SIBI, MUKUND P.

NITROGEN-15 NMR. I. CHEMICAL SHIFTS OF ANILINES, UREAS, AND RELATED COMPOUNDS. II. INVESTIGATION OF NITROGEN-15 - FLUORINE-19 COUPLING CONSTANTS IN ANILINES, AND PYRIDINES

City University of New York PH.D. 1980

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^{15}N NMR. I. CHEMICAL SHIFTS OF ANILINES, UREAS, AND RELATED COMPOUNDS. II. INVESTIGATION OF ^{15}N-^{19}F COUPLING CONSTANTS IN ANILINES, AND PYRIDINES

by

MUKUND P. SIBI

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.

1980

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ABSTRACT

The Object of This Investigation

The main focus of this project is to study the effect of conjugative interactions on ^{15}N chemical shifts, when the extent of conjugation is varied by different physical and chemical means. The study also includes the determination of N-F coupling constants in fluoroanilines and fluoropyridines. The work is divided into six parts as follows:

(1) Introduction

(2) Effect of steric inhibition of conjugation on ^{15}N chemical shifts in 2,6-dialkyl-N,N-dimethylanilines

(3) Effect of 4-substituents on ^{15}N chemical shifts in anilines, N,N-dimethylanilines, 2,6-dimethylanilines 2,6,N,N-tetramethylanilines.

(4) Effect of peri interactions on ^{15}N chemical shifts in 1,8-diaminonaphthalenes.

(5) Effect of alkyl and aryl substitution on ^{15}N chemical shifts in ureas and thioureas.

(6) Determination of ^{15}N-^{19}F coupling constants in fluoroanilines and fluoropyridines.

^{15}N chemical shifts of several 2,6-diakiyl-N,N-dimethylanilines have been determined in order to assess the effect of steric inhibition of lone-pair delocalization. Relative to aniline, N-methylation induces

upfield shifts, in contrast to the expected deshielding on α substitution. As the steric size of the alkyl substituent increases ^{15}N shifts move to higher applied field. These shieldings can be correlated with increased localization of the lone-pair on the nitrogen atom and with a corresponding decrease in lone-pair ionization potentials. Protonation induces changes in chemical shifts which also correlate with the extent of lone-pair delocalization. From the chemical shift data, the torsional angular deviation of the dimethylamino group from the configuration for maximum delocalization has also been estimated.

^{15}N chemical shifts of 4-substituted anilines, N,N-dimethylanilines, 2,6-dimethyl- and N,N,2,6,-tetramethylanilines have been determined to assess electronic effects on chemical shifts. The range of shifts encompassed in the first three series is very similar. The range of shifts in the 2,6,N,N-tetramethylanilines is approximately one half of that in the other three series. Using Taft's Dual Substituent Parameter approach the results have been analyzed. The qualitative contributions of inductive and resonance interactions of each substituent have been discussed in the sterically hindered 2,6,N,N-tetramethylanilines.

^{15}N chemical shifts of several 1,2-diaminobenzenes and 1,8-diaminonaphthalenes have been determined to assess peri

effects on thes shifts. The presence of an ortho amino group in aniline shields the nitrogen resonance. Small and large shieldings due to alkyl and heteroatom substitution are observed in the benzene series. Large deshielding effects are observed in the naphthalenes on peri substituion. Protonation of compounds in which the proton can be held in between two nitrogens result in large shieldings.

^{15}N chemical shifts of urea, thiourea and several alkyl- and aryl ureas and thioureas have been determined at natural-abundance in aprotic solvents. N-methylation induces systematic upfield shifts which contrast with expected downfield shifts. Higher alkyl substitution at the nitrogen induces shifts in the expected order based on aliphatic amines. Multiple regression analysis has been carried out to get α , β , γ , and δ substituent parameters. The snifts of urea and methylureas can be correlated with ionization potential differences between the lone-pair molecular orbitals. Using equations derived for amides and thioamides activation energy barriers for rotation across the C-N bond have been estimated for both ureas and thioureas. There is a very limited and qualitative agreement between the literature and estimated values in ureas.

Two-to-five bond ^{15}N-^{19}F coupling constants in fluoropyridines and fluoroanilines have been determined by using natural-abundance N nmr spectroscopy. The ^{15}N chemical

shifts of the above compounds have also been determined. The coupling constants in fluoropyridines are large and in fluoropyridinium ions the couplings parallel the $^{13}C-^{19}F$ couplings in analogous iso-electronic fluorobenzenes. Coupling constants in fluoroanilines do not exceed 2 Hz. The effect of lone pair, hydrogen bonding and substituents on $^{15}N-^{19}F$ couplings have been assessed.

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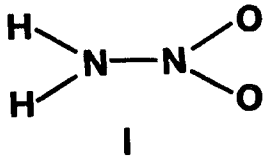
I. INTRODUCTION

Use of natural abundance ^{15}N nuclear magnetic resonance (nmr) spectroscopy in chemistry has become more important in recent years. The presence of nitrogen in a large number of organic and inorganic molecules is the primary reason for the interest in observing this nucleus for the study of molecular structure. Application of the method to structure elucidation began when Ray and Ogg (1) used ^{1}H and ^{14}N nmr spectroscopy to establish the structure of nitramide as the amide of nitric acid (I) rather than as its structural isomer, hyponitrous acid (II).



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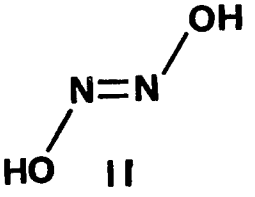


II

In the years following, ^{15}N chemical shifts and relaxation properties were characterized to an increased extent, leading to the present-day exploitation of natural-abundance ^{15}N nmr (2-6).

Comparison Of ^{14}N With ^{15}N

The rate of development of nitrogen nmr spectroscopy has been slow compared with that of proton, carbon, and fluorine (7-9). The slow development can be explained in terms of the greater experimental difficulties encountered with both isotopes of nitrogen. Nitrogen-14, the more abundant isotope (99.65%), has a sensitivity of only 0.00101 that of an equal number of protons in the same magnetic field. Sensitivity in a magnetic resonance experiment is directly proportional to the cube of the magnetogyric ratio, γ which is a function of the magnetic moment and spin quantum number of a nucleus (10).

$$S \quad \alpha \quad \frac{N \quad B_0^2 \quad \gamma^3}{T}$$

Here, N is the total number of nuclei and B_0^2 is the magnetic field strength. Table I lists the different nuclear properties of nitrogen-14 and nitrogen-15 nuclei. From Table I it is evident that the smaller magnetogyric ratios of both ^{14}N and ^{15}N compared to ^{1}H result in decreased sensitivity of the nitrogen nuclei.

Despite its high natural abundance and chemical shift range of several hundred ppm, the chief disadvantage of the ^{14}N nucleus is the spin quantum number I = 1; nuclei with a

spin quantum number greater than 1/2 have a quadrupole moment, which provides an efficient relaxation mechanism. Consequently, except for special cases where the local electrical field gradients are spherically symmetrical (examples of compounds with spherical symmetry are ammonium ions and isonitriles), ^{14}N relaxation times are very short and hence lines very broad. Line widths of up to 1000 Hz have been reported (11) and these result in substantial uncertainties in chemical shift measurements. Line broadening can be decreased to some extent if the spectra are run in dilute solutions, in solvents of low viscosity or at higher temperatures. Under these conditions, the rotational motions of the molecules, which contribute to the molecular correlation times, are increased. because of the direct relationship between correlation times and relaxation rates, the nuclear relaxation rates decrease and the resonances sharpen.

The range of nitrogen chemical shifts for organic compounds is very large (>900 ppm). This factor has been utilized in determination of gross structures of different classes of nitrogen compounds. Small and subtle changes in molecular structure in a particular series of compounds cannot be established using ^{14}N nmr because the uncertainties in chemical shifts are often larger than the substituent effects.

The ^{15}N isotope with a spin of 1/2 does not have a

quadrupole moment and is suitable for high resolution studies. However, the natural abundance of this nucleus is only 0.365% and its sensitivity is only 0.00194 that of an equal number of protons in the same magnetic field (see Table I). Hence, routine detection by earlier available continuous wave (CW) techniques was essentially impossible.

Beginning in 1964, initial ^{15}N studies with enriched compounds were reported by both indirect (INDOR) and direct observation techniques (12). During 1971-72, research groups headed by J. D. Roberts and by E. W. Randall showed that natural-abundance ^{15}N nmr could be a feasible technique. Using time-averaging sweep techniques (13) and pulse-Fourier-transform techniques (14) respectively, the above groups carried out for the first time systematic studies of structurally similar compounds. More recently, the advent of newer spectrometers, improvements in experimental technology, and a better understanding of factors influencing signal strength - exchange processes, relaxation phenomena and the nuclear Overhauser effect - have made natural abundance ^{15}N nmr spectroscopy a chemically useful experimental technique. ^{15}N resonances with enriched material can be observed with little difficulty and natural-abundance spectra can be observed within practical time limits. Later sections discuss some of the experimental methods and molecular properties which affect acquisition of signals.

Table I Comparison of ^{14}N and ^{15}N Nuclear Properties

	^{14}N	^{15}N
Natural abundance	99.64%	0.365%
Spin quantum number	1	1/2
NMR frequency at 2.35 Tesla[a]	7.23 MHz	10.09 MHz
Sensitivity relative to proton for equal number of nuclei	0.00101	0.00194
Sensitivity relative Carbon-13 at natural isotopic abundance	17.22	0.0214
Magnetogyric ratio[b]	1.934×10^{3}	-2.71×10^{3}
Electrical quadrupole moment	1.54×10^{-2}	0

[a]Magnetic field for proton resonance at 100 MHz.

[b]In rad/gauss-sec.

Brief Survey Of Experimental Methods

The Continuous Wave and Indirect Techniques

Nitrogen-15 enrichment, which is often tedious and always expensive, had been widely used for the direct measurement of ^{15}N chemical shifts and coupling constants during the early development of ^{15}N nmr (15). At that time, spectra were obtained by the continuous wave (CW) technique, in which the frequency (or field) is swept through the region of absorption such that nonequivalent nuclei are brought into resonance. In this mode of excitation, only a very narrow band of frequencies contributes to a signal at any one time. Indirect detection of ^{15}N resonances is also possible in enriched compounds where a proton is coupled to a ^{15}N nucleus. The proton signal is continuously observed while a nitrogen frequency is varied until the proton resonance is decoupled. Alternatively, indirect measurement of ^{14}N and ^{15}N chemical shifts can be effected using the INDOR (internuclear double resonance) technique (16).

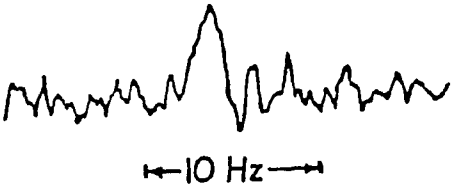
Fourier Transform NMR Techniques

The development of Fourier Transform (FT) nmr spectroscopy has been critical for the growth of ^{15}N nmr (17). Study of low-abundance nuclei like ^{13}C and ^{15}N has been made possible by advances in spectrometer design. because of the

negative magnetogyric ratio of ^{15}N, the typical pulsed FT experimental techniques have to be modified to suit this nucleus. Many comprehensive reviews and books on pulsed FT nmr are available so only a brief description of the experiment is presented here.

The experiment consists of the excitation of the nuclei using a short burst (pulse) of high power (wide band). The nuclei relax after this excitation resulting in a free induction decay (FID) which is in the time domain. In typical experiments a large number of FIDs are accumulated in the computer memory. Fourier transformation of the FIDs results in a spectrum in the frequency domain. The entire excitation and FID collection period commonly requires 1 sec. Typical experiments require 10^3 - 10^4 scans; a practical limit is 10^4 to 10^5 scans.

The FT experiment differs from a CW experiment in that the entire frequency range is monitored simultaneously. The signal strength in a pulse experiment is directly proportional to the number of scans, N, whereas noise is partially averaged out, accumulating with $\sqrt{N}$. Thus the total signal to noise ratio (S:N) increases as a function of $\sqrt{N}$. An idea of the improvement in S:N can be seen in Figure 1 where an FT experiment is compared with a CW experiment (from ref. 8).



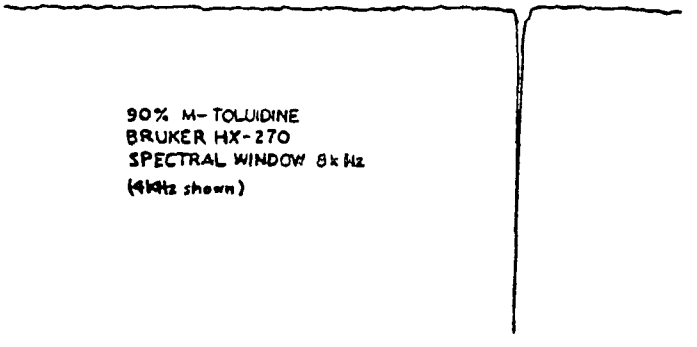


Figure 1. Comparison of a FT Experiment with a CW Experiment.

^{15}N Spin Relaxation

A knowledge of nuclear spin relaxation characteristics is necessary for optimum performance of any FT experiment; such understanding is absolutely critical for successful ^{15}N nmr spectroscopy. The ^{15}N nucleus undergoes spin-lattice (T_1) and spin-spin relaxation (T_2) by the same mechanisms that give rise to ^{1}H and ^{13}C spin relaxation. However, the relative importance of these mechanisms is different for ^{15}N. Also, as a result of the negative magnetogyric ratio (γ) for ^{15}N, simple double resonance experiments may produce undesirable results, such as nulled signals. The relevant relaxation parameters -spin-lattice relaxation time (T_1), spin-spin relaxation time (T_2), and nuclear Overhauser effect (NOE)- are discussed below.

Spin-Lattice Relaxation

The spin-lattice relaxation (T_1) process links nuclear spins with the lattice. The Boltzmann population difference is established by energy exchange between nuclear spins and the lattice. The spin-lattice relaxation for ^{1}H, ^{13}C, and ^{15}N is effected by similar mechanisms. The dipole-dipole mechanism which accounts for all the significant spin-lattice relaxation (18,19) for ^{1}H and for most of the proton bound carbons in ^{13}C nmr, does not necessarily apply for ^{15}N. ^{15}N T_1s vary over a large range from 10 to > 100secs.

Spin-Spin Relaxation

Spin-spin relaxation (T_2) is related to the natural linewidth in the absence of magnetic field inhomogeneity. In ^{15}N nmr the linewidths are controlled by different factors like proton tautomerization, paramagnetic impurities, efficiency of proton decoupling, and B_0 inhomogeneity.

The Nuclear Overhauser Effect

Irradiation at frequencies of protons attached directly to nitrogen results in the collapse of the nitrogen multiplet leading to an increase in the signal intensity of the nitrogen resonance. The intensity of the nitrogen resonance is sometimes greater than that arising from collapse of the N-H multiplet. This intensity change, the nuclear Overhauser effect NOE (20), arises in general when an observed nucleus relaxes via dipole-dipole interactions with another nucleus (commonly proton), whose energy levels are saturated. The maximum obtainable NOE is given by

$$I / I_0 = 1 + \tfrac{1}{2} (\gamma_H / \gamma_X)$$

where I_0 is the intensity without irradiation and I is the intensity with irradiation. For ^{13}C, which relaxes mainly by dipolar interactions with the bound proton(s), the maximum intensity enhancement from the NOE is 200% (Nuclear

Overhauser Enhancement Factor NOEF of 1.98). The negative magnetogyric ratio for ^{15}N results in a negative NOE. The maximum NOEF for ^{15}N is -4.93. Thus, the negative NOE results in an inverted resonance signal for an ^{15}N nucleus. If the ^{15}N nucleus relaxes by other than a dipolar mechanisms the NOEF decreases. A NOEF of -1 results in a nulled signal. Experimental methods like gated decoupling (8) have been developed to overcome this problem. Using this method spectra can be obtained without significant loss in S:N regardless of ^{15}N T_1s. Longer ^{15}N T_1s lengthen the total time needed for a gated decoupling experiment.

^{15}N Chemical Shifts

Since carbon and nitrogen are both second-row nuclei, their shielding is subject to similar electronic and structural effects, and nitrogen shifts generally parallel carbon shifts. The range of chemical shifts for nitrogen (>900 ppm) is slightly greater than that for carbon. For a given class of compounds, additive substituent parameters that have some predictive value (and are similar in magnitude to those for ^{13}C resonances) can be obtained. The lone pair on nitrogen is a feature which distinguishes it from carbon and is useful for structure elucidation. Removal of the lone pair results in changes of the nitrogen shifts. The magnitude and direction of the change of the resonance position are characterstic of a specific type of nitrogen. Nitrogen shifts

are also more sensitive to solvent changes than the resonances of structurally analogous carbons, and this can be exploited for the study of intermolecular interactions.

Various methods have been employed to calculate nitrogen shifts and to relate nitrogen shifts to electron densities. The latter attempts have met with limited success (21). At best, qualitative agreement exists for structurally similar types of nitrogens exhibiting relatively large (50 ppm) chemical shift ranges. More sophisticated ab initio methods using extended basis sets have been impractical for most molecules of organic structural interest (22). When the chemical shift range is very small, the correlation between electron density and shifts is not satisfactory. Chemical shift theory applied to nuclei other than proton does not require the dependence of shifts on electron density (23).

A qualitative framework can be obtained for considering ^{15}N chemical shifts with the aid of semiempirical methods. This is also useful in visualising the effect of the lone pair on ^{15}N shifts. The total nuclear screening constant can be written as

$$\sigma_{tot} = \sigma_{dia}^{loc} + \sigma_{Para}^{loc} + \sigma_{other}$$

In this equation, σ_{dia} is the local diamagnetic screening of the nucleus. This term dominates proton shifts and is related directly to electron density. σ_{para} is the

local paramagnetic term which is negative and requires electrons in orbitals with non-zero angular momentum . The quantity σ_{other} includes all contributions to the screening from other sources than those at the nucleus; anisotropy, field effects, etc. Usually σ_{other} is very small. Both σ_{dia} and σ_{para} may be large, but calculations suggest that σ_{dia} remains relatively constant for a given class of compounds (24,25). Thus, changes in shifts as a function of structure may be attributed to changes in σ_{para}.

σ_{para} can be viewed in terms of three structurally related contributions

$$\sigma_{para} \propto \frac{1}{\Delta E} \cdot \left(\frac{1}{r^3}\right) \cdot \Sigma Q$$

where $\frac{1}{\Delta E}$ is the average excitation energy; $\frac{1}{r^3}$ is the average inverse cube of the (non-s) orbital radius, ΣQ is derived from charge densities and bond orders of all bonding electrons.

The importance of the above factors may be seen from the data in Table II. Removal of the lone pairs in ammonia and methylamine by protonation results in deshielding, probably by removing the diamagnetic screening of the lone pair (26,27). The presence of $n \rightarrow \pi^*$ transitions in an aromatic system (lower ΔE) and increased C-N bond order, can explain the low-lying resonance position of aniline compared with aliphatic amines. The importance of $n \rightarrow \pi^*$ transitions (lower

Table II Illustrative Nitrogen Chemical Shifts[a]

Compound	δ_N, ppm[b]
Ammonia	0.0
Methylamine	2.0
Ammonium Chloride	25.0
Methylamine Hydrochloride	28.0
Anilinium Chloride	48.0
Aniline	52.0
Pyridinium ion	215.0
Pyridine	317.0
Protonated trans-azobenzene	358.0
Trans-azobenzene	508.0

[a]Taken from Reference 8.

[b]Downfield from anhydrous liquid ammonia.

ΔE) and multiple bonding to nitrogen (large Q) results in a large deshielding of the pyridine nitrogen. In general, to the extent that the lone pair exerts a major paramagnetic influence on nitrogen resonance positions, its removal by protonation is expected to result in an upfield displacement of the nitrogen resonance position. This may be seen in the protonation-induced changes in pyridine (-110 ppm) and azobenzene (-150 ppm). The changes on protonation are represented graphically in Figure 2.

Nitrogen chemical shifts of organic compounds can be divided into regions roughly characteristic of the type of nitrogen in a compound (28) (Figure 3). Since there is no discernible isotope effect (29), ^{14}N and ^{15}N chemical shifts can be compared directly.

Aliphatic amines display regular changes in chemical shift with changes in structure. Alkyl substitution at the α position results in a small deshielding, comparable to that of analogous carbon compounds. Beta alkyl substitution results in a large deshielding which is nearly twice the value obtained for carbon in an analogous system. Gamma alkyl substitution results in a small shielding. These have been discussed in some detail elsewhere (8,30).

Spin-Spin Coupling Constants

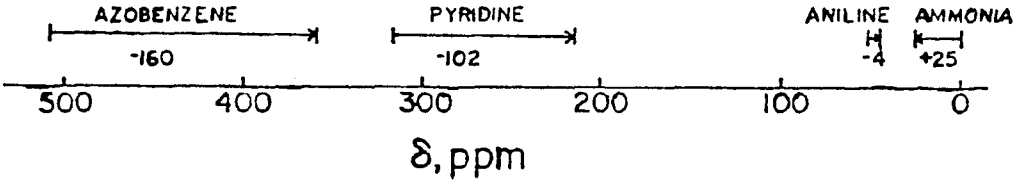


Figure 2. Schematic representation of Protonation Induced Changes (from Table II ref 8).

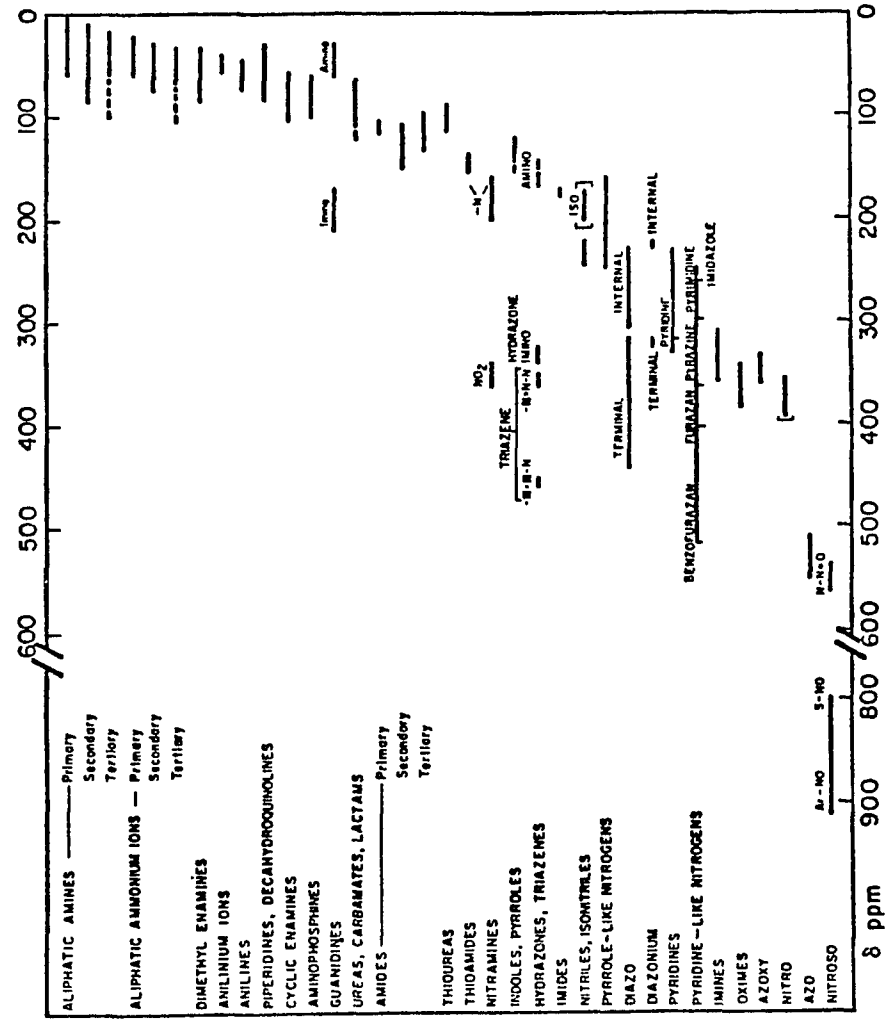


Figure 3. Nitrogen NMR Chemical Shieldings in Organic Compounds (from ref 8).

The drawback of nitrogen-14, the more abundant nucleus, in the determination of coupling constants is its quadrupole moment. Where quadrupole-induced relaxation is rapid, coupling to ^{14}N is generally eliminated. Values obtained from ^{14}N measurements can be converted to the corresponding ^{15}N values by multiplying by the ratio of the magnetogyric ratios, $\gamma_{15N} / \gamma_{14N} = -1.402$

Determination of coupling constants to ^{15}N at natural abundance is not practical except for N-H couplings. In nearly all other cases one needs enriched ^{15}N compounds. Early calculations of nitrogen couplings assumed the dominance of the Fermi contact mechanism, which is the prevailing mechanism for proton and most ^{13}C couplings. Based on this mechanism, qualitative relationships between one-bond couplings and s character have been suggested (31). More recent work suggests that these relationships apply only under limited conditions. One-bond couplings can be geometry dependent. Vicinal couplings to nitrogen display a dependence on geometry analogous to that of carbon and proton. Two-bond couplings to nitrogen can be related to lone-pair orientation. Couplings are large and negative to those nuclei that are close in space to the lone pair, and small and positive to those that are farther removed. Detailed theoretical assessments of coupling mechanisms are hampered by the sensitivity of the calculated values to small changes in geometrical parameters (32-35).

Couplings to nuclei other than proton and carbon have received less theoretical attention. $^{15}N-^{19}F$, (36) $^{15}N-^{31}P$ (37,38), and ^{15}N-metal couplings have been reported (39,40).

The Object of This Investigation

The main focus of this project is to study the effect of conjugative interactions on ^{15}N chemical shifts, when the extent of conjugation is varied by different physical and chemical means. The study also includes the determination of N-F coupling constants in fluoroanilines and fluoropyridines. The work is divided into six parts as follows:

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(6) Determination of $^{15}N-^{19}F$ coupling constants in fluoroanilines and fluoropyridines.

CHAPTER 2

Amines, in which nitrogen is present in its most highly reduced form, may be considered the parents of organonitrogen compounds. They have been studied extensively by many chemical and physical techniques, among which nmr spectroscopy has been widely applied. The nmr method has been particularly valuable in studying intramolecular and intermolecular hydrogen-bonding, and nitrogen inversion in aliphatic and aromatic amines. The properties of aromatic amines, of which aniline is the parent compound, have been studied to a large extent to correlate their behavior with the extent of lone-pair delocalization. The suggested relationships between nuclear magnetic resonance properties and various functions of electron distribution make NMR spectroscopy eminently suitable for this type of study. Particularly when the NMR behavior of the nitrogen nucleus itself is affected, nitrogen NMR spectroscopy has been a useful probe of these phenomena. The general trends and correlations sought by ^{14}N and ^{15}N nmr spectroscopy of amines will be outlined here and then the problem at hand will be discussed.

Ammonia and aliphatic amines lie at the highly shielded end of the spectral range (0-60 ppm). ^{15}N chemical shifts of aliphatic amines have been studied extensively. The effect of alkyl substitution has been analyzed and substituent parameters similar to ones derived for ^{13}C chemical shifts of

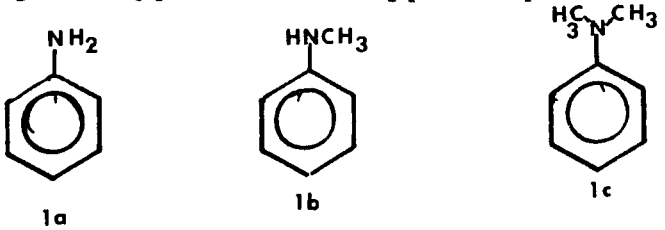
alkanes have been obtained (13,30,41). The effects of solvents on ^{15}N chemical shifts of aliphatic amines have been examined (30). The ^{15}N chemical shifts of aliphatic amines and ^{13}C chemical shifts of alkanes correlate well with each other (30). Protonation of aliphatic amines generally deshields the nitrogen, but the magnitude of this effect is variable. The change on protonation has been shown to depend on solvent (30), counterion (42), concentration(42), and pH (14,42-44). Alicyclic amines display trends analogous to those of the cyclic compounds. The stereochemical dependence of ^{15}N chemical shifts has also been studied in alicyclic amines (30,45).

Nitrogen resonance positions of arylamines are usually deshielded by ~50 ppm from the corresponding aliphatic amines. The deshielding of arylamines has been attributed to the interaction between the nitrogen lone-pair and the adjacent π system. Nitrogen chemical shifts of substituted arylamines have been shown to correlate with π electron densities and Hammett σ constants (46-48). The ^{15}N chemical shifts of anilines also correlate with ^{19}F chemical shifts of the correspondingly substituted fluorobenzenes and ^{13}C chemical shifts of the corresponding toluenes. The nitrogen resonance positions of anilines are not only affected by conjugatively interacting substituents, but also by non-conjugatively interacting methyl groups. Ring methyl substitution in anilines influences the nitrogen resonance positions

in a systematic manner, and this has been related to polarization of the σ network (49-51). The extent of nitrogen lone-pair delocalization can be influenced by different kinds of mechanisms, for example, substituent effects and steric inhibition of resonance. Several experiments have shown that in o-methyl substituted N,N-dimethylanilines nitrogen lone-pair delocalization can be inhibited by steric effects (52-61). Therefore, we have determined the ^{15}N chemical shifts of alkyl substituted N,N-dimethylanilines in order to assess the influence of steric inhibition of conjugation on the resonance positions. We have also studied the effect of protonation on these compounds.

RESULTS AND DISCUSSION

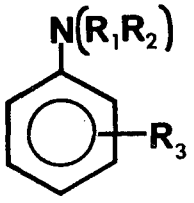
The ^{15}N chemical shifts of compounds 1-5 (see Chart I) are presented in Table III. Table III also includes ^{15}N chemical shifts for the protonated compounds, pK_a's for some of the compounds (52,62), and photoelectron vertical ionization potentials (59,61). Several trends can be seen at the outset. Successive methylation at the nitrogen of aniline (1a → 1b → 1c) displaces the nitrogen resonance positions upfield by 5.3 ppm and 11.9 ppm respectively.



1a 1b 1c

0 -5.3 -11.9

Chart I



1a R_1, R_2, R_3 = H

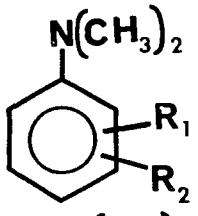
1b R_1, R_3 = H, R_2 = CH_3

1c R_3 = H, R_1, R_2 = CH_3

1d R_3 = 2-CH_3, R_1, R_2 = CH_3

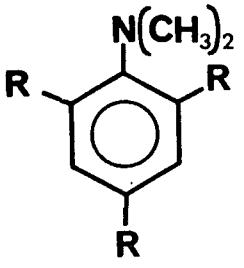
1e R_3 = 3-CH_3, R_1, R_2 = CH_3

1f R_3 = 4-CH_3, R_1, R_2 = CH_3

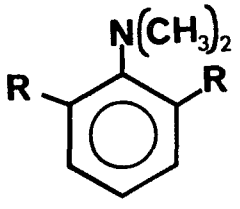


2a R_1 = 2-CH_3, R_2 = 3-CH_3

2b R_1 = 2-CH_3, R_2 = 6-CH_3



3 R = CH_3



4 R = C_2H_5

5 R = i-C_3H_9

Table III ^{15}N Chemical Shifts and Related Data of N,N-Dimethylanilines[a]

Compound	δ_N, ppm[b]	$\Delta\delta_N$[c]	$\Delta\delta_{N'}$[d]	δ_{NH^+}[b,e]	$\Delta\delta_{NH^+}$[f]	pK_a[g]	I.P.$_{\Pi 4}$[h]	I.P.$_{\Pi 2}$[h]
1a	56.43[i]	0	11.9	51.03[i]	-5.4	4.26	8.05	10.61
1b	52.73	-3.7	8.2	44.53	-8.2	4.29	7.65	10.20
1c	44.53	-11.9	0	47.53	+3.0	4.39	7.37	9.80
1d	33.83 (-20.3)[k]	-22.6	-10.7	46.03	12.2	5.15	7.92	9.51
1e	43.63 (-12.0)	-12.8	-0.9	47.53	3.9	4.66	7.24	9.61
1f	41.93 (-12.0)	-14.5	-2.6	46.63	4.7	4.94	7.27	9.55
2a	33.33 (-19.5)	-23.1	-11.2	45.73	12.4	5.25		
2b	17.03 (-33.9)	-39.4	-27.5	46.33	29.3	4.81	7.85	8.85
3	15.33 (-32.2)[l]	-41.1	-29.2	45.63	30.3	5.15[m]		
4	13.03 (-35.1)[n]	-43.4	-31.5	45.73	32.7			
5	10.33 (-37.0)[n]	-46.1	-34.2	44.13	33.8			

[a] Chemical shifts and differences in parts per million.

[b] Chemical shifts were measured with respect to ^{15}N nitromethane and then converted to anhydrous ammonia scale using the equation $\delta_{NH_3} = \delta_{CH_3NO_2} + 380.23$ Positive values denote downfield shifts ref 63.

[c] $\Delta\delta_{N_i} = \delta_i - \delta_{aniline}$ [d] $\Delta\delta_{N_i} = \delta_i - \delta_{1a}$

[e]Chemical shifts of the anilinium ions.

[f]$\Delta\delta_{NH^+} = \delta_{ion} - \delta_{amine}$ = change in chemical shift on protonation.

[g]Ref 52, in 50% ethanol.

[h]Vertical ionization potentials (eV); ref 59-61.

[i]Ref 50.

[i]Ref 51.

[k]Parenthesized values are differences between the substituted N,N-dimethylanilines and the corresponding anilines. Ref 49

[l]$\delta_{mesidine} = 47.53$.

[m]Ref 62.

[n]The chemical shifts of 2,6-diethyl-and 2,6-diisopropylaniline are 48.13 and 47.33 ppm, repectively.

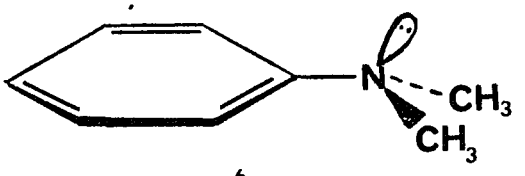
The same direction of change is not seen in the protonated species of the above compounds. On going from protonated 1a to 1b a shielding of the nitrogen is seen, whereas 1b→1c results in a deshielding. This shielding on methylation contrasts markedly with the effects of α-methylation on the ^{13}C chemical shifts of structurally analogous alkylbenzenes (toluene→ethylbenzene→cumene), where downfield shifts of 9 ppm are observed for the substituted carbon (64). In aliphatic amines, α-methylation results in deshielding. An α-substituent parameter of 9 ppm was derived by multiple regression analysis of the primary amine data (13,30,41). There are a few examples of shielding arising from α-methylation in the literature (46,65-68). For example, the nitrogen nucleus of 1,1,3,3-tetramethylurea is shielded by ~12 ppm from that of urea (65). Similarly, the ^{15}N resonance position of N-methylpyrroline is 7.1 ppm to higher applied field than that of the unsubstituted compound (66). Upfield shifts on N-methylation of an aminoglycoside have been reported (67). Nitrogen resonances of N-methylated barbituric acids lie at a higher shielding than those of the unsubstituted compounds (68). Upfield α-methylation shifts are not restricted to cases where a π system can interact with nitrogen. For example, N-methylation of 2,2,6,6-tetramethylpiperidine results in a large shielding of ~30 ppm (46).

As in the case of anilines, ring methyl substitution of

N,N-dimethylaniline shifts the nitrogen resonances to higher field. The effect of 3- and 4-methyl substitution (1e and 1f respectively) parallels the results in anilines (49). However, 2-methyl substitution (1d and 2a) induces an additional 7-8 ppm change over that found in 1c and 1f. This is evident from the parenthesized values in column 2 of Table III, which are expected to partially correct for effects of the methyl groups common to both the anilines and N,N-dimethylanilines. Further methylation at the ortho position (2b and 3) causes additional shielding. The nitrogen shift of 2b is 34 ppm to a higher field than that of 2,6-xylidine. The upfield shift is enhanced by increasing the size of the 2,6-dialkyl groups. This can be seen from the chemical shifts of 4 and 5.

Protonation of 1a and 1b also shields the nitrogen resonance. In compounds 1c-5 the effect of protonation is opposite to that of 1a and 1b, in that the resonances move downfield. With the exception of 5, the chemical shifts of the ions in this series differ by amounts just outside experimental error, averaging 21.5 ppm with a standard deviation of 0.8 ppm. The resonance positions of compounds 1c-5 all lie at higher field than those of the corresponding primary anilines, except for 2b. The ^{15}N chemical shifts of protonated 1a, 1b, and 1c do not parallel ^{13}C chemical shifts of the substituted carbon in the isoelectronic toluene, ethylbenzene, and cumene respectively (64).

The shielding induced by ortho alkyl substitution in 1c can be interpreted in terms of the well established distortion of the dimethylamino group from the optimum conformation 6 for nitrogen lone-pair interaction with the benzene π system.



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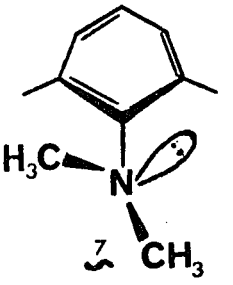
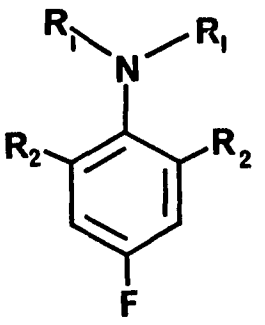


7

In this case, the pyramidal nitrogen is still oriented such that the axis of the lone-pair orbital makes a dihedral angle of 90° with respect to the plane of the ring. Distortions from this geometry has been correlated with changes in basicity (52,53), UV absorption intensities (53), pK_a's of substituted benzoic acids (58), ^{13}C chemical shifts of the para carbon (56), ^{19}F chemical shifts (57), and changes in ^{13}C- H coupling constants (69,70). The increased basicity of 1d, 2a, and 3 relative to 1c, 1e, and 1f can be attributed to greater localization of electron density at nitrogen in the twisted conformation 7. Recently, the pK_a of 2,4,6,-tri-t-butyl-N,N-dimethylaniline has been measured (71). It was concluded from pK_a and UV studies that the nitrogen in this compound is almost completely out of conjugation. The ^{19}F chemical shifts of compounds 8-11 also qualitatively support the data presented in Table III.



8 $R_1 = R_2 = CH_3$

9 $R_1 = CH_3$, $R_2 = H$

10 $R_1 = R_2 = H$

11 $R_1 = H$, $R_2 = CH_3$

The lower field resonance position of ^{19}F in 8 relative to 9 can be attributed to reduced nitrogen lone-pair delocalization. The fluorine in 8 is more delocalized than in 9 resulting in a deshielding of the former compound. There is a qualitative correlation between ^{15}N chemical shifts of 2a, 1c, 1a, and 2,6-xylidine and ^{19}F chemical shifts of 8-11, but no quantitative correlation exists. Similarly, if the ^{19}F and ^{15}N chemical shift differences between corresponding nonmethylated and dimethylanilines are compared, a qualitative but not quantitative parallelism exists. The absence of a direct correlation probably reflects the different degrees to which inductive and mesomeric effects contribute to shifts in the disubstituted compounds compared to the monosubstituted (57).

As alluded to earlier, ^{15}N chemical shifts in many cases have been correlated with ^{13}C chemical shifts. We have tried a similar approach and compared para carbon ^{13}C chemical shifts of anilines with ^{15}N chemical shifts of compounds 1a-5. To the extent that the same factors influence both sets of resonances, the differences between ^{13}C of the dialkyl-N,N-dimethylanilines relative to the primary anilines are expected to reflect largely the electronic effect of the nitrogen. Figure 4 shows a plot of the differences in ^{13}C chemical shifts of the para carbon of the dimethylanilines and the anilines against the ^{15}N chemical shift differences of the same compounds. The ^{13}C chemical shifts of all the

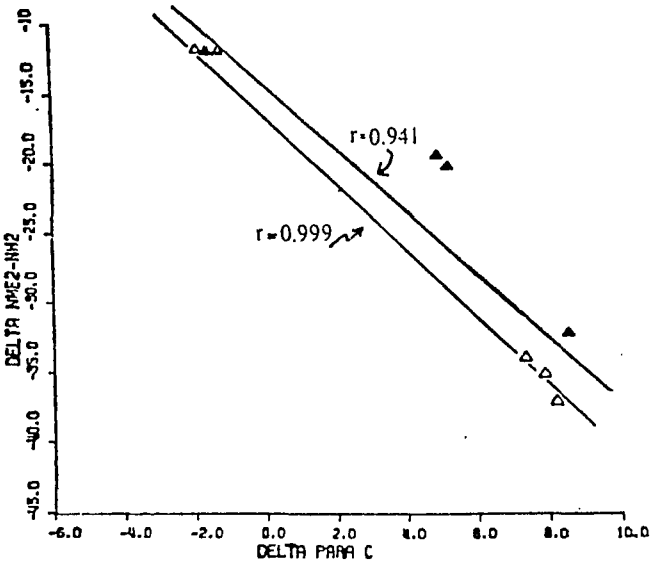


Figure 4. Plot of Nitrogen Shifts of Dialkylanilines vs. Carbon Shifts of C_4. The upper line represents the least-square correlation of allpoints, while the lower line (open triangles) represents the correlation within the 2,6-dialkyl-substituted series 1c, 2b,4, and 5.

compounds except 2b, 4, and 5 are in the literature (56). The scatter exhibited by these points may arise from two sources. First, steric and electronic factors are likely to influence the nitrogen shifts in the less hindered primary anilines to a different extent than in the tertiary compounds and this difference may be compensated only partially by taking the chemical shift differences (parenthesized values in column 2, Table III). Second, the positional influence of the ring alkyl substituents on the ^{13}C and ^{15}N resonances is likely to be different. For example, in 2a the methyl group at C-3 is ortho to C-4 but meta to C-1 which bears the amino group. There is no requirement that the responses of the two positionally different nuclei, ($-C_4$ and NH_2) to a given substituent be the same. The two sets of data show a moderate correlation (see Fig. 4, r= 0.94, slope = 2.3 ppm N/ppm C). To limit the number of variables influencing the shifts, the series 1c, 2b, 4, and 5, where only the nature of the alkyl substituent at C-2 and C-6 is changed, can be examined. Here, electronic perturbations at C-4 and the nitrogen are expected to vary little throughout the series, and the correlation with a limited number of data points is much improved (r=0.999, slope= -2.4 ppm N/ppm C). The slope of -2 obtained in this series indicates that the nitrogen chemical shifts are twice as sensitive as those of carbon. Similar kinds of slopes are obtained for primary aliphatic amines (30). Hence, it is reasonable to suggest that both the nitrogen and C-4 resonance positions

are primarily influenced by common factors, of which the torsional distortion of the dimethylamino group is likely to be dominant.

Further support for the distortion of the dimethylamino group can be obtained by comparison of ^{15}N chemical shifts of 1c, 1d, 2b, and 3 with the ^{119}Sn chemical shifts of substituted trimethyltin compounds (72). The two sets of data correlate well, presumably indicating similar effects (see Figure 5, $r = 0.970$). The upfield ^{15}N resonance positions upon methyl substitution at the 2- or 6- positions in 1-(cycloalkylamino)cyclohexenes have been attributed to distortion of the nitrogen lone-pair from maximum conjugation (73).

The upfield shifts on N-methylation in aniline can be attributed to inhibition of delocalization with an increase in electron density at nitrogen and also to a decrease in C-N π bond character. According to the Karplus-Pople treatment (23) of chemical shifts (Chapter 1), a decrease in the C-N π bond character results in a decrease in the paramagnetic term in the shielding expression and thereby shields the nitrogen. An approach of this type has been used to rationalize the nitrogen shifts in conjugatively substituted

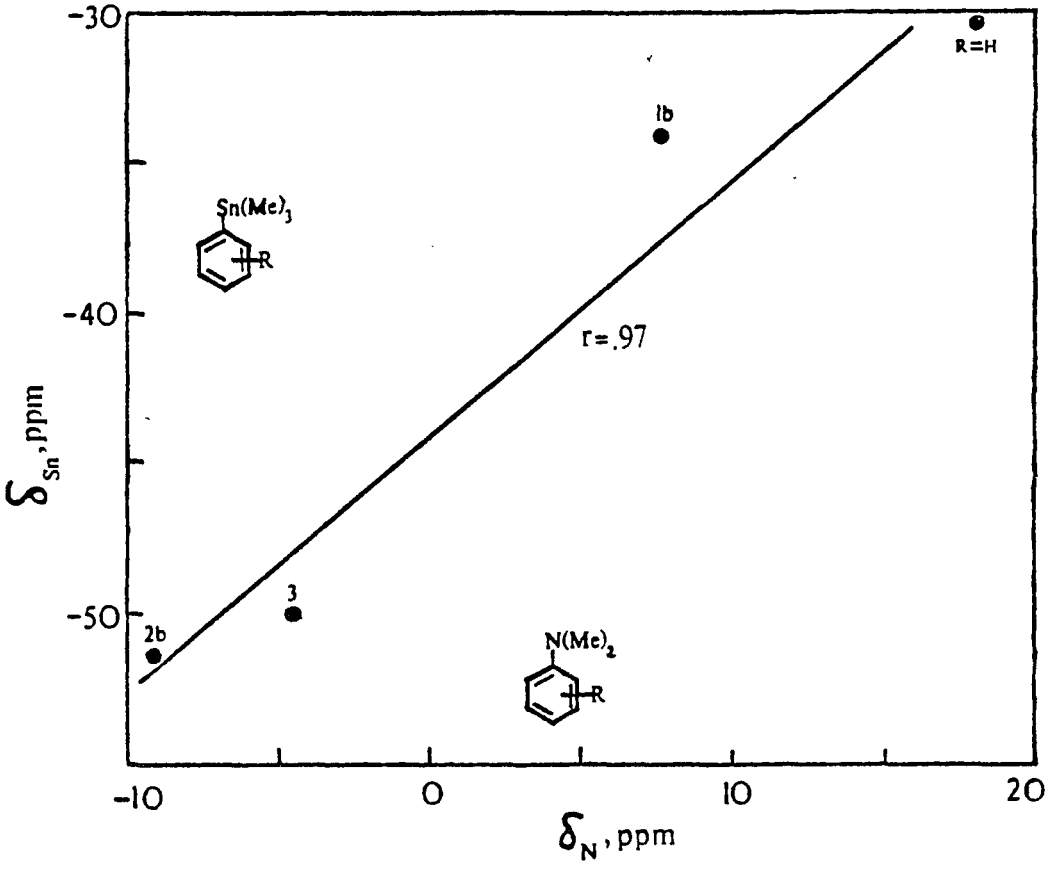


Figure 5. Plot of δ_N, ppm Vs. ^{119}Sn Chemical Shifts.

anilines (46,47,49).

Photoelectron spectroscopy (PES) has been very helpful in the analysis of ^{15}N chemical shift data. The ^{15}N chemical shifts of anilines and the N-methylation effect can be rationalized with the help of vertical ionization potentials obtained by PES (59-61). Photoelectron spectroscopy allows determination of the extent of lone-pair-π orbital overlap, and hence can be related to both δ_N and σ_{para} in the Karplus-Pople formulation. Discussion of these data is helpful in understanding the α-methylation upfield shifts. There are two degenerate benzene highest occupied molecular orbitals of the symmetry type a_2 and b_1. Delocalization of the nitrogen lone pair, which has a b_1 symmetry, into the benzene ring results in an interaction with the HOMO b_1, resulting in a splitting of this level. The a_2 HOMO is affected to a slight extent, presumably because of an inductive effect. These interactions are indicated schematically in Figure 6. Calculations (74) suggest that the first and third ionization bands labelled π_4 and π_2, respectively, (59), may be assigned to those arising by interaction with the nitrogen lone-pair. Hence, the difference between π_4 and π_2 ionization potentials, ΔIP, reflects the extent of lone-pair delocalization. Figure 7 represents schematically the change in π_4 and π_2 with change in alkyl substitution. From Figure 7, it is apparent that both π_4 and π_2 undergo similar changes in all compounds which do not bear ortho

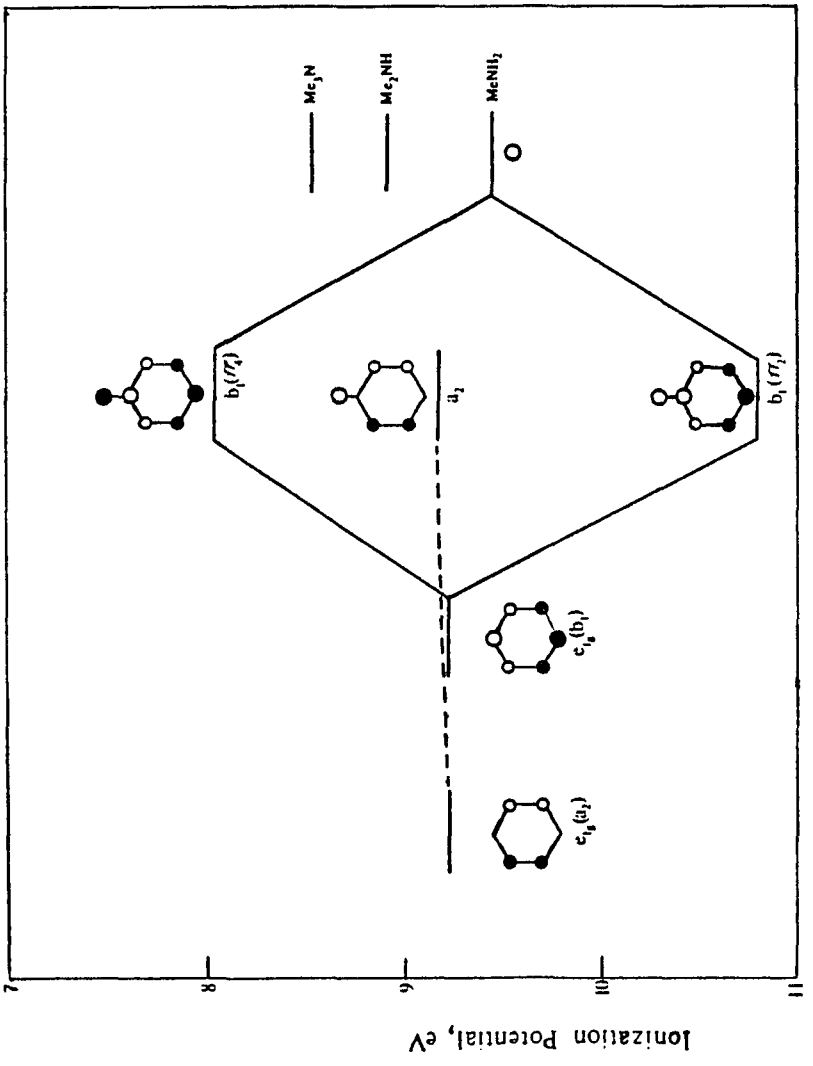


Figure 6. Schematic Representation of the Interaction between the 2p Orbital of an Amine Nitrogen and the HOMOs of Benzene.

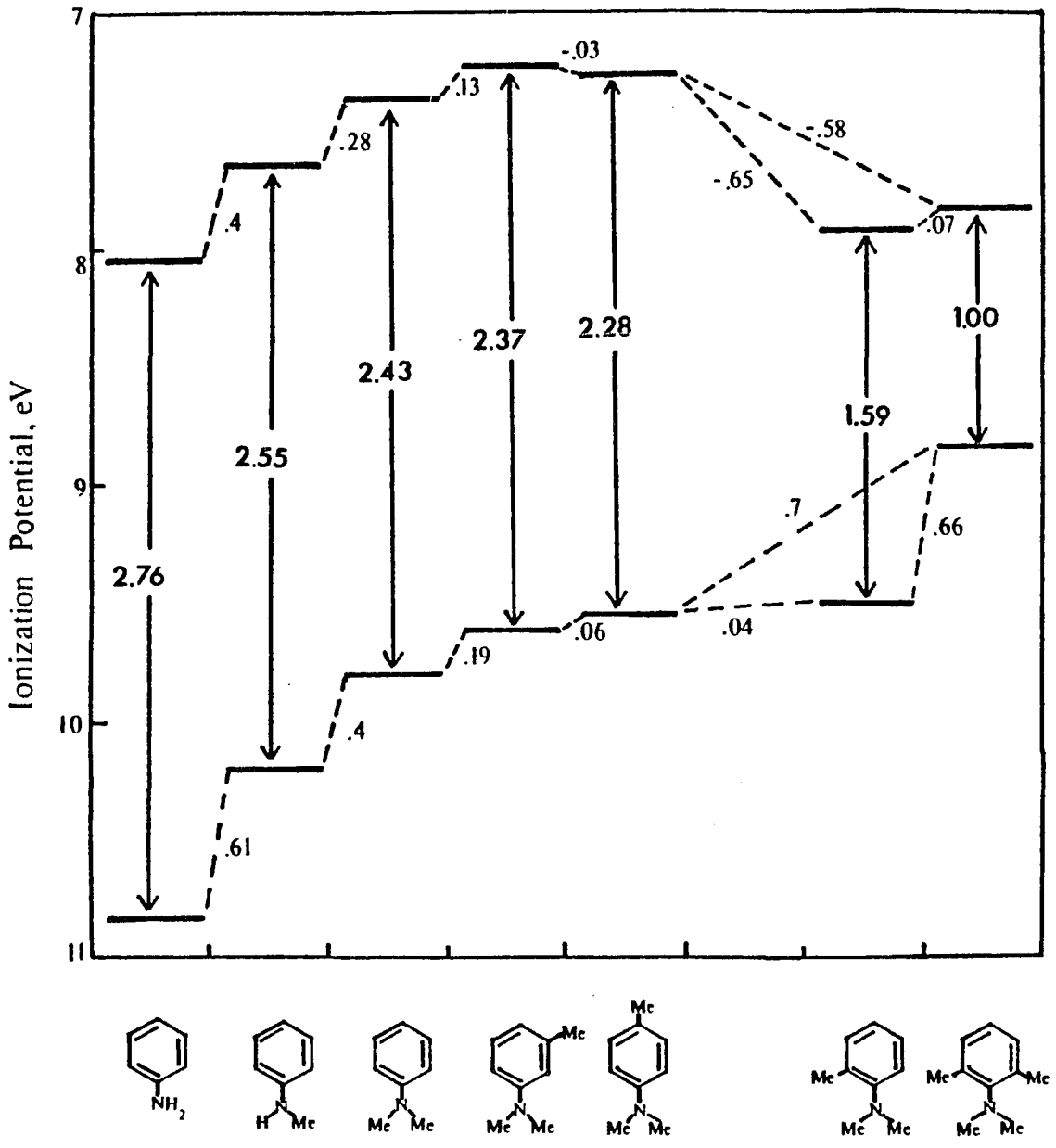


Figure 7. Schematic Representation of the Benzene Orbital Splitting by an Amino Group.

methyl groups (1a, 1b, 1c, 1e, 1f). The change in ionization potentials in the series 1a → 1b → 1c parallels the trend in the series ammonia → methylamine → dimethylamine (75). Substitution in the ortho positions (1c → 1d → 2b) decreases ΔIP progressively. Figure 8 shows a plot of δ_N against ΔIP where the least square line has a correlation coefficient of 0.97 and a slope of 20.6 ppm/eV (lower scale in Fig. 8, dotted lines). Similarly, δ_N correlates moderately well with the π_2 ionization potential; correlation coefficient = 0.95, slope = 20.2 ppm/eV. Overlap population calculations (74) have shown that π_2 has a considerably higher lone-pair character. If aniline (1a) is left out of the correlation arbitrarily, there is an improvement in the correlation coefficient (r = 0.980). The correlations displayed in Figure 8 suggest that both the ΔIPs and the nitrogen shifts reflect the same changes in nitrogen lone-pair delocalization. The near linearity seen for the correlation in Figure 8 can be explained as a dominance of the C-N π bond character (due to 2p-π interaction) in the determination of the nitrogen resonance positions. The preponderance of these factors may account for the high linearity exhibited.

The upfield shifts on N-methylation in the series 1a → 1b → 1c can also be explained with the help of PES. Increasing methyl substitution reduces lone-pair interaction with the ring. The influence is larger on π_2, which has a higher lone-pair character. This may reflect an increase in

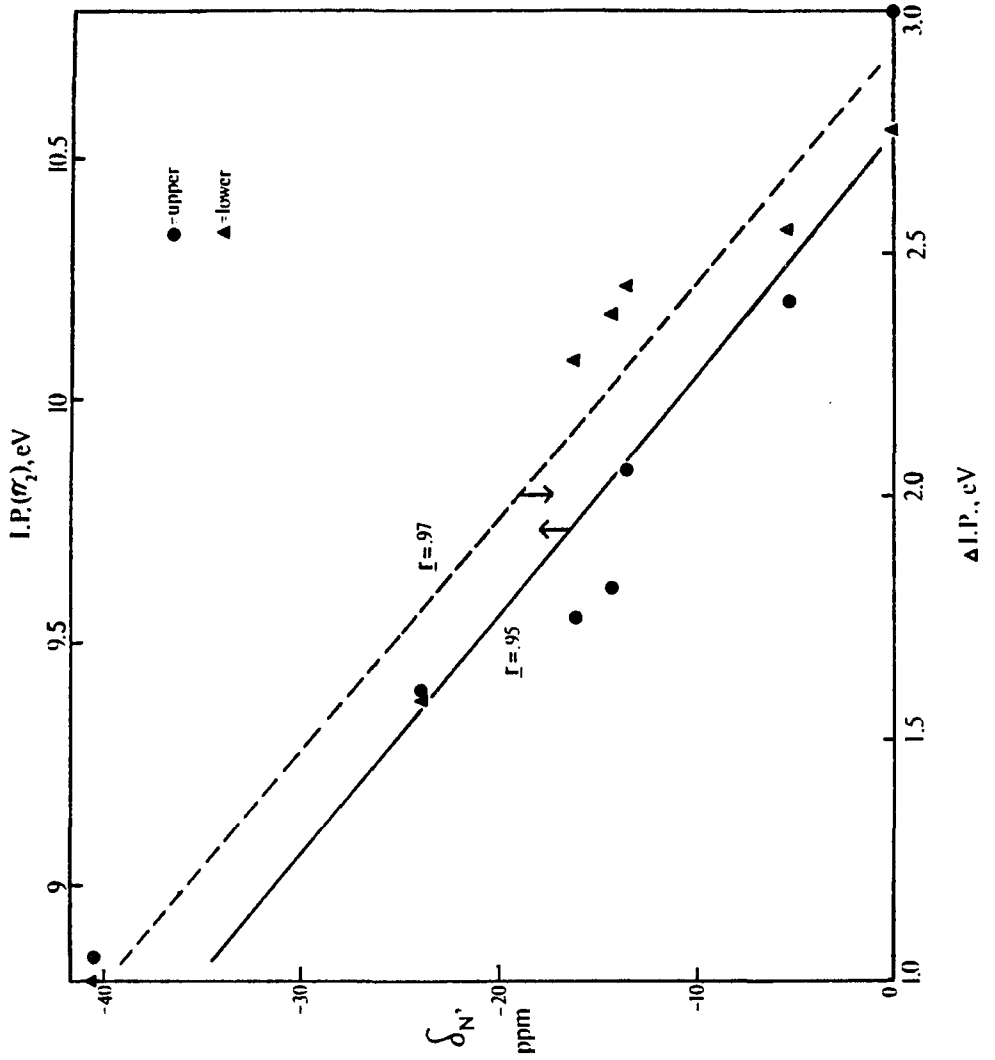


Figure 8. Plot of Nitrogen Chemical Shifts of Dimethylanilines vs. Photoelectron Ionization Potentials.

the energy difference between the unperturbed lone-pair and the benzene b_1 orbital as a function of methyl substitution. The change in δ_N parallels both ΔIP as well as the ionization potential of π_2. The same kind of destabilization of the lone-pair is seen on α methyl substitution in the series ammonia → methylamine → dimethylamine where the ionization potential decreases in the order 10.46 9.64 8.9 eV, respectively (75). A similar approach has been used to explain the upfield shifts seen on N-methylation in formamide, acetamide, and ureas (see Chapter 5). The change in ΔIP displayed by 1d reflects a much larger change in π_4 and only with the second methyl substitution is π_2 affected (1d → 2b). This may arise from more extensive geometrical changes in the dimethylamino group itself in 2b than in 1d, or from an interchange of the relative positions of π_4 and π_2.

The decrease in ΔIP has been correlated with the torsional angle about the C-N bond, giving values of 55 and 65^0 for 1d and 2b respectively. These values are in good agreement with the values estimated from UV data (54), and from pK_a values of substituted benzoic acids (56). Changes in photoelectron ionization potentials have been applied to geometrical studies of nitrobenzenes (61), phenols (59), anisoles (61), and disulfides (76). Ionization potentials have been related to the cosine of the torsional angle θ of the dimethylamino group in compounds 1c, 1d, and 2b (59,60).

Since there is a linear correlation between θ and ΔIP, it is possible to estimate torsional angles in compounds where the chemical shifts are known. The values of δ_N (Table III) for 1c, 1d, and 2b correlate ($r = 0.95$) with $\cos\theta$, giving a slope of 0.22/ppm and an intercept of 0.490. Applying these results to δ_N of 4 and 5, values of 77 and 80° for the torsional angles are obtained. If the parenthesized values for 4 and 5 (column 2 of Table III) are used instead, in order to partially compensate for steric interactions in the primary amines themselves, values of 74 and 77° are obtained for 4 and 5 respectively. Since the experimental values for 1c, 1d, and 2b are estimated to have an uncertainty of 5; both sets of calculated torsional angles are in reasonable agreement with each other. Geometrical changes other than in the torsional angle may be anticipated. The C-N-C bond angles are particularly susceptible to sterically induced distortion and this would be expected to influence shifts. However, the correlation of the nitrogen shifts with other data which themselves are interpretable in terms of torsional angle distortion makes this structural factor likely to exert the major influence.

In general, to the extent that the lone-pair exerts a major paramagnetic influence on nitrogen resonance positions, its removal by protonation is expected to result in shielding of the nitrogen nucleus. This may be seen (Chapter 1) in the protonation induced changes of pyridine (-110 ppm)

and azobenzene (-150 ppm) (12). The upfield shift of -5.4 ppm when aniline is protonated can be attributed to the compensating influence of removal of the nitrogen lone-pair (shielding) and generation of positive charge (deshielding). The effect of generation of a positive charge is seen in the 24 ppm deshielding of the ammonium ion relative to ammonia (12). This has been shown to arise from a change in the diamagnetic part of the chemical shift expression by the presence of a positive charge (26). The upfield shift on protonation of 1b suggests that its lone pair is comparably delocalized, while the downfield shift exhibited by 1c suggests that delocalization is partially inhibited. The larger downfield protonation shifts displayed by the remainder of the series are all consistent with successive attenuation of nitrogen lone-pair delocalization. Although solvent, concentration, and nature of the anion are likely to influence the shifts of the protonated compounds (45), the near constancy of the values for 1c-4 probably reflects structural features to a large extent. It is also interesting that, with the exception of 2b, all the resonances lie at higher field than those of the corresponding primary anilinium ions (51). The slight deviation of the value for 5 may be due to steric effects. The high rotation barrier around the C -N bond in protonated 2b of 16.0 kcal/mol (77) supports this conclusion. The apparent anomalous behavior of N-methylaniline 1b, in view of the correlation with the ionization potential data, must remain without explanation.

CHAPTER 3

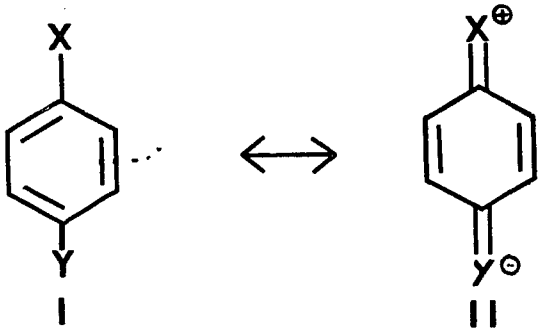
Many properties, chemical and physical, of ring-substituted aromatic compounds depend, at least in part, upon the manner in which ring substituents modify the electronic structure of the molecule (78). Any physical measurement, for example, UV absorption intensities, nmr chemical shifts, that is dependent on the electron distribution in such an aromatic system might therefore be expected to reflect the differences in electronic structure due to the effect of different ring substituents.

The Hammett equation (79), which is the basic equation for the study of substituent effects and linear free energy correlations in organic systems, is shown below.

$$\log k/k_0 = \sigma\rho$$

This equation represents the effect of a substituent on a standard equilibrium, rate of reaction, or any physical property of the system. The value of ρ varies according to the electronic demands of the reaction or the property measured, but is a constant for a fixed set of reaction conditions. The σ constant for a substituent Y (see structure I) in the meta or para position gives a measure of its electronic

effect on the reaction center X.



The σ constant is a measure of the transmission of the substituent electronic effect to the reaction site rather than a measure of its effect on the benzene ring itself. It was recognized earlier that σ values derived by Hammett from p-substituted benzoic acids do not apply for other reactions where X in I is not a carboxylic acid group. This led to the derivation of new σ constants, for example, σ^+ and σ^-, as extremes for cases where the functional group X (see structure I) placed a demand on electrons or had a surplus of them, respectively (80). Taft and his co-workers (81) pioneered attempts to split values into inductive and resonance contributions. The inductive part was considered as the electrical disturbance in the σ bonds and through space, and arose from charge distribution in the substituent. The resonance part consisted of all disturbances observed in the π system of the ring. Thus, the Hammett equation can be written as

$$P_i - P_0 = \sigma_I \rho_I + \sigma_R \rho_R \qquad (1)$$

where P_i is the property measured with the substituent i, P_0 is the property measured with i=H, σ_I is the inductive constant, σ_R the resonance constant, and ρ_I and ρ_R have the same significance as explained for ρ. This approach, named the Dual Substituent Parameter (DSP) analysis, has been used extensively. Similar equations have been derived by Swain and Lupton (82), Bodner and Todd (83), Coulson (84), Yukawa and Tsuno (85), and Dewar (86). There are excellent reviews in the literature on the use of DSP equations for the analysis of chemical reaction data (87,88). It has been shown that the inductive part in equation 1, σ_I, which was derived using aliphatic systems, remains constant for both the aliphatic and aromatic systems (87). In Taft's analysis (87-89) there are four established scales for the resonance parameter σ_R : σ_R^0, $\sigma_{R(BA)}$, σ_R^+, and σ_R^-. The σ^0 values give the relative charge-transfer abilities of substituents attached to an otherwise unperturbed π - system as in monosubstituted benzenes. The $\sigma_{R(BA)}$ scale is appropriate where the probe X (see structure I) is a carboxylic acid group joined to a benzene ring. The terms σ_R^+ and σ_R^- are appropriate to cases where the benzene ring is electron deficient (e.g., p-substituted nitrobenzenes) or electron rich (p-substituted anilines) respectively. Topsom (88) has summarized the advantages of DSP analyses of chemical and spectroscopic data, advantages which usually offset the disadvantage of increasing the number of adjustable parameters.

The effect of substituents in anilines and derivatives has been studied extensively and different properties like basicity, UV absorption intensities, ^1H nmr chemical shifts have been correlated with substituent parameters. Hammett substituent constants (σ) have been shown to be directly proportional to such properties of anilines as base strengtn (90), N-H stretching frequencies (91), and amino proton chemical shifts (92-95). The amino proton chemical shifts in p-substituted anilines have been correlated with electron density at nitrogen (96). The methyl proton chemical shifts of p-substituted N,N-dimethylanilines have been correlated with Hammett σ constants (97). Recently, the methyl proton chemical shifts of p-substituted N,N-dimethylanilines have been correlated with Dewar's F and M constants (98). Likewise, the methyl $^{13}C-H$ coupling constants in p-substituted N,N-dimethylanilines have been correlated with Hammett σ constants (69).

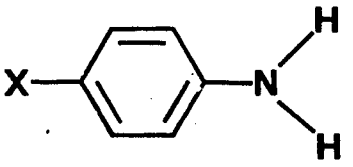
The ^{15}N chemical shifts of p-substituted anilines have been determined and they have been correlated with Hammett σ constants (47). $^1J_{N-H}$ coupling constants in p-substituted anilines have been correlated with Hammett σ constants and have been shown to depend on solvent and hybridization of the nitrogen (99). Taft and co-workers (87) have analyzed Axenrod's aniline data (47) using a DSP approach and have correlated them with σ_R^- , the most appropriate con-

stant. These two sets of data correlate with each other well. Nitrogen nmr spectroscopy is very useful in the analysis of substituent effects in anilines, because the major electronic change is occurring at the nitrogen. Hence, we have determined the ^{15}N chemical shifts of p-substituted anilines (1a-1m) and N,N-dimethylanilines (2a-2m) to assess the effect of substituents on these shifts. In view of our results in 2,6-dialkyl-N,N-dimethylanilines, where the amino group is twisted out of conjugation, we have analyzed the effect of p-substituents on the ^{15}N chemical shifts of 2,6-dimethyl- and 2,6,N,N-tetramethylanilines, (3a-3m) and (4a-4m), respectively. Our interest was to determine whether this analysis would enable us to separate the inductive and resonance contributions of the p-substituent.

RESULTS AND DISSCUSSION

Tables IV-VII list the ^{15}N chemical shifts of compounds 1-4. Table IV, which contains ^{15}N chemical shifts of p-substituted anilines, also lists the pk_a values of some of the compounds (95). Table V contains ^{15}N chemical shifts of p-substituted N,N-dimethylanilines and the ionization potential of the first band in the PES spectrum of some of the compounds (100). Table VIII contains all the regression parameters obtained from the correlation between ^{15}N chemical shifts and σ_I and σ_R using Taft's DSP approach. The correlations presented in Table VIII have been obtained using a

Table IV ^{15}N Chemical Shifts and Related Data for p-Substituted Anilines



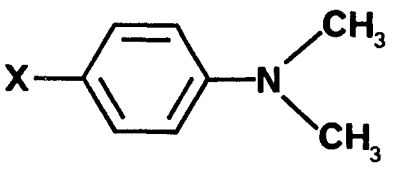
Number	X	δ_N, ppm[a]	$\Delta\delta_N$, ppm[b]	pK_a[c]
1a	H	59.76	0.0	4.69
1b	$N(CH_3)_2$	53.47	-6.29	
1c	OCH_3	54.55	-5.21	5.44
1d	CH_3	57.82	-1.94	5.16
1e	F	55.66	-4.1	4.65
1f	Cl	60.36	+0.6	4.07
1g	Br	61.21	+1.45	3.86
1h	I	62.43	+2.67	
1i	CN	73.18	+13.42	
1j	NO_2	79.48	+19.72	1.04
1k	NH_2	56.01	-3.75	5.34
1l	OH	56.09	-3.27	
1m	COOH	72.34	+12.58	

[a]Resonance positions to lower shielding relative to anhydrous ammonia. Samples were run as $\sim$2 M solutions in DMSO.

[b]$\Delta\delta_N = \delta_{Ni} - \delta_{N\ i=H}$ Positive values denote shifts to lower shielding.

[c]Ref 96.

Table V ^{15}N Chemical Shifts and Related Data for p-Substituted N,N-Dimethylanilines



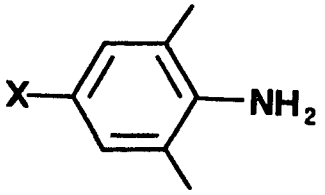
Number	X	δ_N, ppm[a]	$\Delta\delta_N$, ppm[b]	IP, eV[c]
2a	H	44.88	0.0	9.85
2b	$N(CH_3)_2$	42.6	-2.28	10.0
2c	OCH_3	40.77	-4.11	9.24
2d	CH_3	42.76	-2.12	9.59
2e	F	42.73	-2.15	
2f	Cl	49.11	+4.23	7.60
2g	Br	50.08	+5.2	
2h	I	48.26	+3.38	
2i	CN	59.64	+14.76	
2j	NO_2	68.6	+23.72	7.94
2k	NH_2	38.44	-6.44	
2l	OH	[d]	[d]	
2m	COOH	59.64	+14.16	

[a,b] As in Table IV.

[c] Ref. 100.

[d] Not determined.

Table VI ^{15}N Chemical Shifts of p-Substituted 2,6-Dimethyl Anilines

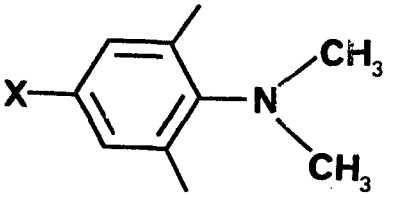


Number	X	δ_N, ppm[a]	$\Delta\delta_N$, ppm[b]
3a	H	55.77	0.0
3b	$N(CH_3)_2$	53.31	-2.4
3c	OCH_3,	51.20	-4.57
3d	CH_3	52.75	-3.02
3e	F	53.1	-2.67
3f	Cl	57.46	+1.69
3g	Br	58.68	+2.91
3h	I	[c]	[c]
3i	CN	72.05	+16.28
3j	NO_2	81.04	+25.27
3k	NH_2	52.26	-3.51
3l	OH	[c]	[c]
3m	COOH	67.80	+12.03

[a,b] As in Table IV.

[c] Not determined.

Table VII ^{15}N Chemical Shifts of p-Substituted 2,6,N,N-Tetramethylanilines



Number	X	δ_N, ppm[a]	$\Delta\delta_N$, ppm[b]
4a	H	16.80	
4b	$N(CH_3)_2$	13.56	-3.24
4c	OCH_3	[c]	[c]
4d	CH_3	15.97	-0.83
4e	F	13.90	-2.90
4f	Cl	[c]	[c]
4g	Br	17.57	+0.77
4h	I	[c]	[c]
4i	CN	18.23	+1.43
4j	NO_2	27.71	+10.91
4k	NH_2	13.67	-3.13
4l	OH	[c]	[c]
4m	COOH	21.53	+4.73

[a,b] As in Table IV.

[c] Not determined.

Table VIII Correlation Parameters for Compounds 1-4 Using DSP Analysis.

Compound	ρ_I	ρ_R	S.D.[a]	R.M.S.[b]	f[c]	λ[d]	n[e]
1	12.95	21.79	0.8012	8.1572	0.098	1.68	10
2	18.05	20.19	1.8623	9.3197	0.199	1.12	9
3[f]	17.29	25.03	1.3532	9.4440	0.136	1.44	8
4	4.18	10.44	2.290	4.405	0.519	2.49	7

[a]S.D. = Standard deviation of calcluted P_i.

[b]R.M.S. = Root mean square value of P_i.

[c]f = S.D./R.M.S.

[d]$\lambda = \rho_R/\rho_I$.

[e]n = Number of points.

[f]Dimethylamino group was not included in the calculation.

multiple regression analysis. The parameters ρ_I and ρ_R are constants obtained from the regression analysis and have the same significance as ρ. The value $\lambda = \rho_I / \rho_R$ indicates the relative importance of resonance and inductive transfer of charge to the observation center, and allows an insight into the property studied. The value f is defined as S.D./R.M.S., where S.D. is the root mean square of the deviations, and R.M.S. is the root mean square of the measured values. It has been suggested that values of $f < 0.1$ indicate excellent fit and values between 0.1 and 0.2 acceptable ones (88). It has been shown that calculation of f is more trustworthy in the analysis of structure-activity relationships than the more conventional correlation coefficient r. (87,101). Calculations performed omit carboxy,hydroxy, and amino substituents. There are no σ_R values for the first two substituents, and Taft has suggested that because the amino substituent can be heavily solvated, its use is not proper (87). In all the calculations performed in this study the minimum basis set requirement (87) is met except in compounds 3 and 4.

The chemical shifts presented in Table IV compare well with the values obtained by Axenrod et al. (47). The Table also contains ^{15}N chemical shifts for six compounds which were not included in the previous study. As observed before, the resonance position of aniline is shifted to higher shielding when an electron donating p-substituent is pre-

sent. Similarly, electron withdrawing p-substituents shift aniline's resonance position to lower field. In the earlier study (47), nitrogen shifts were shown to correlate with the π electron density at nitrogen. The pK_a's of some of the anilines also correlate with the nitrogen chemical shifts (r = 0.97, slope = -5.45). This indicates that differential solvation in this series of compounds does not affect the resonance positions. The results obtained from the regression analysis presented in Table VIII compare well with those obtained by Taft using Axenrod's data (47). The λ value of 1.68 indicates that the resonance contribution of the p-substituent predominates over the inductive contribution. The λ value of 1.68 is similar to λ values obtained for ionization of p-substituted anilinium ions (87), although the two experiments measure two different state properties.

Studies of chemical shifts of p-substituted N,N-dimethylanilines have not been as extensive as those of anilines. N-methylation of aniline results in shifts of the nitrogen resonance to higher field. This has been explained in Chapter 2. The effect of p-substituents in N,N-dimethylanilines is similar to that observed for primary anilines (1a-1m). The range of shifts in compounds 2a-2m is slightly larger than that for 1a-1m. The ρ_I and ρ_R values obtained for N,N-dimethylanilines are higher than those for anilines. This suggests that the total substituent effect

is larger in N,N-dimethylanilines than in anilines. A λ value of 1.11 indicates that the resonance contribution of the substituent is only slightly larger than the inductive contribution. This value is similar to those obtained for ionization of p-substituted N,N-dimethylanilinium ions (87). The f value for dimethylanilines is higher than that obtained for anilines. Recently, the ^{15}N chemical shifts of p-substituted N-phenylaziridines have been analysed (102). N-phenylaziridines, which are structurally similar to N,N-dimethylanilines, show a good correlation with σ_I and $\bar{\sigma_R}$ values. The λ value of 2.52 suggests that resonance interactions predominate even more over inductive effects than in N,N-dimethylanilines. The ^{15}N chemical shifts of some N,N-dimethylanilines do not correlate with the first ionization band in the PES spectrum ($r = 0.83$). This band has been identified to have a large lone-pair character (100). Although there is a poor correlation, a trend does exist.

Introduction of electron donating o-methyl groups in aniline shields the nitrogen. The effect of p-substituents in 2,6-dimethylanilines is similar to that observed for primary anilines. An f value of 0.13 indicates a good correlation between the substituent constants and chemical shifts. The ρ_I and ρ_R values obtained for 2,6-dimethylanilines are larger than those for anilines, which indicates that the total substituent effect is larger in the former than in the latter series. A λ value of 1.44 for 2,6-dimethylanilines,

which is slightly lower than that for anilines, indicates nonetheless a predominance of resonance contributions over the inductive ones.

In 2,6,N,N-tetramethylaniline, the dimethylamino group has been estimated to be twisted out of the benzene plane by 65^0 (see Chapter 2). Introduction of a p-substituent might have been expected to influence the nitrogen mainly via the σ network and thus enable a distinction to be made between inductive and resonance contributions of the substituent compared with those in more highly conjugated anilines. With this aim, we analyzed the effect of p-substituents in 2,6,N,N-tetramethylanilines using the DSP approach. Inspection of Table VIII shows that σ_I and σ_R^- do not correlate with ^{15}N chemical shifts (f = 0.51). Hence, any conclusions drawn from the analysis are debatable although some qualitative trends can be seen. One possible reason for the lack of correlation may be that the degree of twisting of the dimethylamino group depends on the p-substituent. Hence, the extent of resonance vs. inductive contribution to the ^{15}N chemical shift would differ for each compound, and no correlation would be expected. The correlations were also determined using σ_R^0 instead of σ_R^- and the ρ_I and ρ_R values are the same in both cases.

In conclusion, the ^{15}N chemical shifts of p-substituted anilines, N,N-dimethylanilines, and 2,6-dimethylanilines can

be correlated successfully with substituent constants. The lack of correlation in 2,6,N,N-tetramethylanilines shows the limitation of this kind of analysis. A study of 6-substituted benzoquinuclidines where the nitrogen lone pair is known to be orthogonal to the benzene ring could be more rewarding for the separation of inductive and resonance contributions of a substituent.

CHAPTER 4

Substituents at the 1,8-(peri) positions of the planar naphthalene are in much closer proximity than similar substituents in aromatic systems which are located ortho to each other. This geometry has been resposible for the existence of several unique properties of peri-substituted naphthalenes (103). Steric repulsion between bulky substituents at the peri positions can be relieved in principle by stretching of bonds, by in-plane deflection or distortion of the substituent, or by a change in the geometry of the ring itself. Steric effects in naphthalenes have been analysed by crystal structure, UV absorption, nmr chemical shifts, and pK_a measurements. A few crystal structures of peri-substituted naphthalenes have been determined. In 1,8-dinitronaphthalene steric strain is relieved by a twisting of the nitro group by 43^0 from the ring (104,105). Similar twisting of the nitro group has been observed for 1,4,5,8,-tetranitronaphthalene (106). The crystal structures of 1,8-diphenylnaphthalene (107) and 1,4,5,8-tetraphenylnaphthalene (108) have been analyzed. In these compounds the phenyl rings are face-to-face and experience an in-plane splaying of 5^0 away from the normal direction of an exocyclic bond. It has also been shown that in 1,8-diiodonaphthalene the 2,7-hydrogens exert buttressing effects favoring the out-of-plane distortion of the substituent (109). The crystal structure of

1,8-bis(bromomethyl)naphthalene has been analyzed (110). Here, steric strain is relieved by the lengthening of bonds attached to C-1 and C-8 compared to naphthalene, by the in-plane bending of the substituent, and by out-of-plane distortion involving the entire molecule.

Even a proton in the 8-position exerts some steric interaction on a substituent at C-1. This is evidenced by the reduction in ϵ ($\sim$10000) in the UV spectrum of 1-dimethylamino-4-nitronaphthalene compared to 1-amino-4-nitronaphthalene (111). Several authors (112-114) have attributed the low-field position of the 8-proton in 1-substituted naphthalenes to peri effects. The lower electrical dipole moment of 1-dimethylaminonaphthalene compared to 1-aminonaphthalene has been ascribed to peri effects (115). From molar Kerr constant studies of 1-aminonaphthalene, a torsional angle of 28^{0} for the amino group has been suggested (116).

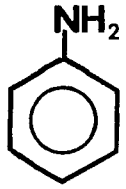
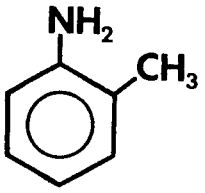
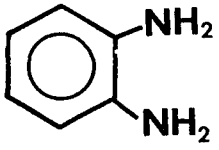
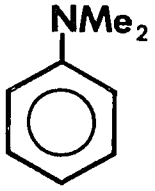
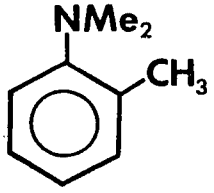
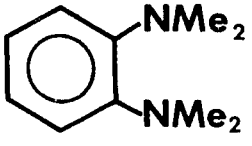
Alder and co-workers have studied the basicity of 1,8-diamino- and 2,7-disubstituted-1,8-diaminonapthalene and have shown that in the latter compounds the amino groups are severely sterically hindered (117,118). 2,7-Dimethoxy-1,8-dimethylaminonaphthalene, with a pK_a of >16, is one of the strongest neutral bases, and this high basicity has been attributed to severe steric crowding (118).

Recently, Schuster and Roberts (119) reported a study of proximity effects on ^{15}N chemical shifts. In this study ^{15}N chemical shifts of 8-substituted-1-aminonaphthalenes and 8-substituted-1-nitronaphthalenes were determined. It was observed that the nitro and amino nitrogens are deshielded upon 8-substitution regardless of the nature of the substituent. The deshielding upon substitution at the 8-position was attributed to steric effects. In view of our study on o-substituted-N,N-dimethylanilines (Chapter 2) where the amino group is twisted out of conjugation, we wished to assess the influence of this alternative kind of steric effect, the peri interaction, on ^{15}N chemical shifts. Thus, we have determined the ^{15}N chemical shifts of 1,8-diaminonaphthalenes, their protonated forms and their structural analogs in the benzene series, namely 1,2-diaminobenzenes.

RESULTS AND DISSCUSSION.

The ^{15}N chemical shifts of 1,2-diaminobenzenes and 1,8-diaminonaphthalenes are presented in Tables IX and X respectively. The Tables also list the ^{15}N chemical shifts of the protonated compounds. The chemical shifts of the compounds were determined as 2M solutions in DMSO. The aniline nitrogen is deshielded in DMSO compared to its resonance position in the pure liquid. Because DMSO is a hydrogen-bond acceptor, it can form strong hydrogen bonds

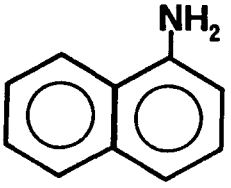
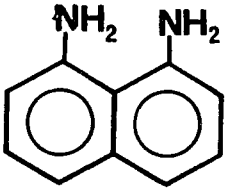
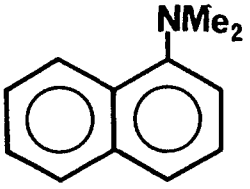
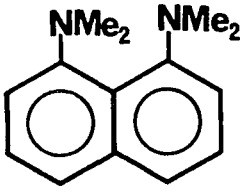
Table IX ^{15}N Chemical Shifts of 1,2-Diaminobenzenes

Compound	Number	δ_N, ppm[a]	δ_{NH^+}, ppm[b]	
	1	59.76	51.03	-8.73
	2	57.94	48.73	-9.21
	3	52.02	50.70	-1.3
	4	44.68	47.53	+2.75
	5	33.83	46.03	+12.2
	6	37.87	32.29	-4.58

[a]Resonance positions to lower shielding relative to anhydrous ammonia. Samples were run as ~2 M solutions in DMSO.

[b]As trifluoroacetates in chloroform: amine:TFA is 1:2 M.

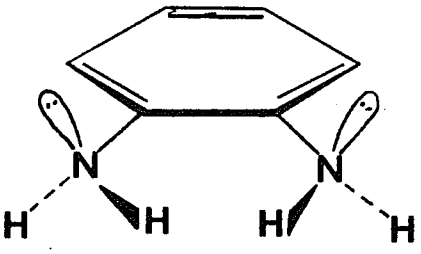
Table X ^{15}N Chemical Shifts of 1,8-Diaminonaphthalenes

Compound	Number	ppm	ppm	
	7	62.55	44.39	-18.16
	8	68.10	48.03	-20.07
	9	35.93	44.64	+8.71
	10	45.36	34.13	-9.77

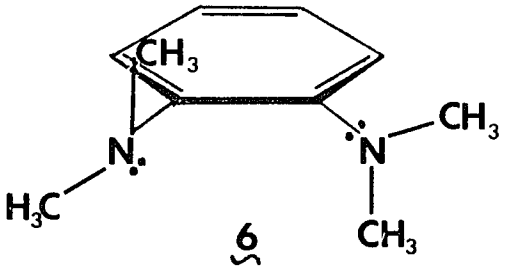
As in Table IX.

with the amino protons, and this is known to deshield the nitrogen. The effect of solvent on the aniline nitrogen resonance position has been studied in detail (120,121). The effect of N-methylation and o-methyl substitution in aniline has already been explained in Chapter 2. Substitution of an ortho amino group in aniline shifts the nitrogen resonance to higher shielding. This may be attributed in part to a reduction of nitrogen lone-pair delocalization by the presence of an additional electron-donating substituent. The change is similar to the upfield shift exhibited by o-toluidine compared to aniline, where an electron-donating methyl group shields the nitrogen. The two amino groups in o-phenylenediamine are γ to each other. A γ substituent which is electronegative generally shields nitrogen (13,41). Thus, the shielding arising from o-amino substitution in aniline can in part be ascribed also to γ effects. Similar upfield shifts are observed in ^{13}C chemical shifts of toluene on o-methyl substitution (122) and the ^{19}F chemical shifts of fluorobenzene on o-fluoro substitution (123). For example, the methyl ^{13}C chemical shift of o-xylene is 1.7 ppm to higher shielding than that of toluene and the ^{19}F chemical shift of o-difluorobenzene is 25.7 ppm to higher shielding than that of fluorobenzene. Substitution of a methyl group at the 2-position in N,N-dimethylaniline results in a large shielding of the nitrogen. This has been attributed to the twisting of the dimethylamino group out of conjugation (see Chapter 2). Similar placement of a dimethylamino group at

C-2 in N,N-dimethylaniline shifts the resonance position upfield but by ~7 ppm. This decrease compared with o-phenylenediamine may be attributed to two factors. First, the electron density in the benzene ring is increased by the presence of an electron donating dimethylamino group, resulting in reduced conjugation. Second, the presence of a bulky dimethylamino group can result in a twisting of the dimethylamino group out of conjugation. Molecular models indicate that there is considerable steric crowding in compound 6 and a conformation (shown below) in which one of the nitrogens is twisted out of conjugation may be a favorable one. The presence of a single resonance for compound 6 implies a time-averaged signal corresponding to the conjugated and non-conjugated dimethylamino groups. This could account for the fact that the nitrogen is not as shielded as that in 2,N,N-trimethylaniline. It is interesting to note that introduction of an amino substituent at the 2-position in aniline and N,N-dimethylaniline induces approximately the same change in chemical shift.



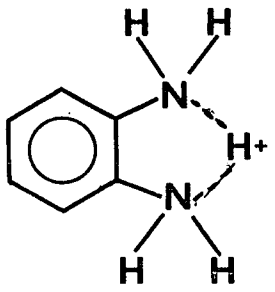
3

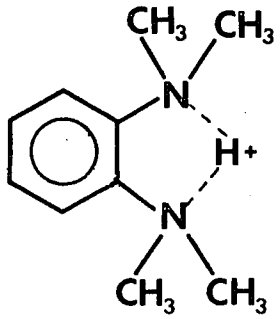


6

Protonation of aniline and o-toluidine leads to shielding of the nitrogens, as was discussed in Chapter 2. The effect of protonation in 3 is also shielding. A shiela-

ing of a larger magnitude is observed for 6. Compounds 3 and 6 are monoprotonated under the experimental conditions used for the study (124).

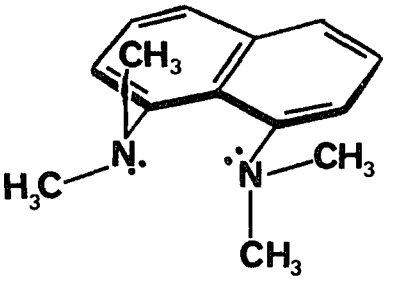




The protonated forms of 3 and 6 can form a stable 5-membered ring. The shielding on protonation of 3 and 6 represents a change in direction opposite to what is displayed by 4. The incorporation of a proton into a five-membered ring in 3 and 6 may be a reason for upfield shifts, although this is highly speculative. This explanation can be slightly substantiated by the deshielding of 5 on protonation. Presumably 5 experiences similar steric interactions as 6 but the proton cannot be a part of a ring. As explained in Chapter 1, the effect of protonation is very much dependent on concentration, pH, and counterion and these factors have not been assessed here. Thus a clear explanation for the upfield shifts in 3 and 6 awaits further experimentation.

Compared to aniline, 1-aminonaphthalene (7) is slightly deshielded. Molar Kerr constant studies indicate that the amino group in the latter compound is twisted out of conjugation by 28^{0} (116). In view of this, deshielding of 7 com-

pared to aniline is remarkable. Conceivably, the second fused benzene ring may induce additional deshielding. N-methylation of 1-aminonaphthalene shields the nitrogen by almost twice the amount (~27 ppm) displayed by N,N-dimethylaniline (~15 ppm) (125). The additional 12 ppm shielding observed for 9 can be attributed to twisting of the bulky dimethylamino group out of conjugation, increasing the nitrogen electron density and decreasing the C-N π bond order. Introduction of an amino group at the 8-position in 7 to give 8 deshields the nitrogen. This effect is oppsite to that observed for m-substitution in aniline, where a very small shielding arises. A deshielding in 10 arises on introduction of a dimethylamino group in the 8-position in 9. This change parallels that noted by Schuster and Roberts (118), cited above. The magnitude of deshielding on going from 9 to 10 is slightly larger than on going from 7 to 8. The crystal structure of 10 has been determined (126) and the most probable conformation is as shown below.



10

Here, the methyl groups are not in the most favorable location to avoid the hydrogens on C-2 and C-7, and the unshared electron pairs are not face-to-face. The presence of a sin-

gle resonance for 10 indicates a time averaged signal. The deshielding on substitution in the peri position seems to be common regardless of the nucleus observed. For example, the ^{13}C resonance position of 1,8-dimethylnaphthalene is ~8 ppm to lower field from that of 1-methylnaphthalene (122). Similarly, the ^{19}F resonance position of 1,8-difluoronaphthalene is ~8 ppm downfield from that of 1-fluoronaphthalene (123).

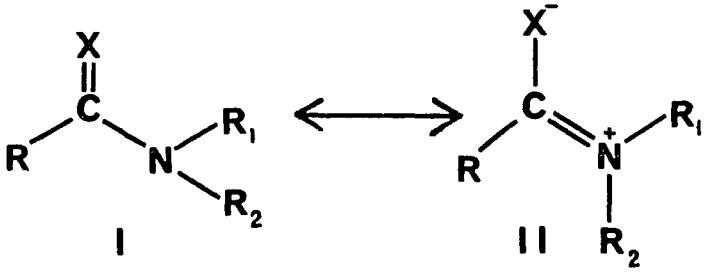
The effect of protonation in the naphthalene series is similar to that in the anilines. Protonation of 7 substantially shields the nitrogen, analogous to the behavior of aniline. By contrast, protonation of 9 results in a deshielding similar to that observed for N,N-dimethylaniline. The effect of protonation on 8 and 10 is in the same direction as that for 3 and 6. A crystal structure for monoprotonated 10 (127) shows that the proton sits between the nitrogens and forms a six-membered ring. The methyl groups are above and below the plane of the ring. ^1H nmr studies of 10 under the experimental conditions used in this study have shown that a proton is held in between the two nitrogens as part of a six-membered ring and that the resonance position of the proton is influenced by concentration and nature of the medium (128). It should be noted that, with admittedly deficient protonated 9 and unprotonated 10 as models, the resonance position of protonated 10 does not correspond to a time averaged signal. The shielding on protonation in 9 and

$\underset{\sim}{10}$ remains a puzzle. Further experimentation is needed to assess these shielding effects.

CHAPTER 5

Compounds containing N-C-O or N-C-S linkages characteristic of amides and polypeptides are important biologically. Ureas are chemically and pharmacologically important because they are effective protein denaturants and because the urea moiety is a structural element in biologically active compounds such as barbiturates and purine bases. The main focus of the different types of analysis of these basic units has been to establish structure-activity relationships. With this knowledge one can then try to analyze properties of larger biologically active molecules.

Amides and related compounds have been studied extensively by nuclear magnetic resonance spectroscopy. The discovery that methyl groups in N,N-dimethylformamide are magnetically non-equivalent gave birth to dynamic nmr studies (129). Most of the nmr studies of these compounds are concerned with the partial double-bond character of the C-N bond. This double-bond character arises from the contribution of resonance structure II to the ground state.



R = Alkyl,Aryl.

X = O, S.

Earlier ^{1}H nmr studies of these compounds have focussed on determinations of isomer ratios (cis and trans isomers in monosubstituted compounds) and on barriers for rotation around the C-N bond (130-133).

With the availability of modern FT nmr spectrometers, amides and related compounds have been extensively studied by ^{13}C, ^{14}N, and ^{15}N nmr spectroscopy. The main focus of ^{13}C nmr studies of these compounds has been to determine chemical shifts of the carbonyl (or thiocarbonyl) carbons with the aim of identifying these fragments in the analysis of polypeptides (134-136). Thioamides and thioureas have also been studied by ^{13}C nmr spectroscopy (137-138).

Nitrogen nmr spectroscopy has been used extensively in the study of N-C=X fragments. The major advantage of nitrogen nmr spectroscopy in studying these compounds is that one can focus on the nitrogen where most of the electronic change is taking place. The effects of alkyl and aryl substitution on ^{15}N chemical shifts of amides have been extensively characterized (138-139). The influence of solvents on amide nitrogen chemical shifts has been studied by ^{15}N nmr (140). Recently, ^{15}N chemical shifts of acetamides have been used as models for studies of peptides (141).

In contrast to amides, considerably less attention has been paid to the nmr spectroscopy of ureas and thioureas.

Some early ^{14}N nmr results on ureas (142,143) and thioureas (144) have been reported. The identification of resonances in unsymmetrically substituted ureas and thioureas by ^{14}N nmr is hampered by the inherently broad signals arising from ^{14}N quadrupolar relaxation. Isolated examples of ^{15}N chemical shifts for urea (138), thiourea (41), and tetramethylurea (142) and its thio analog (138) have been reported, and ^{15}N chemical shifts of urea and methylureas have recently been determined in water (145). However, because no systematic study of structural effects on ^{15}N chemical shifts of these compounds exists, we have measured these quantities in an extensive series of compounds and report these results here.

Besides determining effects of substitution, for comparison and contrast with amides, we also wished to evaluate the suggestion (138,139) that ^{15}N shifts in these materials can be used to determine rotational barriers around the C-N bond. Activation energy barriers for C-N bond rotation in ureas are small and are not easily obtainable by ^{1}H or ^{13}C nmr spectroscopy (146-148). The slightly higher barriers in the thio analogs have been determined by ^{1}H (149) and ^{13}C (150) dynamic nmr spectroscopy. By comparison of the few known experimental values (148,151,152) with those based on the suggested relationship between ^{15}N shifts and rotational barriers, we will assess whether the equations derived for amides give meaningful results in ureas and thioureas.

Recently, Martin and co-workers have determined ^{15}N chemical shifts of some ureas and thioureas and have estimitated rotational barriers using a modified form of their's amide equation (153).

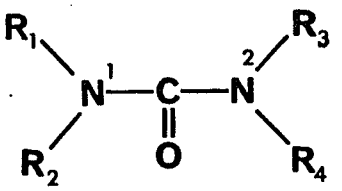
This chapter is divided into two parts. First, the ureas are presented, and then the thioureas.

RESULTS AND DISCUSSION

UREAS

The ^{15}N chemical shifts of ureas 1a-1f (see Chart II) are given in Table XI, which also includes some ^{14}N chemical shifts (142,143), photoelectron vertical ionization potentials for methylureas (154) and ^{13}C chemical shifts of the urea carbonyl carbons, some of which have been reported (155,156). Tables XI and XII list similar data for compounds 2a-2h and 3a-3c (see Charts III and IV) respectively. Solvent affects resonance positions of urea nitrogens to different degrees. The ^{15}N chemical shifts in water of urea and some methylureas reported in the literature (145) do not correspond with those in Table XI. In water, the chemical shifts of the nitrogens in methylurea do not differ. ^{15}N chemical shifts of urea nitrogens in both DMF and DMSO show similar trends although there is a $\sim$1 ppm deshielding effect in DMSO. Dilution from 4M to 2M concentrations in DMF

Chart II



	R_1	R_2	R_3	R_4
1a	H	H	H	H
1b	CH_3	H	H	H
1c	H	CH_3	H	CH_3
1d	CH_3	CH_3	H	H
1e	CH_3	CH_3	CH_3	H
1f	CH_3	CH_3	CH_3	CH_3

Table XI ^{15}N Chemical Shifts and Related Data for Methylureas

Compound	δ_N, ppm[a] 4M DMF[b]	2MDMF[b]	4M DMSO[b]	δ_N, ppm[c]	$\delta_{C=O}$, ppm[d]	I.P$_{\pi_1}$ eV[e]	I.P$_{\pi_2}$ eV[e]
1a	75.00	74.94	77.59	75.0	161.1	10.22	10.78
1b	N_1 = 69.07	68.71	70.09	71.2[g]	159.8	9.21	10.23
	N_2 = 72.94	72.70	75.49	71.1			
1c	66.61	66.65	67.99	69.4[g]	159.5	9.23	9.73
1d	N_1 = 65.57[f]		60.80		159.4	8.27	9.93
	N_2 = 72.70[f]		76.33				
1e	N_1 = 62.92[f]		63.51		159.0	8.80	9.93
	N_2 = 67.62[f]		68.71				
1f	63.51	62.66	63.51	59.7[h]	164.8	8.64	8.98

[a]Measured with respect to external CH_3NO_2, converted to anhydrous ammonia scale (ref 63) via the relationship $\delta_{NH_3} = \delta_{CH_3NO_2} + 380.23$

[b]DMF= N,N-dimethylformamide, DMSO= dimethylsulfoxide.

[c]References 143 and 144; pure liquids except as noted.

[d]Urea carbonyl chemical shift, measured as 2 M solutions

in DMSO, reported with respect to tetramethylsilane.

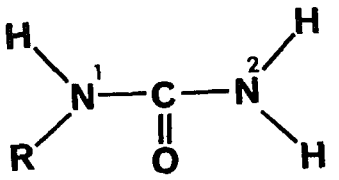
[e]Photoelectron ionization potential, ref 154.

[f]Concentrations not known.

[g]Aqueous solution.

[h]Acetone solution.

Chart III



2a R = C_2H_5

2b R = n-C_3H_7

2c R = i-C_3H_7

2d R = n-C_4H_9

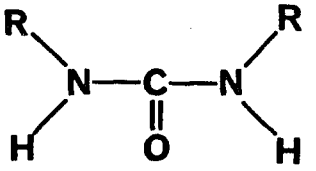
2e R = i-C_4H_9

2f R = t-C_4H_9

2g R = C_6H_5

2h R = $-CH_2CH=CH_2$

Chart IV



3a R = C_2H_5

3b R = n-C_4H_9

3c R = C_6H_5

Table XII ^{15}N Chemical Shift and Related Data for Monosubstituted Ureas

Compound	δ_N, ppm[a] 4 M DMF[b]	2 M DMF[b]	4 M DMSO[b]	$\delta_{^{14}N}$, ppm[c]	$\delta_{C=O}$, ppm[d]
2a	N_1 = 87.22	86.73	88.07	90.7[g]	
	N_2 = 72.94	72.58	72.58	71.1	159.5
2b	N_1 = 83.71	83.35	84.44		
	N_2 = 72.94	72.46	75.12		159.3
2c	N_1 = 100.65	100.77	101.77		
	N_2 = 71.66	73.07	73.07		
2d	N_1 = 83.83	83.59	84.68	90.7	
	N_2 = 72.94	72.63	75.12	67.7	160.0
2e	N_1 = 82.33	81.90			159.2
	N_2 = 73.07	72.58			
2f	N_1 = 103.91[f]	104.69	105.25[f]		158.4
	N_2 = 74.15	73.79	76.33		
2g	N_1 = 105.73	105.61	106.82	99.5[h]	156.6
	N_2 = 77.54	77.06	79.54	69.0	
2h	N_1 = 80.73	80.33	81.3		
	N_2 = 73.31	72.94	75.6		159.3

[a-h]Footnotes as in Table XI

Table XIII ^{15}N Chemical Shifts and Related Data for 1,3-Disubstituted Ureas

Compound	δ_N, ppm[a] 4 M DMF[b]	2 M DMF[b]	2 M DMSO[b]	$\delta_{^{14}N}$, ppm[c]	$\delta_{C=O}$, ppm[d]
3a	84.92	84.68	85.77	89.6	158.2
3b	82.41[f]	82.41	82.31[f]		158.3
3c	107.67[f]	107.67[f]	108.88[f]	104.3[h]	152.6

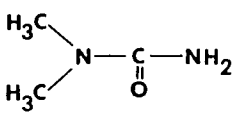
[a-h]As in Table XI.

also seems to have very little efect on urea resonance positions. Comparison with the results in water (145) suggests that hydrogen bonding or association of ureas in a hydrophilic solvent can play a role in influencing the resonance positions as is known to be the case in amides. More experimentation is needed to assess the importance of solvent effects in these compounds.

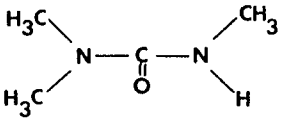
Since amides and ureas are very closely related compounds, it is useful to compare their nitrogen chemical shifts. In general a urea nitrogen is shielded compared to the corresponding amide nitrogen. For example, the ^{15}N chemical shift of formamide (63) lies 40 ppm to lower shielding compared with that of urea. The shielding trend in ureas can be explained by a decrease in nitrogen lone-pair delocalization because of cross-conjugative interaction of the two nitrogens with the carbonyl group. This kind of cross-conjugation is not present in amides. The argument is based on the assumption that nitrogen lone-pair delocalization results in deshielding. Further evidence for this can be seen in the lower field resonance positions of the unsubstituted nitrogen in monoaryl substituted ureas, where an additional pathway for delocalization is available.

The effect of methylation in both urea and formamide leads to some very interesting results. N-methylation results in shielding in both sets of compounds. The direc-

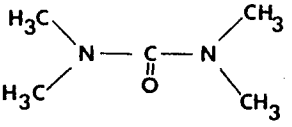
tion of the shielding persists in the series urea → methylurea → tetramethylurea and in formamide → N-mehtyl-formamide → N,N-dimethylformaide (63). N-Methylation of urea to give 1b results in a shielding of 6 ppm of the substituted nitrogen. Further methylation of the substituted nitrogen to give 1d results in an additional but smaller shielding of 3.5 ppm. Methylation of the unsubstituted nitrogen in 1d to give 1e and 1f result in similar shielding effects.



1d



1e

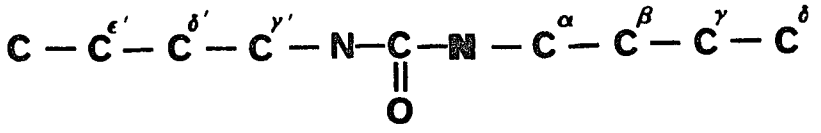


1f

These upfield shifts on methylation contrast with ^{13}C chemical shifts of structurally analogous alkyl ketones, where downfield shifts of ~2.5 ppm for the carbonyl carbon per addition of carbon are observed (157). N-methylation of aliphatic amines deshields the nitrogen. For example, the chemical shift of methylamine is 1.3 ppm to lower shielding compared to that of ammonia. There are a few reports of shielding by α-methylation at nitrogen (13,45,66-66,158). These effects were discussed in Chapter 2.

Alkylation at positions β, γ, and δ to nitrogen in urea leads to shifts expected on the basis of results in saturated amines. β-Alkyl substitution of a urea nitrogen results in a large deshielding similar to that diplayed by

nitrogens in amides (139) and alkylamines (13). Upon γ and δ alkyl substitution a small shielding is observed. Grant and Paul have devised methods to calculate substituent parameters from ^{13}C chemical shifts of alkanes (159,160). Recently, a similar analysis has been carried out for the ^{15}N chemical shift of aliphatic amines (30). Regression analysis of the urea data presented here, following largely the method of Grant and Paul (160), results in the substituent parameters given in Table XIV. Comparison of calculated with observed shifts, gives a correlation coefficient r = 0.995. Owing to the limited data, possible effects of branching were not taken into account. The value for t-butylurea 2f was not included in the regression analysis because of its large deviation from the regression line. The substituent parameters presented in Table XIV are defined according to the structure below.



With the exception of the α-parameter the substituent parameters in Table XIV show trends similar to those of ^{13}C substituent parameters for aliphatic amines. Magnitudes in the latter case are slightly different. For example, the parameter for aliphatic amines is ~2 ppm larger than that for ureas. The small values of γ', δ', and ϵ' obtained show that the chemical shifts of the unsubstituted nitrogens are

Table XIV Substituent Parameters for Alkylureas[b]

Position	Substituent Parameter, ppm[a]		No. of Points Used
α	-4.64	0.40	13
β	16.61	0.56	7
γ	-1.81	0.53	4
δ	-0.67	0.92	2
γ'	-0.99	0.37	12
δ'	0.51	0.58	8
ϵ'	-0.36	0.87	4

[a]Positive values denote shifts to lower field.

[b]Constant value = 72.61 ppm.

Standard deviation 0.96 ppm.

not greatly affected by substitution on the other nitrogen. There is a change in the sign of the α-parameter in the case of ureas. The α-parameter for aliphatic amines is +8.7 (deshielding) and that for urea is -4.64 (shielding). This will be discussed below.

^{14}N and ^{15}N chemical shifts of ureas show similar trends (see Table XI), except for a few values. These few differences may arise from the inherent imprecision in ^{14}N chemical shift measurement, and from differences in measurement conditions. These factors could account for the earlier conclusion, now known to be erroneous, that methyl substitution has no effect on urea nitrogen chemical shifts.

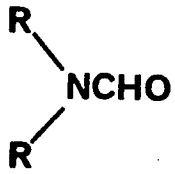
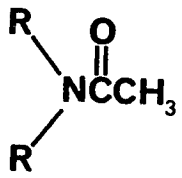
^{13}C chemical shifts of the carbonyl carbon in ureas do not vary much on substitution at nitrogen (see Table XI). The same result was observed for amide carbonyl carbons (139). A plot of ^{15}N chemical shifts of urea nitrogens against the ^{13}C chemical shifts of the corresponding carbonyl carbons results in a very poor correlation ($r<0.8$). One might have expected a good correlation between the two sets of data if they are affected in the same way by nitrogen lone-pair delocalization.

Shielding of the nitrogen nucleus in ureas on methyl substitution can be explained as a reduction in nitrogen lone-pair delocalization into the carbonyl carbon. This reduction

in lone-pair delocalization results in an increase in electron density at the substituted nitrogen atom and also reduces the double bond character in the C-N bond. According to the Karplus-Pople (23) treatment of chemical shifts, a decrease in the double bond character results in a decrease in the paramagnetic term in the shielding expression and thereby shields the nitrogen. As explained in Chapter 1, the paramagnetic term governs the resonance position of nitrogen nucleus. Similar arguments were used in Chapter 2 to explain the upfield α-methylation shifts of methylanilines and nitrogen chemical shifts of conjugatively substituted anilines (46,47,49).

Photoelectron spectroscopy (PES) has been a great asset in rationalization of ^{15}N chemical shifts as has been demonstrated in discussing the upfield shifts in methylanilines (see Chapter 2). The above approach suggests that α-methylation inhibits p-π interaction between the nitrogen lone-pair and the adjacent π system (carbonyl group), possibly by increasing the energy difference between the nitrogen lone-pair and the non-perturbed π system. A similar argument can be used to analyze other conjugated systems. The ^{15}N chemical shifts of formamides and acetamides are analyzed below with the help of PES. The ^{15}N chemical shifts of methyl substituted formamides and acetamides and the ionization potentials arising from the highest occupied molecular orbitals are listed in Table XV. Examination

Table XV ^{15}N Chemical Shifts and Vertical Ionization Potentials for Formamides and Acetamides

Compound	R	R	δ_N, ppm[a,b,c]	IP (Π), eV[d]
	H	H	112.4	10.52
	H	CH_3	109.6	9.87
	CH_3	CH_3	104.8	9.25
	H	H	110.5	10.32
	H	CH_3	106.3	9.68
	CH_3	CH_3	98.3	9.09

[a]Downfield from anhydrous ammonia.

[b]From ref 139.

[c]The chemical shifts were derived from those reported in ref 139 by addition of 378.5 ppm.

[d]Ref 161.

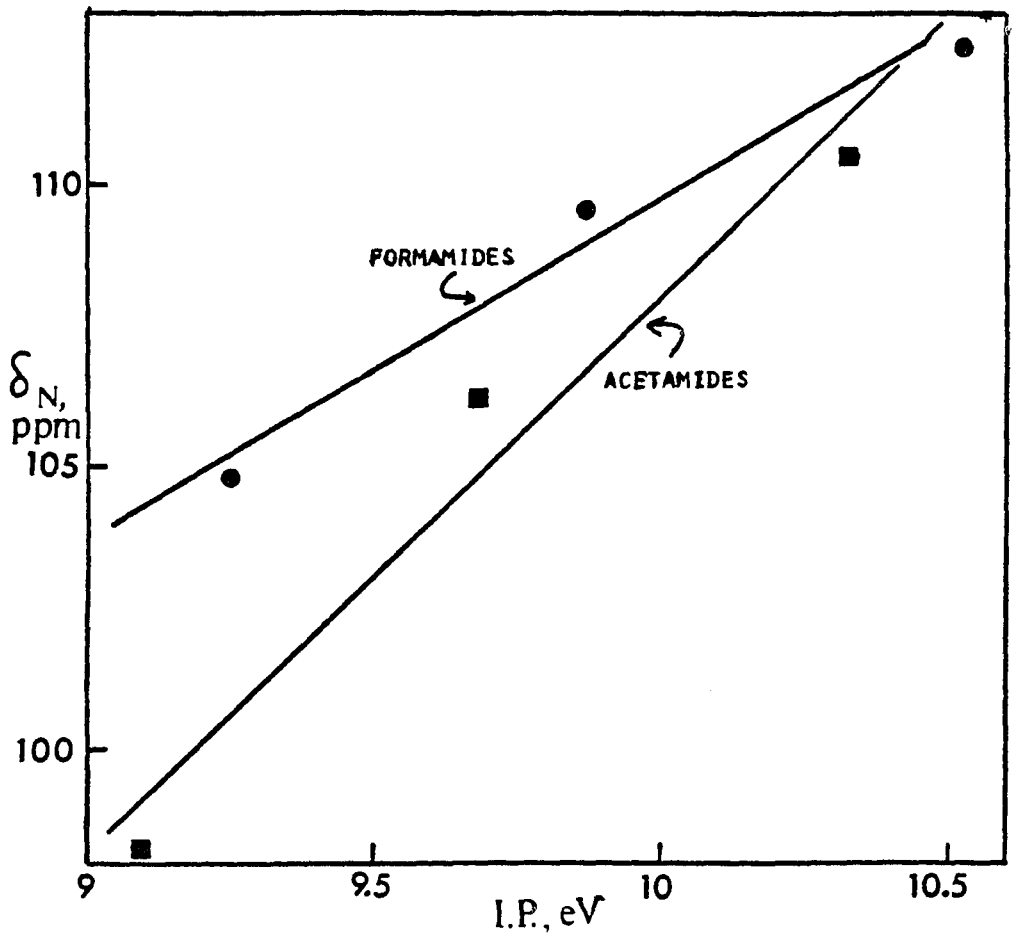
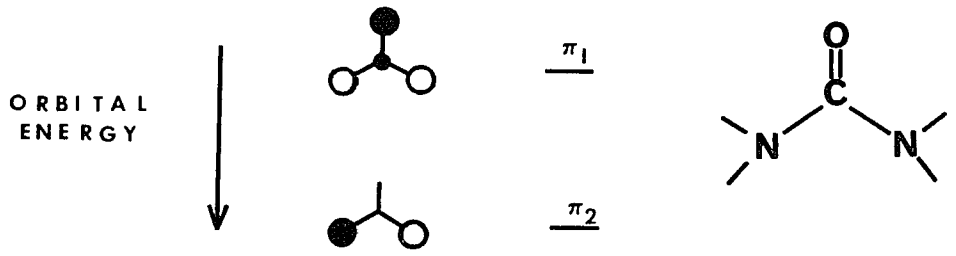


Figure 9. Plot of Ionization Potentials vs. ^{15}N Chemical Shifts of Formamides and Acetamides.

of Table XV shows that the ionization potential of the highest occupied molecular orbital decreases upon methylation. Calculations suggest that this orbital is rather highly localized on nitrogen (161), although recent calculations have indicated that assignment of ionization potentials may be ambiguous (162). The ^{15}N chemical shifts of methyl-substituted formamides and acetamides correlate separately ($r = 0.988$ and $r = 0.980$ respectively) and together ($r = 0.920$) with the photoelectron ionization potentials. Figure 9 shows a plot of these two sets of data. Microwave data for methylated formamides have been reported (163), which indicate that the amide C-N bonds remain torsionally undistorted as a result of methyl substitution. Therefore, the shielding upon methylation and lowering of ionization potentials can be ascribed to the inhibition of p-π interaction as in N-methylated anilines.

We have tried a similar approach to explain the upfield shifts on α-methylation in ureas by seeking a correlation between nitrogen chemical shifts with appropriate ionization potentials. Selection of these is, however, not straightforward. The photoelectron spectra of methylureas have been analyzed in great detail by McGlynn et al. (154). They were able to identify π - type orbitals associated with each nitrogen and estimate the influence of alkyl substitution on lone-pair interaction. As alluded to above, reduction of lone-pair delocalization in urea compared to amides because

of cross-conjugation can be verified by comparing the ionization potential in urea with that of the amide. The lower value for π_1 of the ureas compared to the amides suggests greater localization of electron density at the nitrogen. For example, the value for urea is 0.27 eV less than that for formamide (164). With the help of published data (154) it is possible to approximate the effect of methyl substitution on the ionization potential of each nitrogen separately. This approximation is based on the assumption that the ionization potential which changes more on substitution can be attributed largely to the substituted nitrogen. The π_1 and π_2 orbitals arising from the interaction between the two nitrogens in urea are shown below.



As can be seen from the diagram above both π_1 and π_2 orbitals have electron density on the nitrogen atom. The orbital π_2 which has a larger electron density at nitrogen

is affected to a larger extent on substitution. Methylation results in destabilization of both π_1 and π_2 that is similar to that observed in methylanilines. π_1 displays a saturation effect when nitrogen is completely substituted, while π_2 continues to decrease on further substitution (1d → 1e → 1f). The explanation for the above behavior is that the electron density on π_1 is more heavily localized at the fully substituted nitrogen and further substitution occurs at a site where electron density is low. This enables one to pick out the ionization potential of the nitrogen undergoing substitution and helps in characterizing π_1 and π_2 based on the fact that the nitrogen undergoing substitution also undergoes a large change in ionization potential.

Figure 10 shows a plot of methylurea ^{15}N chemical shifts against ΔIP (see discussion below). The ΔIP differences were derived as follows: for unsymmetrical ureas (1b,1d,1e) the π_1 and π_2 ionization potentials were assigned to the more and less highly substituted nitrogens. The difference between each of these and the corresponding value for urea itself gives ΔIP for each nitrogen. For symmetrical ureas, ΔIP is the difference between the average ionization potential of the substituted urea and the average value for urea itself, 10.53 eV. The I.P. values are listed in Table XI. The δ_N in Figure 10 is the difference in chemical shift of the nitrogen and the value for urea. From Figure 10 it is

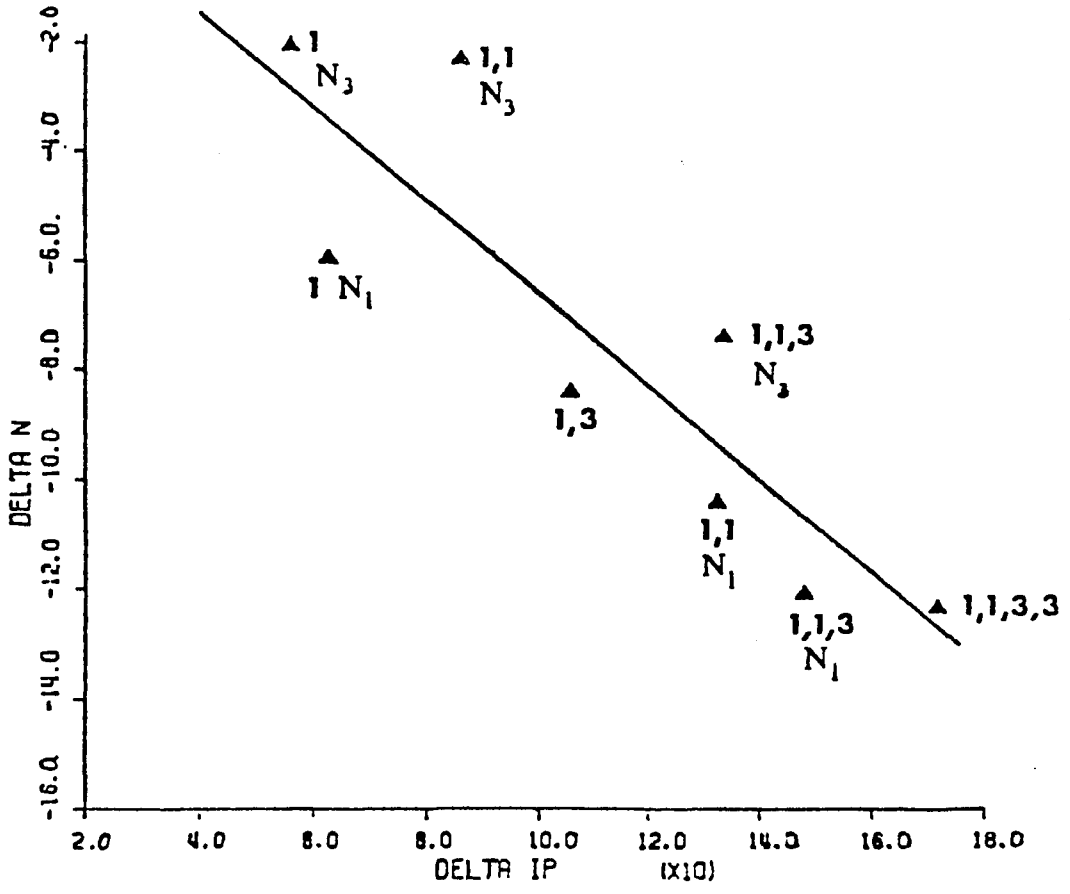


Figure 10. Plot of Methylurea ^{15}N Chemical Shifts vs. Photoelectron Ionization Potentials.

evident that while there is considerable scatter (r = 0.88) a trend exists, and nitrogen shifts can be related in a qualitative manner to ionization potentials. The absence of a clear correlation in Figure 10 may arise because of steric effects in the more highly substituted ureas (1e,1f) which conceivably could inhibit delocalization in a manner reflected differently by the two methods. No structural data are available for 1e or 1f. A crystal structure of tetramethylthiourea has been determined, showing it to be nonplanar (165). The observation of a single resonance for 1f (see Table XI) could be due to two factors. The signal seen may be a time-averaged value between conjugated and non-conjugated nitrogen nuclei or it could reflect a single species in which conjugation of both nitrogens is partially inhibited to the same extent. It is hard to independently assess these factors. The reported low rotational barrier for 1f (150) supports the suggestion of an average value of conjugated and non-conjugated species.

Examination of Table XIV shows that higher alkyl substitution displays similar trends to those displayed by amides. The β-parameter is a large deshielding effect of $\sim$16 ppm, and is almost twice that seen in the ^{13}C carbon shifts of alkanes. Table XIV also shows that the γ parameter is smaller than the γ' parameter, although both have the same sign. This may be due to electronic differences in the intervening bonds as well as conformational differences.

The effect of a phenyl group is large compared to alkyl groups. The phenyl group can delocalize lone-pair electrons and deshields the nitrogen. The large deviation in chemical shift of t-butylurea 2f remains a puzzle.

ACTIVATION ENERGY BARRIERS

As alluded to earlier, an important aspect of the study of amides and related compounds has been to determine rotational barriers by dynamic ^{1}H and ^{13}C nmr spectroscopy. The same techniques have been applied to a lesser extent to determine barriers in ureas. A few scattered data on the barriers have been reported (136,139,150-152). Thus a value of 11.7 kcal/mol was derived from the total line shape analysis of the temperature-dependent urea ^{1}H spectrum (151a). From $T_{1\rho}$ measurements, the rotational barrier for tetramethylurea 1f was estimated to be 6.4 kcal/mol (151b). This value has been confirmed by ^{13}C nmr experiments (150). The main drawback in determination of barriers by ^{1}H nmr lies in the fact that the protons on the alkyl substituent frequently show no magnetic non-equivalence even at low temperatures (148,166).

Recently, ^{15}N chemical shift determinations have been suggested to be useful in evaluating activation energy barriers for C-N bond rotation in amides and derivatives (138,139). The main assumption in this approach is that both ^{15}N chemical shifts and rotational barriers are directly

dependent on the extent of nitrogen lone-pair delocalization in the ground state. This approach appears to give reasonable values for amide rotational barriers, whose values span a fairly large range (139). In order to evaluate this highly empirical approach, equations 1 and 2, which had been derived for amides, have been applied to estimate rotational barriers in alkyl substituted ureas:

$$E_a \text{ (kcal/mol)} = -2.1\ \delta_N + 0.21 \quad (1) \text{ for methylureas}$$

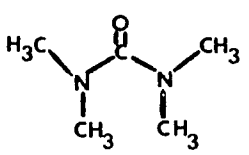
$$E_a \text{ (kcal/mol)} = -7.8\ \delta_N + 0.208 \quad (2) \text{ for other alkyl ureas}$$

Equations 1 and 2 shown above are the same equations derived for amides (139) with slight modification, and have been reformulated to be consistent with the ammonia reference used here.

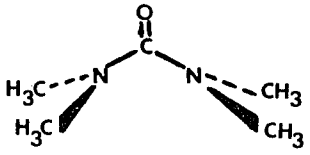
Equation 1 has been derived for evaluation of rotational barriers for the $-NH_2$ group of the monosubstituted urea and for methyl substituted urea. Equation 2 applies to higher alkylureas where the constant term corrects for the substituent effects on the ^{15}N chemical shifts. This method assumes that the substituent effects are independent of rotational barriers.

Direct substitution of the ^{15}N chemical shifts into equa-

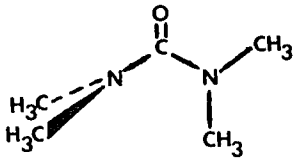
tions 1 and 2 gives values for 1a and 1f which deviate substantially from the measured values (150,151a). In a recent attempt to address this discrepancy, Anet and Ghiaci (150) have suggested that equations 1 and 2 may still be used if appropriately modified. The suggestion of Anet and Ghiaci can be pictorially represented as below for tetramethylurea 1f.



III



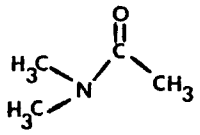
IV



V

The rotational process involves the following. In structure III both nitrogens are conjugated with the carbonyl group. Rotation about both C-N bonds results in structure IV. If one of the nitrogen rotates first, the resulting structure is V. In V the other nitrogen is still conjugated and resembles an amide. The value predicted from equation 1 is the one for structure V. To evaluate E_a the following procedure has to be carried out. First the value obtained from equation 1 is doubled (to obtain E_a for IV) and from this value, the E_a value for the residual amide conjugation is subtracted to get the value for rotation. The above approach is exemplified for compound 1f:

E_a from equation 1 for 1f = 11.2 kcal/mol

E_a for  = 17.3 kcal/mol

E_a for 1f = 2(11.2)-17.3= 5.1 kcal/mol

The values thus obtained for compounds 1a-1f are presented in Table XVI. Equation 1 is very sensitive to ^{15}N chemical shifts. A change of 0.5 ppm in chemical shift results in a change of 1 kcal/mol in E_a. Application of equations 1 and 2 is simple in the case of symmetrical ureas. The values listed in Table XVI agree reasonably well with literature values. The calculation of E_a for 3a and 3b using equation 2 gives values which must be too low. If equation 1 is used to calculate values for 3a and 3b, the results are 10 kcal/mol higher than listed in Table XVI. Use of equation 1 for 3a and 3b is inappropriate because it was derived from data for N-methylated compounds only. Other problems with this method also exist. Application of equation 1 to compounds within a small subset gives results which are exactly opposite to those of experiments. For example, in the series formamide → N-methylformamide → N,N-dimethylformamide the ^{15}N chemical shifts move to higher shielding. Equation 1 predicts a decrease in rotational barrier along this series. Independent measurements have shown that E_a increases in the above series. By contrast, E_a for rotation around the $(H_3C)_2N$ bond of N,N-dimethylbiuret is less than for rotation the H_2N-C bond (152).

Table XVI Calculated Activation Energies of Alkylureas[a]

Compound	E_a (N_1), kcal/mol	E_a (N_2), kcal/mol
1a	10.6	
1b	8.1	8.4
1c	5.6	
1d	6.6	9.0
1e	4.2	6.9
1f	5.1	
2a	4.0	8.4
2b	2.5	8.4
2c	9.5	7.0
2d	2.6	8.4
2e	1.9	8.5
2f	9.9	8.9
3a	1.7	
3b	0.7	

[a]Activation energies for 1a-1f and for the NH_2 group of 2a-2h were calculated using equation 1. Remaining values were derived from equation 2.

Thus it is clear that numerical values obtained from equations 1 and 2 are likely to be inconsistent.

Application of equations 1 and 2 to unsymmetrical ureas is problematic. Following the method of Anet and Ghiaci one must apply appropriate correction values for residual amide rotational barriers. For example, estimation of the barrier for N of 1b requires that the result obtained from equation 1 (12.4 kcal/mol) first be doubled, then be reduced by the rotational barrier for propionamide, the most appropriate isosteric amide. The values for alkylamides fall in the region of 16-18 kcal/mol and depend markedly on solvent (161). A value of 16.7 kcal/mol (based on acetamide) as a correction factor for substituted urea nitrogens and 18.0 kcal/mol (N-ethylacetamide) as correction a factor for unsubstituted nitrogens have been used for unsymmetrical ureas listed in Table XVI. The values for 2a-e appear to be too low. An increase in the size of alkyl substituent (2a →2c →2f) apparently increases E_a. These results are opposite to those obtained in alkyl substituted N,N-dimethylacetamides where an increase in size decreases the rotational barrier (168). The apparent increase in E_a with size also constrasts with results in amides, where an increase in size of an N-alkyl substituent does not affect the rotational barrier to a large extent.

Thus, while ^{15}N chemical shifts may in fact be related to

rotational barriers, quantitative evaluations are questionable. Direct determination by DNMR spectroscopy still remains the most reliable method for evaluating rotational barriers.

THIOUREAS

Thioamides and thioureas have been studied to a lesser extent than their oxo analogs. The proton chemical shifts in thioamides and thioureas are deshielded compared to those of the oxo compounds (132,133). The deshielding has been attributed to the greater anisotropy of thioamides than amides (169,170). The main focus in the study of thioamides and thioureas has been to determine isomer ratios in monosubstituted compounds and to determine rotational barriers. Monosubstituted thioamides exist in both cis and trans configurations. The isomer ratios in several monosubstituted thioamides have been determined (171,172).

^{13}C nmr spectroscopy has been used to characterize some thioamides and thioureas (137,138,173,174). Here, too, the main focus has been determination of rotational barriers (137). ^{14}N chemical shifts of some alkyl and aryl substituted thioamides have been reported (144). A few thioureas have also been studied by both ^{14}N (143) and ^{15}N nmr (138). Activation energies for rotation around the C-N bond in thioamides (175), thioacetamides (167), and thioureas (149)

have been reported.

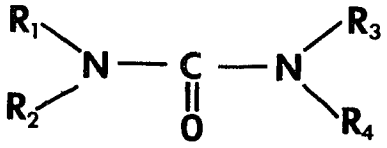
Here, we report a detailed study of ^{15}N chemical shifts of thioureas. We have also estimated activation energies for rotation around the C-N bond using equations derived for amides (138) and have compared them with values in the literature.

RESULTS AND DISCUSSION:

The ^{15}N chemical shifts of compounds 4a-4g (see Chart V) in dimethyl sulfoxide (DMSO) and pyridine are listed in Table XVII. The Table also lists ^{13}C chemical shifts of the thiocarbonyl carbon and reported activation energy barriers. ^{15}N chemical shifts of 4a-4g in DMSO are slightly more deshielded than in pyridine. The trends displayed in each solvent are the same.

It is useful to compare the ^{15}N chemical shifts of thioureas with those of the closely related thioamides and ureas. The ^{15}N nucleus of thiourea (4a) is deshielded by 33 ppm from that of urea. From the few scattered data available for thioamides, it can be seen that the thiourea resonances lie at a higher field than the corresponding thioamides. For example, the resonance of 4f is 60 ppm upfield from that of N,N-dimethylthioformamide (138). The deshielding effect in thioureas compared to ureas has been attributed to low-

Chart V



	R_1	2	R_3	R_4
4a	H	H	H	H
4b	CH_3	H	H	H
4c	CH_3	H	CH_3	H
4d	CH_3	CH_3	H	H
4e	CH_3	CH_3	CH_3	H
4f	CH_3	CH_3	CH_3	CH_3
4g	C_2H_5	H	H	H

Table XVII ^{15}N Chemical Shifts and Related for Alkylthioureas

Compound	δ_N, ppm[a] 2 M DMSO[b]	2 M Pyridine	$\delta_{C=S}$, ppm[c]	E_a, (kcal/mol)[d] $C-N_1$	$C-N_2$
4a	108.39	108.39	176.7	13.7	
4b	N_1 = 101.25	102.95	181.3	14.7	13.3[e] 10.8[f]
	N_2 = 104.93	105.63			
4c	98.59	99.58	181.0	12.7	
4d	N_1 = 98.03				
	N_2 = 99.23	99.93	182.8	12.6	12.0
4e	N_1 = 94.93	93.33			
	N_2 = 100.3	99.83	181.9	10.7	
4f	95.03	93.88	194.0	6.3	
4g	N_1 = 118.92	120.73	182.6		
	N_2 = 105.61	104.53		14.3	13.2[e] 11.2[f]

[a]Measured with respect to external CH_3NO_2, converted to anhydrous ammonia scale via the relationship

$$\delta_{NH_3} = \delta_{CH_3NO_2} + 380.23 \text{ (ref 63)}.$$

[b]DMSO = dimethylsulfoxide

[c]Thiourea carbonyl shift ref 137, except for 4e and 4g. reproted with respect to tetramethylsilane.

[d]Ref 149 and 150.

[e]Trans isomer. [f]Cis isomer.

lying sulfur excited states (174). The shielding of thioureas relative to thioamides is consistent with reduced nitrogen lone-pair delocalization in thioureas, presumably because of competitive cross conjugation of the two nitrogens with the thiocarbonyl group. Further evidence for the cross conjugation in the thioureas can be obtained by comparison of activation energies for rotation around the C-N bond with those of thioamides. The barriers in thioureas are lower than in the corresponding thioamides. For example, the barrier in thioformamide is 6 kcal/mol higher than in thiourea.

As in ureas, N-methylation of thiourea shields the nitrogen. The direction of this change persists in the series 4a $\rightarrow$ 4b $\rightarrow$ 4f. A plot of urea nitrogen shifts against thiourea nitrogen shifts gives a good correlation (r=0.97) indicating very similar methylation effects in both series. The upfield shift on N-methylation of thioureas can be explained in a similar manner to that in ureas. With the limited data available β-alkyl substitution seems to show the normal deshielding effect as in alkylamines and in ureas.

Unlike the case in ureas, the ^{13}C chemical shifts of the thiocarbonyl carbons in thioureas vary on alkyl substitution. A correlation between ^{15}N chemical shifts of thioureas and ^{13}C shifts of their thiocarbonyl carbons was sought

but none seems to exist. One would expect a correlation between these two sets of data if nitrogen lone-pair delocalization affects the two sets of data similarly.

ACTIVATION ENERGY BARRIERS

Dynamic ^{1}H and ^{13}C nmr spectroscopy have been very valuable in the evaluation of rotational barriers in thioamides and thioureas. Literature values are available for several thioformamides (175), thioacetamides (167), and thioureas (149,150). In the thioamides and related systems, barriers about the C-N bond are usually 2-5 kcal/mol higher than in the oxo analogs. For example, the barrier for formamide is 17.8 kcal/mol and that for thioformamide is >20.5 kcal/mol. The increased barrier is presumably due to destabilization of the transition state in which a full carbon-sulfur sulfur double bond must exist. The other factor which influences the barriers is the larger size of the sulfur atom compared to the oxygen. In the series thioformamide —> N-methylthioformamide —> N,N-dimethylthioformamide the barriers increase (>20.5 ⟶ 23.1 ⟶ 24.1). This trend is the same as the one observed for N-methylformamides. By contrast, increasing the size of the alkyl substituent on the thiocarbonyl carbon in thioamides decreases the barrier.

The relationship between ^{15}N chemical shifts and amide rotational barriers (see above) has also been suggested to

apply to thioamides and thioureas (138,139). As shown above, this approach was found not to be very satisfactory for ureas. To further test the method we have estimated the activation energies for rotation around the C-N bond in thioureas. Equation 3, which had been derived for thioamides was used to estimate rotational barriers in thioureas. This equation has been reformulated to be consistent with the ammonia reference used here.

$$E_a \text{ (kcal/mol)} = -23.40 \quad + 0.305 \qquad (3)$$

Direct substitution of ^{15}N chemical shifts from Table XVII into equation 3 gives the calculated rotational barriers listed in Table XVIII, which also lists the literature values. Examination of Table XVIII shows that there is very little correspondence between the literature and estimated values. It was recently suggested that equation 3 can be used with slight modification (150), as discussed above for ureas. The rotational barriers estimated using Anet's modification are all negative. There is no apparent structural explanation for these results, which probably reflect the inherent limitations of the method discussed above.

The ^{13}C chemical shift of the thiocarbonyl carbon correlates only to a fair degree (r=0.92) with literature rotational barriers. There is no correlation of the measured

Table XVIII Calculated Activation barriers for Thioureas

Compound	E_a, (kcal/mol)			
	Estimated[a]		Literature[b]	
	$C-N_1$	$C-N_2$	$C-N_1$	$C-N_2$
4a	8.58		13.7	
4b	7.0	7.8	14.7	13.3[c] 10.8[d]
4c	6.0		12.7	
4d	6.0	6.1	12.6	12.0
4e	4.1	4.3	10.7	
4f	4.3		6.3	
4g	12.19	7.4	14.3	13.2[c] 11.2[d]

[a]Calculated from equation 3 using ^{15}N chemical shifts in DMSO

[b]Ref 149 and 150.

[c]Trans isomer.

[d]Cis isomer.

^{15}N chemical shifts with the literature rotational barriers.

In conclusion, the effect of substituents on thiourea ^{15}N chemical shifts is similar to that in the oxo analogs. The empirical equations derived for determination of rotational barriers completely fails in the case of thioureas.

CHAPTER 6

Measurement and interpretation of nuclear spin-spin coupling constants is important because of their correlation with molecular structure and their potential in structure determination. In the earlier days of nitrogen nmr, coupling constants were determined when they were not eliminated by the ^{14}N quadrupolar relaxation. To increase the applicable range of compounds, enrichment with ^{15}N has been necessary. Values from ^{14}N measurements can be converted to ^{15}N values upon multiplication by $\gamma_{15N}/\gamma_{14N} = -1.402$. Exceptions to the need for ^{15}N enrichment arise when the coupling is to a nucleus of high natural-abundance (^{1}H, ^{31}P, ^{19}F) and the coupled natural-abundance ^{15}N spectrum can be observed. ^{15}N, because of its small magnetic moment, exhibits small coupling constants compared to ^{1}H or ^{13}C. Because γ_{15N} is negative the sign of couplings with ^{15}N are opposite to that with ^{14}N.

The Fermi contact term, which dominates N- H and ^{13}C- H couplings also contributes to a large extent to $^{1}J_{N-H}$ and $^{1}J_{N-C}$ values. Other mechanisms such as orbital motions and spin dipolar interactions can also contribute to nitrogen couplings (8).

Nitrogen-proton couplings have received greatest attention . $^{1}J_{N-H}$ values vary from 75 to 130 Hz depending on the

nature of the nitrogen atom: compounds in which the nitrogen is pyramidal have $^{1}J_{N-H}$ at the lower end of the range, while compounds in which bonding to nitrogen is linear display $^{1}J_{N-H}$ values at the higher end. $^{1}J_{N-H}$ in anilines has been found to vary with solvents and substituents (120,121). $^{1}J_{N-H}$ in amides has also been shown to depend on geometry (177).

$^{2}J_{N-H}$ is smaller in magnitude than $^{1}J_{N-H}$ and is more sensitive to structural variations. The characteristic feature of $^{2}J_{N-H}$ is that in geometrically fixed nitrogens, the coupling is large and negative to a proton close to the lone-pair and small and positive to one which is not. The above factor has been used to establish geometries in different types of nitrogen compounds (178).

Three-bond N-H couplings show a Karplus-type dependency on dihedral angle (179). Vicinal N-H couplings are much larger than geminal ones. In geometrically rigid systems where the nitrogen lone-pair orientation is fixed. $^{3}J_{N-H}$ is related to lone-pair orbital orientation in a parallel manner to $^{2}J_{N-H}$.

$^{1}J_{N-C}$ values are smaller than $^{1}J_{N-H}$ and have been related to s-character, although this has been criticized (8). $^{2}J_{N-C}$ shows a similar dependence on lone-pair orientation as $^{2}J_{N-H}$ does. $^{3}J_{N-C}$ couplings do not vary much and

their dependence on dihedral angle is not evident (180).

Determination of couplings between nitrogen and nuclei other than proton and carbon have been rather infrequent (8,181). There has been no systematic study of couplings to nitrogen with fluorine (N-F) and nitrogen (N-N), although a few reports of ^{15}N-^{19}F couplings are in the literature. $^{1}J_{N-F}$ is usually large and varies from 100-500 Hz depending on the nature of the compound (182). A few $^{2}J_{N-F}$ (183) and $^{3}J_{N-F}$ (184) couplings have also been reported.

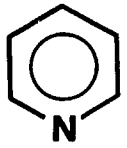
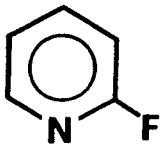
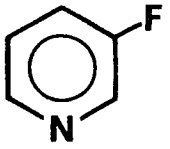
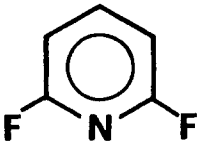
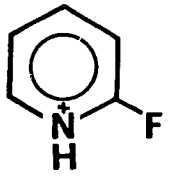
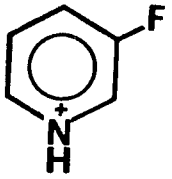
We have carried out a systematic study of ^{15}N-^{19}F couplings in fluoropyridines and fluoroanilines in order to delineate the effects of factors like hydrogen bonding, substituent effects, protonation, and methylation on N-F couplings. These systems were chosen because of the possibility of drawing analogies to N-H couplings in the corresponding pyridines and anilines.

RESULTS AND DISCUSSION.

Fluoropyridines:

^{15}N chemical shifts and ^{15}N-^{19}F coupling constants of fluoropyridines are presented in Table XIX. Compared with pyridine, substitution of a fluorine in the 2-position shields the nitrogen by 41.7 ppm. This is consistent with

Table XIX ^{15}N Chemical Shifts and ^{15}N-^{19}F Coupling Constants in Fluoropyridines

Structure	Number	δ_N, ppm[a]	$^nJ_{N-F}$[b] Hz (n)
	1	317.3	
	2	215.0	
	3	275.9	-52.5 (2)
	4	299.4	3.6 (3)
	5	245.2	-52.3 (2)
	6	221.9[c]	-23.1 (2)
	7	219.9[c]	3.1 (3)

[a]Resonances to lower field from position of anhydrous ammonia.

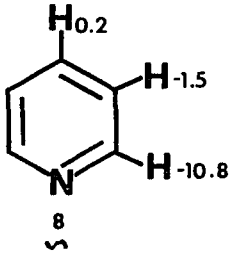
Experimental error ±0.2 ppm.

[b]Experimental uncertainty ±0.2 Hz.

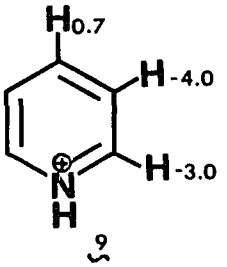
[c]As hydrochlorides in $CHCl_3$.

the fact that conjugatively electron-donating substituents shield nitrogen by an increase of electron density at the site (8,21). Substitution of fluorine at the 3-position also leads to shielding but the magnitude is small. Addition of a second fluorine at the 6-position in compound 2 induces a nearly additive effect. Protonation of pyridine also results in shielding. This is the result of the removal of the lone-pair on nitrogen and an increase of the ΔE term in the chemical shift equation (8). Similar shielding effects are seen on protonation of fluoropyridines although the magnitude of the change is smaller.

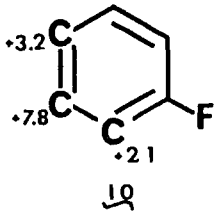
The $^2J_{N-F}$ values measured for 3 are the largest in this series. Protonation of 3 (3 →6) decreases this value. This change is similar to that observed for $^2J_{N-H}$ in pyridine (185), where the coupling decreases from -10.8 Hz to -3.0 Hz on protonation. The $^2J_{N-H}$ value of protonated 3 is similar to $^2J_{C-F}$ (21.0 Hz) in the isoelectronic fluorobenzene (123). The sign of $^2J_{N-F}$ in 3 recently has been determined by spin-spin analysis (186). The fortuitous coincidence of $^2J_{N-F}$ in 6 and $^2J_{C-F}$ in 10 may arise from compensating factors: the smaller value expected for $^2J_{N-F}$ because of the smaller magnetogyric ratio of nitrogen may be increased because of the positive charge at nitrogen.



8

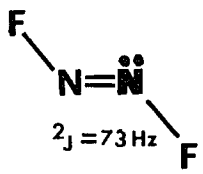


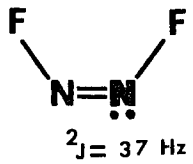
9



10

No further parallelisms exist among 3, 8, 9 and 10 except for the values of ^2J. The change in $^2J_{N-F}$ on protonation of 3 is not proportional to that in $^2J_{N-H}$ when 8 is protonated to 9. This suggests that different mechanisms may operate for the two kinds of couplings. The larger magnitude of $^2J_{N-F}$ compared with $^2J_{N-H}$ in 8 may arise via an additional lone-pair mediated pathway for N-F coupling available to 3 (8). Similar effects of lone-pair orientation are observed in 1,2-difluorodiazines where $^2J_{N-F}$ is larger for the trans than the cis isomer (167).





These results for $^2J_{N-H}$ are consistent with the lone-pair dependence of ^{13}C and ^1H couplings with ^{15}N discussed above. Thus, it is surprising that $^3J_{N-F}$ in 8-fluoroquinoline (2.9 Hz) (188) is indeed smaller than that for 4 (3.6 Hz). This result may indicate that lone-pair orientation may have little effect on $^3J_{N-F}$, or that 4, by virtue of the trans geometry between N and F, has a larger through-bond contribution than does 8-fluoroquinoline.

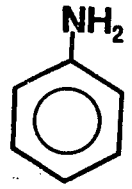
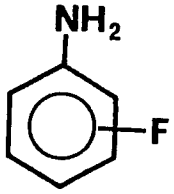
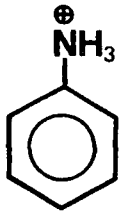
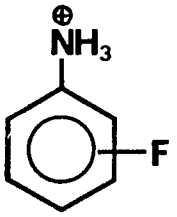
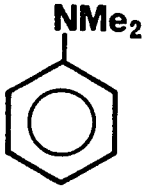
The value of $^3J_{N-F}$ in 4 is smaller than $^2J_{N-F}$. A similar decrease in the magnitude of coupling with distance is also seen in compounds 9 and 10. 4-Fluoropyridine is very unstable and determination of spectral parameters was not possi-

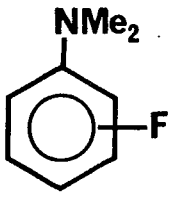
ble. $^4J_{N-F}$ has been shown to be very small or not present in 3,5-dichloro-2,4,6-trifluoropyridine (189). This indicates that the magnitude of $^nJ_{N-F}$ does decrease with distance, which parallels the results for $^nJ_{N-F}$ in pyridine.

Fluoroanilines

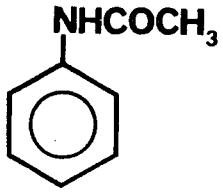
^{15}N chemical shifts and N-F coupling constants of fluoroanilines and derivatives are presented in Table XX. Substitution of a fluorine at carbon 2 or 4 in aniline shields the nitrogen. Similar shielding effects have been observed for other conjugatively interacting substituents (47-49,190). The shielding by two fluorines in 15 is nearly additive. Substition of fluorine in the meta position results in a small shielding (0.6 ppm). Protonation of fluoroanilines consistently leads to shielding. This behavior is similar to that seen on protonation of aniline. Conversion of the primary fluoroanilines (12-15) to their corresponding dimethylamino compounds (22-25) results in a consistent shielding of 8-13 ppm except in compound 25. Shielding of the same type is exhibited by anilines and toluicines and can be attributed to a reduction of lone-pair delocalization by the methyl groups (191). Conversion of the sp^3 nitrogen to an sp^2 nitrogen as in compounds 26 and 31 results in a large deshielding of nearly 40 ppm. This change results from the presence of an additional group ($-\overset{O}{\overset{\|}{C}}-$ or $-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-$) into which the lone-pair can be delocalized. The effects of fluo-

Table X.X ^{15}N Chemical Shifts and $^{15}N-^{19}F$ Coupling Constants in Fluoroanilines

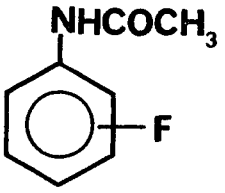
Compound	Number		δ_N, ppm[a]	$^nJ_{N-F}$,[b] Hz (n)
	11		56.5	
	12	2-F	42.3	0 (3)
	13	3-F	55.9	0 (4)
	13	4-F	53.9	1.5 (5)
	15	2,4-F	38.9	1.5 (5)
	16	2-CH_3, 4-F	50.4	1.5 (5)
	17		51.1	
	18	2-F[c]	38.7	1.3 (3)
	19	3-F[c]	45.5	0.2 (4)
	20	4-F	48.3	0.0 (5)
	21		44.6	



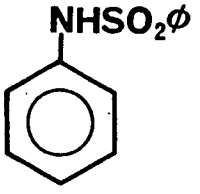
22	2-F	33.7	0.0 (3)
23	3-F	46.6	0.0 (4)
24	2,4 F_2	40.5	0.5 (5)



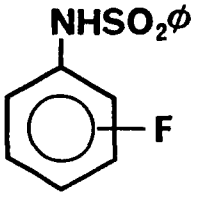
26		138.1	



27	2-F	120.3[d]	1.0 (3)
28	3-F	134.3[d]	0.9 (4)
28	4-F	131.8[d]	0.5 (5)
30	2-CH_3, 4-F	118.1[d]	0.2 (5)



31		132.0[d]	



32	2-F	109.7[d]	1.9 (3)
33	3-F	122.5[d]	0.5 (4)
34	4-F	117.1[d]	0.8 (5)
35	2,4-F_2	108.3[d]	1.3,1.8 (3,5)

[a]Resonances to lower field from anhydrous ammonia.

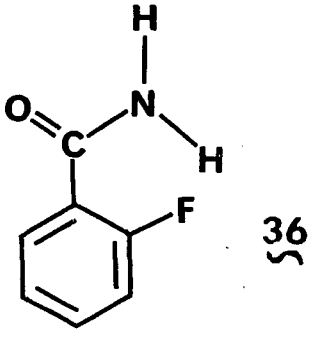
[b]Experimental uncertainty $<$ 0.2 Hz.

[c]As trifluoroacetates in $CHCl_3$.

[d]As solutions in DMSO.

rine on the chemical shifts in compounds 26 and 31 are very similar to the ones in the anilines and is very highly additive.

The most striking thing about N-F couplings in fluoroanilines and its derivatives is tnat the magnitude of the couplings do not exceed 2 Hz. The nature of the nitrogen atom also has very little effect on the coupling. Furthermore, compounds 12-16 display only a five-bond coupling; no measurable three- or four-bond coupling exists. Couplings of 0.1 Hz would have been discernible since the digital resolution during these experiments was 0.06 Hz. The possibility of intramolecular hydrogen-bonding in 12 as a factor in reducing $^{3}J_{N-F}$ can be excluded because the same results are obtained in the N,N-dimethyl derivatives 22-25, where there is no possibility of hydrogen-bonding. Microwave studies have shown that there is very little or no hydrogen-bonding in 12 (192). However, that the lone-pair does play some role in three-bond couplings is seen by the observed value of 1.3 Hz for $^{3}J_{N-F}$ in o-fluoroanilinium ion 18. The role of hydrogen bonding in N-F couplings is ambiguous. In o-fluorobenzamide 36 , $^{4}J_{N-F}$ depends on solvent (36). $^{4}J_{N-F}$ is larger (-7.0 Hz) in $CDCl_3$ than in $(CD_3)_2SO$ (-3.2 Hz).



36

This shows that $^4J_{N-F}$ depends on a conformation that is maintained by means of an intramolecular N-F hydrogen-bond, since the magnitude is smaller in $(CD_3)_2SO$ (less intramolecular hydrogen bonding) than in $CDCl_3$ (more intramolecular hydrogen bonding). In anilinium ions 18-20, the N-F couplings decrease with distance. This pattern can be compared to F-F and C-F couplings in the corresponding difluorobenzenes and isoelectronic fluorotoluenes respectively. In the difluorobenzenes the F-F couplings decrease in the order $^3J_{F-F}$ = 20.1 Hz, $^4J_{F-F}$ = 6.6 Hz, $^5J_{F-F}$ = 12.5 Hz (123). The larger couplings in these compounds can be accounted for by the larger magnetogyric ratio for ^{19}F. The apparent distance dependence of $^nJ_{F-F}$ in difluorobenzenes is opposite to that of $^nJ_{F-F}$ in 18-20 and in 12-14. One reason for the small values of $^4J_{F-F}$ compared with $^5J_{F-F}$ may be lack of conjugative interactions between the two fluorines in the m-difluorobenzene. In the fluorotoluenes $^nJ_{C-F}$ decreases with distance; $^3J_{C-F}$ = 3.8 Hz, $^4J_{C-F}$ =1.8 Hz, $^5J_{C-F}$ =0.0 Hz (193). This behavior indeed parallels that for 18-20. The N-F couplings in acetanilides 27-30 and benzenesulfonamides 32-35, show a slight increase relative to the corresponding anilines. Compounds 27-30 show the same trend in coupling as fluoroanilinium ions, i.e., the couplings decrease with distance. The same trend does not arise in compounds 32-35. The slight increase in couplings in these compounds (27-30, 32-35) may be related to an increase in s character at the nitrogen.

In conclusion, the N-F couplings in fluoropyridines parallel the trends in the N-H couplings of pyridines and the C-F couplings in fluorobenzene but the N-F couplings are slightly larger in magnitude. The magnitudes of N-F couplings in fluoroanilines are very small and further experimentation is needed to establish the role of solvent and self association on these couplings.

EXPERIMENTAL SECTION

This section describes the way the chemical shifts and coupling constants were determined and then describes any of the syntheses involved.

Chapter 2

Natural-abundance ^{13}C and ^{15}N spectra were determined at 25.03 and 10.09 MHz, respectively, by the pulsed Fourier transform method on a JEOL PS/PFT-100 NMR spectrometer equipped with the JEOL EC-100 data system. For ^{13}C spectra, a sweep width of 5.0 KHz over 8K data points was used, and 1000-2000 transients were collected for proton-noise decoupled spectra. Pulse widths corresponding to tip angles of $20-25^{0}$ and a repetition rate of 2.0 sec were employed. The compounds were run using 10-15% deuteriobenzene as internal lock in solution with 2% tetramethylsilane. The chemical shifts were referenced to tetramethylsilane.

Intially, ^{15}N spectra of the free bases were determined using 10-15% deuteriobenzene as internal lock in solution, and were referenced to an external capliary of 2.9 M enriched ammonium chloride in 1 M HCl. It was noted that the resonance positions were solvent sensitive and to overcome this all compounds were run as pure liquids. Subsequently, samples were run using a concentric capillary of ca.20%

enriched nitromethane in deuteriobenzene, which provided the field frequency lock. Under these conditions the resonance position of nitromethane lies at 380.23 ppm to lower field from that of anhydrous liquid ammonia. The experimental measurement uncertainty is estimated to be ±0.2 ppm or better. For ^{15}N spectra of the primary amines, a sweep width of 5.0 kHz over 8K data points was used, and 1000-2000 transients were collected for proton noise decoupled spectra. Pulse widths corresponding to tip angles of 20-25^0 and a repetition rate of 2.0 sec were employed. For tertiary amines, a pulse width corresponding to tip angles of 15-20^0 and a repetition rate of 5 sec were employed and spectras were accumulated overnight to get adequate signal intensities. Chromium tris(acetylacetonate) (ca. 10-20 mg) was added to compounds with tertiary nitrogens to shorten T_1 values.

All compounds except 2a-5 were available commercially. Compounds 2a-5 were prepared by methylation of the primary amine using trimethylphosphate (194). The compounds were characterized by ^1H nmr, infrared spectra, and boiling point comparison with literature values (195).

In a typical synthesis 0.1 mol of the primary amine was heated with 0.104 mol of trimethylphosphate under nitrogen at 160-180 for 3 h. Then the phosphate ester was hydrolysed using 10% NAOH. The resulting solution was extracted with ether. The dimethylanilines were purified by distillation.

CHAPTER 3

The chemical shifts were determined as described above. Spectra for compounds 2j, 4i, 4j were determined at Florida State University.

Compounds 1a-1m, 2a-2d, 2f-2g, 2i-2k, 3a, 3d, 3g are all commercially available. The remaining compounds were prepared according to literature procedures and characterized by comparison with literature melting points and boiling points and ^1H nmr.

Syntheses of 2e and 2h

Compounds 2e and 2h were prepared by methylation of the corresponding primary amines using trimethylphosphate as described in Chapter 2 (196).

Synthesis of 3b

Compound 3b was prepared by methylation of 3,5-dimethyl-4-nitroaniline (57) using trimethylphosphate, as described above. The resulting 3,5-dimethyl-4-nitro-N,N-dimethylaniline was catalytically hyrogenated over Pd/C using a Parr hydrogenator to get 3b (197).

Synthesis of 3c

A mixture of 3,5-dimethyl-4-nitroaniline (4.42 g) (57) concentrated hydrochloric acid (6.0 ml), and water (6.0 ml) was diazotised with sodium nitrite (2.6 g) in water (7.5 ml). After diazotization, the mixture was filtered. The diazonium chloride solution was then added slowly to a hot 25% sulfuric acid (50 ml). The mixture was refluxed for 2 hours and then steam distilled. 3,5-dimethyl-4-nitrophenol was isolated from the distillate by ether extraction. The compound was recrystallized using 95% ethanol. The above compound was refluxed with excess methyl iodide in anhydrous methanol and anhydrous potassium carbonate for 2 days. The mixture was then concentrated and poured into water and extracted with ether. The ether was removed to get 3,5-dimethyl-4-nitroanisole. This was then catalytically hydrogenated overnight in absolute ethanol with Pd/C using a Parr hydrogenater. The catalyst was filtered and ethanol removed. Compound 3c was purified by distillation at reduced pressure (196).

Synthesis of 3e

Compound 3e was prepared from 3,5-dimethyl-4-nitroaniline according to Dewar's procedure (57).

Synthesis of 3f

0.1 mol of 3,5-dimethyl-4-nitroaniline was diazotized as described for 3c and the diazonium chloride was filtered into a solution of cuprous chloride (20 g) in concentrated hydrochloric acid (100 ml) at 60 . The solution was stired for 2 hours and then steam distilled. The stesm distillate was extracted with ether and the ether extract was dried over anhydrous sodium sulfate and filtered. The ether was removed and the resulting 4-chloro-2,6-dimethylnitrobenzene was recrystallized using 95% ethanol. Then it was catalytically hydrogenated as described for 3c. The resulting amino compound after work up was distilled under reduced pressure (199).

Synthesis of 3i

A mixture of 4-bromo-2,6-dimethylaniline (4 g) and cuprous cyanide (2 g) in 100 ml of dry DMF was refluxed for 4 hours. The reaction mixture was then poured into 400 ml of 1 M ferric chloride solution. The solution was extracted using benzene. The benzene extract was dried and the benzene removed. Compound 3i was recrystallized using benzene-hexane (200).

Synthesis of 3j

Compound 3j was prepared according to Wepster's procedure (53).

Synthesis of 3k

Compound 3k was prepared by catalytic hydrogenation of 4-nitro-2,6-dimethylaniline (197).

Synthesis of 3m

Compound 3m was prepared by catalytic reduction of 3,5-dimethyl-4-nitrobenzoic acid (58).

Syntheses of 4a, 4b, 4d, 4e, 4g, 4i, 4j, 4m

The above compounds were prepared by methylation of the corresponding primary anilines using trimethylphosphate (57,58,195,197,201-204).

Synthesis of 4k

Compound 4k was prepared by catalytic reduction of 4j over Pd/C as described above (197).

Chapter 4

The nmr chemical shifts were determined as described in Chapter 2. All the compounds were commercially available.

Chapter 5

The nmr chemical shifts were determined as described in Chapter 2. The spectra for unsymmetrical ureas and thioureas were assigned on the basis of gated decoupling experiments. All the compounds were commercially available.

Chapter 6

The nmr chemical shifts were determined as described in Chapter 2. Coupling constants were determined using a sweep width of 500 Hz over 16K data points, giving a digital resolution of 0.06 Hz, and experimental values are assumed precise to 0.2 Hz. Liquids were determined as neat compounds, and solids as solutions in DMSO (exact concentrations not determined). The anilinium salts were determined as solutions in $CDCl_3$ using a two-equivalent excess of CF_3COOH relative to the amine.

Compounds 1, 3, 4, 5, 6, 7, 11-16, 21, 26, wee commercially available.

Synthesis of 22-25

Compounds 22-25 were prepared by methylation of their repspective primary anilines using trimethylphosphate, as described in Chapter 2 (205).

Synthesis of 27-30

Compounds 27-30 were prepared by acylation of their respective primary anilines using acetyl chloride (205). In a typical synthesis 0.1 mol of the primary amine is dissolved in 25 ml of dry pyridine and dry benzene and 0.1 m of acetyl chloride is added dropwise. After stirring for 1/2 h, the mixture is warmed to 60 on a water bath. The mixture is then poured into water, extracted with benzene and the benzene layer washed with sodium bicarbonate. The resulting benzene solution is evaporated, and the product is recrystallized using a benzene-petroleum ether mixture (205).

Synthesis of 32-35

Compounds 32-35 were prepared by treatment of their respective primary anilines with benzenesulfonyl chloride (206). Similar procedures as above were used. The products were recrystallized using benzene-petroleum ether.

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