Part II of this thesis the configuration and conformations of ^{15}N-nitroso-labeled nitrosoamines and nitrosohydrazines have been investigated.

A brief discussion of some of the fundamental nitrogen nmr con-

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(1) H. A. Thomas, Phys. Rev., 80, 901 (1950).
(2) G. Lindstrom, Phys. Rev., 78, 817 (1950).
(3) W. C. Dickinson, Phys. Rev., 77, 717 (1950).

siderations that may be helpful in explaining some of the experimental observations follows.

Nuclear Parameters and Double Resonance

There are two naturally occurring isotopes of nitrogen, ^{14}N and ^{15}N. The former isotope occurs in nature to the extent of 99.63%, has a nuclear spin, I=1, and therefore has an electric quadrupole moment. The magnetic moment of this nucleus, μ, has been shown to be +0.403562± 10^{-5} nuclear magnetons.[4] The less abundant isotope, ^{15}N, which occurs naturally to the extent of 0.36% has a nuclear spin, I=½, and consequently possesses no electric quadrupole moment. The magnetic moment associated with this nucleus has been shown to be -0.283049± 7×10^{-6} nuclear magnetons.[4]

The presence of an electric quadrupole moment in the nitrogen-14 nucleus limits the lifetimes of the available spin states through quadrupolar induced relaxation. This induced relaxation results not only in considerably broadened nitrogen-14 resonance lines, but also causes broadening in the resonance signals of those nuclei to which it is spin-coupled. Line widths of more than 100Hz[5] are not uncommon and although nitrogen-14 chemical shifts have been measured, the uncertainty due to this broadening has reduced the usefulness of these determinations. It is known[6] that the width of the ^{14}N absorption is related to

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(4) M. R. Baker, C. H. Anderson and N. F. Ramsey, Phys. Rev., 133, A1533 (1964).
(5) D. Herbison-Evans and R. E. Richards, Mol. Phys., 8, 19 (1964).
(6) R. A. Ogg and S. D. Ray, J. Chem. Phys., 26, 1339 (1957).

the field symmetry at the nitrogen atom. Thus, the nitrogen absorptions for $^{14}NH_4^+$ and $(CH_3)^{14}{}_4N^+$ ions give relatively narrow signals while their conjugate bases give broad poorly resolved signals. Examples of narrow line widths in conjunction with lower molecular symmetry have been observed for the nitrogen chemical shifts in isonitriles[7] and the pyridinium ion.[8] However, no systematic method of predicting these cases is known as yet.

Due to the absence of a quadrupole moment, nitrogen-15 magnetic resonance does not suffer from this inherent difficulty. Sharp resonance lines, approaching 1 Hz in width are possible and, in the absence of exchange phenomena, coupling to other nuclei is readily measured. Unfortunately, the low natural abundance of this isotope frequently necessitates the use of enriched samples, which, even then, as a result of the low inherent sensitivity of this nucleus may require extensive spectrum accumulation. Computer averaging to accumulate a spectrum might very will be applicable for the determination of both ^{14}N and ^{15}N resonances as the sensitivities of these nuclei, relative to a proton at constant field are 1.01×10^{-3} and 1.04×10^{-3}, respectively.[9] It is often desirable to have chemical shift and coupling constant data for both ^{14}N and ^{15}N. This may be obtained, for a given compound, from the values for one isotopomer and a knowledge of the ratios of the gyromagnetic constants, $^{15}\gamma/^{14}\gamma$ for the two nuclei. For the two isotopes

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(7) M. Witanowski, Tetrahedron, 23, 4299 (1967).
(8) I. C. Smith and G. Schneider, Can. J. Chem., 39, 1158 (1961).
(9) J. B. Lambert, G. Binsch and J. D. Roberts, Proc. Nat. Acad. Sci., U. S., 51, 735 (1964).

of nitrogen Baldeschwieler[10] found $^{15}\gamma/^{14}\gamma$ to be approximately 1.4. The gyromagnetic constant for a given nucleus represents the proportionality factor between its magnetic moment, μ, and its angular momentum, p, as shown in equation 1.

$$\mu = \gamma p \tag{1}$$

The difficulties normally encountered in the direct observation of nitrogen resonances can be circumvented by the use of the technique of nuclear magnetic double resonance (NMDR).[11] This method is applicable if the proton spectrum of a nitrogen-containing molecule shows evidence of coupling to the nitrogen atom. It involves the application of two different radio frequencies to a sample in a fixed magnetic field. One frequency is used to observe the proton resonance while the second frequency is imposed in the region of nitrogen absorption. When the precise frequency necessary to bring the nitrogen atom into resonance under these conditions is applied the proton multiplet will collapse. Thus, the nitrogen chemical shift may be determined by ascertaining the optimum frequency necessary to effect decoupling. In situations where the proton lines are sufficiently sharp the decoupling frequency, which represents the chemical shift of the nitrogen in question, may be determined to within ± 0.1Hz.[12]

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(10) J. D. Baldeschwieler, J. Chem. Phys., 36, 152 (1962).
(11) J. D. Baldeschwieler and E. W. Randall, Chem. Rev., 63, 81 (1963).
(12) P. Hampson and A. Mathias, Chem. Commun., 825 (1968) and preceding papers.

Clearly, the primary advantage of NMDR is that it allows the measurement of chemical shifts for nuclei of inherently low sensitivity with the convenience of a proton measurement. It is equally clear, however, that this technique may only be applied in those cases where the coupling between nitrogen and a proton is observable.

Some Theoretical Considerations

1. Chemical Shifts

The field, H_o, at which a given nucleus comes into resonance, at constant frequency, ν, is a function of the gyromagnetic ratio of that nucleus and the extent to which the electrons and nucleus of that atom and all the other electrons and nuclei in the molecule interact with the magnetic field. This relationship is shown in equation 2. As indicated

$$\nu = \gamma H_o (1 - \sigma)/2\pi \qquad (2)$$

by this equation the magnetic field experienced by a nucleus is not the applied field, but rather is the difference between the applied field, H_o, and the product of H_o and σ, the screening constant. Present theory[13] treats the total screening, σ_t, as the sum of three terms shown in equation 3. σ_d represents the local diamagnetic term whose

$$\sigma_t = \sigma_d + \sigma_a + \sigma_p \qquad (3)$$

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(13) A. Saika and C. P. Slichter, J. Chem. Phys., 22, 26 (1954); J. A. Pople, Discussions Faraday Soc., 34, 7 (1963).

main contributions come from inner non-bonding orbitals. This part of the screening constant predicts a shift to higher fields with increasing electron density at the atom in question. Recent calculations involving ^{15}N-nitrogen-oxygen compounds[14] suggest the magnitude of the diamagnetic contribution to be approximately 80 ppm. σ_a is the screening which arises from long range shielding by other atoms and whose magnitude has been estimated at 1 ppm. As the range of nitrogen chemical shifts is in excess of 1000 ppm, the greatest contribution to the screening constant is considered to arise from the paramagnetic term, σ_p. Indeed, as a first approximation, nitrogen shifts have been interpreted solely in terms of changes in σ_p.[14] The general expression suggested by Pople[15] for second row elements is shown in equation 4, where ΔE is the mean triplet excitation energy, $\langle r^{-3} \rangle$ is the mean

$$\sigma_p \propto \langle r^{-3} \rangle \Sigma Q_{AB} / \Delta E \qquad (4)$$

value of the inverse cube of the radius for the 2p orbitals of the atom in question, and the terms Q_{AB} contain the elements of charge density and bond order matrix. Attempts at a correlation of nitrogen chemical shifts with $n-\pi^*$ transitions have been made[16] and while rough parallels appear, a more thorough knowledge of the other excited states appears to be necessary. Other studies involving nitroaromatic compounds have

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(14) J. B. Lambert and J. D. Roberts, J. Amer. Chem. Soc., 87, 4087 (1965).

(15) J. A. Pople, Mol. Phys., 7, 301 (1963-64).

(16) D. T. Clark, and J. D. Roberts, J. Amer. Chem. Soc., 88, 745 (1966); T. K. Wu, J. Chem. Phys., 49, 1139 (1968); J. D. Baldeschwieler and E. W. Randall, Proc. Chem. Soc., 303 (1961); J. Mason, Chem. Commun., 357 (1969).

correlated the Q_{AB} terms with nitrogen chemical shifts without reference to either ΔE or $\langle r^{-3} \rangle$.[17] The failure of any one specific term in equation 4 to account for observed chemical shifts is not unreasonable in view of the approximations involved, or it may be that a given result represents some combination of these terms.

2. Coupling Constants

The Ramsey[18] theory of nuclear spin-spin coupling between two atoms, A and B, treats the coupling constant as the sum of three contributing terms shown in equation 5. The first term, J_1, arises from relativistic

$$J_{AB} = J_1 + J_2 + J_3 \qquad (5)$$

effects and is referred to as the "Fermi contact term".[19] The J_2 term is due to the interaction between the nuclear magnetic moments and the magnetic moments of the electrons, while J_3 arises from the magnetic shielding of the direct interaction of nuclear spins by electron orbital motion.

The relative importance of the terms in equation 5 have been estimated from a calculation made by Ishiguro[20] on the HD molecule. Allowing for molecular vibration he found J_3 to be +0.100Hz, J_2 to be +0.202 Hz and J_1, the "contact term", to be +36.837 Hz, thus making the total calculated J (HD) equal to 37.139 Hz. While this value is only

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(17) M. Witanowski, J. Amer. Chem. Soc., 90, 5683 (1968).
(18) N. F. Ramsey, Phys. Rev., 91, 303 (1953).
(19) E. Fermi, Z. Physik., 60, 320 (1930).
(20) E. Ishiguro, Phys. Rev., 111, 203 (1958).

in reasonable agreement with the experimental value of ± 43.0 Hz[21] it indicates that coupling is dominated by J_1, the Fermi contact term. Expressions have been deduced for J_1 by both variation and perturbation techniques,[22] and a specific equation for the one bond coupling of a proton to a magnetic nucleus of second row elements has been derived.[23]

This equation, in simplified form, is shown in equation 6, where

$$J_{HA} \propto S_A S_H / \Delta E \qquad (6)$$

E is the mean triplet excitation energy and S_A and S_H are proportional to the per cent s-character of the orbitals forming the bond. Calculations for NH_3 and the NH_4^+ ion, based on equations of this type, have given only fair results.[24]

If a system is chosen such that a change in molecular structure effects only a change in S_A, we may then correlate the observed change in coupling (neglecting J_2 and J_3) with the hybridization of atom A. A correlation of this type has been made for one-bond ^{13}C-H coupling constants[25] and is shown in equation 7. The adaptation of coupling

$$\% \; s = 0.20 \; J(^{13}C\text{-}H) \qquad (7)$$

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(21) H. Y. Carr and E. M. Purcell, Phys. Rev., 88, 415 (1952).
(22) M. Barfield and D. M. Grant, Advan. in Magnetic Resonance, 1, 149 (1965).
(23) C. Juan and H. Gutowsky, J. Chem. Phys., 37, 2198 (1962).
(24) W. McFarlane, Quart. Rev., 23, 187 (1969) and references therein.
(25) N. Muller and D. E. Pritchard, J. Chem. Phys., 31, 1471 (1959).

constant measurements to the determination of hybridization states has attracted wide use, although this approach has not gone unchallenged. Bond polarities may be as important if not more important than the hybridization in certain cases.[26]

Survey of Nitrogen-15 NMR Literature

In recent years the literature has witnessed an increasing application of nmr studies involving nitrogen-15 labeled molecules to the solution of a wide variety of problems in all areas of chemistry. Recent compilations of nitrogen chemical shifts[9] and coupling constants[27] have provided the impetus for additional studies.

In systems of biological importance ^{15}N spectroscopy promises to be a valuable adjunct. The interaction of Zn^{+2} and Mg^{+2} ion with adenosine triphosphate enriched with ^{15}N at all positions has been studied by Happe and Morales.[28] Five well separated nitrogen resonances were observed and assigned. Addition of Mg^{+2} produced no shift in the nitrogen resonances while Zn^{+2} caused an upfield shift of 5.5 ppm. The surprising conclusion is that Mg^{+2} does not interact with ATP. In studdies concerned with the structures and site of protonation in pyrimidine[29] and cytosine[30] derivatives it has been demonstrated by observation of ^{15}N-H coupling that 1-methylcytosine hydrochloride (I), for

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(26) D. M. Grant and W. M. Litchman, J. Amer. Chem. Soc., 87, 3994 (1965).

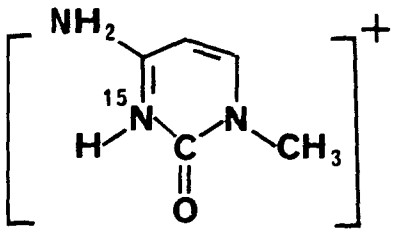
(27) G. Binsch, J. B. Lambert, B. W. Roberts and J. D. Roberts, J. Amer. Chem. Soc., 86, 5564 (1964).

(28) J. A. Happe and M. Morales, J. Amer. Chem. Soc., 88, 2077 (1966).

(29) B. W. Roberts, J. B. Lambert and J. D. Roberts, J. Amer. Chem. Soc., 84, 5439 (1965).

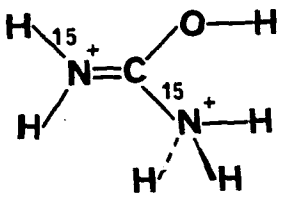
(30) E. D. Becker, H. T. Miles and R. B. Bradley, J. Amer. Chem. Soc., 87, 5575 (1968).

example, is protonated at the 3-N position.



I

In a similar manner Olah and White[31] have demonstrated that, in the presence of strong acid, urea undergoes diprotonation to give a cation whose structure is suggested to be II.



II

In systems capable of tautomeric exchange, nitrogen-15 studies have proved valuable in the assignment of structure and estimation of the

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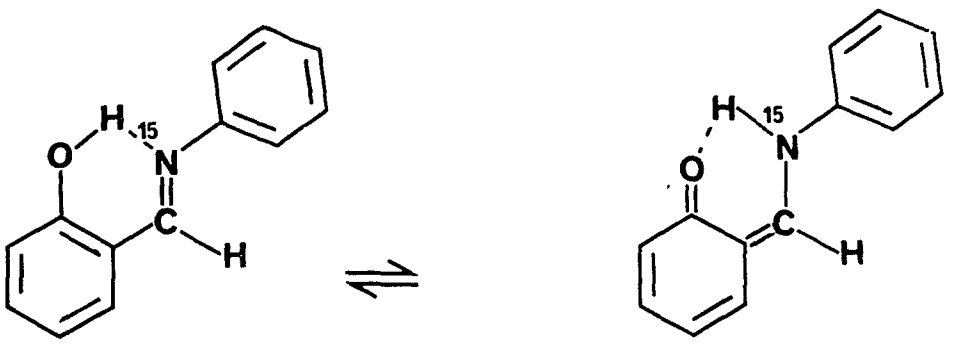
(31) G. A. Olah and A. M. White, J. Amer. Chem. Soc., 90, 6087 (1968).

amount of intramolecular hydrogen bonding. For example, the Schiff base formed from salicylaldehyde and aniline-^{15}N shows an unusually



IIIa IIIb

small J(^{15}N-H) of 13.1 Hz which, it is thought, represents the weighted average of the coupling over two sites in the tautomeric forms IIIa and IIIb.[32] Similarly, the value of 91.5 Hz observed for the one-bond ^{15}N-H coupling in the pyrazolinone, (IV), has been used to distinguish it from structure (V) which otherwise has similar characteristics.[33]

Lehn and co-workers[34] have used the double resonance technique to determine both the relative and absolute signs of nitrogen-15 coupling in oximes and quinoline derivatives. Significantly, the two geminal ^{15}N=CH coupling constants in formaldoxime-^{15}N were found to be of

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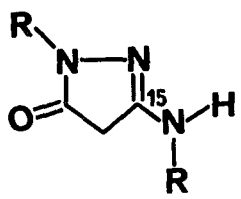
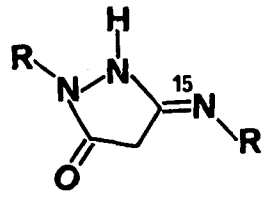
(32) G. O. Dudek, E. P. Dudek, J. Amer. Chem. Soc., 88, 2407 (1966).

(33) G. J. Lestina, G. P. Happ, D. P. Maier and T. H. Regan, J. Org. Chem., 33, 3336 (1968); G. J. Lestina and T. H. Regan, J. Org. Chem., 34, 1685 (1969).

(34) D. Crepaux and J. M. Lehn, Mol. Phys., 14, 547 (1968); D. Crepaux, J. M. Lehn and R. R. Deans, Mol. Phys., 16, 225 (1969).



IV



V

opposite sign.

The possibility that (p-d)π-bonding exists between nitrogen and the directly bonded atoms with empty "d" orbitals in trimethylstannyl, trimethylgermyl and trimethylsilylanilines was tested by an examination of the J(^{15}N-H) values. The failure to observe any significant difference between these couplings and the corresponding coupling in aniline-^{15}N indicates that this type of π-bonding is not important.[35] Finally, by integration of the proton spectra of products derived from phenyldiazonium chloride (from aniline-^{15}N) it was demonstrated[36] that no rearrangement of the type shown on p 13, had occurred as had been previously claimed.[37]

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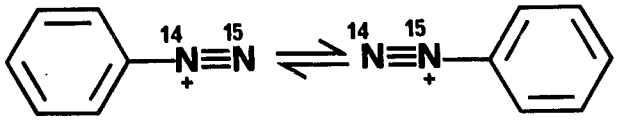
(35) E. W. Randall and J. J. Zuckerman, J. Amer. Chem. Soc., 90, 3167 (1968).

(36) A. K. Bose and I. Kugajevsky, J. Amer. Chem. Soc., 88, 2325 (1966).

(37) J. M. Insole and E. S. Lewis, J. Amer. Chem. Soc., 85, 122 (1963).


14
15
N≡N
+
⇌
14
15
N≡N
+

PART I

AN NMR STUDY OF ANILINE-^{15}N DERIVATIVES

PRESENT INVESTIGATION

Since the first proposal[25] that the magnitude of the one-bond coupling could be related to the hybridization of the nuclei involved, much effort has been expended in testing this hypothesis with emphasis on the study of ^{13}C-H coupling. The results so obtained have been encouraging and usually compare favorably with hybridization conclusions reached by different approaches.

More recently, this hypothesis has been extended to the one-bond ^{15}N-H coupling. Two independent groups suggested similar relationships between the magnitude of the coupling and the % s-character in the bonding orbital of the nitrogen atom. The empirical relationship suggested by Roberts[9] and his co-workers is shown in equation 8. This group

$$\% \; s = 0.43 \; J(^{15}NH) - 6 \qquad (8)$$

assumed the ammonium ion, $^{15}NH_4^+$, and the diphenylketimmonium ion, $Ph_2C{=}^{15}NH_2^+$, to be representative cases of sp^3 and sp^2 nitrogen hybridization having 25% and 33% s-character, respectively.

An essentially identical expression has been suggested by Bourn and Randall[38] based on the $^{15}NH_4^+$ ion and $^{15}NH_3$ as model hybridization cases. This relationship is given in equation 9. The two equations do not differ significantly and with few exceptions predict coupling con-

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(38) A. J. R. Bourn and E. W. Randall, Mol. Phys., 8, 567 (1964).

$$\% \; s = 0.34 \; J(^{15}N\text{-}H) \qquad (9)$$

stants which are in substantial accord with observed values based on the classical hybridization normally expected in a variety of nitrogen-containing functional groups.

For example, equation 8 predicts coupling constants of 72, 90 and 130 Hz for sp^3, sp^2 and sp hybridization situations, respectively. These expectations are supported by the observed coupling constants of 75 Hz in anilinium-^{15}N trifluoroacetate,[39] 88 and 92 Hz in formamide-^{15}N[40] and 130-136 Hz in protonated nitriles[41] as these compounds represent cases for sp^3, sp^2 and sp nitrogen hybridizations, respectively.

It is well know that the relative base strengths of aniline derivatives are markedly dependent on the nature of the ring substituent.[42] The existence of a quantitative correlation between the s-character of the N-H bond and the value of the one-bond coupling constant provided an excellent manner in which the hybridization of the nitrogen in a series of aniline-^{15}N derivatives could be investigated. As relatively little information is presently available on the nature of the nitrogen-15 chemical shifts in compounds of this type, it seemed worthwhile to simultaneously investigate the relationship, if any, that

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(39) M. Bramwell and E. W. Randall, Chem. Commun., 250 (1969).

(40) B. Sunners, L. H. Piette and W. G. Schneider, Can. J. Chem., 38, 681 (1960).

(41) H. Hogeveen, Rec. Trav. Chem. Pays-Bas, 86, 1288 (1968); G. A. Olah and T. E. Kiovsky, J. Amer. Chem. Soc., 90, 4666 (1968).

(42) J. Clark and D. D. Perrin, Quart. Rev., 18, 295 (1964).

might exist between the nature of the bonding to the nitrogen nucleus and the nitrogen-15 chemical shift.

One-Bond ^{15}N-H Coupling Constants

1. Ring-substituted Aniline-^{15}N Derivatives

A series of para-substituted aniline-^{15}N derivatives having a ^{15}N-enrichment of 95% was prepared. The one-bond ^{15}N-H coupling constants in these compounds were determined in chloroform and dimethylsulfoxide solutions using approximately 1 molal concentrations.[43] The sample solutions in most cases were shaken for several hours with dry basic alumina in order to reduce the exchange rate of the ^{15}N-bound protons with traces of water or hydrogen ions in the solutions. These data are presented in Table I, page 18. Examination of these data reveals that the ^{15}N-H coupling constants shows a dependence on both the solvent employed and the nature of the para-substitent.

The solvent dependence of the ^{15}N-H coupling constant in aniline has previously been observed by Becker and Paolillo.[44] These workers attributed the changes in $J(^{15}N\text{-}H)$ in aniline to variations in the hydrogen bonding ability of the solvent. Values were found to range from 78 to 82 Hz going from cyclohexane to dimethylsulfoxide. Similarly,

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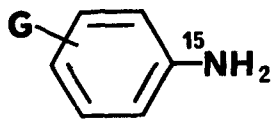
(43) The concentration used in some cases was determined by the limited amount of material available from the synthetic procedure followed. The effect of concentration on the ^{15}N-H coupling constant in the case of aniline in $CDCl_3$ solution was shown to be less than the experimental error, ± 0.2 Hz, over a ten-fold range in concentration.

(44) E. D. Becker and L. Paolillo, 1968, personal communication.

Table I. One-Bond ^{15}NH Coupling Constants in Ring Substituted Anilines.[a]

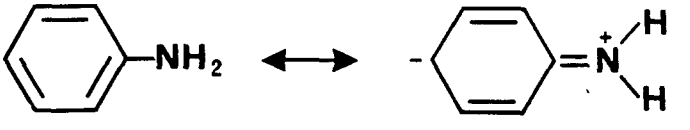


G	$J(^{15}NH)$, Hz DMSO-d_6	$CDCl_3$
4-NMe_2	78.8[b]	74.8
4-NH_2		74.9
4-MeO	79.4	75.6
4-Me	81.4	76.5
4-F	81.6	77.8
4-H	82.6	78.6
4-Cl	83.7	78.9
4-I	84.0	79.7
4-Br	84.0	79.6
2,4-Br_2	86.0	82.7
3,5-Me-4-NO_2	87.0	83.2
2,4,6-Br_3	87.4	
4-NO_2	89.4	86.4
2,4-$(NO_2)_2$	92.6	

[a] Measured as approximately 1 molal solutions at 37-43°. Values are estimated to be ± 0.2 Hz. [b] Measurement made at 10°C.

the one-and two-bond ^{15}N-H coupling constants in formamide-^{15}N have been shown to increase from 88.0 to 95.4 Hz and from 16.4 to 23.3 Hz, respectively, in going from acetone to water.[40] It has been suggested that such changes in the magnitude of the coupling may be attributed to the differences in the hydrogen bonding ability[45] of the solvent as well as changes in the dielectric constant of the medium.[46]

In the case of aniline the $J(^{15}N\text{-}H)$ in chloroform has a value of 78.6 Hz.corresponding to 28% s-character in the hybrid nitrogen orbitals. In dimethylsulfoxide which is a more polar and better hydrogen bonding solvent than chloroform the $J(^{15}N\text{-}H)$ is increased to 82.6 Hz corresponding to 30% s-character. This is equivalent to a partial rehybridization of the nitrogen atom resulting in more extensive delocalization of the nitrogen lone-pair as represented in resonance structures VIa and VIb.



VIa VIb

(45) E. D. Becker, H. T. Miles and R. B. Bradley, J. Amer. Chem. Soc., 87, 5575 (1965).

(46) H. M. Hutton, B. Richardson and T. Schaefer, Can. J. Chem., 45, 1795 (1967).

The substituent dependence of the $J(^{15}N-H)$ in the aniline derivatives listed in Table I, page 18, can be seen to be very similar in either chloroform or dimethylsulfoxide although larger in the latter solvent. Strongly electron withdrawing groups lead to enhanced coupling compared to aniline while electron-donating substituents result in diminished coupling. The importance of the role of the substituent can be illustrated by comparing the $J(^{15}N-H)$ for 2,4-dinitroaniline in dimethylsulfoxide with the results for N,N-dimethyl-p-phenylenediamine. The value of $J(^{15}N-H)$ in 2,4-dinitroaniline is 92.6 Hz corresponding to 34% s-character while the value of 87.8 Hz observed for N,N-dimethyl-p-phenylenediamine corresponds to 28% s-character. Thus, in going from a strongly electron withdrawing substituent to an electron donating substituent the hybridization of the nitrogen atom is changed from virtually sp^2 to a value approximating sp^3 hybridization.

For aniline and other substituted benzenes the importance of π-bonding between the nitrogen lone-pair and the phenyl ring has long been recognized. Recent nuclear quadrupole resonance[47] and microwave[48] studies on aniline in which an H-N-H bond angle of 113° 5' was found have indicated the intermediate nature of the nitrogen hybridization in this amine thus providing additional support for the contention that substantial overlap exists for sp^3 nitrogen. In 2,4-dinitroaniline the observed $J(^{15}N-H)$ of 92.6 Hz supports the view that the nitrogen

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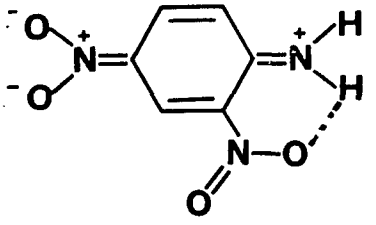
(47) C. T. Yim, M. A. Whitehead and D. H. Lo, Can. J. Chem., 46, 3595 (1968).

(48) D. G. Lister and J. K. Tyler, Chem. Commun., 152 (1966).

pyramid is considerably flattened compared to aniline, where $J(^{15}N\text{-}H)$= 82.6 Hz. Clearly, this must be attributable to the extensively delocalized π-system represented by VII in which hydrogen bonding may also be important. That this should be the situation is not surprising;



VII

however, it is none-the-less gratifying to note that the $J(^{15}N\text{-}H)$ data support these conclusions.

The effect of structural changes on reactions and equilibria involving aromatic compounds has often been expressed in terms of inductive, resonance and steric contributions, with the first two factors dominating if only the meta and para isomers are considered. The Hammett $\sigma\rho$ function[49] relates the effect of a substituent on the electronic environment at a distant reaction site in the molecule. This relationship is shown in equation 10 where K is the rate or equilibrium constant for the substituted derivative, K^o is the rate or equilibrium constant for the corresponding unsubstituted compound, ρ is the reaction

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(49) For reviews see H. H. Jaffe, Chem. Rev., 53, 191 (1953); P. R. Wells, Chem. Rev., 62, 171 (1962).

$$\log K/\log K^{o} = \sigma\rho \qquad (10)$$

constant which measures the sensitivity of the reaction to electrical effects of the substituent, and σ is the substituent constant which measures the ability of the substituent to either donate or withdraw electrons.

The base strengths,[42] N-H stretching frequencies[50] and chemical shifts of the amino protons[51] in ring-substituted aniline derivatives have all been shown to be proportional to the Hammett substituent constant.

A least squares plot of the coupling constant, $J(^{15}N\text{-}H)$, measured in chloroform and dimethylsulfoxide against the Hammett substituent constant for the aniline derivatives is shown in Figure 1, page 23. Except where noted, Hammett substituent constants[52] have been used for meta and para groups while Taft polar substituent constants[53] have been assigned to ortho substituents. It may be seen that, in both solvents, the $J(^{15}N\text{-}H)$ is also proportional to the substituent constant, σ, and

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(50) E. V. Titov, L. M. Litvinenko and N. A. Izamailov, Uktrain. Khim. Zhur., 27, 87 (1961); Chem. Abstr., 55, 20624d (1961).

(51) B. M. Lynch, B. C. MacDonald and J. G. Webb, Tetrahedron, 24, 3598 (1968); T. Yonemoto, B. F. Reynolds, H. M. Hutton and T. Schaefer, Can. J. Chem., 43, 2668 (1965).

(52) L. P. Hammett, "Physical Organic Chemistry", McGraw Hill, New York, 1940, ch 7; A σ value of -0.05 has been assigned to the 4-fluoro group in keeping with the suggestion of Birchall and Jolly; T. Birchall and W. L. Jolly, J. Amer. Chem. Soc., 88, 5439 (1966).

(53) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., John Wiley and Sons Inc., New York, 1956, Ch XIII. For a brief discussion of Taft's approach see J. Hine "Physical Organic Chemistry", 2nd Ed., McGraw Hill, New York, 1962, page 95.

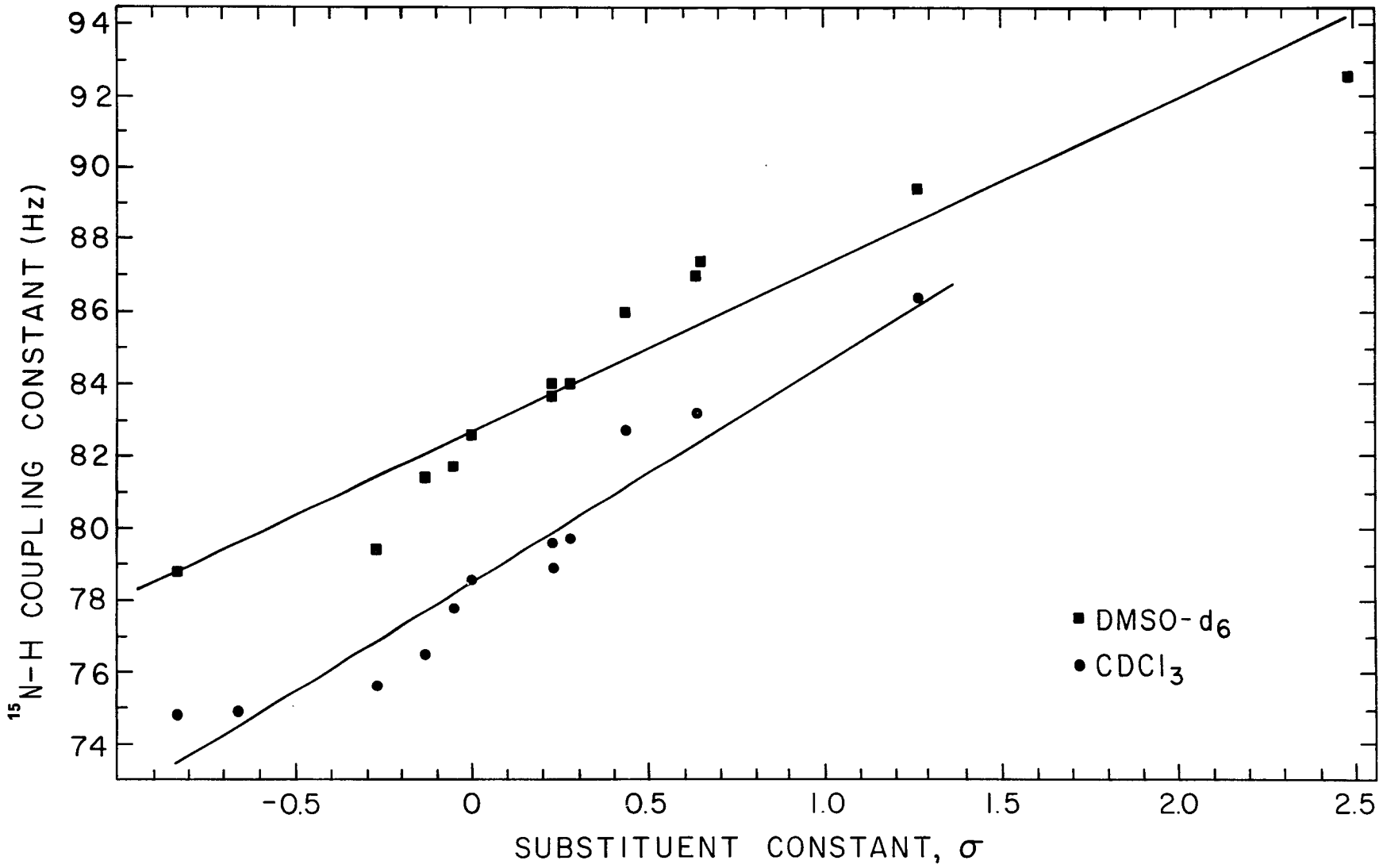

Figure 1. Correlation of the directly bonded nitrogen-15-proton coupling constant in ring substituted anilines with Hammett substituent constant.

that reasonable linearity is observed.[54] The approximate parallel nature of the two plots illustrates that the solvent serves to augment the hybridization at the nitrogen atom without altering the relative electronic effect of the substituents.

That both resonance and inductive effects are operating in these derivatives is illustrated by the magnitude of the dimethylsulfoxide coupling constant for 3,5-dimethyl-4-nitroaniline (87.0 Hz) relative to that for 4-nitroaniline (89.4 Hz). As the cumulative inductive effect of the meta methyl groups on the one-bond coupling constant has been shown to produce a decrease of 0.6 Hz, relative to aniline,[55] an explanation to account for the 2.4 Hz difference in coupling constant may be sought in terms of the relative interaction of the two nitro groups with the π-system of the benzene ring. In the 3,5-dimethyl derivative non-bonded interactions of the nitro-oxygens with the adjacent methyl groups result in a twisting of the nitro-moiety out of the plane of the benzene ring, as shown in VIII. This lack of co-planarity (the angle of twist having been estimated[56] at 55°) effectively prevents contributions of type IX, present in 4-nitroaniline, in which the hybrid nitrogen orbitals have an increased amount of s-character. This decrease in the amount of s-character in 3,5-dimethyl-4-nitroaniline, as

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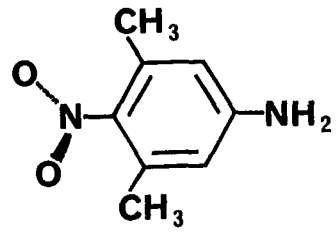
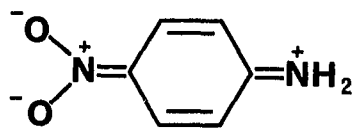
(54) Recently, a similar correlation of the one-bond $J(^{15}N\text{-}H)$ coupling constant with Hammett substituent constant was observed by M. J. Wieder, the City College of New York, for a series of meta-substituted aniline-^{15}N derivatives.

(55) T. Axenrod, P. S. Pregosin, M. J. Wieder and G. W. A. Milne, J. Amer. Chem. Soc., 91, 3681 (1969).

(56) J. P. Schaeffer and T. J. Miraglia, J. Amer. Chem. Soc., 86, 64 (1964); M. J. Dewar and Y. Takeuchi, J. Amer. Chem. Soc., 89, 390 (1967).



VIII



IX

a result of the steric inhibition to resonance, is mirrored in the relatively smaller one-bond coupling.

It has long been recognized that the "normal" Hammett substituent constant for a nitro group provides an inadequate description of this substituent's effect on a reaction center having a much stronger tendency to supply electrons than the carboxylate ion. Accordingly, Hammett proposed the use of a special <u>para</u> constant (σ_p^-), for this substituent, over 60% larger than its normal value (σ_p), for use in reactions of anilines. It is interesting to note that in 3,5-dimethyl-4-nitroaniline, where the resonance interaction of the nitro group is suppressed, the $J(^{15}N\text{-}H)$ correlates well with ordinary σp, whereas in

4-nitroaniline the special σ_p^- value is required.

2. N-Substituted Aniline-^{15}N Derivatives

In an effort to extend our investigations of one-bond ^{15}N-H couplings we next synthesized a group of ^{15}N-alkylanilines. As N-methylaniline is known[42] to have a larger pK_a value than aniline, and since the negative Hammett substituent constant for a methyl group suggests the ability to donate electrons, it was anticipated that a one-bond ^{15}N-H coupling constant lower than the value of 82.6 Hz observed for aniline might be observed.

Figure 2, page 27, shows the nmr spectrum of N-ethylaniline-^{15}N whose one-bond coupling constant in both dimethylsulfoxide and chloroform is shown in Table II, page 28, along with the values for several other N-alkylanilines. In general, it may be seen that N-alkyl groups cause an increase in the one-bond couplings relative to aniline. In Figure 2 the two sets of triplets, spaced 87.5 Hz apart, represent the absorptions for the amino-protons which in this instance are coupled both to the nitrogen-15 atom and the adjacent methylene group. It is interesting to note that the three bond ^{15}N-H coupling to the methyl group (~3Hz) is greater than the two-bond coupling to the methylene group (<1Hz).

The observed one-bond coupling of 87.5 Hz, corresponding to 32% s-character, while not anticipated can be rationalized if one assumes, as a result of the N-alkyl substitution, an increase in the contribution of a resonance structure such as X relative to that for XI in aniline. This increased contribution of the quinoid structure (which produces a relative increase in the % s-character of the nitrogen) compared to aniline may be a consequence of the additional stability of a positive nitrogen atom adjacent to a group capable of donating electrons. Additional support for the increased importance of X is provided by a com-

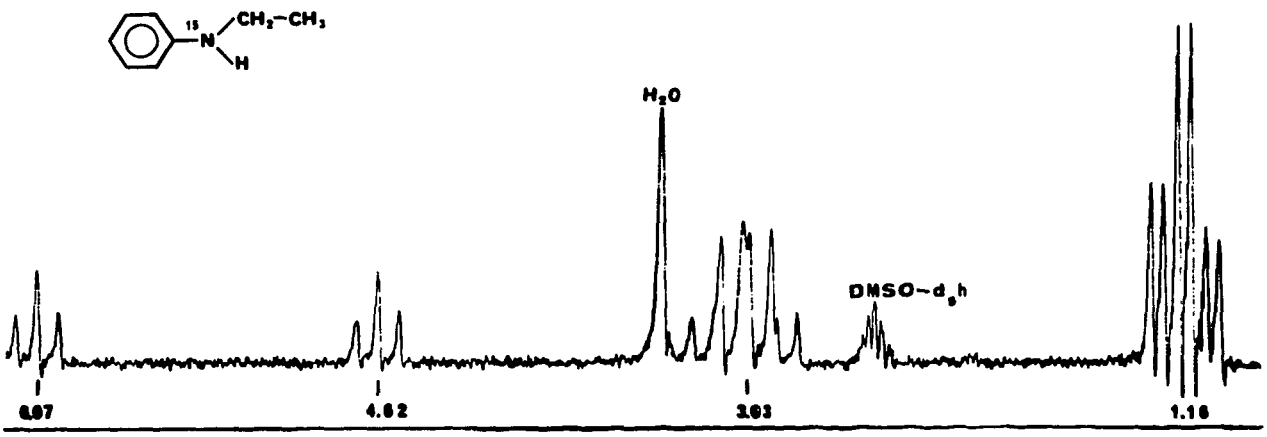
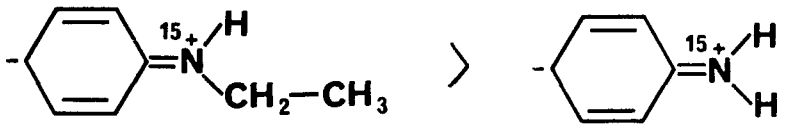


Figure 2. Proton magnetic resonance spectrum of ^{15}N-ethylaniline at 60 MHz.

Table II. One-Bond ^{15}NH Coupling Constants in N-Alkylanilines.[a]

$Ph^{15}NCH_2$-X	J(^{15}NH),Hz		Chemical shift,ppm[b]
X	DMSO-d_6	$CDCl_3$	$^{15}\underline{NH}$
H	87.0	c	5.49
CH_3	87.5	84.3	5.35
$(CH_3)_3C$	87.0	c	5.29
Ph	88.6	86.9	6.10
COPh	88.2	88.2	5.83
CN	88.5	87.7	6.14

[a] Measured as approximately 0.4-1.7m solutions at 37-43°C. [b] Measured from internal tetramethylsilane in DMSO-d_6. [c] Overlap of the amino-proton resonances with other signals prevented an accurate determination of these values.



X XI

parison of the amino-proton dimethylsulfoxide chemical shifts for the N-substituted derivatives shown in Table II (δ 5.29-6.14) with those for the ring substituted derivatives shown in Table VI, page 39 (δ 4.28-5.48, omitting the 4-NO_2 and 2,4-$(NO_2)_2$ compounds). The shift to lower fields is to be expected on two accounts. First, the amino-proton is bound to an atom with a relatively larger amount of positive charge, and second, as a consequence of the relative increase in the planarity of the system, the amino-proton spends additional time in the deshielding region of the benzene ring.

3. Ring Substituted Benzamides.

Electron delocalization in amides causes the rotational barrier about the central C-N bond to be significantly higher than that for a normal C-N single bond.[57] In benzamides such as XII, the two NH protons are not equivalent and consequently have different chemical shifts. It has recently been reported[58] that the rotational barriers in N,N-dimethyl

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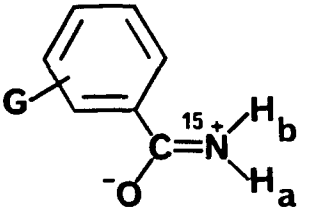
(57) H. S. Gutowsky and C. H. Holm, J. Chem. Phys., 25, 1228 (1956).
(58) L. M. Jackman, T. E. Kavanaugh and R. E. Haddon, Org. Mag. Resonance, 1, 109 (1969).



XII

benzamides are proportional to the Hammett substituent constant. The availability of several ring-substituted derivatives of benzamide-^{15}N permitted us to investigate the effect of substituents on the $J(^{15}N\text{-}H)$ in these compounds. The $J(^{15}N\text{-}H)$ values together with the amino proton chemical shifts are presented in Table III, page 31.

Since the nitrogen atom, shown in XII, is conjugated with the carbonyl function it assumes a relatively high degree of s-character. The observed coupling constants of 88-89 Hz, corresponding to 32% s-character, are in good agreement with those expected for a one-bond coupling of a planar nitrogen. That $J(^{15}NH_b)$ is greater than $J(^{15}NH_a)$ has been observed previously for the cases of formamide-^{15}N and formanilide-^{15}N.[59] While the amino-proton chemical shifts appear to be responsive to a change of the substituent on the benzene ring (a down-

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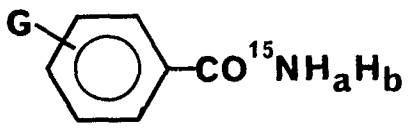
(59) A. J. R. Bourn, D. G. Gilles and E. W. Randall, Tetrahedron, 20, 1811 (1964).

Table III. Proton Chemical Shifts and One-Bond ^{15}N-H Coupling Constants in Benzamides.



G	δ,[b,c] ppm	J[c,d], Hz	δ,[b,c] ppm	J,[c,d] Hz
CH_3	7.25	88.0	7.85[e]	
F	7.43	88.2	7.95	88.6
Cl	7.39	88.2	8.01[e]	
I	7.38	88.1	7.96	89.2
3,5-Me_2-4-NO_2	7.60	88.2	8.01	89.2

[a] H_a is the proton cis to the oxygen atom. [b] From Tetramethylsilane as internal reference. [c] Measured as approximately 1 molal solutions in dimethylsulfoxide-d_6 at 10°C. [d] The error in these measurements is estimated to be ±0.2 Hz. [e] Estimated from the spectrum of the unlabeled material.

field shift of 0.35 ppm is observed for H_a in going from p-toluamide to 3,5-dimethyl-4-nitrobenzamide) the one-bond coupling constants remain essentially unchanged. This is significant in that it suggests that inductive effects, as transmitted through the benzene ring, play a minor role in determining the one-bond coupling in benzamides.

Two and Three-Bond ^{15}N-H Coupling Constants.

As the quadrupole of the nitrogen-14 nucleus broadens the resonances of nuclei coupled to nitrogen through several bonds, substitution of the nitrogen-15 atom facilitates the measurement of geminal and vicinal coupling constants.

Recent research has demonstrated the dependence of both vicinal[60] and geminal[61] coupling constants on the electronegativity of the groups attached to the molecule. Paralleling our studies on one-bond coupling constants we have measured the geminal and vicinal nitrogen-15 proton coupling constants in a series of aniline derivatives with the object of determining the factors which affect these types of coupling.

The effect of incorporating a nitrogen-15 atom at the amine nitrogen on the nmr spectrum of p-nitroaniline is illustrated in Figure 3, page 33. In para-substituted aniline-^{15}N derivatives the upfield half of the AA'BB' pattern of the aromatic proton is further split into a doublet by the nitrogen-15 atom. This coupling of approximately 2 Hz

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(60) I. D. Rae, Aust. J. Chem., 19, 1983 (1966).

(61) A. Bose, I. Kugajevsky, Tetrahedron, 23, 1489 (1967); M. Ohtsuru, K. Tori, J. M. Lehn and R. Seher, J. Amer. Chem. Soc., 91, 1187 (1969).

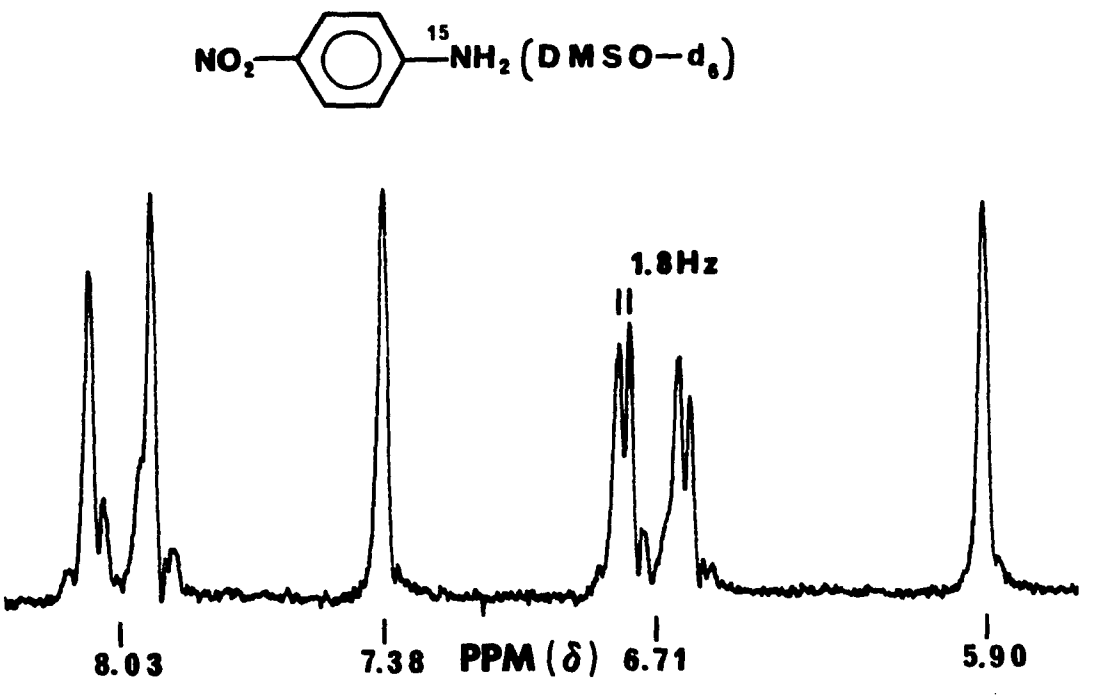

Figure 3. Proton magnetic resonance spectrum of p-nitroaniline-^{15}N at 60 MHz.

is summarized in Table IV, page 35. Coupling between the ^{15}N-nucleus and the more distant meta and para protons is undetectable and thus, the multiplet arising from the protons ortho to the amino nitrogen can easily be identified.

In a recent nmr study of para-substituted acetanilides the coupling J(o-H-H) between aromatic protons was found to be dependent on the Hammett substituent constant.[62] Unfortunately, in view of the small magnitude of this vicinal couplings, no simple relationship between this coupling and the nature of ring substituent is apparent in these anilines. Indeed, the solvent does seem to influence this coupling to a greater extent then does the substituent. It may be seen that this coupling is consistently less (0.1-0.3 Hz) in the dimethylsulfoxide than in chloroform, a situation which is contrary to that for the one-bond ^{15}N-H coupling.

The failure to observe a substituent dependence of the three bond coupling constants in these compounds by no means invalidates the suggestion that such a dependence exists. In fact the observed vicinal ^{15}N-C=C-H coupling in 2,4-dinitroacetanilide (labeled with nitrogen-15 in the amide group) shown in Table V, page 36, suggests that more rewarding results might be forthcoming if the substituents were brought closer to the interacting nuclei.

Chemical Shifts

As we have seen from some of the theoretical considerations on

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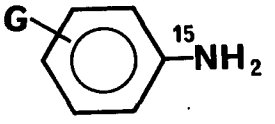
(62) J. Bennett, M. Delmas and J. C. Maire, Org. Mag. Resonance, 1, 319 (1969).

Table IV. Vicinal ^{15}N-C=C-H Coupling Constants[a] in Ring Substituted Anilines.



G	$^3J(^{15}N-H)$[b] DMSO-d_6	$CDCl_3$
CH_3	1.7	1.8
F	1.5	1.8
Cl	1.7	1.9
Br	1.8	1.8
I	1.7	1.8
2,4-Br_2	1.6	1.9
NO_2	1.8	2.0
2,4-$(NO_2)_2$	2.2	

[a] All coupling constants are expressed in Hz. The error in the measurements is estimated at ± 0.2 Hz. [b] This notation, used commonly throughout this dissertation, denotes the coupled nuclei (in parenthesis) and the number of bonds separating them (superscript of J).

Table V. Nitrogen-15-Proton Coupling Constants[a].

Compound	Solvent	$^{2}J(^{15}N-H)$	$^{3}J(^{15}N-H)$
$Ph^{15}N{=}CHPh$	$CDCl_3$	3.9	
$Ph^{15}N{=}CHC(CH_3)_3$	$CDCl_3$	4.2	
2,4-Dinitroacetanilide	DMSO-d_6		1.7[b] , 2.5[c]
$Ph^{15}NHCOCH_3$	$CDCl_3$		1.4

[a] All coupling constants are expressed in Hz. The error in these measurements is estimated at ± 0.2 Hz. [b] Coupling to the methyl group. [c] Coupling to the ortho ring proton.

pages 5-7, the paramagnetic term, ∇p, is believed to make the major contribution to the screening expression. Consequently, it is not surprising that the qualitative trends which have been observed for both ^{14}N and ^{15}N resonances are attributed to some aspect of ∇p. Specifically, for amines and ammonium ions,[63] an explanation for the shift to lower fields resulting from an increase in the number of alkyl groups bonded either directly to the nitrogen atom or to the carbon alpha to the nitrogen has been offered in terms of ΔE, the mean triplet excitation energy. A similar explanation has been invoked to account for the relative nitrogen-14 shifts in trifluoramine oxide, nitrogen trifluoride and related compounds.[64] An upfield shift of the nitrogen-14 resonances in nitroalkanes, with the substitution of increasingly electronegative groups at the alpha carbon, has been observed by Witanowski and coworkers.[65] While not specifically related to any one term in the expression for ∇p, this latter shift, encompassing a range of approximately 300 ppm, is presumably paramagnetic. Recent reports concerned with ^{15}N and ^{14}N ring-substituted nitrobenzenes[66] have related the chemical shift, of the signal associated with the nitro-nitrogen, to the paramagnetic term. In addition it has been shown, by a comparison of the ortho, and para nitro-nitrogen shifts that resonance effects play a subsidiary role to inductive effects in these same nitrobenzenes.[66]

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(63) M. Witanoski and H. Januszewski, Can. J. Chem., 47, 1321 (1969).

(64) J. Mason, Chem. Commun., 357 (1969).

(65) M. Witanowski, T. Urbanski and L. Stefaniak, J. Amer. Chem. Soc., 86, 2569 (1964).

(66) W. Bremser, J. Kroschwitz and J. D. Roberts, J. Amer. Chem. Soc., 91, 6189 (1969); M. Witanowski, L. Stafaniak and G. A. Webb, J. Chem. Soc., B, 1065 (1967).

As part of our studies in this area we have determined the nitrogen-15 chemical shifts in a series of ring substituted aniline-^{15}N derivatives by the double resonance technique. These data are presented in Table VI, page 39, along with the chemical shifts of the amino-protons. The observed range of nitrogen-15 chemical shifts of 37.5 ppm in these anilines is appreciably larger than the ranges of 1, 5 and 24 ppm observed for ^{13}C, ^{15}N and ^{19}F in ring substituted toluenes,[67] nitrobenzenes and fluorbenzenes.[68] It may be seen that these data show a downfield shift of the ^{15}N-resonance with increasing electronegativity of the substituent. In rationalizing the difference in chemical shift for nitrogen in a variety of functional groups, the paramagnetic term, $\overline{\sigma}_p$, is usually considered to dominate the total screening expression.[69] In the present situation the range of chemical shifts in these anilines is comparatively small. Most significantly, it can be seen that the chemical shifts of the corresponding amino protons parallel the nitrogen shifts. This observation is illustrated by the least squares plot of the amino proton chemical shifts against the nitrogen-15 chemical shifts shown in Figure 4 page 40.

It has previously been shown that amino proton chemical shifts in anilines correlate well with Hammett substituent constants[51] and Huckel molecular orbital calculations of electron density at the nitrogen.[70] The nitrogen-15 chemical shifts exhibit a similar trend; the highest

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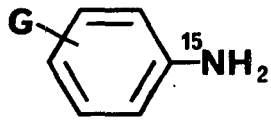
(67) P. C. Lauterbur, Ann, N.Y. Acad. Sci., U.S., 70, 841 (1958).
(68) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson and G. T. Davis, J. Amer. Chem. Soc., 85, 3146 (1963).
(69) E. F. Mooney and P. H. Winston, "Annual Review of Nuclear Magnetic Resonance", Academic Press, New York, 1969, page 125.
(70) B. M. Lynch, Tetrahedron Letters, 1357 (1969).

Table VI. Nitrogen and Amino-Proton Chemical Shifts in Ring-Substituted Aniline-^{15}N Derivatives.



G	Chemical Shift $^{15}\underline{NH}_2$ [a,c]	Chemical Shift $^{15}\underline{NH}_2$ [b,c]
4-MeO	+5.8	4.48
4-Me	+2.7	4.70
4-F	+3.3	4.88
4-H	0.	4.90
4-I	-1.4	5.20
4-Br	-1.0	5.15
4-Cl	-0.3	5.15
2,4-Br_2	-5.8	5.42
3,5-Me_2-4-NO_2	-9.5	5.84
2,4,6-Br_3	-11.7	5.48
4-NO_2	-20.0	6.63
2,4-$(NO_2)_2$	-33.1	8.32

[a] A positive value of the chemical shift indicates a shift upfield from aniline. [b] Values are in ppm relative to tetramethylsilane as an internal standard. All spectra were determined at 60Mc. [c] Spectra were obtained as approximately 1 molal solutions in DMSO-d_6.

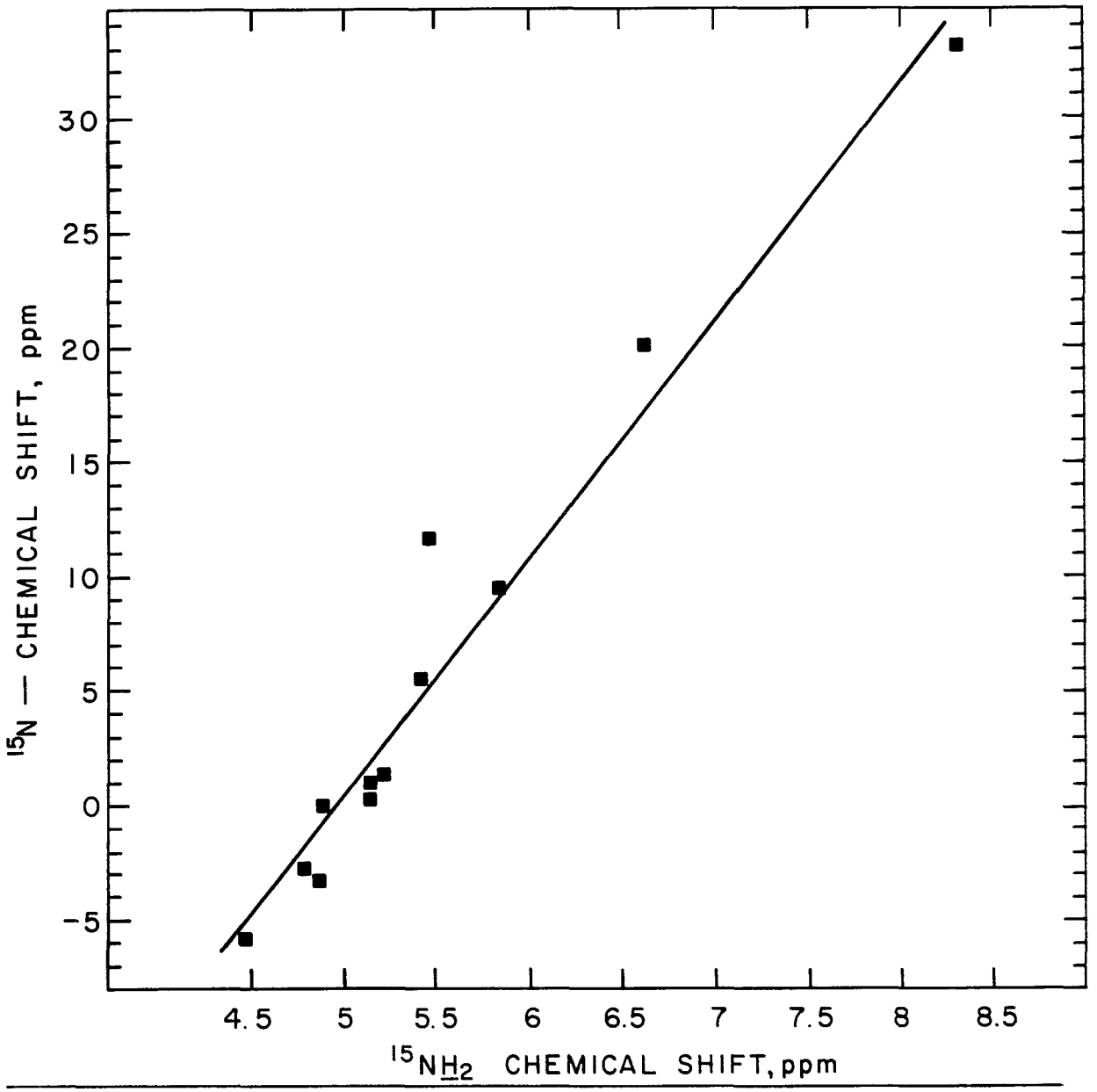


Figure 4. Correlation of the aniline-^{15}N chemical shift in ring substituted anilines with amino-proton chemical shift. Proton chemical shifts are downfield from internal tetramethylsilane. The nitrogen-15 chemical shifts have been referenced against aniline-^{15}N.

field nitrogen absorptions are associated with the most strongly electron donating groups while the lowest field absorptions occur in compounds having strongly electron withdrawing groups. A least squares plot of the nitrogen-15 chemical shift against the Hammett substituent constant is shown in Figure 5, page 42. The approximate linearity of this plot provides evidence for the dependence of the nitrogen chemical shift on the electron density at the nitrogen atom and thus on the relative importance of the diamagnetic term in the total screening within this series of anilines. Recently, a similar dependence of the nitrogen chemical shift on the Hammett substituent constant was found for a series of meta-substituted aniline-^{15}N derivatives.[71]

These results do not preclude the possibility that some combination of both σp and σd is responsible for the relative chemical shifts. Indeed, as a first approximation, the presumed shift to longer wavelength of the $n-\pi^*$ transition in p-nitroaniline, relative to aniline, suggests that there are appreciable changes in ΔE, the mean excitation energy in going from one compound to another. In addition, marked changes in the nitrogen bond order (total number of bonds to a given atom), as a result of increasing double bond character between the nitrogen and the phenyl ring, may also effect the Q_{AB} terms in σp. Thus, while evidence supporting the tentative conclusion has been presented in favor of the importance of diamagnetic effects, other factors may also be contributing.

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(71) T. Axenrod, M. J. Wieder, The City College of New York, 1969 personal communication.

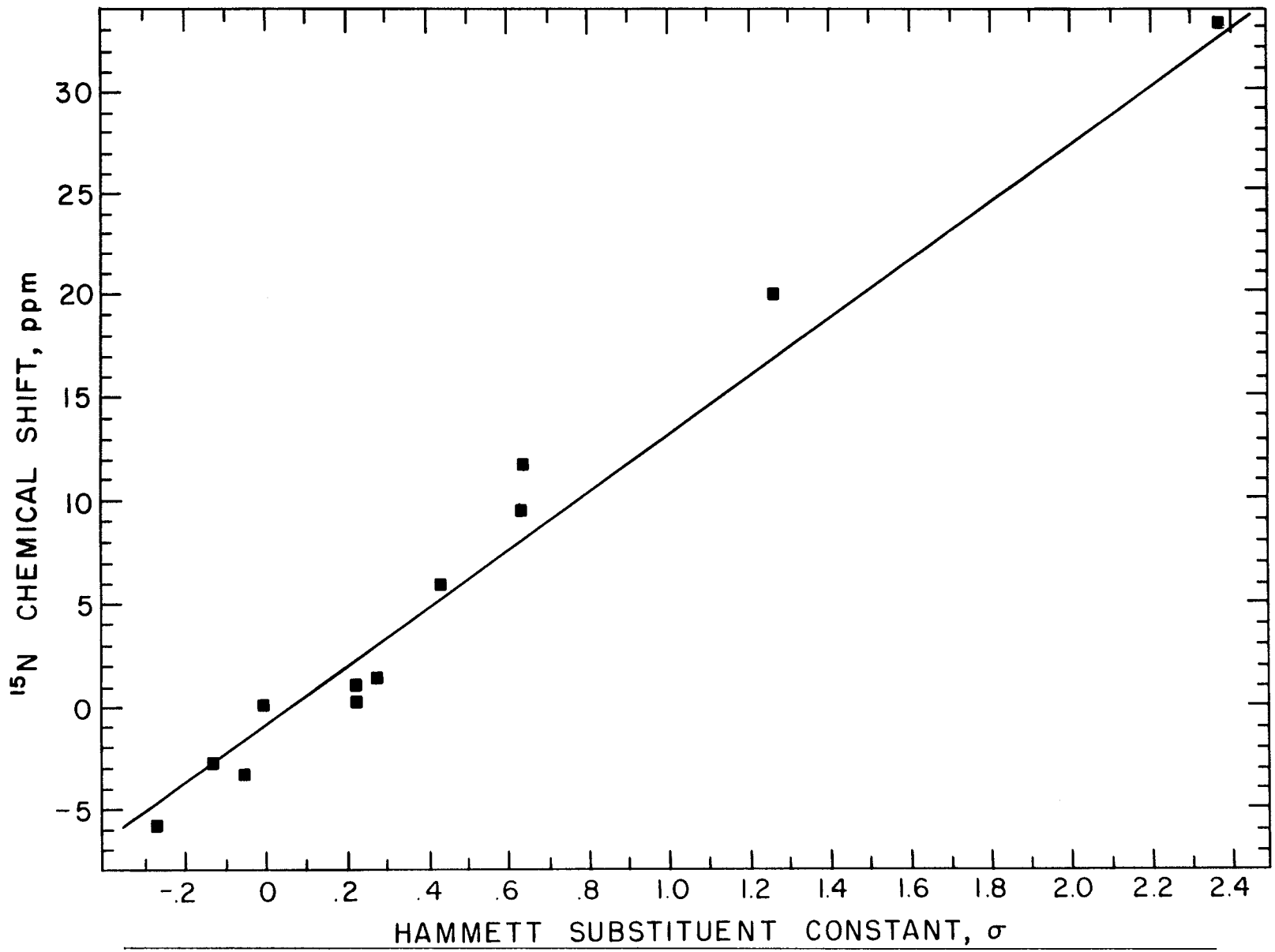

Figure 5. Correlation of the aniline nitrogen-15 chemical shift in ring substituted anilines with Hammett substituent constant.

PART II

CONFIGURATIONAL ASSIGNMENTS IN N-NITROSO-^{15}N AMINES AND HYDRAZINES

PRESENT INVESTIGATION

In certain instances, double bond character between nitrogen and an adjacent atom (e.g. carbon, nitrogen or oxygen) may develop as a result of p-π bonding between the nitrogen and its neighbor. The consequence of such π-bonding is to decrease the rate of rotation about this sigma bond to the point where the two configurational isomers which result may be detected by spectroscopic means. The nuclear magnetic resonance method has been invaluable in the study of those kinetic processes where the interconversion of one configurational isomer to another is relatively slow (50-100 cm^{-1} see^{1}).[72] Amides,[57] nitrites,[73] triazines,[74] aminoboranes[75] and nitrosamines[76] are examples of classes of compounds which fall in this category. In unsymmetrical nitrosamines, the partial π-bond between adjacent nitrogen atoms leads to the existence of the configurational isomers XIII and XIV. Quantum mechanical calculations suggest that polar structures of the type XIII and XIV may contribute up to 49% to both the ground and excited states of the molecule.[77] Recent electron diffraction studies[78] on dimethylnitrosamine

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(72) J. W. Emsley, J. Feeney and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy", Permagon Press Ltd., Oxford, 1965.

(73) P. Tarte, J. Chem. Phys., 20, 1570 (1952).

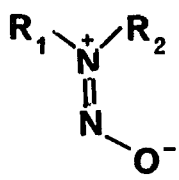
(74) M. K. Akhtar, R. S. McDaniel, M. Feser and A. C. Oehschlager, Tetrahedron, 24, 3899 (1968).

(75) K. Niedenzu and J. W. Dawson, J. Amer. Chem. Soc., 82, 4223 (1960).

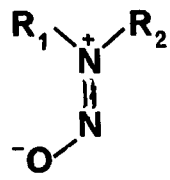
(76) C. E. Looney, W. D. Philips and E. I. Reilly, J. Amer. Chem. Soc., 86, 5564 (1951).

(77) Y. L. Chow and C. J. Colon, Can. J. Chem., 46, 2827 (1968).

(78) L. V. Vilkhor and I. I. Nazarenko, Z. Strukturnoi Khimii, 9, 887 (1968); P. Rademacher and R. Stolevik, Acta. Chem. Scand., 23, 660 (1969).



XIII



XIV

have shown the C-N-C and C-N-N bond angles to be 120° ± 1.5° and the ONN angle to be 118 .18' ± 1' .18'. These data suggest a polar structure for the nitrosamino-moiety in which the oxygen atom is at the negative end of the molecular dipole. The measured dipole moment of 3.98 D. U. for dimethylnitrosamine is consistent with this view.[79] In addition, one may reach similar conclusions from the work of Kuhn and McIntyre[80] and the ^{15}N labeling studies of Axenrod[81] who have clearly demonstrated that nitrosamines are protonated on the oxygen atom in strong acid solution.

Temperature dependent nmr studies on dimethylnitrosamine in both the liquid[82] and vapor states[83] have shown the barrier to rotation about N-N bond to be approximately 21-25 Kcal. Mannschreck and co-workers[84] in connection with their nmr investigations of activation

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(79) J. Tanaka, J. Chem. Soc. Japan, 78, 1647 (1957).
(80) S. J. Kuhn and J. S. McIntyre, Can. J. Chem., 44, 105 (1966).
(81) T. Axenrod, The City College of New York, 1969, personal communication.
(82) D. J. Blears, J. Chem. Soc., 6256 (1964).
(83) L. K. Harris and R. A. Spragg, Chem. Commun., 362 (1967).
(84) A. Mannschreck, H. Muensch and A. Matteus, J. Mol. Spectrosc., 23, 15 (1967).

parameters using line-shapes and equilibration techniques have succeeded in isolating pure rotameric forms of several nitrosamines. The barrier to rotation, as determined by these techniques, has been found to be consistent with the earlier reports.

The substantial barrier to rotation about the N-N bond in nitrosamines gives rise to separate resonances (at room temperature) for groups oriented cis and trans to the nitroso-oxygen atom. This is illustrated in figure 7, page 50 for the spectrum of dimethylnitrosamine. The original workers[76] assigned the upfield resonances to the methyl group trans to the nitroso-oxygen, but this assignment has subsequently been reversed by more recent work in which isomer ratios and solvent effects in unsymmetrical nitrosamines were investigated.[85]

Configurational assignments in nitrosamines are generally based upon consideration of steric effects and the probable anisotropy of the nitrosamino group.[86,87] The former assumes that as one alkyl group in a series of compounds becomes larger, its increased non-bonded interactions with the nitroso-oxygen atom results in a preference for that group to adopt a trans orientation with respect to the oxygen atom. Karabatsos and Taller[85] have observed considerable variations in the chemical shift differences between the protons cis and trans to the nitroso group in dialkylnitrosamines and have attributed this to differences in the conformations adopted by these alkyl groups. These

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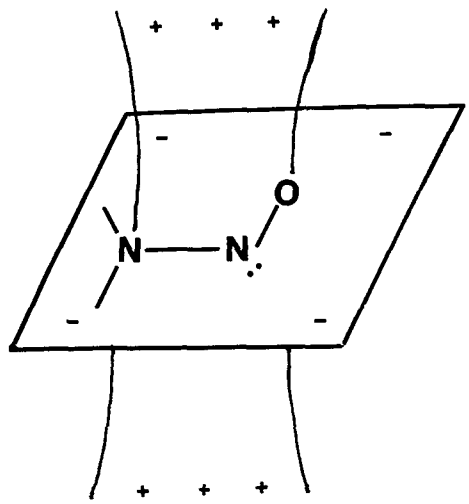
(85) G. J. Karabatsos and R. A. Taller, J. Amer. Chem. Soc., 86, 4373 (1964).
(86) R. K. Harris, J. Mol. Spectrosc., 15, 100 (1965).
(87) R. K. Harris and R. A. Spragg, J. Mol. Spectrosc., 23, 158 (1967).

workers have concluded that the resonances due to α-methyl and α-methylene protons occur at higher fields when oriented cis to the nitroso-oxygen than when trans, while the reverse is true for α-methine protons.

The anisotropy of the nitrosamino-group is such that protons located in the nodal plane of the π-system, denoted as the (-) section of XV, are deshielded relative to those which lie above or below that



XV

plane, in the (+) area.

Three-Bond ^{15}N-N-C-H Coupling Constants

1. N-Nitrosamines

Recent reports by Lehn and co-workers have shown the dependence of geminal ^{15}N-C-H coupling on the orientation of the nitrogen lone-pair in

aldoximes[88] and tetrahydro-1,3-oxazines.[89] In addition, both the geminal and vicinal ^{15}N-H coupling constants in quinoline-^{15}N and some of its derivatives show a variation in going from aprotic solvents to acid media.[90] In general, both vicinal and geminal ^{15}N-H coupling through sp^3-hybridized carbon atoms are small with values[91] falling in the range 0.6-1.4 Hz, however, in situations where the coupling occurs through an sp^2-hybridized carbon, such as in formamides[92] and formamidines[61] significantly enhanced coupling is observed.

These reports suggested that a configurational dependence of the vicinal ^{15}N-H coupling might exist in nitrosamines, in which case such a dependence could be used as a complementary technique by which configurational assignments might be made.

To test this hypothesis, a series of N-nitrosamines and N-nitrosohydrazines, both having a ^{15}N-enrichment of 99 atom % in the nitroso-group, were investigated. In addition, it was decided to determine the nitrogen-15 shifts in each configurational isomer with the intent of gaining some additional insight into the nature of the factors contributing to the shielding of this nucleus.

The spectrum of dimethylnitrosamine-(^{15}N-nitroso) is presented in Figure 6, page 49, and may be compared with that of its ^{14}N-isotopomer

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(88) J. P. Kintzinger and J. M. Lehn, Chem. Commun., 660 (1967).
(89) F. G. Riddell and J. M. Lehn, J. Chem. Soc., B, 1225 (1968).
(90) K. Tori, M. Ohtsuru, K. Aono, Y. Kawazoe and M. Ohnishi, J. Amer. Chem. Soc., 89, 2765 (1967).
(91) G. Binsch, J. B. Lambert, B. W. Roberts and J. D. Roberts, J. Amer. Chem. Soc., 86, 5564 (1964).
(92) M. T. Rogers and L. A. Laplanche, J. Phys. Chem., 69, 3648 (1965); B. Sunners, L. H. Piette and W. G. Schneider, Can. J. Chem., 38, 681 (1960); A. J. R. Bourn and E. W. Randall, J. Mol. Spectrosc., 13, 29 (1964).

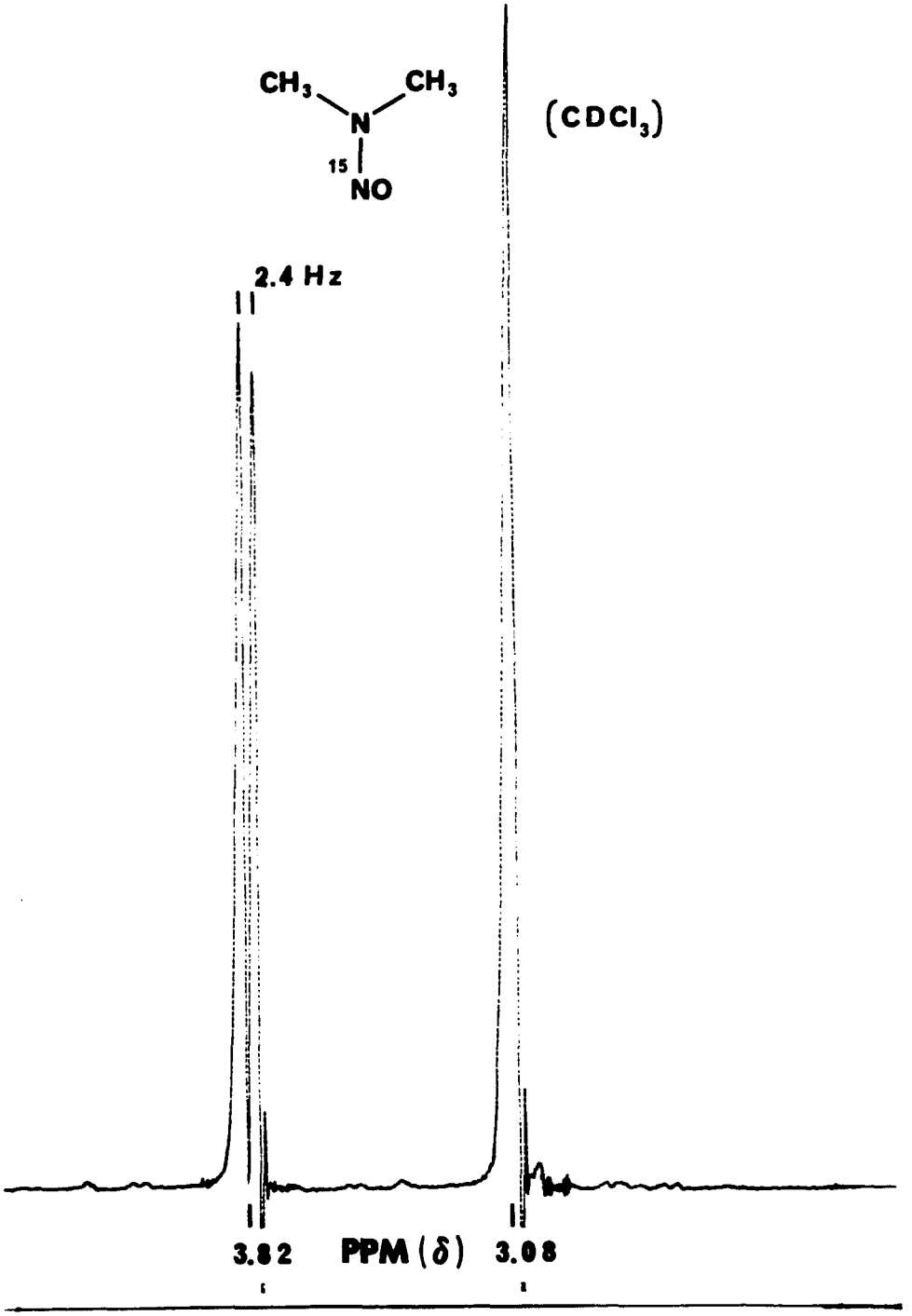

Figure 6. Proton magnetic resonance spectrum of N-nitroso-dimethylamine-(^{15}N-nitroso) at 60 MHz.

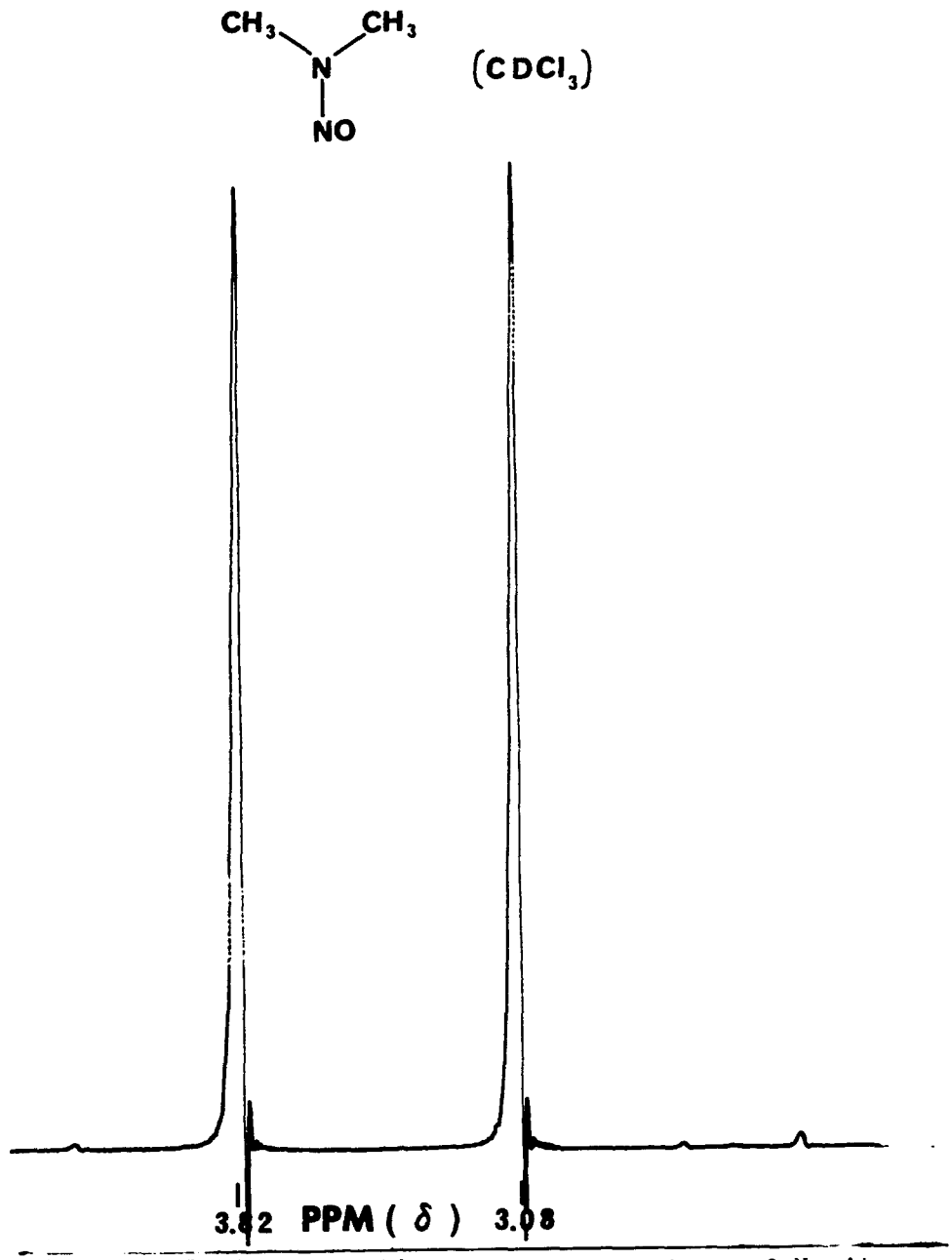

Figure 7. Proton magnetic resonance spectrum of N-nitroso-dimethylamine at 60 MHz.

shown in Figure 7 page 50. The essential difference between these spectra is that the low field resonance at δ 3.82, due to the trans methyl absorption, appears as a doublet in the ^{15}N-isotopomer and as a singlet in the unenriched compound. This observation provides support for our expectation that a significant dependence of the ^{15}N-N-C-H coupling on the orientation of the nitroso-moiety does exist. In Table VII, page 52 there are summarized the proton chemical shifts and the isomer ratios of the several nitrosamines that have been investigated. In Table VIII, page 53, there are presented the $^{3}J(^{15}N-H)$ coupling constants for those nitrosamines which have been enriched in nitrogen-15.

In all cases it may be seen that the ^{15}N-N-C-H coupling to protons oriented trans to the nitroso-oxygen (cis to the nitrogen lone-pair) falls in the range 2.1-3.1 Hz while coupling to protons oriented cis to the nitroso-oxygen is usually undetectable and in no case exceeds 1 Hz. A similar configurational dependence of the $^{3}J(^{15}N-H)$ coupling has recently been reported in such related systems as nitrites[93] and nitrosohydroxylamines.[94] The nmr spectrum of N-nitroso-N-ethylbenzylamine, shown in Figure 8 page 54, is a typical example of an unsymmetrical nitrosamine ($R_1 \neq R_2$). Since the steric requirements for the benzyl and ethyl groups do not differ markedly both isomers are present in almost equal quantities. In each of the two rotamers, the trans benzyl (δ 5.29) and trans (δ 4.13) methylene protons show evidence of coupling

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(93) T. Axenrod, M. J. Wieder and G. W. A. Milne, Tetrahedron Letters, 1397 (1969).

(94) T. Axenrod, M. J. Wieder and G. W. A. Milne, Tetrahedron Letters, 401 (1969).

Table VII. Chemical Shifts of the α-Protons in (Nitroso-^{15}N)-N-Nitrosamines[a,b]

	$R_1R_2N^{15}NO$		R_1		R_2		%
	R_1	R_2	cis	trans	cis	trans	syn/anti[c]
a)	CH_3	CH_3	3.08	3.82	3.08	3.82	50/50
b)	$PhCH_2$	CH_3	4.83	5.32	2.96	3.69	24/76
c)	$PhCH_2$	CH_2Me	4.85	5.29	3.56	4.13	49/50
d)	$PhCH_2$	$CH(Me)_2$	4.77	5.25	4.92	4.58	84/16
e)	$PhCH_2$	$C(Me)_3$	4.84	--			100/0
f)	$PhCH_2$	$PhCH_2$	4.63	5.18	4.63	5.18	50/50
g)	PhCHMe	PhCHMe	6.28	5.00	6.28	5.00	50/50
h)	CH_3	Ph	3.42	—			0/100
i)	$PhCH_2$	Ph	5.17	5.55			4/96
j)	$CH_2C(Me)_3$[d]	Ph[d]	4.00	4.37			13/87
k)	$CH(Me)_2$[d,e]	Ph[d,e]	1.17	1.44			36/64
l)	$C(Me)_3$[d,e]	Ph[d,e]	--	1.59			100/0

[a] Spectra were taken as 10.20% W/W solutions in $CDCl_3$. [b] Measured in ppm from internal tetramethylsilane. [c] syn is the isomer having R_1 cis to the oxygen. [d] Sample not enriched in ^{15}N. [e] Methyl of the t-butyl group.

Table VIII. ^{15}N-N-C-H Coupling Constants in (Nitroso-^{15}N)-N-Nitrosamines

$R_1R_2N^{15}NO$		R_1		R_2	
R_1	R_2	cis	trans	cis	trans
CH_3	CH_3	1.0	2.4	1.0	2.4
$PhCH_2$	CH_3	0.5	2.1	0.8	2.2
$PhCH_2$	CH_2CH_3	0.	2.4	0.8	2.5
$PhCH_2$	$CH(CH_3)_2$	0.	3.1	0.	2.4
$PhCH_2$	$C(CH_3)_3$	0.	-	-	-
$PhCH_2$	$PhCH_2$	0.	2.4	0.	2.4
$PhCHCH_3$	$PhCH\,CH_3$	0.	3.0	0.	3.0
CH_3	Ph	0.8	0.	-	-

[a] All constants are expressed in Hz. [b] The uncertainty in these values is estimated to be ± 0.2 Hz because of broadening and in some cases, partial overlap of peaks.

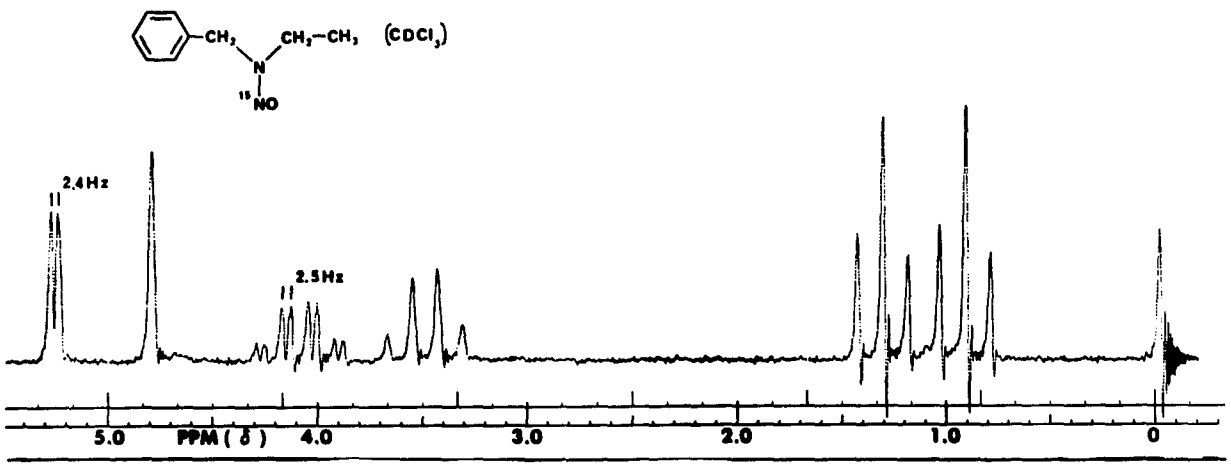


Figure 8. Proton magnetic resonance spectrum of N-nitroso-N-ethylbenzylamine-(^{15}N-nitroso) at 60 MHz.

to the nitrogen-15 nucleus.

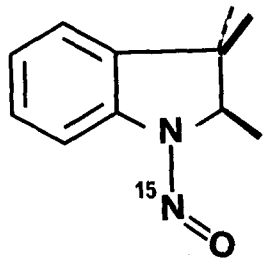
It may been seem from Table VII, page 53, that as the size of the alkyl group in the series of alkylbenzylnitrosamines (entries a-g) is systematically increased the benzyl resonance at δ4.8, increases at the expense of the signal at δ 5.3. The former signal is due to the benzyl protons oriented cis to the nitroso-oxygen whereas the later corresponds to the benzyl protons oriented trans to this same grouping. In the case of N-nitroso-N-t-butylbenzylamine-(^{15}N-nitroso) only one configuration has been detected, which, on the basis of the expected steric requirements for the t-butyl group and the appearance of a singlet for the benzyl absorption has been assigned to the configuration having the nitroso-oxygen trans to the t-butyl group. The observation that N-nitroso-N-methylaniline exists in the configuration having the phenyl group trans to the nitroso group has been noted previously.[76] This has been attributed to the more demanding steric requirement of a benzene ring which is co-planar with the nitrosamino-group and not to a rapid interconversion process which might conceivable lead to an nmr spectrum consistent with the one observed. The former interpretation is almost certainly correct in view of the trend found in the N-nitroso-N-alkyl-aniline series (entries h-l). Here again, an increase in the effective size of the alkyl group R_1, results in the expected decrease in the difference in stability between the two rotameric forms. Additionally, the magnitude of the $^3J(^{15}N\text{-}H)$ coupling to the methyl group (0.8 Hz) in N-nitroso-N-methylaniline-(^{15}N-nitroso) is consistent with a configuration having the nitroso-oxygen cis to the methyl group.

The suggestion, noted previously,[85] that cis α-methine protons resonate at lower field than the corresponding trans proton has been explained in terms of the relative importance of the conformation which

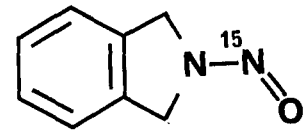
places the α-methine hydrogen in the deshielding plane of the nitrosamine group. This is illustrated for racemic-α,α'-dibenzyldimethylnitrosamine-(^{15}N-nitroso), whose spectrum is shown in Figure 9, page 57. This conformational argument is strengthened by the observation that in this case only the high field quartet, which is presumed to be due to the trans-α-methine proton, shows the $^{3}J(^{15}NH)$ coupling whose magnitude (3.0 Hz) we now recognize to result from a hydrogen oriented trans to the nitroso-oxygen. That this observation for α-methine protons is a general one is indicated by the coupling to the high field signal observed in ^{15}N-nitroso-N-isopropylbenzylamine.

It appears that the specificity of the trans $^{3}J(^{15}N-H)$ coupling in these systems is independent of conformation and relative chemical shift and that magnitude of the coupling constant can be used to unambiguously identify configurational isomers in nitrosamines.

In the course of our investigation several heterocyclic nitrosamines-(^{15}N-nitroso) were prepared whose nmr spectra showed no detectable $^{3}J(^{15}N-H)$ coupling to either the cis or trans α-protons. Specifically, this was observed in N-nitroso-2,3,3-trimethylindoline-(^{15}N-nitroso), (XVI), and N-nitrosoisoindoline-(^{15}N-nitroso), (XVII).



XVI



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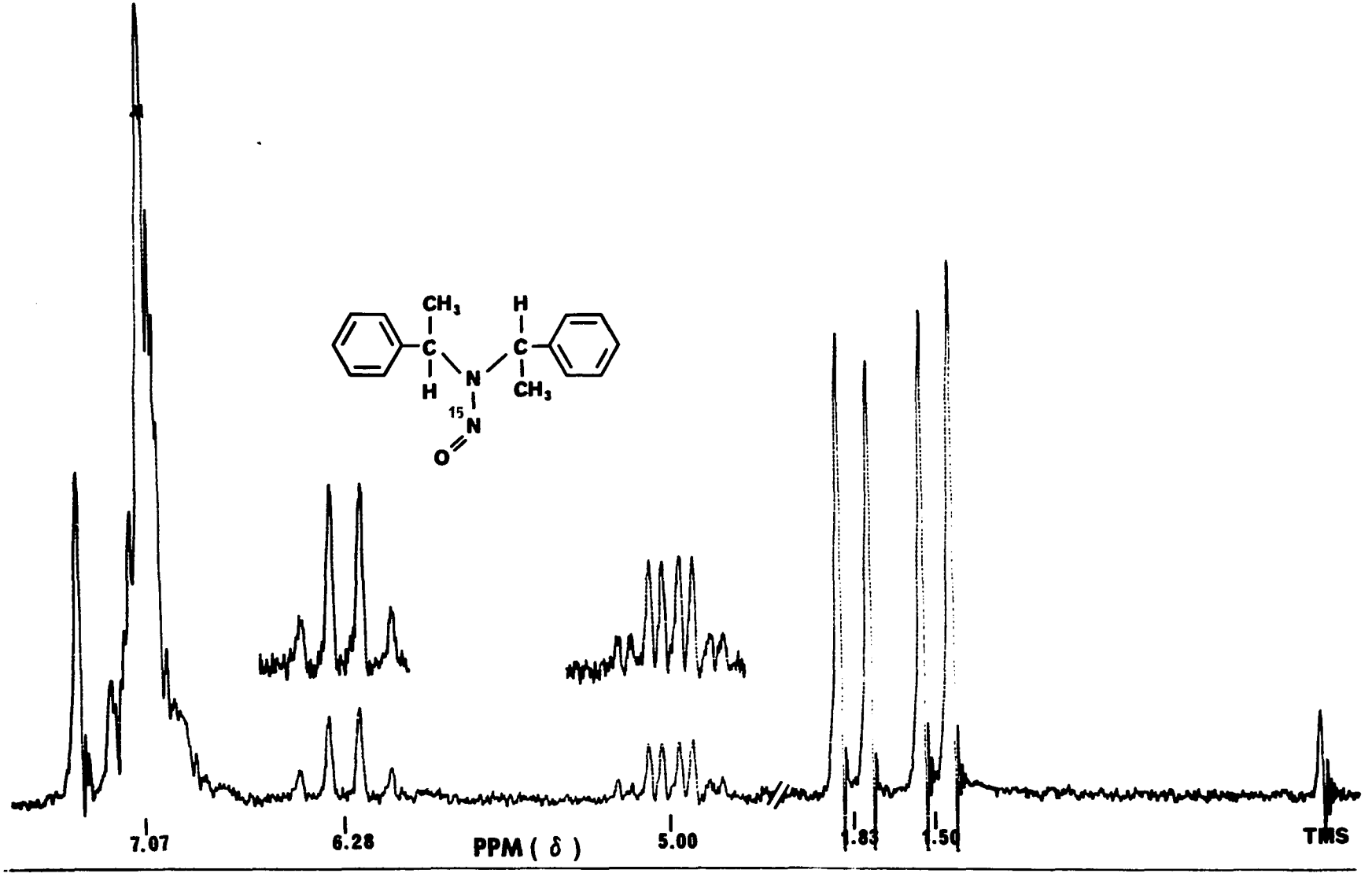
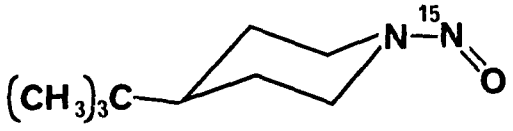


Figure 9. Proton magnetic resonance spectrum of racemic-N-nitroso-α,α-dimethyldibenzylamine-(^{15}Nitroso) at 60 MHz.

These findings suggested that the lack of coupling might be due to an unfavorable dihedral angle between the nitroso-nitrogen-15 atom and the adjacent α-protons. Such an angular dependence has recently been demonstrated for the $^{3}J(^{14}N\text{-}H)$ values in some bicyclic ammonium derivatives[95] and isonitriles.[96] For these compounds a dihedral angle of 60° corresponded to the angle associated with minimum coupling. The rigidity of both XVI and XVII results in (assuming an sp^2 amino-nitrogen) a dihedral angle of approximately 60° which suggests our observations are in reasonable agreement with those found for the ^{14}N-ammonium salts. To test this idea further, 4-t-butyl-N-nitrosopiperidine,XVIII,



XVIII

was prepared. Since the t-butyl group occupies an equatorial position (to minimize non-bonded interactions with axial hydrogens in the 2 and 6 positions) the compound is relatively rigid. Dreiding models suggest that the dihedral angles to the α-axial and α-equatorial protons in this compound are approximately 120° and 0° respectively. Unfortunately, the complexity of the spectra at 60, 100 and even 200 MHz has prevented the

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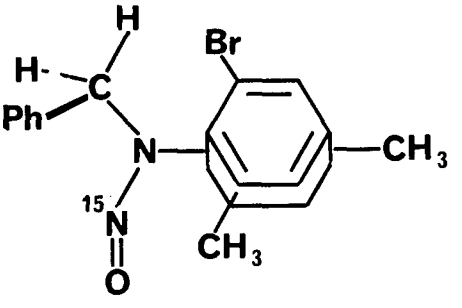
(95) Y. Terui, K. Aono and K. Tori, J. Amer. Chem. Soc., 90, 1069 (1968).

(96) A. A. Bothner-By and R. H. Cox, J. Phys. Chem., 73, 1830 (1969).

unequivocal identification of any coupling to the α-protons. Decoupling experiments are now in progress to simplify the spectra sufficiently so that an upper limit on the ^{15}N-N-C-H coupling in this compound can be estimated.

It has recently been reported[97] that in certain ortho-substituted N-nitrosobenzylanilines, the benzyl protons in each configurational isomer exhibit an AB splitting patterm. For example, the benzyl protons in N-nitroso-N-benzyl-(2-bromo-4,6-dimethyl)-aniline-(^{15}N-nitroso), XIX, appear as a complex multiplet. This complexity, shown in figure 10, page 60, arises from both restricted rotation about the



XIX

aryl-nitrogen bond and $^{3}J(^{15}N\text{-}H)$ coupling in addition to the usual isomerism due to the nitroso-group. As it has been observed that the magnetically non-equivalent α-protons, in acetals[98] exhibit unequal one-

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(97) R. J. Seymour and R. Jones, Tetrahedron Letters, 2021 (1967); A. Mannschreck and H. Muensch, Tetrahedron Letters, 3227 (1968).

(98) L. S. Rattet, L. Mandell and J. H. Goldstein, J. Amer. Chem. Soc., 89, 2253 (1967).

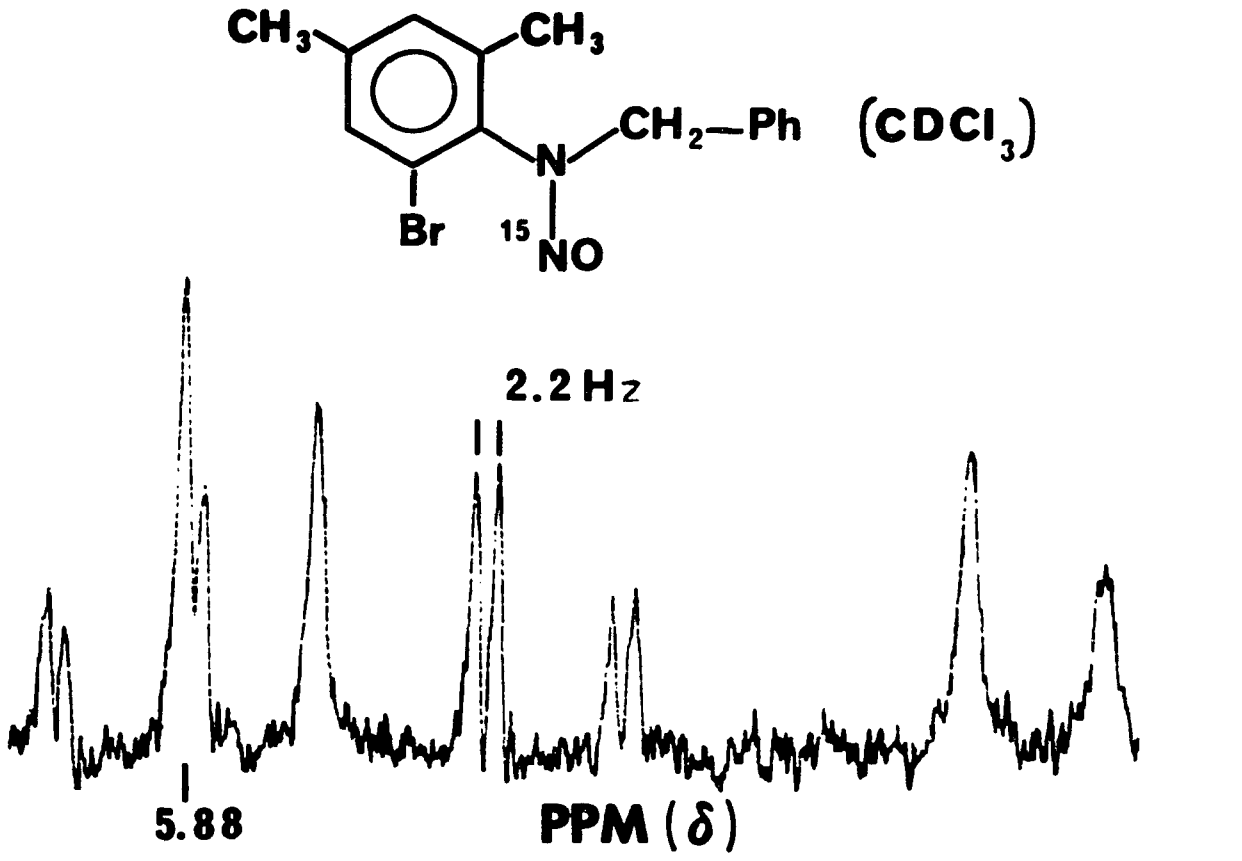


Figure 10. Methylene resonances of N-nitroso-N-benzyl-2-bromo-4,6-dimethylaniline-(^{15}N-nitroso) at 60 MHz.

bond ^{13}C-H coupling it prompted us to investigate several N-nitroso-N-benzylanilines to see if a similar situation exists in these systems. While free rotation of the benzyl group is to be expected, it was hoped that the magnetic non-equivalence of the benzyl protons might be reflected in unequal $^{3}J(^{15}N\text{-}H)$ coupling.

For the case illustrated in Figure 10, page 60, anywhere from eight to sixteen lines for the benzyl protons (assuming no overlapping of peaks) might be observed. The appearance of twelve lines (two of which overlap at δ 5.88) is easily explained. The isomer having the nitroso trans to the benzyl protons gives an AB quartet further split by coupling to the ^{15}N-nitroso-nitrogen, while the isomer having the nitroso cis to the benzyl protons gives only an AB quartet as $^{3}J(^{15}N\text{-}H)$ is approximately 0 Hz. The vicinal couplings observed in the two halves of the AB pattern ($^{3}J(^{15}N\text{-}H)$=2.1 and 2.2 Hz) are essentially the same. Examination of the coupling constants for other compounds of this type, given in Table IX, page 62, shows no discernible difference from those obtained for the other dialkylnitrosamines. The failure to observe a difference may be related to the possibility that a change of several per cent in these coupling constants would go unnoticed due to the relatively small magnitude of the coupling.

2. Nitrosohydrazines

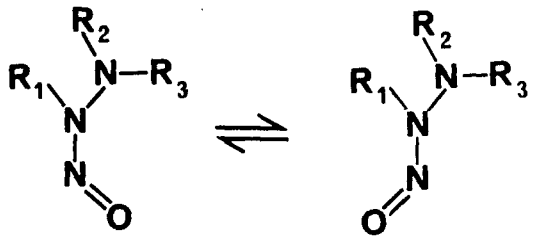
As an extension of our studies on nitrosamines. The nmr properties of N-nitrosohydrazines were investigated. This class of compounds has received relatively little systematic attention beyond the early pre-

Table IX. ^{15}N-N-C-H Coupling Constants in Ortho-Substituted (Nitroso-^{15}N)-N-Nitrosoanilines[a]

$R_1R_2N^{15}NO$			$^3J(^{15}N-H)$, Hz	
R_1	R_2	Solvent	cis[b]	trans[b]
$PhCH_2$	2-ClPh	Acetone-d_6	0.	2.4[c]
$PhCH_2$	2,6-Me_2Ph	$CDCl_3$	0.7	2.5
$PhCH_2$	2-Br-4,6-Me_2Ph	$CDCl_3$	0.	2.1,2.2[d]
$PhCHCH_3$	2,6-Me_2Ph	$CDCl_3$	0.	2.3

[a] The error in these measurements is estimated to be ± 0.2 Hz. [b] The trans configuration is defined as the one having the nitroso-oxygen anti to R_1. [c] Measurement made at -35°C. [d] Coupling constants of CH_AB_A protons.

parative work of Thiele.[99] Although it was expected that appreciable π-bonding between the nitrogen atoms would occur, the existence of configurational isomers XXa and XXb on the nmr time scale has not been dem-



XX a XX b

onstrated previously. Revlative to nitrosamines it was uncertain what effect the replacement of an alkyl group by an amino-group would have on both the degree of p-pπ bonding and the relative stability of each configuration. The nmr spectrum of a representative example, N-nitroso-trimethylhydrazine, at ambient temperature, is shown in Figure 11, page 64. Clearly, both isomers are present, although in unequal quantities. The chemical shifts and coupling constants for a series of N-nitroshydrazines, several of which have been labeled with nitrogen-15 (99 atom % ^{15}N) in the nitroso group are shown in Table X, page 65, and Table XI, page 66, respectively.

An examination of these data reveals that the relative population of isomers is not governed solely by steric considerations as in nitros-

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(99) J. Thiele, Ann., 376, 239 (1910).

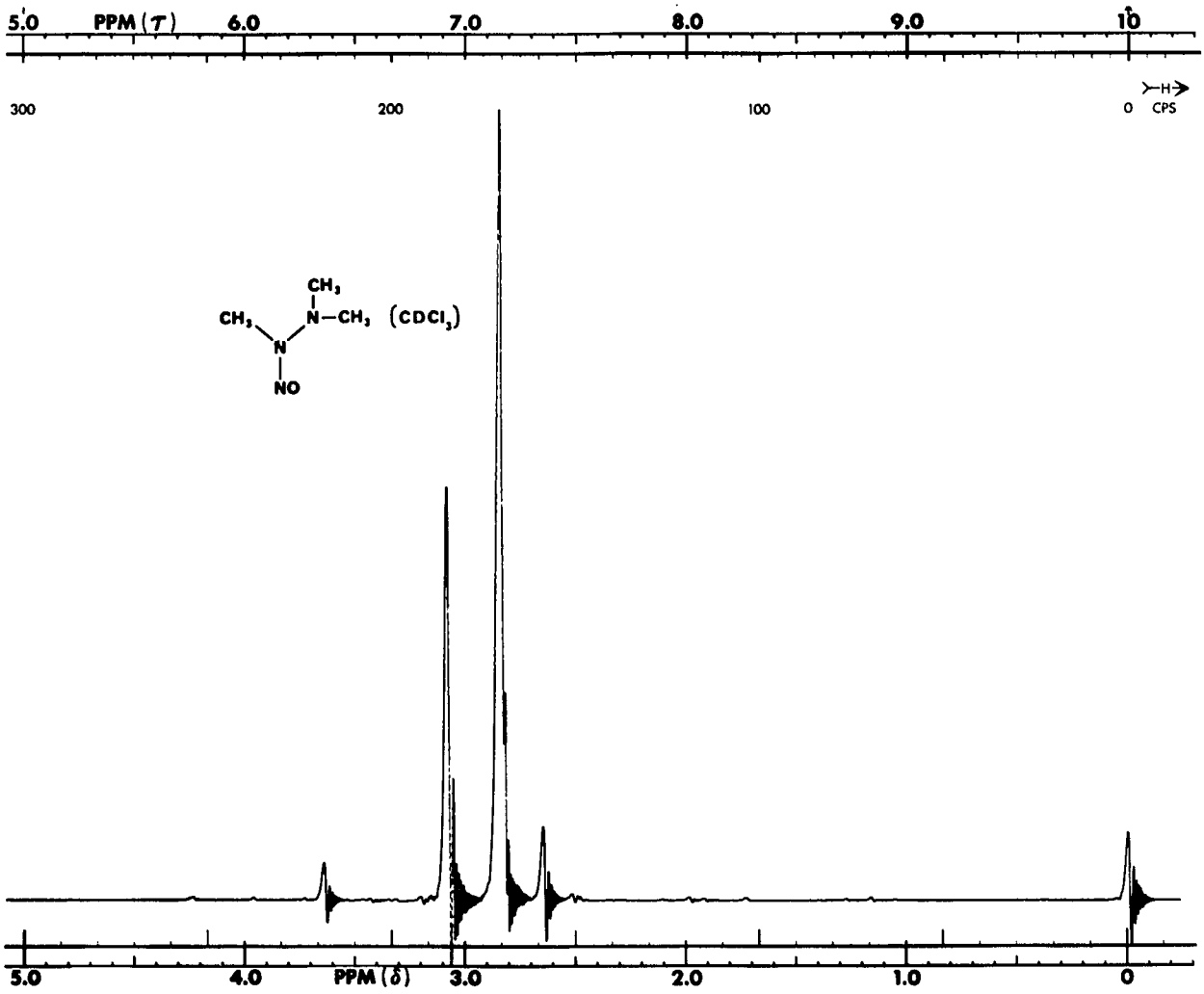

Figure 11. Proton magnetic resonance spectrum of trimethylnitrosohydrazine at 60 MHz.

Table X. Proton Chemical Shifts in cis and trans-(^{15}N-nitroso)-N-Nitrosohydrazines[a,b]

$R_1N(NO)NR_2R_3$			cis[c]			trans[c]			%[d]
R_1	R_2	R_3	R_1	R_2	R_3	R_1	R_2	R_3	trans/cis
CH_3	H	H				3.60	6.10	6.10	100/0
$PhCH_2$	H	H				5.22	5.70	5.70	100/0
$PhCH_2$	CH_3	H				5.20	2.50	2.50	100/0
$PhCH_2$	$PhCH_2$	H				5.14	3.84		100/0
CH_3	$PhCH_2$	H				3.55	3.90		100/0
$PhCH_2$	CH_3	CH_3	4.80	2.62	2.62	5.13	2.85	2.85	21/79
$PhCHCH_3$	CH_3	CH_3	5.42	2.45	2.45	6.01	2.63	2.63	41/59
CH_3	CH_3	CH_3	3.08	2.65	2.65	3.63	2.85	2.85	9/91

[a] Spectra were measured in $CDCl_3$ solution using either a Varian A-60 or HA-100 spectrometer. [b] The trans configuration is defined as the one having the nitroso-oxygen oriented syn to the adjacent aminonitrogen atom. [c] Chemical shift values of the α-protons are reported in ppm relative to tetramethylsilane as internal standard. [d] At magnet temperature, 37°.

Table XI. Coupling Constants in (^{15}N-Nitroso)-N-Nitrosohydrazines[a]

$R_1N(^{15}NO)NR_2R_3$			$^3J(^{15}N-H)$	$^3J(^{15}N-H)$	J(HNCH)
R_1	R_2	R_3	cis	trans	
$PhCH_2$	H	H	-	2.2	
CH_3	$PhCH_2$	H	-	2.2	6.5
$PhCH_2$	$PhCH_2$	H	-	-	6.0[b]
$PhCH_2$	CH_3	H	-	2.2	6.0
$PhCH_2$	CH_3	CH_3	0	2.2	
$PhCHCH_3$	CH_3	CH_3	0	1.9	

[a] All coupling constants expressed Hz. The error in these measurements is estimated at ± 0.2 Hz. [b] Obtained from the unlabeled compound.

amines. It appears that N-nitrosohydrazines may be divided into two categories; those compounds in which either or both R_2 and R_3 are hydrogen, in which case only one isomer is observed,[100] and those in which neither are hydrogen, in which event two isomers are observed.[101] For compounds falling in the latter category steric considerations appear to be the predominating factors, as an increase in the size of R_1 results in an increase in the amount of the isomer having the nitroso-group trans to R_1. In the case of N-nitroso-trimethylhydrazine, figure 11, page 64, the chemical shifts and intensities of the methyl absorptions suggest the isomer having the nitroso-group cis to methyl to be the major component. This assignment is reasonable if one assumes first, that the anisotropic effect of the nitroso-group in nitrosohydrazines is similar to that for nitrosamines and second, that the dimethylamino moiety can be considered roughly equivalent in size to an isopropyl group. The isomer ratio, observed by Karabatsos,[85] of 11% nitroso trans to methyl, 89% nitroso cis to methyl for N-nitroso-N methylisopropylamine, as opposed to 9% nitroso trans to methyl, 91% nitroso cis to methyl for N-nitroso-trimethylhydrazine provides support for the latter assumption.

From Table XI, page 66 it is obvious that the observed ^{15}N-N-C-H

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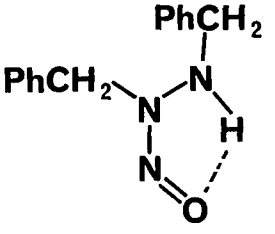
(100) A rapidly interconverting pair is not ruled out but is considered unlikely as the spectra remain essentially unchanged when the temperature is either raised or lowered.

(101) In an attempt to estimate the barrier to rotation, using the equilibration technique, a sample of 1-benzyl-2,2-dimethylnitrosohydrazine was heated in the nmr spectrometer. Initially, the compound exhibits a typical temperature dependent coalescence sequence; however, as the temperature is raised the material begins to decompose, although it does appear that the coalescence temperature is considerably lower than that for nitrosamines.

coupling in N-nitrosohydrazines, (approximately 2 Hz for those isomers having the nitroso-group trans to R_1 and approximately 0 Hz for those isomers having the nitroso-group cis to R_1) are essentially identical to those observed for nitrosamines.

For those nitroshydrazines where either R_2 or R_3 are hydrogen, the presence of only the isomer having the nitroso-group trans to R_1, as determined by the chemical shift of the α-protons and the magnitude of the $^3J(^{15}N\text{-}H)$ coupling, is attributed to preferential stabilization of this configurational isomer by intramolecular hydrogen-bonding. This is illustrated for N-nitrosodibenzylhydrazine, XXI. Additional evidence



XXI

for the proposed hydrogen-bonding comes from the observation of coupling between the N-bound proton and the adjacent benzyl protons. Normally, H-N-C-H coupling is not observed due to the rapid exchange of the hydrogen directly bonded to nitrogen. However, as sumarized in Table XI, page 66; in these N-nitrosohydrazines the hydrogen-bond between the nitroso-oxygen and the amino-hydrogen presumably, slows this exchange sufficiently to allow the 6.0-6.5 Hz coupling to be observed. Addition of D_2O causes the doublet associated with the alkyl group to collapse to a broad singlet, thus confirming that an exchangeable proton is

involved in the coupling.

It might be expected that dimethylsulfoxide, a powerful hydrogen-bonding solvent, would be able to effectively compete with the nitroso group and disrupt the intramolecular hydrogen-bond leading to an equilibrium mixture of configurational isomers. Evidently the intramolecular hydrogen bond in these nitrosohydrazines is quite strong in that the spectrum of N-nitrosobenzylhydrazine, in DMSO-d_6 is essentially unchanged from that in $CDCl_3$. That only one benzyl absorption, at δ 5.27, is observed is interpreted to mean that the isomer present is the one having the nitroso-group trans to the benzyl protons.[102] In support of this assignment it may be noted that the trans benzyl absorption of 2,2-dimethyl-1-benzylnitrosohydrazine appears at δ 5.13.

In conclusion, we suggest that the same dependence of $^3J(^{15}N\text{-}H)$ on the orientation of the nitroso-moiety, demonstrated for nitrosamines, exists in nitrosohydrazines, and that this dependence provides a useful method for the assignment of configurations in nitrosohydrazines.

Nitrogen-15 Chemical Shifts

Data for the chemical shifts of the nitroso-nitrogen atoms in several nitrogen-15 labeled nitrosamines and nitrosohydrazines, as determined by double resonance, are presented in Table XII, page 70. Since these compounds exhibit configurational isomerism due to res-

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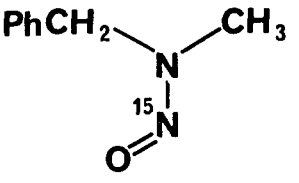
(102) A similar experiment was carried out with N-nitroso-N-benzylhydroxylamine-(^{15}N-nitroso), kindly provided by Mr. M. J. Wieder. In this instance the appearance of only one benzyl absorption, at δ 5.25, was accompanied by coupling of the benzyl protons to the nitroso-nitrogen. The observed coupling constant of 2.6 Hz was identical with the value obtained in $CDCl_3$ solution, thus providing additional evidence that the isomer present is the one having the nitroso trans to the benzyl protons.

Table XII. ^{15}N-Nitroso Nitrogen Chemical Shifts in a Series of N-Nitrosamines.[a,b]

	$R_1R_2N^{15}NO$		Chemical Shift, ppm	
	R_1	R_2	R_1NR_2 | ^{15}NO	R_1NR_2 | ON^{15}
a)	$PhCH_2$	CH_3	2.5	0.
b)	$PhCH_2$	CH_2CH_3	2.5	0.6
c)	$PhCH_2$	$PhCH_2$	1.5	1.5
d)	$PhCH_2$	$CH(CH_3)_2$	6.1	2.0
e)	$PhCHCH_3$	$PhCHCH_3$	5.0	5.0
f)	$PhCH_2$	$C(CH_3)_3$	-	5.4
g)	CH_3	Ph	11.5	-
h)	$PhCH_2$	Ph	9.3	10.5
i)	$PhCH_2$	$N(CH_3)_2$	8.8	10.5
j)	$PhCHCH_3$	$N(CH_3)_2$	9.7	-

[a] Measured in ppm relative to the isomer of N-nitroso-N-methylbenzylamine having the nitroso oriented trans to the methyl group. [b] Obtained as 10-20% w/w solutions in $CDCl_3$. The error in these measurements is estimated at ± 0.1 ppm.

tricted rotation about the N-N bond, it has been possible to measure the chemical shifts of the nitrogen atoms in both rotameric forms. For ease in discussion the chemical shift of the nitroso-^{15}N atom of the isomer of N-nitroso-N-methylbenzylamine having the nitroso-oxygen trans to the α-methyl group, XXII, is taken as an arbitary reference.



XXII

Relative to the large range of chemical shifts associated with the different types of nitrogen functional groups (1000 ppm), the spread of values found for the nitroso-^{15}N nuclei in these compounds encompasses a narrow range of only 11.5 ppm. Specifically, it may be seen in a series of N-alkyl-N-benzylnitrosamines (entries a-f) that as the number of alkyl substituents on the carbon atom alpha to the nitrosamino group is increased, a downfield trend is observed in the nitrogen chemical shifts. This is particularly true in that configurational isomer having the nitroso-oxygen atom oriented trans to the alkyl group and cis to the benzyl group. Data are also presented for two N-alkyl-N-phenyl nitrosamines (entries g and h) and two nitrosohydrazines (entries i and j). However, these data are so few (and in some cases due to only one configurational isomer) that any attempt to rationalize the chemical shifts in these latter systems seems premature. Consequently, the interpretation of the nitroso-^{15}N chemical shifts will be largely restricted to

the N-alkyl-N-benzylnitrosamines (entries a-f).

Of the factors generally considered to contribute to the shielding of nitrogen, the paramagnetic term is usually of major importance where large shifts are involved.[14-16] While significant changes in the paramagnetic contribution cannot be rigorously excluded the $n-\pi^*$ absorptions in these N-alkyl-N-benzylnitrosamines have been identified[103] and are essentially invariant suggesting that at least the change in ΔE in the paramagnetic term is minimal.[104] We also note that the observed changes in chemical shift are in the opposite direction to that expected for a diamagnetic effect due to increasing alkyl substitution. If one assumes that the observed, relatively small, changes in nitrogen chemical shift are not the result of a minor change in ν_p it is reasonable to attempt to correlate these shifts with the long range shielding that the nitrogen atom experiences as a result of some preferred conformation adopted by the molecule.

The suggestion that open chain organic compounds may exist in distinct rotational conformers is not a novel one. For the case of a tetrahedral carbon bonded to a trigonal carbon it is well known that the most favored conformation is that in which a substituent on the tetrahedral carbon eclipses the double bond.[105] While it is not necessarily the smallest substituent on the tetrahedral carbon which eclipses the double bond[106] it is well established that as the size of the tetrahedral

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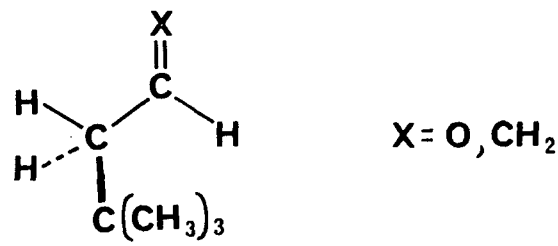
(103) M. Kasha, Discussions Faraday Soc., 9, 14 (1950).

(104) The interpretation of the ultraviolet spectra of these compounds is complicated by the fact that the net absorption is the sum of the absorptions of two different isomers.

(105) R. W. Kilb, C. C. Lin and E. B. Wilson, J. Chem. Phys., 26 1695 (1957); D. R. Herschbach and L. C. Krischer, J. Chem. Phys., 28, 728 (1958).

(106) R. J. Abraham and J. A. Pople, Mol. Phys., 3, 609 (1960).

substituent increases the most favored conformation of the molecule is the one in which the large tetrahedral substituent assumes a gauche position relative to the double bond. Thus both neopentylethylene[107] and 3,3-dimethylbutyraldehyde[108] exist primarily in a conformation such as XXIII.



XXIII

The situation for N-nitrosamines, in which there is appreciable double bond character between the two nitrogens, is somewhat more complex. In addition to the interactions between the double bond and the tetrahedral substituents one must consider the interactions between the alkyl substituents on the tetrahedral carbons alpha to the nitrosamino group. Thus Karabatsos[85] has suggested that the favored conformation of diisopropyl nitrosamine is XXV , in which only one <u>trans</u> β methyl group is eclipsed by a <u>cis</u> β methyl group, as opposed to XXIV, in which both <u>trans</u> β methyl groups are eclipsed.

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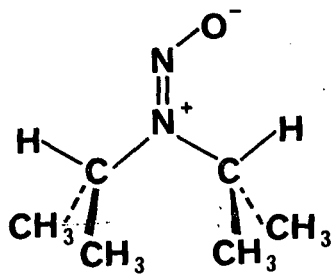
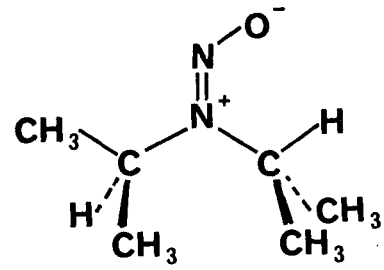
(107) A. A. Bothner-By, C. Naar-Colin and H. Gunther, J. Amer. Chem. Soc., <u>84</u>, 2748 (1962).

(108) G. J. Karabatsos and N. Hsi, J. Amer. Chem. Soc., <u>87</u>, 2864 (1965).



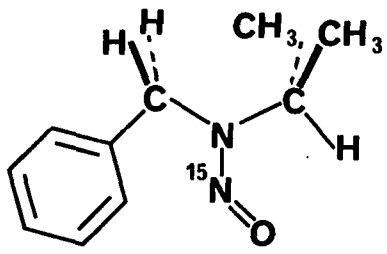
XXIV



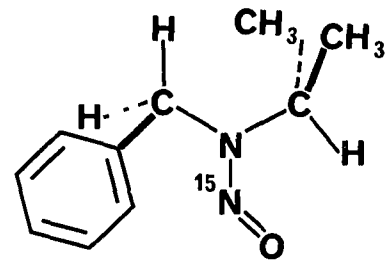
XXV

For N-nitrosamines it has been shown[85] that resonances due to α-methyl and α-methylene protons occur at higher fields when oriented cis to the nitroso-oxygen than when trans, while the reverse is true for α-methine protons. The greater deshielding experienced by the cis-α-methine proton is considered to arise from a highly populated conformation which places the methine proton of the cis alkyl group in the nodal plane of the nitrosamino-group. If this assumption is correct one might expect the isomer of N-nitroso-N-isopropylbenzylamine-(^{15}N-nitroso) having the nitroso group trans to the benzyl group to exist primarily in conformations XXVI-XXVIII. The relative population of these conformations would be expected to be determined by the nature of the 1,3-interactions that arise when the different substituents (phenyl and hydrogen) are brought into juxtaposition with the methyl groups and the N-N bond. Of these conformations, it seems reasonable to assign the greatest contribution to XXVII because of the neatly staggered arrangement of groups and the absence of the eclipsing inter-

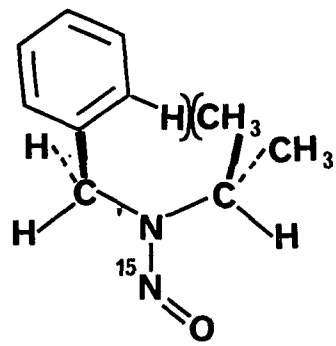
actions in XXVI or steric compression XXVIII.[109]



XXVI



XXVII



XXVIII

The chemical shift of a magnetic nucleus depends not only on its

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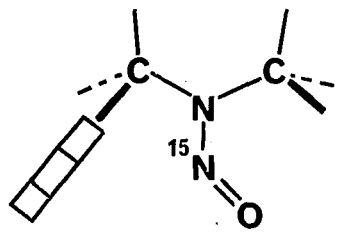
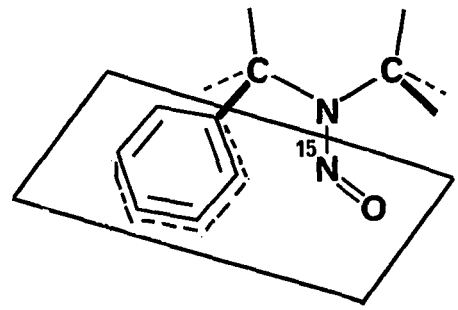
(109) The observation that approximately one third of the molecules of phenylacetaldehyde exist in a conformation in which the phenyl group eclipses the double bond (see footnote 108) suggests that XXVI contributes appreciably.

electronic environment but also on the orientation and anisotropy of neighboring groups. The π -electrons of a phenyl group can have a pronounced effect on the chemical shift of a proton (and presumably other nuclei) located in a different section of a molecule. For example, the chemical shift of the central methylene protons of (1.8) paracyclophane occurs at higher field than the other methylene protons due to the shielding effect of the aromatic ring.[110]

In N-nitroso-N-isopropylbenzylamine conformation XXVII places the phenyl ring in a position to influence the chemical shift of the nitroso-nitrogen (as opposed to a conformation such as XXVIII in which the phenyl ring is oriented away from the nitroso-nitrogen). Structures XXIX and XXX are presented in an effort to estimate the effect of the benzene π-system in XXVII on the chemical shift of the nitroso-nitrogen. In XXIX



XXIX



XXX

where the benzene ring is shown perpendicular to the plane of the nitroso-group it may be seen that only slight shielding by the benzene π-cloud results as the nitroso-nitrogen is situated on the edge of the

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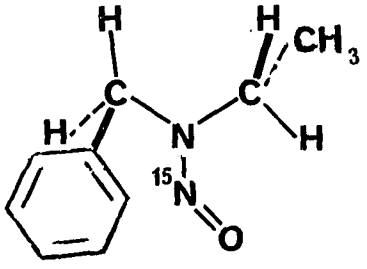
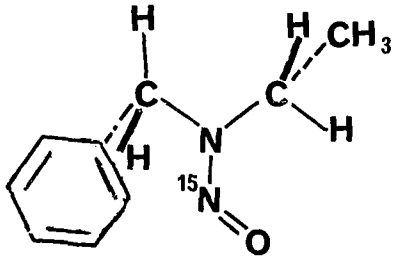
(110) John R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds", Prentic Hall Inc., Englewood Cliffs, New Jersey 1965, p 82.

shielding cone. In XXX, where the benzene ring is co-planar with the nitroso-group, the nitroso-nitrogen lies squarely in the deshielding region of the benzene ring. Summing of the effects of all the presumed positions of the benzene ring relative to the nitroso-nitrogen, results in a net deshielding of the nitrogen-15 atom.[111]

For the isomer of N-nitroso-N-ethylbenzylamine-(^{15}N-nitroso) having the nitroso-oxygen <u>trans</u> to the benzyl group several of the heavily populated conformations are shown in XXXI-XXXIV.



XXXI



XXXII

In conformations XXXIII and XXXIV the π-cloud of the benzene ring is not in a position to affect the nitroso-nitrogen while the orientation of the benzene ring in conformations XXXI and XXXII is similar to that of XXVII with the resulting possibility of deshielding. Assuming that the chemical shift of the nitrogen-15 atom is a reflection of the heavily

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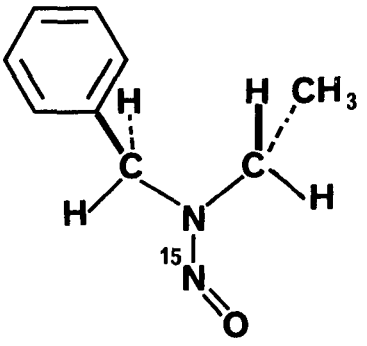
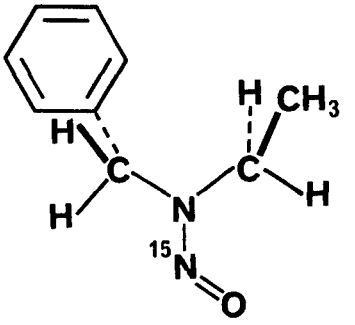
(111) The conclusions concerning both the proximity and the net magnetic anisotropy of the benzene ring relative to the nitroso-nitrogen are based on a qualitative examination of Dreiding models of the compounds in question.



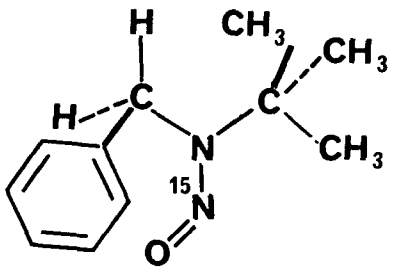
XXXIII



XXXIV

populated conformations of the molecule, the upfield shift (6.1 to 2.5 ppm) observed in going from the isopropyl isomer, shown in XXVI and XXVII, to the ethyl isomer, XXXI-XXXIV, may be attributed to the reduced deshielding of the nitroso-nitrogen by conformations XXXIII and XXXIV. In effect one may consider that conformations of the type XXXIII and XXIV, which are not present in the isopropyl isomer, tend to "dilute" the deshielding of XXXI and XXXII.

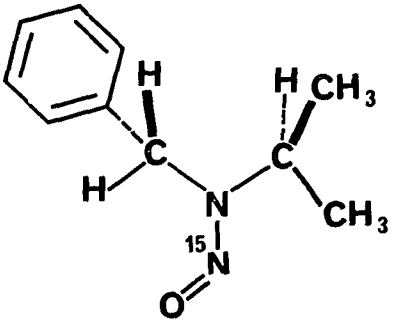
For N-nitroso-N-t-butylbenzylamine-(^{15}N-nitroso), in which the nitroso-oxygen is oriented exclusively cis to the benzyl group, a relative deshielding (5.4 ppm) of the nitroso-nitrogen is observed. This, again, may be explained in terms of the anisotropic effect of the benzene ring. Since there are unfavorable non-bonded interactions of the benzene nucleus with both the nitroso-oxygen and the t-butyl methyl groups the molecule may adopt a staggered conformation similar to XXXV. This conformation situates the phenyl ring in a position from which it



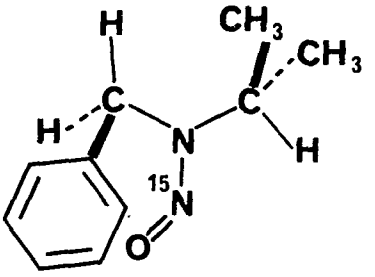
XXXV

may deshield the nitroso-nitrogen. Extending our argument, if substitution of hydrogen for methyl, in XXXV, results in heavily populated conformations from which no deshielding occurs, an upfield shift of the nitroso-nitrogen would be expected. The observed shift (5.4 to 2.0 ppm) in going from N-nitroso-N-t-butylbenzylamine-(^{15}N-nitroso), XXXV, to the isomer of N-nitroso-N-isopropylbenzylamine-(^{15}N-nitroso) having the nitroso-oxygen cis to the benzyl group is in agreement with this expectation and is attributed to the importance of a conformation such as XXXVI which tends to "dilute" the deshielding of XXXVII.

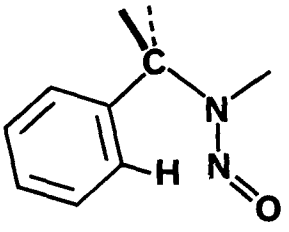
In general it may be noted that the chemical shifts of those isomers having the nitroso-oxygen trans to R_1 appear at lower fields than do those isomers having the nitroso cis to R_1. This is understandable as those isomers falling in the former category have the opportunity to adopt a conformation such as XXXVIII in which the benzene ring and the nitroso group are co-planar. While this eclipsed conformation is not the most favored it is of lower energy than the corresponding co-planar situation, shown in XXXIX, for those isomers having the nitroso cis to



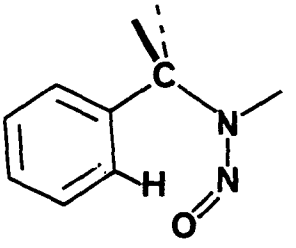
XXXVI



XXXVII



XXXVIII



XXXIX

the benzyl group. The relative stability of XXXVIII over XXXIX results in relatively more co-planarity for isomers of type XXXVIII and thus for greater deshielding of the nitroso-nitrogen atoms in these isomers.

While the data for N-nitrosoanilines are few they are in agreement with our suggestions. Specifically, N-nitroso-N-methylaniline-(^{15}N-nitroso) and N-nitroso-N-benzylaniline-(^{15}N-nitroso) represent situations in which the nitroso-group may be conjugated with the benzene

ring. Such a conjugation would allow for co-planarity of both π-systems, thus locating the nitroso-nitrogen in the deshielding region of the benzene ring. The observed chemical shifts (9.3 to 11.5 ppm) are consistent with this increased deshielding.

In summary we suggest that the nitrogen-15 chemical shifts may be a function of the heavily populated conformations which these compounds adopt and, within each conformation, the extent to which the phenyl ring deshields the nitrogen-15 atom.

As we have attributed changes in the chemical shifts of the nitroso-nitrogen atoms, in these compounds, to the position and anisotropy of the phenyl ring it would be interesting to examine the nitrogen-15 shifts of some dialkylnitrosamines-(^{15}N-nitroso) in which a) the aromatic nucleus is substituted and b) there is no aromatic nucleus.

EXPERIMENTAL

Methods and Materials

Boiling points and melting points are uncorrected. Spectra, except where noted, were obtained on a Varian Model A-60 spectrometer equipped with a variable-temperature probe and V-6040 variable temperature controller. Coupling constants were measured by the audio sideband technique. The uncertainty in these values is estimated at ± 0.2 Hz. Double resonance experiments were performed at the National Institutes of Health on a Varian HR-60 spectrometer modified for field-frequency stabilization through a servo loop operating on the dispersion mode signal from internal tetramethylsilane. A general radio Model 1164-A frequency synthesizer provided both the 60 MHz proton frequency and the decoupling frequency (ca 6.08 MHz in the ^{15}N range). The integrations for those nitrosamines and nitrosohydrazines in which more than one isomer is observed are relative for each isomer.

The data for the nitrogen-15 compounds in this section were obtained from crude reaction products. The nmr data shown below do not include those peaks which arise from the impurities associated with crude materials (i.e. traces of unreacted starting materials).

All starting materials, unless otherwise specified, were commercially available and were used without further purification. Sodium nitrite, 99.0 atom % ^{15}N and ammonium chloride, 97.2 atom % ^{15}N were supplied by Isomet, Inc., Palisades Park, New Jersey. Potassium nitrite, 99.1 atom % ^{15}N was supplied by Ateledyne, Westwood, New Jersey. Aniline, 97.8 atom % ^{15}N and ammonium acetate, 98.4 atom % ^{15}N were supplied by the Junta De Energia Nuclear, Madrid, Spain. DMSO-d_6 and $CDCl_3$ were supplied by Stohler isotope chemical, Inc., Rutherford, New Jersey.

Preparation of Aniline-^{15}N Derivatives

3,5-Dimethyl-4-nitrobenzoic acid. To a refluxing solution of nitromesitylene (64.0 g, 0.388 mol) in 80 ml of concentrated sulfuric acid and 300 ml of glacial acetic was added a solution of chromium trioxide (120.0 g, 1.20 mol) in 400 ml of water over a 90-minute period. Refluxing was continued for an additional hour after which time the reaction mixture was poured on ice and the precipitated solid collected by filtration, washed with water, and dissolved in 100 ml of 10% sodium hydroxide. Filtration to remove unreacted starting material was followed by acidification of the filtrate with 25 ml of concentrated hydrochloric acid. The crude product was collected by filtration, washed with water and recrystallized from 95% ethanol to afford 13.3 g (17.6%) of 3,5-dimethyl-4-nitrobenzoic acid, mp 215-224° (lit.[112] mp 225.5-227°). A second recrystallization from 95% ethanol gave 9.00 g, mp 223-226°.

3,5-Dimethyl-4-nitrobenzoyl chloride. A mixture of 3,5-dimethyl-4-nitrobenzoic acid (3.55 g, 0.0182 mol), thionyl chloride (11.2g, 0.0949 mol) and pyridine (0.250 g, 0.00316 mol) was heated under reflux for 105 minutes. After cooling to room temperature the excess thionyl chloride was removed at reduced pressure on a rotary evaporator. The resulting solid was recrystallized from petroleum ether (bp 30-60°) to afford 2.10 g of 3,5-dimethyl-4-nitrobenzoyl chloride, mp 57-59° (lit.[113] mp 52-53°). An additional 1.10 g of product, mp 55-58°, was obtained

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(112) J. P. Schaeffer and T. J. Miraglia, J. Amer. Chem. Soc., 86, 64 (1964).

(113) D. B. Cosulich, D. R. Seeger, M. J. Fahrenbach, K.H. Collins, B. Roth, M. E. Hultquist, and J. M. Smith, Jr., J. Amer. Chem. Soc., 45, 4675 (1953).

by concentrating the filtrate and recrystallizing the solid which remains. The total yield is 3.20 g (82%); nmr ($CDCl_3$), δ 2.40 (s, 6, m-CH_3), 793 (broad s, 2, ArH).

3,5-Dimethyl-4-nitrobenzamide-^{15}N. A 25 ml three-necked round-bottomed flask was equipped with an inlet for dry nitrogen, a dropping funnel and a reflux condenser fitted with a 10-cm potassium hydroxide drying tube which was connected to a dry-ice trap by means of tygon tubing. A solution of 3,5-dimethyl-4-nitrobenzoyl chloride (0,427 g, 0.00200 mol) in 65 ml 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 of 4 ml of a 1.15M solution of ammonium-^{15}N chloride (0.251 g, 0.00460 mol, 97.2 atom % ^{15}N) to a refluxing solution of 4 ml of 6.25M sodium hydroxide over a 20-minute period. The aqueous solution was heated under reflux for an additional 2 hours and the residual ammonia-^{15}N conducted to the trap by the maintenance of a slow stream of nitrogen for 18 hours. The suspension formed in the trap was filtered and the crude ammonium-^{15}N chloride washed with acetone and the washings combined with the ethereal filtrate. Removal of the solvent at reduced pressure on a rotary evaporator gave 0.351 g (90%) of 3,5-dimethyl-4-nitrobenzamide-^{15}N, mp 167.5-170° (lit.[114] mp 169-170°); nmr (DMSO-d_6), δ 8.01 (d, 1, ^{15}NH), 7.60 (d, 1, ^{15}NH), 2.33 (s, 6, m-CH_3), 7.83 (s, 2, ArH). The recovered ammonium-^{15}N chloride (0.088 g) was

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(114) M. J. S. Dewar and Y. Takeuchi, J. Amer. Chem. Soc., 89, 390 (1967).

used in future preparations.

3,5-Dimethyl-4-nitroaniline-^{15}N. Solid 3,5-dimethyl-4-nitrobenzamide-^{15}N (0.300 g, 0.00154 mol) was added to a solution of sodium hypobromite prepared by the addition of bromine (0.273 g, 0.00171 mol) to 2 ml to 20% sodium hydroxide at 0°. After stirring for 1 minute the temperature of the suspension was raised to 100° over a 30-minute period and maintained at that temperature for 2 hours during which time two 1-ml aliquots of 10% sodium hydroxide were added at 45 minute intervals. The resulting yellow solid was extracted with ether and the ethereal solution dried ($MgSO_4$). Removal of the ether at reduced pressure afforded 0.192 g (75%) of crude yellow produce, mp 128-132° (lit.[115] mp 133°); nmr (DMSO-d_6), δ 5.84 (d, 2, $^{15}NH_2$), 2.19 (s, 6, m-CH_3), 6.31 (m, 2, ArH).

p-Toluamide-^{15}N. The same procedure as that for the preparation of 3,5-dimethyl-4-nitrobenzamide was followed with one modification; the concentration of the aqueous sodium hydroxide in the three-necked flask was changed from 6.25M to 7.50M. From p-toluyl chloride (0.311 g, 0.00201 mol) and ammonium-^{15}N chloride (0.242 g, 0.00444 mol, 97.2 atom % ^{15}N) there was obtained 0.244 g (89%) of crude product, mp 155-163° (lit.[116] mp 165°); nmr (DMSO-d_6), δ 7.85 (d, 1, ^{15}NH), 7.25 (d, 1, ^{15}NH), 2.32 (s, 3, CH_3), 7.42 (m, 4, ArH).

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(115) E. Bamberger, Ann., 443, 207 (1925).

(116) L. McMaster and F. B. Lamgreck, J. Amer. Chem. Soc., 39, 106 (1917).

p-Toluidine-^{15}N. Solid p-toluamide-^{15}N (0.149 g, 0.00110 mol) was added to a solution of sodium hypobromite prepared by the addition of bromine (0.182 g, 0.00115 mol) to 1 ml of 20% sodium hydroxide at 0°. After stirring for 10 minutes at 0°, 1 ml of 10% sodium hydroxide was added and the temperature of the suspension raised to 100° over a 30-minute period and maintained at that temperature for 2 hours. Extraction of the resulting suspension with ether was followed by drying ($MgSO_4$) and concentration at reduced pressure to afford 0.071 g (60%) of crude product, mp 37-41° (lit.[117] mp 45°); nmr (DMSO-d_6), δ 4.70 (d, 2, $^{15}NH_2$), 2.13 (s, 3, CH_3), 6.70 (m, 4, ArH).

p-Anisamide-^{15}N. The same procedure as that for the preparation of 3,5-dimethyl-4-nitrobenzamide-^{15}N was followed. From p-anisoyl chloride (0.512 g, 0.00300 mol) and ammonium-^{15}N acetate (0.496 g, 0.00637 mol, 98.4 atom % ^{15}N) there was obtained 0.381 g (84%) of crude product, mp 158-164° (lit.[118] mp 165-167°).

p-Anisidine-^{15}N. p-Anisidine-^{15}N was prepared by the procedure of Hauser and Renfrow.[119] From p-anisamide-^{15}N (0.366 g, 0.00242 mol), bromine (0.500 g, 0.00313 mol) and 14 ml of 10% sodium hydroxide there was obtained 1.160 g (57%) of crude product, mp 52-56° (lit.[118] mp 56.5-57°); nmr (DMSO-d_6), δ 4.48 (d, 2, $^{15}NH_2$), 3.63 (s, 3, CH_3), 6.70 (m, 4, ArH).

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(117) A. I. Vogel, "Practical Organic Chemistry", 3rd Ed., Longsmans, Green and Co., London, 1956, p 565.

(118) E. S. Lewis and R. E. Halliday, J. Amer. Chem. Soc., 91, 426 (1969).

(119) C. R. Hauser and W. B. Renfrow, J. Amer. Chem. Soc., 59, 121 (1937).

p-Fluorobenzamide-^{15}N. The same procedure as that for the preparation of 3,5-dimethyl-4-nitrobenzamide-^{15}N was followed. From p-fluorobenzoyl chloride (0.295 g, 0.00186 mol) and ammonium-^{15}N chloride (0.232 g, 0.00426 mol) there was obtained 0.240 g (92%) of crude product, mp 156-160° (lit.[120] mp 152-153°); nmr (DMSO-d_6), δ 7.95 (d, 1, ^{15}NH), 7.43 (d, 1, ^{15}NH), 7.77 (m, 4, ArH).

p-Fluoroaniline-^{15}N. The same procedure as that for the preparation of p-toluidine-^{15}N was followed. From p-fluorobenzamide-^{15}N (0.172 g, 0.00123 mol) and aqueous hypobromite (0.231 g bromine in 1 ml 30% sodium hydroxide) there was obtained 0.0.082 g (69%) of crude product; nmr[121] (DMSO-d_6), δ 4.88 (d, 2, $^{15}NH_2$), 6.70 (m, 4, ArH).

p-Chlorobenzamide-^{15}N. The same procedure as that for the preparation of 3,5-dimethyl-4-nitrobenzamide-^{15}N was followed. From p-chlorobenzoyl chloride (0.349 g, 0.00200 mol) and ammonium-^{15}N chloride (0.241 g, 0.00455 mol) there was obtained 0.279 g (95%) of p-chlorobenzamide-^{15}N, mp 173-181.5° (lit.[122] mp 180°); nmr (DMSO-d_6), δ 8.01 (d, 1, ^{15}NH), 7.39 (d, 1, ^{15}NH), 7.78 (m, 4, ArH).

p-Chloroaniline-^{15}N. A modification of the same procedure as that for the preparation of p-toluidine-^{15}N was followed. Before extraction with ether the crude amine was dissolved in 6M hydrochloric acid and insoluble organic materials were removed by extraction with ether. The

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(120) K. C. Joshi and S. Giri, J. Indian Chem. Soc., 37, 423 (1960).
(121) R. E. Richards and T. Schaefer, Proc. Royal Soc., A-246, 429 (1958).
(122) C. H. Kao and Shao-Yuan Ma, J. Chem. Soc., 443 (1931).

amine was then precipitated from the aqueous solution with 20% sodium hydroxide. From p-chlorobenzamide-^{15}N (0.233 g, 0.00149 mol) and aqueous hypobromite (0.275 g bromine in 1.5 ml of 20% sodium hydroxide) there was obtained 0.107 g (52%) of p-chloroaniline-^{15}N, mp 69-71° (lit.[123] mp 70-71°) nmr (DMSO-d_6), δ 5.15 (d, 2, $^{15}NH_2$), 6.82 (m, 4, ArH).

p-Iodobenzamide-^{15}N. The same procedure as that for the preparation of 3,5-dimethyl-4-nitrobenzamide-^{15}N was followed with one modification. The crude amide was washed with n-hexane to remove unreacted acid chloride. From p-iodobenzoyl chloride (0.504 g, 0.00200 mol) and ammonium-^{15}N chloride (0.233 g, 0.00428 mol) there was obtained 0.350 g (71%) of crude product, mp 214-217° (lit.[124] mp 217.6°); nmr (DMSO-d_6), δ 7.96 (d, 1, ^{15}NH), 7.38 (d, 1, ^{15}NH), 7.48 (m, 4, ArH).

p-Iodoaniline-^{15}N. The same procedure as that for the preparation of p-toluidine-^{15}N was followed. From p-iodobenzamide-^{15}N (0.248 g, 0.00100 mol) and aqueous hypobromite (0.181 g bromine in 1 ml 20% sodium hydroxide) there was obtained 0.106 g (48%) of crude product, mp 57-60° (lit.[125] mp 67-68°), nmr (DMSO-d_6), δ 5.20 (d, 2, $^{15}NH_2$), 6.88 (m, 4, ArH).

Acetanilide-^{15}N. A stirred solution of aniline-^{15}N (0.650 g, 0.00691 mol, 97.8 atom % ^{15}N) and acetic anhydride (0.780 g, 0.00780 mol) in 0.660 g of glacial acetic acid was heated under reflux for 1 hour. The hot suspension was then poured on 50 g of ice and the gray solid which precipitated was extracted with chloroform. The chloroform layer was

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(123) C. R. Noller and Poe Liang, J. Amer. Chem. Soc., 54, 670 (1932).

(124) I. Remsen and E. Reid, Amer. Chem. Journal, 21, 290 (1899).

(125) M. Beringer and I. Lillien, J. Amer. Chem. Soc., 82, 725 (1960).

washed successively with 5% aqueous potassium carbonate and water, dried ($MgSO_4$) and concentrated at reduced pressure on a rotary evaporator to afford 0.758 g (82%) of acetanilide-^{15}N, mp 108-112° (lit.[126] mp 113-114°); nmr (acetone-d_6), δ 9.42 (d, 1, ^{15}NH), 2.12 (d, 3, CH_3), 6.90-7.83 (m, 5, ArH).

2,4-Dinitroacetanilide-^{15}N. Solid acetanilide-^{15}N (0.660 g, 0.00485 mol) was added to a stirred solution of 2.2 ml of fuming sulfuric acid (20-23%) cooled to 0°, over a 15-minute period. The reaction mixture was stirred for 1 hour at 0° after which time it was poured on 50 g of ice and the precipitated yellow solid was extracted with chloroform. The chloroform solution was washed successively with 5% potassium carbonate and water, dried ($MgSO_4$) and concentrated at reduced pressure to afford 0.758 g (69%) of crude yellow solid, mp 117.5-120°(lit.[127] mp 121°), nmr ($CDCl_3$), δ 10.62 (d, 1, ^{15}NH), 2.42 (d, 3, CH_3), 8.38-9.20 (m, 3, ArH).

2,4-Dinitroaniline-^{15}N. A stirred suspension of 2,4-dinitroacetanilide-^{15}N (0.131 g, 0.000579 mol) in 12 ml of 70% sulfuric acid was heated at 135° for 2 hours after which time the hot reaction mixture was poured on 33 g of ice. The resulting mixture was made basic with 27 ml of 30% sodium hydroxide and the crude yellow solid was extracted with chloroform. After washing with 5% potassium carbonate and water, the chloroform solution was dried ($MgSO_4$) and concentrated at reduced pressure to afford 0.106 g (99%) of crude product, mp 176-178° (lit.[128]

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(126) A. I. Vogel, "Practical Organic Chemistry", 3rd Ed., Longmans, Green and Co., London, 1956, p 577.

(127) W. Borsche, Ber., 50, 1355 (1917).

(128) A. I. Vogel, "Practical Organic Chemistry", 3rd Ed., Longmans, Green and Co., London, 1956, p 638.

mp 182°); nmr (DMSO-d_6), δ 8.32 (d, 2, $^{15}NH_2$), 8.73 (d, 1, m-ArH), 8.08 (q, 1, m-ArH), 7.13 (q, 1, o-ArH).

N,N-Dimethyl-p-phenylenediamine-^{15}N. N,N-dimethyl-p-phenylenediamine-^{15}N was prepared by the stannous chloride, hydrochloric acid reduction of p-nitroso-N,N-dimethylaniline as described by Jacobs and Heidelberger.[129] The p-nitroso-N,N-dimethylaniline was prepared by the procedure of Vogel[130] and was not isolated but used in the reduction, as the hydrochloride, without further purification. From N,N-dimethylaniline (0.179 g, 0.00148 mol), sodium nitrite-^{15}N (0.121 g, 0.00173 mol, 99.0 atom % ^{15}N) and stannous chloride (0.679 g, 0.00357 mol) there was obtained 0.081 g (40%) of crude product, mp 35-37.5° (lit.[130] mp 38-41°); nmr ($CDCl_3$), δ 2.75 (s, 6, N-$(CH_3)_2$), 3.24 (d, 2, $^{15}NH_2$), 6.63 (m, 4, ArH).

p-Phenylenediamine-^{15}N. Zinc dust (0.722 g, 0.0144 mol) was added to a refluxing suspension of p-nitroaniline-^{15}N (0.346 g, 0.00249 mol, 96.6 atom % ^{15}N) in 0.20 ml of 20% sodium hydroxide and 3 ml of 95% ethanol over a 5 minute period. The resulting red suspension was maintained under reflux for 80 minutes during which time 0.20 ml aliquots of 20% sodium hydroxide were added at 15 minute intervals. After adding 2 ml of ethanol the hot suspension was filtered and the zinc residue washed with hot ethanol. Drying of the ethanolic solution ($MgSO_4$) was

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(129) W. A. Jacobs and M. Heidelberger, J. Biol. Chem., 21, 113 (1915).

(130) A. I. Vogel "Practical Organic Chemistry", 2nd Ed., Longmans, Green and Co., London, 1951, p 550.

followed by concentration at reduced pressure to afford 0.200 g, (74%) of p-phenylenediamine-^{15}N as a red solid, mp 138-141°, (lit.[131] mp 140°); nmr ($CDCl_3$), δ 3.37 (d, 2, ^{15}NH), 3.37 (broad s, 2, ^{15}NH).

Bromination of aniline-^{15}N. To a mechanically stirred solution of aniline-^{15}N (0.470 g, 0.00500 mol, 97.8 atom % ^{15}N) in 15 ml of glacial acetic acid at 0°, was added 5.2 ml of a bromine solution, prepared by the addition of 8.00 g of bromine to 35.0 ml of glacial acetic acid. The resulting yellow suspension was stirred for 100 minutes after which time 35 ml of 30% sodium hydroxide were added and the insoluble organic layer was extracted with 60 ml of ether. The ether layer was washed with an equal volume of water, dried ($MgSO_4$) and concentrated at reduced pressure on a rotary evaporator to afford 0.840 g of yellow oil. The oil was chromatographed on 60 g of alumina slurry packed in hexane. Elution with nine 100-ml portions of benzene-hexane (10 : 90%) followed by concentration at reduced pressure afforded 0.055 g of 2,4,6-tribromoaniline-^{15}N, mp 114-116° (lit.[132] mp 120°). Continued elution with thirteen 100-ml portions of benzene-hexane (20 : 80%) followed by twelve 100-ml portions of benzene-hexane (40 : 60%) afforded in like manner 0.300 g of 2,4-dibromoaniline-^{15}N, mp 78-79.5° (lit.[133] mp 78-79°) and 0.363 g of p-bromoaniline-^{15}N, mp 61-63° (lit.[134] mp 66°), respectively; nmr p-bromoaniline-^{15}N (DMSO-d_6), δ 5.15 (d, 2, $^{15}NH_2$), 6.87 (m, 4,

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(131) E. Hazlet and C. A. Dornfeld, J. Amer. Chem. Soc., 66, 1781 (1944).

(132) A. I. Vogel, "Practical Organic Chemistry", 3rd Ed., Longmans, Green and Co., London, 1956 p 579.

(133) C. Chen, H. Ruan and F. Wu, J. Org. Chem., 30, 2090 (1965).

(134) A. I. Vogel, "Practical Organic Chemistry", 3rd Ed., Longmans, Green and Co., London, 1956, p 580.

ArH); 2,4-dibromoaniline-^{15}N (DMSO-d_6), 5.42 (d, 2, $^{15}NH_2$), 7.52 (d, 1, m-ArH), 7.24 (q, 1, m-ArH), 6.80 (q, 1, o-ArH); 2,4,6-tribromoaniline-^{15}N (DMSO-d_6), 5.48 (d, 2, $^{15}NH_2$), 7.63 (s, 2, ArH).

N-Benzylideneaniline-^{15}N. A solution of benzaldehyde (0.157 g, 0.00149 mol) and aniline-^{15}N (0.140 g, 0.00149 mol, 97.8 atom % ^{15}N) in 0.5 ml of benzene was heated under reflux for 1.75 hours after which time the solvent and all water formed were removed at reduced pressure using a rotary evaporator. The oil which remained crystallized slowly, mp 43-46° (lit.[135] mp 52°); nmr ($CDCl_3$), δ 8.32 (d, 1, CH), 7.00-8.00 (m, 10, ArH).

N-Benzylaniline-^{15}N. To a stirred suspension of lithium aluminum hydride (0.044 g, 0.00166 mol) in 8 ml of anhydrous ether was added a solution of N-benzylideneaniline-^{15}N (0.270 g, 0.00149 mol) in 7 ml of anhydrous ether and the resulting suspension heated under reflux for 18 hours. The mixture was hydrolyzed by the addition of 40 mg of water and the inorganic salts removed by filtration and washed with ether. Concnetration of the combined ethereal solutions gave 0.205 g (75%) of crude product, mp 33-34° (lit.[136] mp 37-38°); nmr (DMSO-d_6), δ 6.10 (d of t, 1, ^{15}NH), 4.23 (d, 2, CH_2), 6.38-7.60 (m, 10, ArH).

Formanilide-^{15}N. A solution of aniline-^{15}N (0.207 g, 0.00220 mol, 97.8 atom %-^{15}N) in 1.5 ml of ethyl formate was heated under reflux for

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(135) Organic Synthesis Coll. Vol. No 1, 2nd Ed., John Wiley and Sons Inc., New York, 1940, p 80.

(136) A. I. Vogel "Practical Organic Chemistry", 2nd Ed., Longmans, Green and Co., London, 1951, p 549.

19 hours. The excess ethyl formate was removed at reduced pressure and the oil which remained was recrystallized from petroleum ether (30-60°) to afford 0.242 g (90%) of product, mp 44-46° (lit. 46.6-47.5°) whose nmr spectrum is in agreement with that of the literature.[138]

N-Methylaniline-^{15}N. N-methylaniline-^{15}N was prepared by a modification of the procedure described by Finholt, Jacobson, Ogard and Thompson.[139] To a suspension of lithium aluminum hydride (0.055 g, 0.00147 mol) in 5 ml of anhydrous ether at 0° was added a solution of formanilide-^{15}N (0.183 g, 0.00150 mol) in 5 ml of anhydrous ether over a 5-minute period. The resulting suspension was maintained under reflux for 18.5 hours and then hydrolyzed with 30 mg of water. The granular inorganic salts were removed by filtration, washed with ether and the combined ethereal filtrates concentrated at reduced pressure. The yellow oil which resulted was dissolved in 6M hydrochloric acid and the aqueous solution successively extracted with ether, neutralized with 2M sodium hydroxide and extracted with fresh ether. Drying ($MgSO_4$) followed by concentration afforded 0.093 g (56%) of yellow oil; nmr (DMSO-d_6), δ 5.49 (d of t, 1, ^{15}NH), 2.65 (d, 3, CH_3), 6.36-7.20 (m, 5, ArH).

N-Ethylaniline-^{15}N. N-Ethylaniline was prepared by the modification of the method of Finholt, Jacobson, Ogard and Thompson[139] described above. From acetanilide-^{15}N (0.272 g, 0.00200 mol) and lithium aluminum

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(137) A. P. de Jonge, D. Van der Ven and Widen Hertog, Rec. Trav. Chem., 75, 5 (1956).

(138) A. J. R. Bourn, D. G. Gillies and E. W. Randall, Tetrahedron, 20, 1811 (1964).

(139) A. E. Finholt, E. C. Jacobson, A. E. Ogard and P. Thompson, J. Amer. Chem. Soc., 77, 4163 (1955).

hydride (0.110 g, 0.00290 mol) there was obtained 0.178 g (73%) of crude product; nmr (DMSO-d_6), δ 5.35 (d of t, 1, ^{15}NH), 3.03 (m, 2, CH_2), 1.16 (sextet, 3, CH_3) 6.40-7.33 (m, 5, ArH).

α-Anilinoacetophenone-^{15}N. A solution of phenacyl bromide (0.151 g, 0.000759 mol) and aniline-^{15}N (0.142 g, 0.00151 mol, 97.8 atom % ^{15}N) in 5 ml of ether was heated under reflux for 7 hours and then stirred at room temperature for an additional 16 hours. The resulting ethereal suspension was washed thoroughly with water, dried ($MgSO_4$) and concentrated at reduced pressure to afford a yellow solid which, after two recrystallizations from ethanol, has mp 92.5-94.5° (lit.[140] mp 93°). The yield is 0.066 g (41%); nmr (DMSO-d_6), δ 5.83 (d of t, 1, ^{15}NH), 4.70 (d, 2, CH_2), 6.60-8.22 (m, 10, ArH).

α-Anilinoacetonitrile-^{15}N. α-Anilinoacetonitrile-^{15}N was prepared by a modification of the procedure described by Engler.[141] A solution of chloroacetonitrile (0.082 g, 0.00109 mol) and aniline-^{15}N (0.180 g, 0.00191 mol, 97.8 atom % ^{15}N) in 0.5 ml of acetonitrile was heated under reflux for 23 hours. After cooling to room temperature 5 ml of ether were added and the resulting solution washed with water. Concentration at reduced pressure afforded 0.068 g (54%) of crude product; nmr (DMSO-d_6), δ 6.14 (d of t, 1, ^{15}NH), 4.20 (d, 2, CH_2), 6.50-7.40 (m, 5, ArH).

Pivaldehyde-anil-^{15}N. Pivaldehyde (0.309 g, 0.00359 mol) was added directly to aniline-^{15}N (0.150 g, 0.00160 mol, 97.8 atom % ^{15}N) and the

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(140) A. Bischler, Ber., 25, 2860 (1892).
(141) E. Engler, Ber., 6, 1003 (1873).

resulting suspension stirred at room temperature for 1 hour. Extraction with ether, drying ($MgSO_4$) and concentration at reduced pressure afforded 0.188g(77%) of crude product; nmr ($CDCl_3$), δ 7.68 (d, 1, CH), 1.17 (s, 9, $(CH_3)_3$-C), 6.80-750 (m, 5, ArH).

N-Neopentylaniline-^{15}N. The same procedure as that for the preparation of N-methylaniline-^{15}N was followed. From pivaldehyde-anil (0.183 g, 0.00113 mol) and lithium aluminium hydride (0.028 g, 0.000737 mol) there was obtained 0.047 g (25%) of yellow oil; nmr (DMSO-d_6), δ 5.29 (d of t, 1, ^{15}NH), 2.80 (d, 2, CH_2), 0.093 (s, 9, $(CH_3)_3$-C), 6.40-7.14 (m, 5, ArH).

Preparation of Nitroso-^{15}N Amines and Hydrazines.

Dimethylnitrosamine-(^{15}N-nitroso). A suspension of dimethylamine hydrochloride (0.225 g, 0.00362 mol) and potassium nitrite-^{15}N (0.185 g, 0.00215 mol, 99.1 atom % ^{15}N) in 0.080 ml of water was acidified to ph 1 with concentrated hydrochloric acid and allowed to stand, with periodic stirring for 50 minutes. After adding sufficient magnesium sulfate to remove the water the crude product was extracted with chloroform and the chloroform extract concentrated at reduced pressure to afford 0.099 g (61%) of dimethylnitrosamine-(^{15}N-nitroso); nmr[85] ($CDCl_3$), δ 3.83 (d, 3, trans-CH_3), 3.08 (d, 3, cis-CH_3).

N-Nitroso-N-t-butylbenzylamine-(^{15}N-nitroso). Concentrated hydrochloric acid was added to a suspension of N-t-butylbenzylamine (0.224 g, 0.00137 mol) in 1 ml of water until a ph 1 was reached, at which point a solution of potassium nitrite-^{15}N (0.088 g, 0.00102 mol, 99.1 atom % ^{15}N) in 0.5 ml of water was added. Stirring for 5 minutes at 65° and for 10 minutes at room temperature was followed sucessively by extraction of the organic layer with ether, drying ($MgSO_4$) and concentration at

reduced pressure to afford 0.143 g (74%) of crude product, mp 44-46° (lit.[142] mp 44.5-46°); nmr ($CDCl_3$), δ 4.87 (broad s, 2, CH_2), 1.57 (s, 9, $(CH_3)_3$-C), 6.85-7.43 (m, 5, ArH).

N-Nitroso-N-ethylbenzylamine-(^{15}N-nitroso). To a solution of N-ethylbenzylamine (0.208 g, 0.00154 mol) in 1 ml of 2.0 M hydrochloric acid at 0° was added a solution of potassium nitrite-^{15}N (0.088 g, 0.00102 mol, 99.1 atom % ^{15}N) in 0.5 ml of water over a 5-minute period. The resulting suspension was allowed to stand at room temperature with periodic stirring for 80 minutes after which time the organic layer was extracted with ether. Drying ($MgSO_4$) of the ethereal solution was followed by concentration at reduced pressure to afford 0.099 g (59%) of crude yellow oil; nmr[85] ($CDCl_3$), δ 5.32 (d, 2, trans-$PhCH_2$), 4.85 (broad s, 2, cis-$PhCH_2$), 4.13 (octet, 2, trans-CH_2-CH_3), 3.56 (octet, 2, cis-CH_2-CH_3), 1.37 (t, 3, trans CH_3), 0.98 (t, 3, cis CH_3), 7.33 (m, 5, ArH).

N-Nitroso-N-isopropylbenzylamine-(^{15}N-nitroso). The same procedure as that for the preparation of N-nitroso-N-t-butylbenzylamine-(^{15}N-nitroso) was followed. From N-isopropylbenzylamine (0.206 g, 0.00138 mol) and potassium nitrite-^{15}N (0.083 g, 0.000965 mol, 99.1 atom % ^{15}N) there was obtained 0.074 g (43%) of a crude product; nmr[85] ($CDCl_3$), δ 5.25 (d, 2, trans-CH_2), 4.77 (s, 2, cis-CH_2), 4.92 (broad sextet, 1, cis-CH), 4.58 (m, 1, trans-CH), 1.43 (d, 6, trans-CH_3), 1.02 (d, 6, cis-CH_3), 7.00-7.45 (m, 5, ArH).

Meso N-Nitroso-α,α'-dimethyldibenzylamine-(^{15}N-nitroso). N-

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(142) L. A. Carpino, A. A. Santilli and R. W. Murry, J. Amer. Chem. Soc., 82, 2728 (1960).

nitroso- , -dimethyldibenzylamine-(^{15}N-nitroso) was prepared by the procedure of Overberger, Marullo and Hiskey.[143] From , -dimethyldibenzylamine (0.339 g, 0.169 mol) and potassium nitrite-^{15}N (0.128 g, 0.00149 mol, 99.1 atom % ^{15}N) there was obtained 0.158 g (55%) of crude product, mp 50-54°; nmr ($CDCl_3$), 6.28 (broad q, 1, cis-CH), 5.00 (d of q, 1, trans-CH), 1.83 (d, 3, trans-CH_3), 1.50 (d, 3, cis-CH_3), 7.07 (m, 5, ArH).

4-t-Butyl-1,1-nitrosopiperidine-(^{15}N-nitroso). The same procedure as that for the preparation of N-nitroso-N-t-butylamine was followed. From 4-t-butylpiperidine (0.201 g, 0.00142 mol) and potassium nitrite-^{15}N (0.095 g, 0.00110 mol, 99.1 atom % ^{15}N) there was obtained 0.071 g (38%) of crude product, mp 52-55° (lit.[77] mp 55-56°).

N-Nitroso-N-methylbenzylamine-(^{15}N-nitroso). The same procedure as that for the preparation of N-nitroso-N-t-butylbenzylamine-(^{15}N-nitroso) was followed. From N-methylbenzylamine (0.267 g, 0.00200 mol) and potassium nitrite-^{15}N (0.087 g, 0.00101 mol, 99.1 atom % ^{15}N) there was obtained 0.060 g (39%) of crude yellow oil, nmr[85] ($CDCl_3$), 5.32 (d, 2, trans-CH_2), 4.83 (broad s, 2, cis-CH_2), 3.69 (d, 3, trans-CH_3), 2.95 (d, 3, cis-CH_3), 7.12-7.58 (m, 5, ArH).

N-Nitroso-N-methylaniline-(^{15}N-nitroso). To a solution of N-methylaniline (0.205 g, 0.00192 mol) in 1 ml of 6M hydrochloric acid was added a solution of potassium nitrite-^{15}N (0.088 g, 0.00102 mol, 99.9 atom % ^{15}N) in 0.5 ml of water. The resulting suspension was stirred for 10 minutes after which time the yellow oil which formed was ex-

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(143) C. G. Overberger, N. P. Marullo and R. G. Hiskey, J. Amer. Chem. Soc., 83, 1374 (1961).

tracted with ether. The ethereal solution was dried (Na_2SO_4) and concentrated at reduced pressure to afford 0.083 g (53%) of crude yellow oil; nmr ($CDCl_3$) δ 3.42 (d, 3, CH_3), 7.28-7.72 (m, 5, ArH).

N-nitroso-N-benzylaniline-(^{15}N-nitroso). The same procedure as that for the preparation of N-nitroso-N-methylaniline-(^{15}N-nitroso) was followed. From N-benzylaniline (0.174 g, 0.000951 mol) and potassium nitrite-^{15}N (0.092 g, 0.000108 mol, 99.1 atom % ^{15}N) there was obtained 0.136 (67%) of a yellow oil; nmr[85] ($CDCl_3$), δ 5.55 (d, 2, trans-CH_2), 5.17 (s, 2, cis-CH_2), 6.87-7.63 (m, 10, ArH).

N-Nitroso-N-neopentylaniline. The same procedure as that for the preparation of N-nitroso-N-methylaniline-(^{15}N-nitroso) was followed. From N-neopentylaniline (0.160 g, 0.000926 mol) and potassium nitrite (0.098 g, 0.00115 mol) there was obtained 0.161 g (90%) of crude product, mp 41-44°. Recrystallization from petroleum ether at 5° afforded needles , mp 44-46°; nmr ($CDCl_3$), δ 0.80 (s, 9, cis$(CH_3)_3$-C), 0.92 (s, 9, trans-$(CH_3)_3$-C), 4.00 (s, 2, cis-CH_2), 4.37 (s, 2, trans-CH_2), 7.45 (m, 5, ArH).

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.58. Found: C, 68.78; H, 8.07; N, 15.15.

N-t-Butylaniline. N-t-butylaniline was prepared by the procedure of Hickenbottom.[144] From t-butyl iodide (37.0 g, 0.200 mol) and aniline (38.0 g, 0.409 mol) there was obtained 2.59 g (8.8%) of t-butylaniline, bp 88-92° (8.4mm; nmr ($CDCl_3$), δ 1.28 (s, 9, $(CH_3)_3$-C), 3.27 (broad s, 1, NH), 6.38-7.12 (m, 5, ArH).

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(144) W. J. Hickenbottom, J. Chem. Soc., 946 (1933).

N-Nitroso-N-t-butylaniline. The same procedure as that for the preparation of N-nitroso-N-methylaniline (^{15}N-nitroso) was followed. From N-t-butylaniline (0.500 g, 0.00201 mol) and potassium nitrite (0.250 g, 0.00201 mol) there was obtained 0.490 g (88%) of crude product, mp 59-61° (lit.[137] mp 61-62°); nmr ($CDCl_3$), δ 1.59 (s, 9, $(CH_3)_3$-C), 6.80-7.60 (m, 5, ArH).

N-Nitroso-N-isopropylaniline. The same procedure as that for the preparation of N-nitroso-N-methylaniline (^{15}N-nitroso) was followed. From N-isopropylaniline (2.70 g, 0.200 mol) and sodium nitrite (0.200 g, 0.0290 mol) there was obtained 3.20 g (98%) of product, bp 74° (0.20mm); nmr[85] ($CDCl_3$), δ 5.12 (m, 2, cis and trans CH), 1.44 (d, 6, trans (CH_3)-CH), 1.17 (d, 6, cis (CH_3)-CH), 6.83-7.72 (m, 5, ArH).

2,3,3-Trimethylindoline. A solution of 2,3,3,-trimethylindole (11.7 g, 0.0736 mol) in 70 ml of absolute ethanol was hydrogenated at 2.9 atm with 174 mg of platinum oxide in Parr apparatus. After the uptake of hydrogen had ceased (6 days,100% of theory) the catalyst was filtered and the filtrate concentrated at reduced pressure to afford 10.7 g (90%) of a red oil which was used without further purification; nmr[145] ($CDCl_3$), δ 3.62 (broad s, 1, NH), 3.38 (q, 1, CH), 1.22 (s, 3, CH_3), 0.98 (s, 3, CH_3), 1.07 (d, 3, CH_3-CH), 6.81 (m, 4, ArH).

N-nitroso-2,3,3-trimethylindoline-(^{15}N-nitroso). To a solution of 2,3,3-trimethylindoline (0.161 g, 0.00100 mol) in 1 ml of 1.2M hydrochloric

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(145) J. L. Mateos, E. Diaz and R. Cetina, Bol. Inst. Quim. Univ. Nacl. Auton. Mex., 14, 61 (1962).

acid was added a solution of potassium-^{15}N (0.099 g, 0.00115 mol, 99.1 atom % ^{15}N) in 1 ml of water over a 15-minute period. The resulting suspension was stirred for 15 minutes after which time the insoluble organic layer was extracted with ether. The ether was dried ($MgSO_4$) and concentrated at reduced pressure to afford 0.170 g (89%) of a red oil; nmr ($CDCl_3$), 4.05 (q, 1, cis-CH), 4.68 (q, 1, trans-CH), 1.16 (d, 3, cis-CH_3-CH), 1.63 (d, 3, trans-CH_3-CH), 1.18 (s, 3, cis-CH_3), 1.35 (s, 3, cis-CH_3), 1.26 (s, 3, trans-CH_3), 1.38 (s, 3, trans-CH_3). The nmr spectrum was identical (excepting ^{15}N coupling) with that of the unlabeled material which has bp 90° (0.10 mm).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.40; H, 7.41, N, 14.77. Found: C, 70.03; H, 7.76; N, 14.42.

N-Nitrosoisoindoline-(^{15}N-nitroso). The same procedure as that for the preparation of 2,3,3-trimethyl-N-nitrosoindoline (^{15}N-nitroso) was followed. From isoindoline (0.124 g, 0.00104 mol) and potassium nitrite-^{15}N (0.128 g, 0.00149 mol, 99.1 atom % ^{15}N) there was obtained 0.045 g (29%) of crude product which on recrystallization from hexane had mp 96-97° (lit.[146] mp 96-97°); nmr ($CDCl_3$), δ 5.63 (s, 2, trans-CH_2), 4.92 (s, 2, cis-CH_2), 7.38 (broad s, 4, ArH).

N-Nitroso-N-benzyl-2-bromo-4,6-dimethylaniline-(^{15}N-nitroso). To a solution of N-benzyl-2-bromo-4,6-dimethylaniline[147] (0.094 g, 0.000323 mol) in 2 ml of 2.5M hydrochloric acid was added a solution of

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(146) S. Gabriel and A. Neumann, Ber., 26, 527 (1893).

(147) Kindly provided by A. Mannschreck, University of Heidelberg, 1968.

sodium nitrite-^{15}N (0.034 g, 0.000486 mol, 99.0 atom % ^{15}N) in 2 ml of water over a 20-minute period. The suspension which formed was stirred for 75 minutes after which time the organic material was extracted with ether. The ether was dried ($MgSO_4$) and concentrated at reduced pressure to afford 0.089 g (85%) of crude product; nmr[148] ($CDCl_3$), δ 1.70 (s, 3, cis-o-CH_3), 2.23 (s, 3, trans-o-CH_3), 5.62 (d of q, 2, trans-CH_2), 5.17 (q, 2, cis-CH_2), 6.78-7.57 (m, 7, ArH).

N-Nitroso-N-benzyl-2-chloroaniline-(^{15}N-nitroso). The same procedure as that for the preparation of N-nitroso-N-benzyl-2-bromo-4,6-dimethylaniline-(^{15}N-nitroso) was followed. From N-benzyl-2-chloroaniline (0.044 g, 0.000433 mol) and potassium nitrite-^{15}N (0.044 g, 0.000518 mol, 99.1 atom % ^{15}N) there was obtained 0.080 g (75%) of crude product; nmr[149] (acetone-d_6), δ 5.68 (m, 2, trans-CH_2), 5.22 (s, 2, cis CH_2), 6.48-7.67 (m, 9, ArH).

N-Nitroso-N-benzyl-2,6-dimethylaniline-(^{15}N-nitroso). The same procedure as that for the preparation of N-nitroso-N-benzyl-2-bromo-4,6-dimethylaniline was followed. From N-benzyl-2,6-dimethylaniline hydrochloride[147] (0.155 g, 0.000628 mol) and potassium nitrite-^{15}N (0.065 g, 0.000756 mol, 99.1 atom % ^{15}N) there was obtained 1.139 g (80%) of crude product; nmr[148] ($CDCl_3$), δ 5.02 (d, 2, cis-CH_2), 5.47 (d, 2, trans-CH_2), 1.69 (s, 6, cis, o-CH_3), 1.90 (s, 6, trans-o-CH_3), 6.77-7.53 (m, 8, ArH).

N-nitroso-N-(α-phenethyl)-2,6-dimethylaniline-(^{15}N-nitroso). The same procedure as that for the preparation of N-nitroso-N-benzyl-2-bromo-4,6-

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(148) A. Mannschreck, University of Heidelberg,1968, personal communication.

(149) R. J. Seymour and R. C. Jones, Tet. Letters, 21, 2021 (1967).

dimethylaniline-(^{15}N-nitroso) was followed. From N-(α-phenethyl)-2,6-dimethylaniline[140] (0.114 g, 0.000507 mol) and sodium nitrite-^{15}N (0.042 g, 0.000609 mol, 99.0 atom % ^{15}N) there was obtained 0.101 g (78%) of crude product, mp 63-70°; nmr[150] ($CDCl_3$), δ 5.98 (q, 1, cis-CH), 5.08 (d of q, 1, trans-CH), 2.15 (d, 3, trans-CH_3CH), 1.51 (d, 3, cis-CH_3-CH), 2.05 (s, 3, trans-o-CH_3), 1.32 (s, 3, trans-o-CH_3), 1.67 (s, 3, cis-o-CH_3), 6.75 (m, 8, ArH). Cis-o-CH_3 obscured by absorption at δ 2.0-2.2.

Benzylhydrazine. Benzylhydrazine was prepared by the procedure of Biel.[151] From benzylchloride (12.6 g, 0.100 mol) and 95% hydrazine (16.8 g, 0.100 mol) there was obtained 7.00 g (57%) of product; bp 98-100° 5.2 mm), nmr ($CDCl_3$), δ 3.80 (s, 2, CH_2), 3.20 (s, NH+NH_2), 7.15 (s, 5, ArH).

Benzylnitrosohydrazine. To a solution of benzylhydrazine (6.10 g, 0.050 mol) in 15 ml of 4M hydrochloric acid at 0° was added a solution of sodium nitrite (6.90 g, 0.100 mol) in 15 ml of water. Stirring for 15 minutes was followed successively by extraction with ether, drying (Na_2SO_4) and concentration at reduced pressure to afford 4.00 g (53%) of crude product. Recrystallization from ethanol gave a pale yellow solid; mp 69-71° (lit.[152] mp 71°), nmr ($CDCl_3$), δ 5.70 (broad s, 2, NH_2), 5.13 (s, 2, CH_2), 7.43 (s, 5, ArH).

Methylenedimethylhydrazine. Methylenedimethylhydrazine was prepared

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(150) A. Mannschreck and A. Muensch, Tet. Letters, 3227 (1968).
(151) J. H. Biel, J. Amer. Chem. Soc., 81, 2805 (1959).
(152) A. Wohl and C. Oesterlin, Ber., 33, 2740 (1900).

by the method described by Class, Aston and Oakwood.[153] From unsymmetrical dimethylhydrazine (15.0 g, 0.250 mol) and 37% aqueous formaldehyde (20.3 g, 0.250 mol) there was obtained 16.5 g (92%) of product; bp 66-70° (lit.[153] bp 72° (730mm)); nmr ($CDCl_3$), δ 6.05 (broad s, 2, CH_2=N), 2.77 (s, 6, $(CH_3)_2N$).

Trimethylhydrazine. Trimethylhydrazine was prepared by the method described by Class, Aston and Oakwood.[153] From methylenedimethylhydrazine (7.20 g, 0.100 mol) and lithium aluminum hydride (1.10 g, 0.389 mol) was obtained 7.00 g (95%) of product; bp 62-63°, (lit.[153] bp 60°(735 mm)), nmr ($CDCl_3$), δ 2.51 (s, 3, N-CH_3), 2,38 (s, 6, N-$(CH_3)_2$), 2.27 (broad s, 1, NH).

Trimethylnitrosohydrazine. Trimethylnitrosohydrazine was prepared by the method described by Graefe.[154] From trimethylhydrazine (2.20 g, 0.0300 mol) and sodium nitrite (6.21 g, 0.0900 mol) there was obtained 2.15 g (70%) of a product; bp 70-71° (45mm), lit.[154] bp 41-42° (10mm)) nmr ($CDCl_3$), δ 3.65 (s, 3, trans-N-CH_3), 3.08 (s, 3, cis-N-CH_3), 2.65 (s, 6, trans-N-$(CH_3)_2$), 2.85 (s, 6, cis-N-$(CH_3)_2$).

Methylnitrosohydrazine. Methylnitrosohydrazine was prepared by the method described by Thiele.[99] From methylhydrazine (7.50 g, 0.163 mol) and potassium nitrite (38.3 g, 0.451 mol) there was obtained 3.55 g (34%) of product; mp 43-45° (lit.[99] mp 45°); nmr ($CDCl_3$) δ 6.07 (broad s, 2, NH_2), 3.70 (s, 3, CH_3).

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(153) J. B. Class, J. S. Aston and T. S. Oakwood, J. Amer. Chem. Soc., 75, 2937 (1953).
(154) A. E. Graefe, J. Org. Chem., 23, 1230 (1958).

Benzaldehyde Methylhydrazone. To a well stirred solution of benzaldehyde (10.5 g, 0.100 mol) in 30 ml of anhydrous ether was added a solution of methylhydrazine (4.60 g, 0.100 mol) in 30 ml of anhydrous ether over a 5-minute period. The turbid solution which results was stirred for 30 minutes at room temperature, dried ($MgSO_4$), and concentrated at reduced pressure to afford 11.47 g of crude product. Distillation gave 8.45 g (63%) of benzaldehyde methylhydrazone bp 95-98° (2.0mm) (lit.[155] bp 130-131°(18mm)); nmr ($CDCl_3$), δ 5.27 (broad s, 1, NH), 2.96 (s, 3, CH_3), 7.12-7.77 (m, 6, CH and ArH).

Benzalmethylnitrosohydrazine. The same procedure as that for the preparation benzylnitrosohydrazine was followed. From Benzaldehyde methylhydrazone (0.142 g, 0.00106 mol) and potassium nitrite (0.182 g, 0.00214 mol) there was obtained 0.105 g (61%) of crude product. Recrystallization from hexane-chloroform gave yellow crystals, mp 73-76° (lit.[99] mp 77-78°); nmr ($CDCl_3$), δ 3.43 (s, 3, CH_3), 7.23-7.88 (m, 6, ArH and CH).

1-Benzyl-2-methylhydrazine. A solution of benzaldehyde methylhydrazone (6.70 g, 0.0500 mol) in 70 ml of absolute ethanol was shaken under hydrogen at 2.7 atm with 225 mg of 10% palladium on charcoal in a Parr hydrogenator. After the uptake of hydrogen had ceased (2.5 hours, 96% of theory) the catalyst was removed by filtration and the filtrate concentrated at reduced pressure. Distillation of the remaining oil gave 4.45 g (65%) of product, bp 77° (1.3mm); nmr ($CDCl_3$),

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(155) D. Todd, J. Amer. Chem. Soc., 71, 1353 (1949).

δ 3.61 (s, 2, CH_2), 3.17 (s, 2, NH), 2.58 (s, 3, CH_3), 7.33 (s, 5, ArH).

2-Benzyl-1-methyl-1-nitrosohydrazine. 2-Benzyl-1-methyl-1-nitrosohydrazine was prepared by the procedure of Thiele.[99] From methylnitrosohydrazine (0.755 g, 0.0107 mol) and benzylchloride (1.29 g, 0.102 mol) there was obtained 1.08 g (64%), of crude product, mp 49-52°; nmr ($CDCl_3$), δ 4.07 (d, 2, CH_2), 3.55 (s, 3, CH_3), 7.15 (s, 5, ArH).

2-Methyl-1-benzylnitrosohydrazine. 2-Methyl-1-benzylnitrosohydrazine was prepared by the procedure of Thiele.[99] From benzylnitrosohydrazine (0.900 g, 0.00738 mol) and dimethyl sulfate (4.67 g, 0.0371 mol) there was obtained 0.895 g (89%) of crude product; nmr ($CDCl_3$), δ 5.28 (s, 2, CH_2), 2.50 (s, 3, CH_3), 7.77 (s, 5, ArH).

Nitrosation of 1-benzyl-2-methylhydrazine. To a solution of 1-benzyl-2-methylhydrazine (0.144 g, 0.00106 mol) in 5.5 ml of 0.2M hydrochloric acid was added a solution of potassium nitrite-^{15}N (0.088 g, 0.00102 mol, 99.1 atom % ^{15}N) in 1 ml of water. After stirring for 25 minutes the organic layer was extracted with ether. Drying ($MgSO_4$) and concentration at reduced pressure gave 0.045 g of an oil whose nmr spectrum shows it to a mixture of benzalmethylnitrosohydrazone, 2-benzyl-1-methylnitrosohydrazine and 2-methyl-1-benzylnitrosohydrazine.

2-Benzyl-1,1-dimethylhydrazine. A solution of benzaldehyde dimethylhydrazone[156] (14.8 g,0.100 mol) in 50 ml of absolute ethanol was shaken under hydrogen at 3.4 atm with 100 mg of 5% palladium on charcoal in a Parr hydrogenator. After the uptake of hydrogen had ceased (1.5 hours,

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(156) Kindly provided by Mr. L. Loew, The City College of New York, 1968.

98% of theory) the catalyst was removed by filtration and the filtrate concentrated at reduced pressure. Distillation of the remaining oil gave 9.36 g (62%) of product, bp 55-56° (0.88mm) (lit.[157] bp 61-62° (0.55mm)); nmr ($CDCl_3$), δ 3.90 (s, 2, CH_2), 2.51 (broad s, 1, NH), 2.43 (s, 6, N-$(CH_3)_2$), 7.15-7.50 (m, 5, ArH).

2,2-Dimethyl-1-benzylnitrosohydrazine-(^{15}N-nitroso). The same procedure as that for the preparation of benzylnitrosohydrazine, was followed. From 2-benzyl-1,1-dimethylhydrazine (0.217 g, 0.00145 mol) and potassium nitrite-^{15}N (0.082 g, 0.000953, 99.1 atom % ^{15}N) there was obtained 0.140 (88%) of crude product; nmr ($CDCl_3$), δ 5.13 (d, 2, trans-CH_2), 4.81 (broad s, 2, cis-CH_2), 2.86 (s, 6, cis-$(CH_3)_2$), 2.62 (s, 6, trans-$(CH_3)_2$), 7.20-7.50 (m, 5, ArH).

Acetophenonedimethylhydrazone. A solution of acetophenone (24.0 g, 0.200 mol), 1,1-dimethylhydrazine (24.0 g, 0.400 mol) and p-toluenesulfonic acid monohydrate (0.025 g, 0.00013 mol) was heated under reflux for 16.5 hours, after which time the resulting emulsion was dried ($MgSO_4$) and the excess hydrazine removed at reduced pressure. Distillation of the oil which remains afforded 28.9 g (89%) of product, bp 87-90° (4.2mm); nmr ($CDCl_3$), δ 2.45 (s, 6, N-$(CH_3)_2$), 2.45 (s, 3,=C-CH_3), 6.87-7.47 (m, 5, ArH).

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.04; H, 8.69; N, 17.24. Found: C, 73.95; H, 8.74; N, 17.08.

2-(α-Phenethyl-1-dimethylhydrazine. A solution of acetophenone-

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(157) R. L. Hinman, J. Org. Chem., 21, 1177 (1956).

dimethylhydrazone (9.10 g, 0.0561 mol) in 75 ml of absolute ethanol was shaken under hydrogen at 2.9 atm with 220 mg of 10% palladium on charcoal in a Parr hydrogenator. After the uptake of hydrogen had ceased (2 hours, 88% of theory) the catalyst was removed by filtration and the filtrate concentrated at reduced pressure. Distillation of the remaining oil gave 7.93 g (86%) of product, bp 65-67° (1.8mm); nmr ($CDCl_3$), δ 2.42 (s, 6, N-$(CH_3)_2$), 2.13 (broad s, 1, NH), 3.92 (q, 1, CH), 1.28 (d, 3, CH_3), 7.17-7.47 (m, 5, ArH).

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.05. Found: C, 73.50; H, 9.51; N, 17.17.

1-(α-Phenethyl)-2,2-dimethylnitrosohydrazine-(^{15}N-nitroso). The same procedure as that for the preparation of benzylnitrosohydrazine was followed. From 2-(α-phenethyl)-1,1-dimethylhydrazine (0.162 g, 0.000982 mol) and potassium nitrite-^{15}N (0.092 g, 0.00107 mol) there was obtained 0.055 g (29%) of crude product; nmr ($CDCl_3$), δ 6.35 (q, 1, cis-CH), 5.70 (d of q, 1, trans-CH), 2.77 (s, 6, cis-N-$(CH_3)_2$), 2.58 (s, 6, trans-N-$(CH_3)_2$), 1.48 (d, 3, cis-CH_3), 1.75 (d, 3, trans-CH_3), 7.22-7.58 (m, 5, ArH).