

Fractions 12–21 (0.155 g) when worked up in the same manner yielded the analytical sample of IIIb, mp 121–123°. The mass spectrum showed a molecular ion at  $m/e$  274; ir (KBr) 6.65, 7.4, 8.6, 12.85, and 13.8  $\mu$ ;  $\lambda_{\text{max}}^{\text{MeOH}}$  388 (11,000), 262 (13,400), and 235  $m\mu$  ( $\epsilon$  27,700). *Anal.* Calcd for  $\text{C}_{11}\text{H}_9\text{O}_3\text{N}_2\text{F}_3$ : C, 48.17; H, 3.28; N, 10.21. Found: C, 48.13; H, 3.18; N, 10.04.

Fractions 22–29 yielded crude IIIa (85 mg). The analytical sample was obtained from ether, mp 130–131°. The mass spectrum showed a molecular ion at  $m/e$  260; ir (KBr) 2.95, 6.75, 7.35, 8.7, 12.95, and 13.75  $\mu$ ;  $\lambda_{\text{max}}^{\text{MeOH}}$  386 (10,200), 267 (16,100), and 236  $m\mu$  ( $\epsilon$  25,700). *Anal.* Calcd for  $\text{C}_{10}\text{H}_7\text{O}_3\text{N}_2\text{F}_3$ : C, 46.15; H, 2.70; N, 10.77. Found: C, 46.09; H, 2.73; N, 10.71.

**2-Methyl-3-trifluoromethylquinoxaline 1-Oxide (V).** 2-Methyl-3-trifluoromethylquinoxaline 1,4-dioxide (0.73 g, 0.003 mole) was suspended in water (3 ml). To this suspension a solution of sodium dithionite (1.56 g, 0.009 mole) in water (2 ml) was added dropwise while stirring. The product (0.21 g, 30% yield) precipitated out of the resulting solution. Ether–hexane crystallization gave the analytical sample, mp 142–144°. The mass spectrum showed a molecular ion at  $m/e$  228; ir (KBr) 6.3, 6.65, 7.35, 8.0, 8.90, 9.70, 13.00, and 13.80  $\mu$ ;  $\lambda_{\text{max}}^{\text{MeOH}}$  322 (8100) and 240  $m\mu$  ( $\epsilon$  35,200). *Anal.* Calcd for  $\text{C}_{10}\text{H}_7\text{ON}_2\text{F}_3$ : C, 52.36; H, 3.07; N, 12.28. Found: C, 52.38; H, 3.18; N, 12.00.

**2-Bromomethyl-3-trifluoromethylquinoxaline 1-Oxide (IV).** Bromine (0.8 g, 0.005 mole) was dissolved in methylene chloride (5 ml) and was added dropwise to a refluxing solution of 2-methyl-3-trifluoromethylquinoxaline 1,4-dioxide (1.2 g, 0.005 mole) in the same solvent (15 ml). The reaction was refluxed overnight. The dried residue was crystallized several times from methanol to yield the analytical sample (0.125 g, 8% yield), mp 130–131°. The mass spectrum showed two molecular ions at  $m/e$  308 and 306; ir (KBr) 6.30, 6.65, 7.30, 8.50, 9.90, 10.70, 12.85, and 13.82  $\mu$ ;

$\lambda_{\text{max}}^{\text{MeOH}}$  330 (2400) and 245  $m\mu$  ( $\epsilon$  11,000). *Anal.* Calcd for  $\text{C}_{10}\text{H}_6\text{ON}_2\text{BrF}_3$ : C, 39.08; H, 1.95; N, 9.11. Found: C, 38.78; H, 1.93; N, 9.01.

**2-Methyl-3-trifluoromethylquinoxaline (VI).** 2-Methyl-3-trifluoromethylquinoxaline 1,4-dioxide (0.19 g, 0.0008 mole) was suspended in water (2 ml). To this suspension a solution of sodium dithionite (0.630 g, 0.0036 mole), in water (2 ml), was added dropwise while stirring. After a few hours the reaction was extracted with chloroform, which was dried, filtered, and evaporated to dryness. The residue (0.10 g) was sublimed at room temperature to yield the pure sample, mp 80–82° (lit. 83–84°).<sup>20</sup> The mass spectrum showed a molecular ion at  $m/e$  212.

**3,4-Dihydro-2-methyl-3-trifluoromethylquinoxaline (VII).** 2-Methyl-3-trifluoromethylquinoxaline 1,4-dioxide (0.63 g, 0.00026 mole) was dissolved in 50% aqueous methanol (5 ml). A solution of sodium dithionite (0.21 g, 0.0012 mole) in water (1 ml) was added. An immediate precipitate was formed which redissolved upon stirring. The reaction was further stirred for 1.5 hr at room temperature. Evaporation of the methanol under reduced pressure was followed by ether extraction of the aqueous solution. The organic phase was dried, filtered, and evaporated to dryness to yield a gum which crystallized from ether–hexane (0.015 g), mp 122–127°. The mass spectrum showed a molecular ion at  $m/e$  214. No further purification by crystallization was possible since the compound was air oxidized to VI.

**Acknowledgment.** The author wishes to thank Professor Joseph B. Lambert and Dr. Philip D. Hammen for their helpful discussion, and Mr. Leo B. Keith for his technical assistance.

(20) A. Sykes and J. C. Tatlow, *J. Chem. Soc.*, 2393 (1957).

## Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. Substituent Effects on $^{15}\text{N}$ –H Coupling Constants and Nitrogen Chemical Shifts in Aniline Derivatives

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**Abstract:** Substituent effects on one-bond  $^{15}\text{N}$ –H couplings and nitrogen chemical shifts in a series of aniline- $^{15}\text{N}$  derivatives have been examined. Electron-withdrawing substituents are found to cause an increase in the magnitude of  $^1J(^{15}\text{N}$ –H) and a downfield shift of the nitrogen resonance. These observations are interpreted in terms of a change in hybridization and a concomitant decrease in  $\pi$  electron density at nitrogen.

It has long been recognized that, among other properties, the basicity of aniline is significantly altered by the presence of a ring substituent. Since anilinium ion formation requires the donation of the nitrogen lone pair to a proton, any structural feature which tends to reduce the electron density at nitrogen will decrease its proton affinity, whereas any factor which enhances this density will have the opposite effect. These same considerations should be reflected in the nuclear magnetic resonance parameters of aniline and its ring-substituted derivatives. This paper is concerned with the effect of substituents on the one-bond  $^{15}\text{N}$ –H coupling constants and nitrogen-15 chemical shifts in aniline derivatives.<sup>1</sup>

In the absence of overriding anisotropic effects, the chemical shifts of the carbon atoms in a benzene ring and of any atom attached to it should reflect the electron density at the position in question. It is generally considered that a substituent alters the  $\pi$  electron density of the aromatic ring by both resonance and inductive interactions and that the latter effects are transmitted to ring protons or side chain atoms by successive and diminishing polarization of the intervening  $\sigma$  bonds or by a through-space field effect.<sup>2</sup> The

(1) For a preliminary report of this work see, T. Axenrod, P. S. Pregosin, M. J. Wieder, and G. W. A. Milne, *J. Amer. Chem. Soc.*, **91**, 3681 (1969).

(2) M. J. S. Dewar and Y. Takeuchi, *ibid.*, **89**, 390 (1967).

agreement between Hückel LCAO calculations and  $p$ -hydrogen<sup>3</sup> and  $p$ -<sup>13</sup>C shifts<sup>4</sup> in monosubstituted benzenes supports the contention that, in aromatic systems, the chemical shifts arise mainly from changes in the  $\pi$  electron density.<sup>5</sup> The investigation of the influence of substituents on the <sup>15</sup>N-H coupling and nitrogen chemical shifts in aniline derivatives should provide an additional probe with which to gain insight into the nature and mechanism of the transmission of electronic effects in these systems.

**Coupling Constants.** Since the first proposal that the magnitude of one-bond <sup>13</sup>C-H coupling<sup>6</sup> could be related to hybridization, this hypothesis has been the subject of extensive investigation.<sup>7</sup> From the Ramsey theory of indirect spin coupling,<sup>8</sup> the coupling constant between bonded nuclei will show a dependence on the  $s$  character in the bond if, as is generally accepted, the coupling mechanism is dominated by the Fermi contact term. For closely related compounds this correlation has been quite reasonable, whereas in systems where the nominal hybridization of carbon presumably remains unchanged but the electronegativity of the elements to which it is bonded varies, the correspondence is less than satisfactory.<sup>9</sup>

On the assumption of the dominance of the Fermi contact term and the constancy of  $\Delta E$ , the average electronic excitation energy, this hypothesis has recently been extended to include the dependence of one-bond <sup>15</sup>N-H coupling on the hybridization of nitrogen.<sup>10,11</sup>

An empirical expression,<sup>10</sup>  $\%s = 0.43 \text{ } ^1J(^{15}\text{NH}) - 6$ , relating the per cent  $s$  character in the <sup>15</sup>N-H bond to the one-bond coupling constant has been derived.<sup>12</sup> Observed magnitudes of these <sup>15</sup>N-H coupling constants fall in the range 61–136 Hz<sup>13</sup> and in the majority of cases this relationship affords good qualitative agreement between the measured coupling constants and the expected nitrogen hybridization based on other structural considerations. Typical values for the three different hybridizations are: 75 Hz in ammonium ions ( $sp^3$ ),<sup>13</sup>  $\sim 90$  Hz in amides and pyridinium ion ( $sp^2$ ),<sup>13</sup> and  $\sim 136$  Hz in protonated nitriles ( $sp$ ).<sup>14</sup>

Of the two isotopes of nitrogen, <sup>14</sup>N has an electric quadrupole moment, which frequently leads to increased relaxation rates of nuclei to which it is spin-coupled with consequent line broadening and loss of coupling information. To circumvent these difficulties, a series of aniline-<sup>15</sup>N derivatives having a nitrogen-15 enrichment of 95 atom % was prepared.

(3) H. P. Figeys and R. Flammang, *Mol. Phys.*, **12**, 581 (1967).

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(7) For leading references see: L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press Ltd., London, 1969, p 345.

(8) N. F. Ramsey, *Phys. Rev.*, **91**, 301 (1953).

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

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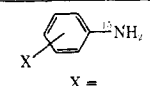
(12) For a similar expression based on different model compounds, see ref 11.

(13) R. L. Lichter, in "Determination of Organic Structures by Physical Methods," Vol. 3 F. C. Nachod and W. D. Phillips, Ed., Academic Press, New York, N. Y., in press.

(14) H. Hogveen, *Recl. Trav. Chim. Pays-Bas*, **86**, 1228 (1967); G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **90**, 6088 (1968); and G. A. Olah and T. E. Kiosky, *ibid.*, **90**, 4666 (1968).

The anilines chosen for study were primarily those having meta and para substituents with only a few having substituents in the ortho position.<sup>15</sup> The one-bond <sup>15</sup>N-H coupling constants which were determined in dimethyl- $d_6$  sulfoxide and deuteriochloroform solutions from the proton spectra are summarized in Table I.

**Table I.** <sup>15</sup>N-H Coupling Constants in Ring-Substituted Aniline Derivatives

 X =	$^1J(^{15}\text{NH})^a$	
	DMSO- $d_6$	CDCl <sub>3</sub>
2,4-(NO <sub>2</sub> ) <sub>2</sub>	92.6	
4-NO <sub>2</sub>	89.4	
2,4,6-(Br) <sub>3</sub>	87.4	85.5
4-NO <sub>2</sub> ,3,5-(Me)	87.0	83.2
3-NO <sub>2</sub>	86.2	83.0
2,4-(Br) <sub>2</sub>	86.0	82.7
3-CF <sub>3</sub>	85.1	81.0
3-Br	85.3	80.5
3-Cl	85.1	80.9
3-I	84.4	80.4
3-F	84.2	80.1
4-I	84.0	79.7
4-Br	84.0	79.6
3,5-(MeO) <sub>2</sub>	83.6	79.5
4-Cl	83.7	78.9
3-MeO	83.0	79.4
H	82.6	78.6
3-Me	82.0	78.2
3,5-(Me) <sub>2</sub>	82.1	77.5
4-F	81.6	77.8
4-Me	81.4	76.5
4-MeO	79.4	75.6
4-NH <sub>2</sub>		74.9
4-N(Me) <sub>2</sub>	78.8	74.8

<sup>a</sup> All constants are expressed in hertz and are accurate to  $\pm 0.2$  Hz.

It was frequently necessary to treat the aniline solutions with anhydrous basic alumina to remove traces of acid which catalyzed <sup>15</sup>N-H exchange. In the case of the dimethylamino substituent it was also necessary to reduce the temperature to 10° to eliminate exchange effects, while even these treatments failed in the case of  $p$ -phenylenediamine in DMSO. Otherwise, all spectra were measured at ambient probe temperature (37°).

Approximately 1  $M$  solutions were used except where solubility made this impossible. In such cases saturated solutions were employed. To determine the effect of concentration on the <sup>15</sup>N-H coupling constants the concentration of aniline-<sup>15</sup>N in deuteriochloroform was varied between 0.4 and 2.2  $M$ . Within this range, the observed coupling constants were found to be independent of concentration, and presumably this is also true for the dimethyl sulfoxide solutions.

Inspection of the data in Table I shows that the <sup>15</sup>N-H coupling constants are dependent on both the solvent employed and the nature of the ring substituent. The solvent dependence of the  $^1J(^{15}\text{NH})$  in aniline has previously been observed by Paolillo and Becker,<sup>16</sup> who found that  $^1J(^{15}\text{NH})$  increases regularly with increase in the hydrogen bonding ability of the solvent, although other solvent interactions may also be important. In the case of aniline,  $^1J(^{15}\text{NH})$  in chloroform

(15) A full report on ortho-substituted anilines will be presented at a later date.

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

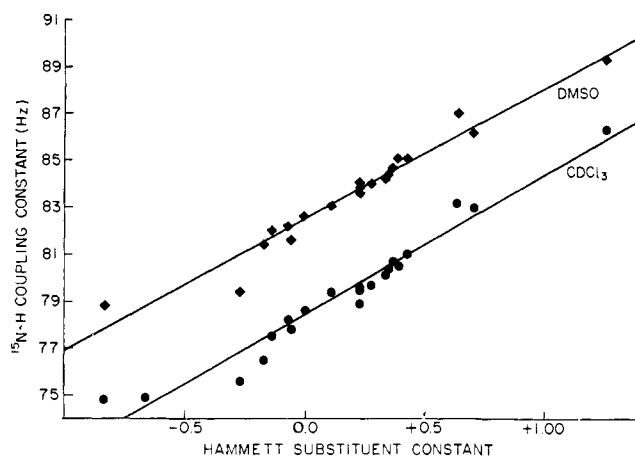
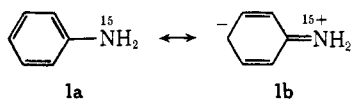


Figure 1. Correlation of one-bond  $^{15}\text{N-H}$  coupling constants in ring-substituted aniline- $^{15}\text{N}$  derivatives with Hammett substituent constants.

has a value of 78.6 Hz which corresponds to 28%  $s$  character in the hybrid nitrogen orbital. In dimethyl sulfoxide which is a more polar and better hydrogen bonding solvent  $J(^{15}\text{NH})$  is increased to 82.6 Hz corresponding to 30%  $s$  character.<sup>17</sup> For aniline and other conjugated systems, the importance of  $\pi$  bonding between the nitrogen lone pair and the phenyl ring has long been recognized. The  $J(^{15}\text{NH})$  values for aniline are intermediate between those expected for a tetrahedral ( $\text{sp}^3$ ) and trigonal ( $\text{sp}^2$ ) nitrogen and suggest that in the more polar solvent there is more extensive delocalization of the nitrogen lone pair as represented in resonance structures 1a and 1b.



The substituent dependence of  $J(^{15}\text{NH})$  in these aniline derivatives may be seen to be very similar in either solvent, although the magnitude of the coupling is consistently greater in dimethyl sulfoxide.<sup>18</sup> Strongly electron-withdrawing groups lead to enhanced  $^{15}\text{N-H}$  coupling compared with aniline whereas electron-donating substituents result in diminished coupling. The importance of the role of the substituent can be illustrated by comparing  $J(^{15}\text{NH})$  for 2,4-dinitroaniline with the value for  $N,N$ -dimethyl- $p$ -phenylenediamine. In dimethyl sulfoxide the values are 92.6 (34%  $s$  character) and 78.8 Hz (28%  $s$  character), respectively. Thus, in going from a strongly electron-withdrawing substituent to one that is strongly electron donating, the nitrogen hybridization is changed from virtually  $\text{sp}^2$  to  $\text{sp}^3$ . This is consistent with recent nuclear quadrupole resonance studies which indicate greater pyramidal character at the nitrogen atom in  $p$ -phenylenediamine<sup>19</sup> than in aniline.

Substituent effects involving aromatic compounds are often expressed in terms of inductive, resonance, and steric contributions. The first two factors dominate if only meta and para substituents are considered. In

(17) Calculated from the relationship given in ref 10. These values can only be regarded as approximate.

(18) Similar observations in acetone solutions have been reported by M. R. Bramwell and E. W. Randall, *Chem. Commun.*, 250 (1969).

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

general inductive and resonance effects of different substituents present in the molecule are considered to be additive and  $pK_a$  values of aromatic amines have been correlated with the Hammett  $\sigma$  constants of the substituents.<sup>20</sup> Similarly, the N-H stretching frequencies in anilines<sup>21</sup> and the C-H coupling constants in the methyl group of toluene derivatives<sup>22</sup> have been shown to be proportional to the Hammett substituent constants.

Least-squares plots of the coupling constant  $J(^{15}\text{NH})$ , measured in chloroform and in dimethyl sulfoxide, against the Hammett substituent constant for the aniline derivatives are shown in Figure 1. It may be seen that, in both solvents,  $J(^{15}\text{NH})$  is proportional to the substituent constant,  $\sigma$ , and that reasonable linearity is observed. The parallel nature of the two plots illustrates that the solvent serves to augment the coupling without altering the relative electronic effect of the substituents.

The presence of a halogen atom in the meta position reduces the basicity of aniline, although there is almost no difference between the effects produced by fluorine, chlorine, bromine, and iodine. The influence of meta halogens on  $J(^{15}\text{NH})$  is very similar. On the other hand, although a para halogen atom also decreases the basicity the effect is much smaller, a fluorine substituent even causing an increase. Qualitatively, the same effect on  $J(^{15}\text{NH})$  is observed. Thus, while there is little difference in the inductive effect of the halogens on the electron density at the nitrogen atom, the resonance effect from the para position is considered to follow the order  $\text{F} > \text{Br} > \text{Cl} > \text{I}$ . This conclusion previously reached from basicity considerations is now supported by the observed substituent effects on  $J(^{15}\text{NH})$ . Significantly, microwave studies indicate that  $p$ -fluoroaniline<sup>23</sup> has greater pyramidal character at the amino group than does aniline.<sup>24</sup> Analogous behavior is shown by other substituents, for example, methyl groups have electron-donating effects as evidenced by slightly decreased  $^{15}\text{N-H}$  coupling in  $m$ - and  $p$ -toluidine compared with aniline.

The importance of resonance and inductive effects is further illustrated by a comparison of  $J(^{15}\text{NH})$  in dimethyl sulfoxide for 3,5-dimethyl-4-nitroaniline (87.0 Hz) and 4-nitroaniline (89.4 Hz). The cumulative effect of the meta methyl groups can only account for a decrease of 0.5 Hz out of the 2.4 Hz difference that is observed. Maximum conjugation of mesomerically interacting substituents requires that these groups be coplanar and in the case of 4-nitroaniline leads to enhanced trigonal  $\text{sp}^2$  hybridization at the amino nitrogen. This condition, however, is subject to steric influences. In 3,5-dimethyl-4-nitroaniline nonbonded interactions between the oxygen atoms of the nitro group and the adjacent methyl groups cause the nitro group to be twisted out of the plane of the ring resulting in a diminution of its resonance interaction with the amino group.<sup>25</sup> It is in-

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(25) 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).

interesting to note that the  $^{15}\text{N-H}$  coupling constant observed for 3,5-dimethyl-4-nitroaniline is comparable to that of 3-nitroaniline, in which inductive effects are normally considered to be dominant. The observed coupling constant reflects this steric inhibition and although  $^1J(^{15}\text{NH})$  for 4-nitroaniline can be correlated with the exalted  $\sigma^-$  value for the nitro group the use of the usual  $\sigma$  value<sup>26</sup> seems justified for the case of 3,5-dimethyl-4-nitroaniline.

In the course of this work spin coupling between the nitrogen-15 atom and the adjacent ortho protons was observed. The nmr spectrum of 4-nitroaniline is illustrated in Figure 2. In general, the upfield half of the AA'BB' pattern for the aromatic protons in para-substituted aniline- $^{15}\text{N}$  derivatives is further split into a doublet by the nitrogen-15 atom. Longer range coupling between the  $^{15}\text{N}$  nucleus and the more distant meta and para protons is not observed. This observation may have some diagnostic value in the identification and assignment of signals arising from protons ortho to the amino nitrogen. The magnitude of the coupling between the nitrogen and the ortho proton shows no obvious dependence on the nature of the ring substituent. Typical values are given in Table II.

**Table II.** Vicinal  $^{15}\text{NC}=\text{CH}$  Coupling Constants in Some Ring-Substituted Anilines

X =	$^3J(^{15}\text{N-H})^a$	
	DMSO	$\text{CDCl}_3$
2,4-(NO <sub>2</sub> ) <sub>2</sub>	2.2	
4-NO <sub>2</sub>	1.8	2.0
2,4-(Br) <sub>2</sub>	1.6	1.9
4-I	1.7	1.8
4-Br	1.8	1.8
4-Cl	1.7	1.9
4-F	1.5	1.8
4-CH <sub>3</sub>	1.7	1.8

<sup>a</sup> All coupling constants are expressed in hertz. The error is  $\pm 0.2$  Hz.

**Chemical Shifts.** Nitrogen chemical shifts are influenced by factors different from those that determine proton chemical shifts.<sup>13</sup> Wu<sup>27</sup> has used the Pople theory<sup>28</sup> of chemical shielding to calculate nitrogen chemical shifts. The total shielding is taken as  $\sigma_{\text{total}} = \sigma_{\text{D}} + \sigma_{\text{P}} + \sigma_{\text{F}}$ , where  $\sigma_{\text{D}}$  is the diamagnetic contribution arising from the rotation of the electron cloud around the nucleus,  $\sigma_{\text{P}}$  is the paramagnetic contribution resulting from the mixing of ground and excited states in the magnetic field due to increased orbital angular momentum in nonspherically symmetrical molecules, and  $\sigma_{\text{F}}$  is the long-range effect of other atoms in the molecule and it includes contributions from all other sources such as neighbor anisotropy, ring currents, and solvent effects.

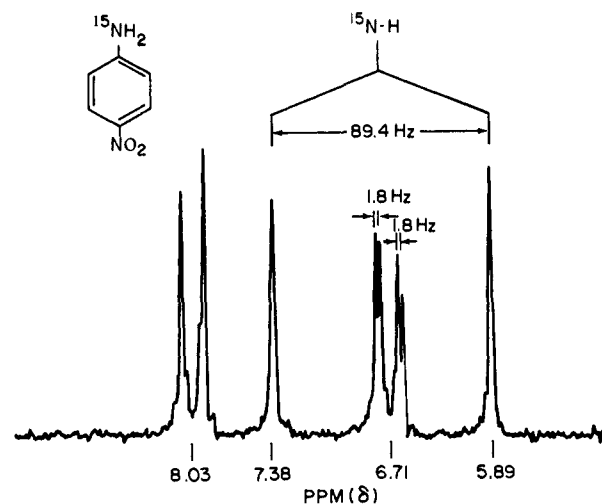
The large range of chemical shifts ( $\sim 1000$  ppm) observed for nitrogen is considered to be determined by changes in the paramagnetic term; the diamagnetic contribution and long-range effects are assumed to be negligible. This view is supported by much experimental evidence,<sup>29</sup> although in considering small changes within

(26) H. H. Jaffe, *Chem. Rev.*, **53**, 250 (1953).

(27) T. K. Wu, *J. Phys. Chem.*, **49**, 1139 (1968); **51**, 3622 (1969).

(28) J. A. Pople, *J. Chem. Phys.*, **37**, 53, 60 (1962).

(29) B. E. Holder and M. P. Klein, *ibid.*, **23**, 1956 (1955); B. M. Schmidt, L. C. Brown, and D. Williams, *J. Mol. Spectrosc.*, **2**, 539



**Figure 2.** The 60-MHz proton magnetic resonance spectrum of 4-nitroaniline- $^{15}\text{N}$  in dimethyl sulfoxide measured relative to TMS.

a given class of compounds neglect of the diamagnetic term may not be justified.<sup>30</sup> The paramagnetic term,  $\sigma_{\text{P}}$ , is considered to arise primarily from the effect of multiple bonds of nitrogen and the mean excitation energy,  $\Delta E$ .

The direct observation of nitrogen-15 resonances is rendered difficult by the inherent low sensitivity of this nucleus. In order to make accurate measurements of nitrogen chemical shifts which might be interpreted in terms of substituent effects we have used  $^1\text{H}\{^{15}\text{N}\}$  double resonance to provide  $^1\text{H}$  sensitivity in the determination of  $^{15}\text{N}$  resonance frequencies in the present series of  $^{15}\text{N}$ -enriched anilines. The nitrogen-15 chemical shifts along with the corresponding amino proton chemical shifts are summarized in Table III.

It is apparent from the data in Table III that the range of nitrogen-15 chemical shifts in these anilines is relatively narrow ( $\sim 39$  ppm) when compared with the overall range of about 1000 ppm found for nitrogen-15 in different classes of compounds. Moreover, in these aniline derivatives it can be seen that the amino proton chemical shifts parallel those of the nitrogen-15 nucleus. The ring substituents have a qualitatively similar effect on both of these chemical shifts; electronegative substituents produce a downfield shift in each case whereas electron-donating groups induce shifts to higher field. A least-squares plot of the nitrogen-15 chemical shifts *vs.* the amino proton chemical shifts which illustrates this correlation is shown in Figure 3. The effect of substituents on the amino proton chemical shifts has been the subject of extensive investigation<sup>31</sup> and it has been shown that these shifts are linearly related to the Hammett substituent constant in DMSO,<sup>32</sup> among other solvents. Hammett substituent constants are generally accepted as a measure of  $\pi$  electron density variation at ring or exocyclic positions in substituted benzenes<sup>32</sup>

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(32) B. M. Lynch, B. C. Macdonald, and J. K. G. Webb, *Tetrahedron*, **24**, 3595 (1968).

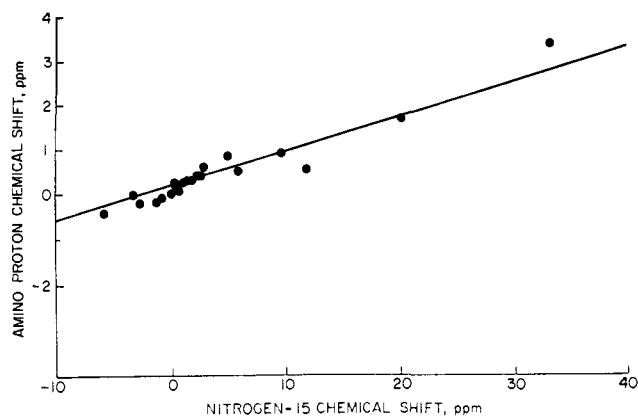
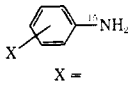


Figure 3. Correlation of amino proton chemical shifts with amino nitrogen chemical shifts for aniline- $^{15}\text{N}$  derivatives measured in dimethyl sulfoxide.

and Hückel calculations correlating amino proton chemical shifts, base strength, and Hammett substituent constants for substituted anilines have recently been reported.<sup>33</sup> A plot of these  $\pi$  electron densities against

Table III. Nitrogen-15 and Amino Proton Chemical Shifts in Ring-Substituted Aniline Derivatives

 X =	Chemical shifts <sup>a</sup>	
	$^{15}\text{N}^b$	$\text{NH}_2^c$
2,4-(NO <sub>2</sub> ) <sub>2</sub>	32.7	3.42
4-NO <sub>2</sub>	19.7	1.73
2,4,6-(Br) <sub>3</sub>	11.5	0.58
3,5-Me <sub>2</sub> ,4-NO <sub>2</sub>	9.4	0.94
2,4-(Br) <sub>2</sub>	5.8	0.52
3-NO <sub>2</sub>	4.9	0.85
3-CF <sub>3</sub>	2.7	0.62
3-Cl	2.5	0.40
3-Br	2.3	0.40
3-I	1.7	0.30
4-I	1.4	0.30
4-Br	1.0	0.25
3-MeO	0.7	0.07
3,5-(MeO)	0.3	0.15
4-Cl	0.3	0.25
H	0.0	0.0
3-Me	-0.8	-0.07
3,5-Me <sub>2</sub>	-1.2	-0.17
4-Me	-2.6	-0.20
4-F	-3.3	-0.02
4-MeO	-5.8	-0.42

<sup>a</sup> Chemical shifts were obtained for dimethyl sulfoxide solutions and are reported in parts per million relative to aniline. A positive value of the chemical shift indicates a shift downfield from aniline.

<sup>b</sup>  $^{15}\text{N}$  chemical shift of aniline is 16.6 ppm downfield from  $(\text{CH}_3)_4\text{N}^+\text{I}^-$  (internal) [E. D. Becker, *J. Magn. Resonance*, **4**, 142 (1971)].

<sup>c</sup>  $^{15}\text{N}$  resonance frequency of aniline is 6.080112 MHz in magnetic field where  $^1\text{H}$  resonance of TMS (internal) is exactly 60 MHz.

<sup>d</sup>  $^1\text{H}$  chemical shift of  $\text{NH}_2$  in aniline is 4.90 ppm downfield from TMS (internal).

the observed nitrogen-15 chemical shifts is shown in Figure 4. The parallel behavior of the nitrogen-15 chemical shifts and amino proton shifts indicates that similar factors are responsible for the substituent effects on their respective chemical shifts and that the  $\pi$  electron density is the single most important consideration. Our results could also be explained in terms of a simple change in the electron density in the diamagnetic term.

(33) B. M. Lynch, *Tetrahedron Lett.*, 1357 (1969).

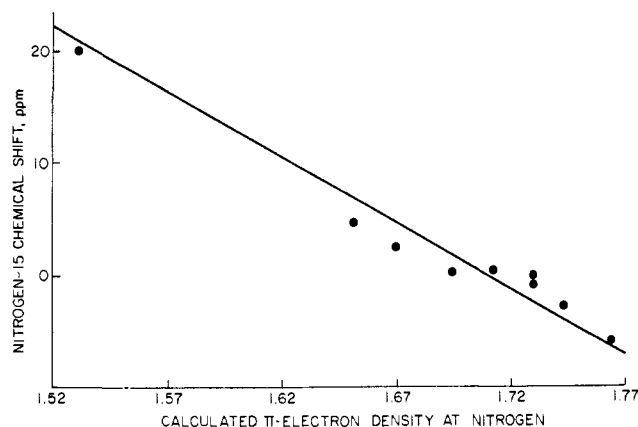


Figure 4. Correlation of nitrogen-15 chemical shifts in aniline derivatives with calculated  $\pi$  electron densities at nitrogen.

However, in simple amines alkyl substitution on nitrogen has the effect of shifting the nitrogen resonance downfield,<sup>13</sup> contrary to what would have been expected if the diamagnetic term were of major importance.

If the paramagnetic term,  $\sigma_P$ , dominates the overall shielding of the nitrogen in these anilines the observed chemical shifts may be qualitatively rationalized. Since the paramagnetic term depends, in part, on bonding to nitrogen the degree of conjugation of the nitrogen lone pair might be expected to be important in influencing the chemical shift. Indeed, the downfield shifts in the ammonium ion and aniline compared with ammonia have been attributed to the decreased shielding due to the lone pair that results from protonation in the one case and delocalization over the aromatic system in the other.<sup>34</sup> Similarly, conjugation of the nitrogen lone pair has been observed as a downfield shift of the resonance in amides,<sup>35</sup> ureas,<sup>36</sup> and thioamides<sup>37</sup> which show variations consistent with the degree of delocalization.

Thus it is reasonable to attribute the downfield shift induced by electronegative substituents in these aniline derivatives to increased  $p-\pi$  interaction between the nitrogen lone pair and the aromatic ring resulting in decreased  $\pi$  electron density at the nitrogen with concomitant deshielding. This view is in accord with the earlier suggestion made by Witanowski and Januszewski to explain the chemical shifts in some conjugated amines.<sup>38</sup>

## Experimental Section

Unless otherwise specified all the isotopically labeled anilines used in this investigation were prepared by a Hofmann rearrangement of the corresponding benzamide- $^{15}\text{N}$ . The various benzamide- $^{15}\text{N}$  derivatives were obtained from the reaction of ammonia- $^{15}\text{N}$  (95%  $^{15}\text{N}$ ) with the appropriate acid chloride which was prepared from the commercially available benzoic acid. The synthesis of *m*-anisidine- $^{15}\text{N}$  which is representative is described in detail.

***m*-Anisoyl Chloride.** A solution of *m*-anisic acid (15.25 g, 0.100 mol) in thionyl chloride was heated under reflux for 2.5 hr. The excess thionyl chloride was removed at reduced pressure and the remaining oil was distilled to give 13.40 g (0.078 mol) of *m*-anisoyl chloride, bp 65–66° (0.2 mm), lit.<sup>39</sup> bp 243–244° (760 mm).

(34) J. B. Lambert, G. Binsch, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, **51**, 735 (1964).

(35) P. Hampson and A. Mathias, *Mol. Phys.*, **11**, 541 (1966); and M. Witanowski, *J. Amer. Chem. Soc.*, **90**, 5683 (1968).

(36) P. Hampson and A. Mathias, *J. Chem. Soc. B*, 674 (1968).

(37) P. Hampson and A. Mathias, *Mol. Phys.*, **13**, 361 (1967).

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

(39) F. Ullmann and I. Goldberg, *Ber.*, **35**, 2813 (1902).

*m*-Anisamide-<sup>15</sup>N. *m*-Anisoyl chloride (0.4265 g, 0.00250 mol) dissolved in 75 ml of ether was cooled in a Dry Ice-acetone bath. Ammonia-<sup>15</sup>N was generated by the dropwise addition over a 20-min period of a solution of ammonium-<sup>15</sup>N chloride (0.2870 g, 0.00526 mol) in 5.0 ml of water to a 5.0-ml solution of 1 M sodium hydroxide maintained at 95° in a 25-ml three-necked flask fitted with a reflux condenser, dropping funnel, and gas inlet tube through which nitrogen was admitted. The evolved ammonia-<sup>15</sup>N was swept from the generation flask through a potassium hydroxide drying tube by a slow stream of nitrogen and finally passed into the cold ethereal solution of anisoyl chloride. Nitrogen flow was discontinued after 5 hr and the reaction mixture was maintained at Dry Ice-acetone temperature overnight. The ethereal mixture was brought to room temperature and the suspended ammonium-<sup>15</sup>N chloride was recovered by filtration and washed with acetone. Concentration of the combined ether-acetone filtrate and washing the resulting crude solid with hexane to remove traces of unreacted acid chloride gave 0.2510 g (0.00165 mol) of crystalline *m*-anisamide-<sup>15</sup>N, mp 131–133°, lit.<sup>40</sup> mp 132–134°.

*m*-Anisidine-<sup>15</sup>N. A solution of sodium hypobromite was prepared by the dropwise addition of bromine (0.2160 g, 0.00135 mol) to an ice-cold stirred solution of sodium hydroxide (0.2620 g, 0.0065 mol) in 5.0 ml of water. After 5 min *m*-anisamide-<sup>15</sup>N was added and the suspension was vigorously stirred at 0° for 20 min at which time a clear yellow solution had resulted. The reaction mixture was slowly heated to 95° and maintained at that temperature for 1.5 hr. The reaction mixture was cooled to room temperature and the dark organic layer was extracted with three 10-ml portions of ether. The combined ethereal extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give 0.1285 g (0.00104 mole) of *m*-anisidine-<sup>15</sup>N as dark oil. The nmr spectrum showed no detectable impurities and consequently the material was used without further purification.

*p*-Phenylenediamine-<sup>15</sup>N<sub>1</sub> was prepared by zinc dust reduction of *p*-nitroaniline-<sup>15</sup>N<sub>1</sub> as described by Hazlet and Dornfeld.<sup>41</sup>

(40) K. V. Levshina and S. I. Sergievskaya, *Zh. Obshch. Khim.*, **24**, 905 (1954).

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

*N,N*-Dimethyl-*p*-phenylenediamine-<sup>15</sup>N<sub>1</sub>. *N,N*-Dimethylaniline was converted to *p*-(nitroso-<sup>15</sup>N)-*N,N*-dimethylaniline as described by Vogel<sup>42</sup> and then reduced by the method of Jacobs and Heidelberger.<sup>43</sup>

**Bromination of Aniline-<sup>15</sup>N.** To a stirred solution of aniline-<sup>15</sup>N (0.470 g, 0.00500 mol) in 15.0 ml of glacial acetic acid at 0° was added dropwise 5.2 ml of a solution prepared by dissolving 8.00 g of bromine in 35.0 ml of glacial acetic acid. The resulting yellow suspension was stirred for an additional 1.5 hr followed by the addition of 35.0 ml of 30% sodium hydroxide solution. The organic layer was extracted with 60 ml of ether, washed with an equal volume of water, dried (MgSO<sub>4</sub>), and concentrated to give 0.840 g of yellow oil. The oil was chromatographed on 60 g of basic alumina. Elution with 900 ml of hexane-benzene (9:1) afforded 0.055 g of 2,4,6-tribromoaniline-<sup>15</sup>N, mp 116–118°, lit.<sup>44</sup> mp 120°. Successive elution with 1.3 l. of hexane-benzene (4:1) gave 0.300 g of 2,4-dibromoaniline-<sup>15</sup>N, mp 78–79.5°, lit.<sup>45</sup> mp 78–79°, and finally 1.2 l. of hexane-benzene (3:2) gave 0.363 g of 4-bromoaniline-<sup>15</sup>N, mp 63–64°, lit.<sup>44</sup> mp 66°.

**Nmr Spectra.** Coupling constant measurements were made with either a Varian HA-100 spectrometer or a Varian A-60A spectrometer using side band interpolation. The accuracy of these determinations is ±0.2 Hz. Proton chemical shifts were measured directly from the A-60A charts, with an estimated accuracy of ±2 Hz (±0.03 ppm). No attempt was made to correct the data to infinite dilution.

<sup>15</sup>N chemical shifts were measured by <sup>1</sup>H{<sup>15</sup>N} double resonance (spin tickling or decoupling) with a Varian HR-60 spectrometer modified for internal field/frequency lock. <sup>1</sup>H and <sup>15</sup>N frequencies were derived from a single frequency synthesizer, as described previously.<sup>16</sup> The frequencies for optimum tickling or decoupling were determined to ±1 Hz or better.

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

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

(44) A. I. Vogel, ref 42, 3rd ed, 1956, p 579.

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