NITROGEN-15 MAGNETIC RESONANCE SPECTROSCOPY. I. CONFIGURATIONAL ASSIGNMENTS BASED ON STEREOSPECIFIC THREE BOND ^{15}N-H COUPLING. II. SUBSTITUENT EFFECTS ON ONE BOND ^{15}N-H COUPLING AND NITROGEN-15 CHEMICAL SHIFTS.

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.

1971

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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Dissertation Abstract

NITROGEN-15 MAGNETIC RESONANCE SPECTROSCOPY

by

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The utility of pmr and ^{15}N-nmr spectroscopy as a means of investigating molecular structure in various nitrogen-containing systems which have been enriched with nitrogen-15 is discussed. In Part I, configurational assignments are made for N-nitrosohydroxylamines, alkyl nitrites, and phenylhydrazones based on the stereospecificity of vicinal $^{15}N{=}N{-}C{-}H$, $^{15}N{=}O{-}C{-}H$, and $^{15}N{=}C{-}C{-}H$ coupling, respectively. In Part II, $^{1}J(^{15}NH)$ values in a series of <u>meta</u>- and <u>para</u>-substituted anilines show a linear correlation with Hammett substituent constants. The lack of a substituent effect on $^{1}J(^{15}NH)$ values in a series of protonated anilines, protonated quinolines, and protonated N-benzylideneanilines indicates that the substituent dependence of $^{1}J(^{15}NH)$ in ring-substituted anilines may be attributed primarily to substituent induced changes in the hybridization of the amino nitrogen atom. Substituent hydrogen bonding abilities in a series of <u>ortho</u>-substituted anilines are evaluated on the basis of $\Delta^{1}J(^{15}NH)$ values, where $\Delta^{1}J(^{15}NH) = {}^{1}J(^{15}NH)_{DMSO} - {}^{1}J(^{15}NH)_{CDCl_3}$. Amino proton nonequivalence in 2-nitro-4-chloroaniline-^{15}N and 2-nitroaniline-^{15}N at low temperature is interpreted in terms of restricted rotation about the

amino nitrogen - aryl carbon bond. The substituent dependence of the amino proton splitting pattern in ortho-substituted ^{15}N-benzamides is interpreted in terms of restricted rotation about the aryl - carbonyl bond in this system. Substituent effects on nitrogen-15 chemical shifts in ring-substituted anilines, quinolines, and N-benzylideneanilines are discussed.

Acknowledgements

I would like to express my deepest gratitude to Professor Theodore Axenrod for guiding, encouraging, being patient with, and trusting in this author.

I would like to thank Dr. Paul S. Pregosin, who, during the early stages of this work, set an example for this author, provided timely advice and assistance, and helped make our shared laboratory experience a memorable and rewarding one.

I would like to express my appreciation to the members of my thesis guidance committee for their many helpful suggestions during both the course of this research and in the preparation of this manuscript.

Finally, I would like to thank the Department of Chemistry of The City College of C.U.N.Y. for enabling this author to earn a living during the course of this research.

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INTRODUCTION

Scope

Since the rapid development of high resolution nmr spectroscopy in the late 1950's, it has been recognized that spin-spin coupling and chemical shift data may serve as sensitive probes in the investigation of molecular structure. It is the purpose of this dissertation to discuss the utility of pmr and ^{15}N-nmr spectroscopy as a means of investigating molecular structure in various nitrogen-containing systems which have been enriched with nitrogen-15.

In Part I, the configurational dependence of three-bond ^{15}N-H coupling in a series of N-nitrosohydroxylamines, alkyl nitrites, and phenylhydrazones is discussed. In Part II, substituent effects on one-bond ^{15}N-H coupling and nitrogen-15 chemical shifts are examined.

Nuclear Parameters

Of the two naturally occurring isotopes of nitrogen, nitrogen-14 has a natural abundance of 99.635%, whereas nitrogen-15 occurs to the extent of only 0.365%. The more abundant isotope, nitrogen-14, has a spin quantum number of I=1 and possesses a nuclear quadrupole moment which frequently causes broadening of the resonance lines of those nuclei to which it is spin-coupled. If the environment of the quadrupolar ^{14}N-nucleus is sufficiently symmetrical however, there will be no net electric field gradient at the nucleus and quadrupole broadening effects will be minimized. Thus, for the tetrahedrally symmetrical ammonium and tetramethylammonium ions, narrow ^{14}N-resonances are observed, whereas in unsymmetrical

ammonium salts, quadrupole induced relaxation is responsible for broad hydrogen and nitrogen resonance lines.[1] Indeed, in all but the most symmetrical of environments, the limited lifetime of ^{14}N-spin states may lead to ^{14}N-line widths as large as 1000 Hz.[2]

Exceptions to the above generalization have been noted in the case of the pyridinium ion,[3] isocyanides,[4] methyl nitrate,[5] and N,N-dimethylnitramine,[5] where, despite low molecular symmetry, small electric field gradients exist and fairly sharp ^{14}N-resonances are observed. Unfortunately, such cases cannot be predetermined at present, and in general, ^{14}N-line widths cannot be predicted. By contrast, nitrogen-15, which has a spin quantum number of $I=\frac{1}{2}$, possesses no quadrupole moment and may exhibit line widths narrower than 1 Hz. Thus, although quadrupole broadening effects obscure coupling and mitigate against accurate ^{14}N-chemical shift determinations, ^{15}N-coupling constants and chemical shifts may be measured with a high degree of accuracy.

The chemical shift of nitrogen-15 is related to that of

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(1) R. A. Ogg and J. D. Ray, J. Chem. Phys., 25, 1285 (1956); 26, 1339 (1957); 26, 1452 (1957).

(2) H. Januszewski and M. Witanowski, Can. J. Chem., 47, 1321 (1969).

(3) I. C. Smith and W. G. Schneider, ibid, 39, 1158 (1961).

(4) I. D. Kuntz, P. von R. Schleyer, and A. Allerhand, J. Chem. Phys., 35, 1533 (1961); M. Witanowski, Tetrahedron, 23, 4299 (1967).

(5) E. D. Becker, R. B. Bradley, and T. Axenrod, J. Magn. Resonance, in press.

nitrogen-14 by the ratio of the respective magnetogyric ratios of the two nuclei. The magnetogyric ratio, γ, is defined as the ratio of the nuclear magnetic moment to the angular momentum (eq 1). The magnetic moments, u, of the ^{14}N- and

$$\gamma = u/p \qquad (1)$$

^{15}N-nuclei have been calculated[6] to be +0.403562 and -0.283049 nuclear magnetons, respectively. Based on the observed nitrogen resonances in the $^{15}NH_4^+$ and $^{14}NH_4^+$ ions, at constant field strength, $^{15}\gamma/^{14}\gamma$ has been calculated[7] to be $1.4027548 \pm 2 \times 10^{-7}$. More recently, an investigation of nitrogen chemical shifts in isotopomers of tetramethylammonium iodide, benzyl isocyanide, methyl nitrate, and N,N-dimethylnitramine has shown[5] that $^{15}\gamma/^{14}\gamma$ is $1.40275694 \pm 6 \times 10^{-8}$.

Nitrogen Chemical Shifts

For a given nucleus, the relationship between the resonance frequency, v, and the applied magnetic field, H_o, is shown in eq 2. At constant frequency, it may be seen that

$$v = \gamma H_o(1 - \sigma_t)/2\pi \qquad (2)$$

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(6) M. R. Baker, C. H. Anderson, and N. F. Ramsey, Phys. Rev., 133, A1533 (1964).

(7) L. W. Anderson, F. M. Pipkin, and J. C. Baird, ibid, 116, 87 (1959); J. D. Baldeschwieler, J. Chem. Phys., 36, 152 (1962).

the field at which a nucleus resonates is a function of both the magnetogyric ratio characteristic of that nucleus and the screening constant, σ_t. Chemical shift theory[8] treats the total screening constant (eq 3) as the sum of diamagnetic,

$$\sigma_{total} = \sigma_d + \sigma_p + \sum\sigma_{other} \qquad (3)$$

σ_d, paramagnetic, σ_p, and all other (anisotropic, ring current, medium effects, etc.) contributions to the overall shielding experienced by the nucleus.

The diamagnetic term is directly related to local atomic electron density and is considered to arise from electron currents around the nucleus induced by the external magnetic field. It is a function of the ground state only.

The paramagnetic contribution to nuclear shielding is considered to arise from deviations from spherical symmetry and attendant changes in orbital angular momentum. Such deviations in electronic symmetry may be the result of unshared electron pairs, in which case the nucleus experiences shielding, or electronegative substituents, in which case the nucleus experiences deshielding. Furthermore, the magnitude of the paramagnetic term is inversely proportional to the mean electronic excitation energy, ΔE, and as such, is

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(8) A. Saika and C. P. Slichter, J. Chem. Phys., 22, 26 (1954); M. Karplus and J. A. Pople, ibid, 38, 2803 (1963); J. A. Pople, Discuss. Faraday Soc., 34, 7 (1963).

a function of both the ground and excited states of the molecule. Since σ_p is inversely proportional to the energy required to promote ground state electrons to low-lying excited states, nuclei involved in conjugation or multiple bonding resonate at lower fields than nuclei in saturated systems. In the series, ammonia ⟶ aniline ⟶ pyridine ⟶ azobenzene, as ΔE decreases, the paramagnetic contribution to deshielding increases and causes the nitrogen resonance to shift downfield.

In general, magnetic shielding of nitrogen nuclei has been explained in terms of the dominance of the paramagnetic term.[9] Experimental evidence in support of this assumption has come from correlations of nitrogen chemical shifts with the energies involved in n - π^* transitions.[10] For example, a study of nitrogen chemical shifts and absorption maxima in a series of nitrogen - oxygen compounds reported[11] a 576 ppm range of shift values. Of the 576 ppm, it has been calculated[11,12] that only 80 ppm is attributable to diamagnetic

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(9) B. E. Holder and M. P. Klein, J. Chem. Phys., 23, 1956 (1955); B. M. Schmidt, L. C. Brown, and D. Williams, J. Mol. Spectrosc., 2, 551 (1958); 3, 30 (1959); D. Herbison-Evans and R. E. Richards, Mol. Phys., 8, 19 (1964).

(10) J. D. Baldeschwieler and E. W. Randall, Proc. Chem. Soc., 303 (1961); V. M. S. Gil and J. N. Murrell, Trans. Faraday Soc., 60, 248 (1964); T. K. Wu, J. Chem. Phys., 49, 1139 (1968); J. Mason, Chem. Commun., 357 (1969).

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

(12) S. I. Chan, M. R. Baker, and N. F. Ramsey, Phys. Rev., 136, A1224 (1964); S. I. Chan and A. S. Dubin, J. Chem. Phys., 46, 1745 (1967).

shielding. Significantly, proton chemical shifts, which are dominated by σ_d, are confined to a relatively small range compared to the overall range of nitrogen chemical shifts (ca. 900-1000 ppm). Because of the apparent dominance of σ_p in determining nitrogen chemical shifts, the third term of eq 3 has received little attention.

The measurement of nitrogen chemical shifts by direct observation is complicated by the low sensitivity, at constant field strength, of the ^{14}N-nucleus (1.01×10^{-3}) and ^{15}N-nucleus (1.04×10^{-3}) relative to that of the proton (1.00). In addition, the ease of saturation and long relaxation times associated with these nuclei further complicate direct chemical shift measurements. Despite these difficulties, compilations of nitrogen-14[13] and nitrogen-15[14] chemical shifts have appeared in the literature.

The ^{15}N-chemical shifts discussed in Part II of this

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(13) B. M. Schmidt, L. C. Brown, and D. Williams, J. Mol. Spectrosc., 2, 539 (1958); 2, 551 (1958); 3, 30 (1959); D. Herbison-Evans and R. E. Richards, Mol. Phys., 8, 19 (1964); J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Oxford, 1965, vol. 2, pp. 1034-1036; E. F. Mooney and P. H. Winson, "Annual Review of Nuclear Magnetic Resonance Spectroscopy," ed. E. F. Mooney, Academic Press, New York, 1969, vol. 2, p. 125; M. Witanowski and H. Januszewski, Can. J. Chem., 47, 1321 (1969).

(14) J. B. Lambert, G. Binsch, and J. D. Roberts, Proc. Nat. Acad. Sci. U. S., 51, 735 (1964); E. D. Becker and L. Paolillo, J. Magn. Resonance, 2, 168 (1970); R. L. Lichter, "Determination of Organic Structures by Physical Methods," ed. F. C. Nachod and W. D. Phillips, Academic Press, New York, vol. 3, in press.

thesis were determined by the technique of $H\{^{15}N\}$ heteronuclear spin-decoupling.[15] To accomplish heteronuclear spin-decoupling, it is necessary to irradiate the two interacting nuclei simultaneously at their resonance frequencies. The proton spectrum under examination is obtained by irradiation with the usual small rf field, H_1, while the heteronucleus, in this instance, nitrogen-15, is subjected to a strong rf field, H_2, at its characteristic resonance frequency. As the resonance frequency of the heteronucleus is approached, the proton multiplet will be perturbed. The precise frequency required to maximize the decoupling effect is the resonance frequency of the heteronucleus from which the desired chemical shift is obtained. Because advantage is taken of the relatively high sensitivity of ^1H, heteronuclear spin-decoupling is a particularly expedient method of measuring the chemical shift of nuclei with inherently low sensitivities. A more detailed description of the ^{15}N-heteronuclear spin-decoupling experiment appears in the Experimental section.

Unlike proton chemical shifts which are generally measured relative to tetramethylsilane, nitrogen chemical shifts have been expressed in the literature in various ways. For example, the nitrogen resonances of the ammonium ion,[16]

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(15) J. D. Baldeschwieler and E. W. Randall, Chem. Rev., 63, 81 (1963).

(16) B. M. Schmidt, L. C. Brown, and D. Williams, J. Mol. Spectrosc., 2, 539 (1958); 2, 551 (1958); 3, 30 (1959).

the nitrate ion,[17] and nitromethane[18] have been used as standard references for nitrogen chemical shifts. Recently, Becker has reviewed this subject[19] and has proposed that nitrogen chemical shifts be uniformly referenced against internal tetramethylammonium iodide.

Spin-Spin Coupling

The theory of spin-spin coupling as developed by Ramsey[20] and others[21] evaluates coupling between two nuclei as the sum of three terms: (1) the nuclear spin-electron orbital interaction, (2) the dipole-dipole interaction between nuclear magnetic moments and electronic magnetic moments, and (3) the Fermi contact interaction[22]

$$J_{total} = J_1 + J_2 + J_3 \qquad (4)$$

The relative importance of these terms can be judged from Ishiguro's[23] calculation for the HD molecule where it was found that J_1 (HD) = 0.100 Hz, J_2 (HD) = 0.202 Hz, and

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(17) D. Herbison-Evans and R. E. Richards, Mol. Phys., 8, 19 (1964); J. B. Lambert, G. Binsch, and J. D. Roberts, Proc. Nat. Acad. Sci. U. S., 51, 735 (1964).

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

(19) E. D. Becker, J. Magn. Resonance, in press.

(20) N. F. Ramsey and E. M. Purcell, Phys. Rev., 85, 143 (1952); N. F. Ramsey, ibid, 91, 303 (1953).

(21) M. Karplus and D. M. Grant, Proc. Nat. Acad. Sci. U. S., 45, 1269 (1959); D. E. O'Reilly, J. Chem. Phys., 36, 274 (1962).

(22) E. Fermi, Z. Physik, 60, 320 (1930).

(23) E. Ishiguro, Phys. Rev., 111, 203 (1958).

J_3 (HD) = 36.837 Hz. The calculated ^1J(HD) value of 37.139 Hz compares favorably with an experimental value of 43.0 Hz.[24] Particularly noteworthy is the dominance of the Fermi contact term. The contribution of this term to the spin coupling interaction between two nuclei is directly proportional to the product of the s-electron densities at the respective nuclei of the orbitals forming the bond and inversely proportional to the mean triplet excitation energy[25]

$$J_{nn'} \propto s_n s_{n'} / \Delta E \qquad (5)$$

Generally, investigations of one bond spin coupling have been concerned primarily with hydrogen and a second nucleus, since the hybridization of the hydrogen atom is assumed to remain constant. A relationship (eq 6) between $^1J(^{13}CH)$ values and carbon hybridization has been derived by Muller and Pritchard[26] based on molecular orbital theory and by Juan and Gutowsky[27] based on valence bond theory. More recent

$$s = 0.20\ ^1J(^{13}CH) \qquad (6)$$

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(24) H. Y. Carr and E. M. Purcell, ibid, 88, 415 (1952).
(25) H. M. McConnell, J. Chem. Phys., 24, 460 (1956); C. J. Jameson and H. S. Gutowsky, ibid, 40, 1714 (1964).
(26) N. Muller and D. E. Pritchard, ibid, 31, 768 (1959); ibid, 31, 1471 (1959).
(27) C. Juan and H. S. Gutowsky, ibid, 37, 2198 (1962).

studies have shown that the electronegativity of substituents[28] or changes in the effective nuclear charge on the carbon atom[29] may also affect the magnitude of one bond ^{13}C-H coupling constants.[30]

The quadrupole moment associated with the ^{14}N-nucleus and the attendant broadening of resonance signals of nitrogen substituents made the extension of one bond coupling constant studies to the problem of nitrogen hybridization difficult. Two independent groups of workers, however, were able to relate the percent s-character in the N-H bond to the magnitude of one bond ^{15}N-H coupling. Roberts and coworkers[31] derived eq 7 on the basis of observed $^{1}J(^{15}NH)$ values of 73.2 Hz and 92.6 Hz for $^{15}NH_4Cl$ and $(Ph)_2C=^{15}NH_2^+Cl^-$, respectively. The former $^{1}J(^{15}NH)$ value was chosen to correspond to 25% s-character (sp^3), whereas the latter value was chosen to correspond to 33.3% s-character (sp^2). An equivalent expression (eq 8), based on slightly different model

$$s = 0.43\ ^{1}J(^{15}NH) - 6 \qquad (7)$$

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(28) R. M. Hammaker, ibid, 43, 1843 (1965); L. Lundazzi and F. Taddei, Spectrochim. Acta, 23A, 841 (1967).

(29) D. M. Grant and W. M. Litchman, J. Amer. Chem. Soc., 87, 3994 (1965); C. H. Yoder, R. H. Tuck, and R. E. Hess, ibid, 91, 539 (1969).

(30) For a summary of pertinent references, see G. E. Maciel, J. W. McIver, Jr., N. S. Ostlund, and J. A. Pople, ibid, 92, 1 (1970).

(31) G. Binsch, J. B. Lambert, B. W. Roberts, and J. D. Roberts, ibid, 86, 5564 (1964).

compounds, has been derived by Bourn and Randall.[32]

$$s = 0.34\ {}^{1}J({}^{15}NH) \qquad (8)$$

In accord with representative ${}^{1}J({}^{15}NH)$ values of 74 Hz, 92 Hz, and 134 Hz for sp^3, sp^2, and sp hybridized nitrogen, respectively, ${}^{1}J({}^{15}NH)$ values of 75.0 Hz for anilinium trifluoroacetate,[33] 96.0 Hz for quinolinium fluorosulfonate,[34] and 130-136 Hz for protonated nitriles[35] have been reported. Indeed, the magnitude of one bond ${}^{15}N$-H coupling, or the lack of such coupling, has been utilized in studies of tautomeric equilibria,[35-38] in the differentiation and identification of tautomeric forms,[39-46] and in studies concerned with

---

(32) A. J. Bourn and E. W. Randall, Mol. Phys., 8, 567 (1964).
(33) M. R. Bramwell and E. W. Randall, Chem. Commun., 250 (1969).
(34) T. Axenrod, M. J. Wieder, G. Berti, and P. L. Barili, J. Amer. Chem. Soc., 92, 6066 (1970).
(35) H. Hogeveen, Rec. Trav. Chem. Pays-Bas, 86, 1288 (1967); G. A. Olah and T. E. Kiovsky, J. Amer. Chem. Soc., 90, 4666 (1968).
(36) G. O. Dudek and E. P. Dudek, ibid, 86, 4283 (1964); ibid, 88, 2407 (1966).
(37) G. O. Dudek and E. P. Dudek, Tetrahedron, 23, 3245 (1967).
(38) V. Bekarek, K. Rothschein, P. Vetesnik, and M. Vecera, Tetrahedron Lett., 3711 (1968).
(39) A. K. Bose and I. Kugajevsky, J. Amer. Chem. Soc., 88, 2325 (1966).
(40) G. Klose and E. Uhlemann, Tetrahedron, 22, 1373 (1966).
(41) G. J. Lestina, G. P. Happ, D. P. Maier, and T. H. Regan, J. Org. Chem., 33, 3336 (1968).
(42) G. J. Lestina and T. H. Regan, ibid, 34, 1685 (1969).

sites of protonation.[47-50]

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(43) P. B. Fischer, B. L. Kaul, and H. Zollinger, Helv. Chim. Acta, 51, 1449 (1968).

(44) L. Mester, G. Vass, A. Stephen, and J. Parello, Tetrahedron Lett., 4053 (1968).

(45) L. Mester, A. Stephen, and J. Parello, ibid, 4119 (1968).

(46) L. Mester and G. Vass, ibid, 3847 (1969).

(47) B. W. Roberts, J. B. Lambert, and J. D. Roberts, J. Amer. Chem. Soc., 87, 5439 (1965).

(48) E. D. Becker, H. T. Miles, and R. B. Bradley, ibid, 87, 5575 (1965).

(49) G. A. Olah and A. M. White, ibid, 90, 6087 (1968).

(50) G. A. Olah and R. H. Schlosberg, ibid, 90, 6464 (1968).

PART I

CONFIGURATIONAL ASSIGNMENTS BASED ON STEREOSPECIFIC THREE BOND ^{15}N-H COUPLING

The phenomenon of hindered internal rotation in organic molecules has been investigated by a variety of physical methods,[51] including dipole moment measurements, electron diffraction studies, Raman and infrared spectroscopy. Nuclear magnetic resonance spectroscopy has proved to be a particularly valuable means of studying isomerism resulting from rotational barriers in the range 5-25 kcal/mole.[52] When the energy of activation for internal rotation is in this range, rapid equilibration between the individual rotamers generally precludes their physical isolation. However, if the rate of interconversion is slow on the nmr timescale, separate resonances for each rotamer in the resulting equilibrium mixture may be observed.

For molecules containing the X-Y=Z moiety, double bond character in the X-Y bond, arising from electron delocalization, is possible. In amides,[53] aminoboranes,[54] alkyl ni-

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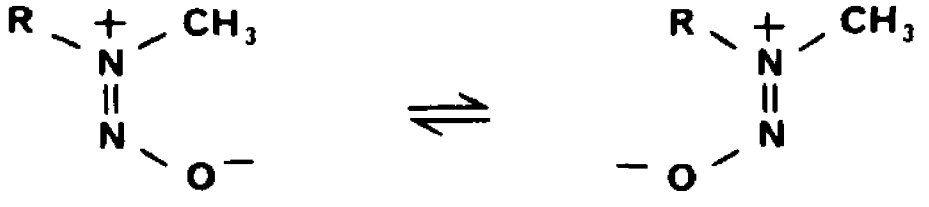
(51) S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, New York, 1954.

(52) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Oxford, 1965; G. Binsch, "Topics in Stereochemistry," Interscience, New York, 1968, vol. 3, p. 97; H. Kessler, Angew. Chem. Internat. Ed., 9, 219 (1970).

(53) W. D. Phillips, J. Chem. Phys., 23, 1363 (1955); H. S. Gutowsky and C. H. Holm, ibid, 25, 1228 (1956); W. D. Phillips, Ann. N. Y. Acad. Sci., 70, 817 (1958); W. J. Kowalewski and D. G. de Kowalewski, J. Chem. Phys., 32, 1272 (1960).

(54) K. Niedenzu and J. W. Dawson, J. Amer. Chem. Soc., 82, 4223 (1960); G. E. Ryschkewitsch, W. S. Brey, Jr., and A. Saji, ibid, 83, 1010 (1961); D. Imbery, A. Jaeschke, and H. Friebolin, Org. Magn. Resonance, 2, 271 (1970).

trites,[55] and nitrosamines,[56] restricted rotation about partial double bonds leads to configurational isomerism. Generally, configurational assignments for these systems are based on nmr observed changes in the equilibrium composition of a mixture of syn and anti isomers as the bulk of one of the substituents on the partial double bond is systematically varied. For example, in nitrosamines (1a and 1b), as R in-



(1a) (1b)

(R = methyl, ethyl, isopropyl, tert-butyl)

creases in size from a methyl to a tert-butyl group, the equilibrium shifts to favor structure (1a), the configuration in which the larger alkyl group is oriented <u>trans</u> to the nitroso oxygen atom.[57]

Within the last few years, there have been reports indi-

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(55) W. D. Phillips, C. E. Looney, and C. P. Spaeth, <u>J. Mol. Spectrosc.</u>, <u>1</u>, 35 (1957); H. W. Brown and D. P. Hollis, <u>ibid</u>, <u>13</u>, 305 (1964).

(56) C. E. Looney, W. D. Phillips, and E. I. Reilly, <u>J. Amer. Chem. Soc.</u>, <u>79</u>, 6136 (1957); G. J. Karabatsos and R. A. Taller, <u>ibid</u>, <u>86</u>, 4373 (1964).

(57) G. J. Karabatsos and R. A. Taller, <u>ibid</u>, <u>86</u>, 4373 (1964).

cating that the magnitude of ^{15}N-proton spin-spin coupling is, at least in part, dependent upon the stereochemistry of the nitrogen atom. In aldoximes,[58] tetrahydro-1,3-oxazines,[59] oxaziridines,[60] and aziridines,[61] geminal ^{15}N-C-H coupling has been shown to be stereospecific. In each of these systems, α-protons oriented cis with respect to the ^{15}N-lone pair of electrons exhibit larger $^{2}J(^{15}NH)$ values than the corresponding trans α-protons.

Similarly, systems containing the ^{15}N=X-C-H moiety might be expected to exhibit stereospecific vicinal ^{15}N=X-C-H coupling. This hypothesis was first tested by Axenrod and Pregosin who showed that the magnitude of ^{15}N=N-C-H coupling in N-nitrosamines[62] and N-nitrosohydrazines[63] was dependent upon the orientation of the ^{15}N-nitroso nitrogen lone pair of electrons and that syn/anti assignments for N-nitroso compounds could be made based on the stereospecificity of ^{15}N=N-C-H coupling.

In the present study, an attempt will be made to determine the feasibility of making configurational assignments for

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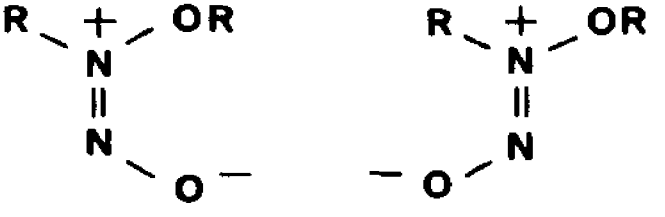
(58) J. P. Kintzinger and J. M. Lehn, Chem. Commun., 660 (1967).
(59) F. G. Riddell and J. M. Lehn, J. Chem. Soc. (B), 1224 (1968).
(60) D. M. Jerma, D. R. Boyd, L. Paolillo, and E. D. Becker, Tetrahedron Lett., 1483 (1970).
(61) M. Ohtsuru and K. Tori, ibid, 4043 (1970).
(62) T. Axenrod, P. S. Pregosin, and G. W. A. Milne, Chem. Commun., 702 (1968).
(63) T. Axenrod, P. S. Pregosin, and G. W. A. Milne, Tetrahedron Lett., 5293 (1968).

N-nitrosohydroxylamines, alkyl nitrites, and phenylhydrazones based on vicinal $^{15}N{=}N{-}C{-}H$, $^{15}N{=}O{-}C{-}H$, and $^{15}N{=}C{-}C{-}H$ coupling, respectively, and in so doing, test whether $^{15}N{=}X{-}C{-}H$ coupling is generally stereospecific.

N-Nitrosohydroxylamines

Beyond the early preparative work[64-67] and some recent investigations of thermal decomposition[68,69] and rearrangement,[70] much of the chemistry of N-nitrosohydroxylamines has been limited to metal chelate studies.[71]

Although it has not been demonstrated previously, N-nitrosohydroxylamines, by analogy with N-nitrosamines[56] and N-nitrosohydrazines,[63] might be expected to exhibit configurational isomerism (II-a and II-s) due to restricted rotation



(II-a) (II-s)

(64) R. Behrend and E. König, Ann., 263, 217 (1891).
(65) R. Behrend and R. Lindner, ibid, 275, 133 (1893).
(66) E. Bamberger, Ber., 27, 1548 (1894).
(67) A. B. Boese, L. W. Jones, and R. T. Major, J. Amer. Chem. Soc., 53, 3530 (1931).
(68) T. Koenig and M. Deinzer, ibid, 88, 4518 (1966).
(69) T. Koenig and M. Deinzer, ibid, 90, 7014 (1968).
(70) T. Koenig, T. Fithian, M. Tolela, S. Markwell, and D. Rogers, J. Org. Chem., 84, 952 (1969).
(71) H. J. Backer, Ahrens Sammlung, 18, 359 (1912).

about the N-NO bond. Furthermore, the successful application of stereospecific $^{15}N{=}N{-}C{-}H$ coupling to the problem of making configurational assignments for N-nitrosamines[62] and N-nitrosohydrazines[63] suggested that an ^{15}N-labeling study might serve as the basis for making heretofore unreported configurational assignments for N-nitrosohydroxylamines.

In order to test this hypothesis, a series of N-nitroso-O,N-dialkylhydroxylamines-(^{15}N-nitroso) was prepared and a study of their nmr spectra was undertaken. α-Proton chemical shifts and equilibrium isomer ratios for the several N-nitrosohydroxylamines examined are summarized in Table I.

Unlike N-nitrosamines and N-nitrosohydrazines, individual resonance signals for anti (II-a) and syn (II-s) configurational isomers of N-nitrosohydroxylamines are observed only at low temperatures, where the fraction of molecules undergoing rotation about the N-NO bond is small. This suggests that the N-N bond of N-nitrosohydroxylamines has considerably less double bond character than that in N-nitrosamines and N-nitrosohydrazines and that the greater electron withdrawing ability of an alkoxy group relative to that of an alkyl or dialkylamino group results in decreased electron delocalization over the nitrosamino moiety. This explanation is consistent with the observation that $(CF_3)_2NNO$ exhibits restricted rotation about the N-NO bond at low temperature,[72]

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(72) S. Andreades, J. Org. Chem., 27, 4167 (1962).

Table I. Isomer Ratios and Chemical Shift Values in Syn and Anti N-Nitrosohydroxylamines[a]

$R_1N(NO)OR_2$		anti		syn			anti/syn
R_1	R_2	R_1	R_2	R_1	R_2	T, °C[b]	%
CH_3	CH_3	3.91	3.87	3.46	4.13	-30	80/20
CH_3	$PhCH_2$	3.52	4.92	3.19	5.16	-25	85/15
$PhCH_2$	CH_3	5.31	3.62	5.06	3.96	-40	92/8
$PhCH_2$	$PhCH_2$	5.62	5.05	5.45	5.39	-40	95/5[c]
$CH_3\underline{CH}_2$	$PhCH_2$	3.99	4.99	3.9[d]	--[d]	-20	98/2
$Ph(CH_3)C\underline{H}$	CH_3	5.71	3.58			+35[e]	100/0
$PhCH_2$	H	5.20	9.83			+35[e]	100/0

[a] Spectra were measured in $CDCl_3$ solution in ppm (δ) from internal TMS using a Varian A60 spectrometer. [b] Temperature at which measurements were made. [c] In N,N-dimethylformamide solution. [d] Obscured by the methylene resonance of the anti isomer. [e] Spectra not temperature-dependent.

whereas N,N-dialkylnitrosamines exhibit restricted rotation at room temperature.

Table II presents the $^{15}N{=}N{-}C{-}H$ coupling constants for the labeled N-nitrosohydroxylamines investigated. In a typical case, the temperature-dependent nmr spectrum of N-nitroso-N-methyl-O-benzylhydroxylamine is shown in Figure I. At room temperature, the nmr spectrum of this compound shows two broad singlets at δ 3.50 and δ 4.96 which are in the ratio 3:2 and are assigned to the N-methyl and O-benzyl methylene protons, respectively. At -20°C, the distinct resonance signals of the N-methyl and O-benzyl methylene protons in the equilibrium mixture of configurational isomers are observed. An examination of the corresponding low temperature spectrum of the ^{15}N-isotopomer reveals that the larger N-methyl signal at δ 3.52 exhibits vicinal $^{15}N{=}N{-}C{-}H$ coupling of 2.2 Hz, whereas the smaller N-methyl signal at δ 3.19 does not exhibit such coupling.

If the observed dependence of the magnitude of geminal $^{15}N{-}C{-}H$ coupling on lone pair orientation is also valid for vicinal $^{15}N{=}N{-}C{-}H$ coupling, configurational assignments in the N-nitrosohydroxylamine series may be made based on the difference in the magnitude of syn and anti $^{15}N{=}N{-}C{-}H$ coupling constants. Thus, the coupled N-methyl group is assigned the orientation <u>cis</u> to the ^{15}N-nitroso nitrogen lone pair of electrons and corresponds to the <u>anti</u> (III-<u>a</u>) isomer. The uncoupled N-methyl group is assigned the orientation <u>trans</u> to the ^{15}N-lone pair and corresponds to the <u>syn</u> (III-<u>s</u>) isomer.

Table II. Vicinal Coupling Constants in N-(^{15}N-Nitroso)-Hydroxylamines

$R_1N(^{15}NO)OR_2$		$^3J(^{15}NH)$		
R_1	R_2	anti	syn	T, °C[c]
CH_3	CH_3	2.0	0.7	-30
CH_3	$PhCH_2$	2.2	0.7[d]	-25
$PhCH_2$	CH_3	2.0	0	-40
$PhCH_2$	$PhCH_2$	2.0	0	-40
$CH_3\underline{CH}_2$	$PhCH_2$	2.1	-	+35
$Ph(CH_3)\underline{CH}$	CH_3	1.6	-	+35
$PhCH_2$	H	2.6	-	+35

[a] All coupling constants are expressed in Hz. [b] The uncertainty in these values is estimated to be ±0.2 Hz. [c] Temperature at which measurements were made. [d] This coupling constant is not evident from Figure I; $^3J(^{15}NH)$ was obtained from the corresponding 100 Hz expanded spectrum.

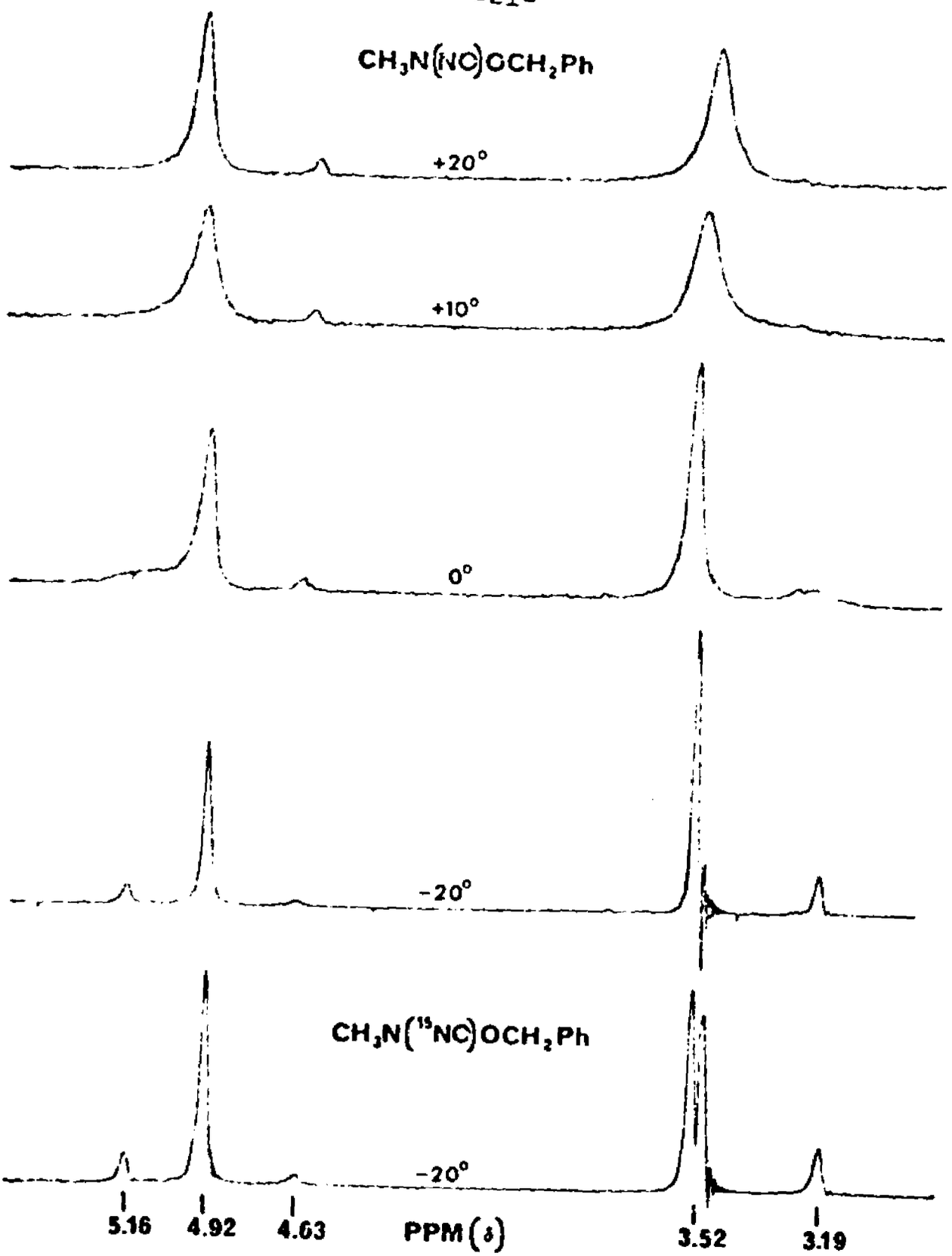
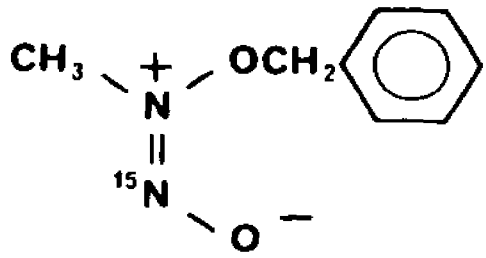
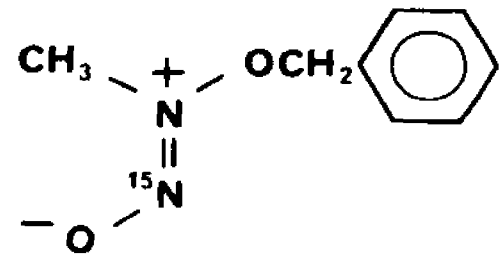


Figure I. Temperature-dependent 60-MHz nmr spectrum of N-nitroso-N-methyl-O-benzylhydroxylamine.



(III-a)



(III-s)

A particularly illustrative example of the utility of stereospecific $^{15}N{=}N{-}C{-}H$ coupling in making configurational assignments for N-nitrosohydroxylamines is the case of N-nitroso-O,N-dimethylhydroxylamine. As shown in Figure II, the low temperature nmr spectrum of this compound consists of four singlets at δ 3.46, δ 3.87, δ 3.91, and δ 4.13. Although it is clear that the resonances at δ 3.87 and δ 3.91 and at δ 3.46 and δ 4.13, respectively, correspond to the N- and O-methyl groups in the two different configurational isomers, unequivocal assignments are not possible. However, an examination of the corresponding low temperature spectrum of the ^{15}N-compound, shown in Figure III, reveals that the resonance signal at δ 3.91 is a 2.0 Hz doublet, whereas that at δ 3.46 is a 0.7 Hz doublet. Based on the configurational dependence of $^{15}N{=}N{-}C{-}H$ coupling, the 2.0 Hz doublet at δ 3.91 and the 0.7 Hz doublet at δ 3.46 correspond to the N-methyl resonances of the anti (IV-a) and syn (IV-s) isomers, respectively.

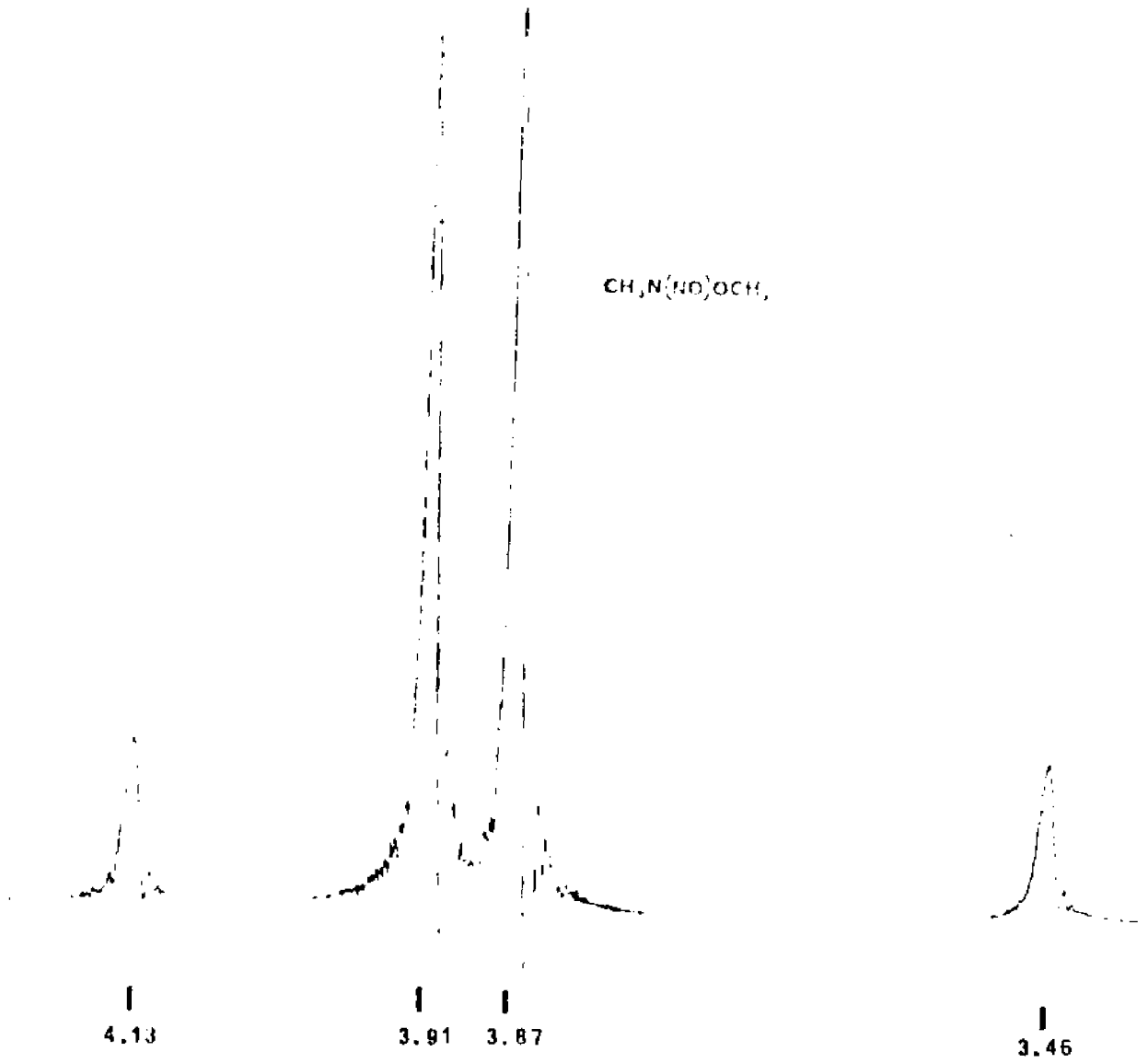


Figure II. 60 MHz pmr spectrum of N-nitroso-O,N-dimethylhydroxylamine at -30°C.

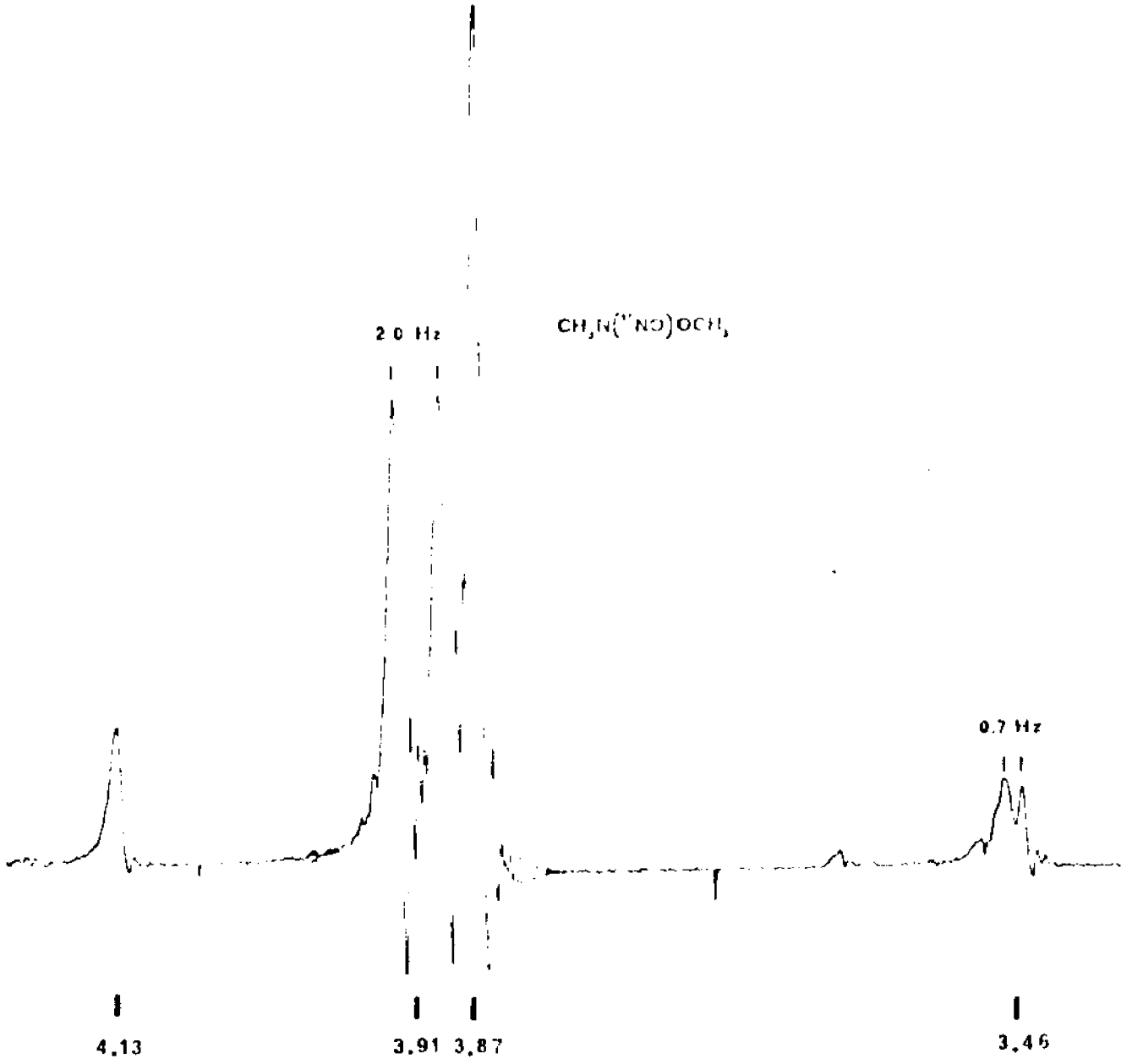
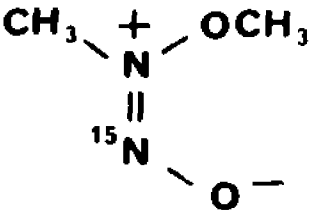
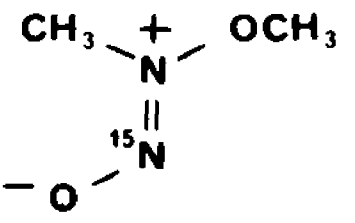


Figure III. 60 MHz pmr spectrum of N-(^{15}N-nitroso)-O,N-dimethylhydroxylamine at -30°C.

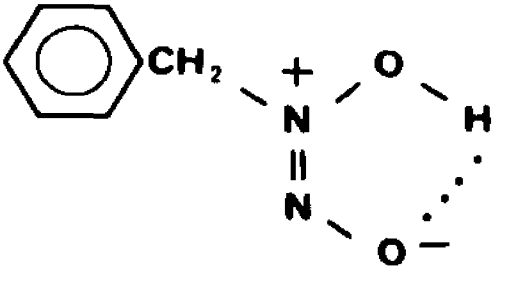


(IV-a)



(IV-s)

It is interesting to note (Table I) that steric factors alone do not determine the equilibrium isomer ratios in N-nitrosohydroxylamines. Low temperature nmr studies reveal the presence of only one configurational isomer in the spectrum of N-nitroso-N-benzylhydroxylamine, whereas the spectrum of N-nitroso-N-benzyl-O-methylhydroxylamine reveals the presence of both syn and anti isomers. The fact that the N-benzyl methylene resonance of N-nitroso-N-benzylhydroxylamine-(^{15}N-nitroso) appears as a temperature independent 2.6 Hz doublet indicates the presence of only the anti isomer. The absence of the syn isomer may be attributed to the importance of intramolecular hydrogen bonding, possible only in the anti (V-a) configuration. An analogous situation has been observed



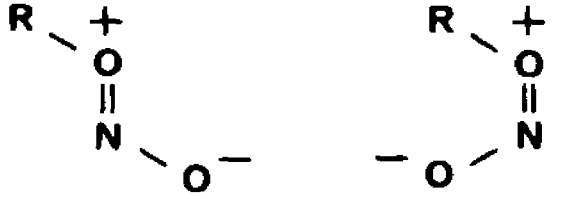
(V-a)

in N-nitrosohydrazines.[63]

It may be pointed out that the configurational assignments made for N-nitrosamines,[62] N-nitrosohydrazines,[63] and presently for N-nitrosohydroxylamines, based on the stereospecificity of $^{15}N{=}N{-}C{-}H$ coupling, are in accord with assignments made by Karabatsos and Taller[57] for N-nitrosamines based on steric arguments and on the anisotropy of the nitrosamino moiety.[73]

Alkyl nitrites

Evidence for rotational isomerism in alkyl nitrites has been provided by infrared and ultraviolet spectroscopies,[74] dipole moment measurements,[75] and nuclear magnetic resonance spectroscopy.[76] Separate resonances for anti (VI-a) and syn



(VI-a) (VI-s)

(VI-s) configurational isomers may be observed at low tem-

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(73) R. K. Harris, J. Mol. Spectrosc., 15, 100 (1965); R. K. Harris and R. A. Spragg, ibid, 23, 158 (1967); Y. L. Chow, Angew. Chem. Internat. Ed., 6, 75 (1967).

(74) L. D'or and P. Tarte, J. Chem. Phys., 19, 1064 (1951); P. Tarte, Bull. Soc. Chem. Belg., 60, 227 (1951); P. Tarte, J. Chem. Phys., 20, 1570 (1952); R. N. Hazeldine and J. Jander, J. Chem. Soc., 691 (1954); R. N. Hazeldine and B. J. H. Mattison, ibid, 4172 (1955).

(75) T. Chiba, Bull. Chem. Soc. Jap., 20, 505 (1955); R. F. Grant, D. W. Davidson, and P. Gray, J. Chem. Phys., 33, 1713 (1960).

peratures consistent with an energy barrier to rotation about the O-NO bond of 6-10 kcal/mole.[77]

Early configurational assignments for alkyl nitrites were based on the assumption that intramolecular hydrogen bonding in the syn (VI-s) isomer would shift the α-proton resonances downfield relative to those of the corresponding anti (VI-a) isomer.[76] Moreover, it was argued that since one nitrite isomer had an α-proton chemical shift similar to that observed in the corresponding alcohol and ether, that isomer had to be the anti (VI-a) form, since the chemical shift of the α-protons of the syn (VI-s) isomer would be expected to be strongly influenced by the proximity of the nitroso oxygen atom.[78] Assignments based on these earlier arguments have been reversed on the basis of more recent steric and anisotropy considerations presented by Brown and Hollis.[79]

Although vicinal $^{15}N{=}N{-}C{-}H$ coupling had been shown to be configuration dependent,[62,63,80] it was still unknown whether or not related, but heretofore unreported, vicinal $^{15}N{=}O{-}C{-}H$ coupling would exhibit the same stereospecificity. Accordingly, a series of alkyl nitrites having an ^{15}N-enrichment of

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(76) L. H. Piette, J. D. Ray, and R. A. Ogg, J. Chem. Phys., 26, 1341 (1957).

(77) L. H. Piette and W. A. Anderson, ibid, 30, 899 (1959); P. Gray and L. W. Reeves, ibid, 32, 1878 (1960).

(78) W. D. Phillips, C. E. Looney, and C. P. Spaeth, J. Mol. Spectrosc., 1, 35 (1957).

(79) H. W. Brown and D. P. Hollis, ibid, 13, 305 (1964).

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

99.0 atom % was prepared and their nmr spectra were examined. Table III summarizes the α-proton chemical shifts and equilibrium isomer ratios for the several labeled alkyl nitrites investigated. Table IV presents the time-averaged room temperature $^{15}N{=}O{-}C{-}H$ coupling constants and the individual syn and anti $^{15}N{=}O{-}C{-}H$ coupling constants measured at -75°C.

The temperature dependent nmr spectra of the benzyl nitrite isotopomers, shown in Figure IV, are representative of the alkyl nitrites examined. In each case, the time-averaged room temperature α-proton resonances are resolved into the individual syn and anti α-proton resonances of the equilibrium mixture of isomers at low temperature. From the nmr spectrum of benzyl nitrite-(^{15}N) at -75°C, it may be seen that the benzyl methylene resonance at δ 6.03 exhibits $^{15}N{=}O{-}C{-}H$ coupling of 2.4 Hz, whereas the smaller benzyl methylene resonance at δ 4.93 exhibits no $^{15}N{=}O{-}C{-}H$ coupling.

The observed difference in the magnitude of anti and syn $^{3}J(^{15}NH)$ coupling in the alkyl nitrite series is confirmation that vicinal $^{15}N{=}O{-}C{-}H$ coupling, like vicinal $^{15}N{=}N{-}C{-}H$ coupling, is configuration dependent and that substitution of oxygen for nitrogen as the intervening atom has little effect on the magnitude of such coupling.

By analogy with the configurational assignments made for the N-nitroso systems,[62,63,80] the 2.4 Hz doublet at δ 6.03 in the low temperature nmr spectrum of benzyl nitrite-(^{15}N) is assigned to the methylene protons oriented <u>cis</u> with res-

Table III. Chemical Shift Values and Equilibrium Isomer Ratios in Syn and Anti Alkyl Nitrites[a,b]

R-ONO	anti	syn	anti/syn
$(CH_3)_3CCH_2C\underline{H}_2$	5.22	4.08	1.4
$PhC\underline{H}_2$	6.03	4.93	2.0
$PhCH_2C\underline{H}_2$	5.20	4.08	2.4
$Ph(CH_3)C\underline{H}$	6.48	5.60	4.9
$Ph(CH_3CH_2)C\underline{H}$	6.42	5.53	6.5

[a] Spectra were measured in $CDCl_3$ solution in ppm (δ) from internal TMS using a Varian A60 spectrometer. [b] All measurements were made at -75°C.

Table IV. Vicinal Coupling Constants in ^{15}N-Alkyl Nitrites[a,b]

	$^3J(^{15}NH)$		
	+35°C	-75°C	
R-O^{15}NO	average	anti	syn
$(CH_3)_3CCH_2C\underline{H}_2$	1.7	2.4	0
$PhC\underline{H}_2$	1.7	2.4	0
$PhCH_2C\underline{H}_2$	1.8	2.3	0
$Ph(CH_3)C\underline{H}$	1.9	2.4	0
$Ph(CH_3CH_2)C\underline{H}$	2.1	2.1	0

[a] All coupling constants are expressed in Hz. [b] The uncertainty in these values is estimated to be ±0.2 Hz.

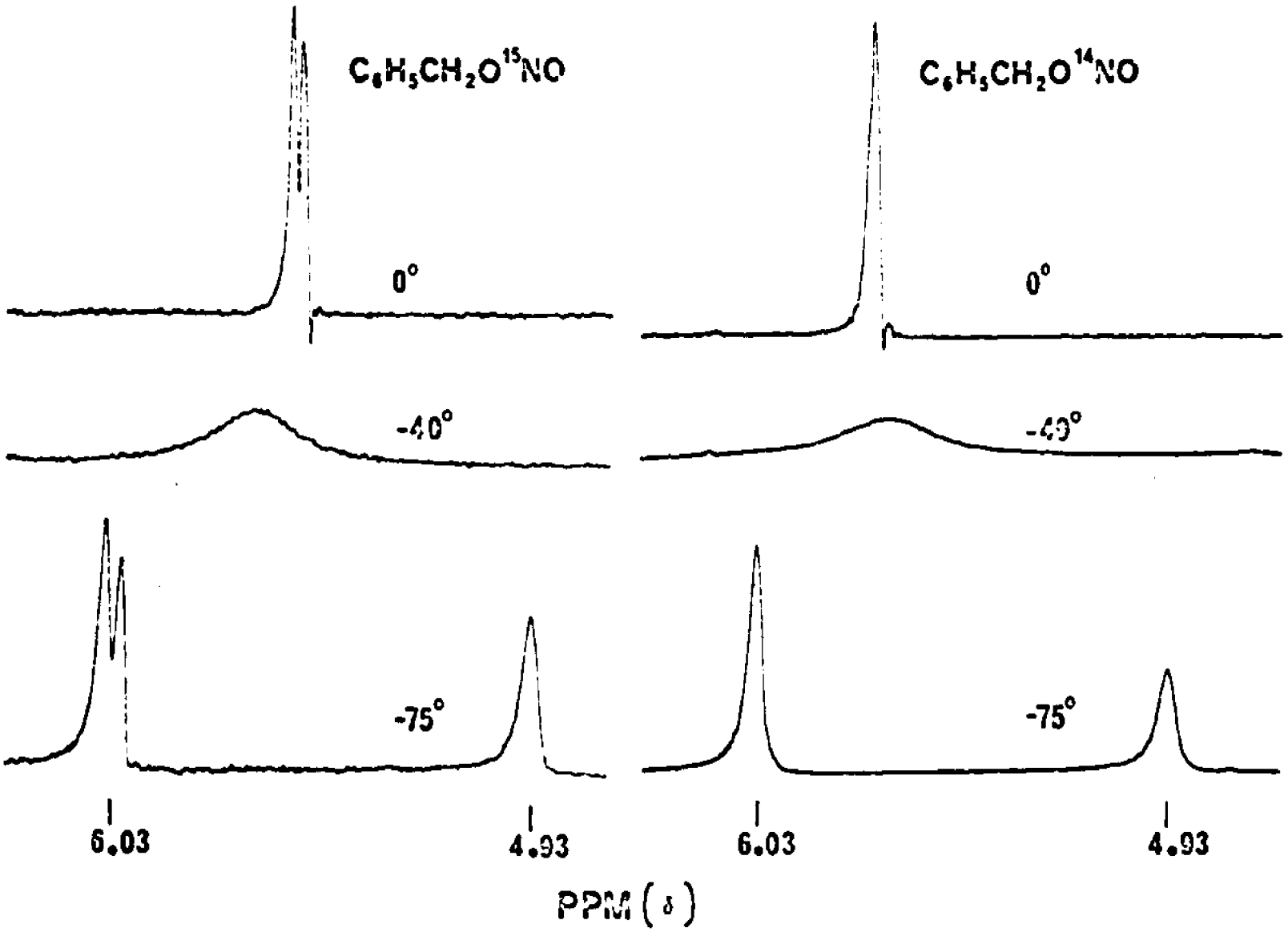


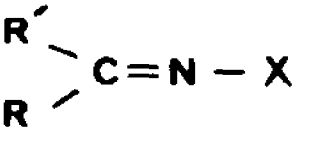
Figure IV. Temperature-dependent 60-MHz nmr spectrum of benzyl nitrite.

pect to the nitroso nitrogen lone pair of electrons and corresponds to the anti (VI-a) isomer. The singlet at δ 4.93 is assigned to the methylene protons oriented trans with respect to the nitroso nitrogen lone pair and corresponds to the syn (VI-s) isomer.

The assignment of the larger α-proton signal to the anti isomer is in accord with the expected greater stability of the anti (VI-a) configuration relative to the syn (VI-s) configuration with regard to lone pair-lone pair repulsions[81] and is consistent with the configurational assignments made by Brown and Hollis[79] based on steric and anisotropy considerations.

Phenylhydrazones

Configurational assignments for compounds with the general structure (VII) shown below have been made[82-84] on the



(VII)

(X = NH_2, NHR, $NHCONH_2$, $NHCSNH_2$, OH)

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(81) N. L. Owen and N. Sheppard, Proc. Chem. Soc., 264 (1964).

(82) G. J. Karabatsos, R. A. Taller, and F. M. Vane, J. Amer. Chem. Soc., 85, 2326 (1963).

(83) G. J. Karabatsos and R. A. Taller, ibid, 85, 3624 (1963).

(84) G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, ibid, 86, 3351 (1964).

basis of steric arguments, chemical shift considerations, and solvent effects. The observed configurational dependence of three bond ^{15}N-H coupling in N-nitrosamines,[62] N-nitrosohydrazines,[63] N-nitrosohydroxylamines,[80] and alkyl nitrites[85] suggested that vicinal ^{15}N=C-C-H coupling in the class of compounds represented by (VII) might be stereospecific and might thus serve as the basis for making configurational assignments for this system.

In order to test this hypothesis, several representative ^{15}N-enriched phenylhydrazones were prepared and their nmr spectra were examined. A summary of isomer ratios and α-proton chemical shifts is presented in Table V. Syn and anti ^{15}N=C-C-H coupling constants are presented in Table VI.

An examination of the methyl proton resonances of acetone phenylhydrazone-(^{15}N), Figure V, reveals that the magnitude of the ^{15}N=C-C-H coupling is indeed configuration dependent. In order to relate the magnitude of the vicinal ^{15}N=C-C-H coupling to ^{15}N-lone pair orientation, it was necessary to examine the nmr spectrum of a labeled phenylhydrazone known to exist in only one configuration. Figure VI shows the alkyl resonances of pinacolone phenylhydrazone-(^{15}N). This phenylhydrazone exists as the <u>syn</u> (VIII-<u>s</u>) isomer.[83] Since the α-methyl group is oriented <u>trans</u> to the ^{15}N-lone pair in this configuration, the smaller of the two previously noted (Fig-

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(85) T. Axenrod, M. J. Wieder, and G. W. A. Milne, <u>Tetrahedron Lett.</u>, 1397 (1969).

Table V. Isomer Ratios and Chemical Shifts[a] in ^{15}N-Phenylhydrazones

$R_1R_2C=^{15}NNHPh$		syn		anti		syn/anti[b]
R_1	R_2	R_1	R_2	R_1	R_2	%
CH_3	CH_3	1.81	1.93	1.93	1.81	50/50[c]
$(CH_3)_3C$	CH_3	1.05	1.70			100/0[c]
$PhCH_2$	H	3.37	6.35	2.69	---[d]	76/24[e]

[a] Chemical shifts are expressed in ppm (δ) relative to internal TMS. [b] For a summary of solvent dependent phenylhydrazone isomer ratios, see G. J. Karabatsos and R. A. Taller, J. Amer. Chem. Soc., 85, 3624 (1963). [c] In DMSO-d_6. [d] Obscured by the aromatic proton resonances. [e] In benzene-d_6.

Table VI. Vicinal Coupling Constants in ^{15}N-Phenylhydrazones

$R_1R_2C{=}^{15}NNHPh$		$^3J(^{15}NH)$[a,b]		
R_1	R_2	cis-CH_n	trans-CH_n	Solvent
CH_3	CH_3	3.8	1.8	DMSO-d_6
$(CH_3)_3C$	CH_3	---	1.8	DMSO-d_6
$PhCH_2$	H[c]	3.6	2.2	Benzene-d_6

[a] Coupling constants are accurate to ±0.2 Hz. [b] The terms cis and trans denote the orientation of the α-alkyl group relative to the ^{15}N-lone pair of electrons. [c] In addition to the vicinal coupling constants reported in this table, trans $^{15}N{=}C{-}H$ coupling of 3.5 Hz was observed. The corresponding cis geminal proton resonance was obscured by the aromatic proton resonances.

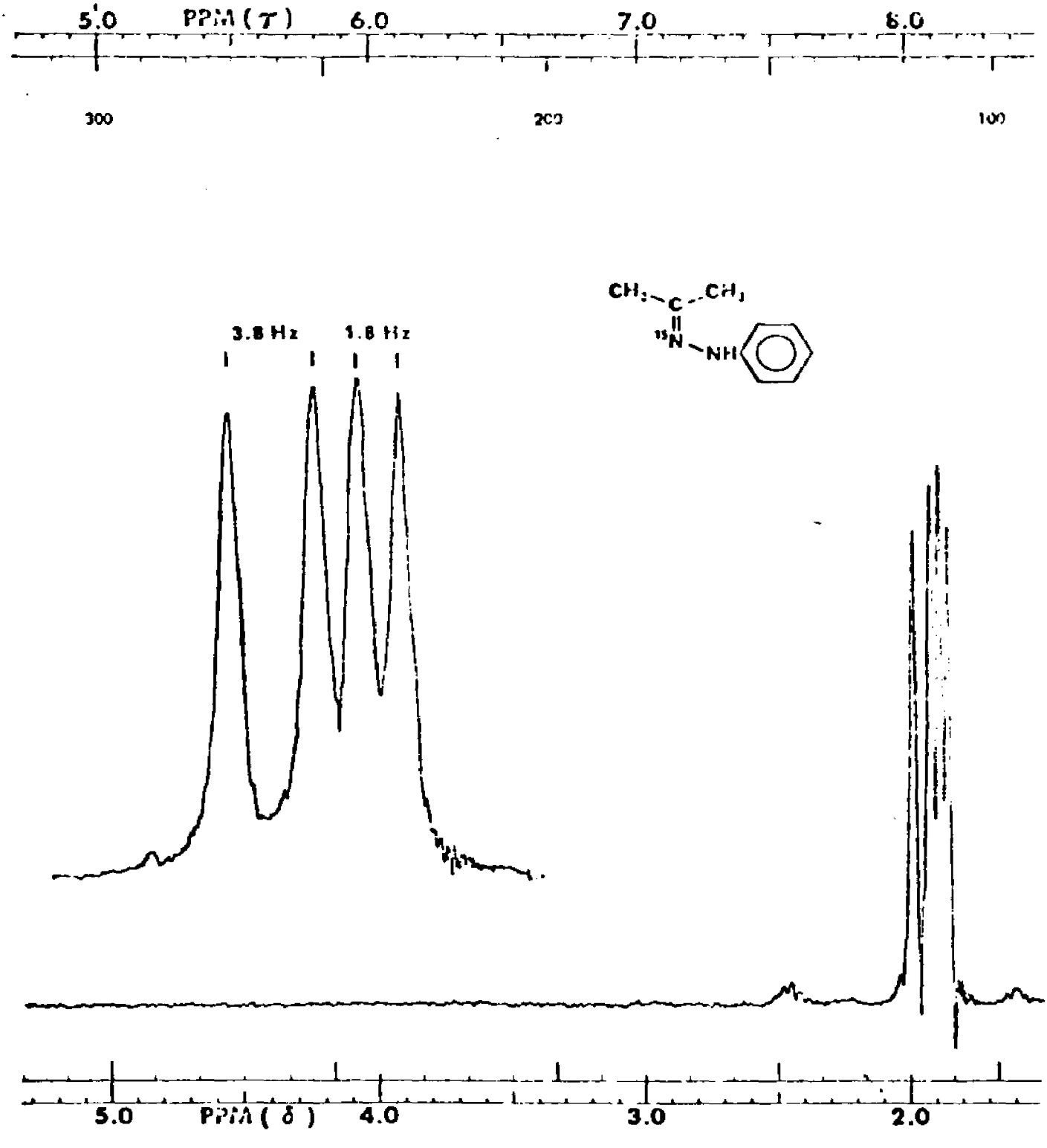


Figure V. Methyl proton resonances of ^{15}N-acetone phenylhydrazone at 60 MHz.

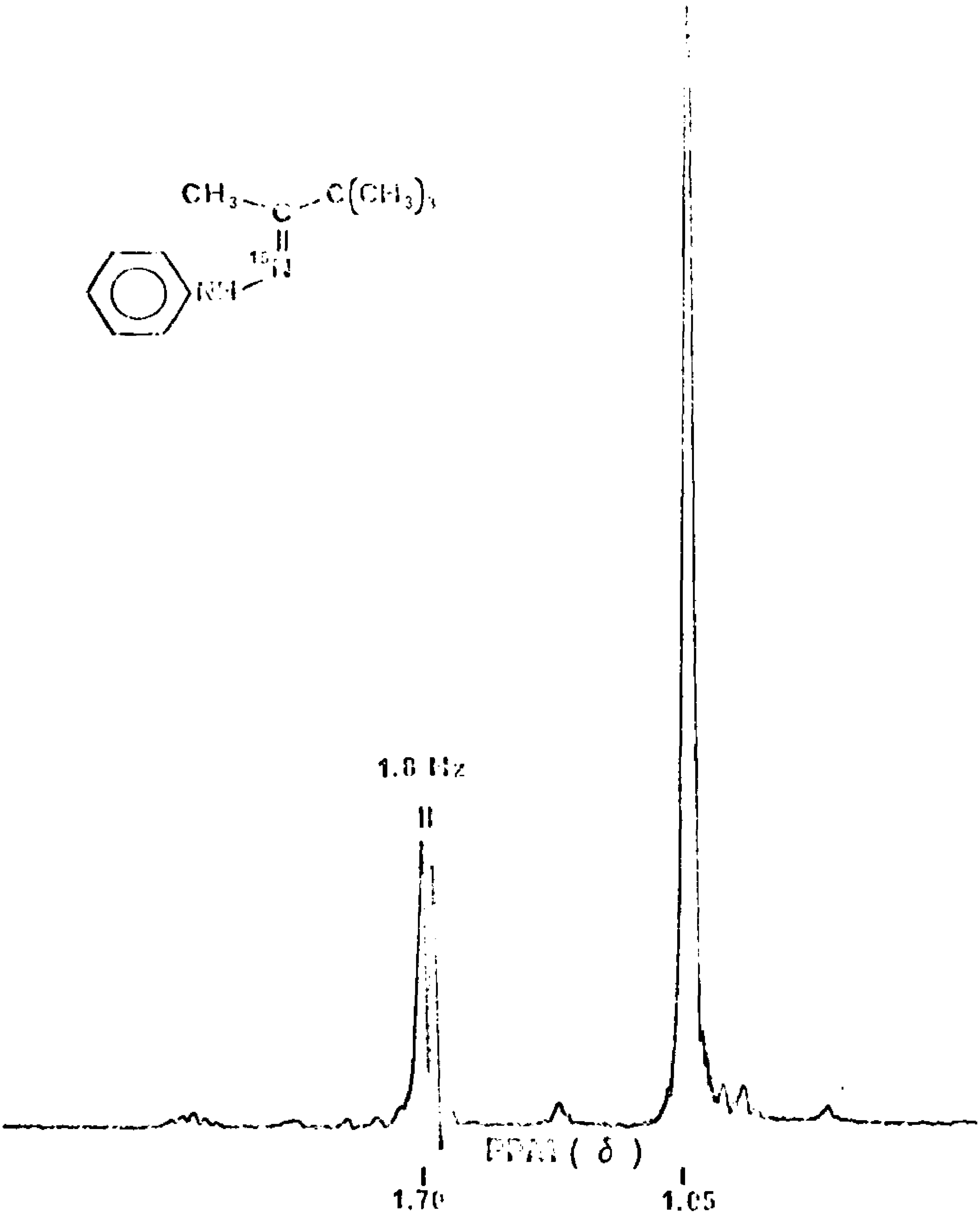
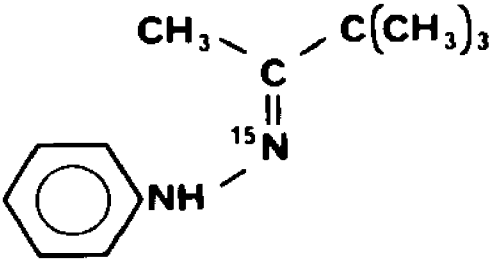


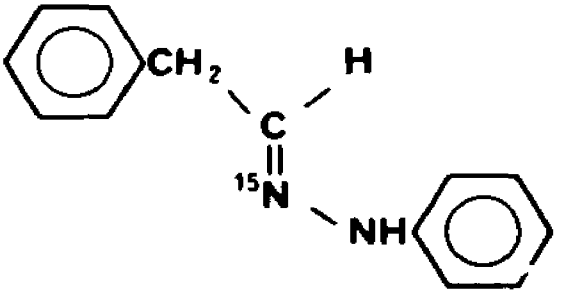
Figure [illegible] of ^{15}N, [illegible] phenylhydrazone at [illegible].



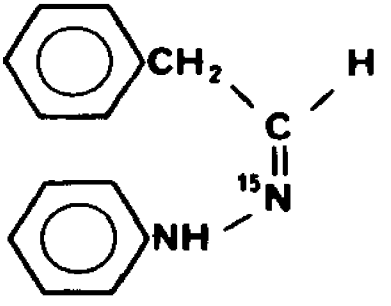
(VIII-s)

ure V) ^{15}N=C-C-H coupling constants (1.8 Hz) is observed in the present case.

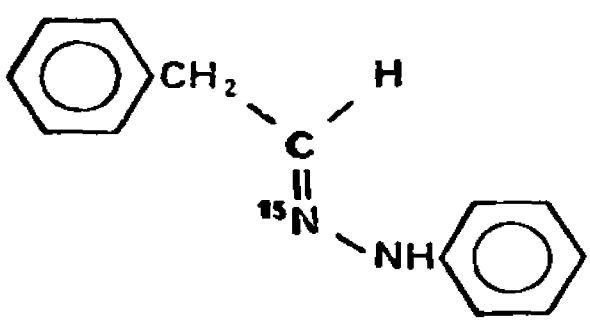
As a final illustrative example, the benzyl methylene resonances of phenylacetaldehyde phenylhydrazone-(^{15}N) are shown in Figure VII. Based on the difference in the magnitude of the observed ^{15}N=C-C-H coupling constants, the methylene resonance at δ 3.37, exhibiting 3.6 Hz ^{15}N=C-C-H coupling, is assigned to the <u>syn</u> (IX-s) isomer, whereas the methylene resonance at δ 2.89, exhibiting 2.2 Hz ^{15}N=C-C-H coupling, is assigned to the <u>anti</u> (IX-a) isomer. The assignment of the lar-

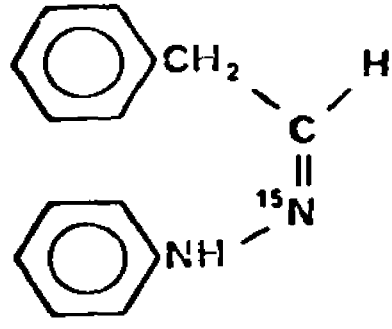


(IX-s)



(IX-a)





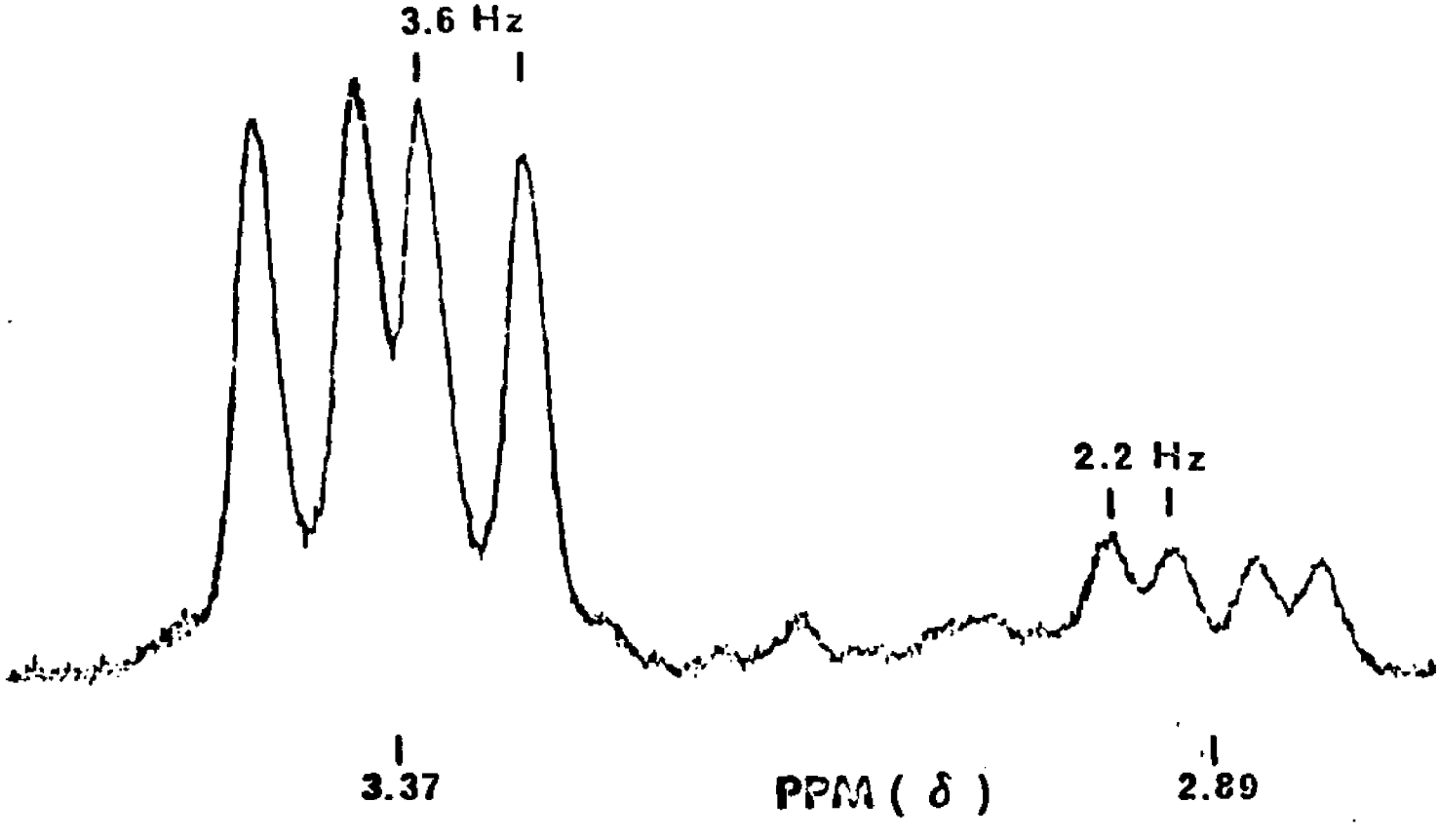
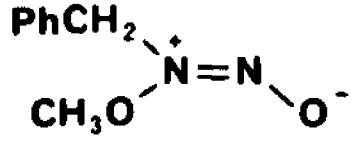


Figure VII. Methylene proton resonances of ^{15}N-phenylacetaldehyde phenylhydrazone at 60 MHz.

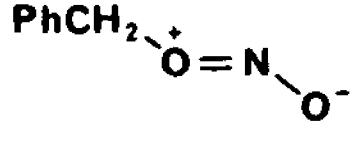
ger downfield benzyl methylene resonance to the syn (IX-s) isomer is consistent with the expected greater stability of the configuration in which the two largest substituents are oriented trans with respect to one another.

In conclusion, the magnitude of vicinal $^{15}N{=}X{-}C{-}H$ coupling has been shown to be configuration dependent in N-nitrosohydroxylamines, alkyl nitrites, and phenylhydrazones and may serve as the basis for making configurational assignments for these systems.

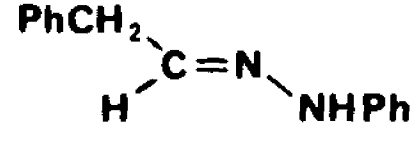
Note Added In Proof. Although the configurational descriptors cis/trans and syn/anti are widely employed in nomenclature to describe double-bond stereoisomerism, the resulting names are often ambiguous because these descriptors have not been defined according to any generally accepted universally applicable rules. Unambiguous specification of stereoisomerism about a double bond is now possible using a new set of descriptors, E (from the German entgegen) and Z (from the German zusammen),[(i)] which are based on the chirality sequence rules of Cahn, Ingold, and Prelog.[(ii)] Application of the E-Z convention to the systems discussed in Part I is illustrated below:



(Z)



(E)



(E)

(i) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, J. Amer. Chem. Soc., 90, 509 (1968).

(ii) R. S. Cahn, C. K. Ingold, and V. Prelog, Angew. Chem. Internat. Ed., 5, 385 (1966).

PART II

SUBSTITUENT EFFECTS ON ONE BOND ^{15}N-H COUPLING AND NITROGEN-15 CHEMICAL SHIFTS

Many properties, both physical and chemical, of ring-substituted aromatic compounds depend, at least in part, upon the manner in which the ring substituents modify the electronic structure of the molecule.[86] Any physical measurement which is dependent upon the electron distribution in such an aromatic system might therefore be expected to reflect differences in electronic structure due to the effect of different ring substituents.

The utilization of one bond ^{15}N-H coupling in the investigation of nitrogen hybridization in N-substituted anilines[87,88] suggested that a study of $^{1}J(^{15}NH)$ in a series of ring-substituted anilines might provide some insight into the nature of substituent-dependent changes in the electron distribution at the amino nitrogen atom. Furthermore, since both $^{1}J(^{15}NH)$ values and Hammett substituent constants[89] are functions of electron distribution, it seemed reasonable to inquire whether a relationship between the two exists.

Ring-substituted ^{15}N-anilines

In the present investigation, a series of ^{15}N-enriched

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(86) A. R. Katritzky and R. D. Topsom, Angew. Chem. Internat. Ed., 9, 87 (1970) and references cited therein.

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

(88) P. S. Pregosin, Ph. D. Dissertation, City College of the City University of New York, 1970.

(89) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1940, chaps. 3, 4, and 7; H. H. Jaffe, Chem. Rev., 53, 191 (1953); P. R. Wells, ibid, 63, 171 (1963); S. Ehrenson, Progr. Phys. Org. Chem., 2, 195 (1964); C. D. Ritchie and W. F. Sager, ibid, 2, 323 (1964).

(99.0 atom %) meta- and para-[90] substituted anilines was prepared and a study of their $^{1}J(^{15}NH)$ values in $CDCl_3$ and DMSO was undertaken. A summary of $^{1}J(^{15}NH)$ values for the several anilines examined is presented in Table VII.

An inspection of the data in Table VII reveals that the magnitude of $^{1}J(^{15}NH)$ in both solvents is dependent upon the nature of the ring substituent. Although the trend of increasing $^{1}J(^{15}NH)$ values is essentially the same in both solvents, the magnitude of the coupling is consistently greater in DMSO. Based on the nitrogen hybridization relationships[31,32] discussed earlier and the measured $^{1}J(^{15}NH)$ values shown in Table VII, the range of percent s-character in the ^{15}N-H bond of the ring-substituted anilines is calculated to be 26-31% in $CDCl_3$ and 28-32% in DMSO and, as such, is indicative of amino nitrogen hybridization intermediate between sp^3 and sp^2.

Hammett substituent constants have been shown to be directly proportional to such properties of anilines as base strength,[91] as well as N-H stretching frequencies[92] and amino

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(90) The para-substituted ^{15}N-anilines were investigated by P. S. Pregosin (88) and, as a matter of convenience for the reader, the results of that study are included in the present discussion.

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

(92) M. S. C. Flett, Trans. Faraday Soc., 44, 767 (1948); S. Califano and R. Moccia, Gazz. Chim. Ital., 86, 1014 (1956); 87, 58 (1957); P. J. Krueger and H. W. Thompson, Proc. Roy. Soc. (London) Ser. A, 243, 143 (1957); 250, 22 (1959); P. J. Krueger, Can. J. Chem., 40, 2300 (1962).

Table VII. One Bond ^{15}N-H Coupling Constants in Ring-Substituted Anilines.

Substituent[b]	$^1J(^{15}NH)$[a] $CDCl_3$	DMSO	$\sigma_{m,p}$[c]
4-NO_2	86.4	89.4	+1.27
4-NO_2, 3,5-$(CH_3)_2$	83.2	87.0	+0.64
3-NO_2	83.0	86.2	+0.71
3-CF_3	81.0	85.1	+0.43[d]
3-Br	80.5	85.1	+0.39
3-Cl	80.7	84.7	+0.37
3-I	80.4	84.4	+0.35
3-F	80.1	84.2	+0.34
4-I	79.7	84.0	+0.28
4-Br	79.6	84.0	+0.23
3,5-$(OCH_3)_2$	79.5	83.6	+0.24
4-Cl	78.9	83.7	+0.23
3-OCH_3	79.4	83.0	+0.12
H	78.6	82.6	0.00
3-CH_3	78.2	82.2	-0.07
3,5-$(CH_3)_2$	77.5	82.0	-0.14
4-F	77.8	81.6	+0.06
4-CH_3	76.5	81.4	-0.17
4-OCH_3	75.6	79.4	-0.27
4-$N(CH_3)_2$	74.8	78.8	-0.83[d]

[a] All coupling constants are expressed in Hz and are accurate to ±0.2 Hz. [b] Where possible, measurements were made with ca. 1.0 molal solutions, otherwise saturated solutions were used. [c] Values cited are from ref (97). [d] Values cited are from D. H. McDaniel and H. C. Brown, J. Org. Chem., 23, 420 (1958).

proton chemical shifts.[93]

In order to evaluate the effect of ring substituents on the magnitude of one bond ^{15}N-H coupling in the present series of labeled anilines, the $CDCl_3$ and DMSO $^1J(^{15}NH)$ values were plotted against the appropriate Hammett substituent constants. A least squares plot of the data is shown in Figure VIII. An examination of Figure VIII shows that there is an excellent linear correlation between the $^1J(^{15}NH)$ values measured in $CDCl_3$ and DMSO and the Hammett substituent constants. Thus, the presence of electron-withdrawing substituents may be seen to increase the magnitude of $^1J(^{15}NH)$, whereas the presence of electron-donating substituents may be seen to have the reverse effect. The parallel nature of the two plots is indicative of the fact that the electron donating or attracting ability of any one substituent relative to another in the series is independent of the solvent system.

To the extent that electron delocalization via p-π overlap is important in anilines, the enhancement of $^1J(^{15}NH)$ in DMSO relative to $CDCl_3$ may be attributed, in part, to the ability of the higher dielectric constant solvent[94] to stabilize charge separation in structures such as (X), although

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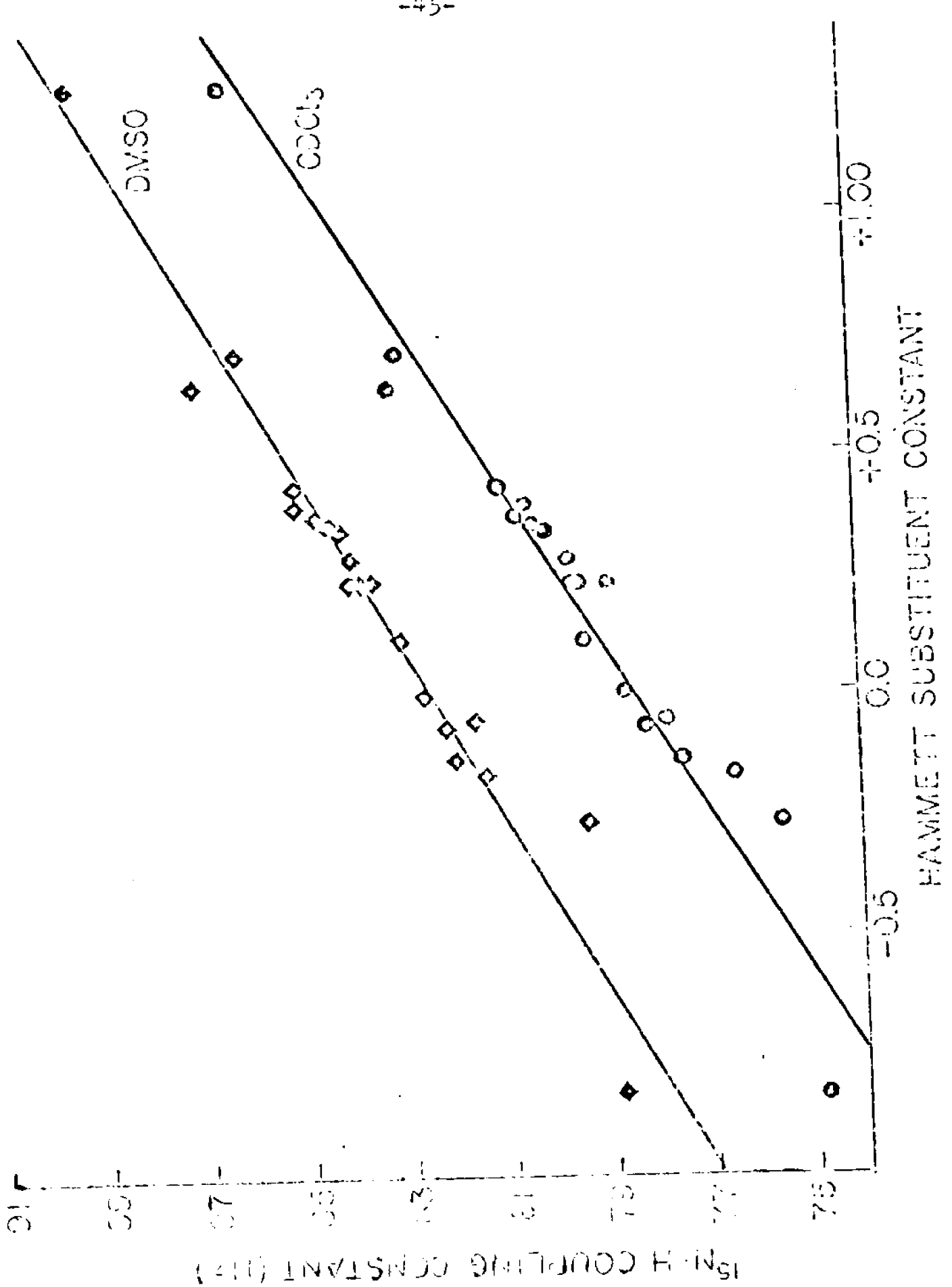
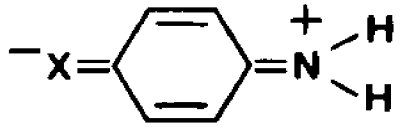
(93) W. F. Reynolds, Ph. D. Dissertation, University of Manitoba, 1963; L. K. Dyall, Aust. J. Chem., 17, 419 (1964); T. Yonemoto, W. F. Reynolds, H. M. Hutton, and T. Schaefer, Can. J. Chem., 43, 2668 (1965); B. M. Lynch, B. C. Macdonald, and J. G. K. Webb, Tetrahedron, 24, 3595 (1968).

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


DMSO
CDCl3
HAMMETT SUBSTITUENT CONSTANT
+1.00
+0.5
0.0
-0.5
^{15}N-H COUPLING CONSTANT (Hz)

other factors, such as the hydrogen bonding ability of the



(X)

solvent,[95] may also be important.

That both conjugative and inductive effects are important in ring-substituted anilines may be illustrated by a comparison of $^{1}J(^{15}NH)$ values in DMSO for 4-nitroaniline (89.4 Hz), 3,5-dimethyl-4-nitroaniline (87.0 Hz), 3-nitroaniline (86.2 Hz), aniline (82.6 Hz), and 3,5-dimethylaniline (82.0 Hz). Relative to aniline, the cumulative effect of 3,5-dimethyl substitution is to decrease the magnitude of one bond ^{15}N-H coupling by 0.6 Hz. Relative to 4-nitroaniline, however, 3,5-dimethyl substitution leads to a 2.4 Hz decrease in coupling. This inconsistency may be attributed to steric inhibition of resonance in 3,5-dimethyl-4-nitroaniline.

In 4-nitroaniline, coplanarity between the nitro group and the benzene ring leads to direct conjugation between the nitro group and the amino group and to enhanced sp^2 hybridi-

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(95) R. J. Ouellette, ibid, 43, 707 (1965); E. D. Becker, H. T. Miles, and R. B. Bradley, J. Amer. Chem. Soc., 87, 5575 (1965); J. G. Traynham and G. A. Knesel, J. Org. Chem., 31, 3350 (1966); E. D. Becker and L. Paolillo, J. Magn. Resonance, 2, 168 (1970).

zation of the amino nitrogen atom. In 3,5-dimethyl-4-nitroaniline, non-bonded interactions between the oxygen atoms of the nitro group and the adjacent methyl groups force the nitro group out of the plane of the aromatic ring and minimize its resonance interaction with the amino group[96] thereby decreasing the sp^2-character of the amino nitrogen atom.

It is noteworthy that the $CDCl_3$ and DMSO ^{15}N-H coupling constants of 4-nitroaniline are best correlated by the use of a σ^- value,[97] indicative of direct conjugation with the measurement center, whereas the corresponding $^1J(^{15}NH)$ values of 3,5-dimethyl-4-nitroaniline are best correlated with a normal σ value, consistent with steric inhibition of resonance and the dominance of the inductive effect in this compound. It is not surprising then that the $^1J(^{15}NH)$ values of 3,5-dimethyl-4-nitroaniline are more nearly comparable to those of 3-nitroaniline than 4-nitroaniline.

$^1J(^{15}NH)$ in systems of fixed nitrogen hybridization

Although the substituent dependence of $^1J(^{15}NH)$ in ring-substituted anilines has been explained[33,98] in terms of changes in the hybridization of the amino nitrogen atom, other substituent effects may contribute to overall changes

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(96) J. P. Schaefer and T. J. Miraglia, J. Amer. Chem. Soc., 86, 64 (1964); M. J. S. Dewar and Y. Takeuchi, ibid, 89, 390 (1967).

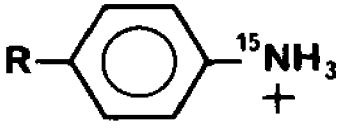
(97) H. H. Jaffe, Chem. Rev., 53, 250 (1953).

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

in the magnitude of one bond ^{15}N-H coupling.

For example, Grant and Litchman have calculated[99] that, in simple aliphatic halides, changes in $^{1}J(^{13}CH)$ can be accounted for in terms of substituent electronegativities which alter the effective nuclear charge on the carbon atom and that changes in the hybridization of the carbon atom are not necessarily involved. Yoder, Tuck, and Hess have explained[100] the substituent dependence of $^{1}J(^{13}CH)$ in ring-substituted toluenes-α-^{13}C in similar fashion. In view of these studies, the substituent dependence of $^{1}J(^{15}NH)$ in the ring-substituted anilines might be explained in terms of substituent-induced changes in the effective nuclear charge on the amino nitrogen atom and not necessarily in terms of changes in the amino nitrogen hybridization.

To provide information which would bear on these points, a study of $^{1}J(^{15}NH)$ in systems of fixed nitrogen hybridization was undertaken. Table VIII presents the $^{1}J(^{15}NH)$ values that were measured in a series of protonated anilines (XI),



(XIa, R = NO_2)
(XIb, R = H)

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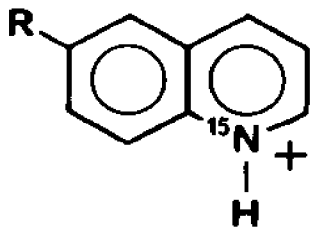
(99) D. M. Grant and W. Litchman, ibid, 87, 3994 (1965).
(100) C. H. Yoder, R. H. Tuck, and R. E. Hess, ibid, 91, 539 (1969).

Table VIII. One Bond ^{15}N-H Coupling in Systems of Fixed Nitrogen Hybridization.

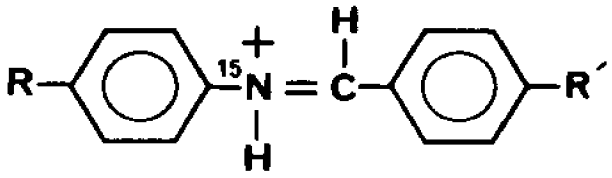
Compound	$^{1}J(^{15}NH)$[a,b,c]	Solvent
XIa	77.1	$HFSO_3$
	76.0	H_2SO_4
XIb	76.9	$HFSO_3$
	76.0	H_2SO_4
XIIa	96.5	$HFSO_3$
XIIb	96.0	$HFSO_3$
XIIc	96.0	$HFSO_3$
XIIIa[d]	92.0	$HFSO_3$
XIIIb	91.9	$HFSO_3$
XIIIc	91.5	$HFSO_3$
XIIId	91.5	$HFSO_3$
XIIIe	91.5	$HFSO_3$
XIIIf	91.5	$HFSO_3$

[a] All coupling constants are expressed in Hz and are accurate to ±0.5 Hz. [b] The $^{1}J(^{15}NH)$ values measured in H_2SO_4 were reported in ref.(34). [c] In the protonated quinolines (XIIa-c), cis H-^{15}N=C-H coupling was observed to be 7.5 Hz; in the protonated N-benzylideneanilines (XIIIa-f), trans H-^{15}N=C-H coupling was observed to be 17.8 Hz. [d] A sample of this compound was kindly provided by Dr. T. Axenrod.

protonated quinolines (XII), and protonated N-benzylidene-anilines (XIII).



(XIIa, R = NO_2)
(XIIb, R = H)
(XIIc, R = CH_3)



(XIIIa, R = NO_2, R' = H)
(XIIIb, R = H , R' = NO_2)
(XIIIc, R = H , R' = Cl)
(XIIId, R = H , R' = H)
(XIIIe, R = H , R' = CH_3)
(XIIIf, R = CH_3, R' = H)

It will be noted from an examination of Table VIII that, within each series, the magnitude of $^1J(^{15}NH)$ is virtually unaffected by the nature of the ring substituent. Thus, the anilinium ions (XIa and XIb) exhibit $^1J(^{15}NH)$ values characteristic of sp^3-hybridized nitrogen, whereas the quinolinium ions (XIIa-c) and the benzylideneanilinium ions (XIIIa-f) exhibit $^1J(^{15}NH)$ values characteristic of sp^2-hybridized nitrogen.

These observations suggest that the substituent dependence of $^1J(^{15}NH)$ in the ring-substituted anilines can be attributed primarily to substituent induced changes in the hybridization of the amino nitrogen atom.

Intramolecular hydrogen bonding in o-substituted ^{15}N-anilines

Nmr evidence for the existence of hydrogen bonding has come primarily from chemical shift investigations of the proton(s) involved in the hydrogen-bonded complex X-H···Y,[101] although recent reports indicate that new insights may be provided by chemical shift studies of the heteronuclei which serve as the proton donors (X) and acceptors (Y).[102]

To the extent that hydrogen bonding might be expected to alter the nature of the X-H bond, one-bond X-H spin coupling could conceivably act as a probe for the detection of hydrogen bonding. In light of the reported solvent dependence of $^{1}J(^{15}NH)$ in aniline[103] and its ring-substituted derivatives,[98] it seems reasonable to inquire whether an investigation of one-bond ^{15}N-H coupling in a series of ortho-substituted anilines might serve as a basis for evaluating the relative hydrogen bonding abilities of the various ortho substituents.

In order to test this hypothesis, a series of ortho-

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(101) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Oxford, 1965, vol. 1, p. 534.

(102) A. Loewenstein and Y. Margalit, J. Phys. Chem., 69, 4152 (1965); H. Saito, K. Nukada, H. Kato, T. Yonezawa, and K. Fukui, Tetrahedron Lett., 111 (1965); A. E. Florin and M. Alei, Jr., J. Chem. Phys., 47, 4268 (1967); A. E. Florin and M. Alei, Jr., J. Phys. Chem., 73, 863 (1969); J. Reuben, J. Amer. Chem. Soc., 91, 5725 (1969); W. M. Litchman, M. Alei, Jr., and A. E. Florin, ibid, 91, 6574 (1969); 92, 4828 (1970); H. Saito and K. Nukada, ibid, 93, 1072 (1971); H. Saito, Y. Tanaka, and K. Nukada, ibid, 93, 1077 (1971).

(103) L. Paolillo and E. D. Becker, J. Magn. Resonance, 2, 168 (1970).

substituted anilines having an ^{15}N-enrichment of 99 atom % was prepared and the one-bond ^{15}N-H coupling constants in $CDCl_3$ and DMSO were measured. A summary of $^1J(^{15}NH)$ values and amino proton chemical shifts is presented in Table IX.

It is readily apparent from an examination of Table IX that, as had been the case in the meta and para series of ^{15}N-anilines, $^1J(^{15}NH)$ values in the ortho series of anilines are also substituent and solvent dependent. Thus, the ability of the solvent or the ring substituent to foster delocalization of the amino nitrogen lone pair of electrons and enhance the sp^2-character of the ^{15}N-H bond is reflected in the magnitude of ^{15}N-H coupling.

Of particular interest however, is the set of $\Delta^1J(^{15}NH)$ values.[104] It will be noted that as the electron withdrawing ability of the ortho substituent increases, the difference in the observed coupling constants in $CDCl_3$ and DMSO becomes quite small. For example, $\Delta^1J(^{15}NH)$ for ortho-nitroaniline is 0.7 Hz, whereas for meta- and para-nitroaniline $\Delta^1J(^{15}NH)$ is 3.2 Hz and 3.0 Hz, respectively.[105]

Significantly, since it is generally acknowledged that ortho-nitroanilines are intramolecularly hydrogen bonded in $CDCl_3$ and intermolecularly hydrogen bonded in DMSO,[106] and

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(104) $\Delta^1J(^{15}NH) = {}^1J(^{15}NH)_{DMSO} - {}^1J(^{15}NH)_{CDCl_3}$

(105) See Table VII.

(106) I. D. Rae, Chem. Commun., 519 (1966); I. D. Rae, Aust. J. Chem., 20, 1173 (1967).

Table IX. ^{15}N-H Coupling Constants and Amino Proton Chemical Shifts in some ortho-Substituted Anilines.

Substituent[c]	$^1J(^{15}NH)$[a] $CDCl_3$	$^1J(^{15}NH)$[a] DMSO	$\Delta^1J(^{15}NH)$	$\Delta\nu_{NH_2}$[b] $CDCl_3$	$\Delta\nu_{NH_2}$[b] DMSO
2-NO_2, 4-Cl	91.1	91.8	0.7	6.11	7.56
2-NO_2	90.3	91.0	0.7	6.16	7.40
2-COPh	88.1	89.3	1.2	6.15	7.16
2-Cl, 4-NO_2	89.2	90.5	1.3	4.91	6.86
2,4,6-$(Br)_3$[d]	85.5	87.4[d]	1.9	4.30	5.48[d]
2-CF_3	83.6	86.5	2.9	4.11	5.46
2-Br	81.4	84.3	2.9	4.01	5.16
2-OCH_3	79.4	82.3	2.9	3.75	4.60
2-F	80.1	83.5	3.4	3.66	4.98
2-H	78.6	82.6	4.0	3.56	4.80

[a] All coupling constants are expressed in Hz and are accurate to ±0.2 Hz. [b] Amino proton chemical shifts are expressed in ppm (δ) relative to TMS. [c] Where possible, measurements were made on ca. 1.0 molal solutions, otherwise saturated solutions were used. [d] See ref. (88).

since it has also been reported that both intra-[107] and intermolecular[108] hydrogen bonding in ring-substituted anilines enhance the electron donating ability of the amino group, the $\Delta^1J(^{15}NH)$ values of Table IX may be considered to reflect the strength of the intramolecular hydrogen bond in $CDCl_3$. Thus, for a strongly electron withdrawing ortho-substituent, the enhancement of sp^2-character in the ^{15}N-H bond due to intramolecular hydrogen bonding in $CDCl_3$ will be comparable to that due to intermolecular hydrogen bonding in DMSO, and consequently, $\Delta^1J(^{15}NH)$ for that substituent will be small. On this basis, the order of substituent hydrogen bonding abilities may be seen to be: $NO_2 > C{=}O > CF_3$, Br, $OCH_3 > F$.

It is interesting to note that a moderately strong intramolecular hydrogen bond exists in 2-chloro-4-nitroaniline, whereas only a weak interaction is indicated in 2-bromo- and 2-fluoroaniline. Apparently, in 2-chloro-4-nitroaniline, the hydrogen bonding ability of the ortho-chloro substituent is substantially enhanced by the increased acidity of the amino protons due to the resonance interaction between the amino group and the powerfully electron withdrawing para-nitro group. Recent infrared evidence supports this view.[109]

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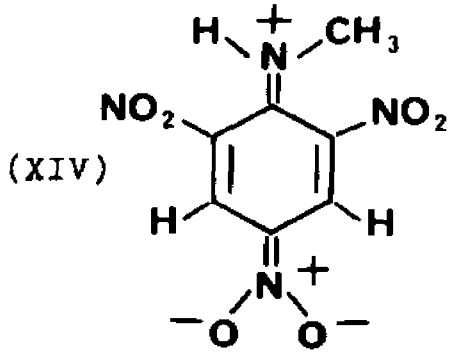
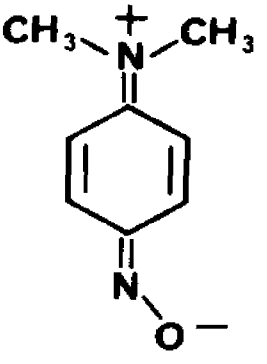
(107) P. J. Krueger, Can. J. Chem., 40, 2300 (1962).
(108) B. M. Lynch, B. C. Macdonald, and J. G. K. Webb, Tetrahedron, 24, 3595 (1968).
(109) L. K. Dyall, Aust. J. Chem., 23, 947 (1970); C. Madec, J. Lauransan, and P. Saumagne, J. Phys. Chem., 75, 1157 (1971).

Restricted rotation in ortho-substituted ^{15}N-anilines

NMR studies have shown that the ring protons in N-methyl-2,4,6-trinitroaniline[110] (XIV) and the methyl groups in p-nitroso-N,N-dimethylaniline[111] (XV) are nonequivalent at



(XIV)



(XV)

low temperature. These observations have been interpreted in terms of restricted rotation about the amino nitrogen - aryl carbon bond. By analogy, delocalization of the amino nitrogen lone pair of electrons in ring-substituted anilines should manifest itself in double bond character in the amino nitrogen - aryl carbon bond and should lead to the nonequivalence of the amino protons.

In an attempt to demonstrate this point,[112] acetone solutions of several representative ortho-substituted ^{15}N-anilines were prepared and an investigation of their low temperature nmr spectra was undertaken.

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(110) J. Heidberg, J. A. Weil, G. A. Janusonis, and J. K. Anderson, J. Chem. Phys., 41, 1033 (1964).

(111) R. K. Mackenzie and D. D. MacNicol, Chem. Commun., 1299 (1970).

(112) An unsuccessful attempt to demonstrate amino proton nonequivalence in unlabeled 2-nitroaniline was made by I. Yamaguchi and S. Brownstein, J. Phys. Chem., 67, 525 (1963).

In each of the anilines investigated, the $^{15}NH_2$ signal was observed to be temperature dependent with respect to chemical shift and line shape. Amino proton nonequivalence, however, was evident only in the low temperature pmr spectra of 2-nitro-4-chloroaniline-^{15}N and 2-nitroaniline-^{15}N, shown in Figures IX and X, respectively. In all other instances, the sample solutions froze (-105°C) before amino proton nonequivalence could be detected.

As Figures IX and X reveal, the amino proton resonances of 2-nitro-4-chloroaniline-^{15}N and 2-nitroaniline-^{15}N, at low temperature, consist of <u>two</u> sets of ^{15}N-H doublets. Unfortunately, the aromatic proton resonances obscure, either partially (Figure IX) or totally (Figure X), the upfield signals in each set so that only the downfield signals are clearly visible. In addition to being non-isochronous at low temperature, the amino protons also exhibit 2.2 Hz geminal H_a-^{15}N-H_b coupling.[113]

The detection of amino proton nonequivalence in <u>ortho</u>-substituted anilines requires that the amino nitrogen - aryl carbon bond exhibit considerable double-bond character. This fact is borne out by the $^1J(^{15}NH)$ values for 2-nitro-4-chloroaniline-^{15}N and 2-nitroaniline-^{15}N, presented in Table X, which reflect[31,32] the essentially complete sp^2-hybridization of the amino nitrogen in these compounds.

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(113) See H. Kamei, <u>Bull. Chem. Soc. Jap.</u>, <u>38</u>, 1212 (1965) for a report of 2.2-2.5 Hz geminal H-N-H coupling in some amides.

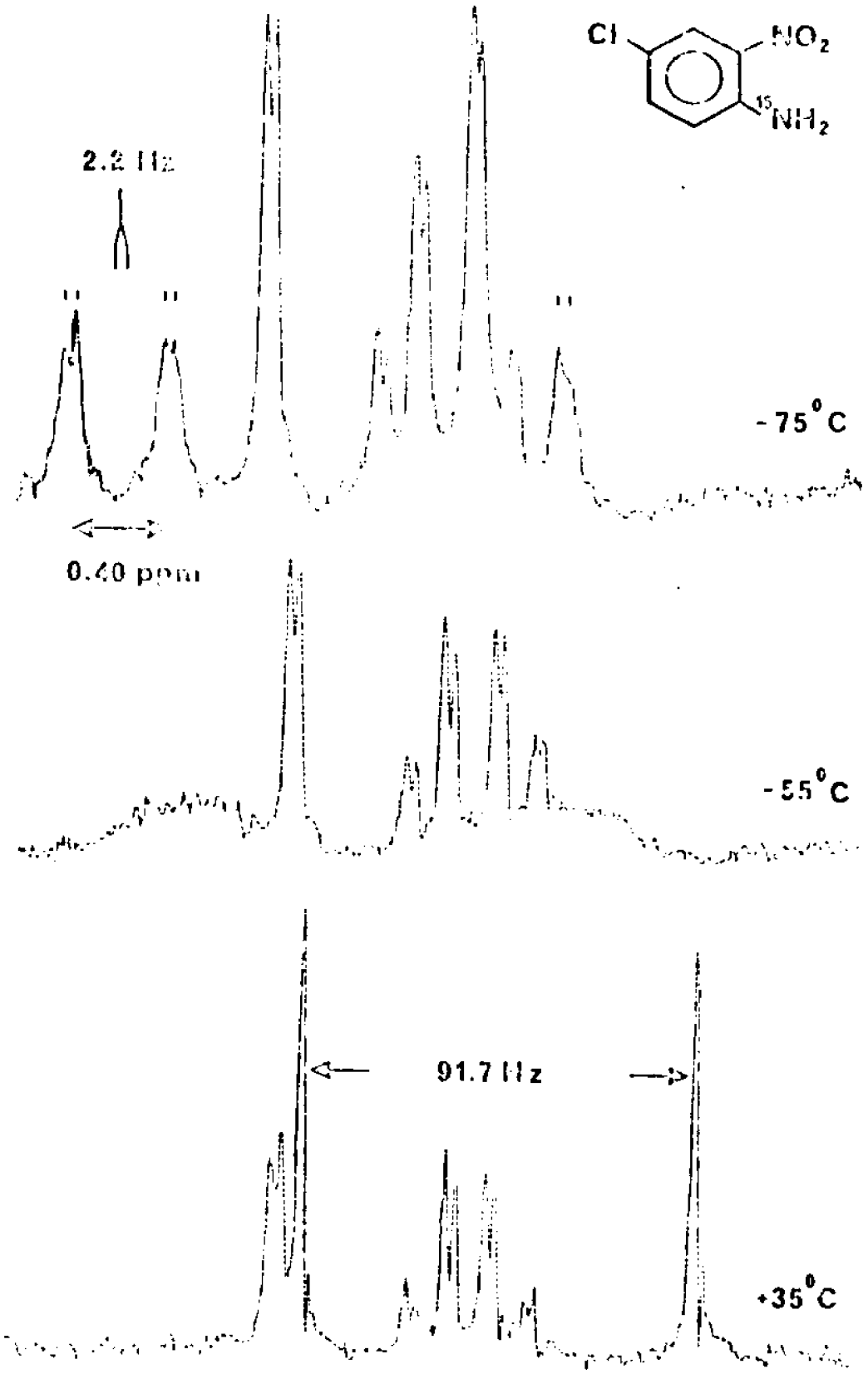


Figure 12. Temperature-dependent 60 MHz pmr spectrum of 2-nitro-4-chloroaniline-^{15}N in acetone.

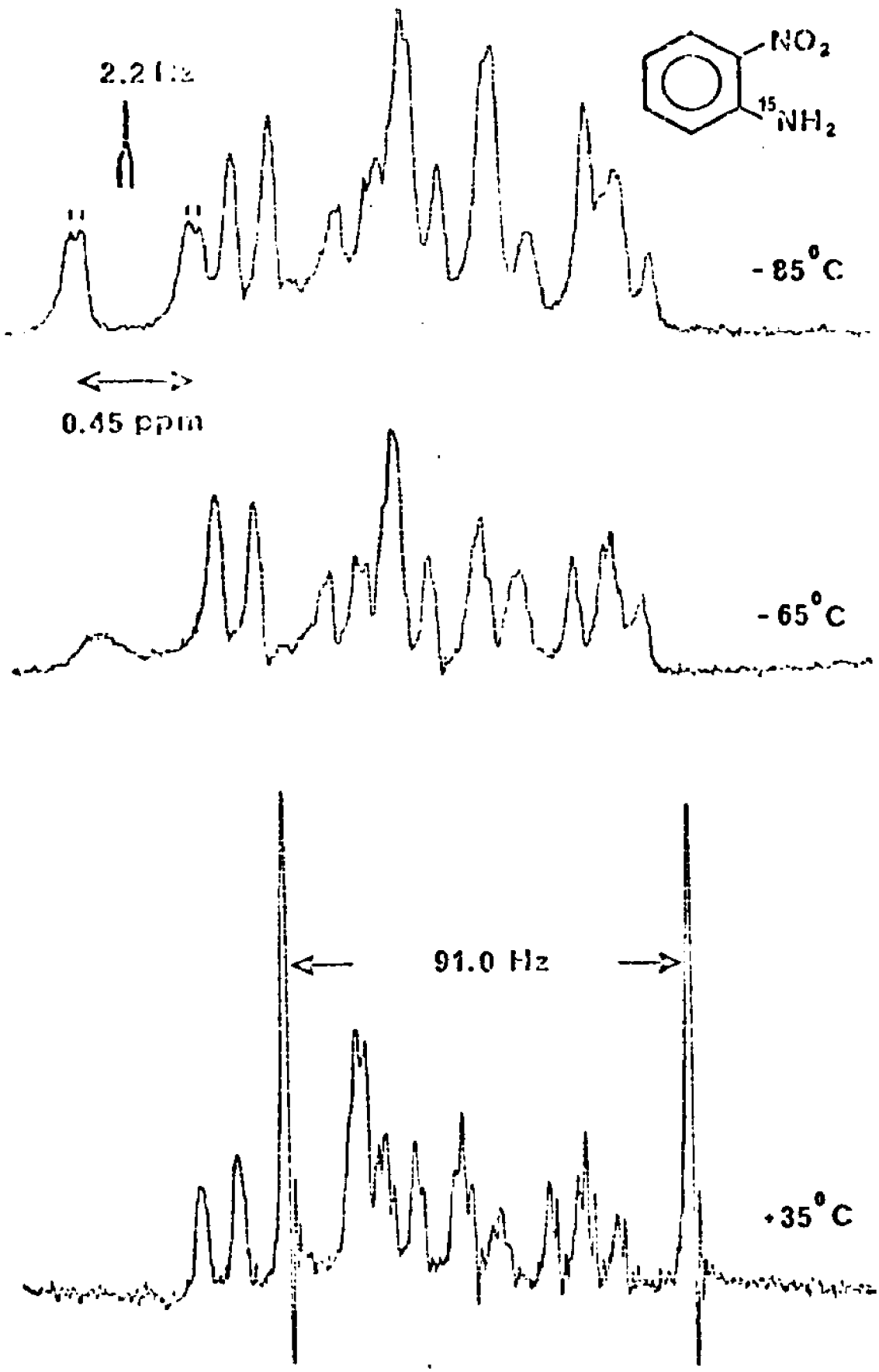


Figure X. Temperature-dependent 60 MHz pmr spectrum of 2-nitroaniline-^{15}N in acetone.

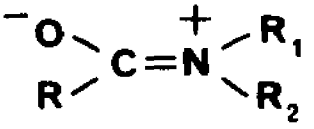
Table X. $^{1}J(^{15}NH)$ Values of some <u>ortho</u>-Substituted Anilines in Acetone.

Substituent[a]	$^{1}J(^{15}NH)$[b]
2-NO_2, 4-Cl	91.7
2-NO_2	91.0[c]
2-Cl, 4-NO_2	90.4
2,4,6-$(Br)_3$	87.3
2-CF_3	86.4
2-Br	84.2
2-OCH_3	81.7
2-H	81.4

[a] Measurements were made with ca. 1 molal solutions. [b] All coupling constants are expressed in Hz and are accurate to ±0.2 Hz. [c] $^{1}J(^{15}NH)$ in this instance was obtained from the INDOR spectrum.

Substituent effects in ^{15}N-benzamides

Delocalization of the nitrogen lone pair of electrons over the N-C=O moiety in amides leads to double bond character in the central C-N bond[114] and to the geometric and magnetic nonequivalence of substituents on the nitrogen atom even when $R_1 = R_2$ (XVI). Furthermore, the rigidity of the



(XVI)

planar amide framework leads to the possibility of restricted rotation in amides about bonds other than the central C-N linkage.[115]

Recently, nonequivalence of the geminal methylene protons in ortho-substituted and unsymmetrically ortho-disubstituted N,N-dibenzylbenzamides (XVII) was interpreted in terms of restricted rotation about the aryl - carbonyl bond.[116] Although the possibility for it exists, restricted rotation about the aryl - carbonyl bond in primary benzamides has not been reported previously.

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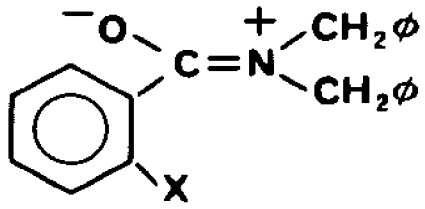
(114) H. S. Gutowsky and C. H. Holm, J. Chem. Phys., 25, 1228 (1956); M. T. Rogers and J. C. Woodbrey, J. Phys. Chem., 66, 540 (1962).

(115) For a recent review of amides, see W. E. Stewart and T. H. Sidall, Chem. Rev., 70, 517 (1970) and references cited therein.

(116) A. H. Lewin and M. Frucht, Tetrahedron Lett., 1079 (1970); A. H. Lewin, M. Frucht, and F. A. Bovey, ibid, 1083 (1970).



(XVII)

The availability of a series of ring-substituted ^{15}N-benzamides[117] having an ^{15}N-enrichment of 99 atom % provided an opportunity to investigate this possibility. Additionally, it was of interest to determine whether or not substituent electronic effects are transmitted through the carbonyl group to the amino group. A summary of $^{1}J(^{15}NH)$ values and amino proton chemical shifts for the ^{15}N-benzamides examined is presented in Table XI.

The observed range of $^{1}J(^{15}NH)$ values, ca. 88-90 Hz, is characteristic of sp^2-hybridized nitrogen and is consistent with the expectation of double bond character in the central amide bond. Because the amino nitrogen lone pair is extensively delocalized over the N-C=O moiety, no significant ring substituent effect on one-bond ^{15}N-H coupling is observed in the ^{15}N-benzamides, in contrast to the situation that exists in ring-substituted ^{15}N-anilines.

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(117) The ^{15}N-benzamides were precursors in the syntheses of the labeled anilines.

Table XI. One Bond ^{15}N-H Coupling and Amino Proton Chemical Shifts in Ring-Substituted Benzamides.

Substituent[a]	$^1J(^{15}NH)$[b] Upfield	$^1J(^{15}NH)$[b] Downfield	$\Delta\nu_{NH_2}$[c] Upfield	$\Delta\nu_{NH_2}$[c] Downfield
3-CF_3	88.7	89.1	464	500
3-Br	88.2	88.8	465	499
3-Cl	88.1	-[d]	461	495[e]
3-F	88.2	-[d]	459	490[e]
3,5-$(OCH_3)_2$	-[d]	89.1	452[e]	489
3-OCH_3	88.0	-[d]	455	490[e]
3-H	87.8	-[d]	451	488[e]
3-CH_3	88.1	-[d]	449	486[e]
3,5-$(CH_3)_2$	88.0	88.8	448	483
2-NO_2, 4-Cl	88.2	89.6	467	493
2-Cl, 4-NO_2	88.4	90.0	474	490
2-NO_2	88.4	89.6	465	492
2-CF_3	88.7	89.7	466	486
2-Br	88.2	90.0	455	472

[a] Measurements were made at +10°C using 1.0-1.5 molal DMSO solutions. [b] Coupling constants are expressed in Hz and are accurate to ±0.2 Hz. [c] Chemical shifts are expressed in Hz relative to TMS at 60 MHz and are accurate to ±1.0 Hz. [d] ^{15}NH signal hidden by aromatic proton resonances. [e] An approximate value based on a $^1J(^{15}NH)$ value of 89±1 Hz.

It will also be noted that, for a given ring substituent, $^{1}J(^{15}NH)$ for the downfield amino proton is slightly larger than that for the upfield amino proton. A similar observation in the case of ^{15}N-formamide has been explained in terms of the difference in the ^{15}N-H bond lengths in this molecule.[118] By analogy, the stronger spin-coupling interaction in ^{15}N-benzamides would be expected in the shorter ^{15}N-H bond.

Although the effect of ring substituents on one bond ^{15}N-H coupling in the benzamide series is negligible, the amino proton resonances are markedly influenced by both the position and nature of the ring substituent. Figures XI-XIV illustrate this point.

The amino proton splitting pattern of 3,5-dimethylbenzamide-^{15}N, shown in Figure XI, is typical of that observed for the meta-substituted ^{15}N-benzamides and consists simply of two ^{15}N-H doublets. In addition to one bond ^{15}N-H coupling, Figure XII shows that the amino protons of 2-bromobenzamide-^{15}N exhibit 2.0 Hz geminal H_a-^{15}N-H_b coupling.[113] The amino proton splitting pattern of 2-methoxybenzamide-^{15}N, shown in Figure XIII, consists of two AB quartets separated by ca. 88 Hz, whereas that of 2-fluorobenzamide-^{15}N, shown in Figure XIV, is barely recognizable.

The general effect of meta- versus ortho-substitution on the ^{15}N-amino proton resonances is illustrated in Figure XV.

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

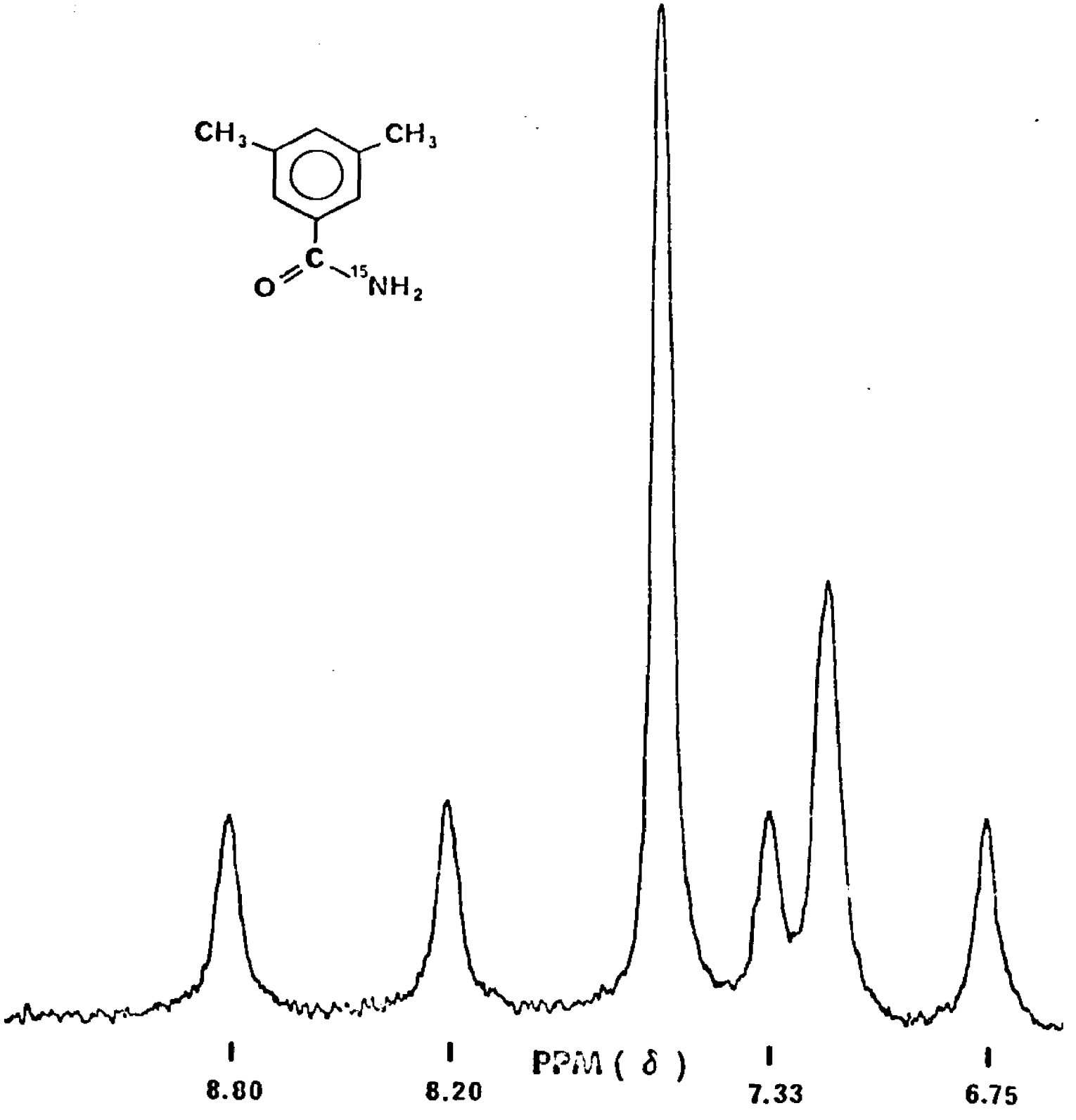


Figure XI. 60 MHz pmr spectrum of ^{15}N-3,5-dimethylbenzamide in DMSO at +10°C.

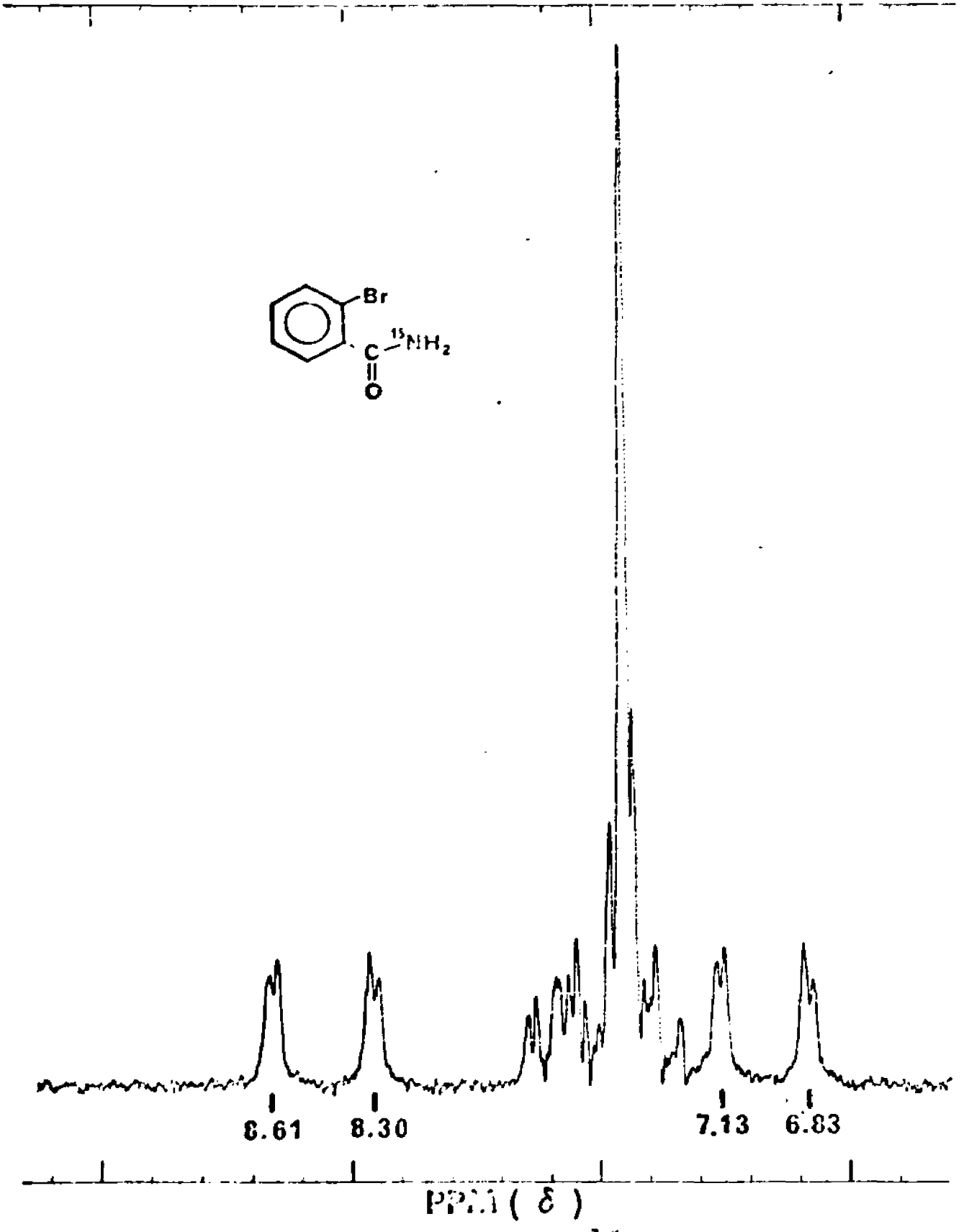


Figure XII. 60 MHz pmr spectrum of ^{15}N-o-bromobenzamide in DMSO at +10°C.

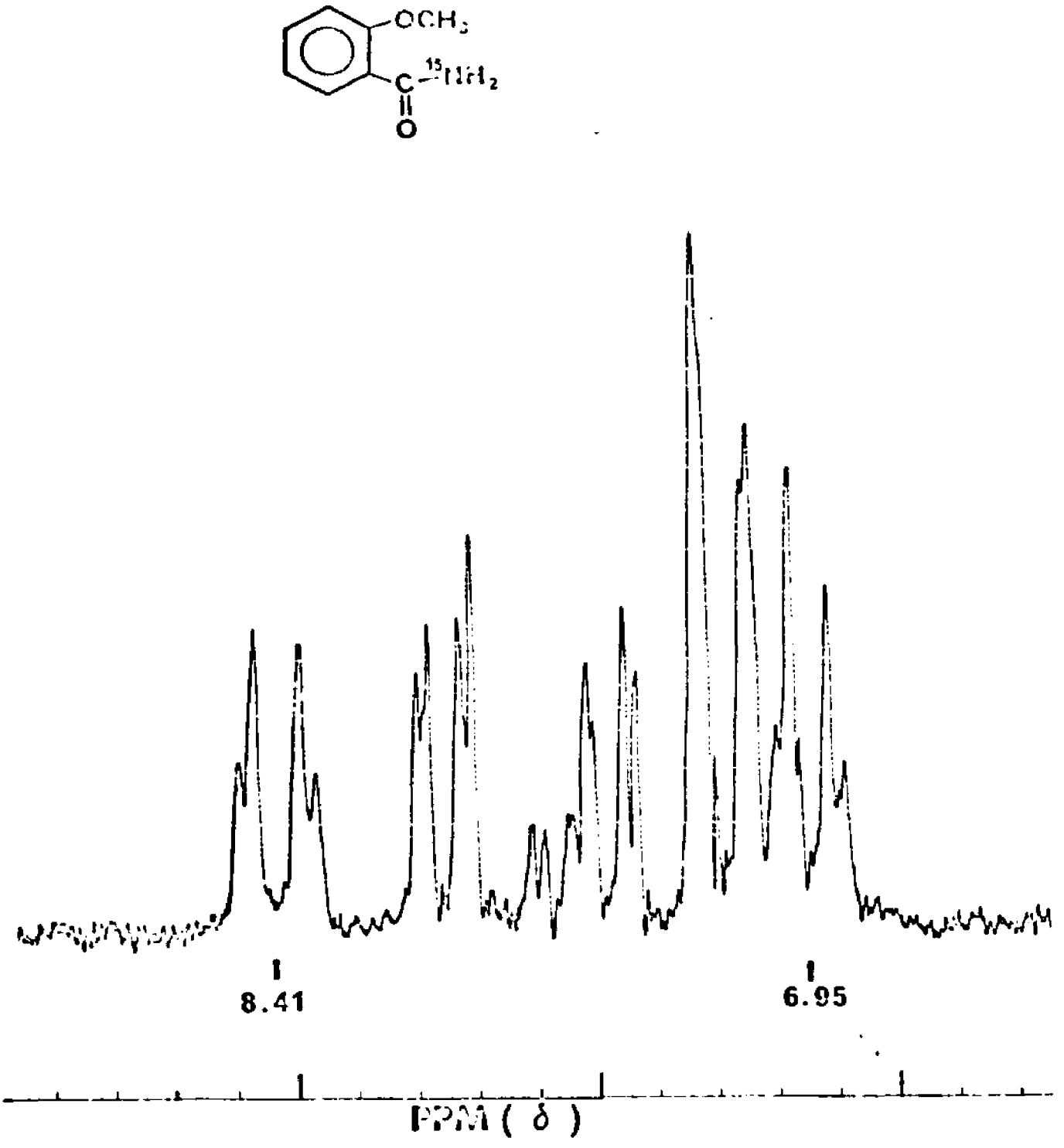
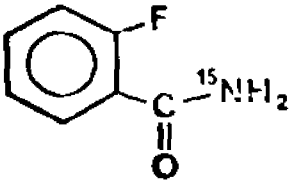


Figure XIII. 60 MHz pmr spectrum of ^{15}N-o-methoxybenzamide in DMSO at +10°C.



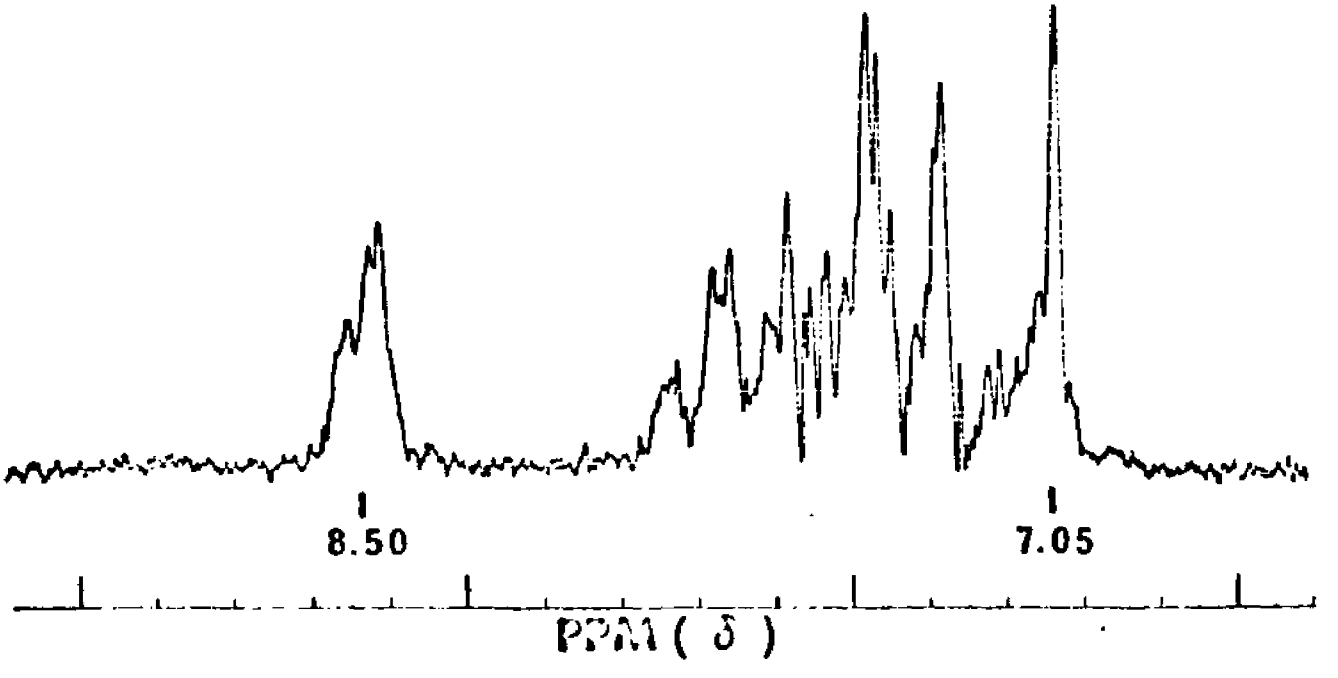


Figure XIV. 60 MHz pmr spectrum of ^{15}N-o-fluorobenzamide in DMSO at +10°C.

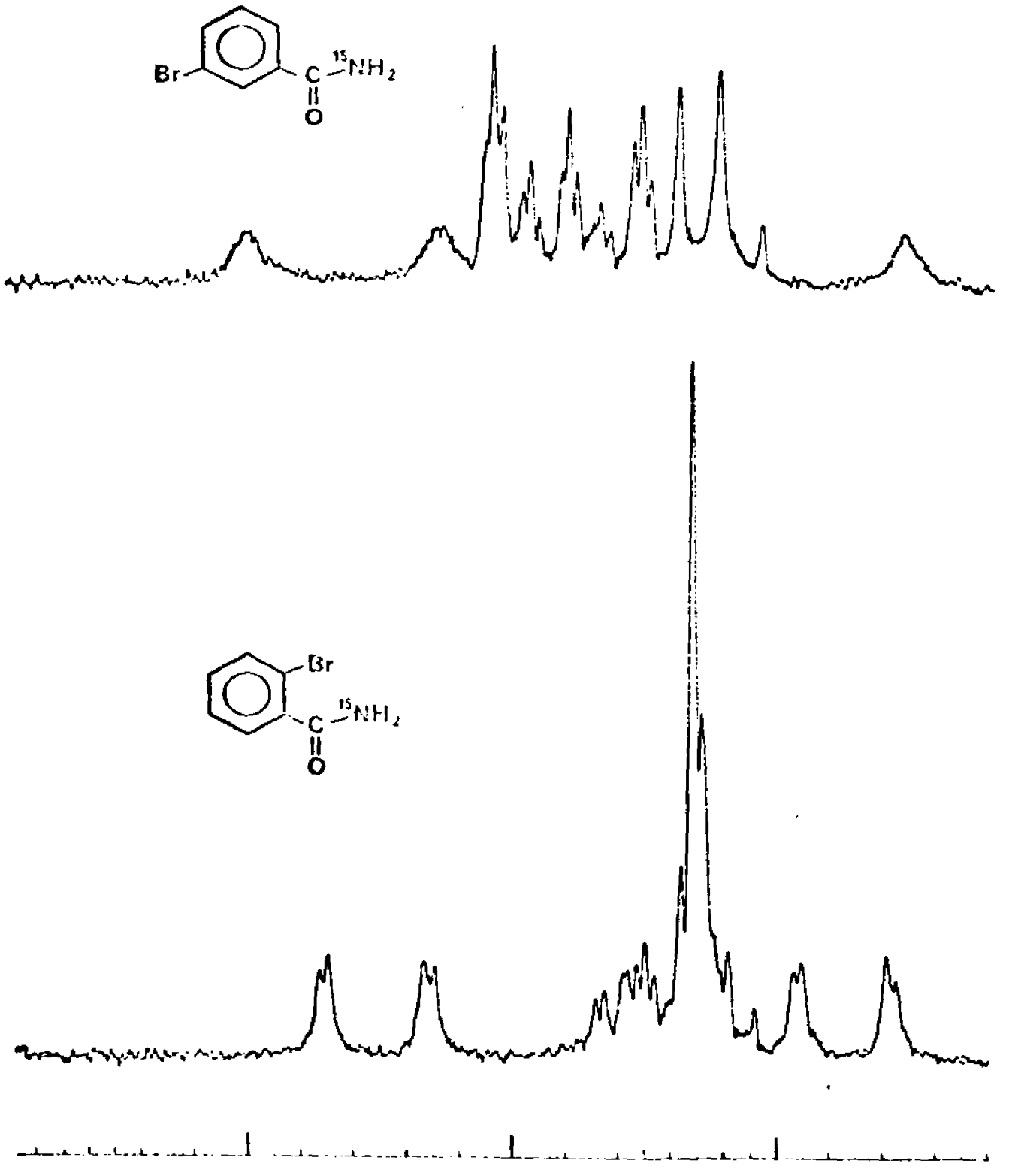
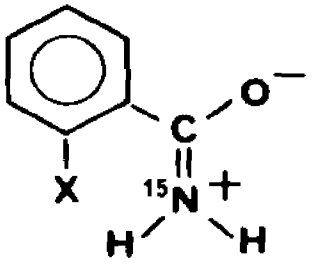


Figure XV. 60 MHz pmr spectra of ^{15}N-o- and p-bromobenzamide in DMSO at ca. +35°C.

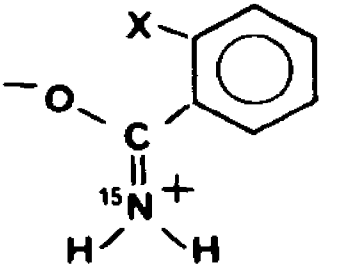
It can be seen that, at probe temperature (ca. +35°C), the amino proton resonances of the ortho-substituted ^{15}N-benzamide are much better resolved than those of the corresponding meta isomer.

The preceding observations may be reasonably explained in terms of the following model: In meta- and para-[88] substituted ^{15}N-benzamides, cross-conjugation between the benzene π-network and the N-C=O moiety results in insufficient double bond character in the central C-N amide bond at room temperature to fully resolve the amino proton resonances. However, in ortho-substituted ^{15}N-benzamides, non-bonded interactions involving the ortho substituent force the benzene ring out of the N-C=O plane. The resultant decrease in orbital overlap between the π-systems of the benzene ring and the carbonyl group tends to enhance the double bond character of the central C-N amide linkage and, consequently, leads to well resolved amino proton resonances at room temperature.

The extent to which the benzene ring is forced out of the N-C=O plane is determined by the severity of the non-bonded interactions the ortho substituent experiences. Of the two limiting orientations the ortho substituent can assume, the position next to the anti amino proton (XVIIIa) is preferred over that next to the carbonyl oxygen atom (XVIIIb). This preference is indicated by the trend of the amino proton splitting patterns shown in Figures XII-XIV, whereby the increasing proximity of the ortho substituent ($F > OCH_3 > Cl$, Br,



(XVIIIa)



(XVIIIb)

CF_3, and NO_2) to the anti amino proton results in lone pair shielding of this proton approximating that experienced by the amino proton adjacent to the electron-rich carbonyl oxygen atom and leads to increasingly greater deviations from first-order splitting in the amino proton resonances.

Apparently, in ortho-substituted primary benzamides, lone pair - lone pair repulsions between the ortho substituent and the carbonyl oxygen atom are more severe than steric repulsions between the ortho substituent and the anti amino proton, in contrast to the situation that exists in ortho-substituted N,N-dibenzylbenzamides (XVII)[116] where the ortho substituent favors the position adjacent to the carbonyl oxygen atom over that adjacent to the anti N-methylene protons. Finally, lone pair - lone pair repulsions between the ortho substituent and the carbonyl oxygen atom in ortho-substituted primary benzamides are severe enough to cause restricted rotation about the aryl - carbonyl bond.

Substituent effects on ^{15}N-chemical shifts :

In light of reported substituent effects, or lack thereof, on ^{15}N-H coupling in ring-substituted anilines[33,98] and related aniline derivatives,[34] it seems reasonable to inquire to what extent ^{15}N-chemical shifts in these systems are dependent upon the nature of the ring substituent. The ^{15}N-chemical shifts subsequently presented were obtained by $^{1}H\{^{15}N\}$ double resonance techniques and, in each series, are expressed in ppm relative to the unsubstituted parent compound.

Ring-substituted anilines

Although amino proton chemical shifts in ring-substituted anilines have been the subject of extensive investigation,[119] there has been a dearth of information regarding nitrogen chemical shifts in this system. A summary of nitrogen-15 and amino proton chemical shifts in a series of meta- and para-[88] substituted anilines is presented in Table XII.

An examination of Table XII reveals that whereas the range of amino proton chemical shifts is ca. 2 ppm, the corresponding range of ^{15}N-chemical shifts is ca. 26 ppm. Qualitatively, this observation is consistent with the dominant role diamagnetic and paramagnetic shielding effects play in determining ^{1}H and ^{15}N chemical shifts, respectively. In com-

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(119) H. Suhr, Z. Elektrochem., 66, 466 (1962); L. K. Dyall, Aust. J. Chem., 17, 419 (1964); T. Yonemoto, W. F. Reynolds, H. M. Hutton, and T. Schaefer, Can. J. Chem., 43, 2668 (1965).

Table XII. Nitrogen-15 and Amino Proton Chemical Shifts in meta- and para-Substituted Anilines.[a]

Substituent	Nitrogen-15[b]	NH_2[c]	$\Delta\nu$, ppm[d] ^{15}N	NH_2
4-NO_2	6,080,029.0	6.63	-20.0	-1.83
3,5-$(Me)_2$, 4-NO_2	6,079,966.0	5.84	- 9.5	-1.04
3-NO_2	6,079,938.5	5.80	- 4.9	-1.00
3-CF_3	6,079,925.5	5.52	- 2.8	-0.72
3-Cl	6,079,924.0	5.30	- 2.5	-0.50
3-Br	6,079,923.0	5.30	- 2.3	-0.50
3-I	6,079,919.5	5.20	- 1.8	-0.40
4-I	6,079,917.5	5.20	- 1.4	-0.40
4-Br	6,079,915.0	5.15	- 1.0	-0.35
3-OMe	6,079,913.0	4.97	- 0.7	-0.17
4-Cl	6,079,911.0	5.15	- 0.3	-0.35
3,5-$(OMe)_2$	6,079,911.0	5.00	- 0.3	-0.20
H	6,079,909.0	4.80	0.0	0.00
3-Me	6,079,904.0	4.83	+ 0.8	-0.03
3,5-$(Me)_2$	6,079,901.5	4.73	+ 1.3	+0.07
4-Me	6,079,893.0	4.70	+ 2.7	+0.10
4-OMe	6,079,874.0	4.48	+ 5.8	+0.32

[a] Measurements were made on ca. 1.0 molal DMSO solutions. [b] Chemical shift values are expressed in Hz relative to TMS at 60 MHz. [c] Chemical shift values are expressed in ppm (δ) relative to TMS. [d] Substituent chemical shifts are expressed in ppm relative to aniline-^{15}N.

parison to the overall range of nitrogen chemical shifts (ca. 1000 ppm) however, the 26 ppm range of aniline ^{15}N-chemical shift values is quite small and could conceivably arise from diamagnetic, rather than paramagnetic, effects.[120] Indeed, nitrogen chemical shifts in ring-substituted nitrobenzenes have been explained in terms of inductive, rather than π-electron conjugative, effects.[121]

In order to better understand the nature of the substituent effect on the ^{15}N-chemical shift in the aniline series, the set of ^{15}N-chemical shift values was plotted against the corresponding set of amino proton chemical shifts. It can be seen from the least squares plot of the data, shown in Figure XVI, that a fairly good linear relationship exists between the two sets of shift values. Hence, those factors which determine amino proton chemical shifts in ring-substituted anilines also play a significant role in determining the ^{15}N-amino nitrogen chemical shifts.

Since amino proton chemical shifts in ring-substituted anilines have been correlated with Hammett substituent constants[108] and, more recently, with calculated values of the π-electron density at the amino nitrogen atom,[122] it seems

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(120) R. Grinter and J. Mason, J. Chem. Soc. (A), 2196 (1970); L. O. Andersson, J. Mason, and W. van Bronswyk, ibid, 296 (1970); A. J. Sadlej, Org. Magn. Resonance, 2, 63 (1970).

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

(122) B. M. Lynch, Tetrahedron Lett., 1357 (1969).

NITROGEN-15 CHEMICAL SHIFT, ppm
-30
-20
-10
0
+10
AMINO PROTON CHEMICAL SHIFT, ppm

reasonable to interpret the observed substituent effect on the ^{15}N-chemical shift in terms of the ability of the ring-substituent to alter the π-electron density at the amino nitrogen atom. Thus, the downfield shift caused by electron withdrawing substituents is due to an increased p-π interaction between the nitrogen lone pair and the aromatic π-network which leads to decreased π-electron density at the amino nitrogen atom.

This view is consistent with the nitrogen chemical shift studies of Witanowski and Januszewski[2] on conjugated amines and with the conclusions reached from a consideration of one-bond ^{15}N-H coupling in this system. Inasmuch as σ_p is, in part, dependent upon nitrogen conjugation, the ^{15}N-chemical shifts in the meta- and para-substituted anilines are apparently determined by paramagnetic effects.

A summary of nitrogen-15 and amino proton chemical shifts in a series of ortho-substituted anilines is presented in Table XIII. It can be seen that the substituent effect on ^{15}N-chemical shifts in the ortho series is qualitatively similar to that found in the meta and para series of anilines.

N-Benzylideneanilines and Quinolines

To the extent that substituent π-electron conjugative effects play a significant role in determining nitrogen chemical shifts in systems in which the nitrogen atom is part of a conjugated π-network, the magnitude of the substituent effect should depend upon the nature of the π-system. That

Table XIII. Nitrogen-15 and Amino Proton Chemical Shifts in <u>ortho</u>-Substituted Anilines.[a]

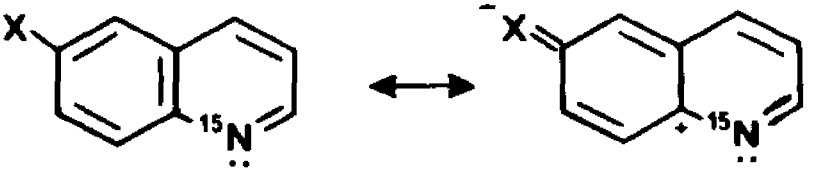
Substituent	Nitrogen-15[b]	ν NH_2[c]	$\Delta\nu$, ppm[d] ^{15}N	NH_2
2-NO_2, 4-Cl	9,120,243.8	7.08	-16.93	-2.76
2-NO_2	9,120,231.9	6.96	-15.63	-2.64
2-Cl, 4-NO_2	9,120,228.2	6.20	-15.22	-1.88
2,4,6-$(Br)_3$	9,120,195.3	5.23	-11.61	-0.91
2-COPh	9,120,188.9	6.81	-10.91	-2.49
2-Br	9,120,127.7	4.81	- 4.20	-0.49
2-CF_3	9,120,107.7	5.05	- 2.01	-0.73
2-H	9,120,089.4	4.32	0.00	0.00
2-OCH_3	9,119,994.4	4.27	+10.42	+0.05

[a] Measurements were made on ca. 1.0 molal acetone-h_6 solutions. [b] Nitrogen-15 chemical shifts were obtained from the INDOR spectra and are expressed in Hz relative to acetone-h_6 at a lock frequency of 89,999,809.7 ± 0.2 Hz. Nitrogen-15 chemical shifts are accurate to ±0.5 Hz. [c] Proton chemical shifts are expressed in ppm (δ) relative to TMS. [d] Substituent chemical shifts are expressed in ppm relative to aniline-^{15}N.

this is clearly the case is evident from an examination of Table XIV, in which a summary of ^{15}N-chemical shifts in a series of ring-substituted N-benzylideneanilines and quinolines is presented.

Although ^{15}N-chemical shifts in the imine series are substituent dependent, ^{15}N-chemical shifts in the quinoline series are relatively unaffected by the nature of the ring substituent. The difference in the order of magnitude of the substituent effect in the two series may be rationalized in terms of the ability of the ring substituent to conjugate effectively with the ^{15}N-atom.

In the quinoline series, direct π-electron conjugative effects between the ring substituent and the ^{15}N-atom are not possible (XIX). Thus, the ca. 3 ppm range of ^{15}N-chemical



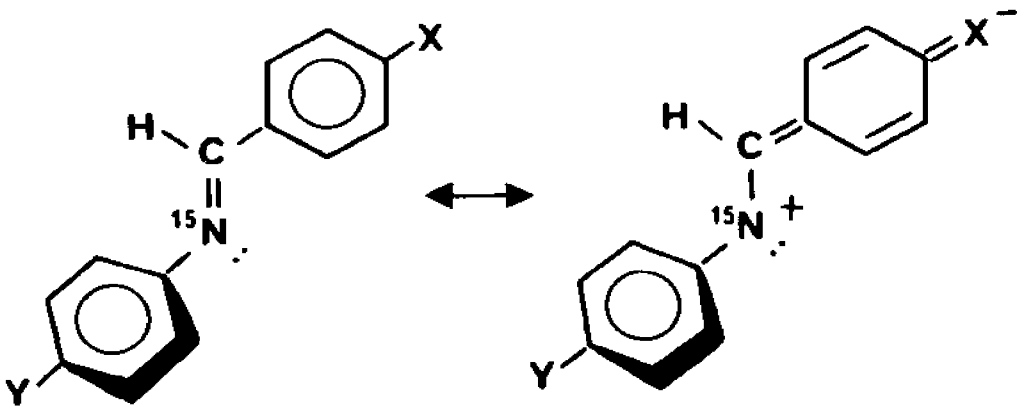
(XIX)

shifts is determined primarily by substituent inductive effects. In the imine series however, the benzal phenyl ring substituent may directly alter the π-electron density at the imino nitrogen atom (XX). It is interesting to note that benzal phenyl ring substituents have a more pronounced effect on the ^{15}N-chemical shift than anilino phenyl ring sub-

Table XIV. Relative Nitrogen-15 Chemical Shifts[a] in Ring-Substituted Quinolines and N-Benzylideneanilines.

Compound	$\Delta\nu_{^{15}N}$
(XIX) X = CH_3	+ 1.30
(XIX) X = H	0.00
(XIX) X = NO_2	- 2.20
(XX) X = CH_3, Y = H	+ 3.68
(XX) X = H , Y = CH_3	+ 1.02
(XX) X = H , Y = H	0.00
(XX) X = Cl , Y = H	- 1.72
(XX) X = NO_2, Y = H	-13.62

[a] Substituent chemical shifts are expressed in ppm relative to the unsubstituted parent compound in each series.



(XX)

stituents. This observation is consistent with recent reports[123] which indicate that the anilino phenyl ring is not coplanar with the benzalamino π-system.

(123) K. Tabei and E. Saito, Bull. Chem. Soc. Jap., 42, 1440 (1969); M. A. El-Bayoumi, M. El-Aasser, and F. Abdel-Halim, J. Amer. Chem. Soc., 93, 586 (1971).

EXPERIMENTAL

Methods and Materials

With the exception of the temperature-dependent nmr spectra shown in Figures IX and X, which were obtained using a Jeolco Model JNM-C-60 HL nmr spectrometer, the nmr spectra presented in Parts I and II were obtained using a Varian Associates Model A-60 nmr spectrometer equipped with a variable-temperature probe and a V-6040 temperature controller.

The ^{15}N-chemical shifts presented in Table XII were obtained by the "spin-tickling" technique using a Varian Associates Model HR-60 nmr spectrometer equipped with a General Radio Model 1164-A frequency synthesizer. This technique requires that the ^{15}N-decoupling frequency be fixed while the ^{1}H-region is swept. By properly adjusting the power to the decoupling channel, the signal(s) of the proton(s) coupled to the ^{15}N-nucleus will be perturbed only when the decoupling frequency corresponds to the ^{15}N-resonance frequency. The assistance of Dr. E. D. Becker of the National Institutes of Health in performing this experiment is gratefully acknowledged.

The ^{15}N-chemical shifts presented in Table XIII were obtained by the INDOR method using a Bruker HFX-90 nmr spectrometer. This technique requires that the resonance frequency of the proton(s) coupled to the ^{15}N-nucleus be fixed while the ^{15}N-region is swept. The result is an ^{15}N-nmr spectrum from which the ^{15}N-chemical shift may be measured. Since the reference lock signal (internal lock system) of the

Bruker HFX-90 nmr spectrometer is modulated at ca. 4.22 KHz, it is possible to obtain ^{15}N-chemical shift values relative to the upper or lower side band of the lock signal instead of the center band. Thus, in order to maintain the consistency of a series of ^{15}N-shift values, care must be taken to lock on the same band of the reference signal for each sample in the series. In Table XIII, for example, all ^{15}N-chemical shifts are referenced against the <u>center</u> band of acetone-h_6 at a lock frequency of 89,999,809.7 ± 0.2 Hz.

The relative ^{15}N-chemical shifts presented in Table XIV were obtained by the "spin-tickling" technique using a Bruker HFX-90 nmr spectrometer. Because a frequency counter capable of measuring frequencies in both the ^{1}H and ^{15}N regions of the spectrum was not available at the time this experiment was performed, it was not possible to measure ^{15}N-chemical shifts referenced against a proton standard. The data in Table XIV are consequently presented as substituent chemical shifts only. The assistance of Mr. Jack Landis in teaching this author the operation of the Bruker HFX-90 nmr spectrometer is gratefully acknowledged.

Melting points were taken on a Thomas-Hoover melting point apparatus. Melting points and boiling points are uncorrected. Commercially available starting materials were used without further purification. All nmr solvents were obtained from Stohler Isotope Chemicals, Incorporated. $HFSO_3$ was obtained from Diaprep Incorporated. Potassium nitrite (99.1 atom % ^{15}N) was obtained from Ateledyne Corporation.

Sodium nitrite (99.0 atom % ^{15}N) was obtained from Isomet, Incorporated. Ammonium chloride (99.3 atom % ^{15}N), ammonium acetate (97.5 atom % ^{15}N), aniline (98.8 atom % ^{15}N), and *p*-nitroaniline (48.6 atom % ^{15}N) were obtained from the Junta de Energia Nuclear, Madrid. Elemental analyses were performed by Galbraith Laboratories, Inc. and Schwarzkopf Microanalytical Laboratory.

Preparation of N-Nitroso-O,N-Dialkylhydroxylamines-(^{15}N-Nitroso) :

Ethyl N-benzyloxycarbamate. Ethyl N-benzyloxycarbamate was prepared by a modification of the procedure described by Fuller and King.[124] O-Benzylhydroxylamine hydrochloride (6.40 g, 0.040 mol) was added to a solution of sodium carbonate (6.36 g, 0.060 mol) in 50 ml of water. Ethyl chloroformate (4.30 g, 0.040 mol) was then slowly added to the vigorously stirred solution, and after three hours of continued stirring at room temperature, the reaction mixture was acidified with 6N HCl and was extracted with ether. The extract was dried over anhydrous sodium sulfate followed by removal of the solvent at reduced pressure to give 6.80 g of a colorless oil. Distillation of the oil yielded 4.80 g (0.024 mol) of product, bp 131°-132°C (1.2 mm), lit.[125] bp 126°-128°C (0.5 mm); nmr ($CDCl_3$), δ 1.20 (t, 3, J = 7.0 Hz), δ 4.12 (q, 2, J = 7.0 Hz), δ 4.82 (s, 2, CH_2), δ 7.35 (s, 5, ArH), δ 8.20 (broad s, 1, NH).

Ethyl N-benzyloxy-N-methylcarbamate. Ethyl N-benzyloxy-N-methylcarbamate was prepared by a modification of the procedure described by Jones and Fleck.[126] Ethyl N-benzyloxycarbamate (3.90 g, 0.020 mol) was added to a solution of

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(124) A. Fuller and H. King, J. Chem. Soc., 963 (1947).
(125) B. Nicolaus, G. Pagani, and E. Testa, Helv. Chim. Acta, 45, 1381 (1962).
(126) L. W. Jones and E. E. Fleck, J. Amer. Chem. Soc., 50, 2024 (1928).

potassium hydroxide (1.15 g, 0.020 mol) in 40 ml of absolute ethanol. The stirred solution was then slowly treated with methyl iodide (2.84 g, 0.020 mol) resulting in an immediate precipitate of potassium iodide. After the reaction mixture was stirred overnight at room temperature, it was heated under reflux for two hours, cooled, and filtered. Concentration of the filtrate at reduced pressure gave a viscous, green oil in which a pale yellow solid was suspended. The concentrate was washed with water to dissolve the suspended solid and was then extracted with ether. Subsequent drying of the ether extract over anhydrous sodium sulfate for one hour followed by removal of the ether at reduced pressure gave a light green oil which was distilled to give 3.10 g (0.015 mol) of product, bp 110°-112°C (1.0-1.1 mm), lit.[125] bp 97°-98°C (0.6 mm); nmr ($CDCl_3$), δ 1.25 (t, 3, J = 7.0 Hz), δ 3.05 (s, 3, N-CH_3), δ 4.20 (q, 2, J = 7.0 Hz), δ 4.85 (s, 2, CH_2), δ 7.40 (s, 5, ArH).

N-Methyl-O-benzylhydroxylamine. Ethyl N-benzyloxy-N-methylcarbamate (8.60 g, 0.040 mol) was added to a solution of sodium hydroxide (6.40 g, 0.160 mol) in 60 ml of 50% aqueous ethanol. After the reaction mixture was heated under reflux for three hours, it was cooled to room temperature and diluted with a saturated aqueous salt solution. Subsequent extraction of the diluted reaction mixture with ether, drying of the extract over anhydrous sodium sulfate, and removal of the ether at reduced pressure gave 5.20 g of a light green

oil. Distillation of the oil yielded 4.00 g (0.029 mol) of product, bp 59°-60°C (1.25-1.30 mm), lit.[125] bp 94°-95°C (15 mm); nmr ($CDCl_3$), δ 2.68 (s, 3, N-CH_3), δ 4.68 (s, 2, O-CH_2), δ 5.10 (broad s, 1, NH), δ 7.31 (s, 5, ArH).

N-Nitroso-N-methyl-O-benzylhydroxylamine-(^{15}N-nitroso). To a suspension of N-methyl-O-benzylhydroxylamine (0.1350 g, 0.98 mmol) in 2 ml of water, 0.10 ml (1.2 mmol) of conc. hydrochloric acid was added. The resulting solution was cooled to 0°C and treated with a solution of potassium nitrite-^{15}N (0.0860 g, 1.00 mmol, 99.1 atom % ^{15}N) in 1 ml of water over a fifteen minute period. The reaction mixture was stirred at 0°C for an additional fifteen minutes before the yellow organic layer was extracted with 4-5 ml of ether. After drying over anhydrous sodium sulfate for fifteen minutes, the extract was transferred to a pre-weighed centrifuge cone where the ether was removed by gently blowing a stream of nitrogen into the cone. The yield of labeled product, a yellow oil, was 0.1290 g (0.77 mmol); nmr ($CDCl_3$), δ 3.50 (broad s, 3, N-CH_3), δ 5.00 (s, 2, O-CH_2), δ 7.35 (s, 5, ArH).
Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.81; H, 6.07; N, 16.88. Found: C, 57.97; H, 6.18; N, 16.70.

Ethyl N-benzyloxy-N-ethylcarbamate. The procedure for the preparation of ethyl N-benzyloxy-N-methylcarbamate was followed. From ethyl N-benzyloxycarbamate (6.83 g, 0.035 mol), ethyl iodide (5.46 g, 0.035 mol), and potassium hydroxide (2.02 g, 0.036 mol) there was obtained 6.40 g of

crude product, a light green oil. Distillation of the oil yielded 4.80 g (0.021 mol) of product, bp 117°-119°C (1.2-1.4 mm); nmr ($CDCl_3$), δ 1.20 (q, 6, J = 7.0 Hz), δ 3.50 (q, 2, J = 7.0 Hz), δ 4.20 (q, 2, J = 7.0 Hz), δ 4.86 (s, 2, CH_2), δ 7.40 (s, 5, ArH).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.54; H, 7.69; N, 6.27. Found: C, 64.32; H, 7.72; N, 6.45.

N-Ethyl-O-benzylhydroxylamine. The procedure for the preparation of N-methyl-O-benzylhydroxylamine was followed. From ethyl N-benzyloxy-N-ethylcarbamate (4.46 g, 0.020 mol) and sodium hydroxide (3.20 g, 0.080 mol) there was obtained 2.60 g (0.017 mol) of product, bp 63°-64°C (1.6 mm), lit.[127] bp 135°C (70 mm); nmr ($CDCl_3$), δ 1.08 (t, 3, J = 7.0 Hz), δ 2.90 (q, 2, J = 7.0 Hz), δ 4.70 (s, 2, O-CH_2), δ 5.16 (s, 1, NH), δ 7.38 (s, 5, ArH).

N-Nitroso-N-ethyl-O-benzylhydroxylamine-(^{15}N-nitroso). The procedure for the preparation of N-nitroso-N-methyl-O-benzylhydroxylamine-(^{15}N-nitroso) was followed. From N-ethyl-O-benzylhydroxylamine (0.1560 g, 1.03 mmol), potassium nitrite-^{15}N (0.0930 g, 1.08 mmol, 99.1 atom % ^{15}N), and conc. hydrochloric acid (0.10 ml, 1.2 mmol) there was obtained 0.1440 g (0.79 mmol) of labeled product, a yellow oil; nmr ($CDCl_3$), δ 1.22 (t, 3, J = 7.0 Hz), δ 3.98 (octet, 2, J = 7.0 Hz, J = 2.0 Hz), δ 5.00 (s, 2, O-CH_2), δ 7.36 (s, 5, ArH).

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(127) R. Behrend and K. Leuchs, Ann., 257, 237 (1890).

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.97; H, 6.72; N, 15.54. Found: C, 59.94; H, 6.80; N, 14.94.

Ethyl N-methoxycarbamate. The procedure for the preparation of ethyl N-benzyloxycarbamate was followed. From O-methylhydroxylamine hydrochloride (16.70 g, 0.200 mol), ethyl chloroformate (21.60 g, 0.200 mol), and sodium carbonate (33.00 g, 0.310 mol) there was obtained 20.15 g of a clear, colorless oil. Distillation of the oil yielded 17.55 g (0.147 mol) of product, bp 54°-57°C (0.8-1.0 mm), lit.[128] bp 186°-188°C (760 mm); nmr ($CDCl_3$), δ 1.30 (t, 3, J = 7.0 Hz), δ 3.75 (s, 3, O-CH_3), δ 4.22 (q, 2, J = 7.0 Hz).

Ethyl N-methoxy-N-benzylcarbamate. The procedure for the preparation of ethyl N-benzyloxy-N-methylcarbamate was followed. From ethyl N-methoxycarbamate (11.90 g, 0.100 mol), benzyl chloride (12.65 g, 0.100 mol), and potassium hydroxide (5.60 g, 0.100 mol) there was obtained 15.85 g of a colorless oil. Distillation of the oil yielded 11.40 g (0.054 mol) of product, bp 108°-110°C (1.7-1.8 mm); nmr ($CDCl_3$), δ 1.25 (t, 3, J = 7.0 Hz), δ 3.59 (s, 3, O-CH_3), δ 4.25 (q, 2, J = 7.0 Hz), δ 4.65 (s, 2, N-CH_2), δ 7.35 (s, 5, ArH).

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.13; H, 7.24; N, 6.69. Found: C, 63.03; H, 7.04; N, 7.18.

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(128) L. W. Jones and R. T. Major, J. Amer. Chem. Soc., 52, 677 (1930).

N-Benzyl-O-methylhydroxylamine. The procedure for the preparation of N-methyl-O-benzylhydroxylamine was followed. From ethyl N-methoxy-N-benzylcarbamate (10.45 g, 0.050 mol) and sodium hydroxide (7.00 g, 0.175 mol) there was obtained 6.50 g of a colorless oil. Distillation of the oil yielded 4.15 g (0.030 mol) of product, bp 56°-59°C (1.4-1.6 mm); nmr ($CDCl_3$), δ 3.45 (s, 3, O-CH_3), δ 3.97 (s, 2, N-CH_2), δ 5.00 (broad s, 1, NH), δ 7.32 (s, 5, ArH).

Anal. Calcd for $C_8H_{11}NO$: C, 70.03; H, 8.09; N, 10.21. Found: C, 70.43; H, 8.45; N, 9.71.

N-Nitroso-N-benzyl-O-methylhydroxylamine-(^{15}N-nitroso). The procedure for the preparation of N-nitroso-N-methyl-O-benzylhydroxylamine-(^{15}N-nitroso) was followed. From N-benzyl-O-methylhydroxylamine (0.1334 g, 0.97 mmol), potassium nitrite-^{15}N (0.0878 g, 1.02 mmol, 99.1 atom % ^{15}N), and conc. hydrochloric acid (0.10 ml, 1.2 mmol) there was obtained 0.1430 g (0.85 mmol) of labeled product, a yellow oil; nmr ($CDCl_3$), δ 3.66 (s, 3, O-CH_3), δ 5.22 (d, 2, J = 2.0 Hz), δ 7.35 (s, 5, ArH).

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.81; H, 6.07; N, 16.88. Found: C, 57.71; H, 6.00; N, 16.44.

Ethyl N-methoxy-N-(1-phenylethyl)carbamate. The procedure for the preparation of ethyl N-benzyloxy-N-methylcarbamate was followed. From ethyl N-methoxycarbamate (7.80 g, 0.065 mol), 1-phenylethyl chloride (9.10 g, 0.065 mol), and potassium hydroxide (3.70 g, 0.066 mol) there was obtained

13.00 g of a clear, yellow oil. Distillation of the oil yielded 4.50 g (0.020 mol) of product, bp 107°-108°C (1.2 mm); nmr ($CDCl_3$), δ 1.22 (t, 3, J = 7.0 Hz), δ 1.59 (d, 3, J = 7.0 Hz), δ 3.50 (s, 3, O-CH_3), δ 4.20 (q, 2, J = 7.0 Hz), δ 5.27 (q, 1, J = 7.0 Hz), δ 7.35 (m, 5, ArH).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.54; H, 7.69; N, 6.27. Found: C, 63.91; H, 7.80; N, 5.82.

N-(1-Phenylethyl)-O-methylhydroxylamine. The procedure for the preparation of N-methyl-O-benzylhydroxylamine was followed. From ethyl N-methoxy-N-(1-phenylethyl)carbamate (4.00 g, 0.018 mol) and sodium hydroxide (2.40 g, 0.060 mol) there was obtained 1.85 g of a clear, green oil. Distillation of the oil yielded 1.32 g (0.0087 mol) of product, bp 62°-64°C (1.1 mm); nmr ($CDCl_3$), δ 1.32 (d, 3, J = 7.0 Hz), δ 3.45 (s, 3, O-CH_3), δ 4.13 (q, 1, J = 7.0 Hz), δ 5.40 (broad s, 1, NH), δ 7.32 (s, 5, ArH).

Anal. Calcd for $C_9H_{13}NO$: C, 71.47; H, 8.61; N, 9.26. Found: C, 71.30; H, 8.69; N, 9.83.

N-Nitroso-N-(1-phenylethyl)-O-methylhydroxylamine-(^{15}N-nitroso). The procedure for the preparation of N-nitroso-N-methyl-O-benzylhydroxylamine-(^{15}N-nitroso) was followed. From N-(1-phenylethyl)-O-methylhydroxylamine (0.1580 g, 1.05 mmol), potassium nitrite-^{15}N (0.0970 g, 1.12 mmol, 99.1 atom % ^{15}N), and conc. hydrochloric acid (0.10 ml, 1.2 mmol) there was obtained 0.1705 g (0.94 mmol) of labeled product, a yellow oil; nmr ($CDCl_3$), δ 1.75 (d, 3, J = 7.0 Hz), δ 3.59 (s, 3, O-CH_3),

δ 5.72 (octet, 1, J = 7.0 Hz, J = 1.6 Hz), δ 7.35 (s, 5, ArH). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.97; H, 6.72; N, 15.54. Found: C, 59.96; H, 6.46; N, 15.44.

N-Nitroso-O,N-dimethylhydroxylamine-(^{15}N-nitroso). The procedure described by Boese, Jones, and Major[129] was followed. From O,N-dimethylhydroxylamine hydrochloride (0.1142 g, 1.15 mmol) and potassium nitrite-^{15}N (0.1040 g, 1.16 mmol, 99.1 atom % ^{15}N) there was obtained 0.0900 g (0.99 mmol) of labeled product, a yellow oil; nmr ($CDCl_3$), δ 3.72 (broad s, 3, CH_3), δ 3.87 (broad s, 3, CH_3).

O,N-Dibenzylhydroxylamine. O,N-Dibenzylhydroxylamine was prepared by a modification of the procedure described by Jones and Fleck.[126] To a well stirred solution of ethyl N-hydroxycarbamate (9.35 g, 0.089 mol) and potassium hydroxide (11.00 g, 0.196 mol) in 100 ml of absolute ethanol, 25.00 g (0.197 mol) of benzyl chloride were added. After twenty four hours of stirring at room temperature, the reaction mixture, with potassium chloride in suspension, was heated under reflux for one hour, and then was cooled and filtered. The filtrate was washed with a dilute, aqueous sodium hydroxide solution to remove any unreacted ethyl N-benzyloxycarbamate and ethyl N-hydroxycarbamate. The organic layer was extracted with ether and dried over anhydrous sodium sulfate. Concentration

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(129) A. B. Boese, L. W. Jones, and R. T. Major, ibid, 53, 3530 (1931).

of the extract at reduced pressure yielded 17.95 g of crude ethyl N-benzyloxy-N-benzylcarbamate which was used without further purification in the next step of the synthesis. The crude ester was added to a solution of sodium hydroxide (10.10 g, 0.252 mol) in 80 ml of 50% aqueous ethanol, and the mixture was heated under reflux for two hours. After cooling to room temperature, the reaction mixture was concentrated at reduced pressure, diluted with a saturated aqueous salt solution, and extracted with ether. Subsequent drying of the extract over anhydrous sodium sulfate followed by removal of the ether at reduced pressure gave 13.00 g of an orange oil. Distillation of the oil yielded 1.60 g (0.0075 mol) of O,N-dibenzylhydroxylamine, bp 133°-134°C (1.2 mm), lit.[126] bp 145°-146°C (3.0 mm); nmr ($CDCl_3$), δ 3.98 (s, 2, $N-CH_2$), δ 4.62 (s, 2, $O-CH_2$), δ 5.47 (broad s, 1, NH), δ 7.25 (s, 10, ArH).

N-Nitroso-O,N-dibenzylhydroxylamine-(^{15}N-nitroso). The procedure for the preparation of N-nitroso-N-methyl-O-benzylhydroxylamine-(^{15}N-nitroso) was followed. From O,N-dibenzylhydroxylamine (0.1070 g, 0.502 mmol), potassium nitrite-^{15}N (0.0465 g, 0.539 mmol, 99.1 atom % ^{15}N), and conc. hydrochloric acid (0.05 ml, 0.6 mmol) there was obtained 0.0935 g (0.385 mmol) of labeled product, a creamy-white solid, mp 68°- 72°C, lit.[130] mp 73°-74°C; nmr ($CDCl_3$), δ 4.88 (s, 2,

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(130) R. Behrend and R. Lindner, Ann., 275, 134 (1893).

O-CH_2), δ 5.11 (d, 2, J = 2.0 Hz), δ 7.32 (d, 10, ArH).

N,N-Dibenzylhydroxylamine. N,N-Dibenzylhydroxylamine was prepared by a modification of the procedure described by Jones and Sneed.[131] To a solution of hydroxylamine hydrochloride (14.30 g, 0.206 mol) and benzyl chloride (50.60 g, 0.400 mol) in 200 ml of 70% ethanol, 60.00 g (0.566 mol) of sodium carbonate was added. The well stirred reaction mixture was then heated under reflux for three hours. After cooling, the reaction mixture was diluted with 500 ml of cold water in order to dissolve the inorganic salts present and to precipitate the product from solution. The resulting suspension was suction filtered to give 34.00 g of crude product, a white solid, mp 118°-121°C. Recrystallization from 95% ethanol yielded 23.57 g (0.111 mol) of N,N-dibenzylhydroxylamine, mp 122°-123°C, lit.[132] mp 122°-123°C; nmr ($CDCl_3$), δ 3.59 (s, 4, N-CH_2), δ 7.22 (s, 10, ArH).

N-Benzylbenzaldoxime. N-Benzylbenzaldoxime was prepared by a modification of the procedure described by Cope and Haven.[133] A suspension of N,N-dibenzylhydroxylamine (23.57 g, 0.111 mol) and red mercuric oxide (56.00 g, 0.248 mol) in 200 ml of 75% ether - 25% methylene chloride was stirred at room temperature for twenty four hours. The reaction mixture was then

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(131) L. W. Jones and C. N. Sneed, J. Amer. Chem. Soc., 39, 677 (1917).

(132) E. Muller and H. Metzger, Chem. Ber., 89, 406 (1956).

(133) A. Cope and A. Haven, Jr., J. Amer. Chem. Soc., 72, 4896 (1950).

filtered, and the filtrate was concentrated at reduced pressure to give crude product, mp 75°-78°C. Recrystallization from 95% hexane - 5% acetone yielded 15.00 g (0.071 mol) of N-benzylbenzaldoxime, mp 81°-83°C, lit.[133] mp 81.5°-83.5°C; nmr ($CDCl_3$), δ 4.99 (s, 2, N-CH_2), δ 7.20-7.50 (m, 9, ArH + CH), δ 8.10-8.32 (m, 2, ArH).

N-Benzylhydroxylamine. The procedure described by Jones and Sneed[131] was followed. Concentrated hydrochloric acid (40 ml, 0.48 mol) was added to N-benzylbenzaldoxime (15.00 g, 0.071 mol), and steam was passed through the mixture until no benzaldehyde was detected in the distillate. After concentrating the reaction mixture to ca. 25-30 ml by distilling some of the excess hydrochloric acid, the concentrate was cooled to room temperature and made neutral by the addition of sodium carbonate. The neutral reaction mixture was then filtered. The filtrate was cooled to 0°C and was made alkaline by the addition of more sodium carbonate. A white precipitate formed after the basic filtrate had cooled at 0°C for 1-2 hours. The precipitate was collected and suction air dried to give 4.20 g (0.034 mol) of product, mp 52°-55°C, lit.[133] mp 56°-58°C; nmr ($CDCl_3$), δ 4.83 (s, 2, N-CH_2), δ 6.20 (broad s, 2, NHOH), δ 7.28 (s, 5, ArH).

N-Nitroso-N-benzylhydroxylamine-(^{15}N-nitroso). To a suspension of N-benzylhydroxylamine (0.1875 g, 1.52 mmol) in 3 ml of water, 0.15 ml (1.8 mmol) of conc. hydrochloric acid were added. Addition of a solution of potassium nitrite-^{15}N

(0.1347 g, 1.56 mmol, 99.1 atom % ^{15}N) in 1 ml of water to the cooled (0°C) hydrochloride solution resulted in the formation of a white, crystalline precipitate. After stirring the reaction mixture for thirty minutes, the precipitate was collected, washed with cold water, and suction air dried to yield 0.1272 g (0.83 mmol) of labeled product, mp 76°-78°C, lit.[132] mp 76°-77°C; nmr ($CDCl_3$), δ 5.18 (d, 2, J = 2.6 Hz), δ 7.38 (s, 5, ArH), δ 9.70 (broad s, 1, OH).

Preparation of ^{15}N-enriched Alkyl nitrites :

The following general procedure was used to prepare the labeled alkyl nitrites subsequently described. A solution of conc. sulfuric acid and alkyl alcohol in 1-2 ml of water, cooled to 0°C, was treated over a fifteen minute period with a solution of sodium nitrite-^{15}N in 1-2 ml of water. After an additional fifteen minutes at 0°C, with occasional stirring, the reaction mixture, a green nitrite layer atop a clear aqueous layer, was extracted with ether. The extract was dried over anhydrous, granular sodium sulfate and was then transferred to a pre-weighed centrifuge cone. Removal of the ether by gently blowing a stream of nitrogen into the cone yielded the labeled alkyl nitrite.

Benzyl nitrite-^{15}N. From benzyl alcohol (0.1405 g, 1.30 mmol), conc. sulfuric acid (0.05 ml, 0.9 mmol), and sodium nitrite-^{15}N (0.1260 g, 1.80 mmol, 99.0 atom % ^{15}N) there was obtained 0.0745 g (0.540 mmol) of product, a green oil; nmr ($CDCl_3$), δ 5.65 (d, 2, J = 1.7 Hz), δ 7.32 (s, 5, ArH).

2-Phenylethyl nitrite-^{15}N. From 2-phenylethanol (0.1590 g, 1.30 mmol), conc. sulfuric acid (0.05 ml, 0.9 mmol), and sodium nitrite-^{15}N (0.1260 g, 1.80 mmol, 99.0 atom % ^{15}N) there was obtained 0.1035 g (0.68 mmol) of product, a green oil; nmr ($CDCl_3$), δ 2.92 (t, 2, J = 7.0 Hz), δ 4.83 (sextet, 2, J = 7.0 Hz, J = 1.8 Hz), δ 7.20 (s, 5, ArH).

Anal. Calcd for $C_8H_9NO_2$: C, 63.53; H, 6.01; N, 9.27. Found: C, 63.73; H, 6.27; N, 8.86.

1-Phenylethyl nitrite-^{15}N. From 1-phenylethanol (0.1525 g, 1.25 mmol), conc. sulfuric acid (0.06 ml, 1.1 mmol), and sodium nitrite-^{15}N (0.1400 g, 2.00 mmol, 99.0 atom % ^{15}N) there was obtained 0.0925 g (0.61 mmol) of product, a green oil; nmr (toluene-d_8), δ 1.34 (d, 3, J = 7.0 Hz), δ 6.15 (octet, 1, J = 7.0 Hz, J = 1.8 Hz), δ 7.10 (s, 5, ArH).

1-Phenylpropyl nitrite-^{15}N. From 1-phenylpropanol (0.1700 g, 1.25 mmol), conc. sulfuric acid (0.06 ml, 1.1 mmol), and sodium nitrite-^{15}N (0.1400 g, 2.00 mmol, 99.0 atom % ^{15}N) there was obtained 0.1285 g (0.77 mmol) of product, a green oil; nmr (toluene-d_8), δ 0.75 (t, 3, J = 7.0 Hz), δ 1.80 (quintet, 2, J = 7.0 Hz), δ 6.00 (sextet, 1, J = 7.0 Hz, J = 2.1 Hz), δ 7.10 (s, 5, ArH).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.40; H, 6.72; N, 8.48. Found: C, 65.57; H, 7.06; N, 7.83.

3,3-Dimethyl-1-butyl nitrite-^{15}N. 3,3-Dimethyl-1-butyl nitrite-^{15}N was prepared by a slight modification of the general procedure described previously. A solution of 3,3-di-

methyl-1-butanol (0.1326 g, 1.30 mmol) and conc. sulfuric acid (0.06 ml, 1.1 mmol) in 1 ml of water, at 0°C, was treated over a fifteen minute period with a solution of sodium nitrite-^{15}N (0.1400 g, 2.00 mmol, 99.0 atom % ^{15}N) in 2 ml of water. After an additional fifteen minutes at 0°C, with occasional stirring, the green nitrite layer was carefully drawn off by pipette and transferred to a pre-weighed centrifuge cone containing a minimum amount of anhydrous sodium sulfate. The yield of labeled product was 0.1320 g (1.00 mmol); nmr ($CDCl_3$), δ 1.00 (s, 9, t-butyl), δ 1.65 (t, 2, J = 7.0 Hz), δ 4.71 (sextet, 2, J = 7.0 Hz, J = 1.7 Hz).

Anal. Calcd for $C_6H_{13}NO_2$: C, 54.90; H, 10.01; N, 10.68. Found: C, 55.04; H, 10.19; N, 9.96.

Preparation of ^{15}N-enriched Phenylhydrazones :

Phenylhydrazine-(^{15}N-amino). Phenylhydrazine-(^{15}N-amino) was prepared[134] in the following manner: To a suspension of aniline (0.5580 g, 6.00 mmol) in 1 ml of water, at 0°C, 1.60 ml (19.2 mmol) of conc. hydrochloric acid was added. The resulting solution was then treated over a five minute period with an ice-cold solution of sodium nitrite-^{15}N (0.4350 g, 6.20 mmol, 99.0 atom % ^{15}N) in 3 ml of water. After all of the sodium nitrite-^{15}N had been added, the diazonium salt solution was stirred for an additional five minutes at 0°C before being added, as rapidly as possible, to an ice-cold solution of

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(134) Organic Syntheses, coll. vol. I, 2nd ed., John Wiley and Sons, Inc., New York, 1941, p. 442.

sodium sulfite (3.80 g, 0.030 mol) in 15 ml of water. Upon addition of the diazonium salt solution to the sodium sulfite solution, the reaction mixture turned bright orange-red. The reaction mixture was then gradually heated to a bath temperature of ca. 70°-75°C at which point sufficient conc. hydrochloric acid was added to make the solution acid to litmus. The acidified reaction mixture was heated at 70°-75°C for two hours, after which time, 20 ml of conc. hydrochloric acid was added to the hot solution and heating was discontinued. As the the reaction mixture cooled to room temperature, a crystalline precipitate formed. After cooling the reaction mixture in Dry Ice for five minutes, the suspension was suction filtered. The white crystalline solid so obtained was dissolved in 10 ml of water and the resulting solution was made basic by the addition of sodium hydroxide. Subsequent extraction of the basic reaction mixture with three 10 ml portions of ether, followed by drying of the extract over anhydrous sodium sulfate and removal of the ether at reduced pressure yielded 0.3600 g (3.30 mmol) of phenylhydrazine-(^{15}N-amino); nmr ($CDCl_3$), δ 4.85 (broad s, 3, NH-$^{15}NH_2$), δ 6.50-7.40 (m, 5, ArH).

Acetone phenylhydrazone-^{15}N. A solution of phenylhydrazine-(^{15}N-amino) (0.1430 g, 1.30 mmol) in 5 ml of reagent grade acetone was heated under reflux for two hours, after which time, the excess acetone was removed at reduced pressure to give 0.1675 g (1.12 mmol) of labeled product, a red oil; nmr

(DMSO-d_6), δ 1.80 (d, 3, J = 1.8 Hz), δ 1.93 (d, 3, J = 3.8 Hz), δ 6.50-7.30 (m, 5, ArH), δ 8.37 (broad s, 1, NH).

Pinacolone phenylhydrazone-^{15}N. A solution of phenylhydrazine-(^{15}N-amino) (0.0875 g, 0.800 mmol) and pinacolone (0.0800 g, 0.800 mmol) in 5 ml of absolute ethanol was heated under reflux for three hours, after which time, the solvent was removed at reduced pressure to give 0.1205 g (0.630 mmol) of labeled product, a red oil; nmr (DMSO-d_6), δ 1.06 (s, 9, t-butyl), δ 1.70 (d, 3, J = 1.8 Hz), δ 6.40-7.20 (m, 5, ArH), δ 8.25 (broad s, 1, NH).

Phenylacetaldehyde phenylhydrazone-^{15}N. A solution of phenylhydrazine-(^{15}N-amino) (0.1095 g, 1.00 mmol) and phenylacetaldehyde (0.1200 g, 1.00 mmol) in 6 ml of benzene was heated under reflux for four hours, after which time, the solvent was removed at reduced pressure to give 0.1900 g (0.900 mmol) of labeled product, a viscous red oil; nmr (benzene-d_6), δ 2.89 (q, CH_2, J = 5.2 Hz, J = 2.2 Hz), δ 3.37 (q, CH_2, J = 5.8 Hz, J = 3.6 Hz), δ 6.35 (sextet, CH=^{15}N, J = 5.8 Hz, J = 3.5 Hz), δ 6.50-7.80 (m, 12, ArH + NH + CH=^{15}N).

Preparation of Benzoyl chlorides :

The following general procedure was used to prepare the several meta and ortho substituted benzoyl chlorides described below. After the appropriately substituted benzoic acid was heated under reflux with an excess of thionyl chloride for two hours, the bath temperature was raised slightly and most of the excess thionyl chloride was removed by distillation.

Any remaining thionyl chloride was removed at reduced pressure. The residue was then distilled under vacuum or was recrystallized.

m-Anisoyl chloride. From m-anisic acid (15.25 g, 0.100 mol) and thionyl chloride (35.70 g, 0.300 mol) there was obtained 13.40 g (0.078 mol) of product, bp 65°-66°C (0.2 mm), lit.[135] bp 243°-244°C (760 mm); nmr ($CDCl_3$), δ 3.82 (s, 3, O-CH_3), δ 7.10-7.82 (m, 4, ArH).

3,5-Dimethylbenzoyl chloride. From 3,5-dimethylbenzoic acid (15.20 g, 0.100 mol) and thionyl chloride (35.70 g, 0.300 mol) there was obtained 15.15 g (0.090 mol) of product, bp 61°-63°C (0.2-0.3 mm), lit.[136] bp 109°C (10 mm); nmr ($CDCl_3$), δ 2.28 (s, 6, CH_3), δ 7.18 (broad s, 1, ArH), δ 7.58 (broad s, 2, ArH).

3,5-Dimethoxybenzoyl chloride. From 3,5-dimethoxybenzoic acid (12.80 g, 0.070 mol) and thionyl chloride (25.00 g, 0.210 mol) there was obtained 8.70 g (0.044 mol) of product, bp 98°-99°C (0.25-0.30 mm), lit.[137] bp 157°-158°C (16 mm); nmr ($CDCl_3$), δ 3.75 (s, 6, O-CH_3), δ 6.63 (t, 1, ArH), δ 7.10 (d, 2, ArH).

m-Iodobenzoyl chloride. From m-iodobenzoic acid (12.40 g, 0.050 mol) and thionyl chloride (17.85 g, 0.150 mol) there

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(135) F. Ullmann and I. Goldberg, Ber., 35, 2813 (1902).
(136) M. Weiler, ibid, 32, 1910 (1899).
(137) F. Mauthner, J. Prakt. Chem., 87, 405 (1913).

was obtained 10.54 g (0.039 mol) of product, bp 75°-76°C (0.20-0.25 mm), lit.[138] bp 159°-160°C (23 mm).

o-Nitrobenzoyl chloride. From o-nitrobenzoic acid (8.35 g, 0.050 mol) and thionyl chloride (17.85 g, 0.150 mol) there was obtained 8.33 g (0.045 mol) of product, bp 95°C (0.25 mm), lit.[139] bp (Warning!) 120°C (2 mm).

o-Benzoylbenzoyl chloride. From o-benzoylbenzoic acid (22.65 g, 0.100 mol) and thionyl chloride (35.70 g, 0.300 mol) there was obtained, after recrystallization from anhydrous ether, 17.10 g (0.070 mol) of product, mp 65°-69°C, lit.[140] mp 70°C.

2-Nitro-4-chlorobenzoyl chloride. From 2-nitro-4-chlorobenzoic acid (2.00 g, 0.010 mol) and thionyl chloride (3.57 g, 0.030 mol) there was obtained 1.90 g (0.0087 mol) of product, mp 35°-37°C, lit.[141] mp 34°C.

2-Chloro-4-nitrobenzoyl chloride. From 2-chloro-4-nitrobenzoic acid (4.05 g, 0.020 mol) and thionyl chloride (7.15 g, 0.060 mol) there was obtained 3.52 g (0.016 mol) of product, bp 85°C (0.05 mm), lit.[142] bp 182°C (34 mm).

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(138) J. B. Cohen and H. S. Raper, J. Chem. Soc. (Trans.), 85, 1273 (1904).

(139) N. C. Cook and F. C. Whitmore, Chem. Eng. News, 23, 2394 (1945). A danger of explosion during the distillation of o-nitrobenzoyl chloride is reported.

(140) A. Haller and A. Guyot, Bull. Soc. Chim. Fr., 25, 54 (1901).

(141) J. B. Cohen and H. P. Armes, J. Chem. Soc. (Trans.), 89, 458 (1906).

(142) C. V. Gheorghiu, L. Stoiescu-Crivetz, and L. Mandasescu, Acad. Rep. Populare Romine, Studii Cercetari Chim., 4, 39 (1956); Chem. Abstr., 51, 1891h (1957).

Preparation of ring-substituted ^{15}N-Benzamides :

The following general procedure was adopted for the preparation of the ring-substituted ^{15}N-benzamides described below. A 25 ml three-necked flask was fitted with a gas inlet adapter, a dropping funnel, and a reflux condenser. In order to trap moisture, two sodium hydroxide drying tubes, joined by an adapter, were connected to the reflux condenser at one end and, by means of a female joint and tygon tubing, to a trap at the other end. A constant flow of nitrogen gas through the system served to carry the $^{15}NH_3$, generated in the reaction flask, into the trap containing an ethereal solution of the ring-substituted benzoyl chloride at Dry Ice - acetone temperatures. The labeled ammonia was liberated by adding, dropwise over a fifteen minute period, an aqueous solution of ammonium chloride-^{15}N (99.3 atom % ^{15}N) to a preheated aqueous solution of sodium hydroxide (bath temperature 95°-100°C). After the reaction flask was heated for 4-5 hours, the oil bath was removed and the nitrogen flow was discontinued. The trap and its contents were left in the Dry Ice - acetone bath overnight before being brought to room temperature the following morning. The resulting suspension was filtered through fluted filter paper, and the ammonium chloride-^{15}N that remained in the filter paper was washed with acetone. Concentration of the combined ether - acetone filtrate at reduced pressure yielded the crude ^{15}N-benzamide. The crude product was washed with hexane to remove any unre-

acted acid chloride and was then suction air dried. Most of the ^{15}N-benzamides described below were of acceptable purity at this stage, however, where necessary, a recrystallization was performed. The ammonium chloride-^{15}N recovered from the filter paper was re-used.

m-Anisamide-^{15}N. From m-anisoyl chloride (0.4265 g, 2.50 mmol), ammonium chloride-^{15}N (0.2870 g, 5.26 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.2400 g, 6.00 mmol) there was obtained 0.2510 g (1.65 mmol) of labeled product, mp 131°-133°C, lit.[143] mp 134°C.

m-Toluamide-^{15}N. From m-toluyl chloride (0.3892 g, 2.50 mmol), ammonium chloride-^{15}N (0.2890 g, 5.30 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.2320 g, 5.80 mmol) there was obtained 0.2580 g (1.90 mmol) of labeled product, mp 91°-93°C, lit.[144] mp 96°C.

m-Chlorobenzamide-^{15}N. From m-chlorobenzoyl chloride (0.4375 g, 2.50 mmol), ammonium chloride-^{15}N (0.2890 g, 5.30 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.2320 g, 5.80 mmol) there was obtained 0.3030 g (1.94 mmol) of labeled product, mp 129°-131°C, lit.[145] mp 133°-134°C.

m-Bromobenzamide-^{15}N. From m-bromobenzoyl chloride (0.5475 g, 2.50 mmol), ammonium chloride-^{15}N (0.2890 g, 5.30 mmol, 99.3

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(143) O. L. Brady and F. P. Dunn, J. Chem. Soc. (Trans.), 123, 1802 (1923).
(144) P. Grammaticakis, Compt. Rend., 255, 1456 (1962).
(145) V. Hach and J. Strof, Chem. Listy, 46, 306 (1952).

atom % ^{15}N), and sodium hydroxide (0.2320 g, 5.80 mmol) there was obtained 0.3630 g (1.80 mmol) of labeled product, mp 148° -151°C, lit.[146] mp 153°-155°C.

3,5-Dimethylbenzamide-^{15}N. From 3,5-dimethylbenzoyl chloride (0.4200 g, 2.50 mmol), ammonium chloride-^{15}N (0.2890 g, 5.30 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.2320 g, 5.80 mmol) there was obtained 0.2590 g (1.72 mmol) of labeled product, mp 136°-137°C, lit.[147] mp 135.0°-135.5°C.

3,5-Dimethoxybenzamide-^{15}N. From 3,5-dimethoxybenzoyl chloride (0.5025 g, 2.50 mmol), ammonium chloride-^{15}N (0.2890 g, 5.30 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.2320 g, 5.80 mmol) there was obtained 0.3866 g (2.12 mmol) of labeled product, mp 138°-141°C, lit.[137] mp 148°-149°C.

m-Iodobenzamide-^{15}N. From m-iodobenzoyl chloride (0.6650 g, 2.50 mmol), ammonium chloride-^{15}N (0.2895 g, 5.31 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.2320 g, 5.80 mmol) there was obtained 0.4375 g (1.60 mmol) of labeled product, mp 185° -186°C, lit.[148] mp 185°-186°C.

m-Trifluoromethylbenzamide-^{15}N. From m-trifluoromethylbenzoyl chloride (0.9405 g, 4.50 mmol), ammonium chloride-^{15}N (0.5451 g, 10.00 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.4000

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(146) S. L. Shapiro, V. A. Parrino, and L. Freedman, J. Amer. Chem. Soc., 81, 3728 (1959).

(147) E. Gryszkiewicz-Trochimowski, W. Schmidt, and O. Gryszkiewicz-Trochimowski, Bull. Soc. Chim. Fr., 593 (1948).

(148) J. Arotsky, R. Butler, and A. C. Darby, Chem. Commun., 650 (1966).

g, 10.00 mmol) there was obtained 0.4105 g (2.15 mmol) of labeled product, mp 116°-119°C, lit.[149] mp 123°C.

m-Nitrobenzamide-^{15}N. From m-nitrobenzoyl chloride (0.8160 g, 4.40 mmol), ammonium chloride-^{15}N (0.5451 g, 10.00 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.4000 g, 10.00 mmol) there was obtained 0.6230 g of crude product, mp 120°-125°C. A recrystallization from chloroform yielded 0.4530 g (2.71 mmol) of labeled product, mp 137°-140°C, lit.[150] mp 141°C.

m-Fluorobenzamide-^{15}N. From m-fluorobenzoyl chloride (0.3965 g, 2.50 mmol), ammonium chloride-^{15}N (0.2890 g, 5.30 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.2320 g, 5.80 mmol) there was obtained 0.2315 g (1.65 mmol) of labeled product, mp 125°-130°C, lit.[151] mp 130°C.

o-Fluorobenzamide-^{15}N. From o-fluorobenzoyl chloride (0.3965 g, 2.50 mmol), ammonium chloride-^{15}N (0.2890 g, 5.30 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.2320 g, 5.80 mmol) there was obtained 0.2190 g (1.56 mmol) of labeled product, mp 108°-111°C, lit.[152] mp 116°C.

o-Bromobenzamide-^{15}N. From o-bromobenzoyl chloride (0.5475 g, 2.50 mmol), ammonium chloride-^{15}N (0.2890 g, 5.30 mmol, 99.3

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(149) P. Buu-Hoi, N. D. Xuong, and N. V. Bac, Compt. Rend., 257, 3182 (1963).

(150) O. L. Brady and A. D. Whitehead, J. Chem. Soc., 2936 (1927).

(151) A. F. Holleman and J. H. Slothouwer, Rec. Trav. Chim. Pays-Bas, 33, 330 (1914).

(152) G. Schiemann and H. G. Baumgarten, Ber., 70, 1421 (1937).

atom % ^{15}N), and sodium hydroxide (0.2320 g, 5.80 mmol) there was obtained 0.3820 g (1.90 mmol) of labeled product, mp 155° -158°C, lit.[153] mp 158°-159°C.

o-Trifluoromethylbenzamide-^{15}N. From o-trifluoromethylbenzoyl chloride (0.7285 g, 3.47 mmol), ammonium chloride-^{15}N (0.4200 g, 7.70 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.3120 g, 7.80 mmol) there was obtained 0.4680 g (2.45 mmol) of labeled product, mp 158°-163°C, lit.[149] mp 160°-161°C.

o-Anisamide-^{15}N. From o-anisoyl chloride (0.4265 g, 2.50 mmol), ammonium acetate-^{15}N (0.4135 g, 5.30 mmol, 97.5 atom % ^{15}N), and sodium hydroxide (0.2320 g, 5.80 mmol) there was obtained 0.3000 g (1.98 mmol) of labeled product, mp 124°-126°C, lit.[154] mp 129°-130°C.

o-Nitrobenzamide-^{15}N. From o-nitrobenzoyl chloride (0.7400 g, 4.00 mmol), ammonium chloride-^{15}N (0.4535 g, 8.40 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.3400 g, 8.50 mmol) there was obtained 0.5515 g (3.30 mmol) of labeled product, mp 171° -176°C, lit.[155] mp 177°C.

o-Benzoylbenzamide-^{15}N. o-Benzoylbenzamide-^{15}N was prepared by a slight modification of the general procedure described earlier. o-Benzoylbenzoyl chloride, due to its insolubility

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(153) J. S. Pizey and R. L. Wain, J. Sci. Food Agr., 10, 577 (1959).

(154) P. Grammaticakis, Bull. Soc. Chim. Fr., 924 (1964).

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

in ether, was dissolved in methylene chloride instead. After the reaction flask was removed from the oil bath and the nitrogen flow was discontinued, the trap and its contents were kept in the Dry Ice - acetone bath overnight and were brought to room temperature the following morning. In order to ensure completion of reaction, the trap was kept at room temperature for twenty four hours before the suspension was filtered. From o-benzoylbenzoyl chloride (0.7340 g, 3.00 mmol), ammonium chloride-^{15}N (0.3380 g, 6.20 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.2640 g, 6.60 mmol) there was obtained, after a recrystallization from toluene, 0.4250 g (1.88 mmol) of labeled product, mp 156°-160°C, lit.[156] mp 165°C.

2-Nitro-4-chlorobenzamide-^{15}N. From 2-nitro-4-chlorobenzoyl chloride (0.7040 g, 3.20 mmol), ammonium acetate-^{15}N (0.5070 g, 6.50 mmol, 97.5 atom % ^{15}N), and sodium hydroxide (0.2800 g, 7.00 mmol) there was obtained 0.6025 g (3.00 mmol) of labeled product, mp 168°-172°C, lit.[157] mp 172°C.

2-Chloro-4-nitrobenzamide-^{15}N. From 2-chloro-4-nitrobenzoyl chloride (1.1000 g, 5.00 mmol), ammonium chloride-^{15}N (0.5615 g, 10.30 mmol, 99.3 atom % ^{15}N), and sodium hydroxide (0.4400 g, 11.00 mmol) there was obtained 0.8900 g (4.42 mmol) of labeled product, mp 162°-165°C, lit.[158] mp 172°C.

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(156) C. Graebe and F. Ullmann, Ann., 291, 11 (1896).
(157) G. Heller, Ber., 49, 546 (1916).
(158) A. Grohmann, ibid, 24, 3813 (1891).

Preparation of ring-substituted ^{15}N-Anilines :

The procedure described for the synthesis of m-anisidine-^{15}N was followed for the preparation of the ^{15}N-anilines subsequently described. The purity of the liquid ^{15}N-anilines was verified by comparing the nmr spectrum of the labeled aniline with that of its commercially available ^{14}N-isotopomer.

m-Anisidine-^{15}N. To a solution of sodium hydroxide (0.2620 g, 6.55 mmol) in 4-5 ml of water, cooled to 0°C, 0.2160 g (1.35 mmol) of bromine was added with efficient stirring. The resulting solution was stirred at 0°C for five minutes prior to the addition of m-anisamide-^{15}N (0.2000 g, 1.31 mmol). The suspension was then vigorously stirred at 0°C for an additional twenty minutes until a clear yellow solution had formed. The solution was gradually heated in an oil bath to a temperature of 95°C and was kept at that temperature for 1.5 hours. After the reaction mixture was cooled to room temperature, the organic layer was extracted with three 10 ml portions of ether. Subsequent drying of the extract over anhydrous sodium sulfate and removal of the ether at reduced pressure yielded 0.1285 g (1.04 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 3.65 (d, 2, J = 79.4 Hz, $^{15}NH_2$), δ 3.70 (s, 3, O-CH_3), δ 6.25 (m, 3, ArH), δ 7.03 (broad t, 1, ArH); nmr (DMSO-d_6), δ 3.65 (s, 3, O-CH_3), δ 4.96 (d, 2, J = 83.0 Hz, $^{15}NH_2$), δ 6.18 (m, 3, ArH), δ 6.93 (broad t, 1, ArH).

m-Toluidine-^{15}N. From m-toluamide-^{15}N (0.2080 g, 1.53 mmol),

sodium hydroxide (0.3020 g, 7.55 mmol), and bromine (0.2640 g, 1.65 mmol) there was obtained 0.1280 g (1.18 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 2.23 (s, 3, CH_3), δ 3.50 (d, 2, J = 78.2 Hz, $^{15}NH_2$), δ 6.20-6.65 (m, 3, ArH), δ 7.00 (m, 1, ArH); nmr (DMSO-d_6), δ 2.16 (s, 3, CH_3), δ 4.83 (d, 2, J = 82.2 Hz, $^{15}NH_2$), δ 6.35 (m, 3, ArH), δ 6.90 (m, 1, ArH).

m-Chloroaniline-^{15}N. From m-chlorobenzamide-^{15}N (0.2505 g, 1.60 mmol), sodium hydroxide (0.3200 g, 8.00 mmol), and bromine (0.2725 g, 1.70 mmol) there was obtained 0.1710 g (1.32 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 3.66 (d, 2, J = 80.7 Hz, $^{15}NH_2$), δ 6.35-7.20 (m, 4, ArH); nmr (DMSO-d_6), δ 5.31 (d, 2, J = 84.1 Hz, $^{15}NH_2$), δ 6.35-7.18 (m, 4, ArH).

m-Bromoaniline-^{15}N. From m-bromobenzamide-^{15}N (0.3000 g, 1.50 mmol), sodium hydroxide (0.3000 g, 7.50 mmol), and bromine (0.2560 g, 1.60 mmol) there was obtained 0.1905 g (1.10 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 3.66 (d, 2, J = 80.5 Hz, $^{15}NH_2$), δ 6.41-7.13 (m, 4, ArH); nmr (DMSO-d_6), δ 5.30 (d, 2, J = 85.1 Hz, $^{15}NH_2$), δ 6.46-7.12 (m, 4, ArH).

3,5-Dimethylaniline-^{15}N. From 3,5-dimethylbenzamide-^{15}N (0.1950 g, 1.30 mmol), sodium hydroxide (0.2600 g, 6.50 mmol), and bromine (0.2240 g, 1.40 mmol) there was obtained 0.1185 g (0.970 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 2.21 (s, 6, CH_3), δ 3.48 (d, 2, J = 77.5 Hz, $^{15}NH_2$), δ 6.30 (broad s, 2, ArH), δ 6.40 (broad s, 1, ArH); nmr (DMSO-d_6), δ 2.10 (s, 6, CH_3), δ 4.73 (d, 2, J = 82.0 Hz, $^{15}NH_2$), δ 6.20 (broad s, 3, ArH).

3,5-Dimethoxyaniline-^{15}N. From 3,5-dimethoxybenzamide-^{15}N (0.2730 g, 1.50 mmol), sodium hydroxide (0.3000 g, 7.50 mmol), and bromine (0.2560 g, 1.60 mmol) there was obtained 0.1980 g (1.29 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 3.70 (d, 2, J = 79.5 Hz, $^{15}NH_2$), δ 3.73 (s, 6, O-CH_3), δ 5.90 (m, 3, ArH); nmr (DMSO-d_6), δ 3.66 (s, 6, O-CH_3), δ 5.00 (d, 2, J = 83.6 Hz, $^{15}NH_2$), δ 5.70-6.20 (m, 3, ArH).

m-Iodoaniline-^{15}N. From m-iodobenzamide-^{15}N (0.3720 g, 1.50 mmol), sodium hydroxide (0.3000 g, 7.50 mmol), and bromine (0.2560 g, 1.60 mmol) there was obtained 0.2390 g (1.08 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 3.61 (d, 2, J = 80.4 Hz, $^{15}NH_2$), δ 6.40-7.20 (m, 4, ArH); nmr (DMSO-d_6), δ 5.20 (d, 2, J = 84.4 Hz, $^{15}NH_2$), δ 6.40-7.10 (m, 4, ArH).

m-Trifluoromethylaniline-^{15}N. From m-trifluoromethylbenzamide-^{15}N (0.3824 g, 2.00 mmol), sodium hydroxide (0.4000 g, 10.00 mmol), and bromine (0.3360 g, 2.10 mmol) there was obtained 0.2160 g (1.32 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 3.78 (d, 2, J = 81.0 Hz, $^{15}NH_2$), δ 6.70-7.30 (m, 4, ArH); nmr (DMSO-d_6), δ 5.51 (d, 2, J = 85.1 Hz, $^{15}NH_2$), δ 6.70-7.40 (m, 4, ArH).

m-Nitroaniline-^{15}N. Instead of extracting the reaction mixture with ether, the orange crystals of m-nitroaniline-^{15}N that formed as the reaction flask cooled to room temperature were collected by suction filtration, washed with 2-3 ml of cold water, and suction air dried. From m-nitrobenzamide-^{15}N (0.3343 g, 2.00 mmol), sodium hydroxide (0.4000 g, 10.00

mmol), and bromine (0.3680 g, 2.30 mmol) there was obtained 0.1400 g (1.01 mmol) of product, mp 108°-111°C, lit.[159] mp 114°C; nmr ($CDCl_3$), δ 4.01 (d, 2, J = 83.0 Hz, $^{15}NH_2$), δ 6.80-7.85 (m, 4, ArH); nmr (DMSO-d_6), δ 5.80 (d, 2, J = 86.2 Hz, $^{15}NH_2$), δ 6.80-7.60 (m, 4, ArH).

m-Fluoroaniline-^{15}N. From m-fluorobenzamide-^{15}N (0.1820 g, 1.30 mmol), sodium hydroxide (0.2600 g, 6.50 mmol), and bromine (0.2240 g, 1.40 mmol) there was obtained 0.1400 g (1.25 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 3.67 (d, 2, J = 80.1 Hz, $^{15}NH_2$), δ 6.20-7.30 (m, 4, ArH); nmr (DMSO-h_6), δ 5.30 (d of d, 2, J = 84.2 Hz, J = 0.9 Hz, $^{15}NH_2$), δ 6.10-7.30 (m, 4, ArH).

o-Fluoroaniline-^{15}N. From o-fluorobenzamide-^{15}N (0.1680 g, 1.20 mmol), sodium hydroxide (0.2400 g, 6.00 mmol), and bromine (0.2080 g, 1.30 mmol) there was obtained 0.0850 g (0.760 mmol) of product, a red oil; nmr ($CDCl_3$), δ 3.66 (d, 2, J = 80.1 Hz, $^{15}NH_2$), δ 6.30-7.20 (m, 4, ArH); nmr (DMSO-h_6), δ 4.98 (d, 2, J = 83.5 Hz, $^{15}NH_2$), δ 6.25-7.20 (m, 4, ArH).

o-Bromoaniline-^{15}N. From o-bromobenzamide-^{15}N (0.3005 g, 1.50 mmol), sodium hydroxide (0.3000 g, 7.50 mmol), and bromine (0.2560 g, 1.60 mmol) there was obtained 0.2060 g (1.18 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 4.01 (d, 2, J = 81.4 Hz, $^{15}NH_2$), δ 6.40-7.49 (m, 4, ArH); nmr (DMSO-d_6), δ 5.16 (d, 2, J = 84.3 Hz, $^{15}NH_2$), δ 6.30-7.48 (m, 4, ArH).

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(159) S. Kubota, K. Nara, and S. Onishi, J. Pharm. Soc. Jap., 76, 801 (1956).

o-Trifluoromethylaniline-^{15}N. From o-trifluoromethylbenzamide-^{15}N (0.3825 g, 2.00 mmol), sodium hydroxide (0.4000 g, 10.00 mmol), and bromine (0.3360 g, 2.10 mmol) there was obtained 0.2480 g (1.52 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 4.11 (d, 2, J = 83.6 Hz, $^{15}NH_2$), δ 6.55-7.58 (m, 4, ArH); nmr (DMSO-h_6), δ 5.46 (d, 2, J = 86.5 Hz, $^{15}NH_2$), δ 6.45-7.49 (m, 4, ArH).

o-Anisidine-^{15}N. From o-anisamide-^{15}N (0.2280 g, 1.50 mmol), sodium hydroxide (0.3000 g, 7.50 mmol), and bromine (0.2560 g, 1.60 mmol) there was obtained 0.1470 g (1.18 mmol) of product, a dark oil; nmr ($CDCl_3$), δ 3.75 (d, 2, J = 79.4 Hz, $^{15}NH_2$), δ 3.78 (s, 3, O-CH_3), δ 6.75 (m, 4, ArH); nmr (DMSO-d_6), δ 3.76 (s, 3, O-CH_3), δ 4.60 (d, 2, J = 82.3 Hz, $^{15}NH_2$), δ 6.70 (m, 4, ArH).

o-Nitroaniline-^{15}N. The labeled product was extracted from the reaction mixture with three 10 ml portions of chloroform instead of ether. From o-nitrobenzamide-^{15}N (0.3345 g, 2.00 mmol), sodium hydroxide (0.4000 g, 10.00 mmol), and bromine (0.4000 g, 2.50 mmol) there was obtained 0.2305 g (1.65 mmol) of product, a low melting red solid, mp 45°-50°C, lit.[160] mp 71°-73°C; nmr ($CDCl_3$), δ 6.16 (d, 2, J = 90.3 Hz, $^{15}NH_2$), δ 6.50-8.16 (m, 4, ArH); nmr (DMSO-d_6), δ 6.50-8.10 (m, 4, ArH), δ 7.40 (d, 2, J = 91.0 Hz, $^{15}NH_2$).

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(160) D. A. Kinsley and S. G. P. Plant, J. Chem. Soc., 4814 (1956).

o-Benzoylaniline-^{15}N. As the reaction mixture cooled to room temperature, brown crystals of o-benzoylaniline-^{15}N formed in the reaction flask. The crystalline solid was collected by suction filtration, washed with 2-3 ml of water, and was suction air dried. From o-benzoylbenzamide-^{15}N (0.3390 g, 1.50 mmol), sodium hydroxide (0.3000 g, 7.50 mmol), and bromine (0.2560 g, 1.60 mmol) there was obtained 0.2365 g (1.18 mmol) of product, mp 90°-96°C, lit.[161] mp 110°-111°C; nmr ($CDCl_3$), δ 6.15 (d, 2, J = 88.1 Hz, $^{15}NH_2$), δ 6.30-8.10 (m, 9, ArH); nmr (DMSO-d_6), δ 7.16 (d, 2, J = 89.3 Hz, $^{15}NH_2$), δ 6.40-8.30 (m, 9, ArH).

2-Chloro-4-nitroaniline-^{15}N. The labeled product was extracted from the reaction mixture with three 10 ml portions of 90% ether - 10% tetrahydrofuran. From 2-chloro-4-nitrobenzamide-^{15}N (0.5025 g, 2.50 mmol), sodium hydroxide (0.5000 g, 12.50 mmol), and bromine (0.4480 g, 2.80 mmol) there was obtained 0.3510 g (2.03 mmol) of product, mp 97°-100°C, lit.[162] mp 107°C; nmr ($CDCl_3$), δ 4.91 (d, 2, J = 89.2 Hz, $^{15}NH_2$), δ 6.76 (d of d, 1, J = 9.0 Hz, J = 1.9 Hz, ArH), δ 8.00 (d of d, 1, J = 9.0 Hz, J = 2.5 Hz, ArH), δ 8.21 (d, 1, J = 2.5 Hz, ArH); nmr (DMSO-h_6), δ 6.86 (d, 2, J = 90.5 Hz, $^{15}NH_2$), δ 6.87 (d of d, 1, J = 9.0 Hz, J = 1.8 Hz, ArH), δ 7.97 (d of d, 1, J = 9.0 Hz, J = 2.5 Hz, ArH), δ 8.08 (d, 1, J = 2.5 Hz, ArH).

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(161) C. Graebe and F. Ullmann, Ann., 291, 13 (1896).
(162) F. D. Chattaway, K. J. P. Orton, and R. C. T. Evans, Ber., 33, 3061 (1900).

2-Nitro-4-chloroaniline-^{15}N. From 2-nitro-4-chlorobenzamide-^{15}N (0.3000 g, 1.50 mmol), sodium hydroxide (0.3000 g, 7.50 mmol), and bromine (0.2880 g, 1.80 mmol) there was obtained 0.2460 g of crude product, a viscous, red oil. Column chromatography of the oil on 35 g of silica gel packed in benzene - hexane (1:1), eluting first with 225 ml of benzene - hexane (1:1), 150 ml of benzene, and finally with 125 ml of benzene (product fraction), yielded, after removal of the solvent at reduced pressure, 0.1735 g (1.00 mmol) of product, mp 111°-113°C, lit.[163] mp 116°-117°C; nmr ($CDCl_3$), δ 6.11 (d, 2, J = 91.1 Hz, $^{15}NH_2$), δ 6.80 (d of d, 1, J = 9.0 Hz, J = 2.0 Hz, ArH), δ 7.32 (d of d, 1, J = 9.0 Hz, J = 2.5 Hz, ArH), δ 8.12 (d, 1, J = 2.5 Hz, ArH); nmr (DMSO-d_6), δ 7.06 (d of d, 1, J = 9.0 Hz, J = 2.0 Hz, ArH), δ 7.43 (d of d, 1, J = 9.0 Hz, J = 2.5 Hz, ArH), δ 7.56 (d, 2, J = 91.8 Hz, $^{15}NH_2$), δ 7.95 (d, 1, J = 2.5 Hz, ArH).

Preparation of ^{15}N-Quinolines :

Acetanilide-^{15}N. An aqueous solution of aniline-^{15}N hydrochloride was prepared by mixing aniline-^{15}N (0.8200 g, 8.80 mmol, 98.8 atom % ^{15}N) with conc. hydrochloric acid (0.75 ml, 8.9 mmol) in 15 ml of water. Acetic anhydride (1.1080 g, 10.86 mmol), followed immediately by a solution of sodium acetate (1.3200 g, 16.10 mmol) in 4 ml of water, were then added to the well stirred hydrochloride solution. After the

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(163) F. D. Chattaway, K. J. P. Orton, and R. C. T. Evans, ibid, 33, 3059 (1900).

resulting suspension was stirred for fifteen minutes at 0°C, the white precipitate was collected by suction filtration, washed with three 5 ml portions of cold water, and suction air dried for one hour. The yield of acetanilide-^{15}N, mp 109°-113°C, lit.[164] mp 114°-115°C, was 1.0160 g (7.47 mmol).

p-Nitroacetanilide-^{15}N. A mixture of acetanilide-^{15}N (0.7500 g, 5.50 mmol), glacial acetic acid (0.7800 g, 13.00 mmol), and conc. sulfuric acid (2.7600 g, 0.0281 mol) was stirred at room temperature until a clear solution was obtained. The reaction solution was then cooled to 0°C and slowly treated with a chilled solution of conc. nitric acid (0.4968 g, 5.52 mmol, 70% HNO_3) and conc. sulfuric acid (0.3750 g, 3.82 mmol). After all of the nitrating solution had been added, the reaction solution was stirred at room temperature for one hour and then was poured into 15 ml of ice-water. The resulting yellow precipitate was collected by suction filtration, washed with three 10 ml portions of cold water, and suction air dried for one hour. A recrystallization of the crude product from 80% methanol - 20% water yielded 0.5200 g (2.87 mmol) of p-nitroacetanilide-^{15}N, mp 211°-214°C, lit.[165] mp 214°-216°C.

6-Nitroquinoline-^{15}N. 6-Nitroquinoline-^{15}N was prepared by a modification of the procedure described by Haskelberg.[166]

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(164) A. I. Vogel, "Practical Organic Chemistry," 3rd ed., Longmans, Green, and Co., London, 1959, p. 577.
(165) Ibid, p. 581.
(166) L. Haskelberg, J. Org. Chem., 12, 434 (1947).

After gently heating a mixture of p-nitroacetanilide-^{15}N (0.4500 g, 2.50 mmol), arsenic pentoxide (0.4940 g, 1.90 mmol), glycerol (0.9210 g, 10.00 mmol), and conc. sulfuric acid (0.6750 g, 6.75 mmol) under reflux for 2.5 hours at a bath temperature of 155°C, the resulting red-brown syrup was cooled to room temperature and poured into 20 ml of water. An orange-brown precipitate was obtained by treating the diluted reaction mixture with conc. ammonium hydroxide until basic. The crude product was collected by suction filtration, washed with 25 ml of cold water, and suction air dried for two hours. Sublimation of the crude product at 90°-95°C (0.05 mm) gave 0.2230 g (1.27 mmol) of 6-nitroquinoline-^{15}N, a yellow crystalline solid, mp 140°-145°C, lit.[166] mp 150°C; nmr ($CDCl_3$), δ 7.58 (octet, 1, ^{15}N=C-C-H), δ 7.99-8.83 (m, 4, ArH), δ 9.10 (octet, 1, ^{15}N=C-H).

Quinoline-^{15}N. A mixture of aniline-^{15}N (0.2820 g, 3.00 mmol, 98.8 atom % ^{15}N), glycerol (0.8295 g, 9.00 mmol), arsenic pentoxide (0.4685 g, 1.80 mmol), and conc. sulfuric acid (0.7800 g, 7.85 mmol) was gently heated under reflux at a bath temperature of 160°C for 4.5 hours. The resulting brown syrup was then cooled to room temperature and was poured into 20 ml of water. After making the diluted reaction mixture basic with sodium hydroxide, the organic layer was extracted with three 10 ml portions of ether. Subsequent drying of the extract over anhydrous sodium sulfate followed by removal of the ether at reduced pressure yielded 0.1055 g (0.810 mmol)

of quinoline-^{15}N. The purity of the labeled product was verified by comparing its nmr spectrum with that of an authentic sample of quinoline; nmr ($CDCl_3$), δ 7.15 (octet, 1, $^{15}N{=}C{-}C{-}\underline{H}$), δ 7.30-8.25 (m, 5, ArH), δ 8.87 (octet, 1, $^{15}N{=}C{-}\underline{H}$).

<u>6-Methylquinoline-^{15}N.</u> A mixture of ^{15}N-<u>p</u>-toluidine[167] (0.2675 g, 2.50 mmol), glycerol (0.7000 g, 7.50 mmol), arsenic pentoxide (0.4000 g, 1.50 mmol), and conc. sulfuric acid (0.6500 g, 6.60 mmol) was gently heated under reflux at a bath temperature of 165°C for 4.5 hours. The resulting black syrup was cooled to room temperature and poured into 25 ml of water. The diluted reaction mixture was made basic with sodium hydroxide and the organic layer was extracted with three 10 ml portions of ether. Subsequent drying of the extract over anhydrous sodium sulfate and removal of the ether at reduced pressure yielded 0.0775 g (0.540 mmol) of 6-methylquinoline-^{15}N. The purity of the labeled product was verified by comparing its nmr spectrum with that of an authentic sample of 6-methylquinoline; nmr ($CDCl_3$), δ 2.47 (s, 3, CH_3), δ 7.27 (octet, 1, $^{15}N{=}C{-}C{-}\underline{H}$), δ 7.36-8.16 (m, 4, ArH), δ 8.81 (octet, 1, $^{15}N{=}C{-}\underline{H}$).

<u>Preparation of ^{15}N-Benzylideneanilines :</u>

<u>N-Benzylideneaniline-^{15}N.</u> A mixture of aniline-^{15}N (0.1880 g, 2.00 mmol, 98.8 atom % ^{15}N) and benzaldehyde (0.2125 g, 2.00

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(167) The sample was kindly provided by Dr. P. Pregosin.

mmol) in 6 ml of reagent grade benzene was heated under reflux for two hours. Subsequent removal of the solvent at reduced pressure and recrystallization of the crude product from petroleum ether yielded 0.2550 g (1.40 mmol) of N-benzylideneaniline-^{15}N, mp 49°-52°C, lit.[168] mp 52°-53°C; nmr ($CDCl_3$), δ 7.00-7.70 (m, 8, ArH), δ 7.72-8.10 (m, 2, ArH), δ 8.45 (d, 1, J = 3.8 Hz, ^{15}N=C-H).

N-p-Nitrobenzylideneaniline-^{15}N. The procedure for the preparation of N-benzylideneaniline-^{15}N was followed. From aniline-^{15}N (0.2350 g, 2.50 mmol, 98.8 atom % ^{15}N) and p-nitrobenzaldehyde (0.3775 g, 2.50 mmol) there was obtained, after a recrystallization from 95% hexane - 5% chloroform, 0.5200 g (2.29 mmol) of N-p-nitrobenzylideneaniline-^{15}N, mp 87°-90°C, lit.[168] mp 92°-93°C; nmr ($CDCl_3$), δ 7.35 (m, 5, ArH), δ 8.20 (q, 4, ArH), δ 8.55 (d, 1, J = 3.8 Hz, ^{15}N=C-H).

N-p-Methylbenzylideneaniline-^{15}N. The procedure for the preparation of N-benzylideneaniline-^{15}N was followed. From aniline-^{15}N (0.1886 g, 2.00 mmol, 98.8 atom % ^{15}N) and p-tolualdehyde (0.2405 g, 2.00 mmol) there was obtained 0.3795 g (1.95 mmol) of N-p-methylbenzylideneaniline-^{15}N, mp 39°-43°C, lit.[169] mp 41°C; nmr ($CDCl_3$), δ 2.36 (s, 3, CH_3), δ 7.28 (m, 7, ArH), δ 7.80 (d, 2, ArH), δ 8.40 (d, 1, J = 3.8 Hz,

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(168) K. Tabei and E. Saitou, Bull. Chem. Soc. Jap., 42, 1440 (1969).

(169) H. H. Keasling and F. W. Schueler, J. Amer. Pharm. Assoc., 39, 87 (1950).

^{15}N=C-H).

N-p-Chlorobenzylideneaniline-^{15}N. The procedure for the preparation of N-benzylideneaniline-^{15}N was followed. From aniline-^{15}N (0.1886 g, 2.00 mmol, 98.8 atom % ^{15}N) and p-chlorobenzaldehyde (0.2810 g, 2.00 mmol) there was obtained 0.4015 g (1.86 mmol) of N-p-chlorobenzylideneaniline-^{15}N, mp 59°-62°C, lit.[168] mp 63.5°-64.5°C; nmr ($CDCl_3$), δ 7.00-8.00 (m, 9, ArH), δ 8.40 (d, 1, J = 3.8 Hz, ^{15}N=C-H).

N-Benzylidene-p-toluidine-^{15}N. The procedure for the preparation of N-benzylideneaniline-^{15}N was followed. From ^{15}N-p-toluidine[167] (0.1190 g, 1.10 mmol) and benzaldehyde (0.1170 g, 1.10 mmol) there was obtained 0.1960 g (1.00 mmol) of N-benzylidene-p-toluidine-^{15}N. The purity of the labeled product was verified by comparing its nmr spectrum with that of an authentic sample of the ^{14}N-isotopomer; nmr ($CDCl_3$), δ 2.23 (s, 3, CH_3), δ 7.10 (s, 4, ArH), δ 7.30 (m, 3, ArH), δ 7.80 (m, 2, ArH), δ 8.30 (d, 1, J = 3.7 Hz, ^{15}N=C-H).

Preparation of 2,4,6-Tribromoaniline-^{15}N. 2,4,6-Tribromoaniline-^{15}N was prepared by the procedure described by Vogel.[170] To an ice-cold solution of aniline-^{15}N (0.1880 g, 2.00 mmol, 98.8 atom % ^{15}N) in 1-2 ml of glacial acetic acid, a solution of bromine (0.9600 g, 6.10 mmol) in 1-2 ml of glacial acetic acid was slowly added. The thick red paste which formed was stirred at 0°C for ca. 5-10 minutes before an excess of ice-water was added to it resulting in the precipitation of the product. The tan precipitate was collected by suction filtration, washed with cold water, and air dried for thirty minutes to give 0.4145 g (1.34 mmol) of 2,4,6-tribromoaniline-^{15}N, mp 118°-121°C, lit.[170] mp 120°-122°C; nmr ($CDCl_3$), δ 4.30 (d, 2, J = 85.5 Hz, $^{15}NH_2$), δ 7.49 (s, 2, ArH); nmr (acetone-h_6), δ 5.23 (d, 2, J = 87.3 Hz, $^{15}NH_2$), δ 7.55 (s, 2, ArH).

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(170) A. I. Vogel, "Practical Organic Chemistry," 3rd ed., Longmans, Green, and Co., London, 1959, p. 579.